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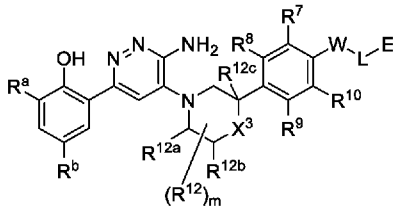
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(54) Title: SMARCA2 DEGRADERS AND USES THEREOF



(A)

(57) Abstract: The present disclosure provides compounds represented by Formula (A), or a pharmaceutically acceptable salt and/or stereoisomer thereof: (A), wherein R^a, R^b, R^7, R^8, R^9, R^{10}, R^{12}, R^{12a}, R^{12b}, R^{12c}, m, X^3, W, L, and E are as defined in the specification. Compounds represented by Formula (A) are SMARCA2 protein degraders and are thus useful for treating cancer and other diseases.

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SMARCA2 DEGRADERS AND USES THEREOF

BACKGROUND

Field

[0001] The present disclosure provides Proteolysis Targeting Chimera (PROTAC) compounds and the use of such PROTAC compounds for the treatment of diseases or disorders dependent on SMARCA2 in mammals. Degradation of SMARCA2 may provide, for example, an anti-tumor effect. The present disclosure thus provides the use of SMARCA2 degraders and pharmaceutical compositions comprising SMARCA2 degraders for the treatment of cancer. It also provides intermediate compounds that may be useful in the preparation of such PROTACs.

Background

[0002] Traditional "small molecule" drugs reversibly (or sometimes irreversibly) bind to a target protein as a means of modulating a given biological activity. In contrast, PROTACs bind to their target proteins reversibly, but then bring about the target protein's degradation. Having achieved this effect, the PROTAC is in theory able to repeat this process with another target protein. Accordingly, unlike traditional small molecule inhibitors, the PROTAC-driven degradation mechanism can in theory operate in a sub-stoichiometric manner - meaning that more modest exposures of a PROTAC compound could still achieve a desired level of efficacy *in vivo*. In practice, this means that the degradation power (DC_{50} and D_{max}) of a PROTAC may have an improved effect over that reflected by its binding affinity.

[0003] PROTAC molecules are described as having three parts - (1) a part that is capable of binding to the protein to be degraded, (2) a second part that is capable of binding to an E3 ubiquitin ligase, and (3) a linker that connects parts (1) and (2) together. In use, the PROTAC binds to both the target protein and E3 ubiquitin ligase simultaneously to form a ternary complex. The E3 ligase then recruits an E2 conjugating enzyme to the ternary complex, which ubiquitinates the target protein. This has the effect of labelling the target protein for degradation by the cell's proteasome machinery. A PROTAC can then dissociate from the target protein and initiate another cycle of this process in a catalytic manner. Meanwhile, the ubiquitinated target proteins are recognized by the cell's proteasome machinery and are then degraded by it. This PROTAC-mediated approach may be valuable as a method of treating certain diseases, including cancer.

[0004] SMARCA4 is a frequently mutated in several tumor types - including lung, liver, colon, skin, bladder, esophageal, gastric, brain, endometrial, cervical and ovarian cancers. Furthermore, it has been established that SMARCA2 is essential for growth of tumors harboring such SMARCA4 mutations. Accordingly, selective suppression of SMARCA2 has been proposed as a therapeutic strategy against cancers that may include SMARCA4 mutations. Accordingly, selective suppression of SMARCA2 may be useful against a number of cancer types, including lung, liver, colon, skin, bladder, esophageal, gastric, brain, endometrial, cervical and ovarian cancers.

[0005] WO2019/207538 discloses certain PROTAC compounds described as "SMARCA 2/4 degraders" and WO2020251969 discloses PROTAC compounds which target one or more of SMARCA2, SMARCA4 and PB1. WO2019/195201 also discloses 'bifunctional' compounds described as modulators of SMARCA2. WO2019/213005 relates to compounds that are said to degrade PBRM1. WO2018/144649 and WO2021/053495 also disclose certain PROTAC molecules. WO2021/053555 discloses glue degrader compounds which bind to the E3 ubiquitin ligase, cereblon.

[0006] As part of developing a PROTAC against cancer, there is a need to develop further PROTAC compounds with a combination of beneficial/improved properties that make them more suitable for use as a therapeutic drug for human use. Properties of interest during pharmaceutical discovery and development may relate to selectivity profile, absorption/bioavailability, distribution, metabolism, elimination, toxicity and side-effect profile, stability, manufacturability and so on.

BRIEF SUMMARY

[0007] In one aspect, the present disclosure provides PROTAC compounds represented by any one of Formulae (A), (IA), or (I)-(XVI), below, and the pharmaceutically acceptable salts thereof, or stereoisomers thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 1, below, and the pharmaceutically acceptable salts thereof or stereoisomers thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 2, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 3, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 4, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 5, below, and the pharmaceutically acceptable salts thereof. Compounds having any one of Formulae (A), (IA), or (I)-(XVI), and the pharmaceutically acceptable salts thereof, or stereoisomers thereof, and the PROTAC compounds of Compound List 1, Compound List 2, Compound List 3, Compound List 4 and/or Compound List 5, and the pharmaceutically acceptable salts thereof, or stereoisomers thereof, are collectively referred to as "Compounds of the Disclosure" or individually as a "Compound of the Disclosure." Compounds of the Disclosure exhibit protein degradation activity against SMARCA2. Compounds of the Disclosure also may have a beneficial degree of selectivity to minimize certain undesirable off-target degradation activities. As such, Compounds of the Disclosure may be useful in the treatment of cancer.

[0008] Compounds of the Disclosure also may have a surprisingly beneficial combination of properties of relevance in the context of pharmaceutical discovery and development. Structural features found in all three regions of a PROTAC have the potential to operate (collectively or in some cases separately) towards delivering a beneficial combination and/or balance of such additional beneficial properties. Avoidance of

off-target activity in pharmaceutical development is often important to avoid or reduce unwanted toxicities, side-effects or other problems with tolerability when used in patients

[0009] As well as being degraders of SMARCA2, Compounds of the Disclosure have a surprising and beneficial combination of properties relating, for example, to chemical and metabolic stability, e.g. in human microsomes and to hydrolysis at pH 7.4, and selectivity against SALL4 and/or Ikaros (IKZF1) – which is expected to provide an improved safety profile for use *in vivo*. Without wishing to be bound by any particular theory, it is believed that degradation of SALL4 and Ikaros (IKZF1) amongst others may risk serious unwanted effects in humans, for example, developmental toxicities or bone marrow toxicities.

[0010] Also, in this regard, it has been found that molecules that degrade SMARCA2 can often also degrade SMARCA4, which is regarded as an undesirable off-target activity. Compounds of the Disclosure may show a beneficial selectivity profile by achieving a potent degree of degradation against SMARCA2 while having a margin of selectivity, i.e., relatively lower degradation, against SMARCA4. In a similar manner in the development of a SMARCA2 PROTAC for use in cancer, it is also regarded as beneficial to have a potent degree of degradation against SMARCA2 while having a good margin of selectivity, i.e., relatively lower degradation, against PBRM1. Compounds of the Disclosure may show a beneficial selectivity profile between SMARCA2 and PBRM1. Thus, in combination, Compounds of the Disclosure may show high potency against SMARCA2 while simultaneously achieving a beneficial selectivity profile with respect to SALL4 and/or Ikaros (IKZF1), and in some cases a surprisingly beneficial margin of selectivity against SMARCA4 and/or PBRM1.

[0011] In another aspect, the present disclosure provides pharmaceutical compositions comprising a Compound of the Disclosure and one or more pharmaceutically acceptable excipients.

[0012] In another aspect, the present disclosure provides methods of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0013] In another aspect, the present disclosure provides methods of reducing SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0014] In another aspect, the present disclosure provides methods of treating cancer in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0015] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in degrading SMARCA2 protein in a human.

[0016] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in reducing SMARCA2 protein in a human.

[0017] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in treating cancer in a human.

[0018] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[0019] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for reducing SMARCA2 protein in a human.

[0020] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for treating cancer in a human.

[0021] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

[0022] In another aspect, the present disclosure provides intermediates used to prepare Compounds of the Disclosure.

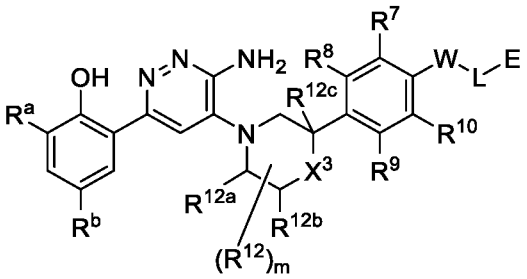
[0023] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION

I. Compounds of the Disclosure

[0024] Many embodiments of this disclosure are detailed throughout the specification.

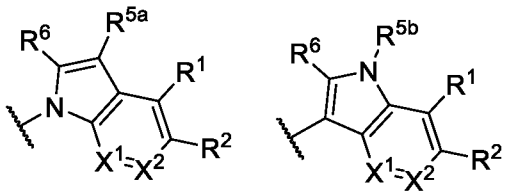
[0025] In one embodiment, Compounds of the Disclosure are compounds having Formula (A), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(A),

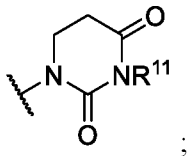
wherein:

[0026] E is:



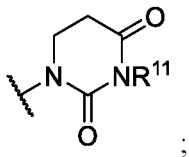
E-1 or E-2 ;

[0027] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

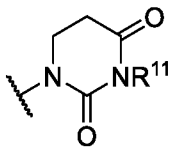
[0028] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

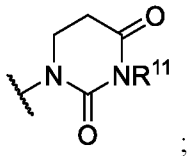
[0029] with the provisos:

[0030] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[0031] (ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

[0032] R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

[0033] X^1 is CR^3 or N;

[0034] R^3 is hydrogen, halogen, or (C_1-C_6)alkyl;

[0035] X^2 is CR^4 or N;

[0036] R^4 is hydrogen, halogen, or (C_1-C_6)alkyl;

[0037] R^{5a} is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl;

[0038] R^{5b} is hydrogen, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl;

[0039] R^6 is hydrogen, (C_1-C_6)alkyl, or cyano;

[0040] X^3 is $-(CR^{13a}R^{13b})_n-$ or -O-;

[0041] n is 0 or 1

[0042] each R^{13a} and R^{13b} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

[0043] L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;

[0044] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[0045] G^2 is (C_1-C_6)alkylenyl, -C(=O)-, or a direct bond;

[0046] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[0047] G^4 is (C_1-C_6)alkylenyl or a direct bond;

[0048] W is -C(=O)-, $-CH_2-$, or a direct bond;

[0049] R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0050] R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0051] R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0052] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0053] each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

[0054] m is 0, 1, 2, 3, or 4;

[0055] R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

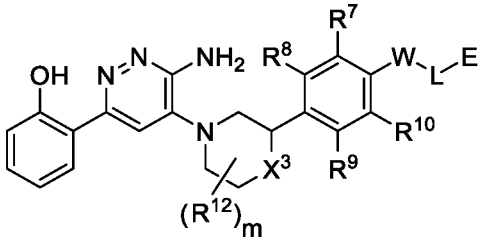
[0056] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl;

[0057] R^{12c} is hydrogen or halogen;

[0058] R^a is hydrogen or halogen; and

[0059] R^b is hydrogen or halogen.

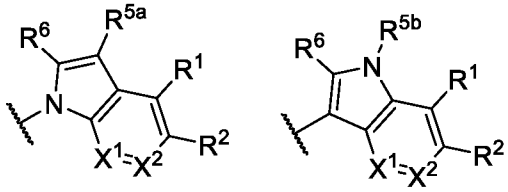
[0060] In another embodiment, Compounds of the Disclosure are compounds having Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



(I),

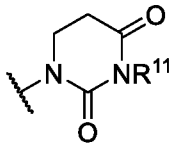
wherein:

[0061] E is:



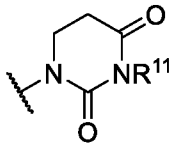
E-1 or E-2 ;

[0062] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

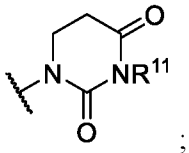
[0063] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

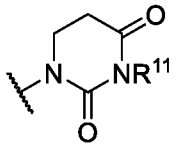
with the provisos:

[0064] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[0065] (ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

[0066] R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

[0067] X^1 is CR^3 or N;

[0068] R^3 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[0069] X^2 is CR^4 or N;

[0070] R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[0071] R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

[0072] R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

[0073] R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

[0074] X^3 is $-(CR^{13a}R^{13b})_n-$ or -O-;

[0075] n is 0 or 1

[0076] each R^{13a} and R^{13b} is independently H, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[0077] L is $-G^1$-G^2-G^3-G^4-, wherein G^1 is attached to W;

[0078] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[0079] G^2 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[0080] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[0081] G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[0082] W is -C(=O)-;

[0083] R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[0084] R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

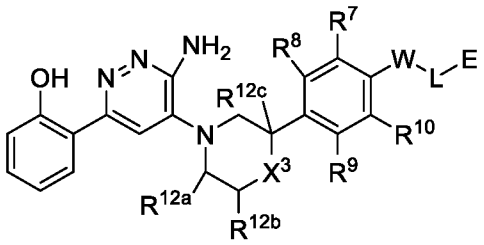
[0085] R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[0086] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0087] each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

[0088] m is 0, 1, 2, 3, or 4.

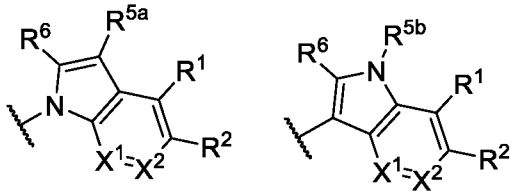
[0089] In another embodiment, Compounds of the Disclosure are compounds having Formula (IA), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(IA),

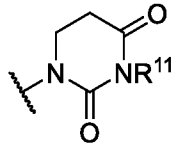
wherein:

[0090] E is:



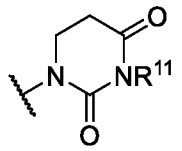
E-1 or E-2 ;

[0091] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

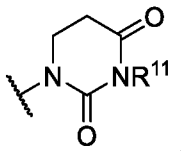
[0092] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

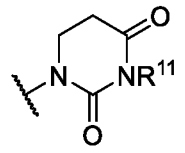
with the provisos:

[0093] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[0094] (ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

[0095] R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

[0096] X^1 is CR^3 or N;

[0097] R^3 is hydrogen, halogen, or (C_1-C_6)alkyl;

[0098] X^2 is CR^4 or N;

[0099] R^4 is hydrogen, halogen, or (C_1-C_6)alkyl;

[0100] R^{5a} is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl;

[0101] R^{5b} is hydrogen, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl;

[0102] R^6 is hydrogen, (C_1-C_6)alkyl, or cyano;

[0103] X^3 is -$(CR^{13a}R^{13b})_n$- or -O-;

[0104] n is 0 or 1

[0105] each R^{13a} and R^{13b} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

[0106] L is -G^1-G^2-G^3-G^4-, wherein G^1 is attached to W;

[0107] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[0108] G^2 is (C_1-C_6)alkylenyl, -C(=O)-, or a direct bond;

[0109] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[0110] G^4 is (C_1-C_6)alkylenyl or a direct bond;

[0111] W is -C(=O)-, -CH_2-, or a direct bond;

[0112] R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0113] R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0114] R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

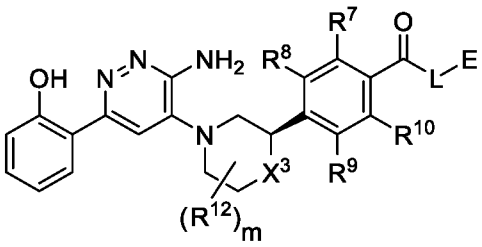
[0115] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[0116] R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

[0117] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl ; and

[0118] R^{12c} is hydrogen or halogen.

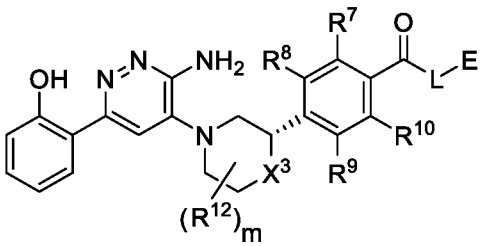
[0119] In another embodiment, Compounds of the Disclosure are compounds having Formula (II):



(II),

[0120] wherein R^7, R^8, R^9, R^{12}, m, E, L, and X^3 are as defined in connection with Formula (I).

[0121] In another embodiment, Compounds of the Disclosure are compounds having Formula (III):



(III),

[0122] wherein R^7, R^8, R^9, R^{12}, m, E, L, and X^3 are as defined in connection with Formula (I).

[0123] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X^3 is -($CR^{13a}R^{13b}$)-.

[0124] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R13a and R13b are hydrogen.

[0125] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R13a and R13b are fluoro.

[0126] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R13a is methyl or methoxy; and R13b is hydrogen.

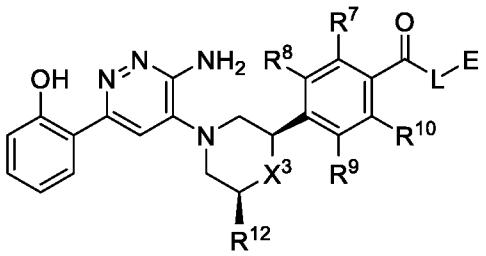
[0127] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X3 is -O-.

[0128] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein m is 0.

[0129] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein m is 2.

[0130] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein m is 1.

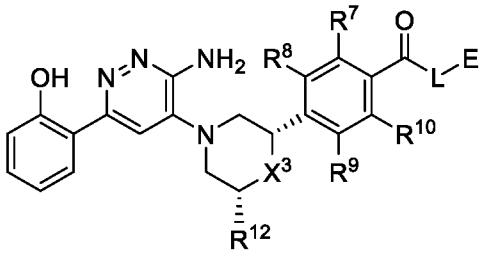
[0131] In another embodiment, Compounds of the Disclosure are compounds having Formula (IV):



(IV),

[0132] wherein R^7, R^8, R^9, R^{12}, E, L, and X^3 are as defined in connection with Formula (I).

[0133] In another embodiment, Compounds of the Disclosure are compounds having Formula (V):

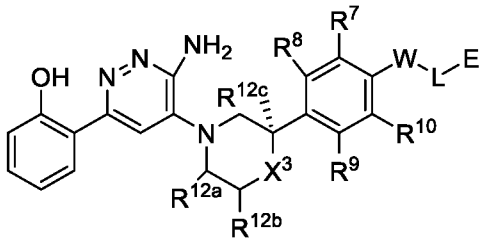


(V),

[0134] wherein R^7, R^8, R^9, R^{12}, E, L, and X^3 are as defined in connection with Formula (I).

[0135] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(V), or a pharmaceutically acceptable salt thereof, wherein each R^{12} is fluoro, methyl, ethyl, or methoxy.

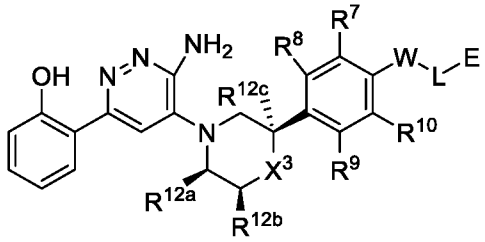
[0136] In another embodiment, Compounds of the Disclosure are compounds having Formula (VIII):



(VIII),

[0137] wherein R^7, R^8, R^9, R^{10}, R^{12a}, R^{12b}, R^{12c}, X^3, W, L, and E are as defined in connection with Formula (IA).

[0138] In another embodiment, Compounds of the Disclosure are compounds having Formula (IX):

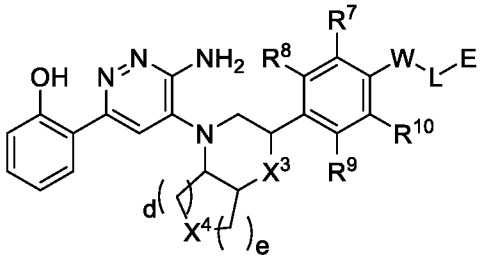


(IX),

[0139] wherein R^7, R^8, R^9, R^{10}, R^{12a}, R^{12b}, R^{12c}, X^3, W, L, and E are as defined in connection with Formula (IA).

[0140] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), (VIII), or (IX), or a pharmaceutically acceptable salt thereof, wherein R^{12a} is hydrogen and R^{12b} is hydrogen, fluoro, methyl, ethyl, or methoxy.

[0141] In another embodiment, Compounds of the Disclosure are compounds having Formula (X):



(X),

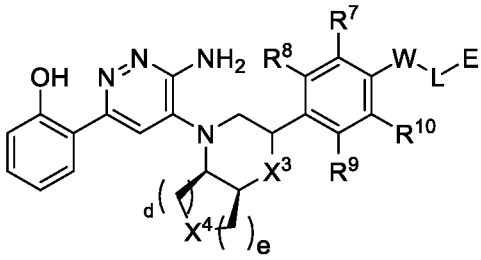
wherein:

[0142] X^4 is O;

[0143] d and e are independently 1 or 2; and

[0144] R^7, R^8, R^9, R^{10}, X^3, W, L, and E are as defined in connection with Formula (IA).

[0145] In another embodiment, Compounds of the Disclosure are compounds having Formula (XI):



(XI),

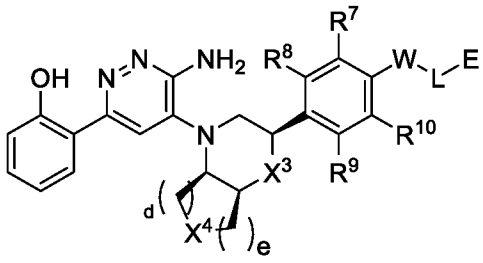
wherein:

[0146] X^4 is O;

[0147] d and e are independently 1 or 2; and

[0148] R^7, R^8, R^9, R^{10}, X^3, W, L, and E are as defined in connection with Formula (IA).

[0149] In another embodiment, Compounds of the Disclosure are compounds having Formula (XII):



(XII),

wherein:

[0150] X^4 is O;

[0151] d and e are independently 1 or 2; and

[0152] R^7, R^8, R^9, R^{10}, X^3, W, L, and E are as defined in connection with Formula (IA).

[0153] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein E is E-1.

[0154] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is hydrogen.

[0155] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is $(C_1$-$C_6)$alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[0156] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is methyl, ethyl, isopropyl, or $-CF_3$.

[0157] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is $(C_3$-$C_6)$cycloalkyl.

[0158] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is cyclopropyl.

[0159] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl.

[0160] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is cyano.

[0161] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl.

[0162] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl.

[0163] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein E is E-2.

[0164] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5b} is hydrogen.

[0165] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5b} is $(C_1$-$C_6)$alkyl.

[0166] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5b} is methyl.

[0167] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof wherein R^{5b} is $(C_3$-$C_6)$cycloalkyl.

[0168] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{5b} is cyclopropyl or cyclobutyl.

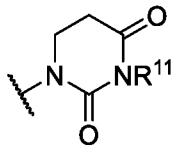
[0169] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.

[0170] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^6 is $(C_1$-$C_6)$alkyl.

[0171] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^6 is cyano.

[0172] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein:

[0173] R^1 is:



; and

[0174] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

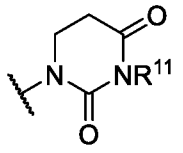
[0175] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[0176] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, fluoro, or methyl.

[0177] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{11} is hydrogen.

[0178] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein:

[0179] R^2 is:



; and

[0180] R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

[0181] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[0182] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen, fluoro, or methyl.

[0183] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{11} is hydrogen.

[0184] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^3.

[0185] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[0186] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^3 is halogen.

[0187] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^3 is fluoro.

[0188] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^3 is $(C_1\text{-}C_6)$alkyl.

[0189] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

[0190] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

[0191] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^4.

[0192] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

[0193] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.

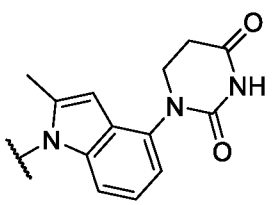
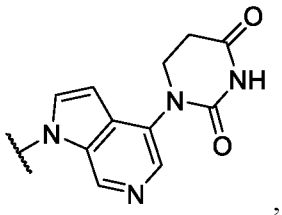
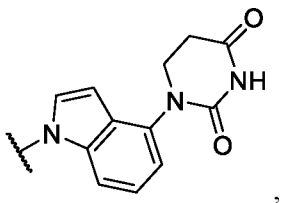
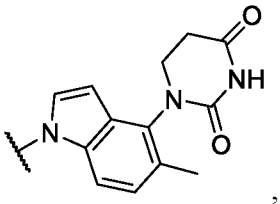
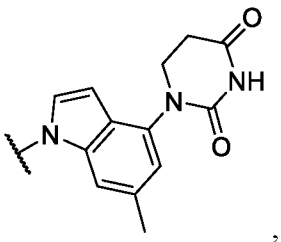
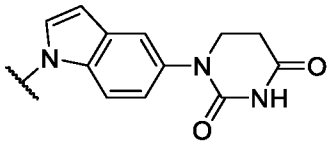
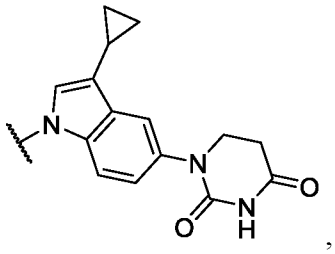
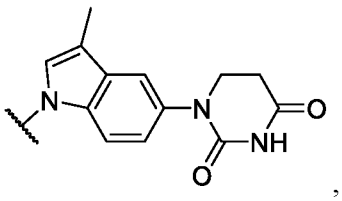
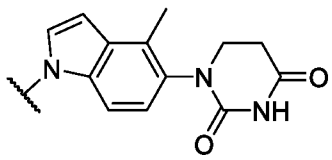
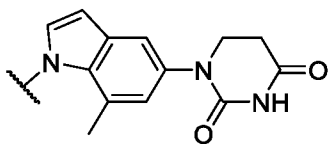
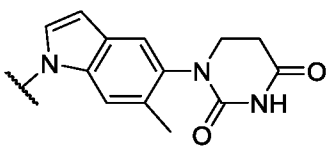
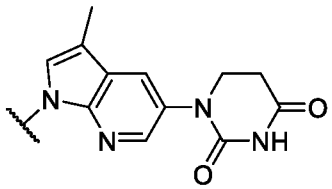
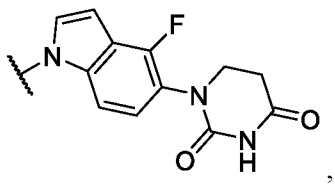
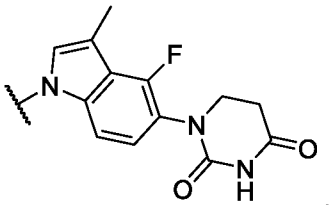
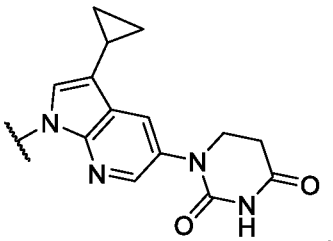
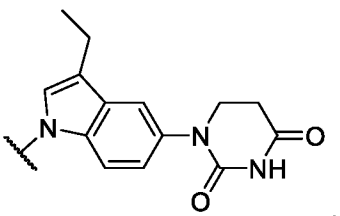
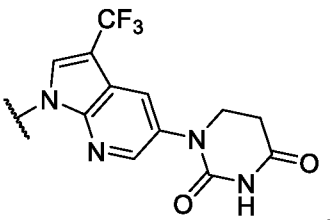
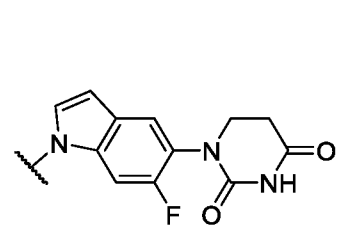
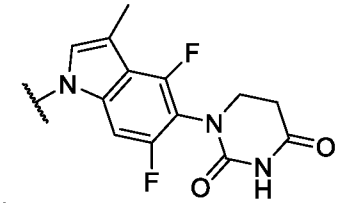
[0194] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^4 is fluoro.

[0195] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^4 is $(C_1\text{-}C_6)$alkyl.

[0196] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl.

[0197] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein X^2 is N.

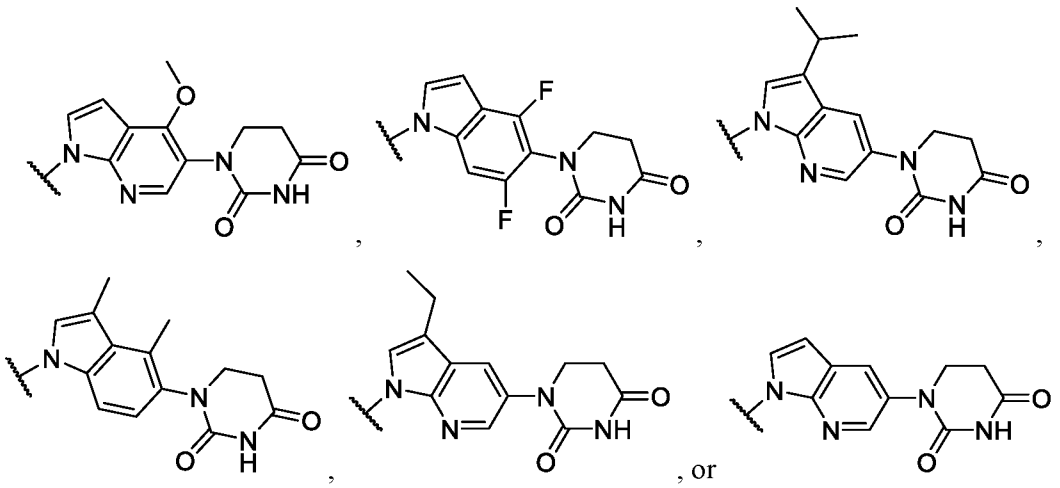
[0198] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein E-1 is:


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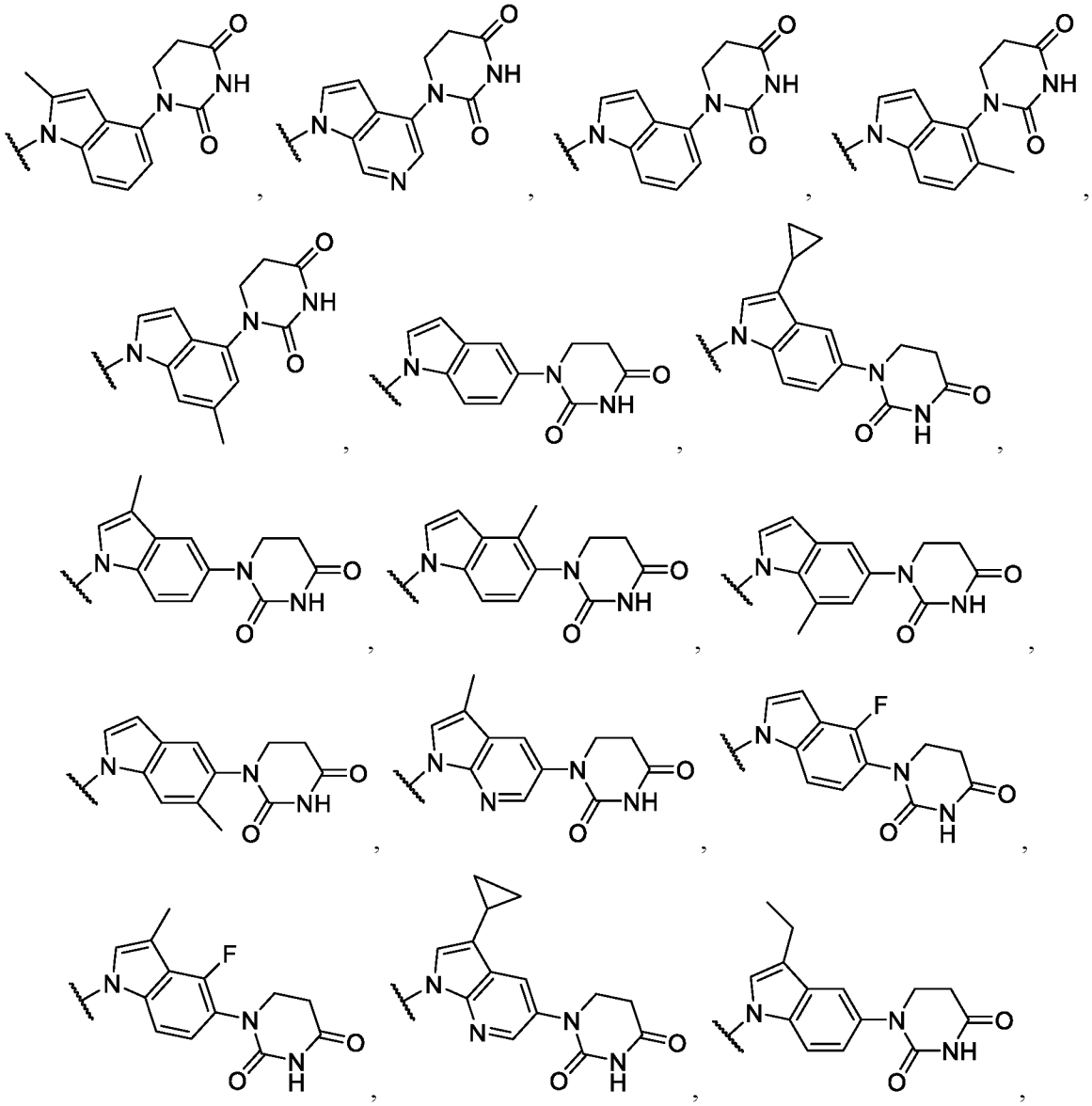
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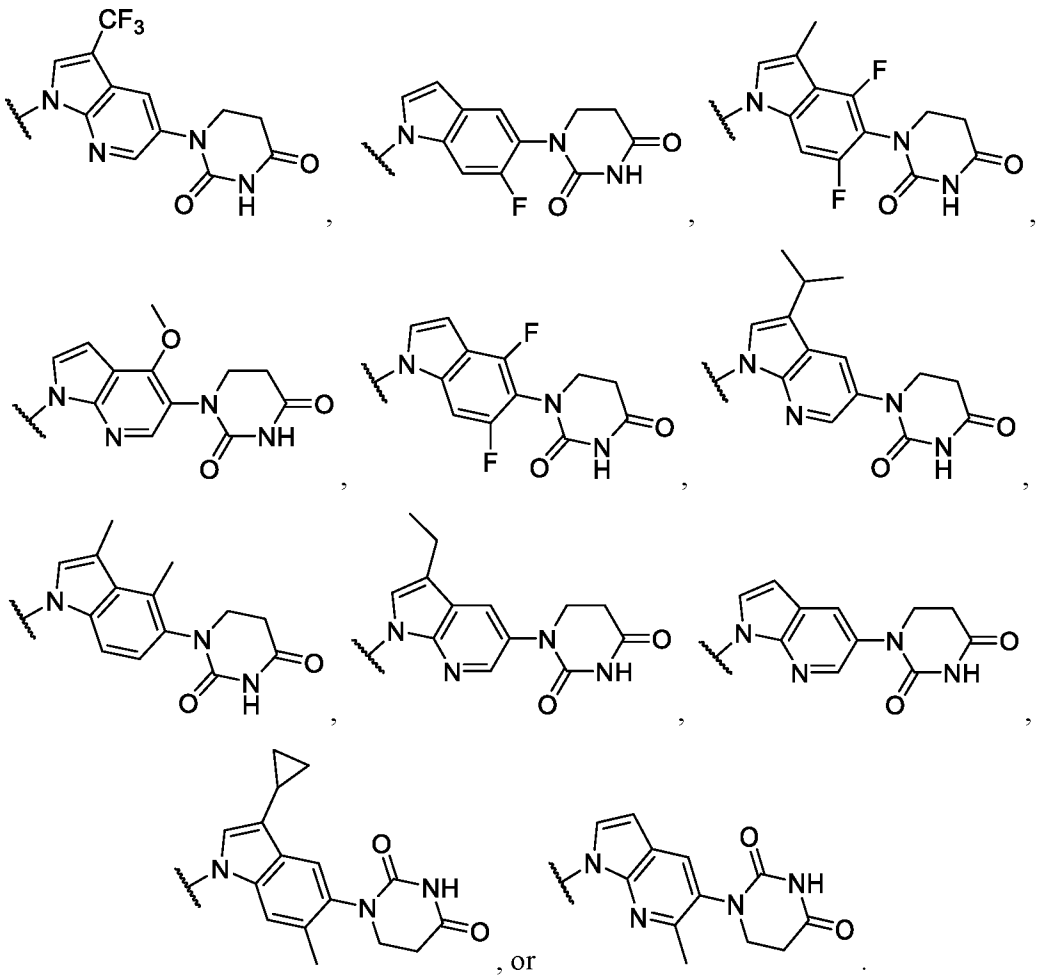
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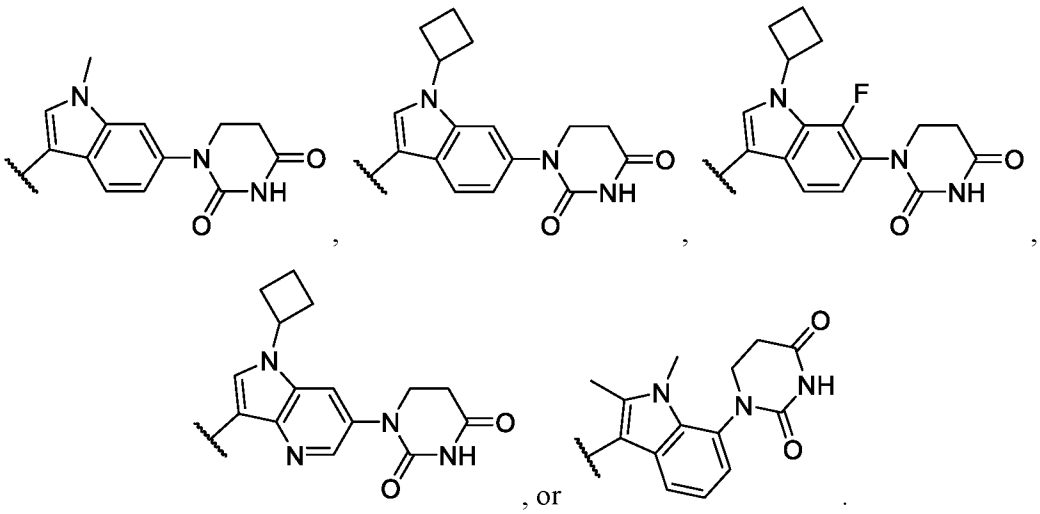


[0199] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein E-1 is:





[0200] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein E-2 is:

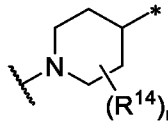


[0201] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^1 is 4-

to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[0202] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein:

[0203] G^1 is:



[0204] each R^{14} is independently halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

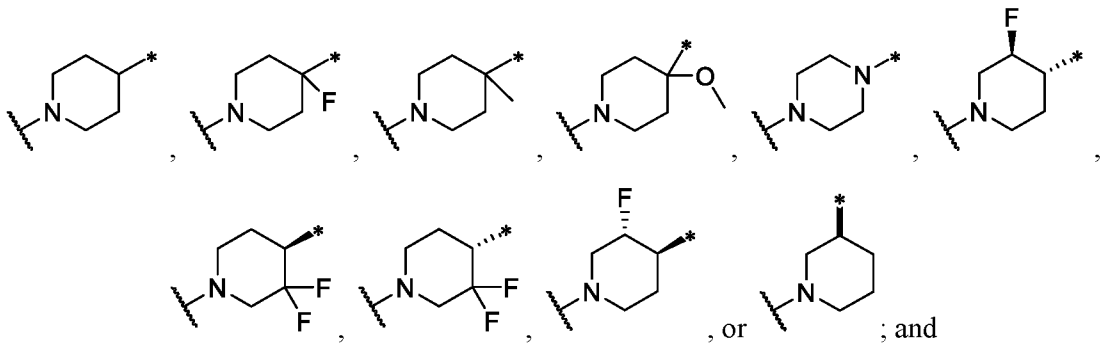
[0205] n is 0, 1, 2, or 3; and

[0206] the bond marked with an "*" is attached to G^2.

[0207] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein n is 0.

[0208] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{14} is fluoro, methyl, or methoxy; and n is 1, or 2.

[0209] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^1 is:

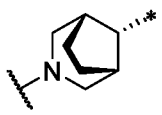


[0210] the bond marked with an "*" is attached to G^2.

[0211] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^1 is (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[0212] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^1 is a 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[0213] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^1 is:


; and

[0214] the bond marked with an "*" is attached to G^2.

[0215] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^2 is a direct bond.

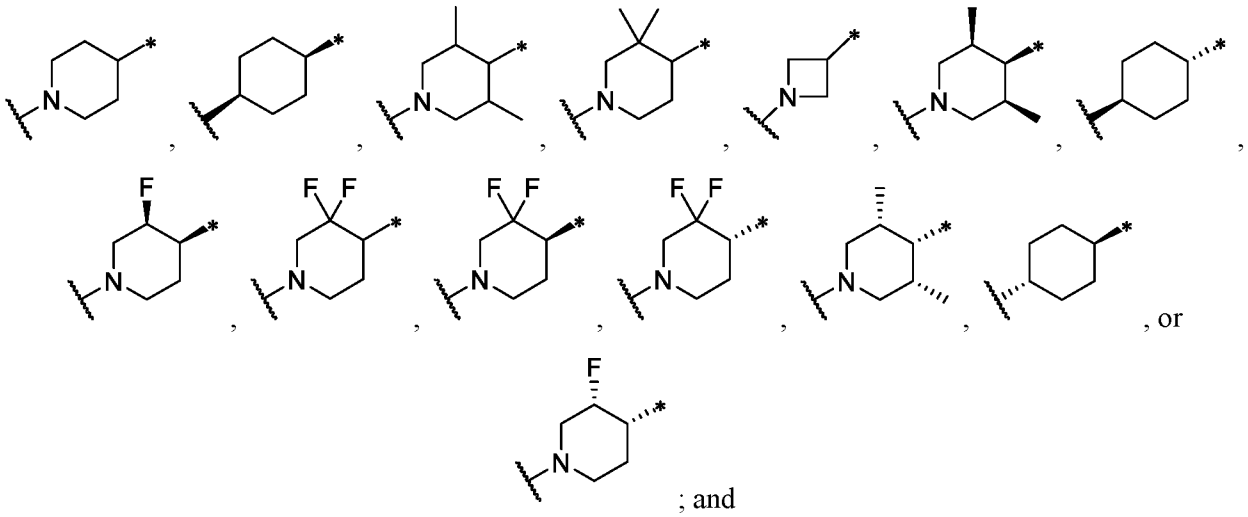
[0216] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^2 is $(C_1\text{-}C_6)$alkylenyl.

[0217] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^2 is -CH_2- or –$CH(CH_3)$-.

[0218] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^2 is –C(=O)-.

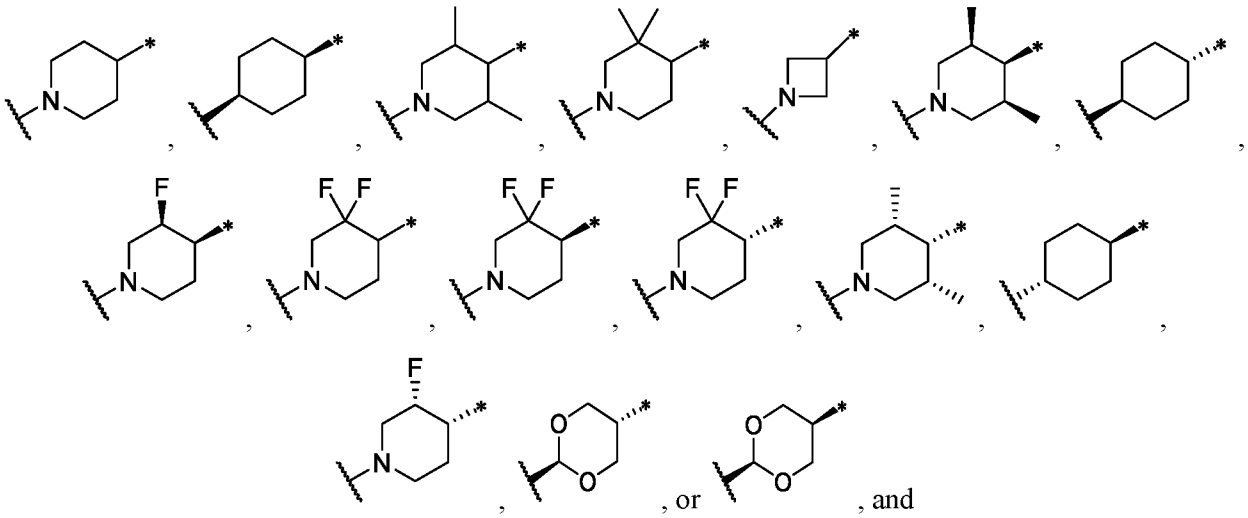
[0219] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V) or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[0220] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:


; and

[0221] the bond marked with an "*" is attached to G^4.

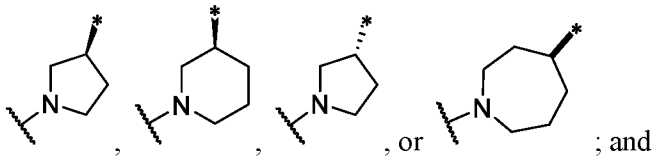
[0222] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V) or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0223] the bond marked with an "*" is attached to G^4.

[0224] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

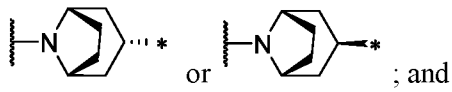
[0225] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0226] the bond marked with an "*" is attached to G^4.

[0227] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

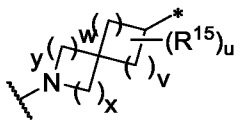
[0228] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0229] the bond marked with an "*" is attached to G^4.

[0230] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein:

[0231] G^3 is:


;

[0232] each R^{15} is independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

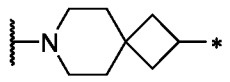
[0233] u is 0, 1, 2, or 3;

[0234] v, w, x, and t are independently 1, 2, or 3; and

[0235] the bond marked with an "*" is attached to G^4.

[0236] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein v, w, x, and y are independently 1 or 2.

[0237] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:


; and

[0238] the bond marked with an "*" is attached to G^4.

[0239] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V) or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is:


; and

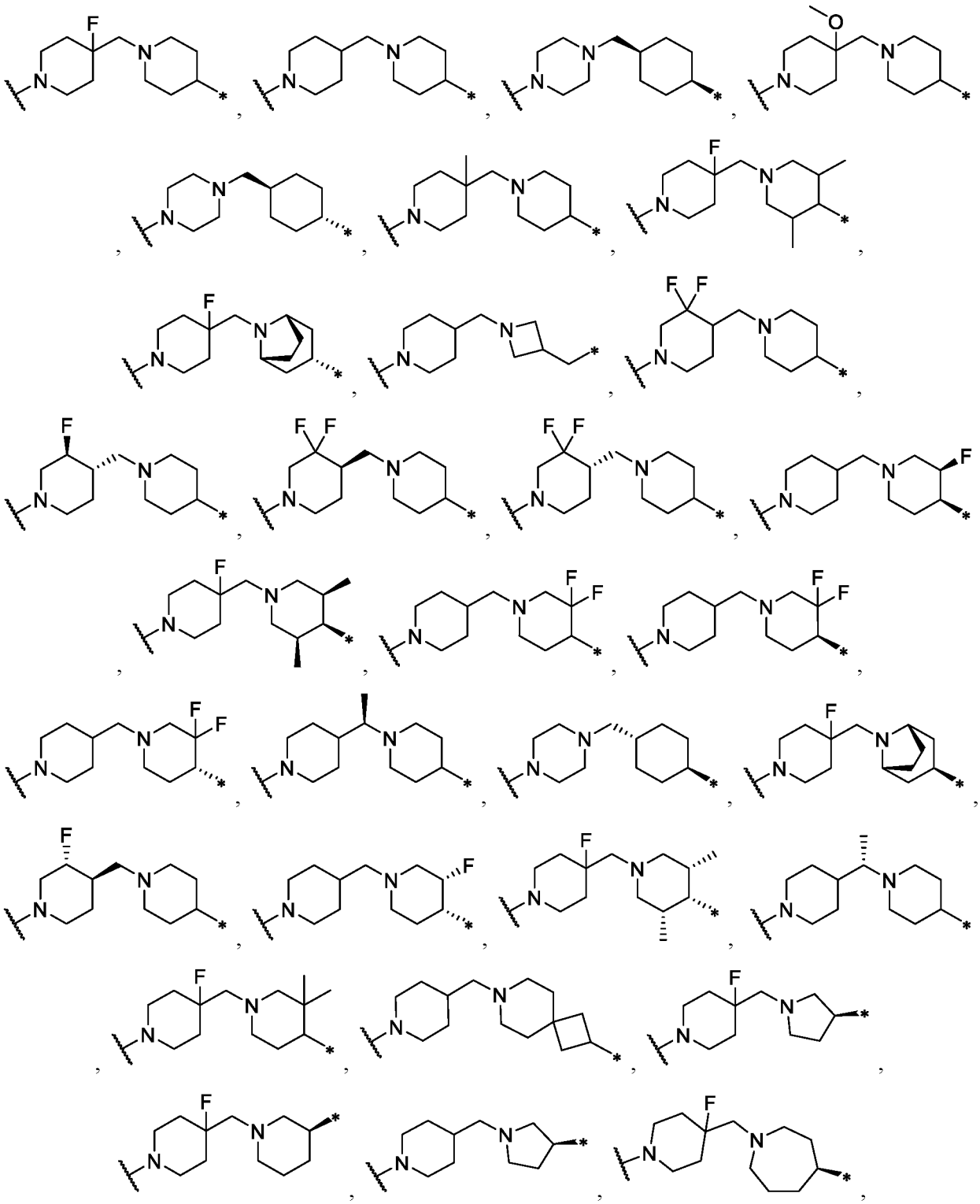
[0240] the bond marked with an "*" is attached to G^4.

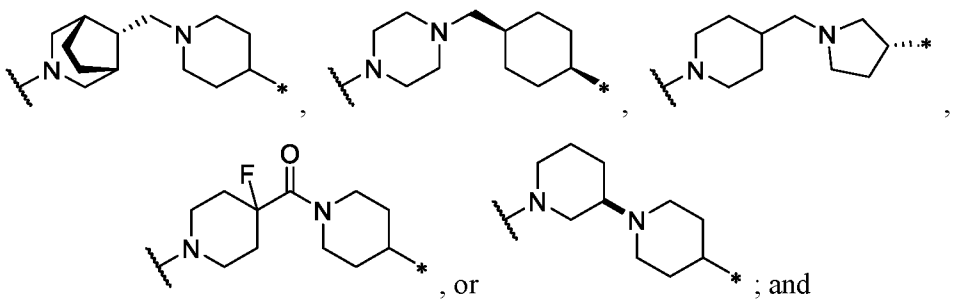
[0241] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V) or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^3 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[0242] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^4 is $(C_1\text{-}C_6)$alkylenyl.

[0243] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein G^4 is a direct bond.

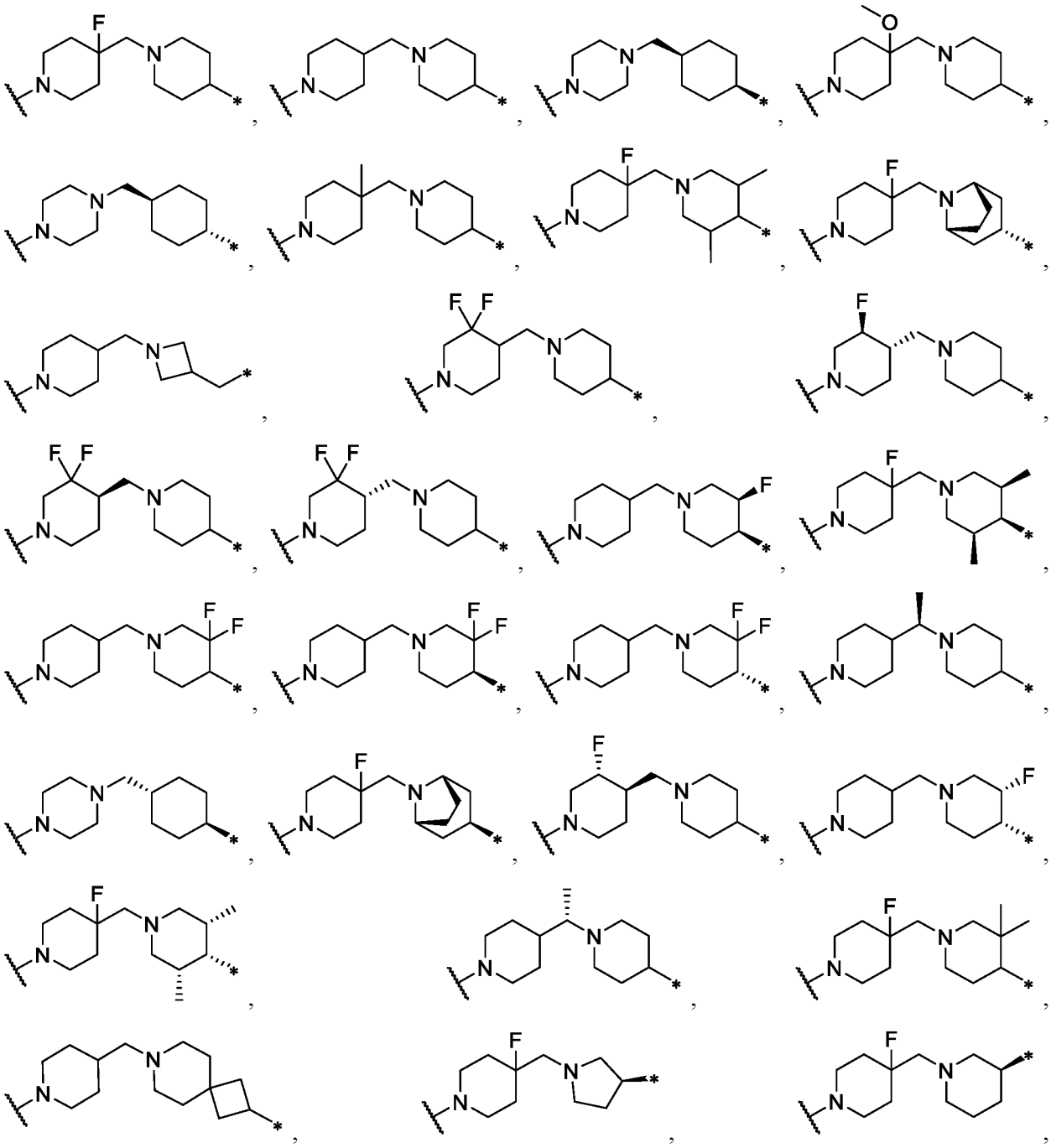
[0244] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein L is:

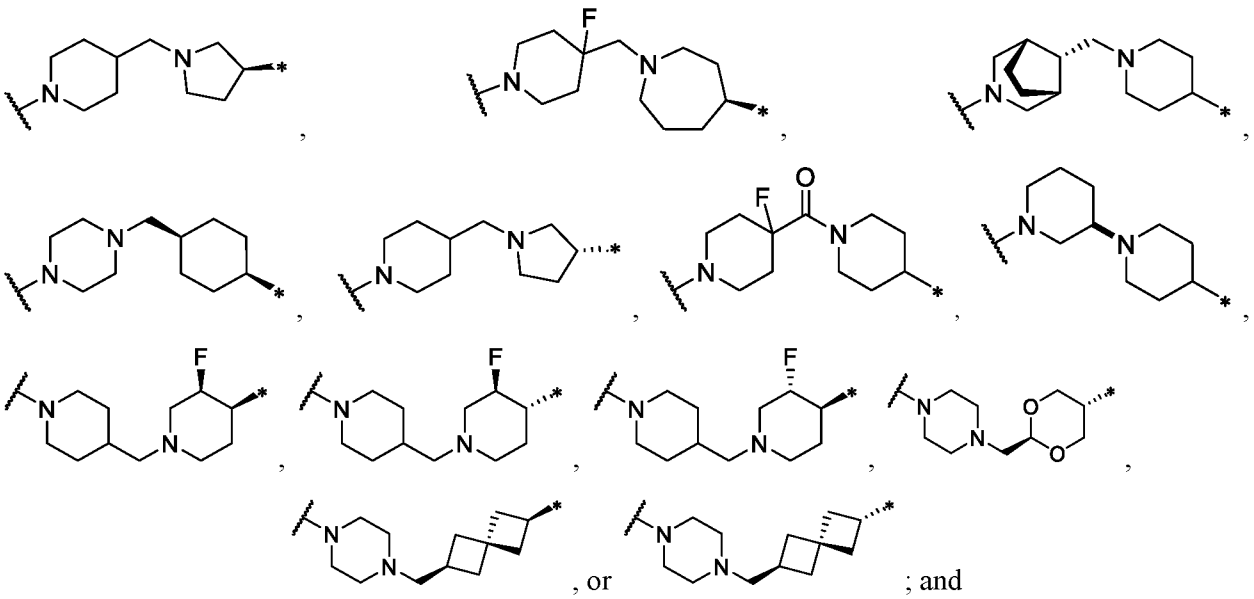




[0245] the bond marked with an "*" is attached to E.

[0246] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein L is:





[0247] the bond marked with an "*" is attached to E.

[0248] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[0249] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen or $(C_1$-$C_6)$alkyl.

[0250] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7 is fluoro or methyl.

[0251] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^8, R^9, and R^{10} are hydrogen.

[0252] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^8 is halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[0253] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^8 is halogen or $(C_1$-$C_6)$alkyl.

[0254] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^8 is fluoro or methyl.

[0255] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7, R^9, and R^{10} are hydrogen.

[0256] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^9 is halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[0257] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^9 is halogen.

[0258] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^9 is fluoro.

[0259] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7, R^8, and R^{10} are hydrogen.

[0260] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{10} is halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[0261] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{10} is halogen.

[0262] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^{10} is fluoro.

[0263] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7, R^8, and R^9 are hydrogen.

[0264] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (I)-(V), or (VIII)-(XII), or a pharmaceutically acceptable salt thereof, wherein R^7, R^8, R^9, and R^{10} are hydrogen.

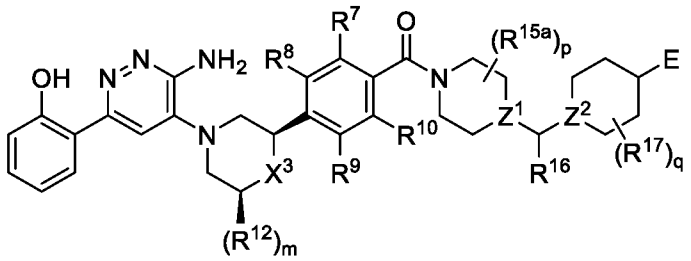
[0265] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (VIII), or (IX), or a pharmaceutically acceptable salt thereof, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[0266] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), (IA), (VIII), or (IX), or a pharmaceutically acceptable salt thereof, wherein R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl.

[0267] In another embodiment, Compounds of the Disclosure are compounds having Formulae (A), wherein R^a is fluoro and R^b is hydrogen.

[0268] In another embodiment, Compounds of the Disclosure are compounds having Formulae (A), wherein R^a is hydrogen and R^b is fluoro.

[0269] In another embodiment, Compounds of the Disclosure are compounds having Formula (VI):



(VI),

wherein:

[0270] R^{15a} is fluoro;

[0271] p is 0, 1, or 2;

[0272] Z^1 is CR^{15b} or N;

[0273] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[0274] R^{16} is hydrogen or methyl;

[0275] Z^2 is CH or N;

[0276] R^{17} is fluoro or methyl;

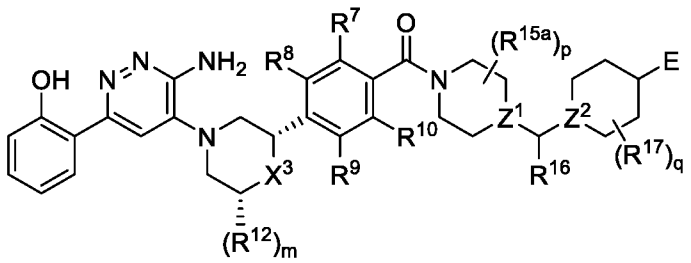
[0277] q is 0, 1, or 2;

[0278] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[0279] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, -CF_3, cyclopropyl, methoxy, or cyano; and

[0280] X^3 and E are as defined in connection with Formula (I).

[0281] In another embodiment, Compounds of the Disclosure are compounds having Formula (VII):



(VII),

wherein:

[0282] R^{15a} is fluoro;

[0283] p is 0, 1, or 2;

[0284] Z^1 is CR^{15b} or N;

[0285] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[0286] R^{16} is hydrogen or methyl;

[0287] Z^2 is CH or N;

[0288] R^{17} is fluoro or methyl;

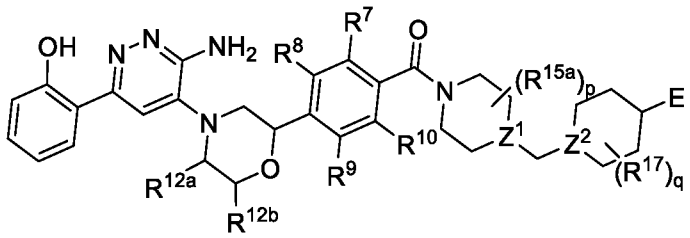
[0289] q is 0, 1, or 2;

[0290] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[0291] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano; and

[0292] X^3 and E are as defined in connection with Formula (I).

[0293] In another embodiment, Compounds of the Disclosure are compounds having Formula (XIII):



(XIII),

wherein:

[0294] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[0295] R^{12a} and R^{12b} are independently hydrogen or methyl;

[0296] R^{15a} is fluoro;

[0297] p is 0, 1, or 2;

[0298] Z^1 is CR^{15b} or N;

[0299] R^{15b} is hydrogen or fluoro;

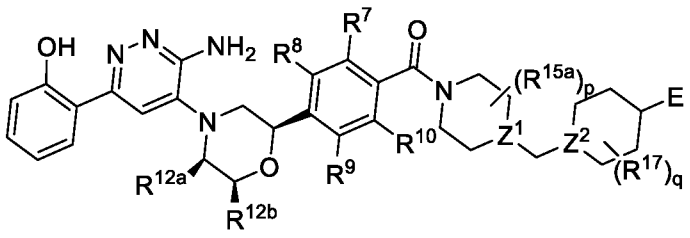
[0300] Z^2 is CH or N;

[0301] R^{17} is fluoro;

[0302] q is 0, 1, or 2; and

[0303] E is as defined in connection with Formula (IA).

[0304] In another embodiment, Compounds of the Disclosure are compounds having Formula (XIV):



(XIV),

wherein:

[0305] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[0306] R^{12a} and R^{12b} are independently hydrogen or methyl;

[0307] R^{15a} is fluoro;

[0308] p is 0, 1, or 2;

[0309] Z^1 is CR^{15b} or N;

[0310] R^{15b} is hydrogen or fluoro;

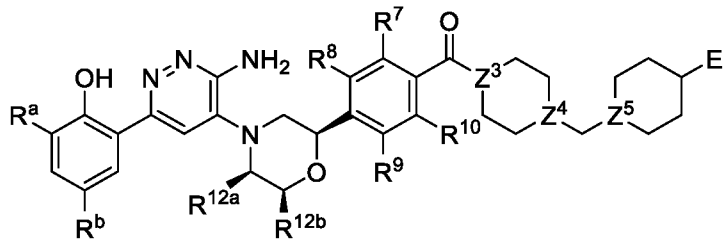
[0311] Z^2 is CH or N;

[0312] R^{17} is fluoro;

[0313] q is 0, 1, or 2; and

[0314] E is as defined in connection with Formula (IA).

[0315] In another embodiment, Compounds of the Disclosure are compounds having Formula (XV):



(XV)

wherein:

[0316] R^a and R^b are independently hydrogen or fluoro;

[0317] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[0318] R^{12a} and R^{12b} are independently hydrogen or methyl; or

[0319] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form a 5-membered heterocycloalkyl;

[0320] Z^3 is CH or N.

[0321] Z^4 is CR^{15b} or N;

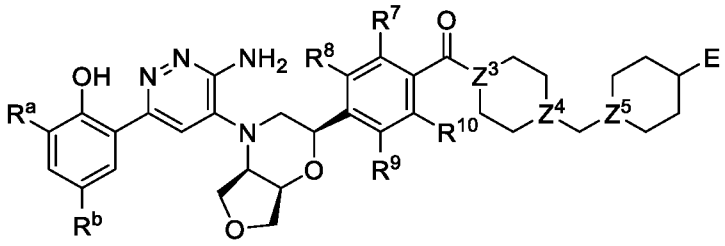
[0322] R^{15b} is hydrogen or fluoro;

[0323] Z^5 is CH or N; and

[0324] E is as defined in connection with Formula (A).

[0325] In another embodiment, Compounds of the Disclosure are compounds having Formula (XV), wherein R^{12a} and R^{12b} are independently hydrogen or methyl.

[0326] In another embodiment, Compounds of the Disclosure are compounds having Formula (XVI):



(XVI),

[0327] wherein R^a, R^b, R^7, R^8, R^9, R^{10}, Z^3, Z^4, Z^5, and E are as definied in connection with Formula (XV).

[0328] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound Lists 1-5, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof. In the Compound Lists, a compound having an "*" in its chemical name indicates that the absolute configuration and/or relative configuration at that position of the molecule has not yet been confirmed. For example, "ethyl (*R**)-4-(pyrrolidin-3-yl)benzoate" indicates that the compound may be ethyl (*R*)-4-(pyrrolidin-3-yl)benzoate or ethyl (*S*)-4-(pyrrolidin-3-yl)benzoate. *See* Intermediates 18d and 18de of EXAMPLE 18. It is to be understood that if a compound has two or more "*" in its chemical name the compound may be one of the several possible stereoisomers, e.g., entantiomers and/or diastereomers. Thus, for example, "1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione" indicates the compound may be 1-(1-(1-((1-(4-((3*R*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione or 1-(1-(1-((1-(4-((3*S*,5*S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione. *See* EXAMPLE 29. Likewise, "1-(1-(1-(((3*R*,4*R*)-1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione" indicates the compound may be 1-(1-(1-(((3*R*,4*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione or 1-(1-(1-(((3*R*,4*R*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione. *See* EXAMPLE 142.

[0329] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 1, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

Compound List 1

[0330] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0331] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0332] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0333] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0334] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0335] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0336] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0337] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0338] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0339] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0340] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0341] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0342] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0343] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0344] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0345] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0346] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0347] (S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0348] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0349] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0350] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0351] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0352] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0353] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0354] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0355] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0356] (R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0357] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0358] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0359] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0360] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0361] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0362] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0363] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0364] (R)-1-(3-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0365] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0366] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0367] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0368] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0369] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0370] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0371] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0372] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0373] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0374] rac-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0375] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0376] (R)-1-(3-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0377] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0378] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0379] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0380] (R)-2-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

[0381] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0382] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0383] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0384] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0385] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0386] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0387] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0388] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0389] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0390] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0391] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0392] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0393] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0394] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0395] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0396] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0397] (R)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0398] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0399] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0400] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

[0401] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0402] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0403] (R)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0404] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0405] (S)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0406] (S)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0407] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0408] (R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0409] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0410] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0411] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0412] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0413] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0414] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0415] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0416] (S)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0417] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0418] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0419] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0420] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0421] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0422] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0423] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0424] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0425] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0426] (R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0427] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0428] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0429] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0430] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0431] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0432] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0433] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0434] rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0435] rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0436] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0437] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0438] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0439] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0440] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0441] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0442] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0443] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0444] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0445] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0446] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0447] 1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0448] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0449] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0450] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0451] 1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0452] rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0453] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0454] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0455] 1-(1-((1R,3s,5S)-8-((1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0456] 1-(1-((1R,3s,5S)-8-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0457] 1-(1-(1-((1-(4-((3R*,5S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0458] (R)-1-(1-((1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0459] 1-(1-(1-(-1-(1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0460] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0461] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0462] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0463] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0464] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0465] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0466] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0467] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0468] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0469] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0470] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0471] 1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0472] (R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1H-indol-7-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0473] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0474] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0475] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0476] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0477] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0478] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0479] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0480] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0481] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0482] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0483] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; or

[0484] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0485] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0486] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0487] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0488] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0489] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0490] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0491] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0492] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0493] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0494] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0495] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0496] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0497] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0498] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0499] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0500] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0501] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0502] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0503] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0504] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0505] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0506] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0507] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0508] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0509] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0510] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0511] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0512] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0513] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0514] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0515] 1-(1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0516] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0517] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0518] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0519] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0520] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0521] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0522] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0523] 1-(1-(1-((1-(4-((2S,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0524] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0525] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0526] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0527] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0528] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0529] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0530] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0531] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0532] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0533] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0534] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0535] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0536] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0537] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0538] 1-(1-(1-(((S*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0539] 1-(1-(-1-((1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0540] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0541] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0542] 1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0543] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0544] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0545] 1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0546] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0547] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0548] rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0549] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0550] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0551] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0552] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0553] 1-(1-(1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0554] rel-1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0555] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0556] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0557] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0558] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0559] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0560] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0561] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; or

[0562] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0563] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 2, or a pharmaceutically acceptable salt thereof, or stereoisomer thereof.

Compound List 2

[0564] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0565] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0566] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0567] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0568] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0569] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0570] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0571] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0572] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0573] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0574] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0575] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0576] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0577] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0578] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0579] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0580] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0581] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0582] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0583] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0584] rac-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0585] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0586] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0587] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0588] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0589] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0590] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0591] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0592] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0593] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0594] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0595] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

[0596] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0597] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0598] (S)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0599] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0600] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0601] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0602] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0603] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0604] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0605] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0606] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0607] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0608] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0609] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0610] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0611] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0612] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0613] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0614] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0615] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0616] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0617] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0618] rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0619] rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0620] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0621] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0622] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0623] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0624] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0625] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0626] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0627] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0628] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0629] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0630] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0631] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0632] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0633] 1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0634] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0635] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0636] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0637] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0638] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0639] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0640] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0641] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0642] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0643] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0644] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0645] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0646] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0647] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0648] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0649] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0650] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0651] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0652] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0653] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0654] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0655] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0656] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0657] (R)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0658] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0659] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0660] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0661] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0662] 1-(1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0663] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0664] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0665] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0666] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0667] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0668] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0669] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0670] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0671] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0672] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0673] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0674] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0675] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0676] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0677] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0678] 1-(1-(1-(((S*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0679] 1-(1-(-1-((1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0680] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0681] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0682] 1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0683] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0684] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0685] 1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0686] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0687] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0688] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0689] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0690] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0691] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0692] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0693] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0694] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0695] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0696] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0697] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0698] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; or

[0699] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0700] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 3, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

Compound List 3

[0701] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0702] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0703] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0704] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0705] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0706] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0707] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0708] (R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0709] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0710] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0711] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0712] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0713] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0714] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0715] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0716] (R)-2-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

[0717] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0718] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0719] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0720] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0721] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0722] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0723] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0724] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0725] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0726] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0727] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0728] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0729] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0730] 1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0731] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0732] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0733] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0734] 1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0735] rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0736] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0737] 1-(1-(1-((1-(4-((3R*,5S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0738] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0739] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0740] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0741] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0742] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0743] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0744] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0745] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0746] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0747] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0748] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0749] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0750] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0751] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0752] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0753] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0754] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0755] 1-(1-(1-((1-(4-((2R,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0756] 1-(1-(1-((1-(4-((2S,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0757] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0758] rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0759] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0760] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0761] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; or

[0762] 1-(1-(1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0763] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 4, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

Compound List 4

[0764] 1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)pyrrolidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0765] 1-(1-((3S*,4R*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0766] 1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0767] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0768] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0769] 1-(1-((S)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0770] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0771] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0772] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0773] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0774] 1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0775] 1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0776] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0777] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0778] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0779] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0780] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0781] (S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0782] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0783] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0784] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0785] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0786] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0787] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0788] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione

[0789] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0790] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0791] 1-(1-((1R,4r)-4-((4-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0792] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0793] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0794] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0795] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0796] rac-1-(1-((1R,4r)-4-((4-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0797] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0798] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0799] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0800] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0801] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0802] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0803] 1-(1-((1R,4r)-4-((4-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0804] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0805] 1-(1-(1-((1-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0806] rac-1-(1-(1-((1-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0807] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0808] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0809] 1-(1-(1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0810] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0811] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0812] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0813] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0814] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0815] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0816] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0817] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0818] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0819] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0820] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0821] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0822] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0823] 1-(1-((1R,4r)-4-((4-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0824] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0825] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0826] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0827] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0828] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0829] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0830] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0831] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0832] (R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0833] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0834] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0835] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0836] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0837] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0838] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0839] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0840] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0841] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0842] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0843] 1-(1-((R)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0844] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0845] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0846] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0847] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0848] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0849] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0850] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0851] 1-(1-(1-((1-(4-((2R*,6R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0852] 1-(1-((1S,4s)-4-((4-(4-((R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0853] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0854] (R)-1-(1-(1-(1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)-4-fluoropiperidine-4-carbonyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0855] 1-(1-((S*)-1'-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-[1,3'-bipiperidin]-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0856] (R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0857] (R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0858] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; or

[0859] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0860] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 5, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

Compound List 5

[0861] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0862] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0863] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0864] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0865] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0866] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0867] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0868] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0869] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0870] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0871] 1-(1-((1*R*,4*s*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0872] 1-(1-((1*R*,4*s*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0873] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0874] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0875] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0876] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0877] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0878] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0879] 1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0880] 1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0881] 1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0882] 1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0883] 1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0884] 1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0885] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0886] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0887] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0888] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0889] 1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

[0890] 1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

[0891] 1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

[0892] 1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

[0893] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0894] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0895] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0896] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[0897] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0898] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0899] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0900] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0901] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0902] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0903] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0904] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0905] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0906] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0907] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0908] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0909] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0910] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0911] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0912] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0913] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0914] 1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0915] 1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0916] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0917] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0918] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0919] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0920] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0921] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0922] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0923] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0924] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0925] 1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0926] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0927] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0928] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0929] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0930] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0931] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0932] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0933] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0934] 1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0935] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0936] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0937] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0938] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0939] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0940] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0941] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0942] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0943] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0944] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0945] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0946] 1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0947] 1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0948] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0949] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0950] 1-(1-((3*S*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0951] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0952] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0953] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0954] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0955] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0956] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0957] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0958] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0959] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0960] 1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0961] 1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0962] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0963] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0964] 1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0965] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0966] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0967] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0968] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0969] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0970] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0971] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0972] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0973] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0974] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3,5-difluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

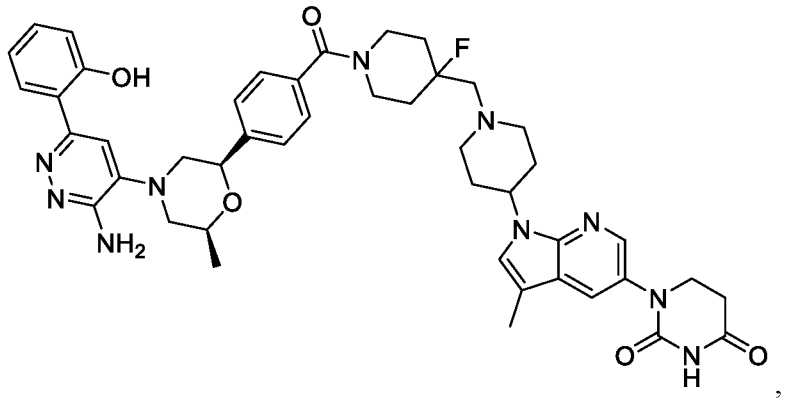
[0975] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0976] 1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

[0977] 1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione; or

[0978] 1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

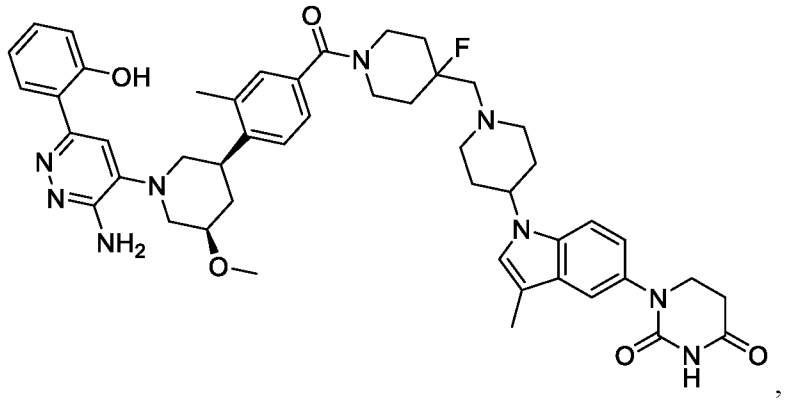
[0979] In another embodiment, a Compound of the Disclosure is:



,

[0980] or a pharmaceutically acceptable salt thereof.

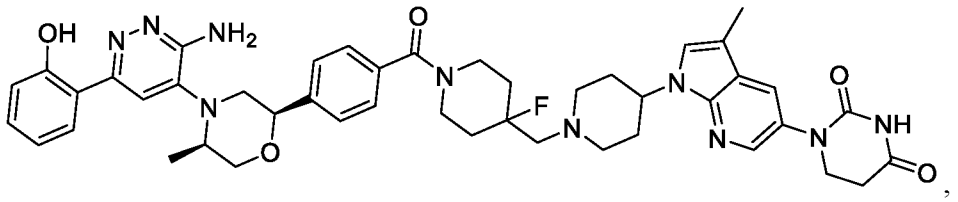
[0981] In another embodiment, a Compound of the Disclosure is:



,

[0982] or a pharmaceutically acceptable salt thereof.

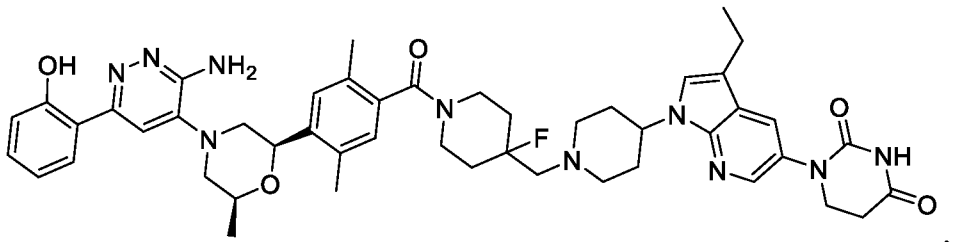
[0983] In another embodiment, a Compound of the Disclosure is:



,

[0984] or a pharmaceutically acceptable salt thereof.

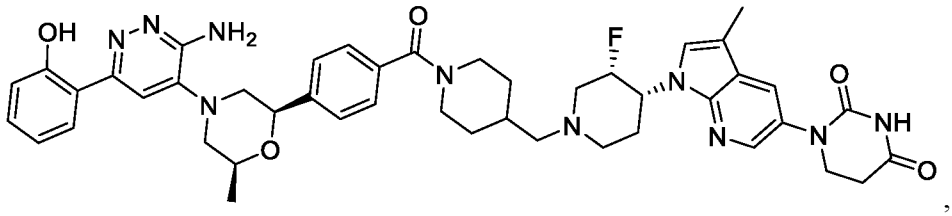
[0985] In another embodiment, a Compound of the Disclosure is:



,

[0986] or a pharmaceutically acceptable salt thereof.

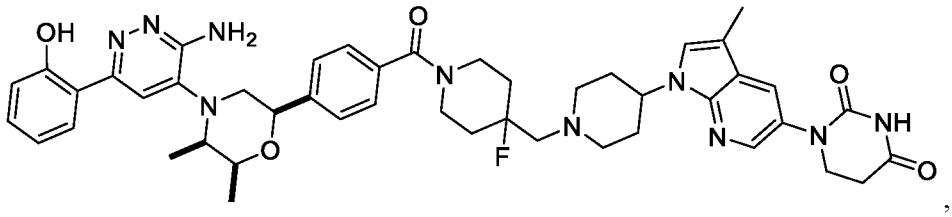
[0987] In another embodiment, a Compound of the Disclosure is:



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[0988] or a pharmaceutically acceptable salt thereof.

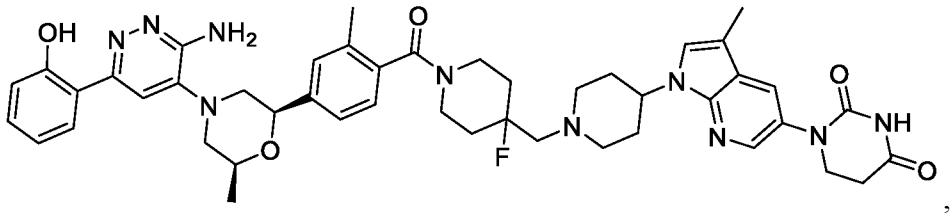
[0989] In another embodiment, a Compound of the Disclosure is:



,

[0990] or a pharmaceutically acceptable salt thereof.

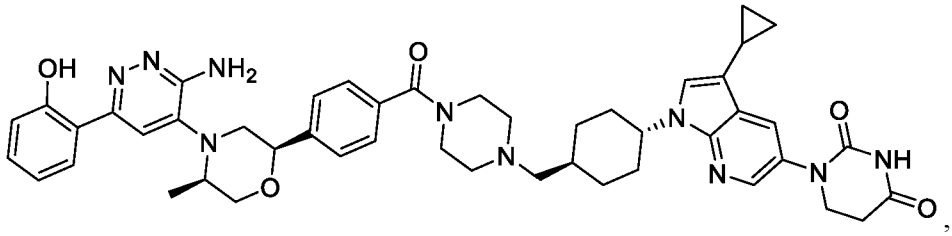
[0991] In another embodiment, a Compound of the Disclosure is:



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[0992] or a pharmaceutically acceptable salt thereof.

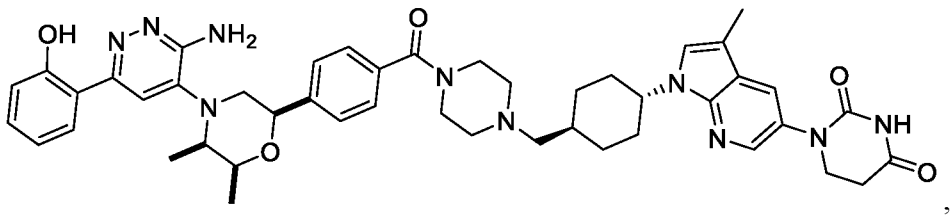
[0993] In another embodiment, a Compound of the Disclosure is:



,

[0994] or a pharmaceutically acceptable salt thereof.

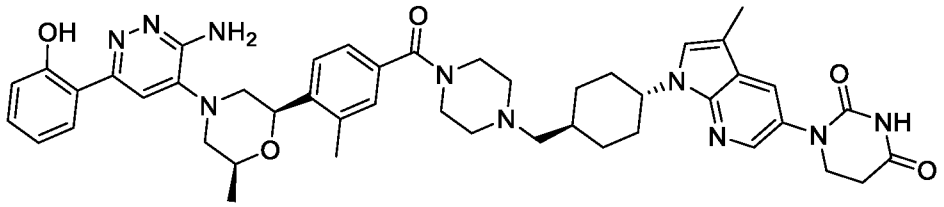
[0995] In another embodiment, a Compound of the Disclosure is:



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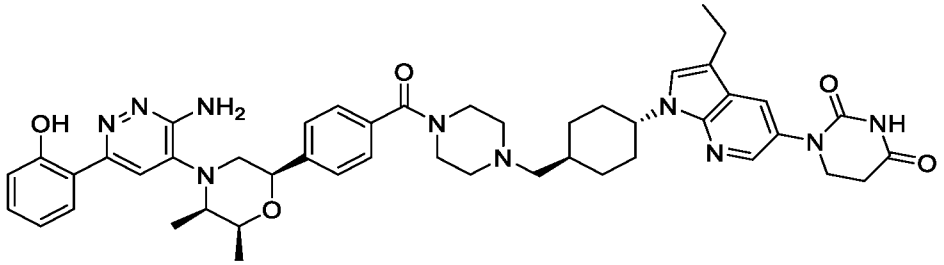
[0996] or a pharmaceutically acceptable salt thereof.

[0997] In another embodiment, a Compound of the Disclosure is:



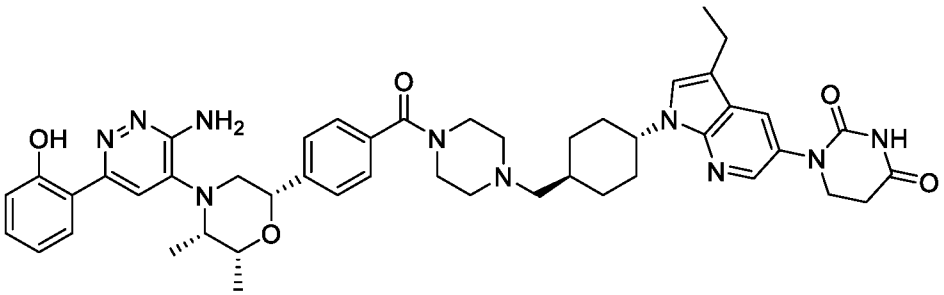
[0998] or a pharmaceutically acceptable salt thereof.

[0999] In another embodiment, a Compound of the Disclosure is:



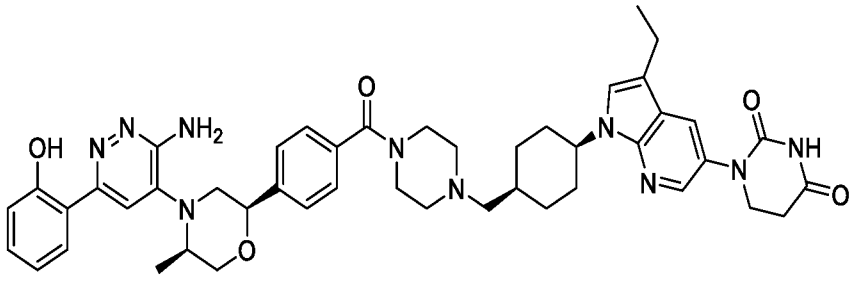
[1000] or a pharmaceutically acceptable salt thereof.

[1001] In another embodiment, a Compound of the Disclosure is:



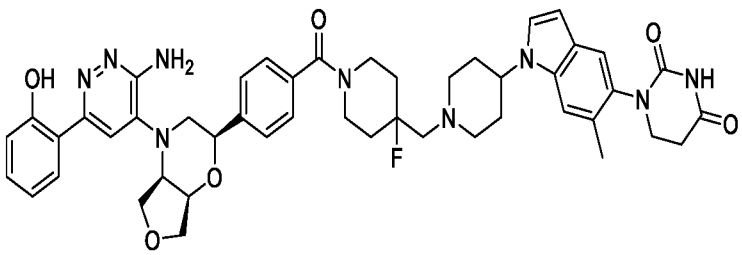
[1002] or a pharmaceutically acceptable salt thereof.

[1003] In another embodiment, a Compound of the Disclosure is:



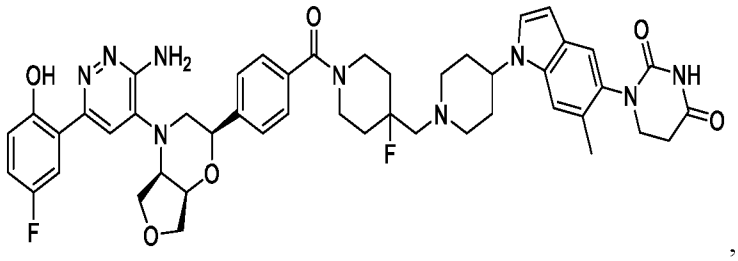
[1004] or a pharmaceutically acceptable salt thereof.

[1005] In another embodiment, a Compound of the Disclosure is:



[1006] or a pharmaceutically acceptable salt thereof.

[1007] In another embodiment, a Compound of the Disclosure is:



,

[1008] or a pharmaceutically acceptable salt thereof.

[1009] In another embodiment, the present disclosure provides pharmaceutical compositions comprising a Compound of the Disclosure and one or more pharmaceutically acceptable excipients.

[1010] Compounds of the Disclosure may have one or more chiral centres and it will be recognised that such compounds may be prepared, isolated and/or supplied with or without the presence of one or more of the other possible enantiomeric and/or diastereomeric isomers of the compounds, or that such isomers may be provided in any relative proportions. The preparation of enantioenriched or enantiopure and/or diastereoenriched or diastereopure compounds may be carried out by standard techniques of organic chemistry that are well known in the art, for example by synthesis from enantioenriched or enantiopure starting materials, and/or by use of an appropriately enantioenriched or enantiopure catalyst during synthesis, and/or by resolution of a racemic or partially enriched mixture of stereoisomers, for example via chiral chromatography. The scope of the present disclosure includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. It is to be understood that the present disclosure includes all combinations and subsets of the particular groups defined hereinabove.

[1011] In one embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, wherein the Compound of the Disclosure is present within the composition with a diastereomeric excess (%de) of ≥ 55%.

[1012] In another embodiment, the %de in the above-mentioned composition is ≥ 90%.

[1013] In another embodiment, the %de in the above-mentioned composition is ≥ 95%.

[1014] In another embodiment, the %de in the above-mentioned composition is ≥ 98%.

[1015] In another embodiment, the %de in the above-mentioned composition is ≥ 99%.

[1016] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, wherein the Compound of the Disclosure is present within the composition with an enantiomeric excess (%ee) of ≥ 55%.

[1017] In another embodiment, the %ee in the above-mentioned composition is ≥ 90%.

[1018] In another embodiment, the %ee in the above-mentioned composition is ≥ 95%.

[1019] In another embodiment, the %ee in the above-mentioned composition is ≥ 98%.

[1020] In another embodiment, the %ee in the above-mentioned composition is ≥ 99%.

[1021] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, wherein the Compound of the Disclosure is present within the composition with an enantiomeric excess (%ee) of ≥ 90% and a diastereomeric excess (%de) of ≥ 90%.

[1022] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, wherein the the %ee and %de of the Compound of the Disclosure take any combination of values, e.g., the %ee is ≥5% and the %de is ≥ 80%; the %ee is ≥5% and the %de is ≥ 90%; the %ee is ≥5% and the %de is ≥ 95%; the %ee is ≥ 5% and the %de is ≥ 98%; the %ee is ≥ 95% and the %de is ≥ 95%; the %ee is ≥ 98% and the %de is ≥ 98%; or the %ee is ≥ 99% and the %de is ≥ 99%.

[1023] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 66, 1-19, (1977) or those listed in P.H. Stahl and C.G. Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley- VCH/VHCA (2011) (see http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html).

[1024] Suitable pharmaceutically acceptable salts can include acid or base addition salts.

[1025] Such base addition salts can be formed by reaction of a Compound of the Disclosure with the appropriate base, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by a variety of methods, including crystallisation and filtration.

[1026] Such acid addition salts can be formed by reaction of a Compound of the Disclosure with the appropriate acid, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by a variety of methods, including crystallisation and filtration.

[1027] Salts may be prepared *in situ* during the final isolation and purification of a Compound of the Disclosure. If a basic compound of a Compound of the Disclosure is isolated as a salt, the corresponding free base form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic base. Similarly, if a Compound of the Disclosure containing a carboxylic acid or other acidic functional group is isolated as a salt, the corresponding free acid form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic acid.

[1028] It will be understood that if a Compound of the Disclosure contains two or more basic moieties, the stoichiometry of salt formation may include 1, 2 or more equivalents of acid. Such salts would contain 1, 2 or more acid counterions, for example, a dihydrochloride salt.

[1029] Stoichiometric and non-stoichiometric forms of a pharmaceutically acceptable salt of a Compound of the Disclosure are included within the scope of the specification, including sub-stoichiometric salts, for example where a counterion contains more than one acidic proton.

[1030] Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphorate, glycolate, hexylresorcinate, hippurate, hydrabamine (*N*,*N*′-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicyclate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

[1031] Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N*,*N*'-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolildine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, tromethamine (*tris*(hydroxymethyl)aminomethane), and zinc.

[1032] The present disclosure also includes isotopically-labeled compounds, which are identical to a Compound of the Disclosure except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into Compounds of the Disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I.

[1033] Compounds of the Disclosure that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the disclosure. Isotopically-labeled compounds of the disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly used for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron

emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be used in some circumstances. Isotopically labeled Compounds of the Disclosure can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[1034] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a comprising a Compound of the Disclosure and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts). The excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof, i.e., the patient.

II. Methods of Use

[1035] It is known that SMARCA4 mutations may be present in certain tumor/cancer types, including lung, liver, colon skin, bladder, cervical and ovarian tumors/cancers, and that SMARCA2 is essential for growth of tumors containing such SMARCA4 mutations. Accordingly, Compounds of the Disclosure may be of value as anti-cancer agents / anti-tumor agents, in particular against cancer/tumor types known to harbor SMARCA4 mutations, for example, lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, liver cancer, cervical cancer, and ovarian cancer.

[1036] Compounds of the Disclosure may also be of value against cancer types/tumors sensitive to the degradation of SMARCA2, for example, lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, liver cancer, cervical cancer, and ovarian cancer.

[1037] Compounds of the Disclosure may also be of value as anti-tumor agents, in particular as selective inhibitors of the proliferation, survival, motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of tumor growth and survival and to inhibition of metastatic tumor growth. In particular, Compounds of the Disclosure may be of value as anti-proliferative and anti-invasive agents in the containment and/or treatment of solid tumor disease.

[1038] Compounds of the Disclosure may also be useful in the prevention or treatment of those tumors which are sensitive to degradation of SMARCA2 and that are involved in the signal transduction steps which lead to the proliferation and survival of tumor cells and the migratory ability and invasiveness of metastasising tumor cells. Further, Compounds of the Disclosure may be useful in the prevention or treatment of those tumors which are mediated alone or in part by degradation of SMARCA2, i.e., the compounds may be used to produce an SMARCA2 degradation effect in a subject, e.g., a warm-blooded animal, e.g., a human, in need of such treatment.

[1039] In one embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of cancer.

[1040] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a solid tumor.

[1041] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a SMARCA2-sensitive tumor type.

[1042] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of tumor types that harbor SMARCA4 mutations.

[1043] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1044] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of SMARCA4-mutated cancer.

[1045] The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous or intramuscular dosing). The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients that are well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. *See, e.g.*, Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[1046] The amount of the Compound of the Disclosure that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the subject being treated and the particular route of administration.

[1047] The size of the dose for therapeutic or prophylactic purposes of Compounds of the Disclosure will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

[1048] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use as a medicament.

[1049] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in therapy.

[1050] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in a method of treatment of the human or animal body by therapy.

[1051] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the production of an anti-proliferative effect, for example, in a warm-blooded animal such as a human.

[1052] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the production of an anti-proliferative effect, for example, in a warm-blooded animal such as a human.

[1053] In another embodiment, the present disclosure provides a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1054] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use as an anti-invasive agent in the containment and/or treatment of solid tumor disease, for example, in a warm-blooded animal such as a human.

[1055] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumor disease, for example, in a warm-blooded animal such as a human.

[1056] In another embodiment, the present disclosure provides a method for producing an anti-invasive effect by the containment and/or treatment of solid tumor disease, in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1057] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of cancer, for example, in a warm-blooded animal such as a human.

[1058] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of cancer, for example, in a warm-blooded animal such as a human.

[1059] In another embodiment, the present disclosure provides a method for the prevention or treatment of cancer in a warm-blooded animal, such as a human, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1060] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of solid tumor(s), for example, in a warm-blooded animal such as a human.

[1061] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of solid tumor(s), for example, in a warm-blooded animal such as a human.

[1062] In another embodiment, the present disclosure provides a method for the prevention or treatment of solid tumor(s) in a warm-blooded animal, such as a human, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1063] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of tumor types that are sensitive to degradation of SMARCA2.

[1064] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of those tumor types that are sensitive to degradation of SMARCA2.

[1065] In another embodiment, the present disclosure provides a method for the prevention or treatment of those tumor types that are sensitive to degradation of SMARCA2, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. Tumor types that are sensitive to degradation of SMARCA2 include, for example, lung tumor, liver tumor, colon tumor, skin tumor, bladder tumor, cervical tumor and ovarian tumor.

[1066] In another embodiment, the d present isclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in providing a degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[1067] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for providing a degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[1068] In another embodiment, the present disclosure provides a method for providing a degrading effect on SMARCA2 in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1069] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in providing a selective degrading effect on SMARCA2 in, for example, a warm-blooded animal such as man.

[1070] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for providing a selective degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[1071] In another embodiment, the present disclosure provides a method for providing a selective degrading effect on SMARCA2 in a warm-blooded animal, such as man, in need of such effect, which comprises administering an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. SMARCA2 has been found to be essential for growth of tumors containing SMARCA4 mutations and certain tumor/cancer types are associated with such SMARCA4 mutations.

[1072] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of tumor types that harbor SMARCA4 mutations.

[1073] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of those tumor types that harbor SMARCA4 mutations.

[1074] In another embodiment, the present disclosure provides a method for the prevention or treatment of those tumor types that harbor SMARCA4 mutations in a warm-blooded animal, such as man, in need of such prevention or treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. Tumor types known to harbor SMARCA4 mutations include lung tumors, liver tumors, colon tumors, skin tumors, bladder tumors, cervical tumors and ovarian tumors, e.g., lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, cervical cancer and ovarian cancer.

[1075] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1076] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1077] In another embodiment, the present disclosure provides a method for treating lung, liver, colon, skin, bladder, cervical or ovarian cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[1078] In another embodiment where cancer is mentioned herein, the cancer is lung cancer.

[1079] In another embodiment where cancer is mentioned herein, the cancer is liver cancer.

[1080] In another embodiment where cancer is mentioned herein, the cancer is colon cancer.

[1081] In another embodiment where cancer is mentioned herein, the cancer is skin cancer.

[1082] In another embodiment where cancer is mentioned herein, the cancer is bladder cancer.

[1083] In another embodiment where cancer is mentioned herein, the cancer is cervical cancer.

[1084] In another embodiment where cancer is mentioned herein, the cancer is ovarian cancer.

[1085] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a SMARCA4-mutated cancer.

[1086] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a SMARCA4-mutated cancer.

[1087] In another embodiment, the present disclosure provides method for treating a SMARCA4-mutated cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

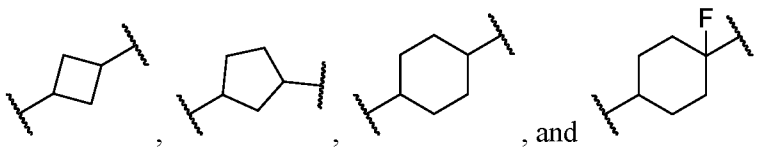
III. Definitions

[1088] As used herein, the term "alkyl" represents a saturated, straight or branched hydrocarbon moiety having the specified number of carbon atoms. The term "(C_1-C_6)alkyl" refers to an alkyl moiety containing from 1 to 6 carbon atoms. Exemplary alkyls include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, pentyl, and hexyl.

[1089] The term "alkylenyl" as used herein by itself or part of another group refers to a divalent form of an alkyl group having the specified number of carbon atoms. For example, the term "(C_1-C_6)alkylenyl" refers to an alkylenyl moiety containing from 1 to 6 carbon atoms. The alkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and (C_1-C_6)alkoxy. Exemplary alkylenyl groups include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2(CH_2)_2CH_2$-, and -$CH_2(CH_2)_3CH_2$-.

[1090] "Alkoxy" refers to a group containing an alkyl radical, defined hereinabove, attached through an oxygen linking atom. The term "(C_1-C_6)alkoxy" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 6 carbon atoms attached through an oxygen linking atom. Exemplary "(C_1-C_6)alkoxy" groups useful in the present specification include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *s*-butoxy, isobutoxy, and *t*-butoxy.

[1091] The term "cycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a cycloalkyl group having the specified number of carbon atoms in the ring. For example, the term "(C_3-C_6)cycloalkylenyl" refers to an cycloalkylenyl moiety containing from 3 to 6 carbon atoms in the ring. The cycloalkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, cyano, and (C_1-C_6)alkoxy. Exemplary cycloalkylenyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexy:

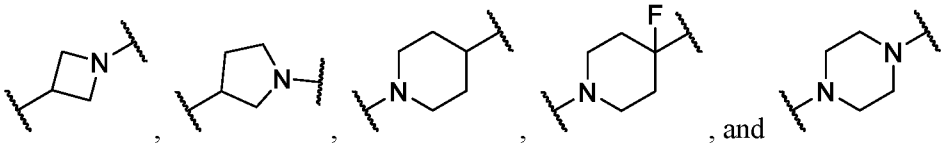


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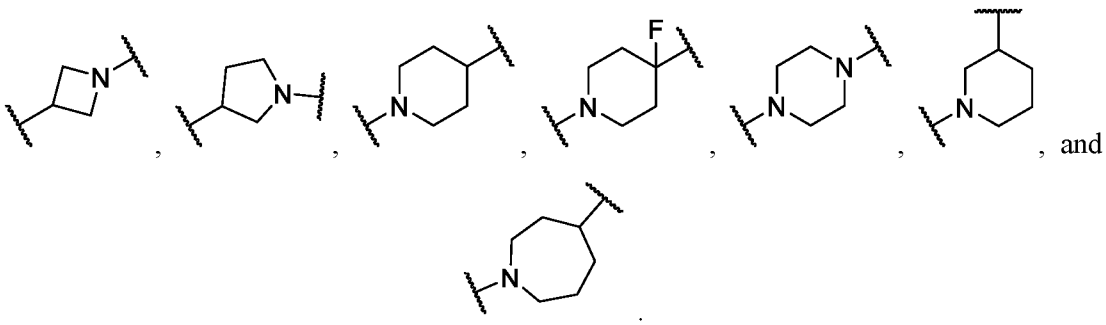
[1092] The term "heterocycloalkyl" as used herein by itself or part of another group refers to group or moiety comprising a non-aromatic, monovalent, monocyclic, bicyclic, or spirocyclic radical, which is

saturated or partially unsaturated, having 4- to 11-ring atoms, which includes carbon and one or two or or three heteroatoms selected independently from oxygen, sulfur, and/or nitrogen. In one embodiment, the heterocycloalkyl includes carbon and one or two heteroatoms.

[1093] The term "4- to 6-membered heterocycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a monocyclic or bicyclic heterocycloalkyl having 4, 5, or 6 ring atoms, which includes carbon and one or two heteroatoms selected independently from oxygen, sulfur, and/or nitrogen. The 4- to 6-membered heterocycloalkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, cyano, or (C_1-C_6)alkoxy. In one embodiment, the 4- to 6-membered heterocycloalkylenyl is a divalent form of an optionally substituted azetidine. In another embodiment, the the 4- to 6-membered heterocycloalkyleny is a divalent form of an optionally substituted piperidinyl. In another embodiment, the heterocycloalkyleny is a divalent form of an optionally substituted piperazinyl. Exemplary heterocycloalkylenyl groups include, but are not limited to:

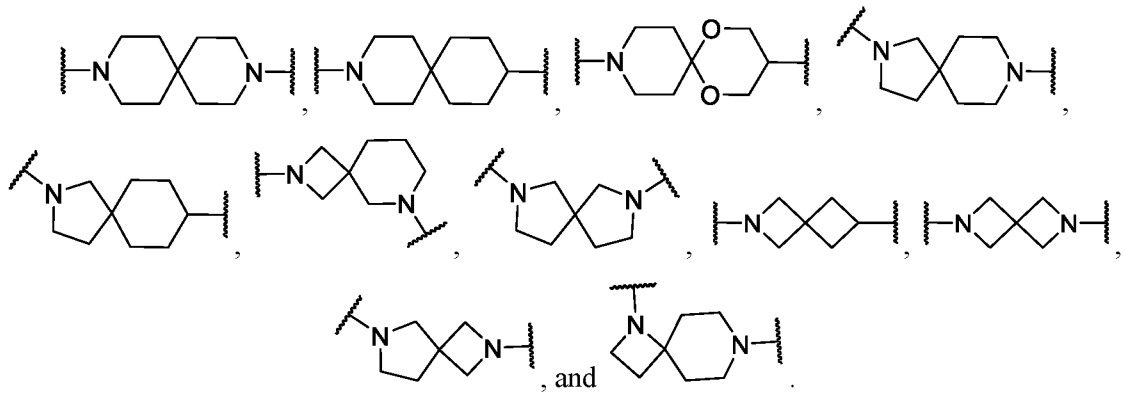


[1094] The term "4- to 7-membered heterocycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a monocyclic or bicyclic heterocycloalkyl having 4, 5, 6, or 7 ring atoms, which includes carbon and one or two heteroatoms selected independently from oxygen, sulfur, and/or nitrogen. The 4- to 7-membered heterocycloalkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, cyano, or (C_1-C_6)alkoxy. In one embodiment, the 4- to 7-membered heterocycloalkylenyl is a divalent form of an optionally substituted azetidine. In another embodiment, the the 4- to 7-membered heterocycloalkyleny is a divalent form of an optionally substituted piperidinyl. In another embodiment, the heterocycloalkyleny is a divalent form of an optionally substituted piperazinyl. In another embodiment, the heterocycloalkyleny is a divalent form of an optionally substituted azepane. Exemplary heterocycloalkylenyl groups include, but are not limited to:



[1095] The term "7- to 11-membered heterocycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a bicyclic or spirocyclic heterocycloalkyl having 7, 8, 9, 10, or 11 ring atoms, which includes carbon and one, two, or three heteroatoms selected independently from oxygen,

sulfur, and/or nitrogen. Exemplary 7- to 11-membered heterocycloalkylenyl groups include, but are not limited to:



[1096] "Aryl" refers to optionally substituted monocyclic, fused bicyclic, or fused tricyclic groups having 6 to 14 carbon atoms and having at least one aromatic ring that complies with Hückel's Rule. Examples of "aryl" groups are phenyl, naphthyl, indenyl, dihydroindenyl, anthracenyl, phenanthrenyl, and the like.

[1097] "Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryls useful in the present specification include, but are not limited to, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuryl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, benzothienyl, indolizinyl, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, pyrazolopyridinyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 5-membered "heteroaryl" groups include furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, and isothiazolyl. Examples of 6-membered "heteroaryl" groups include oxo-pyridyl, pyridinyl, pyridazinyl, pyrazinyl, and pyrimidinyl. Examples of 6,6-fused "heteroaryl" groups include quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 6,5-fused "heteroaryl" groups include benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, indolizinyl, indolyl, isoindolyl, and indazolyl.

[1098] As used herein, "5- or 6-membered heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic radical, containing 5 or 6 ring atoms, including at least one carbon atom and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Selected 5-membered heteroaryl groups contain one nitrogen, oxygen, or sulfur ring heteroatom, and optionally contain 1, 2, or 3 additional nitrogen ring atoms. Selected 6-membered heteroaryl groups contain 1, 2, or 3 nitrogen ring heteroatoms. Illustrative examples of 5- or 6-membered heteroaryl groups useful in the present specification include, but are not limited to furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, and triazinyl.

[1099] The terms "halogen" and "halo" represent fluoro, chloro, bromo, or iodo substituents.

[1100] "Hydroxy" as used herein by itself or as part of a group refers to the radical -OH.

[1101] The term "cyano" as used herein by itself or as part of a group refers to the radical -CN.

[1102] As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur and includes both event(s) that occur and event(s) that do not occur. As such, use of the term "optionally" includes instances where the feature is present, and also instances where the feature is not present. For example, "methyl optionally substituted by one or more F" includes $-CH_3$, $-CH_2F$, $-CHF_2$ and $-CF_3$.

[1103] In present disclosure, a group such as "A-B-C" where B is defined as "a direct bond" equates to "A-C," i.e., where A and C are directly linked to each other by a covalent bond.

[1104] The term “substituted” means that one or more hydrogens on the designated atom or group is replaced by the indicated substituent(s) provided that any atom(s) bearing such substituent(s) maintains its permitted valency where the skilled person understands that the standard valencies of carbon, nitrogen and oxygen are 4, 3 and 2 respectively.

[1105] "Pharmaceutically acceptable" refers to those compounds (including salts), materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[1106] As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject.

[1107] The term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician

[1108] The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or

disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a Compound of the Disclosure may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

[1109] Compounds of the Disclosure may have asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure encompasses the preparation and use of all such possible stereoisomeric forms, as well as their racemic and resolved forms, and mixtures thereof. The enantiomers and diastereomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are also encompassed by the present disclosure.

[1110] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers, atropisomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[1111] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[1112] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction. Enantiomers may be separated by chiral chromatography using methods well known in the art.

[1113] The term "racemic" or "racemate" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

[1114] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., R or S.

[1115] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem 68*:2193 (1996), unless otherwise indicated.

[1116] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{obs}/[\alpha]_{max}) * 100$, where $[\alpha]_{obs}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{max}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography, or optical polarimetry. Compounds of the Disclosure that are racemic can be separated by chiral HPLC, e.g., using a CHIRALPAK IE column. In one embodiment, Compounds of the Disclosure

or Intermediates of the Disclosure have an ee of about 70% or more, e.g., about 80% or more, about 90% or more, about 91% or more, about 92% or more, about 93% or more, about 94% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more.

[1117] The terms "enantiomerically pure" or "enantiopure" refer to a sample of a chiral substance all of whose molecules (within the limits of detection) have the same chirality sense.

[1118] The terms "enantiomerically enriched" or "enantioenriched" refer to a sample of a chiral substance whose enantiomeric ratio is greater than 50:50. Enantiomerically enriched compounds may be enantiomerically pure. Certain compounds of the Disclosure are enantioenriched.

[1119] The term "diastereomeric excess" or "de" refers to a measure for how much of one diastereomer is present compared to another, and is defined by analogy to enantiomeric excess. Determination of diastereomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy and column chromatography.

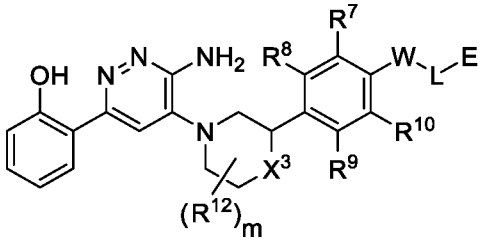
[1120] The term "diastereoenriched enriched" refer to a sample of a chiral substance whose diastereomeric ratio is greater than 50:50. Diastereoenriched enriched compounds may be diastereomerically pure. Certain compounds of the Disclosure are diastereoenriched.

[1121] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

IV. Particular Embodiments

[1122] The present disclosure also provides the following particular embodiments.

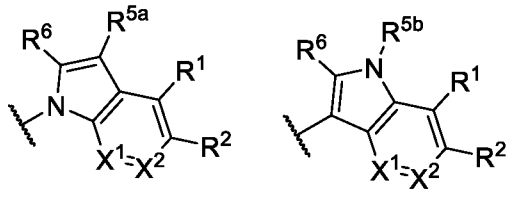
[1123] Embodiment 1. A compound having Formula (I), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(I),

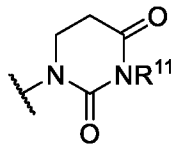
wherein:

[1124] E is:



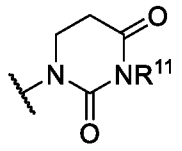
E-1 or E-2 ;

[1125] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

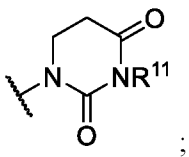
[1126] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or



;

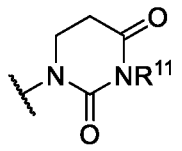
with the provisos:

[1127] (i) when R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^2 is:



; and

[1128] (ii) when R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^1 is:



;

[1129] R^{11} is hydrogen or $-(C_1\text{-}C_6)$alkyl-O-P(=O)-$(OH)_2$;

[1130] X^1 is CR^3 or N;

[1131] R^3 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[1132] X^2 is CR^4 or N;

[1133] R^4 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[1134] R^{5a} is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl;

[1135] R^{5b} is hydrogen, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl;

[1136] R^6 is hydrogen, $(C_1\text{-}C_6)$alkyl, or cyano;

[1137] X^3 is $-(CR^{13a}R^{13b})_n$- or -O-;

[1138] n is 0 or 1

[1139] each R^{13a} and R^{13b} is independently H, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

[1140] L is $-G^1\text{-}G^2\text{-}G^3\text{-}G^4$-, wherein G^1 is attached to W;

[1141] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano; 7- to 11-

membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[1142] G^2 is (C_1-C_6)alkylenyl or a direct bond;

[1143] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[1144] G^4 is (C_1-C_6)alkylenyl or a direct bond;

[1145] W is -C(=O)-;

[1146] R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1147] R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

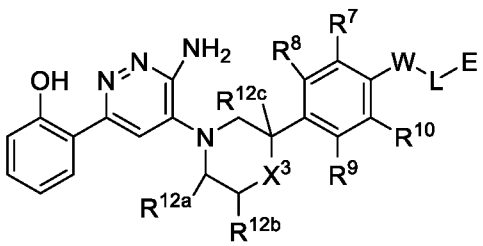
[1148] R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1149] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1150] each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

[1151] m is 0, 1, 2, 3, or 4.

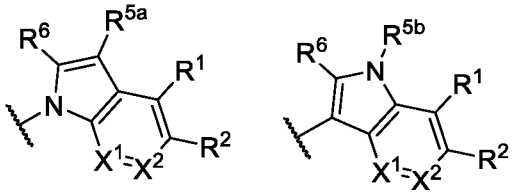
[1152] Embodiment 2. A compound of Formula (IA), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(IA),

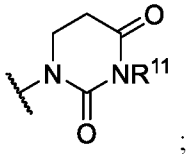
wherein:

[1153] E is:



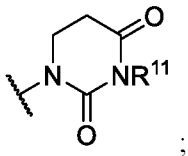
E-1 or E-2 ;

[1154] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

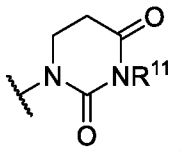
[1155] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

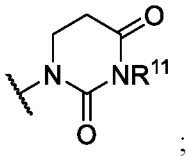
[1156] with the provisos:

[1157] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[1158] (ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

[1159] R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

[1160] X^1 is CR^3 or N;

[1161] R^3 is hydrogen, halogen, or (C_1-C_6)alkyl;

[1162] X^2 is CR^4 or N;

[1163] R^4 is hydrogen, halogen, or (C_1-C_6)alkyl;

[1164] R^{5a} is hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl;

[1165] R^{5b} is hydrogen, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl;

[1166] R^6 is hydrogen, (C_1-C_6)alkyl, or cyano;

[1167] X^3 is -$(CR^{13a}R^{13b})_n$- or -O-;

[1168] n is 0 or 1

[1169] each R^{13a} and R^{13b} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

[1170] L is -G^1-G^2-G^3-G^4-, wherein G^1 is attached to W;

[1171] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[1172] G^2 is (C_1-C_6)alkylenyl, -C(=O)-, or a direct bond;

[1173] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano; or (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[1174] G^4 is (C_1-C_6)alkylenyl or a direct bond;

[1175] W is -C(=O)-, -CH_2-, or a direct bond;

[1176] R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1177] R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1178] R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

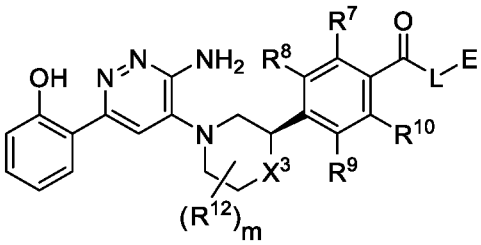
[1179] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1180] R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

[1181] R^{12a} and R12b taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C5-C7)cycloalkyl ; and

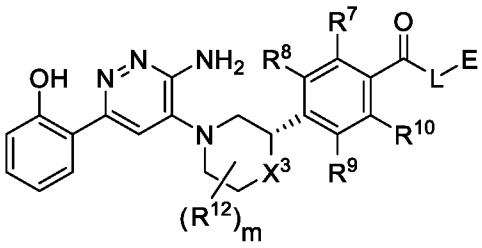
[1182] R^{12c} is hydrogen or halogen.

[1183] Embodiment 3. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 having Formula (II):



(II).

[1184] Embodiment 4. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 having Formula (III):



(III).

[1185] Embodiment 5. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-4, wherein X^3 is -($CR^{13a}R^{13b}$)-.

[1186] Embodiment 6. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{13a} and R^{13b} are hydrogen.

[1187] Embodiment 7. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{13a} and R^{13b} are fluoro.

[1188] Embodiment 8. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{13a} is methyl or methoxy; and R^{13b} is hydrogen.

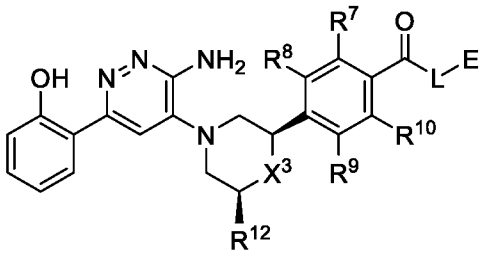
[1189] Embodiment 9. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-4, wherein X^3 is -O-.

[1190] Embodiment 10. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1 or 3-9, wherein m is 0.

[1191] Embodiment 11. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1 or 3-9, wherein m is 2.

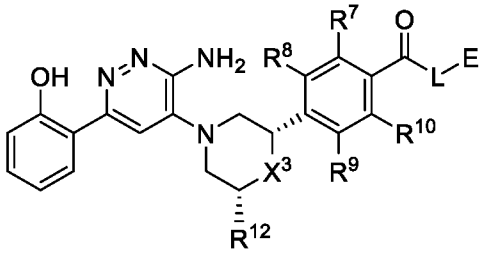
[1192] Embodiment 12. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1 or 3-9, wherein m is 1.

[1193] Embodiment 13. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 12 having Formula (IV):



(IV).

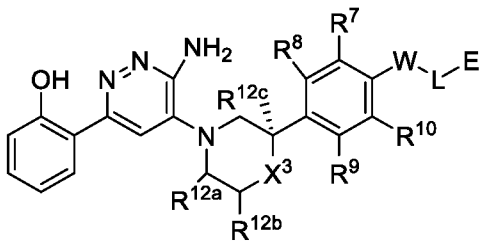
[1194] Embodiment 14. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 12 having Formula (V):



(V).

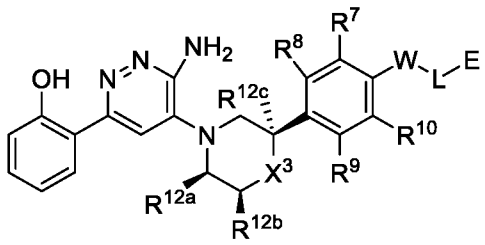
[1195] Embodiment 15. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 12-14, wherein each R^{12} is fluoro, methyl, ethyl, or methoxy.

[1196] Embodiment 16. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2, having Formula (VIII):



(VIII).

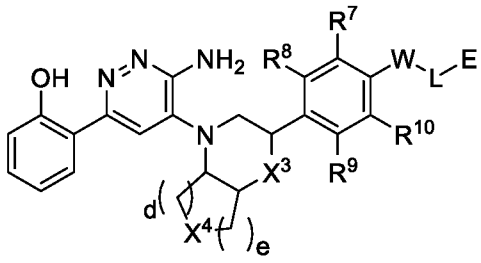
[1197] Embodiment 17. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 2 or 16, having Formula (IX):



(IX).

[1198] Embodiment 18. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 2 or 16-17, wherein R^{12a} is hydrogen and R^{12b} is hydrogen, fluoro, methyl, ethyl, or methoxy.

[1199] Embodiment 19. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to Embodiment 2 having Formula (X):



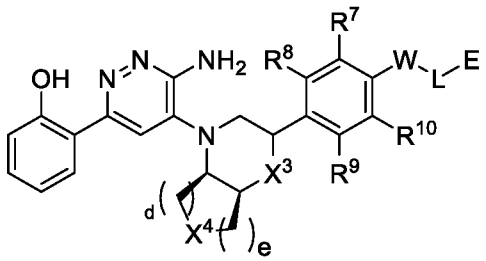
(X)

wherein:

[1200] X^4 is O; and

[1201] d and e are independently 1 or 2.

[1202] Embodiment 20. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2 having Formula (XI):



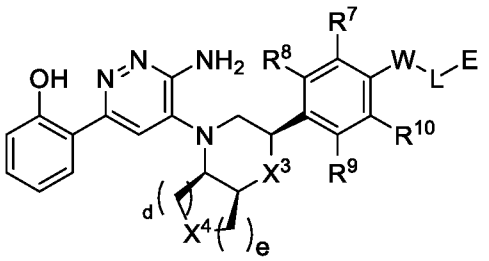
(XI)

wherein:

[1203] X^4 is O; and

[1204] d and e are independently 1 or 2.

[1205] Embodiment 21. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2 having Formula (XII):



(XII)

wherein:

[1206] X^4 is O; and

[1207] d and e are independently 1 or 2.

[1208] Embodiment 22. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-21, wherein E is E-1.

[1209] Embodiment 23. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is hydrogen.

[1210] Embodiment 24. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is (C_1-C_6)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[1211] Embodiment 25. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 24, wherein R^{5a} is methyl, ethyl, isopropyl, or -CF_3.

[1212] Embodiment 26. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is (C_3-C_6)cycloalkyl.

[1213] Embodiment 27. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 26, wherein R^{5a} is cyclopropyl.

[1214] Embodiment 28. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[1215] Embodiment 29. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is cyano.

[1216] Embodiment 30. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[1217] Embodiment 31. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[1218] Embodiment 32. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-21, wherein E is E-2.

[1219] Embodiment 33. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 32, wherein R^{5b} is hydrogen.

[1220] Embodiment 34. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 32, wherein R^{5b} is (C_1-C_6)alkyl.

[1221] Embodiment 35. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 34, wherein R^{5b} is methyl.

[1222] Embodiment 36. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 32, wherein R^{5b} is (C_3-C_6)cycloalkyl.

[1223] Embodiment 37. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 36, wherein R^{5b} is cyclopropyl or cyclobutyl.

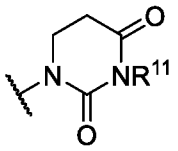
[1224] Embodiment 38. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-37, wherein R^6 is hydrogen.

[1225] Embodiment 39. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-37, wherein R^6 is (C_1-C_6)alkyl.

[1226] Embodiment 40. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-37, wherein R^6 is cyano.

[1227] Embodiment 41. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-40, wherein:

[1228] R^1 is:



; and

[1229] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

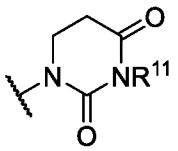
[1230] Embodiment 42. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 41, wherein R^2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[1231] Embodiment 43. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 42, wherein R^2 is hydrogen, fluoro, or methyl.

[1232] Embodiment 44. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 41-43, wherein R^{11} is hydrogen.

[1233] Embodiment 45. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-40, wherein:

[1234] R^2 is:



; and

[1235] R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

[1236] Embodiment 46. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 45, wherein R^1 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[1237] Embodiment 47. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 45, wherein R^1 is hydrogen, fluoro, or methyl.

[1238] Embodiment 48. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 45-47, wherein R^{11} is hydrogen.

[1239] Embodiment 49. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-48, wherein X^1 is CR^3.

[1240] Embodiment 50. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 49, wherein R^3 is hydrogen.

[1241] Embodiment 51. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 49, wherein R^3 is halogen.

[1242] Embodiment 52. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 51, wherein R^3 is fluoro.

[1243] Embodiment 53. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 49, wherein R^3 is $(C_1\text{-}C_6)$alkyl.

[1244] Embodiment 54. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 53, wherein R^3 is methyl.

[1245] Embodiment 55. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-48, wherein X^1 is N.

[1246] Embodiment 56. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-55, wherein X^2 is CR^4.

[1247] Embodiment 57. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 56, wherein R^4 is hydrogen.

[1248] Embodiment 58. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 56, wherein R^4 is halogen.

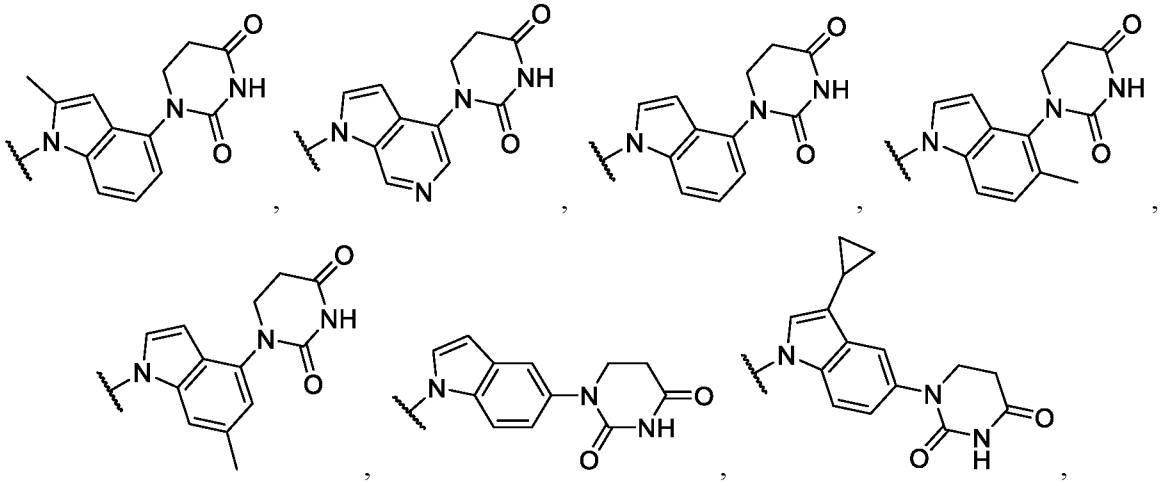
[1249] Embodiment 59. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 58, wherein R^4 is fluoro.

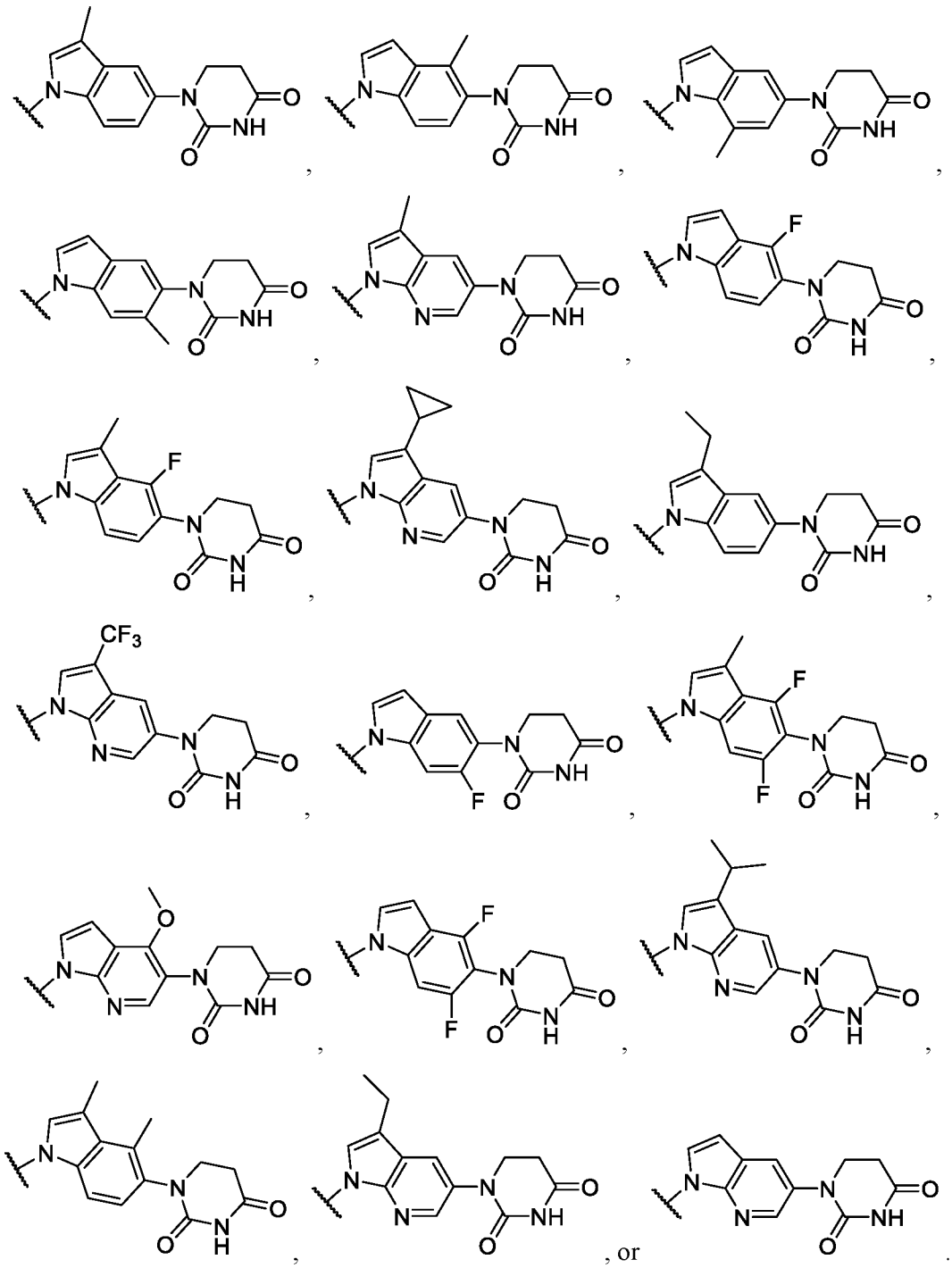
[1250] Embodiment 60. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 56, wherein R^4 is $(C_1\text{-}C_6)$alkyl.

[1251] Embodiment 61. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 60, wherein R^4 is methyl.

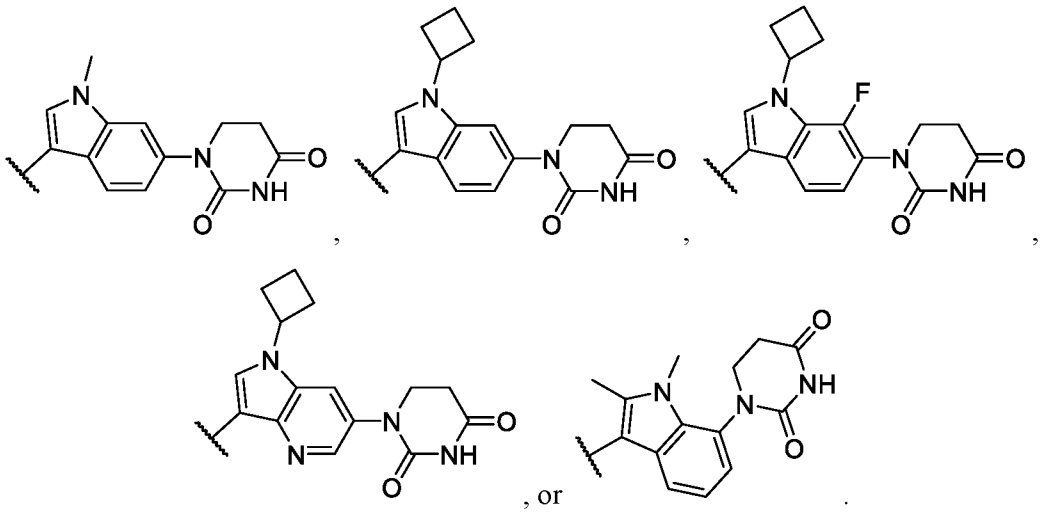
[1252] Embodiment 62. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-55, wherein X^2 is N.

[1253] Embodiment 63. The compound of Embodiment 22, wherein E-1 is:





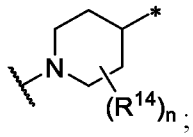
[1254] Embodiment 64. The compound of Embodiment 32, wherein E-2 is:



[1255] Embodiment 65. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-64, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[1256] Embodiment 66. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 65, wherein:

[1257] G^1 is:



[1258] each R^{14} is independently halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

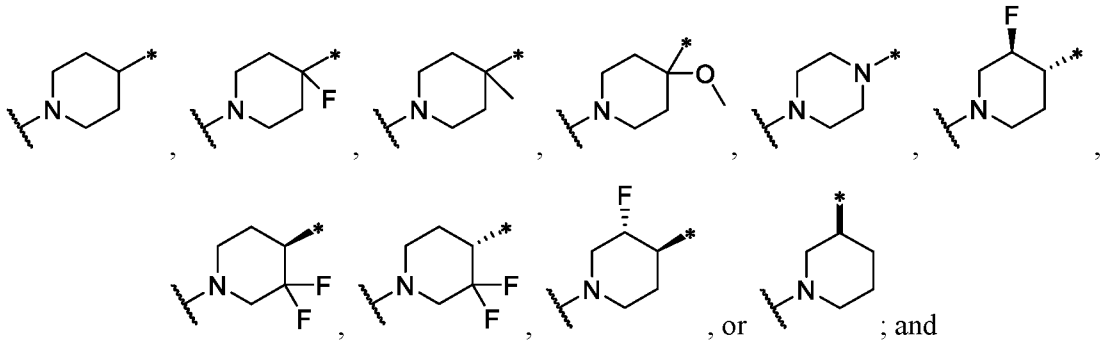
[1259] n is 0, 1, 2, or 3; and

[1260] the bond marked with an "*" is attached to G^2.

[1261] Embodiment 67. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 66, wherein n is 0.

[1262] Embodiment 68. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 66, wherein R^{14} is fluoro, methyl, or methoxy; and n is 1, or 2.

[1263] Embodiment 69. The compound, or pharmaceutically acceptable salt thereof, according Embodiment 65, wherein G^1 is:

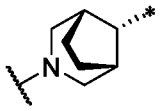


[1264] the bond marked with an "*" is attached to G^2.

[1265] Embodiment 70. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-64, wherein G^1 is $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1266] Embodiment 71. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-64, wherein G^1 is a 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1267] Embodiment 72. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 71, wherein G^1 is:



; and

[1268] the bond marked with an "*" is attached to G^2.

[1269] Embodiment 73. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-72, wherein G^2 is a direct bond.

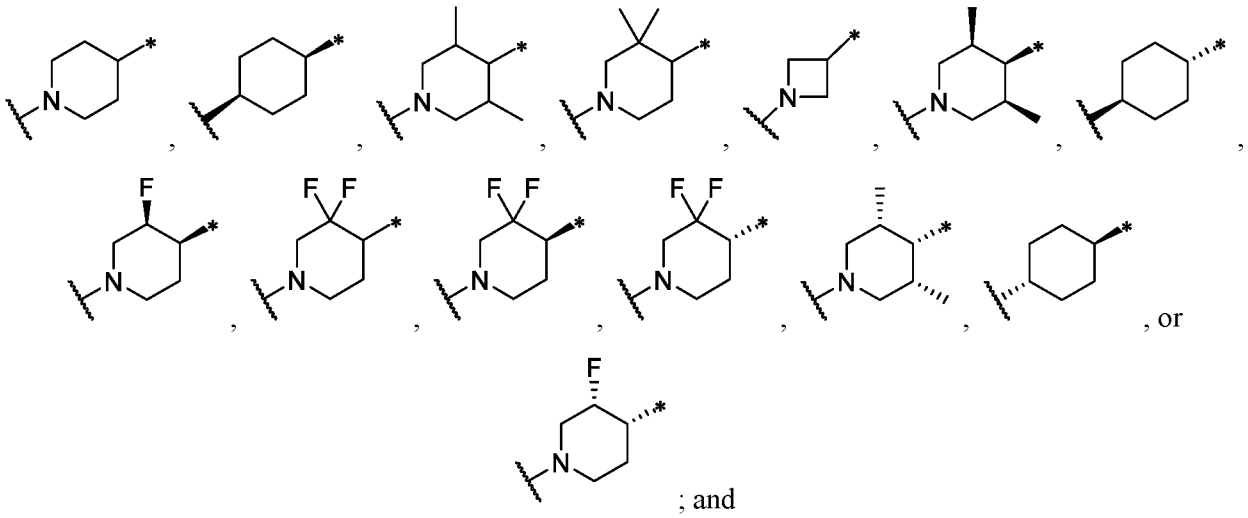
[1270] Embodiment 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-72, wherein G^2 is $(C_1$-$C_6)$alkylenyl.

[1271] Embodiment 75. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 74, wherein G^2 is $-CH_2-$ or $-CH(CH_3)-$.

[1272] Embodiment 76. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1-68, wherein G^2 is $-C(=O)-$.

[1273] Embodiment 77. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1 or 3-76, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1274] Embodiment 78. The compound, or pharmaceutically acceptable salt thereof, according Embodiment 77, wherein G^3 is:

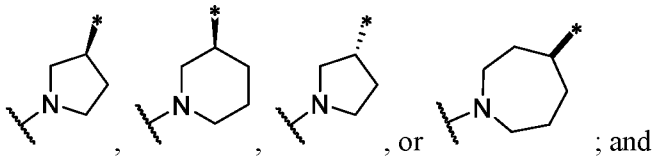


; and

[1275] the bond marked with an "*" is attached to G^4.

[1276] Embodiment 79. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 2-9 or 18-76, wherein G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1277] Embodiment 80. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 79, wherein G^3 is:

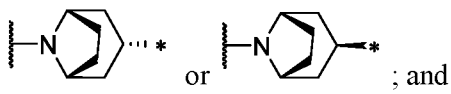


; and

[1278] the bond marked with an "*" is attached to G^4.

[1279] Embodiment 81. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-76, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1280] Embodiment 82. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 81, wherein G^3 is:

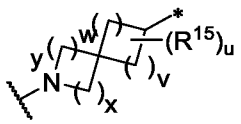


; and

[1281] the bond marked with an "*" is attached to G^4.

[1282] Embodiment 83. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 81, wherein:

[1283] G^3 is:


;

[1284] each R^{15} is independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

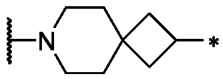
[1285] u is 0, 1, 2, or 3;

[1286] v, w, x, and t are independently 1, 2, or 3; and

[1287] the bond marked with an "*" is attached to G^4.

[1288] Embodiment 84. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 83, wherein v, w, x, and y are independently 1 or 2.

[1289] Embodiment 85. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 84, wherein G^3 is:


; and

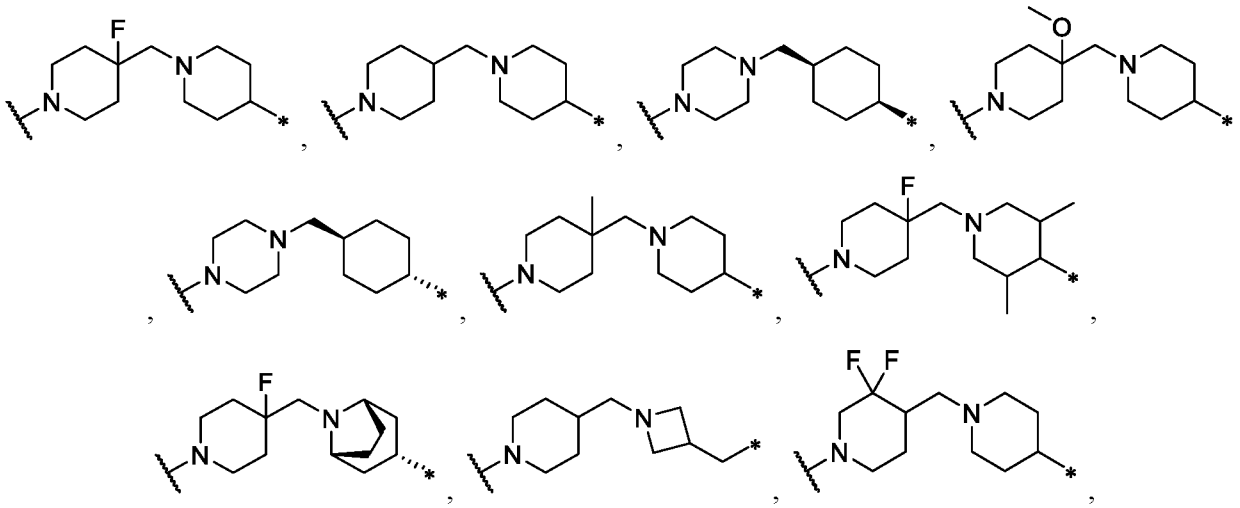
[1290] the bond marked with an "*" is attached to G^4.

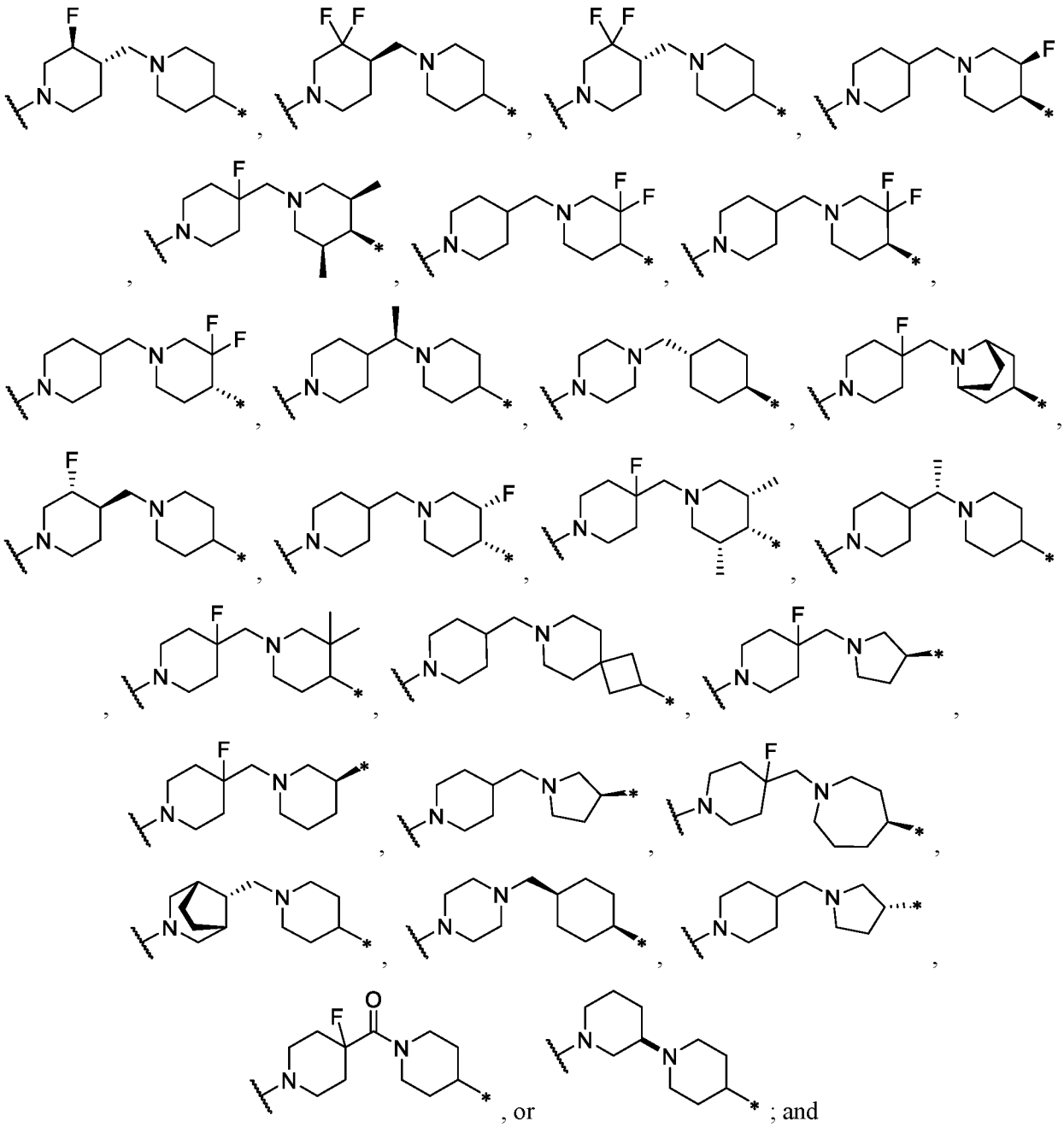
[1291] Embodiment 86. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-76, wherein G^3 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[1292] Embodiment 87. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-86, wherein G^4 is $(C_1\text{-}C_6)$alkylenyl.

[1293] Embodiment 88. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-86, wherein G^4 is a direct bond.

[1294] Embodiment 89. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments 1-64, wherein L is:





[1295] the bond marked with an "*" is attached to E.

[1296] Embodiment 90. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-89, wherein R^7 is halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen.

[1297] Embodiment 91. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 90, wherein R^7 is halogen or (C_1-C_6)alkyl.

[1298] Embodiment 92. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 91, wherein R^7 is fluoro or methyl.

[1299] Embodiment 93. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 90-92, wherein R^8, R^9, and R^{10} are hydrogen.

[1300] Embodiment 94. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-89, wherein R^8 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1301] Embodiment 95. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 94, wherein R^8 is halogen or $(C_1\text{-}C_6)$alkyl.

[1302] Embodiment 96. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 95, wherein R^8 is fluoro or methyl.

[1303] Embodiment 97. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 94-96, wherein R^7, R^9, and R^{10} are hydrogen.

[1304] Embodiment 98. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-89, wherein R^9 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1305] Embodiment 99. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 98, wherein R^9 is halogen.

[1306] Embodiment 100. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 99, wherein R^9 is fluoro.

[1307] Embodiment 101. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 98-100, wherein R^7, R^8, and R^{10} are hydrogen.

[1308] Embodiment 102. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-89, wherein R^{10} is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

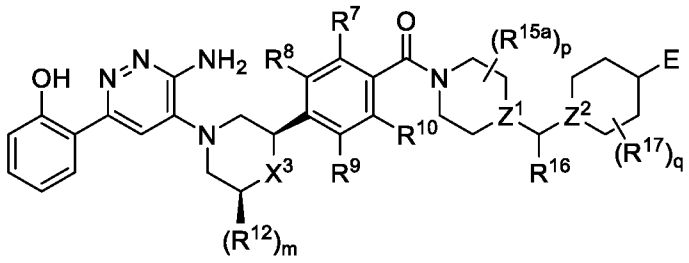
[1309] Embodiment 103. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 102, wherein R^{10} is halogen.

[1310] Embodiment 104. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 103, wherein R^{10} is fluoro.

[1311] Embodiment 105. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 102-104, wherein R^7, R^8, and R^9 are hydrogen.

[1312] Embodiment 106. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-89, wherein R^7, R^8, R^9, and R^{10} are hydrogen.

[1313] Embodiment 107. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1, 5-9, 63, or 64, having Formula (VI):



(VI),

wherein:

[1314] R^{15a} is fluoro;

[1315] p is 0, 1, or 2;

[1316] Z^1 is CR^{15b} or N;

[1317] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[1318] R^{16} is hydrogen or methyl;

[1319] Z^2 is CH or N;

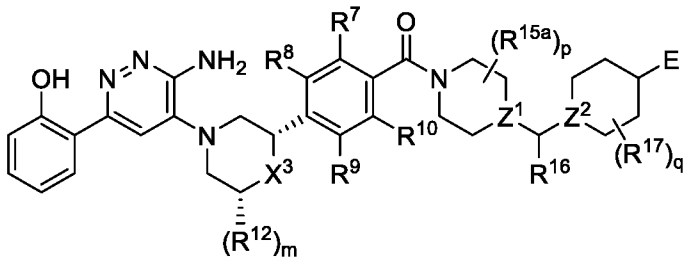
[1320] R^{17} is fluoro or methyl;

[1321] q is 0, 1, or 2;

[1322] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[1323] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

[1324] Embodiment 108. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1, 5-9, 63, or 64, having Formula (VII):



(VII),

wherein:

[1325] R^{15a} is fluoro;

[1326] p is 0, 1, or 2;

[1327] Z^1 is CR^{15b} or N;

[1328] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[1329] R^{16} is hydrogen or methyl;

[1330] Z^2 is CH or N;

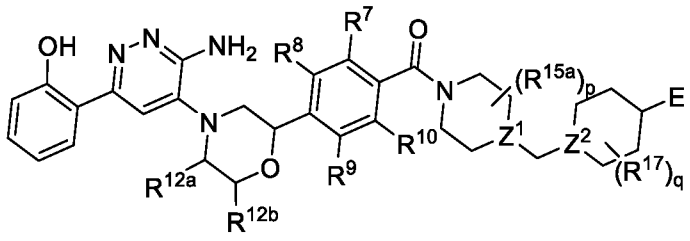
[1331] R^{17} is fluoro or methyl;

[1332] q is 0, 1, or 2;

[1333] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[1334] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

[1335] Embodiment 109. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to Embodiment 2, having Formula (XIII):



(XIII),

wherein:

[1336] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[1337] R^{12a} and R^{12b} are independently hydrogen or methyl;

[1338] R^{15a} is fluoro;

[1339] p is 0, 1, or 2;

[1340] Z^1 is CR^{15b} or N;

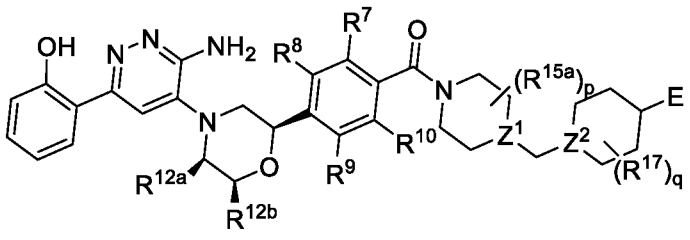
[1341] R^{15b} is hydrogen or fluoro;

[1342] Z^2 is CH or N;

[1343] R^{17} is fluoro; and

[1344] q is 0, 1, or 2.

[1345] Embodiment 110. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2, having Formula (XIV):



(XIV),

wherein:

[1346] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[1347] R^{12a} and R^{12b} are independently hydrogen or methyl;

[1348] R^{15a} is fluoro;

[1349] p is 0, 1, or 2;

[1350] Z^1 is CR^{15b} or N;

[1351] R^{15b} is hydrogen or fluoro;

[1352] Z^2 is CH or N;

[1353] R^{17} is fluoro; and

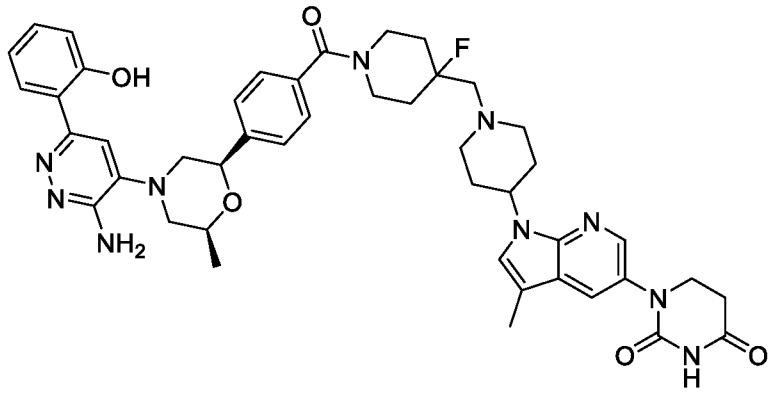
[1354] q is 0, 1, or 2.

[1355] Embodiment 111. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 selected from any one or more of the compounds of Compound List 1, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

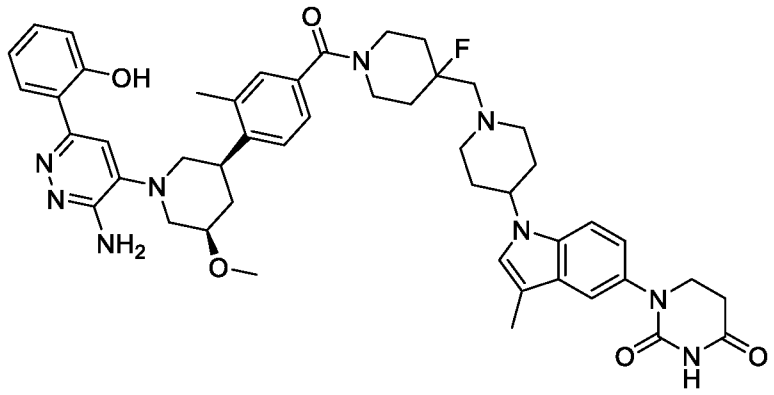
[1356] Embodiment 112. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 selected from any one or more of the compounds of Compound List 2 and/or List 3, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

[1357] Embodiment 113. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2 selected from any one or more of the compounds of Compound List 4, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

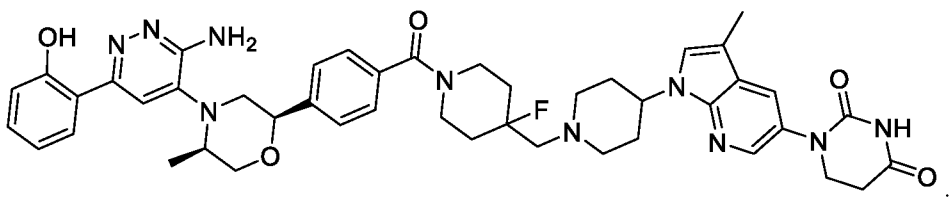
[1358] Embodiment 114. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 111, wherein the compound is:



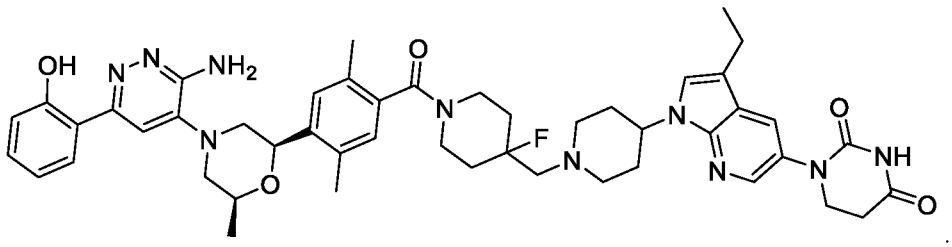
[1359] Embodiment 115. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 111, wherein the compound is:



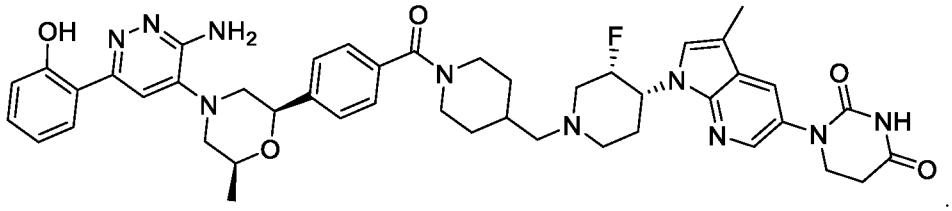
[1360] Embodiment 116. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



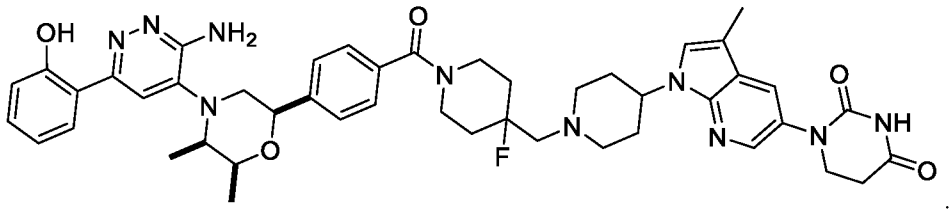
[1361] Embodiment 117. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



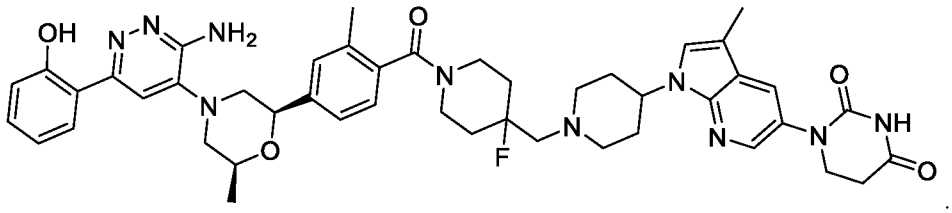
[1362] Embodiment 118. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



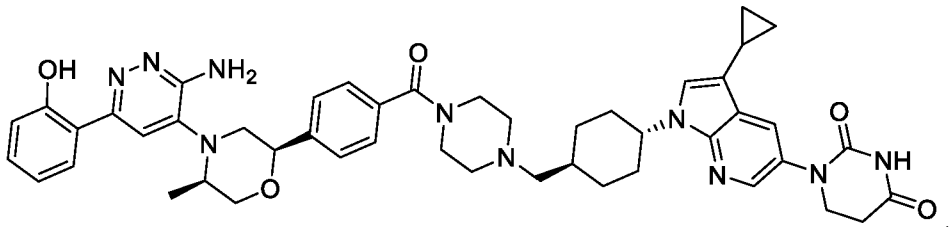
[1363] Embodiment 119. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



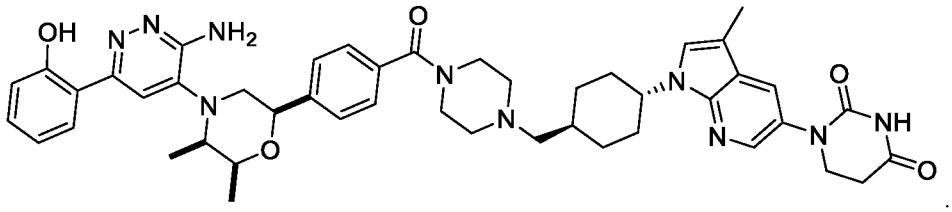
[1364] Embodiment 120. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



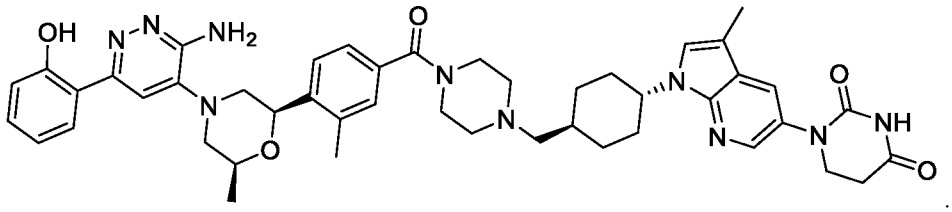
[1365] Embodiment 121. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



[1366] Embodiment 122. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



[1367] Embodiment 123. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 113, wherein the compound is:



[1368] Embodiment 124. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, and a pharmaceutically acceptable excipient.

[1369] Embodiment 125. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124.

[1370] Embodiment 126. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124.

[1371] Embodiment 127. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124.

[1372] Embodiment 128. The method of Embodiment 127, wherein the cancer is a SMARCA2-sensitive cancer.

[1373] Embodiment 129. The method of Embodiment 127, wherein the cancer is a SMARCA2-mutated cancer.

[1374] Embodiment 130. The method of any one of Embodiments 127-129, wherein the cancer is a solid tumor.

[1375] Embodiment 131. The method of any one of Embodiments 127-129, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1376] Embodiment 132. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 for use in degrading SMARCA2 protein in a human.

[1377] Embodiment 133. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 for use in reducing the level of SMARCA2 activity in a human.

[1378] Embodiment 134. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 for use in treating cancer in a human.

[1379] Embodiment 135. The compound for use of Embodiment 134, wherein the cancer is a SMARCA2-sensitive cancer.

[1380] Embodiment 136. The compound for use of Embodiment 134, wherein the cancer is a SMARCA2-mutated cancer.

[1381] Embodiment 137. The compound for use of any one of Embodiments 134-136, wherein the cancer is a solid tumor.

[1382] Embodiment 138. The compound for use of any one of Embodiments 134-136, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1383] Embodiment 139. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[1384] Embodiment 140. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

[1385] Embodiment 141. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-123, or the composition of Embodiment 124 in the manufacture of a medicament for treating cancer in a human.

[1386] Embodiment 142. The compound, or pharmaceutical acceptable salt thereof, for use of Embodiment 141, wherein the cancer is a SMARCA2-sensitive cancer.

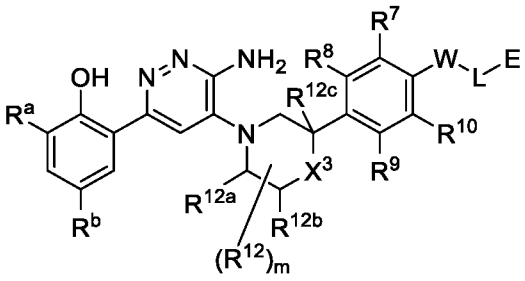
[1387] Embodiment 143. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment 141, wherein the cancer is a SMARCA2-mutated cancer.

[1388] Embodiment 144. The compound for use of any one of Embodiments 141-143, wherein the cancer is a solid tumor.

[1389] Embodiment 145. The compound for use of any one of Embodiments 141-143, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1390] The present disclosure also provides the following particular embodiments.

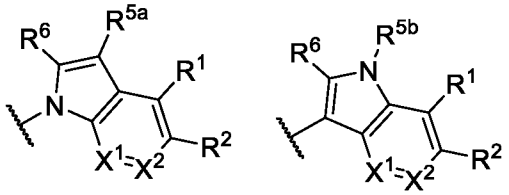
[1391] Embodiment A 1. A compound having Formula (A), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(A),

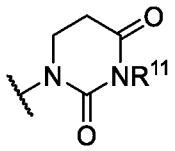
wherein:

[1392] E is:



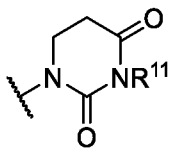
E-1 or E-2 ;

[1393] R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or



;

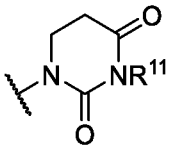
[1394] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or



;

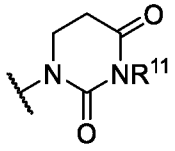
[1395] with the provisos:

[1396] (i) when R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^2 is:



; and

[1397] (ii) when R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^1 is:



;

[1398] R^{11} is hydrogen or -$(C_1\text{-}C_6)$alkyl-O-P(=O)-$(OH)_2$;

[1399] X^1 is CR^3 or N;

[1400] R^3 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[1401] X^2 is CR^4 or N;

[1402] R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[1403] R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

[1404] R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

[1405] R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

[1406] X^3 is $-(CR^{13a}R^{13b})_n-$ or -O-;

[1407] n is 0 or 1

[1408] each R^{13a} and R^{13b} is independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[1409] L is $-G^1$-G^2-G^3-G^4-, wherein G^1 is attached to W;

[1410] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[1411] G^2 is $(C_1$-$C_6)$alkylenyl, -C(=O)-, or a direct bond;

[1412] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[1413] G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[1414] W is -C(=O)-, $-CH_2-$, or a direct bond;

[1415] R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1416] R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1417] R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1418] R^{10} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1419] each R^{12} is independently halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[1420] m is 0, 1, 2, 3, or 4;

[1421] R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

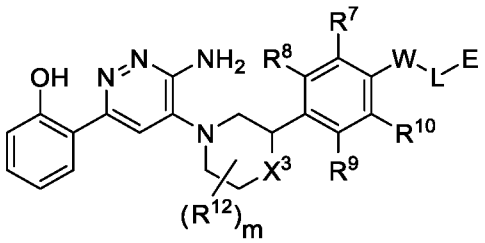
[1422] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl;

[1423] R^{12c} is hydrogen or halogen;

[1424] R^a is hydrogen or halogen; and

[1425] R^b is hydrogen or halogen.

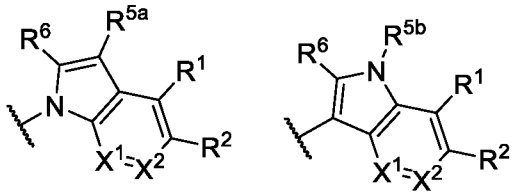
[1426] Embodiment A 2. A compound having Formula (I), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(I),

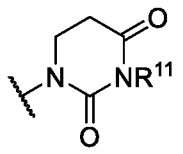
wherein:

[1427] E is:



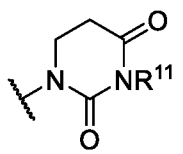
E-1 or E-2 ;

[1428] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

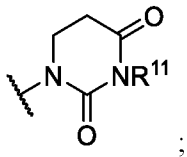
[1429] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

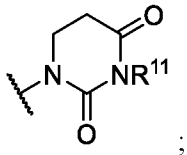
[1430] with the provisos:

[1431] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[1432] (ii) when R^2 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy, then R^1 is:



;

[1433] R^{11} is hydrogen or -$(C_1$-$C_6)$alkyl-O-P(=O)-$(OH)_2$;

[1434] X^1 is CR^3 or N;

[1435] R^3 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[1436] X^2 is CR^4 or N;

[1437] R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[1438] R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

[1439] R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

[1440] R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

[1441] X^3 is -$(CR^{13a}R^{13b})_n$- or -O-;

[1442] n is 0 or 1

[1443] each R^{13a} and R^{13b} is independently H, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[1444] L is -G^1-G^2-G^3-G^4-, wherein G^1 is attached to W;

[1445] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[1446] G^2 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[1447] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally

substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

[1448] G^4 is (C_1-C_6)alkylenyl or a direct bond;

[1449] W is -C(=O)-;

[1450] R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1451] R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

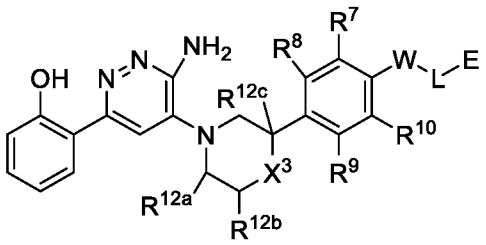
[1452] R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1453] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[1454] each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

[1455] m is 0, 1, 2, 3, or 4.

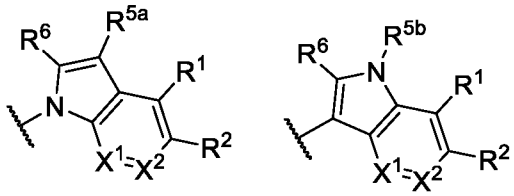
[1456] Embodiment A 3. A compound having Formula (IA), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(IA),

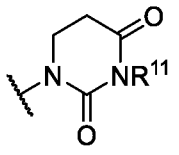
wherein:

[1457] E is:



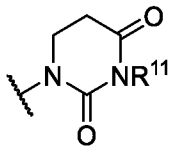
E-1 or E-2 ;

[1458] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

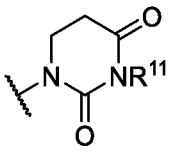
[1459] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

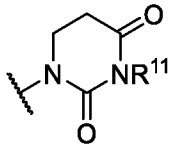
[1460] with the provisos:

[1461] (i) when R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^2 is:



; and

[1462] (ii) when R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^1 is:



;

[1463] R^{11} is hydrogen or $-(C_1\text{-}C_6)$alkyl-O-P(=O)-$(OH)_2$;

[1464] X^1 is CR^3 or N;

[1465] R^3 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[1466] X^2 is CR^4 or N;

[1467] R^4 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[1468] R^{5a} is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl;

[1469] R^{5b} is hydrogen, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl;

[1470] R^6 is hydrogen, $(C_1\text{-}C_6)$alkyl, or cyano;

[1471] X^3 is $-(CR^{13a}R^{13b})_n$- or -O-;

[1472] n is 0 or 1

[1473] each R^{13a} and R^{13b} is independently hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

[1474] L is $-G^1\text{-}G^2\text{-}G^3\text{-}G^4$-, wherein G^1 is attached to W;

[1475] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano; or $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

[1476] G^2 is $(C_1\text{-}C_6)$alkylenyl, -C(=O)-, or a direct bond;

[1477] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[1478] G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[1479] W is -C(=O)-, $-CH_2-$, or a direct bond;

[1480] R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1481] R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1482] R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

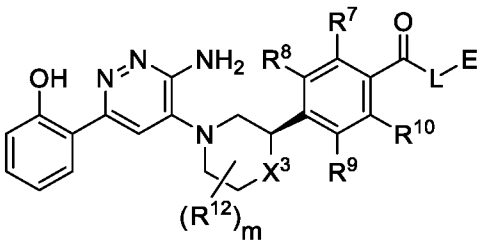
[1483] R^{10} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[1484] R^{12a} and R^{12b} are each independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen; or

[1485] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted $(C_5$-$C_7)$cycloalkyl ; and

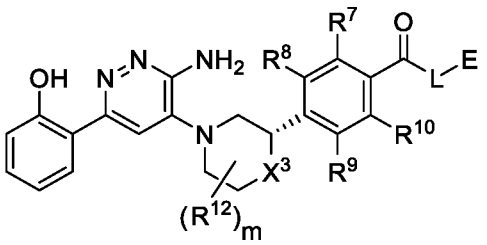
[1486] R^{12c} is hydrogen or halogen.

[1487] Embodiment A 4. The compound, or pharmaceutically acceptable salt thereof, according to Embodiments A 1 or 2 having Formula (II):



(II).

[1488] Embodiment A 5. The compound, or pharmaceutically acceptable salt thereof, according to Embodiments A 1 or 2 having Formula (III):



(III).

[1489] Embodiment A 6. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X^3 is -($CR^{13a}R^{13b}$)-.

[1490] Embodiment A 7. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 6, wherein R^{13a} and R^{13b} are hydrogen.

[1491] Embodiment A 8. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 6, wherein R^{13a} and R^{13b} are fluoro.

[1492] Embodiment A 9. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 6, wherein R^{13a} is methyl or methoxy; and R^{13b} is hydrogen.

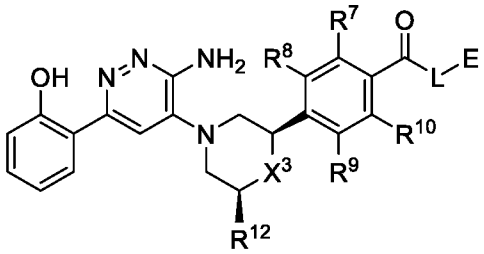
[1493] Embodiment A 10. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X^3 is -O-.

[1494] Embodiment A 11. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 2, or 4-10, wherein m is 0.

[1495] Embodiment A 12. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 2, or 4-10, wherein m is 2.

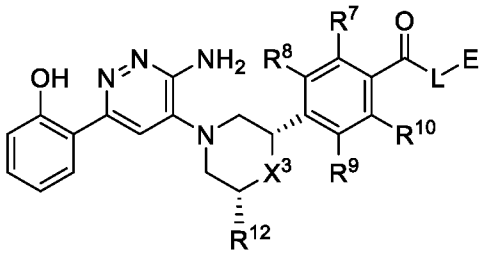
[1496] Embodiment A 13. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 2, or 4-10, wherein m is 1.

[1497] Embodiment A 14. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 2 having Formula (IV):



(IV).

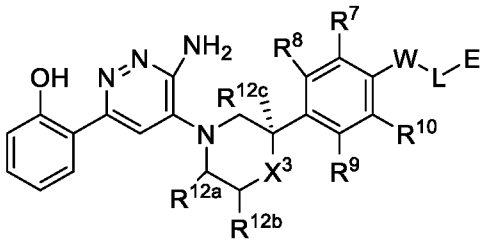
[1498] Embodiment A 15. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 2 having Formula (V):



(V).

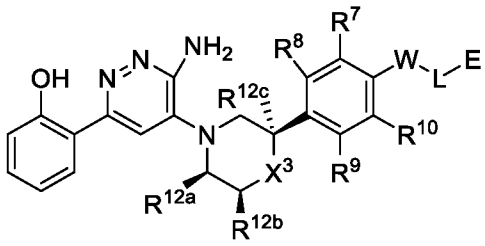
[1499] Embodiment A 16. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 13-15, wherein each R^{12} is fluoro, methyl, ethyl, or methoxy.

[1500] Embodiment A 17. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 3, having Formula (VIII):



(VIII).

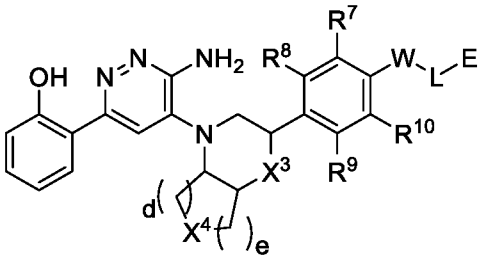
[1501] Embodiment A 18. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 3 or 17, having Formula (IX):



(IX).

[1502] Embodiment A 19. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 3, 17, or 18, wherein R^{12a} is hydrogen and R^{12b} is hydrogen, fluoro, methyl, ethyl, or methoxy.

[1503] Embodiment A 20. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to Embodiment A 3 having Formula (X):



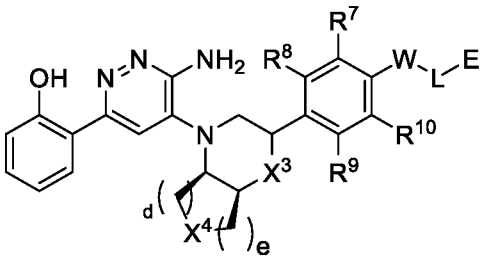
(X)

wherein:

[1504] X^4 is O; and

[1505] d and e are independently 1 or 2.

[1506] Embodiment A 21. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 3 having Formula (XI):



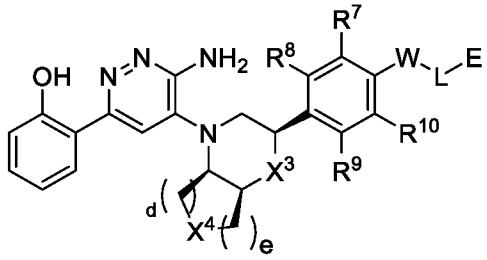
(XI)

wherein:

[1507] X^4 is O; and

[1508] d and e are independently 1 or 2.

[1509] Embodiment A 22. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 3 having Formula (XII):



(XII)

wherein:

[1510] X^4 is O; and

[1511] d and e are independently 1 or 2.

[1512] Embodiment A 23. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-22, wherein E is E-1.

[1513] Embodiment A 24. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is hydrogen.

[1514] Embodiment A 25. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is $(C_1\text{-}C_6)$alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[1515] Embodiment A 26. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 25, wherein R^{5a} is methyl, ethyl, isopropyl, or $-CF_3$.

[1516] Embodiment A 27. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is $(C_3\text{-}C_6)$cycloalkyl.

[1517] Embodiment A 28. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 27, wherein R^{5a} is cyclopropyl.

[1518] Embodiment A 29. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

[1519] Embodiment A 30. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is cyano.

[1520] Embodiment A 31. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

[1521] Embodiment A 32. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 23, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

[1522] Embodiment A 33. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-22, wherein E is E-2.

[1523] Embodiment A 34. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 33, wherein R^{5b} is hydrogen.

[1524] Embodiment A 35. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 33, wherein R^{5b} is $(C_1\text{-}C_6)$alkyl.

[1525] Embodiment A 36. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 35, wherein R^{5b} is methyl.

[1526] Embodiment A 37. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 33, wherein R^{5b} is $(C_3\text{-}C_6)$cycloalkyl.

[1527] Embodiment A 38. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 37, wherein R^{5b} is cyclopropyl or cyclobutyl.

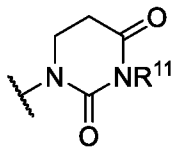
[1528] Embodiment A 39. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-38, wherein R^6 is hydrogen.

[1529] Embodiment A 40. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-38, wherein R^6 is $(C_1\text{-}C_6)$alkyl.

[1530] Embodiment A 41. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-38, wherein R^6 is cyano.

[1531] Embodiment A 42. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-41, wherein:

[1532] R^1 is:



; and

[1533] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

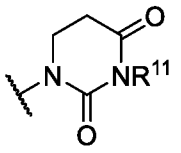
[1534] Embodiment A 43. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 42, wherein R^2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[1535] Embodiment A 44. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 43, wherein R^2 is hydrogen, fluoro, or methyl.

[1536] Embodiment A 45. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 42-44, wherein R^{11} is hydrogen.

[1537] Embodiment A 46. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-41, wherein:

[1538] R^2 is:



; and

[1539] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy.

[1540]

[1541] Embodiment A 47. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 46, wherein R^1 is hydrogen, halogen, or (C_1-C_6)alkyl.

[1542] Embodiment A 48. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 46, wherein R^1 is hydrogen, fluoro, or methyl.

[1543] Embodiment A 49. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 46-48, wherein R^{11} is hydrogen.

[1544] Embodiment A 50. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-49, wherein X^1 is CR^3.

[1545] Embodiment A 51. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 50, wherein R^3 is hydrogen.

[1546] Embodiment A 52. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 50, wherein R^3 is halogen.

[1547] Embodiment A 53. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 52, wherein R^3 is fluoro.

[1548] Embodiment A 54. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 50, wherein R^3 is (C_1-C_6)alkyl.

[1549] Embodiment A 55. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 54, wherein R^3 is methyl.

[1550] Embodiment A 56. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-49, wherein X^1 is N.

[1551] Embodiment A 57. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-56, wherein X^2 is CR^4.

[1552] Embodiment A 58. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 57, wherein R^4 is hydrogen.

[1553] Embodiment A 59. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 57, wherein R^4 is halogen.

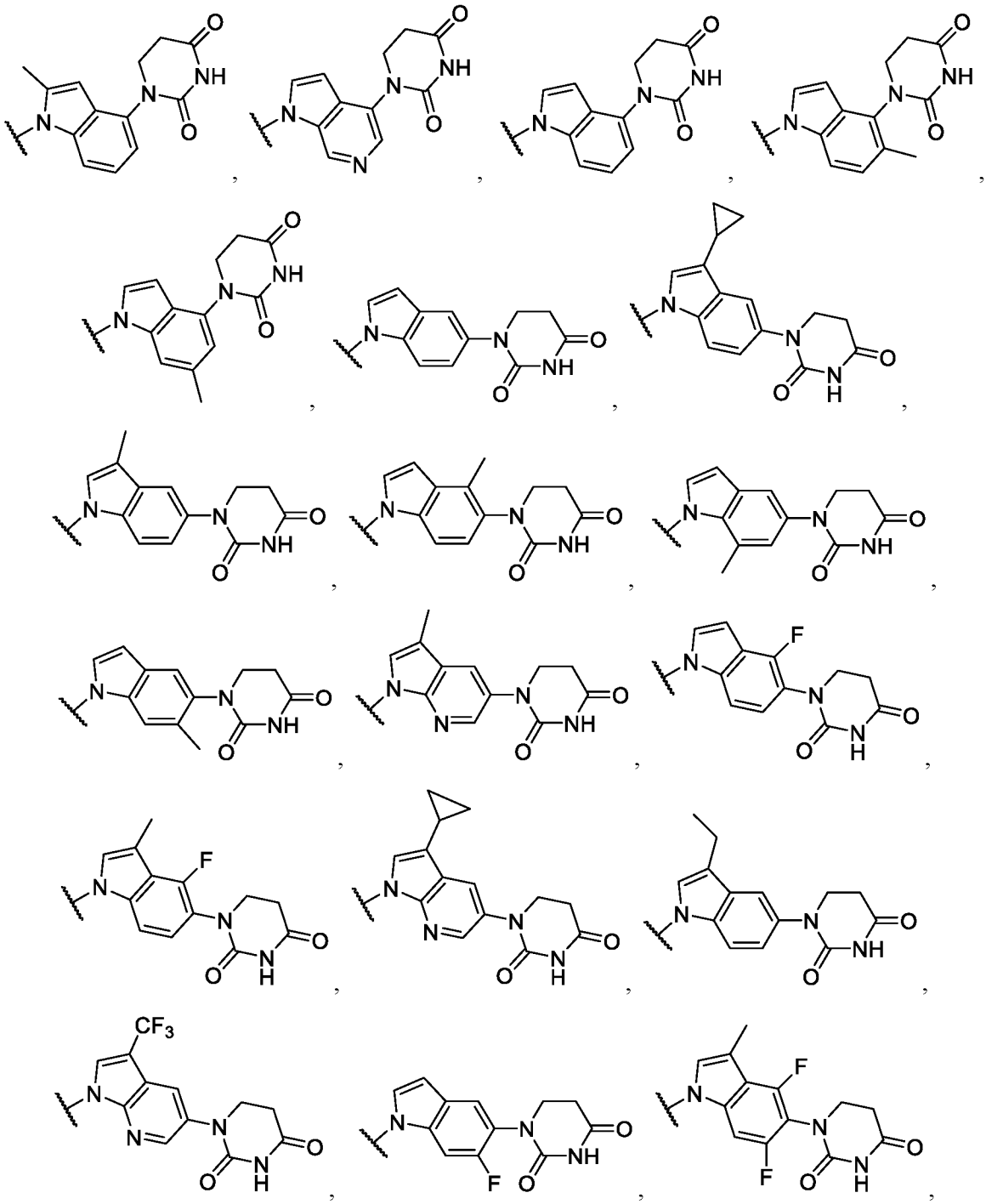
[1554] Embodiment A 60. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein R^4 is fluoro.

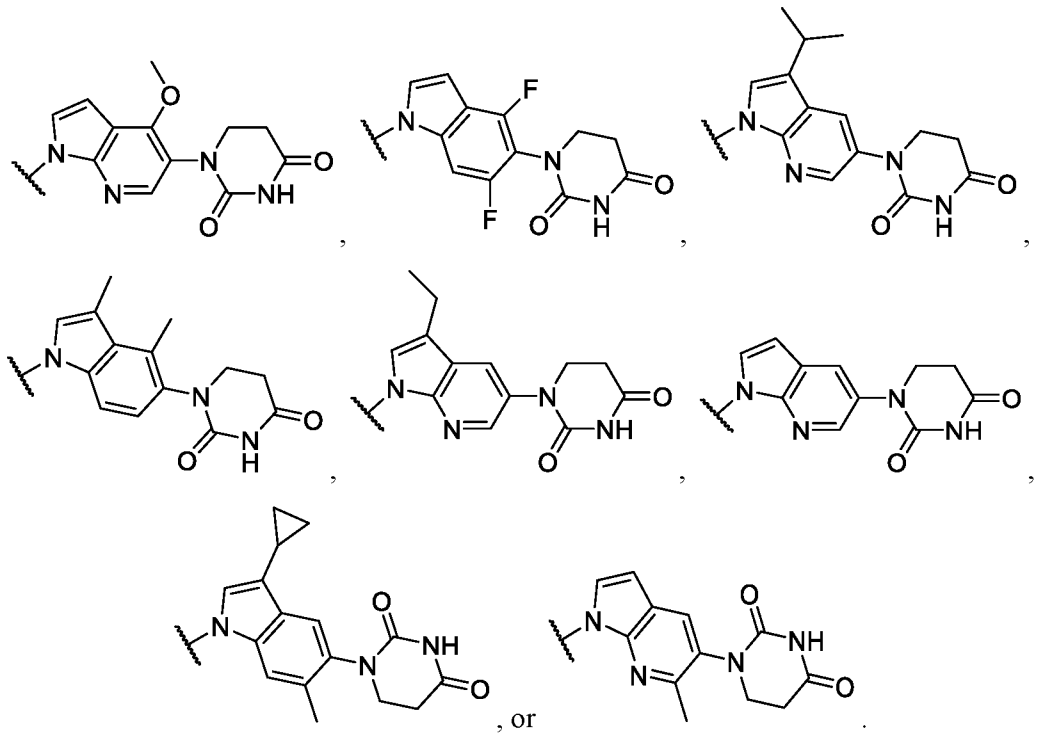
[1555] Embodiment A 61. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 57, wherein R^4 is (C_1-C_6)alkyl.

[1556] Embodiment A 62. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 61, wherein R^4 is methyl.

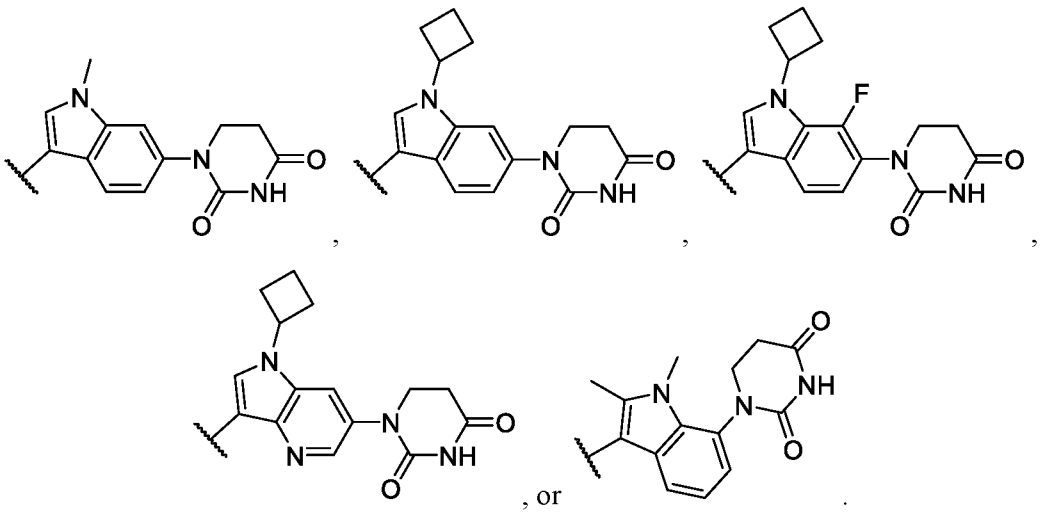
[1557] Embodiment A 63. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-56, wherein X^2 is N.

[1558] Embodiment A 64. The compound of Embodiment A 23, wherein E-1 is:





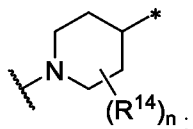
[1559] Embodiment A 65. The compound of Embodiment A 33, wherein E-2 is:



[1560] Embodiment A 66. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-65, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[1561] Embodiment A 67. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 66, wherein:

[1562] G^1 is:



[1563] each R^{14} is independently halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

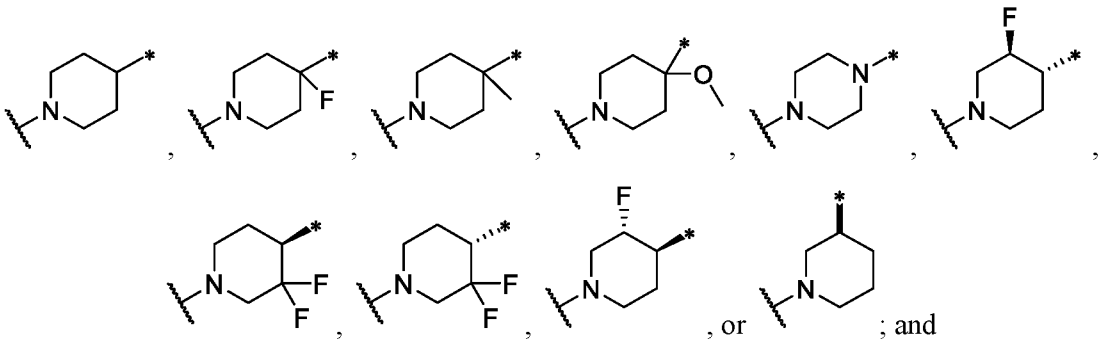
[1564] n is 0, 1, 2, or 3; and

[1565] the bond marked with an "*" is attached to G^2.

[1566] Embodiment A 68. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 67, wherein n is 0.

[1567] Embodiment A 69. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 67, wherein R^{14} is fluoro, methyl, or methoxy; and n is 1, or 2.

[1568] Embodiment A 70. The compound, or pharmaceutically acceptable salt thereof, according Embodiment A 66, wherein G^1 is:



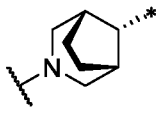
, or ; and

[1569] the bond marked with an "*" is attached to G^2.

[1570] Embodiment A 71. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-65, wherein G^1 is (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[1571] Embodiment A 72. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-65, wherein G^1 is a 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[1572] Embodiment A 73. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 72, wherein G^1 is:



; and

[1573] the bond marked with an "*" is attached to G^2.

[1574] Embodiment A 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-73, wherein G^2 is a direct bond.

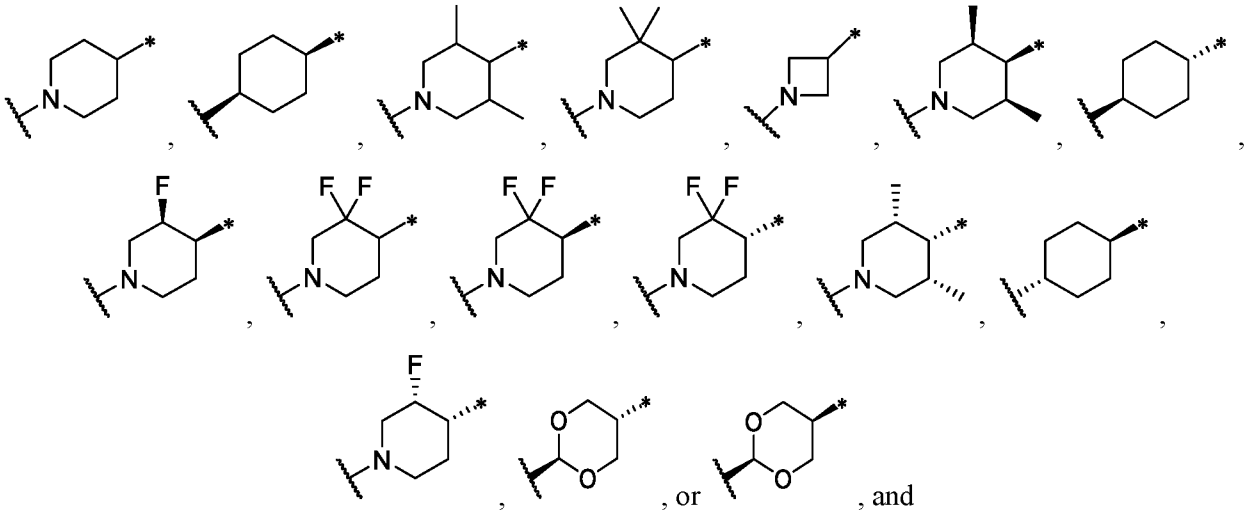
[1575] Embodiment A 75. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-73, wherein G^2 is (C_1-C_6)alkylenyl.

[1576] Embodiment A 76. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 75, wherein G^2 is -CH_2- or –$CH(CH_3)$-.

[1577] Embodiment A 77. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1-73, wherein G^2 is –C(=O)-.

[1578] Embodiment A 78. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-73, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1579] Embodiment A 79. The compound, or pharmaceutically acceptable salt thereof, according Embodiment A 78, wherein G^3 is:

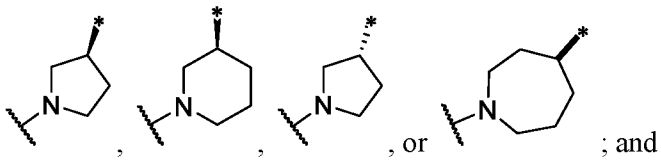


, and

[1580] the bond marked with an "*" is attached to G^4.

[1581] Embodiment A 80. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-77, wherein G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1582] Embodiment A 81. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 80, wherein G^3 is:



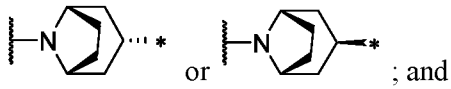
; and

[1583] the bond marked with an "*" is attached to G^4.

[1584]

[1585] Embodiment A 82. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-77, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano.

[1586] Embodiment A 83. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 82, wherein G^3 is:

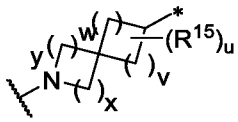


; and

[1587] the bond marked with an "*" is attached to G^4.

[1588] Embodiment A 84. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 82, wherein:

[1589] G^3 is:



;

[1590] each R^{15} is independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

[1591] u is 0, 1, 2, or 3;

[1592] v, w, x, and t are independently 1, 2, or 3; and

[1593] the bond marked with an "*" is attached to G^4.

[1594] Embodiment A 85. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 84, wherein v, w, x, and y are independently 1 or 2.

[1595] Embodiment A 86. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 85, wherein G^3 is:



; and

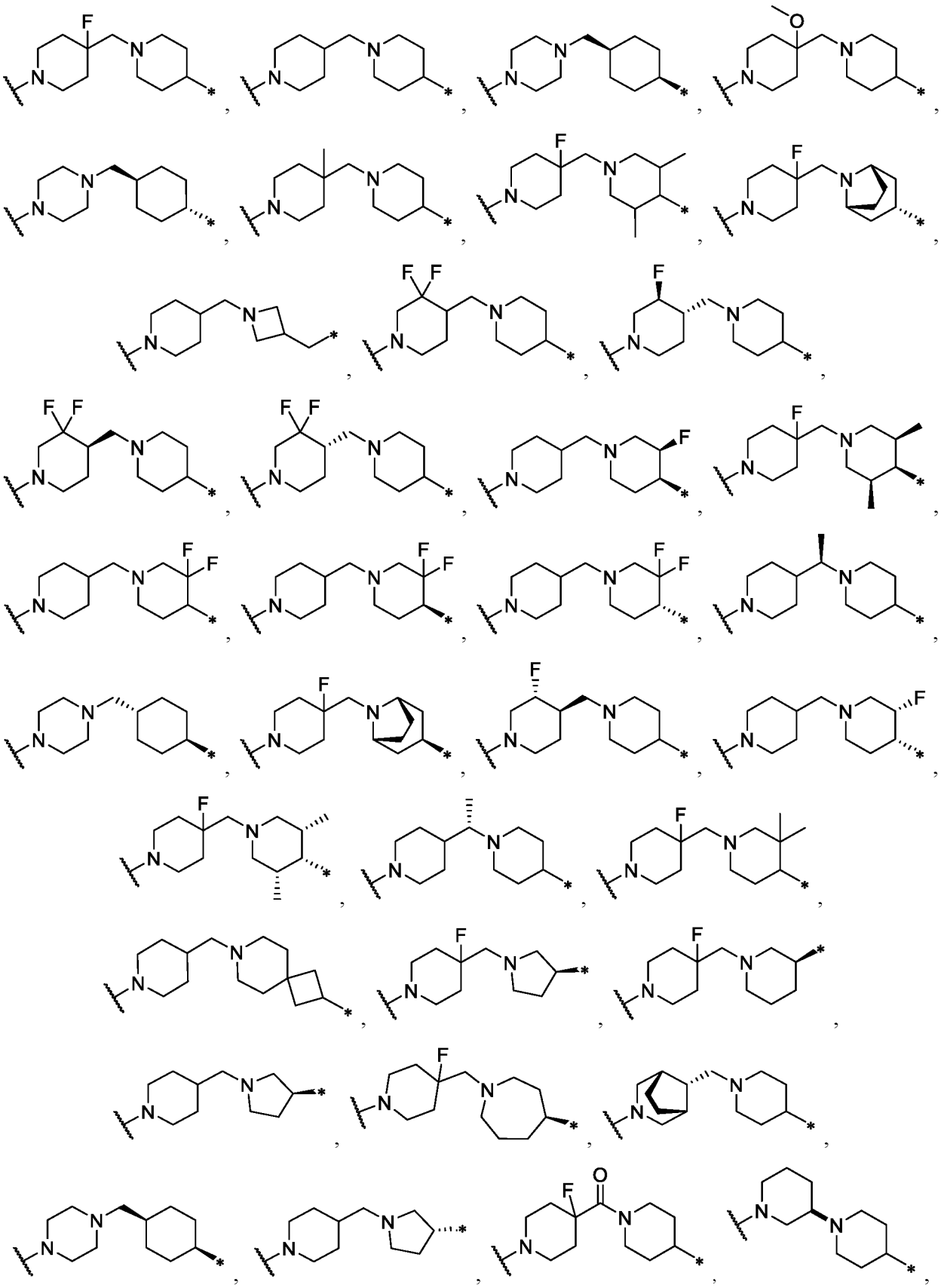
[1596] the bond marked with an "*" is attached to G^4.

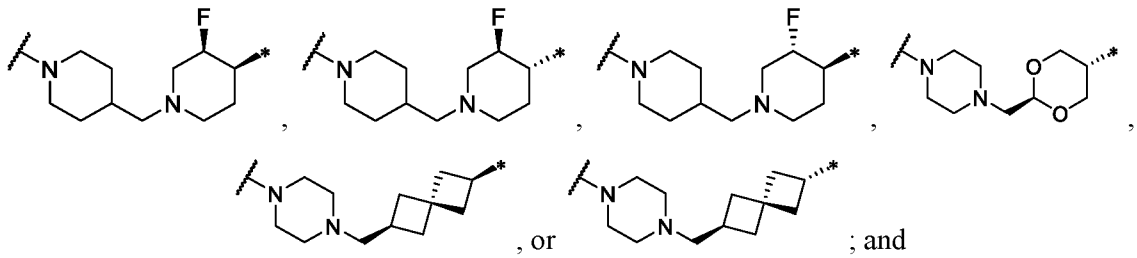
[1597] Embodiment A 87. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-77, wherein G^3 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[1598] Embodiment A 88. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-87, wherein G^4 is $(C_1\text{-}C_6)$alkylenyl.

[1599] Embodiment A 89. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-87, wherein G^4 is a direct bond.

[1600] Embodiment A 90. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments A 1-65, wherein L is:





, or ; and

[1601] the bond marked with an "*" is attached to E.

[1602] Embodiment A 91. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-90, wherein R^7 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1603] Embodiment A 92. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 91, wherein R^7 is halogen or $(C_1\text{-}C_6)$alkyl.

[1604] Embodiment A 93. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 92, wherein R^7 is fluoro or methyl.

[1605] Embodiment A 94. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 91-93, wherein R^8, R^9, and R^{10} are hydrogen.

[1606] Embodiment A 95. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-90, wherein R^8 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1607] Embodiment A 96. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 95, wherein R^8 is halogen or $(C_1\text{-}C_6)$alkyl.

[1608] Embodiment A 97. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 96, wherein R^8 is fluoro or methyl.

[1609] Embodiment A 98. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 95-97, wherein R^7, R^9, and R^{10} are hydrogen.

[1610] Embodiment A 99. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-90, wherein R^9 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1611] Embodiment A 100.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 99, wherein R^9 is halogen.

[1612] Embodiment A 101.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 100, wherein R^9 is fluoro.

[1613] Embodiment A 102.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 99-101, wherein R^7, R^8, and R^{10} are hydrogen.

[1614] Embodiment A 103.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-90, wherein R^{10} is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[1615] Embodiment A 104.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 103, wherein R^{10} is halogen.

[1616] Embodiment A 105.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 104, wherein R^{10} is fluoro.

[1617] Embodiment A 106.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 103-105, wherein R^7, R^8, and R^9 are hydrogen.

[1618] Embodiment A 107.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-90, wherein R^7, R^8, R^9, and R^{10} are hydrogen.

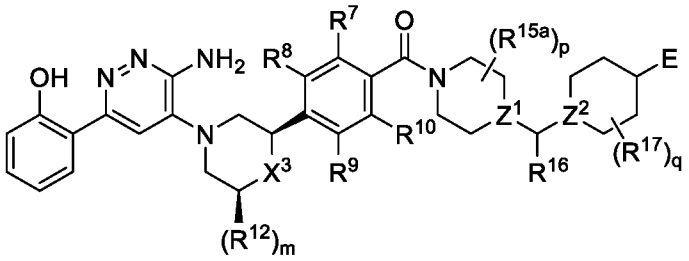
[1619] Embodiment A 108.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 6-13, or 23-107, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; and m is 0.

[1620] Embodiment A 109.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 6-13, or 23-107, wherein R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl; and m is 0.

[1621] Embodiment A 110.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 6-13, or 23-109, wherein R^a is fluoro and R^b is hydrogen.

[1622] Embodiment A 111.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 6-13, or 23-110, wherein R^a is hydrogen and R^b is fluoro.

[1623] Embodiment A 112.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 2, 6-10, 64, or 65, having Formula (VI):



(VI),

wherein:

[1624] R^{15a} is fluoro;

[1625] p is 0, 1, or 2;

[1626] Z^1 is CR^{15b} or N;

[1627] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[1628] R^{16} is hydrogen or methyl;

[1629] Z^2 is CH or N;

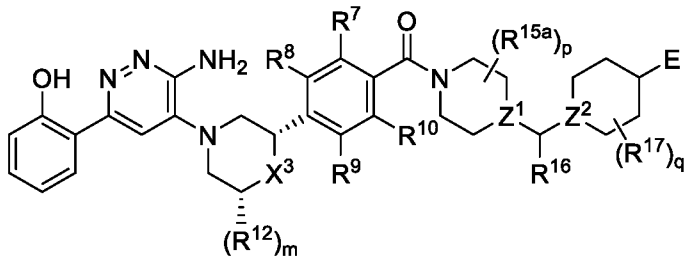
[1630] R^{17} is fluoro or methyl;

[1631] q is 0, 1, or 2;

[1632] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[1633] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

[1634] Embodiment A 113.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 2, 6-10, 64, or 65, having Formula (VII):



(VII),

wherein:

[1635] R^{15a} is fluoro;

[1636] p is 0, 1, or 2;

[1637] Z^1 is CR^{15b} or N;

[1638] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[1639] R^{16} is hydrogen or methyl;

[1640] Z^2 is CH or N;

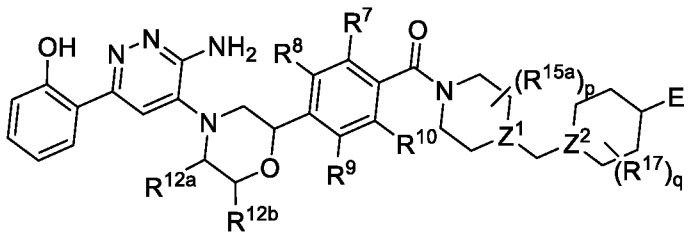
[1641] R^{17} is fluoro or methyl;

[1642] q is 0, 1, or 2;

[1643] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[1644] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

[1645] Embodiment A 114.The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to any one of Embodiments A 3, 64, or 65 having Formula (XIII):



(XIII),

wherein:

[1646] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[1647] R^{12a} and R^{12b} are independently hydrogen or methyl;

[1648] R^{15a} is fluoro;

[1649] p is 0, 1, or 2;

[1650] Z^1 is CR^{15b} or N;

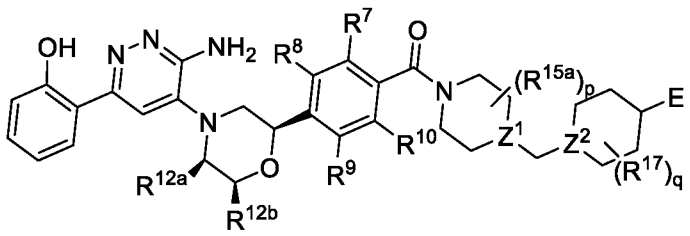
[1651] R^{15b} is hydrogen or fluoro;

[1652] Z^2 is CH or N;

[1653] R^{17} is fluoro; and

[1654] q is 0, 1, or 2.

[1655] Embodiment A 115.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 3, 64, or 65, having Formula (XIV):



(XIV),

wherein:

[1656] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[1657] R^{12a} and R^{12b} are independently hydrogen or methyl;

[1658] R^{15a} is fluoro;

[1659] p is 0, 1, or 2;

[1660] Z^1 is CR^{15b} or N;

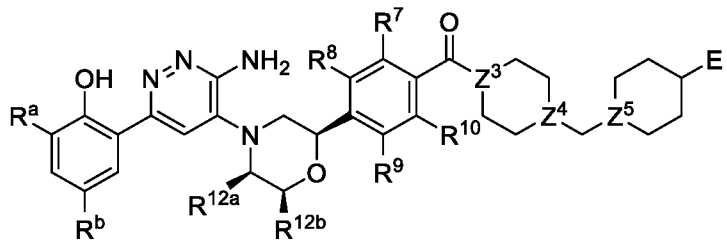
[1661] R^{15b} is hydrogen or fluoro;

[1662] Z^2 is CH or N;

[1663] R^{17} is fluoro; and

[1664] q is 0, 1, or 2.

[1665] Embodiment A 116.The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1, 64, or 65, having Formula (XV):



(XV)

wherein:

[1666] R^a and R^b are independently hydrogen or fluoro;

[1667] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[1668] R^{12a} and R^{12b} are independently hydrogen or methyl; or

[1669] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form a 5-membered heterocycloalkyl;

[1670] Z^3 is CH or N.

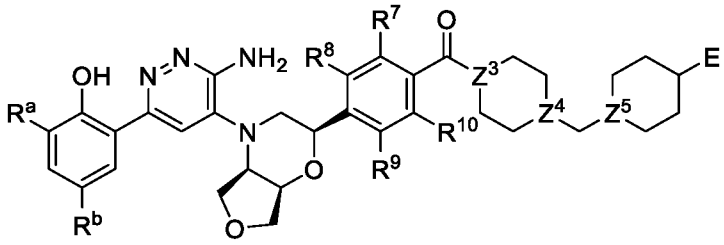
[1671] Z^4 is CR^{15b} or N;

[1672] R^{15b} is hydrogen or fluoro; and

[1673] Z^5 is CH or N.

[1674] Embodiment A 117.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 16, wherein R^{12a} and R^{12b} are independently hydrogen or methyl.

[1675] Embodiment A 118.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 16 having Formula (XVI):



(XVI).

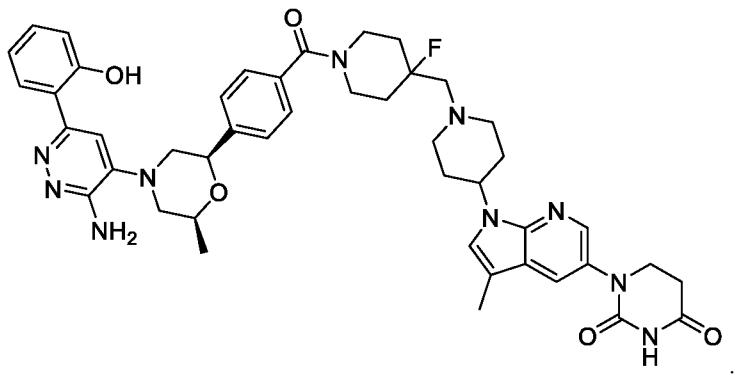
[1676] Embodiment A 119.The compound according to Embodiment A 1 selected from any one or more of the compounds of Compound List 1 and/or Compound List 2, or pharmaceutically acceptable salts thereof.

[1677] Embodiment A 120.The compound according to Embodiment A 1 selected from any one or more of the compounds of Compound List 3, or pharmaceutically acceptable salts thereof.

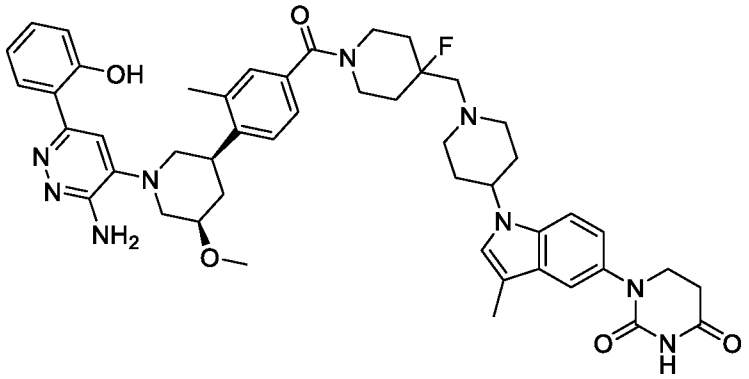
[1678] Embodiment A 121.The compound according to Embodiment A 1 selected from any one or more of the compounds of Compound List 4, or pharmaceutically acceptable salts thereof.

[1679] Embodiment A 122.The compound according to Embodiment A 1 selected from any one or more of the compounds of Compound List 5, or pharmaceutically acceptable salts thereof.

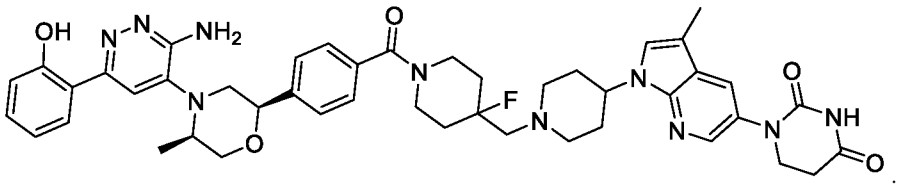
[1680] Embodiment A 123.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 119, wherein the compound is:



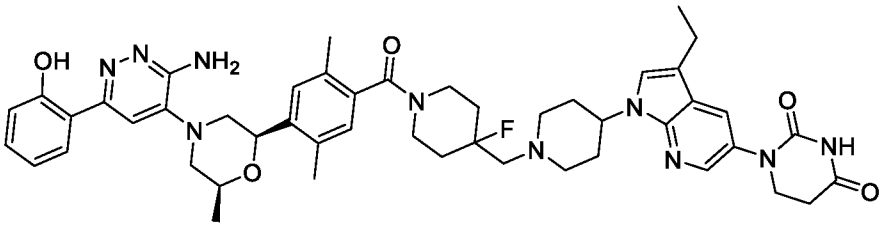
[1681] Embodiment A 124.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 119, wherein the compound is:



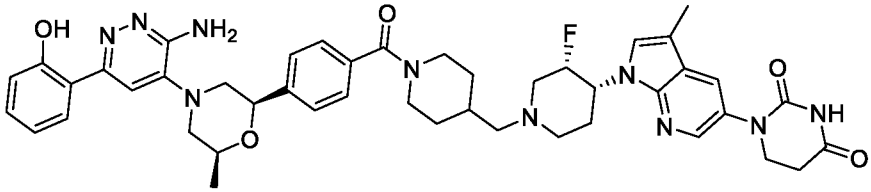
[1682] Embodiment A 125.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



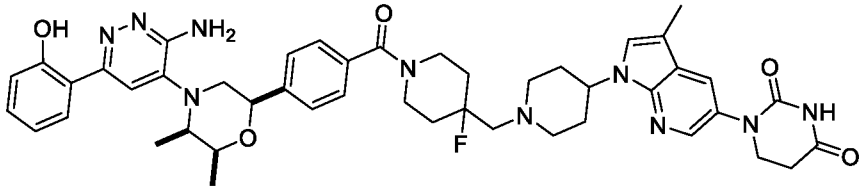
[1683] Embodiment A 126.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



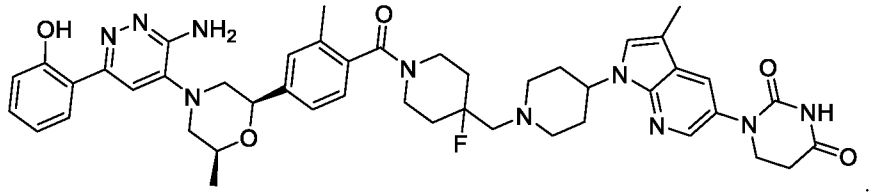
[1684] Embodiment A 127.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



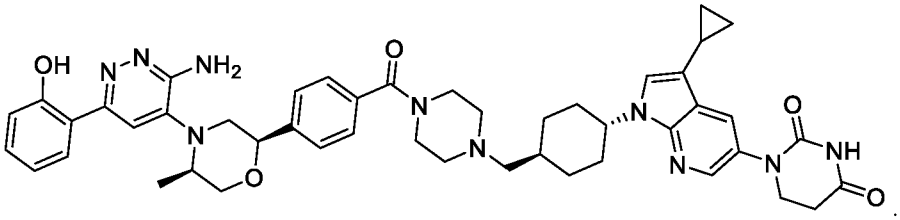
[1685] Embodiment A 128.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



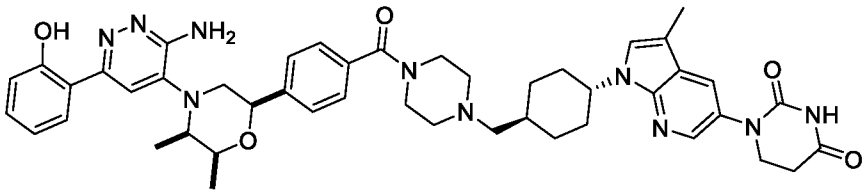
[1686] Embodiment A 129.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



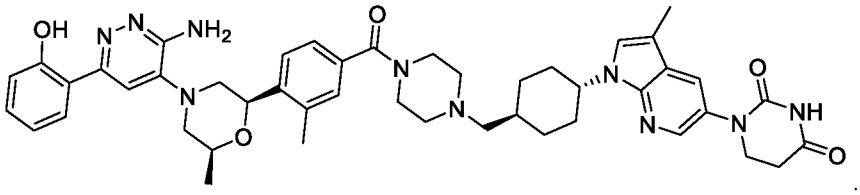
[1687] Embodiment A 130.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



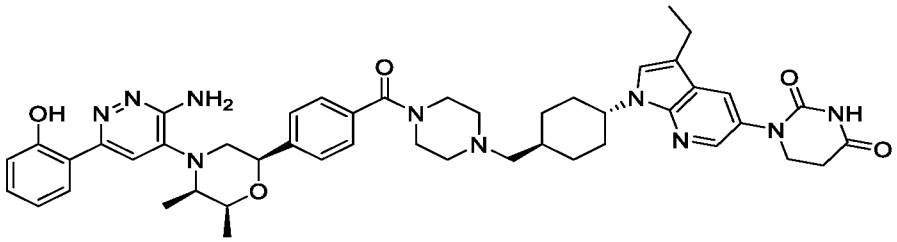
[1688] Embodiment A 131.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



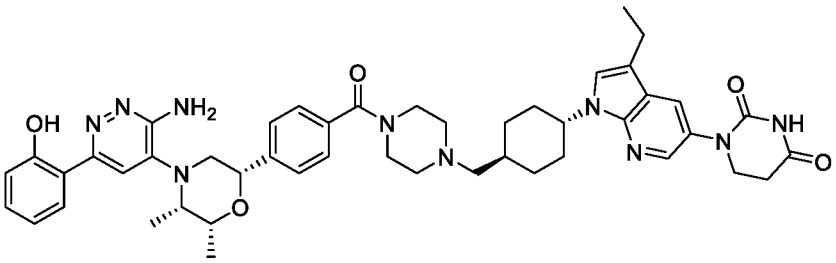
[1689] Embodiment A 132.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 121, wherein the compound is:



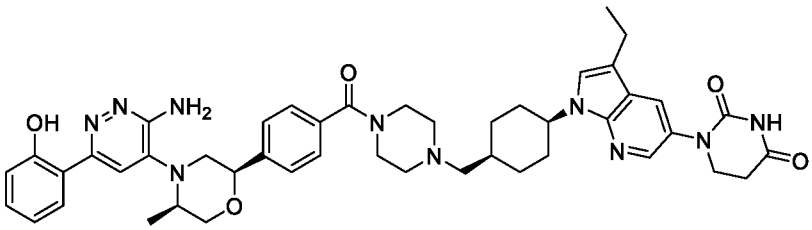
[1690] Embodiment A 133.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 122, wherein the compound is:



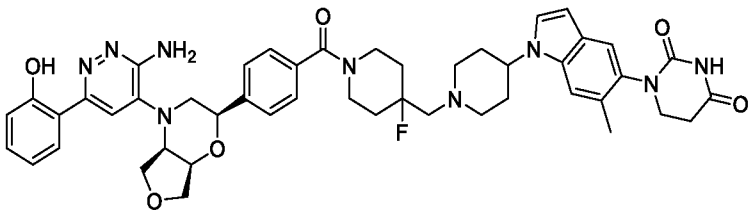
[1691] Embodiment A 134.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 122, wherein the compound is:



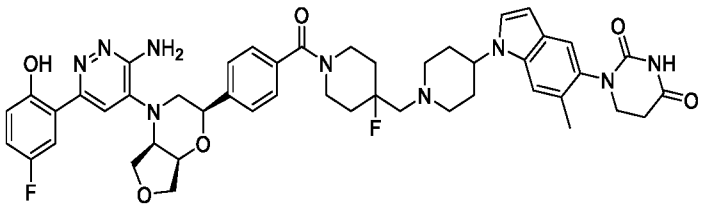
[1692] Embodiment A 135.The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 122, wherein the compound is:



[1693] Embodiment A 136. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 122, wherein the compound is:



[1694] Embodiment A 137. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 122, wherein the compound is:



[1695] Embodiment A 138. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, and a pharmaceutically acceptable excipient.

[1696] Embodiment A 139. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138.

[1697] Embodiment A 140. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or

pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138.

[1698] Embodiment A 141. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138.

[1699] Embodiment A 142. The method of Embodiment A 141, wherein the cancer is a SMARCA2-sensitive cancer.

[1700] Embodiment A 143. The method of Embodiment A 141, wherein the cancer is a SMARCA2-mutated cancer.

[1701] Embodiment A 144. The method of any one of Embodiments A 141-143, wherein the cancer is a solid tumor.

[1702] Embodiment A 145. The method of any one of Embodiments A 141-143, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1703] Embodiment A 146. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 for use in degrading SMARCA2 protein in a human.

[1704] Embodiment A 147. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 for use in reducing the level of SMARCA2 activity in a human.

[1705] Embodiment A 148. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 for use in treating cancer in a human.

[1706] Embodiment A 149. The compound for use of Embodiment A 138, wherein the cancer is a SMARCA2-sensitive cancer.

[1707] Embodiment A 150. The compound for use of Embodiment A 138, wherein the cancer is a SMARCA2-mutated cancer.

[1708] Embodiment A 151. The compound for use of any one of Embodiments A 148-150, wherein the cancer is a solid tumor.

[1709] Embodiment A 152. The compound for use of any one of Embodiments A 148-150, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1710] Embodiment A 153. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[1711] Embodiment A 154. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

[1712] Embodiment A 155. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-137, or the composition of Embodiment A 138 in the manufacture of a medicament for treating cancer in a human.

[1713] Embodiment A 156. The compound, or pharmaceutical acceptable salt thereof, for use of Embodiment A 155, wherein the cancer is a SMARCA2-sensitive cancer.

[1714] Embodiment A 157. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment A 155, wherein the cancer is a SMARCA2-mutated cancer.

[1715] Embodiment A 158. The compound for use of any one of Embodiments A 155-157, wherein the cancer is a solid tumor.

[1716] Embodiment A 159. The compound for use of any one of Embodiments A 155-157, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

EXAMPLES

General Experimental Conditions and Abbreviations

[1717] The following abbreviations are used: *t*-BuBrettPhos = [3,6-dimethoxy-2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]bis(1,1-dimethylethyl)phosphine; *t*-BuBrettPhos Pd G3 = [(2-di-*tert*-butylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate; DCM = dichloromethane; DIPEA = *N,N*-diisopropylethylamine; DMA = *N,N*-dimethylacetamide; DMAP = 4-dimethylaminopyridine; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; Et_2O = diethyl ether; EtOAc = ethyl acetate; EPhos = dicyclohexyl(3-isopropoxy-2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphane; EPhos Pd G4 = palladium catalyst containing EPhos - CAS number: 2132978-44-8; FA = formic acid; FSC = flash silica chromatography; h = hour(s); HATU = (dimethylamino)-*N,N*-dimethyl(3-oxido-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinyl)methaniminium hexafluorophosphate; HPLC = high-performance liquid chromatography; min = minutes; mmol = millimole(s); MeOH = methanol; MeCN = acetonitrile; MTBE = methyl *tert*-butyl ether; NaOAc = sodium acetate; NMR = nuclear magnetic resonance; Pd/C = Palladium on carbon; $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0); $Pd(dppf)Cl_2$ = [1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II); r.t. = room temperature (~18-25°C); RPC = reverse phase chromatography; RP-HPLC = reverse-phase high-performance liquid chromatography; sat. = saturated; SFC = supercritical fluid chromatography; TFA = trifluoroacetic acid; THF = tetrahydrofuran; VCD = vibrational circular dichroism; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; XPhos Pd G3 = (2-dicyclohexyl-phosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)methanesulfonate; $scCO_2$ = supercritical carbon dioxide; DMSO-*d*6 = hexadeuterodimethyl sulfoxide, $CDCl_3$ = deuterochloroform; CD_2Cl_2 = dideuteromethylene chloride; IPA = isopropyl alcohol; PyBop = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; BrettPhos Pd G3 = [(2-di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II)

methanesulfonate; AcOH = acetic acid; EtOH = ethanol; $NaBH(OAc)_3$ = sodium triacetoxyborohydride; Boc = *tert*-butyloxycarbonyl; aq. = aqueous; *t*-BuXPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl; *t*-BuXPhos P G3 = [(2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate; GPhos = (3-(*tert*-butoxy)-2′,6′-diisopropyl-6-methoxy-[1,1′-biphenyl]-2-yl)dicyclohexylphosphane; DMP = Dess–Martin periodinane; DAST = (diethylamine)sulfur trifluoride; TsOH = *p*-toluenesulfonic acid; Ac = acetyl; TBS = *tert*-butyldimethylsilyl; $Pd(dtbpf)Cl_2$ = [1,1′-*bis*(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II); CPhos = 2-dicyclohexylphosphino-2′,6′-*bis*(*N,N*-dimethylamino)biphenyl; CPhos Pd G3 = [(2-Dicyclohexylphosphino-2′,6′-*bis*(N,N-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate; DCE = 1,2-dichloroethane; NMP = *N*-methyl-2-pyrrolidone; GPhos Pd G6 TES = bromo[dicyclohexyl[3-(1,1-dimethylethoxy)-6-methoxy-2',6'-bis(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine](4-((2-(trimethylsilyl)ethoxy)carbonyl)benzen-1-ide)palladium(II); PPTS = pyridinium *p*-toluenesulfonate; NBS = *N*-bromosuccinimide.

[1718] NMR: Proton NMR (^{1}H NMR) was carried out at 300-600 MHz at a temperature in the range from 15-30°C in deuterated-DMSO unless otherwise specified. Standard NMR abbreviations are used: s = single, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt doublet of triplets, ddd = doublet of doublets of doublets, m = multiplet, br = broad.

[1719] Chromatography methods: clean-appearing fractions containing the desired product are generally identified and combined together and then concentrated under reduced pressure. Flash chromatography was performed using straight phase flash chromatography on a SP1™ Purification or SELEKT™ system from Biotage™, CombiFlash™ Rf from ISCO or on Gilson system from Thermo Fisher using normal phase silica FLASH+™ (40M, 25M or 12 M), Sfär Silica HC (5 g, 10 g, 25 g, 100 g, 200 g, 350 g) from Biotage™ or SNAP™ KP-Sil Cartridges (340, 100, 50 or 10), Flash Column silica-CS columns from Agela, with C18-flash columns or standard flash chromatography. RP-HPLC was performed using XSelect or XBridge columns.

[1720] In general, all solvents used were commercially available and of analytical grade. Anhydrous solvents were routinely used for reactions.

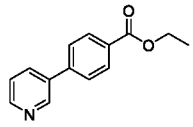
[1721] Concentration of solutions (to partly or fully remove solvent) are generally performed under reduced pressure at r.t. or slightly above.

[1722] The intermediates and examples named below were named using BIOVIA Draw 20.1 or ChemDraw 20.1.1.125. The starting materials were obtained from commercial sources or made via literature routes.

[1723] Compounds of the Disclosure disclosure may be prepared as described in the experimental procedures below, and analogous/similar procedures may be used to prepare other compounds of Formula (I).

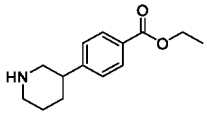
EXAMPLE 1

Intermediate 1a: Ethyl 4-(pyridin-3-yl)benzoate



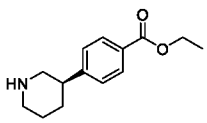
[1724] A solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.0 g, 24.38 mmol), ethyl 4-bromobenzoate (4.0 mL, 24.38 mmol), $Pd(PPh_3)_4$ (2.82 g, 2.44 mmol), Cs_2CO_3 (19.86 g, 60.96 mmol) 1,4-dioxane (94 mL) and water (23.58 mL) was sparged at r.t. for 10 min, then heated to 100°C for 2h. Upon completion, the reaction mixture was cooled to r.t. diluted with EtOAc and water and extracted with EtOAc (3 × 30 mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (6.55 g, 89%) as a colorless oil which solidified upon standing. ^{1}H NMR (DMSO-*d*6): δ 1.34 (3H, t), 4.26-4.42 (2H, q), 7.46-7.56 (1H, m), 7.80-7.93 (2H, m), 8.03-8.07 (2H, m), 8.11-8.19 (1H, m), 8.59-8.70 (1H, m), 8.92-9.01 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 228.4.

Intermediate 1b: *rac*-Ethyl 4-(piperidin-3-yl)benzoate



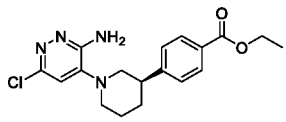
[1725] A solution of Intermediate 1a (2.50 g, 11.00 mmol), 10% Pd/C (1.171 g, 1.10 mmol) and AcOH (110 mL) under N_2 atmosphere was placed under H_2 (1 atm) and stirred at 70°C for 16h. The reaction mixture was filtered through a pad of Celite (washing with MeOH) and concentrated to give a colorless oil. The crude material was then suspended in DCM and basified with sat. aq. $NaHCO_3$. The layers were separated and the aqueous extracts were washed with DCM (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the title compound (2.360 g, 92%) as a brown oil, which solidified upon standing at 0 °C in the refrigerator overnight. ^{1}H NMR (DMSO-*d*6): δ 1.31 (3H, t), 1.42 - 1.52 (1H, m), 1.53 - 1.62 (1H, m), 1.62 - 1.68 (1H, m), 1.83 - 1.91 (1H, m), 2.43 - 2.49 (1H, m), 2.52 - 2.56 (1H, m), 2.63 - 2.72 (1H, m), 2.89 - 3.01 (2H, m), 3.03 - 3.38 (1H, m), 4.30 (2H, q), 7.38 (2H, d), 7.88 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 234.9.

Intermediate 1c: Ethyl (*R*)-4-(piperidin-3-yl)benzoate



[1726] Intermediate 1b (2.00 g, 8.57 mmol) was purified by chiral SFC (Column: IG 30mm × 250 5µm, 0.2% NH_4OH in MeOH) to give the title compound (886 mg, 44% yield, >99% ee) as a light brown oil, which solidified upon standing in the refrigerator at 0°C. Absolute configuration was assigned by VCD.

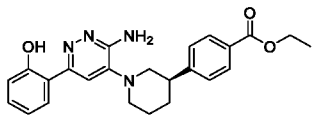
Intermediate 1d: Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)benzoate



[1727] A solution of 4-bromo-6-chloropyridazin-3-amine (89 mg, 0.43 mmol), Intermediate 1c (100 mg, 0.43 mmol), *n*-butanol (0.70 mL), and DIPEA (0.15 mL, 0.86 mmol) was heated up to 110 °C for 16 h. The reaction mixture was cooled to r.t., concentrated under reduced pressure, diluted with EtOAc and sat. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL) before the combined organic extracts were then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to produce an orange oil. Trituration with Et_2O gave the title compound (132 mg, 85%) as an tan solid. ^{1}H NMR (DMSO-*d*6): δ 1.31 (3H, t), 1.58 - 1.72 (1H, m), 1.79 - 1.92 (2H, m), 1.92 - 2.01 (1H, m), 2.60 - 2.75 (2H, m), 3.10 - 3.19 (1H, m), 3.39 - 3.54 (2H, m), 4.24 - 4.38 (2H, m), 6.07 - 6.24 (2H, m), 6.91 - 6.98 (1H, m), 7.41 - 7.54 (2H, m), 7.85 - 7.96 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 361.1.

Intermediate 1e:

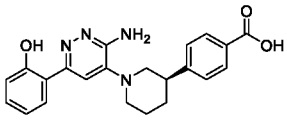
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoate



[1728] A solution of (2-hydroxyphenyl)boronic acid (1.258 g, 9.12 mmol), Intermediate 1d containing 53 mol% DIPEA impurity by NMR (2.43 g, 6.08 mmol), XPhos Pd G3 (0.515 g, 0.61 mmol), XPhos (0.290 g, 0.61 mmol), K_2CO_3 (1.681 g, 12.16 mmol), 1,4-dioxane (24.3 mL) and water (6.1 ml) was sparged with N_2 gas then heated to 95°C for 2h. Upon completion, the reaction mixture was partially concentrated, then extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (2.040 g, 77%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 1.32 (3H, t), 1.62 - 1.77 (1H, m), 1.99 (3H, br s), 2.71 - 2.79 (1H, m), 3.14 - 3.25 (1H, m), 3.51 - 3.60 (2H, m), 4.32 (2H, d), 6.29 (2H, s), 6.89 (2H, br d), 7.17 - 7.27 (1H, m), 7.44 - 7.60 (1H, m), 7.45 - 7.59 (2H, m), 7.94 (4H, br d), 14.17 - 14.32 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 419.1.

Intermediate 1f:

(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoic acid

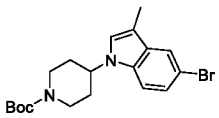


[1729] A solution of Intermediate 1e (2.04 g, 4.69 mmol), EtOH (70.4 mL) and aq. 1 M aq. NaOH (23.46 mL) was stirred at 50°C for 1h. The reaction was cooled to r.t., partially concentrated under reduced pressure and acidified with HCl (pH = 1). The mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated to give the

title compound (1.500 g, 82%) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.68 - 1.79 (1H, m), 1.89 (1H, br s), 1.91 (1H, s), 1.99 (1H, br d), 2.91 (2H, br s), 3.17 (1H, br s), 3.67 (2H, br d), 6.72 - 6.89 (2H, m), 6.93 (1H, s), 6.95 - 7.00 (1H, m), 7.29 - 7.34 (1H, m), 7.48 (2H, d), 7.54 (1H, s), 7.72 - 7.80 (1H, m), 7.92 (2H, d), 12.38 - 13.43 (1H, m); *m/z* (ES^-) $[M-H]^-$ = 389.2.

Intermediate 1g:

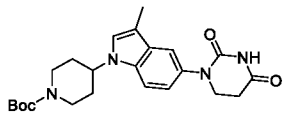
tert-Butyl 4-(5-bromo-3-methyl-indol-1-yl)piperidine-1-carboxylate



[1730] Cs_2CO_3 (16.20 g, 49.72 mmol) was added to a stirred solution of *tert*-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (13.90 g, 49.74 mmol) and 5-bromo-3-methyl-1*H*-indole (5.50 g, 26.18 mmol) in DMF (30 mL) under N_2 at r.t. The resultant mixture was stirred at 95 °C for 8.5 h. The mixture was cooled to r.t. then additional *tert*-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (14.00 g, 50.10 mmol) and Cs_2CO_3 (16.00 g, 49.11 mmol) were added under N_2. The resultant mixture was stirred at 95 °C for 14 h then cooled to r.t. and diluted with EtOAc (200 mL). The mixture was washed with water (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% DCM in hexanes, then 0 to 30% EtOAc in hexanes) gave the title compound (5.85 g, 57%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.50 (9H, s), 1.81-1.95 (2H, m), 2.00-2.07 (2H, m), 2.28 (3H, d), 2.82-2.99 (2H, m), 4.21-4.40 (3H, m), 6.95 (1H, s), 7.16-7.24 (1H, m), 7.28-7.30 (1H, m), 7.69 (1H, d); *m/z* (ES^+) $[M-t\text{Bu}+2H]^+$ = 336.8.

Intermediate 1h:

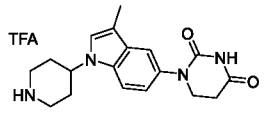
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1731] 1,4-Dioxane (100 mL) was added to a degassed flask Intermediate 1g (4.20 g, 10.68 mmol), Cs_2CO_3 (6.96 g, 21.36 mmol), $Pd_2(dba)_3$ (0.885 g, 0.97 mmol), EPhos (1.028 g, 1.92 mmol) and dihydropyrimidine-2,4(1*H*,3*H*)-dione (3.66 g, 32.03 mmol) at r.t. under argon. The mixture was sparged with argon for five minutes then stirred at 100 °C for 14 h. The mixture was cooled to r.t., diluted with EtOAc (100 mL), filtered through Celite, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (3.06 g, 67%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s), 1.85-1.97 (2H, m), 2.02-2.09 (2H, m), 2.32 (3H, d), 2.85-2.97 (4H, m), 3.93 (2H, t), 4.26-4.40 (3H, m), 7.02 (1H, s), 7.13 (1H, dd), 7.37 (1H, d), 7.40 (1H, s), 7.48 (1H, s); *m/z* (ES^+) $[M+Na]^+$ = 449.2.

Intermediate 1i:

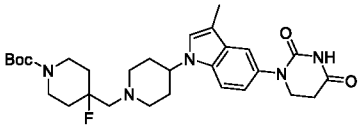
1-(3-Methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1732] TFA (0.289 mL, 3.75 mmol) was added to a solution of Intermediate 1h (80 mg, 0.19 mmol) in DCM (1.0 mL) at r.t. After 1 h the mixture was concentrated under reduced pressure. Et_2O (2 mL) was added and the resultant mixture was sonicated to give a solid precipitate. The supernatant was removed and the solid was dried to give the title compound in the form of a trifluoroacetate salt (83 mg, 100%) as a light pink solid. *m/z* (ES^+) $[M+H]^+ = 326.9$.

Intermediate 1j:

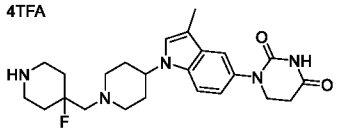
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1733] A mixture of *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (37 mg, 0.16 mmol), NaOAc (33 mg, 0.40 mmol), and Intermediate 1i (35 mg, 0.08 mmol) in THF (1.0 mL) was stirred at 60°C for 25 min and then $NaBH(OAc)_3$ (34 mg, 0.16 mmol) was added. After 0.5h additional *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (37 mg, 0.16 mmol) was added and then after stirring for ten minutes additional $NaBH(OAc)_3$ (20 mg, 0.09 mmol) was added. The mixture was cooled to r.t. and then diluted with DCM (5 mL) and saturated aq. Na_2CO_3 solution (1 mL). The organic layer was separated and the aqueous layer extracted with DCM (2 × 5 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 15% MeOH in DCM) gave the title compound (26 mg, 60%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.40 (9H, s), 1.50-1.67 (2H, m), 1.77-1.88 (4H, m), 1.88-1.98 (2H, m), 2.22 (3H, d), 2.32-2.41 (2H, m), 2.61 (2H, d), 2.71 (2H, t), 2.95-3.09 (4H, m), 3.67-3.81 (4H, m), 4.21-4.29 (1H, m), 7.03 (1H, dd), 7.30 (1H, s), 7.38 (1H, d), 7.45 (1H, d), 10.22 (1H, s); *m/z* (ES^+) $[M+H]^+ = 542.1$.

Intermediate 1k:

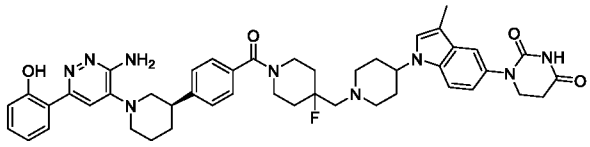
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1734] Prepared in an analogous method to Intermediate 1i starting from Intermediate 1j (39 mg, 0.07 mmol). Et_2O (2 mL) was added and the resultant mixture was sonicated to give a solid precipitate. The solids were filtered off and dried under reduced pressure to give the title compound in the form of a *tetrakis*(trifluoroacetic acid) salt (64 mg, 100%) as a light pink solid. *m/z* (ES^+) $[M+H]^+ = 442.0$.

EXAMPLE 1

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

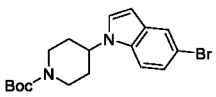


[1735] A solution of Intermediate 1f (47 mg, 0.12 mmol), DMF (1.43 mL), and DIPEA (86 μL, 0.48 mmol) was charged with HATU (54.9 mg, 0.14 mmol) and stirred for 5 min. A solution of Intermediate 1k (130 mg, 0.14 mmol) in DMF (1.43 mL) was added dropwise, and the reaction was stirred at r.t. for 15 min. Purification by RPC (elution gradient: 5 to 50% MeCN in water with 0.1% FA) gave the title compound (19.20 mg, 20%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63-1.81 (3H, m), 1.84-2.05 (9H, m), 2.23 (3H, s), 2.35-2.45 (2H, m), 2.53-2.56 (1H, m), 2.56-2.68 (3H, m), 2.69-2.76 (3H, m), 2.78-2.85 (1H, m), 3.00-3.07 (2H, m), 3.12-3.18 (2H, m), 3.54-3.58 (2H, m), 3.74-3.81 (2H, m), 4.20-4.33 (2H, m), 6.22-6.34 (2H, m), 6.85-6.93 (2H, m), 7.02-7.07 (1H, m), 7.20-7.27 (1H, m), 7.30-7.32 (1H, m), 7.38-7.41 (3H, m), 7.42-7.45 (2H, m), 7.46-7.49 (1H, m), 7.52-7.60 (1H, m), 7.88-7.98 (1H, m), 10.17-10.31 (1H, m), 13.98-14.49 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 814.5.

EXAMPLE 2

Intermediate 2a:

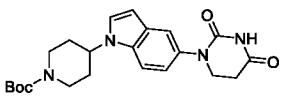
tert-Butyl 4-(5-bromoindol-1-yl)piperidine-1-carboxylate



[1736] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-1*H*-indole (1.0 g, 5.10 mmol). Purification by FSC (elution gradient: 0 to 100% DCM in hexanes) gave the title compound (0.715 g, 37%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.75-1.85 (2H, m), 1.87-1.95 (2H, m), 2.81-3.04 (2H, m), 4.03-4.18 (2H, m), 4.49-4.61 (1H, m), 6.44 (1H, d), 7.23 (1H, dd), 7.53-7.59 (2H, m), 7.72 (1H, d); *m/z* (ES$^+$) $[M-t\text{Bu}+2H]^+$ =323.1.

Intermediate 2b:

tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidine-1-carboxylate

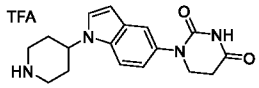


[1737] Intermediate 2a (1.00 g, 2.64 mmol) was added to a degassed mixture of dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.203 g, 10.55 mmol), Cs_2CO_3 (1.718 g, 5.27 mmol), EPhos (0.085 g, 0.16 mmol) and EPhos Pd G4 (0.145 g, 0.16 mmol) in 1,4-dioxane (40 mL) at r.t under N_2. The resultant mixture was stirred at 100 °C for 16 h and then cooled to r.t. The mixture was filtered through Celite, and the solids were washed with 1,4-dioxane (50 mL). The filtrate was concentrated under reduced pressure. Trituration with MTBE gave the title compound (0.850 g, 78%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.77-1.88

(2H, m), 1.89-1.96 (2H, m), 2.71 (2H, t), 2.85-3.06 (2H, m), 3.75 (2H, t), 4.07-4.19 (2H, m), 4.53-4.60 (1H, m), 6.45 (1H, d), 7.07 (1H, dd), 7.45 (1H, d), 7.51-7.58 (2H, m), 10.23 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 413.0.

Intermediate 2c:

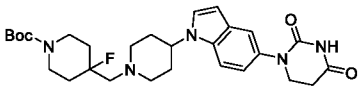
1-(1-(Piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1738] Prepared in an analogous method to Intermediate 1i starting from Intermediate 2b (2.0g, 4.85 mmol). The resultant solid was collected by filtration, washed with MTBE and dried to give the title compound (1.800 g, 80%) as a white solid and trifluoroacetate salt. *m/z* (ES^+) $[M+H]^+$ = 313.0.

Intermediate 2d:

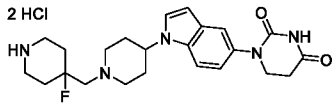
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1739] Prepared in an analogous method to Intermediate 1j starting from Intermediate 2c (500 mg, 1.60 mmol). Purification by FSC (elution gradient: 10 to 100% EtOAc in hexanes) gave the title compound (0.380 g, 45%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.40 (9H, s), 1.51-1.67 (2H, m), 1.79-1.91 (4H, m), 1.92-2.03 (2H, m), 2.34-2.43 (2H, m), 2.54-2.63 (2H, m), 2.71 (2H, t), 2.95-3.12 (4H, m), 3.68-3.79 (4H, m), 4.26-4.39 (1H, m), 6.44 (1H, d), 7.06 (1H, dd), 7.44 (1H, d), 7.49-7.55 (2H, m), 10.23 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 528.3.

Intermediate 2e:

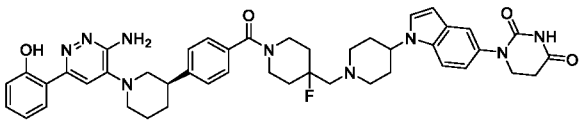
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1740] A solution of Intermediate 2d (750 mg, 1.42 mmol) and 4 M HCl in 1,4-dioxane (10.0 mL, 40 mmol). was stirred at r.t. for 1 h. The mixture was then concentrated under reduced pressure. Trituration with Et_2O gave the title compound as a *bis*(hydrochloric acid) salt (610 mg, 86% yield) as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 428.3.

EXAMPLE 2

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

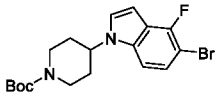


[1741] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 2e (38.3 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (35.4 mg, 68%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.67-2.26 (12H, m), 2.70-2.93 (6H, m), 3.13 (4H, br d), 3.25-3.30 (1H, m), 3.62 (5H, br d), 3.77 (2H, t), 4.20-4.68 (2H, m), 6.49 (3H, br s), 6.88-6.96 (2H, m), 7.06-7.12 (1H, m), 7.25-7.31 (1H, m), 7.37-7.42 (2H, m), 7.44 (2H, s), 7.47-7.49 (1H, m), 7.49-7.54 (1H, m), 7.54-7.60 (2H, m), 7.80-7.91 (1H, m), 10.26-10.32 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 800.1.

EXAMPLE 3

Intermediate 3a:

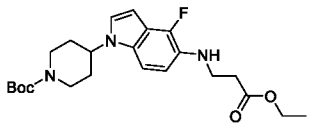
tert-Butyl 4-(5-bromo-4-fluoro-indol-1-yl)piperidine-1-carboxylate



[1742] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-4-fluoro-1*H*-indole (661 mg, 3.09 mmol). Purification by FSC (elution gradient: 10 to 50% DCM in hexanes) gave the title compound (803 mg, 65%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.46-1.50 (9H, s), 1.82-1.94 (2H, m), 1.99-2.09 (2H, m), 2.91 (2H, br s), 4.23-4.41 (3H, m), 6.59 (1H, d), 7.11 (1H, d), 7.21 (1H, d), 7.28 (1H, dd); *m/z* (ES$^+$) $[M+H]^+$ = 397.1.

Intermediate 3b:

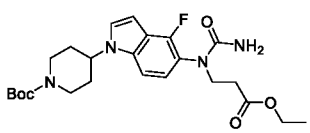
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1743] A solution of Intermediate 3a (1.05 g, 2.64 mmol), ethyl 3-aminopropanoate hydrochloride salt (0.406 g, 2.64 mmol), Cs_2CO_3 (2.58 g, 7.93 mmol), BrettPhos Pd G3 (0.120 g, 0.13 mmol) and 1,4-dioxane (17.62 mL) under N_2 atmosphere was degassed and stirred at 100°C for 16h. After cooling, the reaction was diluted with DCM, filtered through Celite, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.74 g, 64%) as a pale gum. ^{1}H NMR (CD_2Cl_2): δ 1.25 (3H, t), 1.28-1.48 (9H, s), 1.79-1.92 (2H, m), 1.99-2.10 (2H, m), 2.59 (2H, t), 2.89 (2H, br s), 3.48 (2H, q), 3.90 (1H, br s), 4.14 (2H, q), 4.21-4.36 (3H, m), 6.40-6.45 (1H, m), 6.80 (1H, t), 7.03-7.10 (1H, m), 7.09-7.17 (1H, m) ; *m/z* (ES$^+$) $[M+H]^+$ = 434.4.

Intermediate 3c:

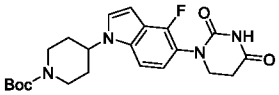
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1744] A solution of Intermediate 3b (700 mg, 1.61 mmol) in DCM (5.0 mL) and AcOH (5.0 mL) was charged with Potassium cyanate (655 mg, 8.07 mmol) and stirred at r.t. for 2.5h. The reaction mixture was diluted with DCM, washed with water, saturated $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (760 mg, 100%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.16 (3H, t), 1.47 (9H, s), 1.81-1.95 (2H, m), 2.02-2.10 (2H, m), 2.58 (2H, br t), 2.92 (2H, br s), 3.90-3.98 (1H, m), 3.98-4.05 (2H, m), 4.27-4.41 (4H, m), 6.65 (1H, d), 7.06 (1H, t), 7.19-7.30 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 477.5.

Intermediate 3d:

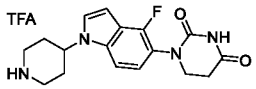
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1745] A solution of Intermediate 3c (0.767 g, 1.61 mmol) in EtOH (6.99 mL) was charged with 21% (w/v) sodium ethoxide in EtOH (1.060 mL, 2.84 mmol). The reaction mixture was stirred at r.t. for 75 min. The mixture was then carefully acidified with aq. 1 M aq. HCl solution. Water was added and aqueous solution was extracted with DCM. The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.520 g, 75%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), δ 1.80-1.90 (2H, m), 1.90-2.00 (2H, m), 2.73 (2H, t), 2.85-3.06 (2H, m), 3.70 (2H, t), 4.06-4.18 (2H, m), 4.52-4.65 (1H, m), 6.55 (1H, d), 7.10-7.15 (1H, m), 7.45 (1H, d), 7.62 (1H, d), 10.37 (1H, s); *m/z* (ES^+) $[M–tBu+2H]^+$ = 375.1.

Intermediate 3e:

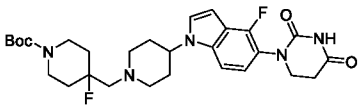
1-(4-Fluoro-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1746] Prepared in an analogous method to Intermediate 1i starting from Intermediate 3d (0.69 g, 1.60 mmol). Trituration with Et_2O gave the title compound (0.650 g, 94%) in the form of a TFA salt as a white solid. *m/z* (ES^+) $[M+H]^+$ = 331.2.

Intermediate 3f:

tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluoro-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

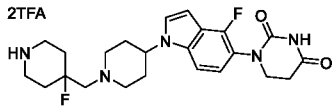


[1747] A solution of Intermediate 3e (111 mg, 0.25 mmol) and *tert*-butyl 4-fluoro-4-formylpiperidine-1-carboxylate (87 mg, 0.38 mmol) in THF (2 mL) was charged with Ti(O*i*-Pr)$_4$ (142 mg, 0.50 mmol). The reaction was stirred at r.t. overnight. $NaBH(OAc)_3$ (159 mg, 0.75 mmol) was added in one portion, and the

reaction mixture was stirred at r.t. for 3h, and the reaction was concentrated under reduced pressure. Purification by FSC (elution gradient: 1 to 4% [400:1 MeOH/NH_4OH] in DCM) gave the title compound (132 mg, 97%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 546.3.

Intermediate 3g:

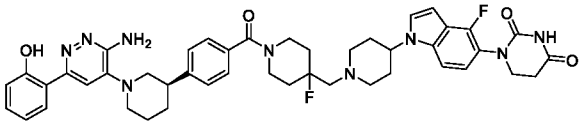
1-(4-Fluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1748] Prepared in an analogous method to Intermediate 1i starting from Intermediate 3f (110 mg, 0.20 mmol). Trituration with Et_2O gave the title compound (131 mg, 97%) in the form of a *bis*-trifluoroacetic acid salt as a white solid. *m/z* (ES^+) $[M+H]^+$ = 446.3.

EXAMPLE 3

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

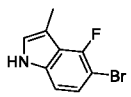


[1749] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 3g (51.8 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (28.6 mg, 55%) as a white solid following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.65-2.31 (12H, m), 2.75 (3H, t), 2.88 (4H, br d), 3.09-3.18 (2H, m), 3.17-3.29 (2H, m), 3.43-3.60 (2H, m), 3.61-3.68 (2H, m), 3.72 (3H, t), 4.22-4.78 (2H, m), 6.47-6.85 (3H, m), 6.90-6.98 (2H, m), 7.12-7.21 (1H, m), 7.26-7.34 (1H, m), 7.41 (2H, s), 7.44 (3H, s), 7.52-7.64 (2H, m), 7.74-7.86 (1H, m), 10.37-10.47 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 818.3.

EXAMPLE 4

Intermediate 4a:

5-Bromo-4-fluoro-3-methyl-1*H*-indole

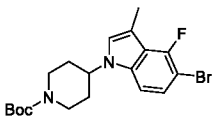


[1750] To a solution of 5-bromo-4-fluoro-1*H*-indole-3-carbaldehyde (1.210 g, 5.0 mmol) and 4-methylbenzenesulfonohydrazide (1.117 g, 6.00 mmol) in DMF (10 mL) and sulfolane (5 mL) was added *p*-toluenesulfonic acid monohydrate (0.141 g, 0.74 mmol). The reaction was heated at 100 °C for 1h. The reaction was cooled to r.t. and $NaBH_3CN$ (1.257 g, 20.00 mmol) was carefully added. The reaction was heated at 100 °C for 2 h. The reaction was cooled to r.t. quenched with aq. 1 M aq. HCl (20 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to

30% EtOAc in hexanes) gave the title compound (1.090 g, 96%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 2.42 (3H, t), 6.95 (1H, s), 7.05 (1H, d), 7.22 (1H, dd), 8.15 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 228.0.

Intermediate 4b:

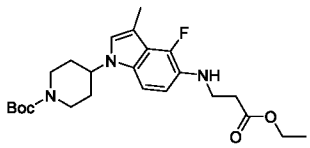
tert-Butyl 4-(5-bromo-4-fluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1751] Prepared in an analogous method to Intermediate 1g starting from Intermediate 4a (1.07 g, 4.69 mmol). Purification by FSC (elution gradient: 20 to 100% DCM in hexanes) gave the title compound (1.100 g, 57%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.45-1.49 (9H, m), 1.83 (2H, br dd), 1.96-2.00 (2H, m), 2.41 (3H, s), 2.88 (2H, br s), 4.19-4.34 (3H, m), 6.92 (1H, s), 7.03 (1H, d), 7.23 (1H, dd); *m/z* (ES^+) $[M+H]^+$ = 411.1.

Intermediate 4c:

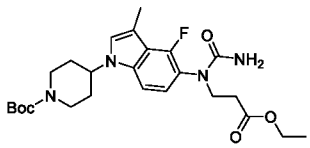
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4-fluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1752] Prepared in an analogous method to Intermediate 3b from Intermediate 4b (1.1 g, 2.67 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.634 g, 53%) as a pale gum. *m/z* (ES^+) $[M+H]^+$ = 448.4.

Intermediate 4d:

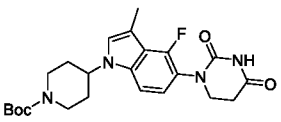
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4-fluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1753] Prepared in an analogous method to Intermediate 3c from Intermediate 4c (700 mg, 1.56 mmol). Concentration under reduced pressure gave the title compound (767 mg, 100%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 492.3.

Intermediate 4e:

tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate

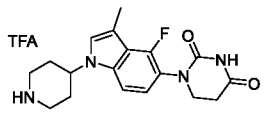


[1754] Prepared in an analogous method to Intermediate 3d from Intermediate 4d (765 mg, 1.56 mmol). Trituration with MeOH gave the title compound (450 mg, 65%) as a white solid. ^{1}H NMR (CD_2Cl_2):

δ 1.47 (9H, s), 1.85 (2H, br dd), 2.02 (2H, br d), 2.42 (3H, s), 2.80-2.85 (2H, m), 2.85-2.96 (2H, m), 3.80 (2H, t), 4.29 (3H, ddt), 6.96 (1H, s), 7.04 (1H, dd), 7.14 (1H, d), 7.47 (1H, s); *m/z* (ES^+) $[2M+H]^+ = 889.5$.

Intermediate 4f:

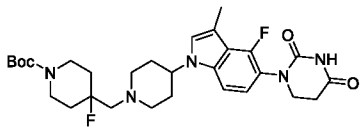
1-(4-Fluoro-3-methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1755] Prepared in an analogous method to Intermediate 1i from Intermediate 4e (450 mg, 1.01 mmol). Concentration *in vacuo* gave the title compound in the form of a trifluoroacetate salt (450 mg, 97%) as a white solid. ^1H NMR (DMSO-*d*6): δ 2.04-2.13 (4H, m), 2.36 (3H, s), 2.73 (2H, t), 3.07-3.17 (2H, m), 3.46 (2H, br d), 3.69 (2H, t), 4.65 (1H, dt), 7.11 (1H, dd), 7.20 (1H, s), 7.37 (1H, d), 8.43 (1H, br d), 8.66 (1H, br d), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+ = 345.2$.

Intermediate 4g:

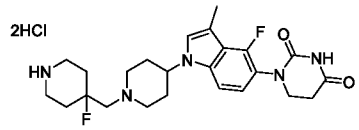
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluoro-3-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1756] Prepared in an analogous method to Intermediate 3f from Intermediate 4f (184 mg, 0.40 mmol). Purification by FSC (elution gradient: 0 to 8% MeOH in DCM) gave the title compound (105 mg, 47%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.44-1.46 (9H, m), 1.55-1.67 (2H, m), 1.86-1.95 (2H, m), 1.94-2.00 (3H, m), 2.01-2.08 (1H, m), 2.36-2.42 (2H, m), 2.42-2.44 (3H, m), 2.49-2.61 (2H, m), 2.83 (2H, t), 3.06-3.16 (4H, m), 3.77-3.82 (2H, m), 3.82-3.91 (2H, m), 4.10-4.18 (1H, m), 6.99-7.04 (2H, m), 7.13 (1H, d), 7.43 (1H, s); *m/z* (ES^+) $[M+H]^+ = 560.3$.

Intermediate 4h:

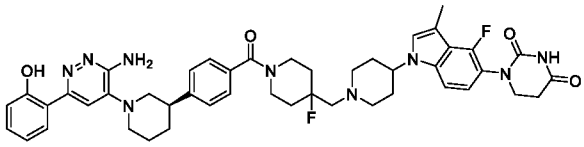
1-(4-Fluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1757] Prepared in an analogous method to Intermediate 2e starting from Intermediate 4g (144 mg, 0.26 mmol). Trituration with EtOAc gave the title compound in the form of a dihydrochloride salt (115 mg, 84%) as a white solid. *m/z* (ES^+) $[M+H]^+ = 460.2$.

EXAMPLE 4

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

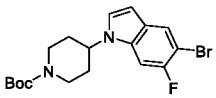


[1758] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 4h (40.8 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (28.4 mg, 53%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.68-2.12 (11H, m), 2.10-2.30 (2H, m), 2.37 (3H, s), 2.71-2.77 (2H, m), 2.78-2.95 (3H, m), 2.93-3.01 (1H, m), 3.09-3.19 (3H, m), 3.20-3.30 (2H, m), 3.43-3.60 (2H, m), 3.70 (4H, br t), 4.16-4.74 (2H, m), 6.49-6.87 (2H, m), 6.90-6.99 (2H, m), 7.07-7.15 (1H, m), 7.21-7.34 (2H, m), 7.41 (3H, s), 7.44 (2H, s), 7.54 (1H, s), 7.74-7.89 (1H, m), 10.41 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 832.5.

EXAMPLE 5

Intermediate 5a:

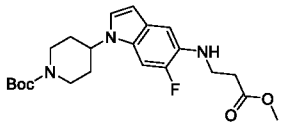
tert-Butyl 4-(5-bromo-6-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1759] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-6-fluoro-1*H*-indole (1070 mg, 5.00 mmol). Purification by RPC (elution gradient: 55 to 90% MeCN in water with 0.1% FA) gave the title compound (820 mg, 41%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.39-1.50 (9H, m), 1.86 (2H, br dd), 1.98-2.07 (2H, m), 2.89 (2H, br s), 4.19-4.41 (3H, m), 6.47 (1H, d), 7.18-7.24 (2H, m), 7.76 (1H, d); *m/z* (ES$^+$) $[M–tBu+2H]^+$ = 341.2.

Intermediate 5b:

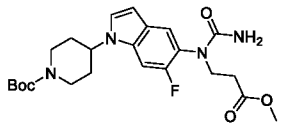
tert-Butyl 4-(6-fluoro-5-((3-methoxy-3-oxopropyl)amino)-1*H*-indol-1-yl)piperidine-1-carboxylate



[1760] Prepared in an analogous manner to Intermediate 3b starting from Intermediate 5a (750 mg, 1.89 mmol) and methyl 3-aminopropanoate, HCl (295 mg, 2.83 mmol). Purification by FSC (elution gradient: 10 to 50% EtOAc in hexanes) gave the title compound (760 mg, 96%) as a gum. ^{1}H NMR (CD_2Cl_2): δ 1.46-1.47 (9H, m), 1.77-1.91 (2H, m), 1.97-2.08 (2H, m), 2.60-2.72 (2H, m), 2.81-2.99 (2H, m), 3.40-3.49 (2H, m), 3.65-3.71 (3H, m), 3.99 (1H, br s), 4.13-4.21 (1H, m), 4.21-4.40 (2H, m), 6.35 (1H, d), 6.87 (1H, d), 7.03-7.08 (1H, m), 7.08-7.11 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 420.5.

Intermediate 5c:

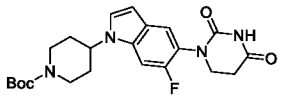
tert-Butyl 4-(6-fluoro-5-(1-(3-methoxy-3-oxopropyl)ureido)-1*H*-indol-1-yl)piperidine-1-carboxylate



[1761] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 5b (760 mg, 1.81 mmol). Concentration *in vacuo* gave the title compound (863 mg, 100%) which was carried forward without further purification. *m/z* (ES^+) $[M+H]^+$ = 463.5.

Intermediate 5d:

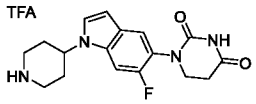
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1762] Prepared in an analogous manner to Intermediate 3d starting from Intermediate 5c (863 mg, 1.81 mmol). Trituration in MeOH gave the title compound (704 mg, 90%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.46-1.50 (9H, m), 1.82-1.95 (2H, m), 2.03-2.09 (2H, m), 2.81-2.87 (2H, m), 2.86-2.99 (2H, m), 3.77-3.82 (2H, m), 4.22-4.40 (3H, m), 6.53 (1H, d), 7.19-7.23 (1H, m), 7.23-7.28 (1H, m), 7.49-7.53 (1H, m), 7.53-7.59 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 331.1.

Intermediate 5e:

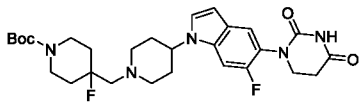
1-(6-Fluoro-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1763] Prepared in an analogous method to Intermediate 1i starting from Intermediate 5d (704 mg, 1.64 mmol). Concentration *in vacuo* gave the title compound in the form of a trifluoroacetate salt (729 mg, 100% yield) as a light yellow solid. *m/z* (ES^+) $[M+H]^+$ = 331.1.

Intermediate 5f:

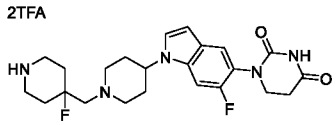
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluoro-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1764] Prepared in an analogous method to Intermediate 3f from Intermediate 5e (754 mg, 1.7 mmol). Purification by FSC (elution gradient: 5 to 50% [9:1 EtOAc/MeOH] in hexanes) gave the title compound (557 mg, 60%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.40-1.45 (9H, m), 1.55-1.67 (2H, m), 1.86-1.96 (2H, m), 1.94-2.10 (4H, m), 2.40 (2H, br t), 2.50 (2H, d), 2.83 (2H, t), 3.03-3.16 (4H, m), 3.77-3.82 (2H, m), 3.82-3.93 (2H, m), 4.06-4.17 (1H, m), 6.52 (1H, d), 7.20 (1H, d), 7.30 (1H, d), 7.43 (1H, s), 7.51 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 546.3.

Intermediate 5g:

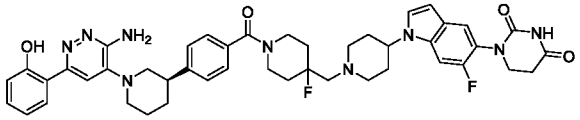
1-(6-Fluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)-dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1765] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 5f (557 mg, 1.02 mmol). Concentration *in vacuo* gave the title compound in the form of a *bis*-trifluoroacetate salt (890 mg, 100%) as a light yellow solid. *m/z* (ES^+) $[M+H]^+$ = 446.3.

EXAMPLE 5

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

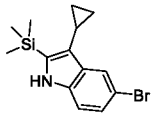


[1766] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (19.5 mg, 0.05 mmol) and Intermediate 5g (47.0 mg, 0.07 mmol). Purification by FSC (elution gradient: 10 to 50% [89:10:1 DCM/MeOH/NH_4OH] in DCM) gave the title compound (23.0 mg, 56%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.62-1.79 (3H, m), 1.81-2.03 (10H, m), 2.33-2.43 (2H, m), 2.56-2.65 (2H, m), 2.67-2.77 (3H, m), 2.77-2.83 (1H, m), 2.95-3.06 (2H, m), 3.07-3.18 (2H, m), 3.51-3.59 (2H, m), 3.65-3.74 (2H, m), 4.18-4.37 (2H, m), 6.30 (2H, s), 6.47 (1H, d), 6.84-6.89 (2H, m), 7.18-7.26 (1H, m), 7.34-7.46 (4H, m), 7.50-7.59 (4H, m), 7.93 (1H, d), 10.39 (1H, s), 14.27 (1H, br.s); *m/z* (ES^+) $[M+H]^+$ = 818.4.

EXAMPLE 6

Intermediate 6a:

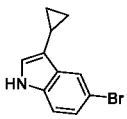
5-Bromo-3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole



[1767] A solution of 4-bromo-2-iodoaniline (0.4 g, 1.34 mmol), 2-cyclopropylethynyl(trimethyl)silane (0.371 g, 2.69 mmol), Na_2CO_3 (0.356 g, 3.36 mmol), LiCl (0.063 g, 1.48 mmol), $PdCl_2(PPh_3)_2$ (0.094 g, 0.13 mmol) and DMF (4 mL) were degassed at r.t. with N_2. The mixture was stirred at 100 °C for 10 h, then cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (0.310 g, 75%) as an off-white solid. ^1H NMR (CD_2Cl_2): δ 0.41-0.46 (9H, m), 0.70-0.77 (2H, m), 0.90-0.99 (2H, m), 1.85-1.93 (1H, m), 7.17-7.25 (2H, m), 7.80-7.85 (1H, m), 7.96-8.12 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 308.1.

Intermediate 6b:

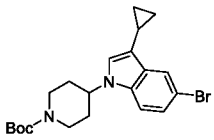
5-Bromo-3-cyclopropyl-1*H*-indole



[1768] 1.0 M tetra-*n*-butylammonium fluoride in THF (1.34 mL, 1.34 mmol) was added to a stirred solution of Intermediate 6a (0.310 g, 1.06) in THF (3 mL). The mixture was stirred at 70 °C for 3 h then cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (0.210 g, 66%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 0.56-0.65 (2H, m), 0.80-0.98 (2H, m), 1.81-1.92 (1H, m), 6.93 (1H, dd), 7.24 (2H, s), 7.85 (1H, s), 8.04 (1H, br s); *m/z* (ES^-) $[M–H]^-$ = 233.9.

Intermediate 6c:

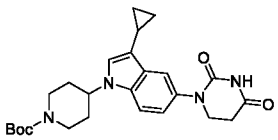
tert-Butyl 4-(5-bromo-3-cyclopropyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1769] Prepared in an analogous method to Intermediate 1g starting from Intermediate 6b (0.248 g, 0.89 mmol). Purification by FSC (elution gradient: 10 to 100% DCM in hexanes) gave the title compound (0.140 g, 37%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 0.55-0.62 (2H, m), 0.84-0.91 (2H, m), 1.47 (9H, s), 1.80-1.91 (3H, m), 1.94-2.03 (2H, m), 2.88 (2H, br s), 4.28 (3H, ddt), 6.91 (1H, s), 7.1-7.28 (2H, m), 7.82 (1H, d); *m/z* (ES^+) $[M–Boc+2H]^+$ = 319.1.

Intermediate 6d:

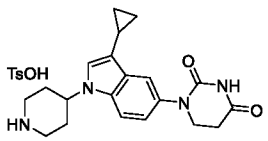
tert-Butyl 4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidine-1-carboxylate



[1770] Prepared in an analogous method to Intermediate 1h starting from Intermediate 6c (0.140 g, 0.33 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (0.112 g, 74%) as a pale yellow solid. ^{1}H NMR (CD_2Cl_2): δ 0.60 (2H, br d), 0.86-0.90 (2H, m), 1.50-1.55 (9H, m), 1.86-1.93 (3H, m), 1.97-2.01 (2H, m), 2.81-2.85 (2H, m), 2.85-2.98 (2H, m), 3.88 (2H, t), 4.23-4.38 (3H, m), 6.95 (1H, s), 7.10 (1H, br d), 7.34-7.38 (1H, m), 7.42 (1H, br s), 7.58 (1H, s); *m/z* (ES^+) $[M–t\text{Bu}+2H]^+$ = 397.2.

Intermediate 6e:

1-(3-Cyclopropyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

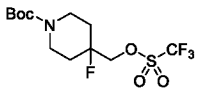


[1771] Intermediate 6d (5.8 g, 12.82 mmol) was added to *p*-toluenesulfonic acid (2.65 g, 15.38 mmol) in MeCN (100 mL) under N_2. The mixture was stirred at 70°C for 4h then cooled to r.t., MTBE (100 mL) was then added, and the mixture was stirred for 0.5h. Additional MTBE was added (50 mL) and the mixture

was then filtered and dried to give the title compound (5.00 g, 74%) as a white solid in the form of a *p*-toluenesulfonic acid salt. *m/z* (ES^+) $[M+H]^+$ = 353.3.

Intermediate 6f:

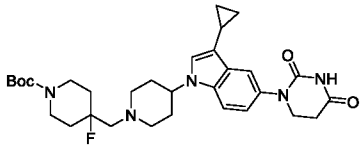
tert-Butyl 4-fluoro-4-(trifluoromethylsulfonyloxymethyl)piperidine-1-carboxylate



[1772] To a solution of *tert*-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (0.100 g, 0.43 mmol) and 2,6-lutidine (0.060 mL, 0.51 mmol) in DCM (0.72 mL) at –5°C was added trifluoromethanesulfonic anhydride (0.076 mL, 0.45 mmol) over 3 min. The mixture was stirred at –5°C for 50 min, then quenched with 1.0 M aq. $NaHSO_4$ (5 mL) and diluted with DCM (20 mL). The layers were separated. The organic layer was washed with 1.0 M aq. $NaHSO_4$ (5 mL), then saturated aq. $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the title compound (0.142 g, 91%) as a light brown oil. ^1H NMR (DMSO-*d*6): δ 1.37-1.45 (9H, m), 1.56-1.76 (2H, m), 1.76-1.90 (2H, m), 2.99 (2H, br s), 3.65-3.96 (2H, m), 4.81-4.96 (2H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 309.8.

Intermediate 6g:

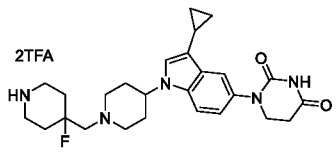
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1773] To a solution of Intermediate 6e (525 mg, 1.00 mmol), Intermediate 6f (731 mg, 2.00 mmol) in 1,4-dioxane (3.6 mL) was added DIPEA (0.524 mL, 3.00 mmol). The reaction was heated to 85 °C for 2 h. Additional DIPEA (0.524 mL, 3.00 mmol) was added and the mixture was stirred at 95 °C for another 6 h. The reaction mixture was then concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (360 mg, 63%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.58-0.65 (2H, m), 0.79-0.88 (2H, m), 1.39-1.43 (9H, m), 1.54-1.68 (2H, m), 1.79-1.90 (5H, m), 1.91-2.01 (2H, m), 2.34-2.43 (2H, m), 2.55-2.64 (2H, m), 2.70-2.76 (2H, m), 2.98-3.15 (4H, m), 3.69-3.75 (2H, m), 3.76-3.82 (2H, m), 4.21-4.31 (1H, m), 7.00-7.10 (1H, m), 7.22-7.29 (1H, m), 7.44-7.48 (1H, m), 7.49-7.53 (1H, m), 10.21-10.28 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 467.6.

Intermediate 6h:

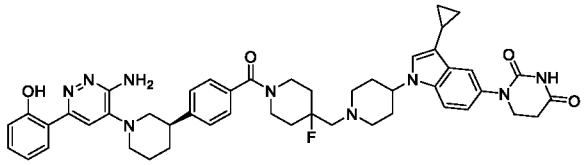
1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1774] Prepared in an analogous method to Intermediate 1i starting from Intermediate 6g (0.028 g, 0.05 mmol). Trituration with Et_2O gave the title compound in the form of a *bis*(trifluoroacetic acid) salt (0.031 g, 89%) as a pale yellow solid. *m/z* (ES^+) $[M+H]^+$ =468.2.

EXAMPLE 6

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

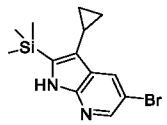


[1775] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 6h (53.4 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (34.0 mg, 61%) as a white solid following lyophilization. ^1H NMR (DMSO-*d6*): δ 0.56-0.66 (2H, m), 0.78-0.89 (2H, m), 1.62-1.80 (3H, m), 1.83-2.13 (10H, m), 2.32-2.47 (1H, m), 2.56-2.68 (1H, m), 2.74 (4H, s), 2.79-2.88 (2H, m), 2.93-3.10 (2H, m), 3.11-3.19 (2H, m), 3.24-3.30 (1H, m), 3.45-3.55 (1H, m), 3.55-3.61 (2H, m), 3.78 (2H, t), 4.12-4.42 (2H, m), 6.34-6.45 (2H, m), 6.86-6.92 (2H, m), 7.04-7.09 (1H, m), 7.20-7.28 (2H, m), 7.40 (2H, s), 7.43-7.46 (2H, m), 7.46-7.50 (1H, m), 7.50-7.52 (1H, m), 7.54-7.57 (1H, m), 7.87-7.95 (1H, m), 10.25-10.31 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 840.5.

EXAMPLE 7

Intermediate 7a:

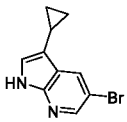
5-Bromo-3-cyclopropyl-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine



[1776] Prepared in an analogous method to Intermediate 6a starting from 5-bromo-3-iodo-pyridin-2-amine (4.00 g, 13.38 mmol) and 2-cyclopropylethynyl(trimethyl)silane (3.70 g, 26.76 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (2.40 g, 58%) as a brown solid. ^1H NMR (DMSO-*d6*): δ 0.38 (9H, s), 0.60-0.68 (2H, m), 0.83-0.96 (2H, m), 1.85 (1H, tt), 8.03 (1H, dd), 8.21 (1H, d), 11.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 309.0.

Intermediate 7b:

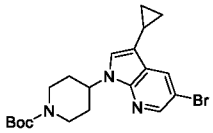
5-Bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine



[1777] Prepared in an analogous method to Intermediate 6b starting from Intermediate 7a (2.40 g, 7.76 mmol). Purification by RPC (elution gradient: 0 to 70% MeCN in water with 0.04% NH_4HCO_3) gave the title compound (1.10 g, 60%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.44-0.52 (2H, m), 0.67-0.77 (2H, m), 1.81 (1H, ddd), 7.12 (1H, s), 8.03-8.06 (1H, m), 8.08-8.11 (1H, m); NH not observed; *m/z* (ES^+) $[M+H]^+$ = 237.2.

Intermediate 7c:

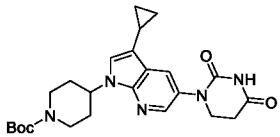
tert-Butyl 4-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1778] Prepared in an analogous method to Intermediate 1g starting from Intermediate 7b (1.10 g, 4.64 mmol). Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.05% NH_4HCO_3) gave the title compound (1.40 g, 72%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.46-0.58 (2H, m), 0.67-0.78 (2H, m), 1.31 (9H, s), 1.64-1.88 (5H, m), 2.60-3.00 (2H, m), 3.90-4.01 (2H, m), 4.60-4.71 (1H, m), 7.38 (1H, s), 8.09 (1H, d), 8.15 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 420.0.

Intermediate 7d:

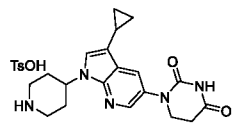
tert-Butyl 4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1779] Prepared in an analogous method to Intermediate 2b starting from Intermediate 7c (0.700 g, 1.67 mmol). Purification by FSC (elution gradient: 0 to 70% EtOAc in petroleum ether) gave the title compound (0.400 g, 53%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.61-0.72 (2H, m), 0.80-0.92 (2H, m), 1.44 (9H, s), 1.79-2.03 (5H, m), 2.77 (2H, t), 2.80-3.00 (2H, m), 3.82 (2H, t), 3.99-4.24 (2H, m), 4.75-4.85 (1H, m), 7.48 (1H, s), 7.96 (1H, d), 8.18 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 454.4.

Intermediate 7e:

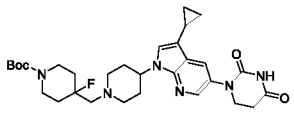
1-(3-Cyclopropyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1780] Prepared in an analogous method to Intermediate 6e starting from Intermediate 7d (5.6 g, 12.35 mmol). Trituration with MTBE gave the title compound (6.00 g, 92%) as a white solid in the form of a *p*-toluenesulfonic acid salt. ^{1}H NMR (DMSO-*d*6): δ 0.62-0.69 (2H, m), 0.85-0.93 (2H, m), 1.95 (1H, tt), 2.04-2.12 (2H, m), 2.23 (2H, td), 2.29 (3H, s), 2.77 (2H, t), 3.07-3.26 (2H, m), 3.44 (2H, d), 3.82 (2H, t), 4.90 (1H, tt), 7.12 (2H, d), 7.29 (1H, s), 7.49 (2H, dd), 7.99 (1H, d), 8.20 (1H, d), 8.34 (1H, d), 8.68 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 354.3.

Intermediate 7f:

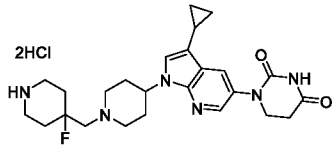
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1781] To a solution of Intermediate 7e (525 mg, 1.00 mmol), Intermediate 6f (730 mg, 2.00 mmol) and 1,4-dioxane (3.5 mL) was added DIPEA (523 µL, 3.00 mmol). The reaction was heated to 90 °C for 24 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (370 mg, 65%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.55-0.72 (2H, m), 0.81-0.91 (2H, m), 1.42 (9H, s), 1.52-1.69 (2H, m), 1.77-1.87 (4H, m), 1.89-1.95 (1H, m), 2.02-2.11 (2H, m), 2.29-2.40 (2H, m), 2.54-2.64 (2H, m), 2.74-2.81 (2H, m), 2.96-3.12 (4H, m), 3.70-3.77 (2H, m), 3.79-3.88 (2H, m), 4.50-4.66 (1H, m), 7.33-7.53 (1H, m), 7.88-8.00 (1H, m), 8.12-8.22 (1H, m), 10.28-10.42 (1H, m); $[M+H]^+$ = 569.5.

Intermediate 7g:

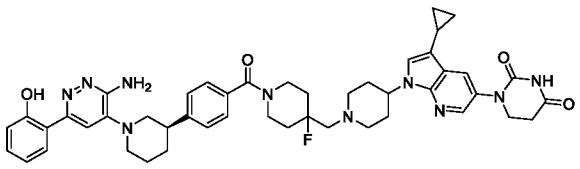
1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1782] Prepared in an analogous method to Intermediate 2e starting from Intermediate 7f (90 mg, 0.16 mmol). Concentration *in vacuo* gave the title compound in the form of a *bis*-hydrochloride salt (0.035 g, 41%) as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 469.3.

EXAMPLE 7:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



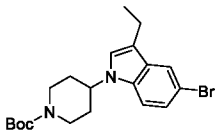
[1783] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (57 mg, 0.15 mmol) and Intermediate 7g (82 mg, 0.18 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (35 mg, 27%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.62-0.71 (2H, m), 0.82-0.89 (2H, m), 1.38-1.47 (1H, m), 1.63-1.81 (4H, m), 1.79-1.96 (6H, m), 1.97-2.14 (4H, m), 2.31-2.43 (2H, m), 2.58-2.68 (2H, m), 2.77 (4H, br s), 2.99-3.08 (2H, m), 3.10-3.22 (2H, m), 3.46-3.59 (2H, m), 3.70-3.78 (1H, m), 3.79-3.86 (2H, m), 4.14-4.29 (1H, m), 4.55-4.65

(1H, m), 6.21-6.39 (2H, m), 6.83-6.94 (2H, m), 7.20-7.30 (1H, m), 7.37-7.47 (4H, m), 7.53-7.60 (1H, m), 7.90-7.99 (2H, m), 8.10-8.21 (1H, m), 10.31-10.44 (1H, m), 14.06-14.48 (1H, m); *m/z* (ES^+) $[M+H]^+$ =841.4.

EXAMPLE 8

Intermediate 8a:

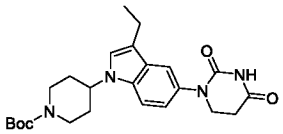
tert-Butyl 4-(5-bromo-3-ethyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1784] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-3-ethyl-1*H*-indole (500 mg, 2.23 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% FA) gave the title compound (278 mg, 30%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, t), 1.44 (9H, s), 1.71-1.95 (4H, m), 2.56-2.73 (2H, m), 2.96 (2H, s), 4.12 (2H, d), 4.40-4.58 (1H, m), 7.19-7.27 (1H, m), 7.36 (1H, s), 7.51(1H, d), 7.67 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 407.1.

Intermediate 8b:

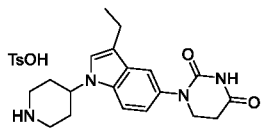
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1785] *t*-BuBrettPhos (71.4 mg, 0.15 mmol) was added to $[Pd(cinnamyl)Cl]_2$ (76 mg, 0.15 mmol), Intermediate 8a (600 mg, 1.47 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (840 mg, 7.36 mmol) and Cs_2CO_3 (960 mg, 2.95 mmol) in 1,4-dioxane (25 mL). The resultant mixture was stirred at 100 °C for 16 h then the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (500 mg, 77%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, t), 1.43 (9H, s), 1.77-1.92 (4H, m), 2.60-2.75 (4H, m), 2.95 (2H, s), 3.75 (2H, t), 4.11 (2H, d), 4.42-4.56 (1H, m), 7.00-7.08 (1H, m), 7.32 (1H, s), 7.42 (1H, d), 7.49 (1H, d), 10.24 (1H, s); *m/z* (ES^+) $[2M+H]^+$ = 881.6.

Intermediate 8c:

1-(3-Ethyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

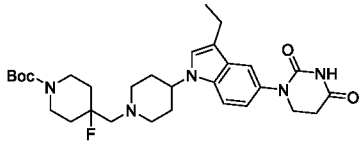


[1786] Prepared in an analogous manner to Intermediate 6e starting from Intermediate 8b (500 mg, 1.13 mmol). Filtration gave the title compound (538 mg, 92%) in the form of a *p*-toluenesulfonic acid salt as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, t), 2.13 (4H, h), 2.29 (3H, s), 2.60-2.81 (4H, m), 3.04-

3.25 (2H, m), 3.46 (2H, d), 3.77 (2H, t), 4.66 (1H, d), 7.03-7.20 (4H, m), 7.46 (1H, d), 7.53 (3H, d), 8.31-8.51 (1H, m), 8.70 (1H, d), 10.27 (1H, s); *m/z* (ES^+) $[M+H]^+ = 341.2$.

Intermediate 8d:

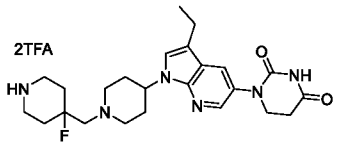
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1787] Prepared in an analogous method to Intermediate 7f starting from Intermediate 8c (1155 mg, 3.16 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (400 mg, 45%) as a yellow solid. ^1H NMR (DMSO-*d*6): δ 0.83-0.88 (1H, m), 1.27 (3H, t), 1.42 (9H, s), 1.53-1.74 (1H, m), 1.77-1.92 (4H, m), 1.98 (2H, d), 2.39 (2H, t), 2.55 (1H, s), 2.61-2.77 (5H, m), 2.95– 3.15 (4H, m), 3.67-3.84 (4H, m), 4.27 (1H, t), 7.02-7.09 (1H, m), 7.31 (1H, s), 7.41-7.51 (2H, m), 10.26 (1H, s); *m/z* (ES^+) $[M+H]^+ = 556.2$.

Intermediate 8e:

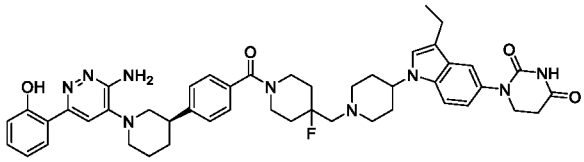
1-(3-Ethyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1788] Prepared in an analogous method to Intermediate 1i starting from Intermediate 8d (300 mg, 61%). Trituration with Et_2O gave the title compound (252 mg, 92%) in the form of a *bis*-trifluoroacetic acid salt as a yellow solid. *m/z* (ES^+) $[M+H]^+ = 456.3$.

EXAMPLE 8

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



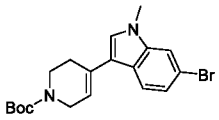
[1789] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (30 mg, 0.08 mmol) and Intermediate 8e (63 mg, 0.09 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (29.9 mg, 47%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.26 (4H, m), 1.64-1.73 (2H, m), 1.74-1.81 (2H, m), 1.84-1.94 (4H, m), 1.94-2.04 (4H, m), 2.33-2.46 (2H, m), 2.73 (3H, s), 2.78-2.86 (2H, m), 3.00-3.09 (2H, m), 3.10-3.19 (2H, m), 3.53-3.60 (2H, m), 3.72-3.80 (2H, m), 4.31-4.35 (1H, m), 6.24-6.36 (2H, m), 6.84-6.92 (2H, m), 7.02-7.09 (1H,

m), 7.21-7.27 (1H, m), 7.29-7.33 (1H, m), 7.37-7.41 (2H, m), 7.43 (2H, s), 7.45-7.50 (2H, m), 7.52-7.57 (3H, m), 7.59-7.65 (1H, m), 7.74-7.81 (2H, m), 7.90-7.96 (1H, m), 9.87-10.47 (1H, m), 13.75-14.60 (1H, m); *m/z* (ES^+) $[M+H]^+$ =828.4.

EXAMPLE 9

Intermediate 9a:

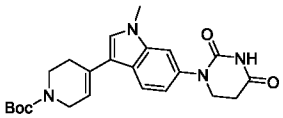
tert-Butyl 4-(6-bromo-1-methyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1790] A solution of 6-bromo-1-methyl-1*H*-indole (748 mg, 3.56 mmol) and 1-Boc-4-piperidone (1419 mg, 7.12 mmol) in toluene (5.23 mL) was charged with a mixture of Et_3Si (1.71 mL, 10.7 mmol), TFA (0.41 mL, 5.34 mmol) and toluene (10.46 mL) dropwise at r.t. The mixture was heated at 55 °C overnight, then cooled r.t. and quenched with saturated aq. $NaHCO_3$ solution. The mixture was extracted with EtOAc and the combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduced pressure Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (0.520 g, 37%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.47 (9H, s), 2.49-2.54 (2H, m), 3.60-3.69 (2H, m), 3.73 (3H, s), 4.09 (2H, q), 6.09 (1H, br s), 7.05 (1H, s), 7.23 (1H, dd), 7.49 (1H, d), 7.72 (1H, d); *m/z* (ES^+) $[M+H]^+$ =391.2.

Intermediate 9b:

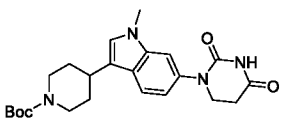
tert-Butyl 4-(6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1791] Prepared in an analogous method to Intermediate 1h starting from Intermediate 9a (310 mg, 0.79 mmol). Purification by FSC (elution gradient: 0 to 5% [400:1 MeOH/NH_4OH] in DCM) gave the title compound (280 mg, 83%) as an off-white solid. ^1H NMR (CD_2Cl_2): δ 1.48 (9H, s), 2.54 (2H, br s), 2.83 (2H, t), 3.65-3.66 (3H, m), 3.76(3H, s), 3.90 (2H, t), 4.10-4.13 (1H, m), 6.12 (1H, br s), 7.02-7.07 (1H, m), 7.12 (1H, s), 7.26 (1H, d), 7.40 (1H, br s), 7.86 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 425.4.

Intermediate 9c:

tert-Butyl 4-(6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indol-3-yl)piperidine-1-carboxylate

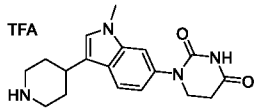


[1792] A solution of Intermediate 9b (0.28 g, 0.66 mmol), 10% Pd/C (0.140 g, 0.07 mmol), MeOH (6.60 mL) and THF (6.60 mL) was degassed and charged with H_2 (1 atm). The reaction was stirred at r.t. for 3 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give

the title compound (0.252 g, 90%), which was carried forward without intermediate purification. ^{1}H NMR (CD_2Cl_2): δ 1.42-1.48 (9H, m), 1.57-1.65 (2H, m), 1.96-2.01 (2H, m), 2.78-2.84 (2H, m), 2.85-3.02 (3H, m), 3.71-3.76 (3H, m), 3.88 (2H, t), 4.15-4.27 (2H, m), 6.87-6.92 (1H, m), 6.95-7.02 (1H, m), 7.22 (1H, d), 7.43-7.54 (1H, m), 7.62 (1H, d); *m/z* (ES^+) $[M–Boc+2H]^+$ = 327.2.

Intermediate 9d:

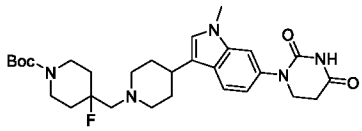
1-(1-Methyl-3-(piperidin-4-yl)-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1793] Prepared in an analogous method to Intermediate 1i starting from Intermediate 9c (251 mg, 0.59 mmol). Trituration with Et_2O gave the title compound (210 mg, 81%) in the form of a TFA salt as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 327.1.

Intermediate 9e:

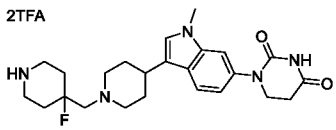
tert-Butyl 4-((4-(6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indol-3-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1794] Prepared in an analogous method to Intermediate 3f from Intermediate 9d (142 mg, 0.32 mmol). Purification by FSC (elution gradient: 0 to 8% MeOH in DCM) gave the title compound (151 mg, 86%) as a white solid.^{1}H NMR (CD_2Cl_2): δ 1.44 (9H, s), 1.53-1.69 (2H, m), 1.73-1.82 (3H, m), 1.86-1.93 (3H, m), 1.95-1.99 (2H, m), 2.34 (3H, br t), 2.45-2.59 (2H, m), 2.81-2.85 (2H, m), 2.99-3.05 (2H, m), 3.06-3.15 (2H, m), 3.72 (3H, s), 3.81-3.85 (1H, m), 3.87-3.92 (2H, m), 6.90 (1H, s), 7.21 (1H, d), 7.54-7.60 (1H, m), 7.60-7.65 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 542.2.

Intermediate 9f:

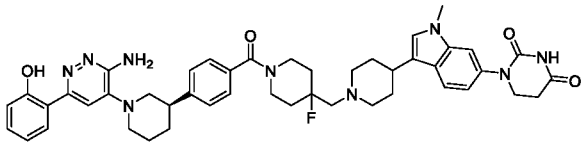
1-(3-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1795] Prepared in an analogous method to Intermediate 1i starting from Intermediate 9e (151 mg, 0.28 mmol). Trituration with Et_2O gave the title compound (171 mg, 92%) in the form of a *bis*(trifluoroacetic acid) salt as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 442.2.

EXAMPLE 9

(*R*)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

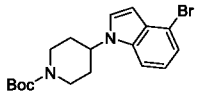


[1796] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 9f (51.4 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (29.2 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.62-2.16 (14H, m), 2.70-2.76 (3H, m), 2.78-2.86 (2H, m), 2.93-3.10 (2H, m), 3.12-3.20 (2H, m), 3.22-3.29 (1H, m), 3.42-3.52 (1H, m), 3.53-3.61 (3H, m), 3.62-3.69 (1H, m), 3.72 (3H, s), 3.80 (2H, s), 4.14-4.52 (1H, m), 6.28-6.42 (2H, m), 6.85-6.92 (2H, m), 6.94-7.04 (1H, m), 7.12-7.18 (1H, m), 7.21-7.28 (1H, m), 7.34-7.37 (1H, m), 7.38-7.41 (2H, m), 7.43-7.47 (2H, m), 7.54-7.57 (1H, m), 7.57-7.65 (1H, m), 7.88-7.95 (1H, m), 10.29-10.35 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 814.4.

EXAMPLE 10

Intermediate 10a:

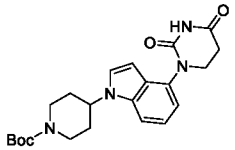
tert-Butyl 4-(4-bromo-1*H*-indol-1-yl)piperidine-1-carboxylate



[1797] 2-(Tributyl-λ^5-phosphanylidene)acetonitrile (92.0 g, 382.56 mmol) was added to a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (77.0 g, 382.56 mmol) and 4-bromo-1*H*-indole (50.0 g, 255.04 mmol) in toluene (500 mL) under N_2 at r.t. The resultant mixture was stirred at 100 °C for 18 h and then cooled to r.t. and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeCN in water with 0.4% NH_4HCO_3) gave the title compound (20.0 g, 21%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.76-2.00 (4H, m), 2.98 (2H, m), 4.13 (2H, d), 4.60 (1H, m), 6.42 (1H, d), 7.08 (1H, t), 7.23-7.28 (1H, m), 7.58-7.74 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 379.1.

Intermediate 10b:

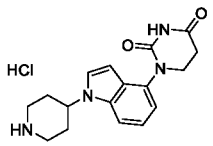
tert-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidine-1-carboxylate



[1798] Prepared in an analogous method to Intermediate 2b starting from Intermediate 10a (1.25 g, 2.64 mmol). Purification by FSC (elution gradient: 0 to 60% EtOAc in petroleum ether) gave the title compound (0.65 g, 60%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s), 1.86-2.01 (2H, m), 2.06-2.14 (2H, m), 2.86-3.00 (4H, m), 3.95 (2H, t), 4.23-4.50 (3H, m), 6.42 (1H, d), 7.06 (1H, d), 7.22-7.27 (2H, m), 7.38 (1H, d), 7.55 (1H, s); *m/z* (ES$^+$) $[M+Na]^+$ = 435.2.

Intermediate 10c:

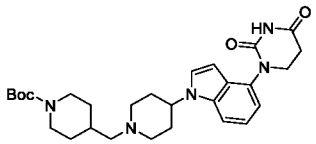
1-(1-(Piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1799] Intermediate 10b (7.0 g, 16.97 mmol) was added to AcOH (20 mL). The resultant mixture was stirred at 100 °C for 72h and then cooled to r.t. and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.4% HCl) gave the title compound (4.50 g, 85%) in the form of a hydrochloride salt as a red solid. ^{1}H NMR (DMSO-*d*6): δ 1.89-2.30 (4H, m), 2.47-2.50 (2H, m), 2.75 (2H, t), 2.99-3.14 (2H, m), 3.76 (2H, t), 4.60-4.77 (1H, m), 6.44 (1H, d), 6.97 (1H, d), 7.16 (1H, t), 7.39 (1H, d), 7.57 (1H, d), 10.33 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 313.2.

Intermediate 10d:

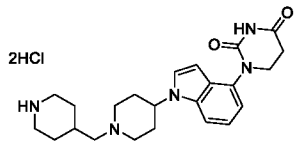
tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1800] *tert*-Butyl 4-formylpiperidine-1-carboxylate (5.53g, 25.62 mmol) was added to a stirred solution of Intermediate 10c (4.00 g, 12.81 mmol) in DCM (103 mL) and IPA (25 mL). The mixture was stirred at r.t for 20 min. $NaBH(OAc)_3$ (134 mg, 64.51 mmol) was then added. The resultant suspension was stirred at r.t for 3 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 8% MeOH in DCM) gave the title compound (4.80 g, 74%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 0.88-1.07 (2H, m), 1.40 (9H, s), 1.72 (3H, d), 1.90-2.09 (4H, m), 2.10-2.27 (4H, m), 2.50-2.77 (4H, m), 2.98 (2H, d), 3.78 (2H, m), 3.94 (2H, d), 4.33-4.50 (1H, m), 6.42 (1H, d), 6.97 (1H, d), 7.15 (1H, m), 7.44-7.59 (2H, m), 10.34 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 510.3.

Intermediate 10e:

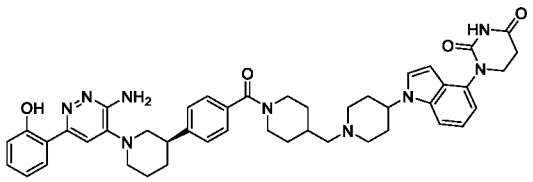
1-(1-(1-(Piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.



[1801] Prepared in an analogous method to Intermediate 2e starting from Intermediate 10d (223 mg, 0.44 mmol), to give the title compound (210 mg, 99% yield) in the form of a dihydrochloride salt as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 410.3.

EXAMPLE 10

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

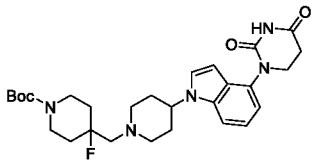


[1802] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (25.0 mg, 0.06 mmol) and Intermediate 10e (36.9 mg, 0.08 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (30.3 mg, 59%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.01-1.16 (2H, m), 1.62-1.74 (2H, m), 1.78-1.90 (3H, m), 1.95 (6H, br s), 2.12-2.21 (2H, m), 2.22-2.30 (2H, m), 2.68-2.73 (1H, m), 2.75-2.80 (3H, m), 2.80-2.83 (1H, m), 2.95-3.02 (2H, m), 3.10-3.19 (1H, m), 3.52-3.58 (2H, m), 3.59-3.69 (1H, m), 3.73 (1H, s), 3.78 (2H, s), 4.33-4.42 (1H, m), 4.43-4.55 (1H, m), 6.28-6.36 (2H, m), 6.39-6.44 (1H, m), 6.87-6.91 (2H, m), 6.94-6.98 (1H, m), 7.12-7.18 (1H, m), 7.21-7.24 (1H, m), 7.32-7.38 (2H, m), 7.39-7.45 (2H, m), 7.49-7.53 (1H, m), 7.53-7.55 (1H, m), 7.55-7.58 (1H, m), 7.91-7.98 (1H, m), 10.31-10.38 (1H, m), 13.90-14.26 (1H, br.s); *m/z* (ES$^+$) $[M+H]^+$ = 782.4.

EXAMPLE 11

Intermediate 11a:

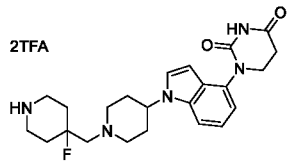
tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1803] Prepared in an analogous method to Intermediate 3f from Intermediate 10c (190mg, 0.61 mmol). Purification by FSC (elution gradient: 0 to 6% MeOH in DCM) to give title compound (200 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.52-1.71 (2H, m), 1.79-1.89 (2H, m), 1.90-1.93 (2H, m), 1.96-2.09 (2H, m), 2.34-2.45 (2H, m), 2.56-2.63 (2H, m), 2.76 (2H, m), 2.93-3.16 (4H, m), 3.67-3.85 (4H, m), 4.30-4.43 (1H, m), 6.42 (1H, d), 6.96 (1H, d), 7.15 (1H, s), 7.45-7.61 (2H, m), 10.20-10.42 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 528.4.

Intermediate 11b:

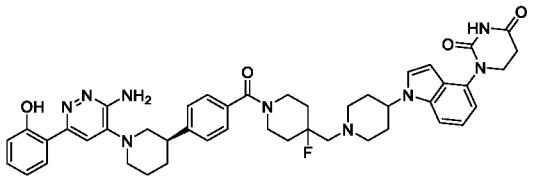
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.



[1804] Prepared in an analogous method to Intermediate 1i starting from Intermediate 11b (40 mg, 0.08 mmol). Concentration *in vacuo* gave the title compound (40 mg, 98% yield) in the form of a *bis*(trifluoroacetic acid) salt as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 428.3.

EXAMPLE 11

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

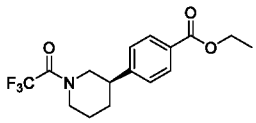


[1805] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (10.0 mg, 0.03 mmol) and Intermediate 11b (20.2 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (7.1 mg, 35%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.65-1.82 (3H, m), 1.85-2.13 (10H, m), 2.39-2.48 (3H, m), 2.59-2.69 (2H, m), 2.71-2.79 (3H, m), 2.80-2.88 (1H, m), 3.01-3.09 (2H, m), 3.10-3.22 (3H, m), 3.53-3.60 (2H, m), 3.78 (2H, s), 4.13-4.45 (2H, m), 6.18-6.38 (1H, m), 6.39-6.45 (1H, m), 6.84-6.92 (2H, m), 6.94-6.99 (1H, m), 7.11-7.18 (1H, m), 7.21-7.28 (1H, m), 7.36-7.41 (2H, m), 7.43-7.46 (2H, m), 7.48-7.54 (2H, m), 7.54-7.59 (1H, m), 7.86-7.97 (1H, m), 10.24-10.36 (1H, m), 14.03-14.47 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 800.4.

EXAMPLE 12

Intermediate 12a:

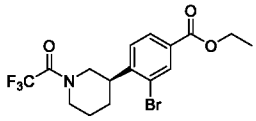
Ethyl (*R*)-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1806] A solution of Intermediate 1c (0.500 g, 2.14 mmol) and THF (4.30 ml) was cooled to 0°C and charged with trifluoroacetic anhydride (0.605 mL, 4.29 mmol) and Et_3N (0.448 mL, 3.21 mmol). The mixture was warmed to r.t., stirred for 0.5 h and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.693 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t), 1.66-1.78 (1H, m), 1.79-1.90 (1H, m), 1.93-2.02 (1H, m), 2.11-2.19 (1H, m), 2.74-2.91 (2H, m), 3.11-3.25 (1H, m), 4.05-4.14 (1H, m), 4.40 (2H, dd), 4.63-4.72 (1H, m), 7.31 (2H, t), 8.04 (2H, dd); *m/z* (ES$^+$) [M+H]$^+$ = 330.2.

Intermediate 12b:

Ethyl (*R*)-3-bromo-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate

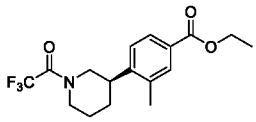


[1807] To a solution of Intermediate 12a (693 mg, 2.10 mmol) and MeCN (4.2 mL) under N_2 was added *N*-bromosuccinimide (936 mg, 5.26 mmol) and $FeCl_3$ (853 mg, 5.26 mmol). The reaction was heated to 100 °C for 18 h. The reaction mixture was dry-loaded onto Celite and purified by FSC (elution gradient: 0 to 50% EtOAc in hexanes) to give the title compound (480 mg, 55%) as a yellow oil. ^{1}H NMR ($CDCl_3$):

δ 1.42 (3H, t), 1.68-1.84 (2H, m), 1.95-2.02 (1H, m), 2.11-2.22 (1H, m), 2.76-2.86 (1H, m), 3.09-3.24 (1H, m), 3.25-3.43 (1H, m), 4.07-4.15 (1H, m), 4.40 (2H, dd), 4.66-4.79 (1H, m), 7.31 (1H, s), 7.95-8.02 (1H, m), 8.27 (1H, br d); *m/z* (ES^+) $[M+H]^+$ = 407.3.

Intermediate 12c:

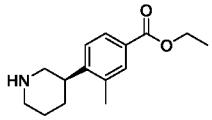
Ethyl (*R*)-3-methyl-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1808] A solution of Intermediate 12b, $Pd(Ph_3P)_4$ (28.3 mg, 0.02 mmol), Me_4Sn (102 μL, 0.73 mmol) and toluene (0.51 mL) was placed under N_2 and heated to 130 °C for 16 h. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (64.5 mg, 77%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.41 (3H, s), 1.68-1.77 (1H, m), 1.79-1.90 (1H, m), 1.94-2.10 (2H, m), 2.37-2.50 (3H, m), 2.70-2.87 (1H, m), 2.95-3.10 (1H, m), 3.12-3.27 (1H, m), 3.96-4.20 (1H, m), 4.33-4.46 (2H, m), 4.57-4.76 (1H, m), 7.23-7.28 (1H, m), 7.84-7.92 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 344.2

Intermediate 12d:

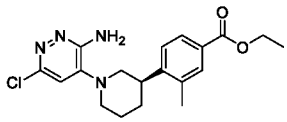
Ethyl (*R*)-3-methyl-4-(piperidin-3-yl)benzoate



[1809] A solution of Intermediate 12c (64 mg, 0.19 mmol) in EtOH (2.004 mL) was charged with K_2CO_3 (129 mg, 0.93 mmol). The reaction mixture was stirred vigorously at r.t. for 16 h. The reaction mixture was filtered through a pad of Celite with EtOH. The filtrate was concentrated under reduced pressure to give the title compound (46 mg, 99% yield), which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 248.1.

Intermediate 12e:

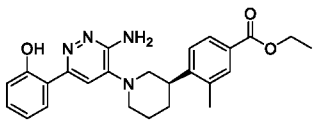
Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-methylbenzoate



[1810] Prepared in an analogous method to Intermediate 1d starting from Intermediate 12d (98 mg, 0.47 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (115 mg, 66% yield) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.27-1.35 (3H, m), 1.54-1.65 (1H, m), 1.80-1.86 (1H, m), 1.87-1.94 (2H, m), 2.42 (3H, s), 2.61-2.76 (2H, m), 3.22-3.29 (1H, m), 3.39-3.51 (2H, m), 4.25-4.34 (2H, m), 6.06-6.18 (2H, m), 6.91-6.97 (1H, m), 7.40-7.45 (1H, m), 7.71-7.79 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 375.1.

Intermediate 12f:

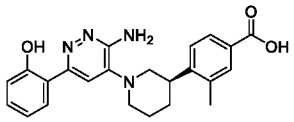
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoate



[1811] Prepared in an analogous method to Intermediate 1e starting from Intermediate 12e (70 mg, 0.19 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1EtOAc/EtOH] in hexanes) gave the title compound (44.2 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.24-1.35 (3H, m), 1.37-1.46 (1H, m), 1.63-1.72 (2H, m), 1.86-1.97 (2H, m), 2.44 (3H, s), 2.70-2.80 (1H, m), 2.81-2.92 (1H, m), 3.47-3.52 (1H, m), 3.58 (1H, s), 4.24-4.35 (2H, m), 6.10-6.35 (2H, m), 6.85-6.91 (2H, m), 7.21-7.27 (1H, m), 7.47-7.52 (1H, m), 7.54-7.57 (1H, m), 7.76-7.81 (2H, m), 7.89-7.94 (1H, m), 13.92-14.34 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 433.2.

Intermediate 12g:

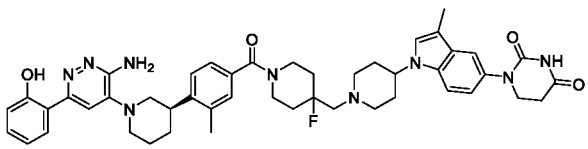
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoic acid



[1812] Prepared in an analogous method to Intermediate 1f starting from Intermediate 12f (68 mg, 0.16 mmol). Filtration gave the title compound (60 mg, 94%) as an brown solid. *m/z* (ES$^-$) [M–H]$^-$ = 403.2.

EXAMPLE 12:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

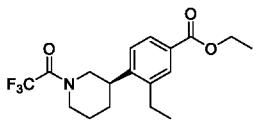


[1813] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (34.0 mg, 0.08 mmol) and Intermediate 1k (91 mg, 0.10 mmol). Purification by FSC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (17.8 mg, 25% yield) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61-1.82 (3H, m), 1.84-1.91 (4H, m), 1.92-2.05 (5H, m), 2.22-2.25 (3H, m), 2.35-2.40 (1H, m), 2.40-2.42 (3H, m), 2.42-2.46 (1H, m), 2.58-2.62 (1H, m), 2.63-2.68 (1H, m), 2.69-2.78 (3H, m), 2.82-2.92 (1H, m), 3.00-3.08 (2H, m), 3.10-3.21 (1H, m), 3.23-3.30 (2H, m), 3.42-3.65 (3H, m), 3.77 (2H, s), 4.18-4.34 (2H, m), 6.27 (2H, s), 6.89 (2H, d), 7.05 (1H, dd), 7.24 (3H, s), 7.31 (1H, s), 7.37-7.42 (2H, m), 7.47 (1H, d), 7.57 (1H, s), 7.90-7.99 (1H, m), 10.24 (1H, s), 13.98-14.55 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 828.4.

EXAMPLE 13

Intermediate 13a:

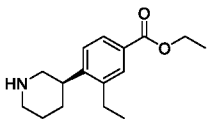
Ethyl (*R*)-3-ethyl-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1814] A solution of Intermediate 12b (100 mg, 0.24 mmol), $Pd(dppf)Cl_2$ (8.96 mg, 0.01 mmol), Cs_2CO_3 (239 mg, 0.73 mmol) and THF (735 μL) was placed under N_2. Et_3B (490 μL, 0.49 mmol) was added in dropwise fashion and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% EtOAc/hexanes) gave the title compound (64 mg, 73%), as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.21-1.32 (3H, m), 1.42 (3H, t), 1.66-1.93 (2H, m), 1.95-2.09 (2H, m), 2.68-2.86 (3H, m), 3.00-3.13 (1H, m), 3.16-3.28 (1H, m), 3.96-4.21 (1H, m), 4.35-4.45 (2H, m), 4.55-4.76 (1H, m), 7.26-7.28 (1H, m), 7.86-7.90 (1H, m), 7.91-7.94 (1H, m); *m/z* (ES^+) $[M+H_3O]^+$ = 376.0.

Intermediate 13b:

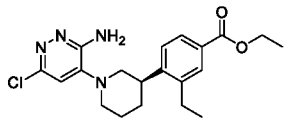
Ethyl (*R*)-3-ethyl-4-(piperidin-3-yl)benzoate



[1815] Prepared in an analogous method to Intermediate 12d starting from Intermediate 13a (64 mg, 0.18 mmol) to give the title compound (46 mg, 99% yield), which was carried forward without purification. *m/z* (ES^+) $[M+H]^+$ = 262.3.

Intermediate 13c:

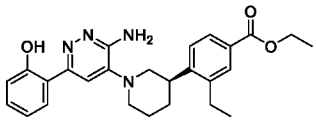
Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoate



[1816] Prepared in an analogous method to Intermediate 1d starting from Intermediate 13b (46.8 mg, 0.18 mmol). Trituration with Et_2O gave the title compound (69.0 mg, 99% yield) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 389.1.

Intermediate 13d:

Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoate

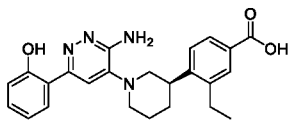


[1817] Prepared in an analogous method to Intermediate 1e starting from Intermediate 13c (69 mg, 0.14 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1EtOAc/EtOH] in hexanes) gave the title compound (32.7 mg, 41%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.19 (4H, d), 1.32 (4H, s), 1.67-1.77 (1H, m), 1.84-1.94 (2H, m), 2.71-2.85 (3H, m), 2.87-2.96 (1H, m), 3.40-3.48 (1H, m), 3.58-3.63 (1H, m),

4.24-4.39 (2H, m), 6.10-6.34 (2H, m), 6.84-6.91 (2H, m), 7.21-7.27 (1H, m), 7.43-7.57 (2H, m), 7.75-7.82 (2H, m), 7.87-7.96 (1H, m), 13.84-14.51 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 447.2.

Intermediate 13e:

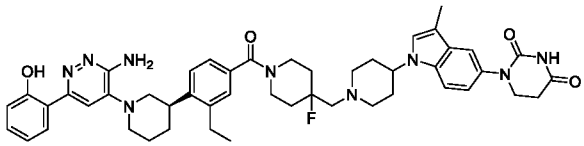
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoic acid



[1818] Prepared in an analogous method to Intermediate 1f starting from Intermediate 13d (32.7 mg, 0.07 mmol). Filtration gave the title compound (29.6 mg, 94%) as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 419.2.

EXAMPLE 13:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

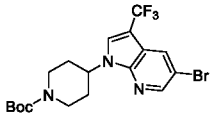


[1819] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 13e (30 mg, 0.07 mmol) and Intermediate 1k (77 mg, 0.09 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (9.8 mg, 16% yield) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.16-1.23 (3H, m), 1.62-1.83 (4H, m), 1.84-1.91 (4H, m), 1.91-2.07 (5H, m), 2.23 (3H, s), 2.34-2.46 (3H, m), 2.59-2.62 (1H, m), 2.63-2.67 (1H, m), 2.68-2.76 (4H, m), 2.77-2.85 (1H, m), 2.89-2.96 (1H, m), 3.00-3.07 (2H, m), 3.09-3.23 (1H, m), 3.40-3.46 (1H, m), 3.48-3.56 (1H, m), 3.59-3.64 (1H, m), 3.73-3.82 (2H, m), 4.20-4.33 (2H, m), 6.18-6.34 (2H, m), 6.84-6.92 (2H, m), 7.03-7.10 (1H, m), 7.21-7.28 (3H, m), 7.30-7.34 (1H, m), 7.38-7.42 (1H, m), 7.43-7.49 (2H, m), 7.53-7.60 (1H, m), 7.89-7.98 (1H, m), 10.21-10.28 (1H, m), 13.82-14.56 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 842.3.

EXAMPLE 14

Intermediate 14a:

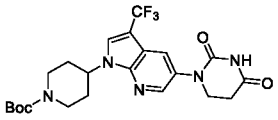
tert-Butyl 4-(5-bromo-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1820] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 1.89 mmol). Purification by FSC (elution gradient: 0 to 70% EtOAc in hexanes) gave the title compound (651 mg, 77%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.95 (4H, br s), 2.80-3.06 (2H, m), 4.04-4.22 (2H, m), 4.82-5.01 (1H, m), 8.25 (1H, d), 8.49-8.53 (2H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 391.5.

Intermediate 14b:

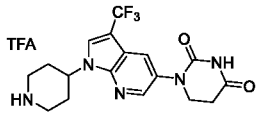
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1821] Prepared in an analogous method to Intermediate 1h from Intermediate 14a (628 mg, 1.40 mmol). Purification by FSC (elution gradient: 0 to 70% EtOAc in hexanes) gave the title compound (296 mg, 44%). ^{1}H NMR (DMSO-*d*6): δ 1.45 (9H, s), 1.92-1.98 (2H, m), 2.00-2.08 (2H, m), 2.78 (2H, t), 2.91-3.07 (2H, m), 3.86 (2H, t), 4.14 (2H, br s), 4.95 (1H, tt), 8.06 (1H, d), 8.41 (1H, d), 8.48 (1H, s), 10.45 (1H, s); *m/z* (ES$^+$) $[M+Na]^+$ = 504.1.

Intermediate 14c:

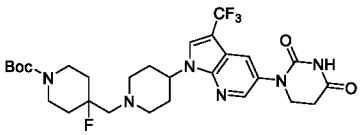
1-(1-(Piperidin-4-yl)-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1822] Prepared in an analogous method to Intermediate 1i starting from Intermediate 14b (296 mg, 0.61 mmol). The solvent was removed under reduced pressure to give the title compound (318 mg, 100%) in the form of a TFA salt as a white solid. *m/z* (ES$^-$) $[M-H]^-$ = 380.0.

Intermediate 14d:

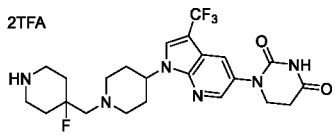
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1823] Prepared in an analogous method to Intermediate 6g from Intermediate 6f (162 mg, 0.44 mmol) and Intermediate 14c (200 mg, 0.40 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (79 mg, 33%) as a brown solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.53-1.71 (2H, m), 1.79-1.97 (4H, m), 2.12-2.24 (2H, m), 2.39 (2H, br t), 2.57-2.66 (2H, m), 2.78 (2H, t), 3.06 (4H, br d), 3.74 (2H, br d), 3.86 (2H, t), 4.68-4.76 (1H, m), 8.05 (1H, s), 8.41 (1H, d), 8.46 (1H, s), 10.45 (1H, s); *m/z* (ES$^+$) $[M+Na]^+$ = 619.2.

Intermediate 14e:

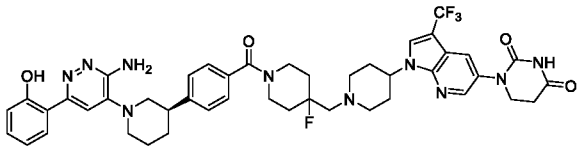
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1824] Prepared in an analogous method to Intermediate 1i starting from Intermediate 14d (79 mg, 0.13 mmol). The solvent was removed under reduced pressure to give the title compound (94 mg, 98%) in the form of a *bis*(trifluoroacetic acid) salt as an off-white solid following lyophilization. *m/z* (ES^+) $[M+Na]^+$ = 519.1.

EXAMPLE 14:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

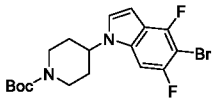


[1825] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (19 mg, 0.05 mmol) and Intermediate 14e (36 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (27 mg, 60%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.64-1.84 (3H, m), 1.85-2.06 (7H, m), 2.15-2.30 (2H, m), 2.36-2.47 (1H, m), 2.58-2.90 (7H, m), 3.02-3.28 (5H, m), 3.59 (3H, br d), 3.86 (2H, t), 4.19-4.36 (1H, m), 4.65-4.85 (1H, m), 6.33-6.50 (2H, m), 6.86-6.95 (2H, m), 7.26 (1H, t), 7.36-7.49 (4H, m), 7.55 (1H, s), 7.89 (1H, br d), 8.05 (1H, d), 8.41 (2H, d), 10.45 (1H, s), 12.50-14.21 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 869.2.

EXAMPLE 15

Intermediate 15a:

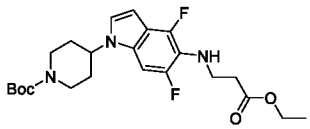
tert-Butyl 4-(5-bromo-4,6-difluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1826] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-4,6-difluoro-1*H*-indole (700 mg, 3.02 mmol). Purification by FSC (elution gradient: 0 to 25% EtOAc in hexanes) gave the title compound (495 mg, 39%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.78-1.88 (2H, m), 1.90-1.95 (2H, m), 2.95 (2H, br s), 4.13 (2H, br d), 4.58 (1H, tt), 6.58 (1H, d), 7.65-7.70 (2H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 360.8.

Intermediate 15b:

tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4,6-difluoro-1*H*-indol-1-yl)piperidine-1-carboxylate

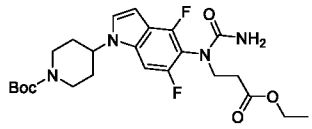


[1827] Prepared in an analogous method to Intermediate 3b from Intermediate 15a (446 mg, 1,12 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (422 mg, 83%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.12-1.18 (3H, m), 1.43 (9H, s), 1.78 (2H, qd), 1.91 (2H,

br d), 2.49-2.50 (2H, m), 2.85-3.02 (2H, m), 3.38 (2H, q), 3.96-3.98 (1H, m), 4.02 (1H, q), 4.07-4.16 (2H, m), 4.27-4.37 (1H, m), 4.45 (1H, tt), 6.38 (1H, d), 7.35 (1H, d), 7.45 (1H, d); *m/z* (ES^+) $[M+Na]^+$ =475.1.

Intermediate 15c:

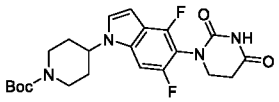
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4,6-difluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1828] Prepared in an analogous method to Intermediate 3c from Intermediate 15b (422 mg, 0.93 mmol) to give the title compound (462 mg, 100%) as a white solid. *m/z* (ES^+) $[M+H]^+$ =496.8.

Intermediate 15d:

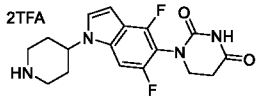
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4,6-difluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[1829] Prepared in an analogous method to Intermediate 3d from Intermediate 15c (462 mg, 0.93 mmol) to give the title compound (236 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.79-1.95 (4H, m), 2.71-2.78 (2H, m), 2.96 (2H, br s), 3.66-3.75 (2H, m), 4.06-4.21 (2H, m), 4.58 (1H, tt), 6.59 (1H, d), 7.58 (1H, d), 7.65 (1H, d), 10.55 (1H, s); *m/z* (ES^-) $[M-H]^-$ = 447.3.

Intermediate 15e:

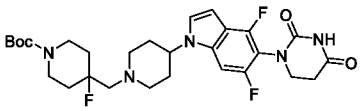
1-(4,6-Difluoro-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1830] Prepared in an analogous method to Intermediate 1i starting from Intermediate 15d (236 mg, 0.53 mmol). The solvent was removed under reduced pressure to give the title compound (288 mg, 95%) in the form of a bis(trifluoroacetic acid) salt as a white solid.^{1}H NMR (DMSO-*d*6): δ 2.07-2.19 (4H, m), 2.69-2.78 (2H, m), 3.05-3.15 (2H, m), 3.47 (2H, br d), 3.64-3.74 (2H, m), 4.65-4.74 (1H, m), 6.63 (1H, d), 7.50 (1H, d), 7.56 (1H, d), 8.52 (1H, br d), 8.74 (1H, br d), 10.54 (1H, s); *m/z* (ES^+) $[M+H]^+$ =349.1.

Intermediate 15f:

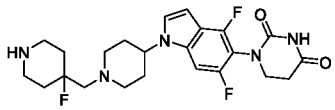
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4,6-difluoro-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1831] Prepared in an analogous method to Intermediate 6g from Intermediate 15e (214 mg, 0.45 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (125 mg, 49%) as a white solid following lyophilization. *m/z* (ES^+) $[M+Na]^+$ = 586.1.

Intermediate 15g:

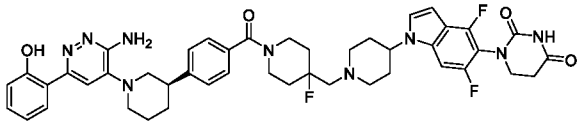
1-(4,6-Difluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1832] Prepared in an analogous method to Intermediate 1i starting from Intermediate 15f (125 mg, 0.22 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (56 mg, 55% yield) as an off-white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.55-1.69 (2H, m), 1.72-1.81 (2H, m), 1.87 (2H, br s), 1.91-2.05 (2H, m), 2.38 (2H, br t), 2.51-2.60 (2H, m), 2.70-2.82 (6H, m), 3.01 (2H, br d), 3.63-3.75 (2H, m), 4.30-4.39 (1H, m), 6.57 (1H, d), 7.53 (1H, d), 7.62 (1H, d), 10.52 (1H, br s); *m/z* (ES^+) $[M+H]^+$ =463.9.

EXAMPLE 15:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

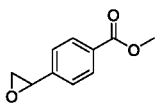


[1833] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (23 mg, 0.06 mmol) and Intermediate 15g (27 mg, 0.06 mmol). Purification by RP-HPLC (elution gradient: 20 to 40% MeCN in water with 0.1% formic acid) gave the title compound (18 mg, 35%), as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63-2.05 (12H, m), 2.42 (2H, br t), 2.59-2.68 (2H, m), 2.74 (3H, br dd), 2.77-2.86 (1H, m), 3.04 (2H, br d), 3.11-3.27 (4H, m), 3.55 (2H, br d), 3.64-3.76 (2H, m), 4.35 (2H, br t), 6.29 (2H, s), 6.58 (1H, d), 6.84-6.92 (2H, m), 7.24 (1H, t), 7.36-7.41 (2H, m), 7.41-7.48 (2H, m), 7.52-7.59 (2H, m), 7.63 (1H, d), 7.94 (1H, d), 10.54 (1H, br s), 13.85-14.54 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 836.6.

EXAMPLE 16

Intermediate 16a:

Methyl 4-(oxiran-2-yl)benzoate

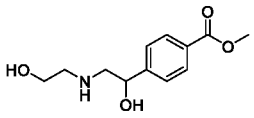


[1834] *m*-CPBA (6.08 g, 24.66 mmol) was added to a solution of methyl 4-vinylbenzoate (2.00 g, 12.33 mmol) in DCM (62 mL). The mixture was stirred at r.t. for 5 h. The reaction mixture was washed with a mixture of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ solution (1:1, 2x), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes)

gave the title compound (1.77 g, 81%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 2.79 (1H, dd), 3.18 (1H, dd), 3.88-3.94 (4H, m), 7.32-7.38 (2H, m), 7.98-8.05 (2H, m).

Intermediate 16b:

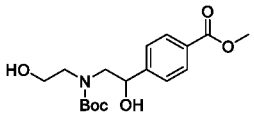
Methyl 4-(1-hydroxy-2-((2-hydroxyethyl)amino)ethyl)benzoate



[1835] A solution of Intermediate 16a (1.06 g, 5.95 mmol) and ethanolamine (3.60 mL, 59.49 mmol) in THF (4.33 mL) was stirred at r.t. for 48 h. The reaction mixture was poured into a mixture of sat. aq. $NaHCO_3$ and brine (1:1). The resulting mixture was extracted with DCM (6x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.13 g, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.53 (3H, br s), 2.77 (1H, dd), 2.82-2.88 (2H, m), 2.95 (1H, dd), 3.72 (2H, t), 3.93 (3H, s), 4.82 (1H, dd), 7.44-7.49 (2H, m), 8.01-8.06 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 240.1.

Intermediate 16c:

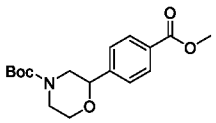
rac-Methyl 4-(2-((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)-1-hydroxyethyl)benzoate



[1836] Boc_2O (0.44 mL, 1.89 mmol) and triethylamine (0.29 mL, 2.06 mmol) were added to a solution of Intermediate 16b (0.41 g, 1.72 mmol) in DCM (7.9 mL) and the mixture was stirred at r.t. for 1 h. The reaction mixture was washed with a mixture of sat. aq. $NaHCO_3$ and brine (1:1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (0.53 g, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.50 (9H, s), 3.01-4.05 (11H, m), 5.04-5.20 (1H, m), 7.46 (2H, br d), 8.02 (2H, br d); *m/z* (ES^+) $[M+H]^+$ = 362.1.

Intermediate 16d:

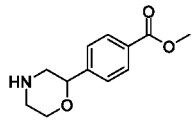
rac-tert-Butyl 2-(4-(methoxycarbonyl)phenyl)morpholine-4-carboxylate



[1837] Diisopropyl azodicarboxylate (0.91 mL, 4.70 mmol) was added dropwise to a solution of Intermediate 16c (1.23 g, 3.61 mmol), PPh_3 (1.28 g, 4.88 mmol) and NEt_3 (1.26 mL, 9.03 mmol) in MTBE (15.9 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min. and at r.t. for 16 h and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.55 g, 47%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.51 (9H, s), 2.82 (1H, br dd), 3.08 (1H, br s), 3.71 (1H, td), 3.83-4.36 (6H, m), 4.45-4.56 (1H, m), 7.48 (2H, d), 8.06 (2H, d); *m/z* (ES^+) $[M–Boc+2H]^+$ = 222.1.

Intermediate 16e:

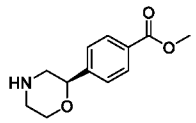
rac-Methyl 4-(morpholin-2-yl)benzoate



[1838] TFA (0.8 mL) was added to a solution of Intermediate 16d (0.15 g, 1.70 mmol) in DCM (3.8 mL) and the mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with DCM (20 mL). Sat. aq. $NaHCO_3$ (20 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the title compound (0.10 g, 98%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 1.85 (1H, br s), 2.76 (1H, dd), 2.87-2.94 (1H, m), 2.96-3.04 (1H, m), 3.09 (1H, dd), 3.79 (1H, td), 3.92 (3H, s), 4.06 (1H, dd), 4.55 (1H, dd), 7.41-7.47 (2H, m), 8.00-8.05 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 222.1.

Intermediate 16f:

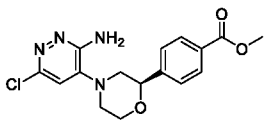
Methyl (*R*)-4-(morpholin-2-yl)benzoate



[1839] Intermediate 16e (0.45 g, 2.01 mmol) was dissolved in MeOH. The resulting solution was purified using the SFC conditions detailed below: Column: Chiralpak ID, 21 × 250 mm, 5µm; mobile phase: 25% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 100 mL/min; BPR: 120 bar; Column temperature: 40°C to afford the title compound that eluted second from the column (0.14 g, 31% yield, 95% ee) as an off-white solid. ^{1}H NMR (DMSO-*d6*): δ 2.45 (1H, dd), 2.58-2.78 (3H, m), 2.95 (1H, dd), 3.60 (1H, td), 3.83 (3H, s), 3.86-3.91 (1H, m), 4.45 (1H, dd), 7.46 (2H, d), 7.91 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 222.1.

Intermediate 16g:

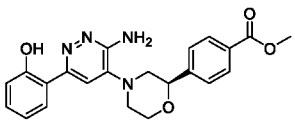
Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)benzoate



[1840] Prepared in an analogous method to Intermediate 1d starting from Intermediate 16f (138 mg, 0.62 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR ($CDCl_3$): δ 2.73 (1H, dd), 2.92 (1H, td), 3.43-3.53 (2H, m), 3.94 (3H, s), 4.00 (1H, td), 4.24 (1H, dt), 4.78 (1H, dd), 5.01 (2H, s), 6.77 (1H, s), 7.49 (2H, d), 8.07 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 349.1.

Intermediate 16h:

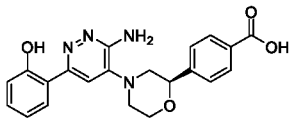
Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoate



[1841] Prepared in an analogous method to Intermediate 1e starting from Intermediate 16g (218 mg, 0.62 mmol). Purification by FSC (elution gradient: 50 to 100% EtOAc in hexanes) gave the title compound (150 mg, 59% over 2 steps) as an orange solid. ^{1}H NMR ($CDCl_3$): δ 2.86 (1H, dd), 3.01 (1H, td), 3.50-3.59 (2H, m), 3.96 (3H, s), 4.05 (1H, td), 4.29 (1H, dd), 4.83 (1H, dd), 4.90 (2H, s), 6.88-6.94 (1H, m), 7.07 (1H, dd), 7.28-7.32 (1H, m), 7.34 (1H, s), 7.53 (2H, d), 7.58 (1H, dd), 8.10 (2H, d), 13.21-14.10 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 407.3.

Intermediate 16i:

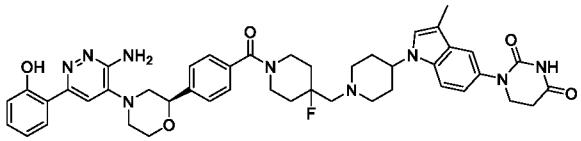
(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoic acid



[1842] Prepared in an analogous method to Intermediate 1f starting from Intermediate 16h (145 mg, 0.36 mmol). The mixture was acidified with 1 M aq. HCl to pH 4. A precipitate formed which was collected by filtration, washed with H_2O and dried *in vacuo* to give the title compound (76 mg, 54%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.85 (1H, br t), 3.08 (1H, br t), 3.45-3.92 (3H, m), 3.96-4.04 (1H, m), 4.11 (1H, br dd), 4.93 (1H, dd), 6.95 (1H, t), 7.05 (1H, d), 7.36 (1H, br t), 7.41-7.79 (6H, m), 7.95 (2H, d), 12.14-13.69 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 393.2.

EXAMPLE 16:

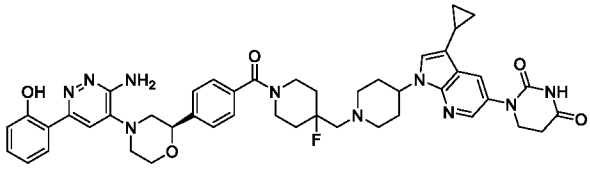
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1843] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 1k (50 mg, 0.06 mmol). Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4OH) gave the title compound (25.1 mg, 60%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.95 (1H, br d), 1.61-2.01 (8H, m), 2.22 (3H, s), 2.39 (2H, br t), 2.57-2.66 (2H, m), 2.71 (2H, t), 2.78 (1H, br t), 2.84-2.92 (1H, m), 3.02 (2H, br d), 3.06-3.18 (1H, m), 3.25-3.32 (1H, m), 3.47 (1H, br d), 3.56 (1H, br d), 3.75 (2H, t), 3.99-4.13 (2H, m), 4.19-4.37 (2H, m), 4.87 (1H, br d), 6.46 (2H, s), 6.82-6.90 (2H, m), 7.03 (1H, dd), 7.22 (1H, t), 7.30 (1H, s), 7.38 (1H, d), 7.40-7.48 (3H, m), 7.49-7.57 (3H, m), 7.93 (1H, d), 10.22 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 816.4.

EXAMPLE 17:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

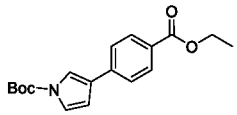


[1844] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and. Intermediate 7g (33 mg, 0.04 mmol). Purification by RPC (elution gradient: 35 to 70% MeCN/water with 0.1% NH_4OH and 10 to 50% MeCN in water with 0.1% FA) gave the title compound (11 mg, 38%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62-0.70 (2H, m), 0.82-0.89 (2H, m), 1.64-2.11 (9H, m), 2.36 (2H, br t), 2.57-2.67 (2H, m), 2.74-2.84 (3H, m), 2.89 (1H, td), 3.04 (2H, br d), 3.10-3.62 (5H, m), 3.82 (2H, t), 4.03-4.15 (2H, m), 4.27 (1H, br d), 4.55-4.66 (1H, m), 4.89 (1H, br d), 6.48 (2H, s), 6.84-6.92 (2H, m), 7.23 (1H, t), 7.41-7.47 (3H, m), 7.51-7.61 (3H, m), 7.89-8.00 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 13.84-14.68 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 843.5.

EXAMPLE 18

Intermediate 18a:

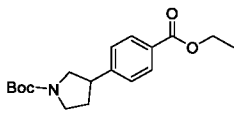
tert-Butyl 3-(4-(ethoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate



[1845] 2 M aq. K_2CO_3 (5.32 mL, 10.63 mmol) was added to a solution of ethyl 4-bromobenzoate (0.81 mg, 3.54 mmol) and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-1-carboxylate (1.04 g, 3.54 mmol) in 1,4-dioxane (17.7 mL). The mixture was sparged with N_2 for 1 min. Pd(dppf)Cl_2·DCM (0.15 g, 0.18 mmol) was added. The reaction was stirred at 100 °C for 40 min. After cooling to r.t. the mixture was diluted with EtOAc (20 mL), washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% EtOAc in hexanes) gave the title compound (0.93 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t), 1.64 (9H, s), 4.39 (2H, q), 6.59 (1H, dd), 7.29-7.35 (1H, m), 7.55-7.64 (3H, m), 8.00-8.08 (2H, m); *m/z* (ES$^+$) $[M–Boc+2H]^+$ = 216.1.

Intermediate 18b:

rac-tert-Butyl 3-(4-(ethoxycarbonyl)phenyl)pyrrolidine-1-carboxylate

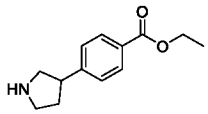


[1846] Pd/C (215 mg, 0.20 mmol, 10 wt% Pd) was added to a solution of Intermediate 18a (318 mg, 1.01 mmol) in ethanol (6.7 mL). The mixture was sparged with H_2 for 5 min. stirred under an atmosphere

of H_2 at r.t. for 80 min. The mixture was sparged with N_2 for 5 min and filtered through a pad of Celite with ethanol. The filtrate was concentrated under reduced pressure to give the title compound (289 mg, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t), 1.50 (9H, br s), 1.96-2.06 (1H, m), 2.31 (1H, br d), 3.28-3.51 (3H, m), 3.54-3.72 (1H, m), 3.78-3.95 (1H, m), 4.39 (2H, q), 7.30-7.36 (2H, m), 8.02 (2H, d); *m/z* (ES^+) $[M+Na]^+$ = 342.1.

Intermediate 18c:

rac-Ethyl 4-(pyrrolidin-3-yl)benzoate



[1847] TFA (0.73 mL, 9.55 mmol) was added to a solution of Intermediate 18b (280 mg, 0.88 mmol) in DCM (2.2 mL). The reaction was stirred at r.t. for 0.5 h and concentrated under reduced pressure. The residue was partitioned between DCM (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer was extracted with DCM (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (183 mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t), 1.90 (1H, dq), 2.30 (1H, dtd), 2.92 (1H, dd), 3.04 (1H, br s), 3.15 (1H, dt), 3.20-3.27 (1H, m), 3.32 (1H, quin), 3.43 (1H, dd), 4.39 (2H, q), 7.33 (2H, d), 8.00 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 220.1.

Intermediate 18d:

Ethyl (*R**)-4-(pyrrolidin-3-yl)benzoate (Isomer 1)

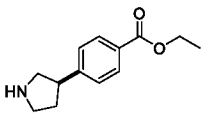
((*absolute configuration not yet confirmed))

and

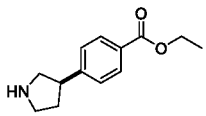
Intermediate 18e:

Ethyl (*R**)-4-(pyrrolidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 1



Isomer 2

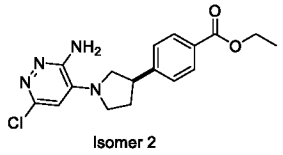
[1848] Intermediate 18c (1.05 g, 4.79 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak ID, 21 × 250 mm, 5μm; mobile phase: 15% MeOH with 0.2% formic acid in $scCO_2$; Flow rate: 75 mL/min; BPR: 100 bar; Column temperature: 40°C to afford Isomer 1 that eluted first from the column (0.26 g, 24% yield, 90% ee) as an off-white solid and Isomer 2 that eluted second from the column (0.23 g, 22% yield, 89% ee) as an off-white solid. Isomer 1: ^{1}H NMR (DMSO-*d*6): δ 1.30 (3H, t), 1.62-1.74 (1H, m), 2.09-2.20 (1H, m), 2.57-2.73 (1H, m), 2.86-2.94 (1H, m), 2.95-3.03 (1H, m), 3.14-3.25 (2H, m), 3.51 (1H, br s), 4.28 (2H, q), 7.40 (2H, d), 7.86 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 220.1. Isomer 2: ^{1}H NMR (DMSO-*d*6): δ 1.30 (3H, t), 1.62-1.74 (1H, m), 2.09-2.20 (1H,

m), 2.57-2.73 (1H, m), 2.86-2.94 (1H, m), 2.95-3.03 (1H, m), 3.14-3.25 (2H, m), 3.51 (1H, br s), 4.28 (2H, q), 7.40 (2H, d), 7.86 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 220.1.

Intermediate 18f:

Ethyl (*R**)-4-(1-(3-amino-6-chloropyridazin-4-yl)pyrrolidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

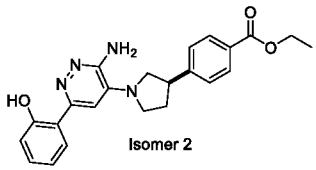


[1849] Prepared in an analogous method to Intermediate 1d starting from Intermediate 18e (234 mg, 1.07 mmol). After cooling to r.t. the reaction mixture was poured into brine and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the title compound as a brown oil as a mixture with 4-bromo-6-chloropyridazin-3-amine. The product was used for the next step without further purification and quantitative yield was assumed. ^1H NMR ($CDCl_3$): δ 1.36-1.40 (3H, m), 2.18 (1H, br d), 2.43-2.53 (1H, m), 3.51-3.60 (2H, m), 3.63-3.68 (2H, m), 3.84-3.91 (1H, m), 4.40 (2H, q), 4.71 (2H, br s), 6.42 (1H, s), 7.35 (2H, d), 8.01-8.09 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 347.2.

Intermediate 18g:

Ethyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

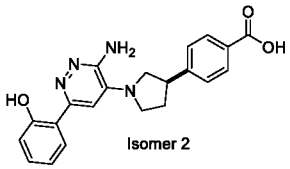


[1850] Prepared in an analogous method to Intermediate 1e starting from Intermediate 18f (370 mg, 1.07 mmol). Purification by FSC (elution gradient: 50 to 100% EtOAc in hexanes) gave the title compound (99 mg, 23%) as a brown solid. ^1H NMR ($CDCl_3$): δ 1.40-1.45 (3H, m), 2.18-2.29 (1H, m), 2.51 (1H, td), 3.56-3.64 (2H, m), 3.68-3.75 (2H, m), 3.87-3.94 (1H, m), 4.37-4.45 (2H, m), 4.61 (2H, br s), 6.87-6.92 (1H, m), 6.95 (1H, s), 7.06 (1H, dd), 7.26-7.31 (1H, m), 7.39 (2H, d), 7.60 (1H, dd), 8.05-8.10 (2H, m), 11.78-14.10 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 405.3.

Intermediate 18h:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

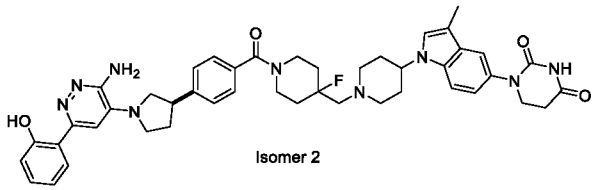


[1851] Prepared in an analogous method to Intermediate 1f starting from Intermediate 18g (99 mg, 0.24 mmol). The mixture was acidified with 1 M aq. HCl to pH 1. A precipitate formed which was collected by filtration, washed with H_2O and dried *in vacuo* to give the title compound (57 mg, 62%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.02-2.13 (1H, m), 2.37-2.46 (1H, m), 3.54-3.63 (1H, m), 3.68 (2H, br t), 3.78-3.86 (1H, m), 3.91 (1H, br dd), 6.03 (2H, br s), 6.83-6.90 (2H, m), 7.11 (1H, s), 7.21-7.27 (1H, m), 7.54 (2H, d), 7.90-7.98 (3H, m), 13.03-14.28 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 377.2.

EXAMPLE 18:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

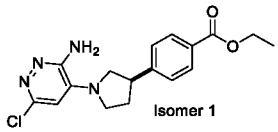
[1852] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 18h (20 mg, 0.05 mmol) and Intermediate 1k (53 mg, 0.06 mmol). Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4OH) gave the title compound (12.9 mg, 30%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63-1.91 (5H, m), 1.92-2.03 (3H, m), 2.05-2.15 (1H, m), 2.23 (3H, s), 2.36-2.46 (3H, m), 2.58-2.68 (2H, m), 2.73 (2H, t), 3.04 (2H, br d), 3.07-3.28 (2H, m), 3.43-3.61 (2H, m), 3.63-3.71 (2H, m), 3.77 (2H, t), 3.79-3.85 (1H, m), 3.89 (1H, dd), 4.10-4.45 (2H, m), 5.99 (2H, s), 6.82-6.91 (2H, m), 7.05 (1H, dd), 7.11 (1H, s), 7.19-7.26 (1H, m), 7.31 (1H, s), 7.38-7.44 (3H, m), 7.44-7.52 (3H, m), 7.93 (1H, d), 10.24 (1H, br s), 14.38-15.21 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 800.5.

EXAMPLE 19

Intermediate 19a:

Ethyl (*R**)-4-(1-(3-amino-6-chloropyridazin-4-yl)pyrrolidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

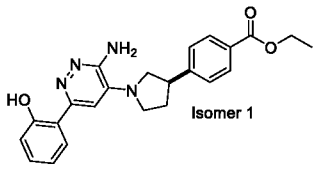
[1853] Prepared in an analogous method to Intermediate 1d starting from Intermediate 18d (50 mg, 0.23 mmol). After cooling to r.t., the reaction mixture was poured into brine and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the title compound as a brown oil as a mixture with 4-bromo-6-chloropyridazin-3-amine. The product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR $CDCl_3$): δ 1.36-1.40

(3H, m), 2.18 (1H, br d), 2.43-2.53 (1H, m), 3.51-3.60 (2H, m), 3.63-3.68 (2H, m), 3.84-3.91 (1H, m), 4.40 (2H, q), 4.71 (2H, br s), 6.42 (1H, s), 7.35 (2H, d), 8.01-8.09 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 347.2.

Intermediate 19b:

Ethyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

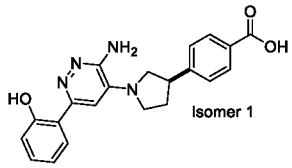


[1854] Prepared in an analogous method to Intermediate 1e starting from Intermediate 19a (79 mg, 0.23 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (37 mg, 40%) as a brown solid. ^1H NMR $CDCl_3$): δ 1.40-1.45 (3H, m), 2.18-2.29 (1H, m), 2.51 (1H, td), 3.56-3.64 (2H, m), 3.68-3.75 (2H, m), 3.87-3.94 (1H, m), 4.37-4.45 (2H, m), 4.61 (2H, br s), 6.87-6.92 (1H, m), 6.95 (1H, s), 7.06 (1H, dd), 7.26-7.31 (1H, m), 7.39 (2H, d), 7.60 (1H, dd), 8.05-8.10 (2H, m), 11.78-14.10 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 405.3.

Intermediate 19c:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

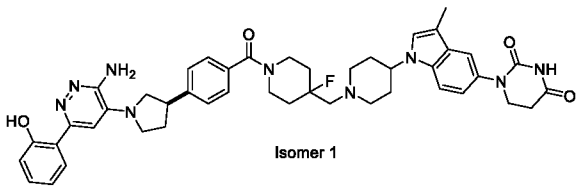


[1855] Prepared in an analogous method to Intermediate 1f starting from Intermediate 19b (37 mg, 0.09 mmol). The mixture was acidified with 1 M aq. HCl to pH 1. A precipitate formed which was collected by filtration, washed with H_2O and dried *in vacuo* to give the title compound (13 mg, 38%) as a brown solid. ^1H NMR (DMSO-*d*6): δ 2.02-2.13 (1H, m), 2.37-2.46 (1H, m), 3.54-3.63 (1H, m), 3.68 (2H, br t), 3.78-3.86 (1H, m), 3.91 (1H, br dd), 6.03 (2H, br s), 6.83-6.90 (2H, m), 7.11 (1H, s), 7.21-7.27 (1H, m), 7.54 (2H, d), 7.90-7.98 (3H, m), 13.03-14.28 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 377.2.

EXAMPLE 19:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

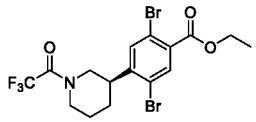


[1856] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 19c (13 mg, 0.03 mmol) and Intermediate 1k (34 mg, 0.04 mmol). Purification by RPC (elution gradient: 30 to 70% MeCN in water with 0.1% NH_4OH) gave the title compound (12.7 mg, 46%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.63-1.91 (5H, m), 1.92-2.03 (3H, m), 2.05-2.15 (1H, m), 2.23 (3H, s), 2.36-2.46 (3H, m), 2.58-2.68 (2H, m), 2.73 (2H, t), 3.04 (2H, br d), 3.07-3.28 (2H, m), 3.43-3.61 (2H, m), 3.63-3.71 (2H, m), 3.77 (2H, t), 3.79-3.85 (1H, m), 3.89 (1H, dd), 4.10-4.45 (2H, m), 5.99 (2H, s), 6.82-6.91 (2H, m), 7.05 (1H, dd), 7.11 (1H, s), 7.19-7.26 (1H, m), 7.31 (1H, s), 7.38-7.44 (3H, m), 7.44-7.52 (3H, m), 7.93 (1H, d), 10.24 (1H, br s), 14.38-15.21 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 800.5.

EXAMPLE 20

Intermediate 20a:

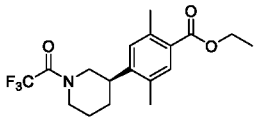
Ethyl (*R*)-2,5-dibromo-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1857] Intermediate 12a (4.00 g, 12.15 mmol), NBS (5.40 g, 30.37 mmol), $FeCl_3$ (4.93 g, 30.37 mmol) and MeCN (24.29 ml) were evenly divided among eight vials, placed under N_2 atmosphere, sealed, and stirred at 100 °C for 16 h. Upon completion, the reactions were combined and concentrated onto celite. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (800 mg, 14%) as a white solid. ^1H NMR ($CDCl_3$): δ 1.43 (3H, t), 1.66 - 1.82 (2H, m), 1.91 - 2.05 (1H, m), 2.08 - 2.23 (1H, m), 2.67 - 2.87 (1H, m), 3.06 - 3.36 (2H, m), 4.04 - 4.17 (1H, m), 4.42 (2H, d), 4.62 - 4.80 (1H, m), 7.50 (1H, d), 8.05 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 487.8.

Intermediate 20b:

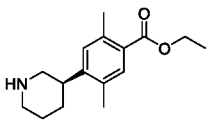
Ethyl (*R*)-2,5-dimethyl-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1858] A solution of Intermediate 20a (487 mg, 1.00 mmol), $Pd(Ph_3P)_4$ (116 mg , 0.10 mmol), Me_4Sn (1073 mg, 6.00 mmol) and toluene (4.0 mL) was placed under N_2 and heated to 130 °C for 16 h. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (320 mg, 90%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.41 (3H, t), 1.67 - 1.78 (1H, m), 1.78 - 1.89 (1H, m), 1.95 - 2.05 (2H, m), 2.34 - 2.41 (3H, m), 2.58 (3H, s), 2.70 - 2.88 (1H, m), 2.90 - 3.04 (1H, m), 3.11 - 3.26 (1H, m), 4.09 - 4.19 (1H, m), 4.32 - 4.44 (2H, m), 4.57 - 4.76 (1H, m), 7.00 - 7.09 (1H, m), 7.72 - 7.81 (1H, m); *m/z* (ES^+) $[M–EtO]^+$ = 312.3.

Intermediate 20c:

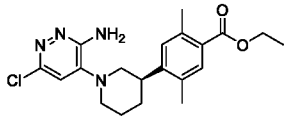
Ethyl (*R*)-2,5-dimethyl-4-(piperidin-3-yl)benzoate



[1859] Prepared in an analogous method to Intermediate 12d starting from Intermediate 20b (320 mg, 0.90 mmol) to give the title compound (234 mg, 100%) as a yellow solid, which was carried forward without further purification. *m/z* (ES^+) $[M+H]^+$ = 262.5.

Intermediate 20d:

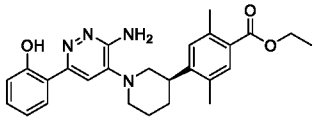
Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoate



[1860] Prepared in an analogous method to Intermediate 1d starting from Intermediate 20c (230 mg, 0.88 mmol) and 4-bromo-6-chloropyridazin-3-amine (367 mg, 1.76 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (228 mg, 67%) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.31 (3H, s), 1.53 - 1.67 (1H, m), 1.77 - 1.97 (3H, m), 2.34 (3H, s), 2.48 (3H, s), 2.60 - 2.69 (1H, m), 2.70 - 2.81 (1H, m), 3.14 - 3.25 (1H, m), 3.36 - 3.53 (2H, m), 4.19 - 4.36 (2H, m), 6.02 - 6.24 (2H, m), 6.90 - 7.03 (1H, m), 7.18 - 7.31 (1H, m), 7.58 - 7.69 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 389.5.

Intermediate 20e:

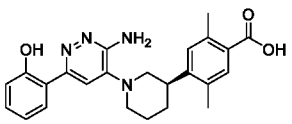
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoate



[1861] Prepared in an analogous method to Intermediate 1e starting from Intermediate 20d (121 mg, 0.88 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (170 mg, 65% yield) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ d 1.31 (3H, s), 1.59 - 1.73 (1H, m), 1.83 - 1.95 (2H, m), 1.97 - 2.04 (1H, m), 2.37 (3H, s), 2.49 - 2.50 (3H, m), 2.67 - 2.78 (1H, m), 2.82 - 2.91 (1H, m), 3.22 - 3.29 (1H, m), 3.42 - 3.50 (1H, m), 3.52 - 3.64 (1H, m), 4.23 - 4.33 (2H, m), 6.23 - 6.32 (2H, m), 6.83 - 6.93 (2H, m), 7.21 - 7.26 (1H, m), 7.26 - 7.30 (1H, m), 7.52 - 7.57 (1H, m), 7.62 - 7.66 (1H, m), 7.90 - 7.96 (1H, m), 14.10 - 14.38 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 447.2.

Intermediate 20f:

(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoic acid

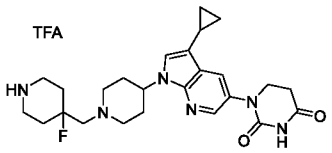


[1862] A solution of Intermediate 20e (170 mg, 0.38 mmol), EtOH (2.5 mL), and 1 M aq. NaOH (2.5 mL, 2.50 mmol) was stirred at 50 °C for 2 h. Upon completion, the reaction mixture was partially concentrated under reduced pressure and acidified with 1 M aq. HCl (2.5 mL). The resultant suspension

was centrifuged and decanted to afford the title compound (155 mg, 97%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.78 (1H, m), 1.83 - 2.08 (3H, m), 2.34 (3H, s), 2.48 - 2.50 (3H, m), 2.81 - 2.97 (1H, m), 2.97 - 3.10 (1H, m), 3.13 - 3.26 (2H, m), 3.54 - 3.68 (1H, m), 3.69 - 3.88 (1H, m), 6.96 (1H, s), 7.00 - 7.05 (1H, m), 7.05 - 7.19 (1H, m), 7.24 (1H, s), 7.33 - 7.40 (1H, m), 7.47 - 7.57 (1H, m), 7.66 (1H, s), 7.67 - 7.72 (1H, m), 12.37 - 12.93 (1H, m) (-OH not observed); *m/z* (ES$^+$) [M+H]$^+$ = 419.5.

Intermediate 20g:

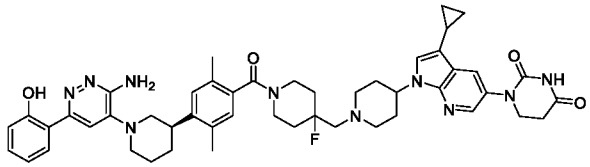
1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1863] Prepared in an analogous method to Intermediate 1i starting from Intermediate 7f (1.00 mg, 1.76 mmol), which gave the title compound (1.62 g, 100%) in the form of a *tetrakis*(trifluoroacetic acid) salt as an brown solid *m/z* (ES$^+$) [M+H]$^+$ = 469.3.

EXAMPLE 20:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

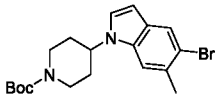


[1864] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 20f (10.0 mg, 0.02 mmol) and Intermediate 20g (22.1 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 60% MeCN in water with 0.1% FA) gave the title compound (6.6 mg, 32%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.69 (2H, m), 0.83 - 0.91 (2H, m), 1.63 - 1.77 (3H, m), 1.85 - 2.02 (9H, m), 2.16 - 2.23 (4H, m), 2.32 - 2.34 (3H, m), 2.39 - 2.41 (3H, m), 2.76 - 2.79 (2H, m), 2.90 - 3.04 (3H, m), 3.16 - 3.21 (2H, m), 3.48 - 3.71 (5H, m), 3.80 - 3.83 (2H, m), 6.89 - 6.98 (3H, m), 6.96 - 7.04 (2H, m), 7.19 - 7.26 (2H, m), 7.27 - 7.37 (2H, m), 7.39 - 7.47 (1H, m), 7.50 - 7.59 (1H, m), 7.73 - 7.81 (2H, m), 7.92 - 8.04 (1H, m), 8.15 - 8.25 (1H, m), 10.35 - 10.42 (1H, m) (-OH not observed); *m/z* (ES$^+$) [M+H]$^+$ = 869.5.

EXAMPLE 21

Intermediate 21a:

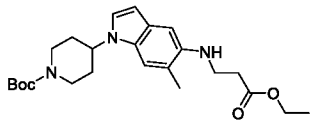
tert-Butyl 4-(5-bromo-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1865] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-6-methyl-1*H*-indole (3.00g, 14.28 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in hexanes) gave an impure white solid. Trituration with Et_2O, filtration through celite, and concentration gave the title compound (1.05g, 19%) as white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.74 - 1.85 (2H, m), 1.88 - 1.98 (2H, m), 2.45 (3H, s), 2.85 - 3.05 (2H, m), 4.03 - 4.22 (2H, m), 4.45 - 4.62 (1H, m), 6.37 - 6.46 (1H, m), 7.45 - 7.53 (1H, m), 7.55 - 7.63 (1H, m), 7.72 - 7.82 (1H, m); *m/z* (ES^+) [M–*t*Bu+2H]+.= 337.0.

Intermediate 21b:

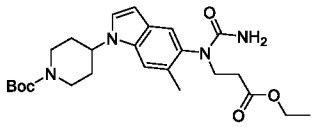
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1866] Prepared in an analogous method to Intermediate 3b starting from Intermediate 21a (1.03 g, 2.62 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) afforded the title compound, (0.840 g, 75%) as a white solid. *m/z* (ES^+) $[M–tBu+2H]^+$ = 374.2.

Intermediate 21c:

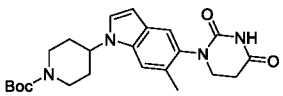
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1867] Prepared in an analogous method to Intermediate 3c starting from Intermediate 21b (840 mg, 1.96 mmol) to afford the title compound (924 mg, 100%) as white foam, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ =473.3.

Intermediate 21d:

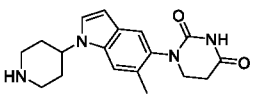
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1868] Prepared in an analogous method to Intermediate 3d starting from Intermediate 21c (924 mg, 1.96 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (590 mg, 71%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.57 (1H, s), 1.75 - 1.87 (2H, m), 1.88 - 1.97 (2H, m), 2.26 (3H, s), 2.82 - 3.09 (2H, m), 3.37 - 3.49 (2H, m), 3.58 - 3.69 (1H, m), 4.03 - 4.22 (2H, m), 4.48 - 4.58 (1H, m), 6.29 - 6.45 (1H, m), 7.31 (1H, s), 7.40 (1H, s), 7.44 (1H, s), 10.01 - 10.50 (1H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 371.1.

Intermediate 21e:

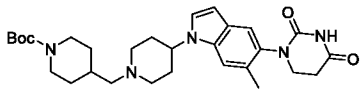
1-(6-Methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1869] Prepared in an analogous method to Intermediate 6e starting from Intermediate 21d (590 mg, 1.38 mmol). The crude product as suspended in 3:1 $CHCl_3$/IPA, washed with sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (260 mg, 58%) as white solid. $[M+H]^+ = 327.1$.

Intermediate 21f:

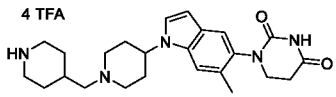
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1870] A solution of Intermediate 21e (100 mg, 0.31 mmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (98 mg, 0.46 mmol), NaOAc (126 mg, 1.53 mmol) and THF (3.06 ml) was stirred at 60 °C for 16 h. The reaction mixture was cooled to r.t., $NaBH(OAc)_3$ (195 mg, 0.92 mmol) was added, and the reaction was stirred for 30 minutes. The reaction mixture was quenched with water and extracted with DCM (3 x10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) afforded the title compound, (33 mg, 21%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 0.91 - 1.03 (2H, m), 1.40 (9H, s), 1.66 - 1.76 (3H, m), 1.92 - 2.04 (3H, m), 2.11 - 2.18 (2H, m), 2.19 - 2.23 (2H, m), 2.28 (3H, s), 2.68 - 2.78 (3H, m), 2.96 - 3.03 (2H, m), 3.37 - 3.40 (1H, m), 3.50 - 3.60 (1H, m), 3.72 - 3.82 (1H, m), 3.87 - 3.99 (2H, m), 4.27 - 4.37 (2H, m), 6.32 - 6.46 (1H, m), 7.39 - 7.44 (2H, m), 7.46 - 7.52 (1H, m), 10.21 - 10.28 (1H, m); *m/z* (ES^+) $[M+H]^+ = 524.6$.

Intermediate 21g:

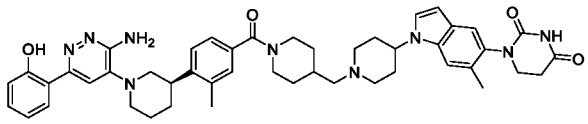
1-(6-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1871] Prepared in an analogous method to Intermediate 1i starting from Intermediate 21f (33.2 mg, 0.06 mmol) to give the title compound (22 mg, 81%) in the form of a *tetrakis*(trifluoroacetic acid) salt, as an brown solid, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+ = 424.3$.

EXAMPLE 21:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

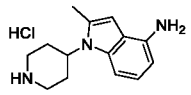


[1872] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 21g (19.3 mg, 0.3 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (9.1 mg, 45%) as a white solid. ^{1}H NMR (DMSO-*d6*): δ 1.06 - 1.15 (2H, m), 1.65 - 1.75 (2H, m), 1.86 - 1.91 (2H, m), 1.93 - 1.97 (4H, m), 1.98 - 2.05 (3H, m), 2.29 (3H, s), 2.41 (4H, s), 2.71 - 2.77 (5H, m), 3.01 (4H, br d), 3.47 - 3.51 (1H, m), 3.55 (2H, br d), 3.58 - 3.62 (1H, m), 3.69 - 3.73 (1H, m), 3.74 - 3.79 (1H, m), 4.26 - 4.40 (2H, m), 4.42 - 4.53 (1H, m), 6.24 - 6.31 (2H, m), 6.39 - 6.43 (1H, m), 6.86 - 6.91 (2H, m), 7.18 - 7.21 (2H, m), 7.22 - 7.26 (1H, m), 7.37 - 7.41 (1H, m), 7.41 - 7.44 (2H, m), 7.45 - 7.49 (1H, m), 7.53 - 7.59 (2H, m), 7.91 - 7.97 (1H, m), 10.20 - 10.28 (1H, m) (-OH was not observed); *m/z* (ES$^+$) $[M+H]^+$ = 810.6.

EXAMPLE 22

Intermediate 22a:

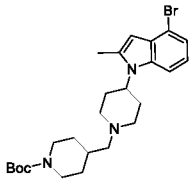
4-Bromo-2-methyl-1-(piperidin-4-yl)-1*H*-indole



[1873] To a stirred solution of 4-bromo-2-methyl-1*H*-indole (0.252 g, 1.2 mmol) in DMF (3 mL) was added *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (0.670 g, 2.40 mmol) and Cs_2CO_3 (0.782 g, 2.40 mmol). The reaction was stirred at 80 °C for 16 h. After cooling to r.t., the mixture was filtered. The filtrate was concentrated under reduced pressure. To the crude residue were added MeOH (2 mL) and 4 M HCl in 1,4-dioxane (1.5 mL, 6.00 mmol). The resulting solution was stirred at r.t. for 3 h and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 30% MeCN in water with 0.1% FA) gave the title compound in the form of a hydrochloride salt (0.074 g, 21%) as a pink solid. *m/z* (ES$^+$) $[M+H]^+$ = 293.0.

Intermediate 22b:

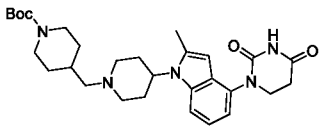
tert-Butyl 4-((4-(4-bromo-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1874] Prepared in an analogous manner to Intermediate 10d starting from Intermediate 22a (74 mg, 0.25 mmol) in DCM (2 mL) and IPA (0.5 mL). Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (0.100 g, 81%) as a yellow oil. *m/z* (ES$^+$) $[M+H]^+$ = 490.3.

Intermediate 22c:

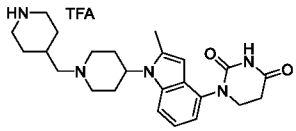
tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1875] A vial was charged with Intermediate 22b (100 mg, 0.20 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (69.8 mg, 0.61 mmol), Cs_2CO_3 (133 mg, 0.41 mmol), $Pd(dba)_2$ (11.7 mg, 0.02 mmol) and EPhos (21.8 mg, 0.04 mmol). The vial was purged with N_2. 1,4-Dioxane (3 mL) was added. The mixture was purged with N_2. The resulting mixture was stirred at 100 °C for 16 h. After cooling to r.t., the mixture was filtered. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.037 g, 35%) as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 524.4.

Intermediate 22d:

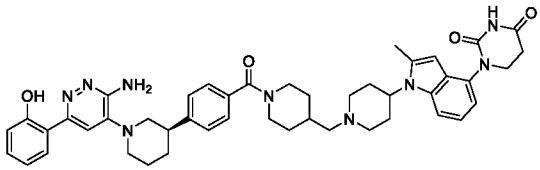
1-(2-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1876] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 22c (2.399 g, 4.58 mmol). Concentration under reduced pressure afforded the title compound as a grey solid in the form of a *tetrakis*(trifluoroacetic acid) salt. ^1H NMR (DMSO-*d*6): δ 1.38 - 1.49 (2H, m), 1.93 - 2.08 (4H, m), 2.14 - 2.31 (1H, m), 2.46 (3H, s), 2.75 (2H, t), 2.78 - 2.99 (4H, m), 3.05 - 3.14 (2H, m), 3.17 - 3.30 (2H, m), 3.35 (2H, br d), 3.70 - 3.78 (4H, m), 4.62 (1H, br t), 6.19 (1H, s), 6.93 (1H, d), 7.03 (1H, t), 7.67 (1H, br d), 8.56 (1H, br d), 8.83 (1H, br d), 10.09 (1H, br s), 10.31 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 424.3.

EXAMPLE 22:

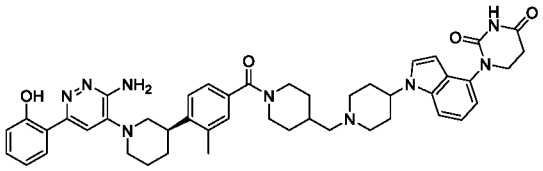
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1877] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (10.0 mg, 0.02 mmol) and Intermediate 22d (22.5 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% FA) gave the title compound (10.3 mg, 51%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.03 - 1.22 (2H, m), 1.61 - 2.08 (10H, m), 2.11 - 2.35 (2H, m), 2.44 (4H, s), 2.59 - 2.66 (1H, m), 2.68 - 2.77 (4H, m), 2.78 - 2.86 (2H, m), 2.96 - 3.19 (4H, m), 3.52 - 3.59 (2H, m), 3.60 - 3.71 (1H, m), 3.72 - 3.78 (2H, m), 4.19 - 4.38 (1H, m), 4.41 - 4.62 (1H, m), 6.13 - 6.18 (1H, m), 6.23 - 6.34 (2H, m), 6.84 - 6.93 (3H, m), 7.02 - 7.09 (1H, m), 7.20 - 7.28 (1H, m), 7.33 - 7.39 (2H, m), 7.42 - 7.46 (2H, m), 7.47 - 7.52 (1H, m), 7.54 - 7.59 (1H, m), 7.88 - 7.98 (1H, m), 10.23 - 10.36 (1H, m)(-OH not reported); *m/z* (ES^+) $[M+H]^+$ = 796.6.

EXAMPLE 23:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

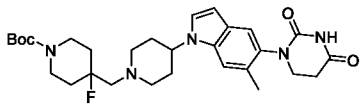


[1878] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (20.0 mg, 0.05 mmol) and Intermediate 10e (31.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (19.6 mg, 47%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.00 - 1.20 (2H, m), 1.60 - 1.78 (2H, m), 1.81 - 1.92 (3H, m), 1.92 - 2.06 (6H, m), 2.11 - 2.34 (4H, m), 2.40 (3H, s), 2.72 - 2.79 (3H, m), 2.82 - 2.89 (1H, m), 2.96 - 3.10 (3H, m), 3.37 - 3.41 (2H, m), 3.47 - 3.51 (1H, m), 3.56 - 3.62 (1H, m), 3.63 - 3.71 (1H, m), 3.75 - 3.81 (2H, m), 4.29 - 4.58 (2H, m), 6.23 - 6.30 (2H, m), 6.38 - 6.45 (1H, m), 6.85 - 6.91 (2H, m), 6.93 - 6.98 (1H, m), 7.12 - 7.17 (1H, m), 7.18 - 7.21 (2H, m), 7.22 - 7.28 (1H, m), 7.36 - 7.42 (1H, m), 7.49 - 7.53 (2H, m), 7.55 - 7.59 (1H, m), 7.90 - 7.98 (1H, m), 10.27 - 10.37 (1H, m), 13.10 - 14.68 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 796.5.

EXAMPLE 24

Intermediate 24a:

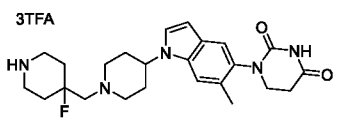
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1879] Prepared in an analogous method to Intermediate 6g starting from Intermediate 21e (160 mg, 0.49 mmol) and Intermediate 6f (322 mg, 0.88 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (61 mg, 23%) as an , colorless solid. ^{1}H NMR (DMSO-*d*6): δ 1.15 - 1.20 (1H, m), 1.41 (9H, s), 1.55 - 1.69 (3H, m), 1.81 - 1.94 (5H, m), 2.28 (3H, s), 2.38 - 2.44 (2H, m), 2.55 - 2.60 (1H, m), 2.62 - 2.65 (1H, m), 2.68 - 2.81 (2H, m), 3.01 - 3.06 (3H, m), 3.52 - 3.57 (1H, m), 3.72 - 3.80 (3H, m), 4.26 - 4.35 (1H, m), 6.30 - 6.45 (1H, m), 7.42 (2H, br s), 7.46 - 7.50 (1H, m), 10.22 - 10.28 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 542.3.

Intermediate 24b:

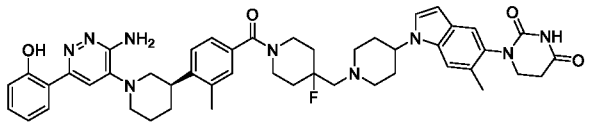
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1880] Prepared in an analogous method to Intermediate 1i starting from Intermediate 24a (60.5 mg, 0.30 mmol) to give the title compound (83 mg, 94%) in the form of a *tris*(trifluoroacetic acid) salt as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 442.5.

EXAMPLE 24:

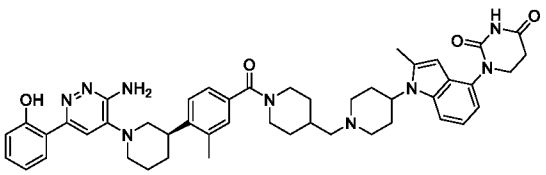
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1881] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol and Intermediate 24b (23.3 mg, 0.3 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (13.8 mg, 67%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.71 (2H, m), 1.72 - 1.81 (1H, m), 1.85 - 2.06 (9H, m), 2.28 (3H, s), 2.35 - 2.39 (1H, m), 2.40 - 2.42 (3H, m), 2.42 - 2.46 (1H, m), 2.54 - 2.58 (2H, m), 2.60 - 2.69 (2H, m), 2.71 - 2.78 (3H, m), 2.84 - 2.92 (1H, m), 3.02 - 3.10 (2H, m), 3.11 - 3.22 (1H, m), 3.24 - 3.29 (1H, m), 3.47 - 3.52 (1H, m), 3.53 - 3.58 (1H, m), 3.58 - 3.63 (1H, m), 3.72 - 3.80 (1H, m), 4.13 - 4.37 (2H, m), 6.20 - 6.38 (2H, m), 6.38 - 6.44 (1H, m), 6.85 - 6.93 (2H, m), 7.24 (3H, br s), 7.42 (3H, br s), 7.45 - 7.50 (1H, m), 7.55 - 7.60 (1H, m), 7.89 - 7.97 (1H, m), 10.23 - 10.29 (1H, m), 14.06 - 14.40 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 828.5.

EXAMPLE 25:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

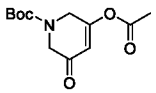


[1882] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10.0 mg, 0.02 mmol) and Intermediate 22d (21.75 mg, 0.02 mmol) Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% FA) gave the title compound (14.2 mg, 71%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.04 - 1.19 (2H, m), 1.59 - 1.72 (1H, m), 1.73 - 1.81 (3H, m), 1.82 - 1.91 (3H, m), 1.92 - 2.04 (2H, m), 2.10 - 2.18 (2H, m), 2.21 - 2.28 (2H, m), 2.40 - 2.42 (3H, m), 2.43 - 2.45 (3H, m), 2.52 - 2.55 (2H, m), 2.71 - 2.78 (3H, m), 2.83 - 2.91 (1H, m), 2.98 - 3.07 (3H, m), 3.46 - 3.51 (1H, m), 3.57 - 3.61 (1H, m), 3.63 - 3.70 (1H, m), 3.72 - 3.76 (2H, m), 4.15 - 4.32 (1H, m), 4.39 - 4.57 (1H, m), 6.11 - 6.19 (1H, m), 6.22 - 6.32 (2H, m), 6.48 - 6.78 (1H, m), 6.84 - 6.93 (3H, m), 7.00 - 7.10 (1H, m), 7.17 - 7.22 (2H, m), 7.23 - 7.28 (1H, m), 7.36 - 7.42 (1H, m), 7.44 - 7.49 (1H, m), 7.53 - 7.61 (1H, m), 7.90 - 8.01 (1H, m), 8.19 - 8.33 (1H, m), 10.21 - 10.35 (1H, m), 14.01 - 14.57 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 810.7.

EXAMPLE 26

Intermediate 26a:

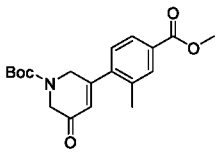
tert-Butyl 5-acetoxy-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



[1883] *tert*-Butyl 3,5-dioxopiperidine-1-carboxylate (10.0 g, 46.90 mmol) in DCM (106 ml) was charged with Et_3N (7.19 ml, 51.59 mmol) and acetyl chloride (4.00 ml, 56.28 mmol) at 0 °C. The reaction mixture warmed to r.t. for 1 h. The reaction was quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM (3 x 20mL). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (11.97g, 100%), as a brown oil which was carried forward without intermediate purification. ^{1}H NMR ($CDCl_3$): δ 1.49 (9H, s), 2.28 (3H, s), 4.10 (2H, s), 4.27 - 4.38 (2H, m), 6.12 - 6.25 (1H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 199.9.

Intermediate 26b:

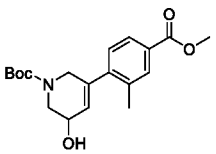
tert-Butyl 5-(4-(methoxycarbonyl)-2-methylphenyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



[1884] A solution of Intermediate 26a (11.9 g, 46.62 mmol), (4-(methoxycarbonyl)-2-methylphenyl)boronic acid (10.0 g, 51.55 mmol), $Pd(OAc)_2$ (0.419 g, 1.86 mmol) and tris(2-methoxyphenyl)phosphane (0.986 g, 2.80 mmol), acetone (85 ml) and water (8.48 ml) was stirred at r.t. for 30 minutes under air. Upon completion, the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (10.58 g, 66%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.51 (9H, s), 2.40 (3H, s), 3.95 (3H, s), 4.18 - 4.25 (2H, m), 4.36 - 4.47 (2H, m), 6.08 - 6.18 (1H, m), 7.18 - 7.30 (1H, m), 7.88 - 7.93 (1H, m), 7.95 - 7.98 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 246.1.

Intermediate 26c:

rac-tert-Butyl 3-hydroxy-5-(4-(methoxycarbonyl)-2-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

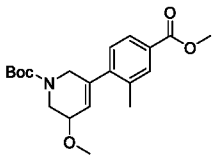


[1885] A solution of Intermediate 26b (500 mg, 1.45 mmol) in MeOH (14.476 ml) was charged with $CeCl_3 \cdot 7H_2O$ (701 mg, 1.88 mmol) and cooled to 0 °C. $NaBH_4$ (71.2 mg, 1.88 mmol) was added over 5 minutes. The resulting mixture was stirred at r.t. for 1 hr. Upon completion, the reaction mixture was quenched with sat. aq. NH_4Cl and partially concentrated under reduced pressure. The resultant suspension

was diluted with water and extracted with DCM. The combined organic extracts were washed with 1 M aq. HCl and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (471 mg, 94%), which was carried forward without intermediate purification. ^{1}H NMR ($CDCl_3$): δ 1.51 (9H, s), 2.02 - 2.29 (2H, m), 2.37 (3H, s), 3.61 - 3.68 (1H, m), 3.69 - 3.78 (1H, m), 3.93 (3H, s), 4.05 - 4.20 (1H, m), 4.32 - 4.43 (1H, m), 5.78 - 5.87 (1H, m), 7.17 - 7.23 (1H, m), 7.82 - 7.87 (1H, m), 7.89 - 7.94 (1H, m); *m/z* (ES^+) $[M–tBu+2H]^+$= 274.1.

Intermediate 26d:

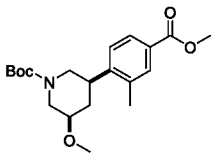
rac-tert-Butyl 3-methoxy-5-(4-(methoxycarbonyl)-2-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1886] A solution of Intermediate 26c (900 mg, 2.59 mmol) in THF (12.8 mL) and DMF (4.2 mL) was cooled to 0 °C. NaH (155 mg, 3.89 mmol) was added. The mixture was stirred at 0 °C for 30 min. MeI (243 µl, 3.89 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h. Upon completion, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with 10% LiCl and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) afforded the title compound, (519 mg, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.50 (9H, br s), 2.38 (3H, s), 3.48 (3H, s), 3.60 - 3.74 (1H, m), 3.93 (4H, s), 3.96 - 4.05 (2H, m), 4.06 - 4.19 (1H, m), 5.77 - 5.84 (1H, m), 7.19 - 7.25 (1H, m), 7.80 - 7.88 (1H, m), 7.89 - 7.94 (1H, m); *m/z* (ES^+) $[M–tBu–OMe+H]^+$ = 274.3.

Intermediate 26e:

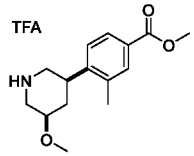
rac-tert-Butyl (3*R*,5*R*)-3-methoxy-5-(4-(methoxycarbonyl)-2-methylphenyl)piperidine-1-carboxylate



[1887] Intermediate 26d (644 mg, 1.78 mmol) in MeOH (8.9 mL) was placed under N_2 atmosphere. 5% $Pd(OH)_2$/C (50% w/w water) (250 mg, 0.18 mmol) and ammonium formate (562 mg, 8.91 mmol) were added. The reaction mixture was stirred for 30 minutes at r.t., filtered through a pad of celite and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) afforded the title compound, (367 mg, 57%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.49 (9H, s), 1.61 - 1.76 (1H, m), 2.25 - 2.35 (1H, m), 2.44 (3H, s), 2.49 - 2.62 (2H, m), 2.89 - 3.03 (1H, m), 3.30 - 3.40 (1H, m), 3.45 (3H, s), 3.92 (3H, s), 4.03 - 4.25 (1H, m), 4.30 - 4.66 (1H, m), 7.16 - 7.33 (1H, m), 7.87 (2H, s); *m/z* (ES^+) $[M–tBu+2H]^+$ = 308.3.

Intermediate 26f:

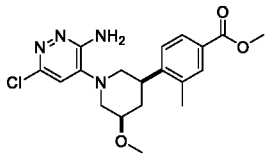
rac-tert-Butyl (*3R,5R*)-3-methoxy-5-(4-(methoxycarbonyl)-2-methylphenyl)piperidine-1-carboxylate



[1888] Prepared in an analogous method to Intermediate 1i starting from Intermediate 26e (811 mg, 2.23 mmol) to give the title compound (843 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil, which was carried forward without intermediate purification.

Intermediate 26g:

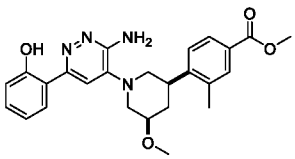
rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-chloropyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoate



[1889] Prepared in an analogous method to Intermediate 1d starting from Intermediate 26f (811 mg, 2.23 mmol) and 4-bromo-6-chloro-pyridazin-3-amine (465 mg, 2.23 mmol). Trituration with diethyl ether gave the title compound (351 mg,) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 - 1.57 (1H, m), 2.17 - 2.28 (1H, m), 2.43 (4H, s), 2.65 - 2.74 (1H, m), 3.25 - 3.32 (1H, m), 3.40 - 3.60 (4H, m), 3.66 - 3.77 (2H, m), 3.84 (3H, s), 6.15 - 6.40 (2H, m), 6.96 - 7.09 (1H, m), 7.41 - 7.51 (1H, m), 7.72 - 7.82 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 391.4.

Intermediate 26h:

rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoate

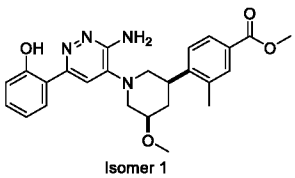


[1890] Prepared in an analogous method to Intermediate 1e starting from Intermediate 26g (350 mg, 0.90 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexane) gave the title compound (250 mg, 62%) as an yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.47 - 1.61 (1H, m), 2.21 - 2.33 (1H, m), 2.42 - 2.47 (3H, m), 2.53 (2H, br s), 2.72 - 2.82 (1H, m), 3.32 (3H, s), 3.42 - 3.49 (1H, m), 3.73 - 3.84 (2H, m), 3.85 (3H, s), 6.20 - 6.39 (2H, m), 6.81 - 6.97 (2H, m), 7.15 - 7.31 (1H, m), 7.42 - 7.53 (1H, m), 7.58 - 7.66 (1H, m), 7.72 - 7.86 (2H, m), 7.91 - 8.02 (1H, m), 13.72 - 14.47 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 449.7.

Intermediate 26i:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))



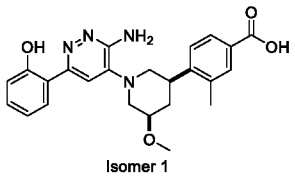
Isomer 1

[1891] Intermediate 26h (250 mg, 0.56 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak OJ 4.6 x 150 mm, 5 mm; mobile phase: 10 to 60% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 4.0 mL/min; BPR: 357 bar; Column temperature: 40°C to afford the title compound that eluted first from the column (56 mg, 22% yield, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 435.6.

Intermediate 26j:

4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))



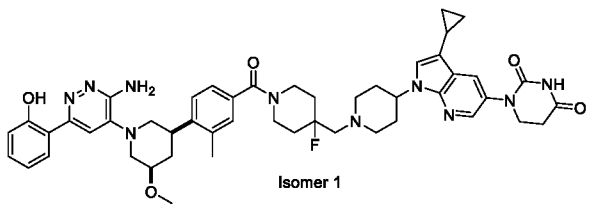
Isomer 1

[1892] Intermediate 26i (56 mg, 0.12 mmol) was stirred in a mixture of MeOH (2 mL) and 1 M aq. NaOH (2 mL, 2.00 mmol) at 50 °C for 1 h. Upon completion, the reaction mixture was partially concentrated under reduced pressure, acidified with 2 M aq. HCl (1.1 mL), centrifuged, and decanted to afford the title compound the title compound (54 mg, 99%) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 435.5.

EXAMPLE 26:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

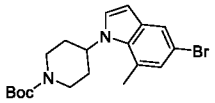
[1893] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (10 mg, 0.02 mmol) and Intermediate 20g (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.8 mg, 50%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.60 - 0.72 (2H, m), 0.85 - 0.92 (2H, m), 1.45 (3H, s), 1.51 - 1.61 (1H, m), 1.63 - 1.76 (1H, m), 1.78 - 1.84 (2H, m), 1.87 - 1.97 (2H, m), 1.99 - 2.18 (3H, m), 2.25 - 2.31 (1H, m), 2.32 - 2.38 (1H, m), 2.42 (3H, s), 2.52 - 2.54 (1H, m), 2.55 - 2.68 (2H, m), 2.75 - 2.79 (2H, m), 2.81 - 2.89 (1H, m), 3.01 - 3.21 (2H, m), 3.22

- 3.29 (1H, m), 3.38 (3H, s), 3.43 - 3.71 (4H, m), 3.73 - 3.79 (1H, m), 3.80 - 3.85 (2H, m), 3.86 - 3.97 (1H, m), 4.13 - 4.38 (1H, m), 4.47 - 4.74 (1H, m), 6.20 - 6.70 (1H, m), 6.83 - 7.01 (2H, m), 7.25 (3H, s), 7.37 - 7.51 (2H, m), 7.55 - 7.65 (1H, m), 7.83 - 8.03 (2H, m), 8.15 - 8.26 (1H, m), 10.35 - 10.48 (1H, m) (-OH not detected); *m/z* (ES^+) $[M+H]^+$ = 885.7.

EXAMPLE 27

Intermediate 27a:

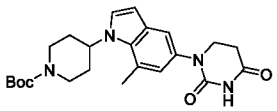
tert-Butyl 4-(5-bromo-7-methyl-indol-1-yl)piperidine-1-carboxylate



[1894] To a mixture of 5-bromo-7-methyl-1*H*-indole (800 mg, 3.81 mmol) in *tert*-amyl alcohol (20.0 mL) at 95°C were added *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (2.66 g, 9.52 mmol) and KO*t*-Bu (1.28 g, 11.4 mmol) in 5 equal potions every 0.5 h. After the final addition, the mixture was stirred at 95 °C for 3 h. After cooling to r.t., the mixture was diluted with MTBE (10 mL), saturated aq. NH_4Cl solution (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with MTBE (10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% DCM in heptane), followed by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (0.373 g, 25%) as a pale brown solid. ^1H NMR (DMSO-*d*6): δ 1.49 (9H, s), 1.74-1.95 (2H, m), 2.07 (2H, d), 2.69 (3H, s), 2.86 (2H, q), 4.32 (2H, s), 4.77 (1H, tt), 6.45 (1H, d), 6.98-7.06 (1H, m), 7.17 (1H, d), 7.58 (1H, d); *m/z* (ES^+) $[M-t\text{Bu}+2H]^+$ = 337.3.

Intermediate 27b:

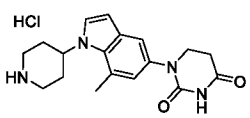
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-7-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1895] Prepared in an analogous method to Intermediate 1h starting from Intermediate 27a (1.05 g, 2.67 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in heptane) gave the title compound (0.550 g, 48%) as a pale yellow solid. ^1H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.83 (2H, qd), 1.97 (2H, s), 2.66-2.75 (5H, m), 2.96 (2H, s), 3.74 (2H, t), 4.11 (2H, d), 4.85 (1H, ddd), 6.45 (1H, d), 6.77-6.87 (1H, m), 7.28 (1H, d), 7.53 (1H, d), 10.23 (1H, s); *m/z* (ES^+) $[M-t\text{Bu}+2H]^+$ = 371.5.

Intermediate 27c:

1-(7-Methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

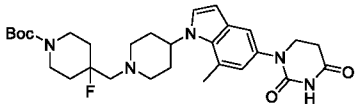


[1896] Intermediate 27b (30 mg, 0.07 mmol) in 1,4-dioxane (0.176 mL) was charged with 4 M HCl in 1,4-dioxane (0.35 mL, 1.4 mmol) and stirred at r.t. for 8 h. The reaction mixture was concentrated, dissolved

in a mixture of DCM and MeOH, treated with sat. aq. $NaHCO_3$, and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (23 mg, 100%) as a pale golden yellow film. *m/z* (ES^+) $[M+H]^+$ = 326.9.

Intermediate 27d:

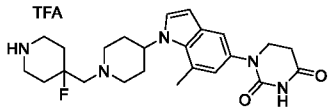
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-7-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1897] Prepared in an analogous method to Intermediate 6g starting from Intermediate 27c (0.026 g, 0.07 mmol) and Intermediate 6f (0.029 g, 0.08 mmol). Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (0.033 g, 84%) as a sticky golden yellow solid. ^1H NMR (DMSO-*d6*): δ 1.36-1.42 (9H, m), 1.56-1.67 (2H, m), 1.79-1.89 (2H, m), 1.89-2.04 (4H, m), 2.32-2.40 (2H, m), 2.61-2.71 (5H, m), 3.04 (2H, br d), 3.28 (2H, br s), 3.72-3.76 (2H, m), 4.65 (1H, br t), 6.45 (2H, br s), 6.82 (2H, br s), 7.21-7.31 (1H, m), 7.54 (2H, br s), 10.24 (2H, s); *m/z* (ES^+) $[M+H]^+$ = 542.3.

Intermediate 27e:

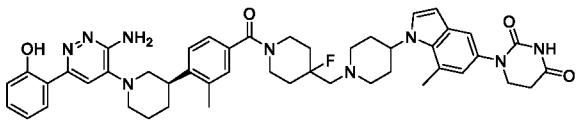
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1898] Prepared in an analogous method to Intermediate 1i starting from Intermediate 27d (73 mg, 0.14 mmol). Lyophilization gave the title compound (104 mg, 98%) as an pink solid. *m/z* (ES^+) $[M+H]^+$ = 442.4.

EXAMPLE 27:

(*R*)-1-(1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

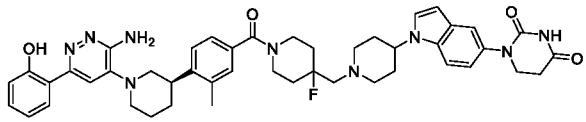


[1899] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 27e (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (9.1 mg, 45%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.61 - 1.79 (3H, m), 1.82 - 2.06 (9H, m), 2.33 - 2.39 (2H, m), 2.41 (3H, s), 2.43 - 2.48 (1H, m), 2.57 - 2.62 (1H, m), 2.63 - 2.66 (1H, m), 2.68 (5H, s), 2.73 - 2.77 (1H, m), 2.83 - 2.91 (1H, m), 3.00 - 3.08 (2H, m), 3.11 - 3.22 (1H, m), 3.24 - 3.29 (2H, m), 3.47 - 3.52 (1H, m), 3.57 - 3.62 (1H, m), 3.70 - 3.78 (2H, m), 4.08

- 4.38 (1H, m), 4.59 - 4.70 (1H, m), 6.21 - 6.35 (2H, m), 6.43 - 6.50 (1H, m), 6.79 - 6.84 (1H, m), 6.86 - 6.92 (2H, m), 7.20 - 7.27 (3H, m), 7.28 - 7.31 (1H, m), 7.38 - 7.45 (1H, m), 7.51 - 7.55 (1H, m), 7.55 - 7.58 (1H, m), 7.89 - 7.98 (1H, m), 10.18 - 10.29 (1H, m), 14.05 - 14.43 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 828.5.

EXAMPLE 28:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

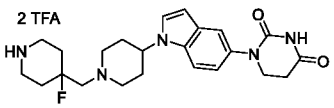


[1900] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (20 mg, 0.05 mmol) and Intermediate 2e (29.6 mg, 0.06 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (29.7 mg, 73%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 2.20 (13H, m), 2.41 (4H, s), 2.54 - 2.68 (1H, m), 2.73 (4H, s), 2.86 - 2.93 (1H, m), 3.02 - 3.23 (3H, m), 3.23 - 3.29 (2H, m), 3.53 (2H, br d), 3.60 - 3.67 (1H, m), 3.74 - 3.80 (2H, m), 4.17 - 4.51 (2H, m), 6.33 - 6.44 (2H, m), 6.44 - 6.50 (1H, m), 6.85 - 6.94 (2H, m), 7.05 - 7.13 (1H, m), 7.20 - 7.30 (3H, m), 7.36 - 7.43 (1H, m), 7.45 - 7.49 (1H, m), 7.51 - 7.59 (3H, m), 7.85 - 7.93 (1H, m), 10.19 - 10.30 (1H, m), 13.00 - 14.44 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 814.5.

EXAMPLE 29

Intermediate 29a:

1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

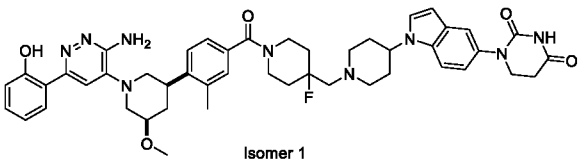


[1901] Prepared in an analogous method to Intermediate 1i starting from Intermediate 2d (2.0 g, 3.79 mmol). Trituration with Et_2O gave the title compound (2.4 g, 97%) in the form of a *bis*(trifluoroacetate) salt as a white solid.^{1}H NMR (DMSO-*d*6): δ 1.89 - 2.03 (3H, m), 2.09 - 2.27 (4H, m), 2.30 - 2.46 (2H, m), 2.68 - 2.76 (2H, m), 3.01 - 3.13 (2H, m), 3.20 - 3.40 (4H, m), 3.43 - 3.74 (4H, m), 3.74 - 3.79 (2H, m), 6.49 - 6.55 (1H, m), 7.08 - 7.15 (1H, m), 7.37 - 7.44 (1H, m), 7.45 - 7.52 (1H, m), 7.58 (1H, d), 8.72 (1H, br s), 8.87 (1H, br s), 10.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 428.3.

EXAMPLE 29:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



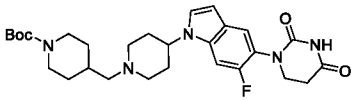
Isomer 1

[1902] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (20 mg, 0.02 mmol) and Intermediate 29a (20 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (8.8 mg, 44%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.48 - 1.60 (1H, m), 1.63 - 1.79 (2H, m), 1.81 - 1.93 (3H, m), 1.95 - 2.05 (3H, m), 2.24 - 2.32 (1H, m), 2.42 (5H, s), 2.46 - 2.49 (1H, m), 2.53 - 2.58 (1H, m), 2.59 - 2.68 (2H, m), 2.70 - 2.74 (2H, m), 2.76 - 2.82 (1H, m), 3.00 - 3.07 (2H, m), 3.09 - 3.17 (1H, m), 3.20 - 3.30 (1H, m), 3.38 (3H, s), 3.42 - 3.47 (1H, m), 3.49 - 3.59 (1H, m), 3.77 (3H, s), 3.82 - 3.89 (1H, m), 4.20 - 4.29 (1H, m), 4.30 - 4.39 (1H, m), 6.32 - 6.40 (2H, m), 6.43 - 6.49 (1H, m), 6.84 - 6.94 (2H, m), 7.02 - 7.11 (1H, m), 7.25 (3H, s), 7.40 - 7.47 (2H, m), 7.55 (2H, s), 7.58 - 7.64 (1H, m), 7.90 - 8.01 (1H, m), 10.28 (1H, s), 13.70 - 14.40 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 844.6.

EXAMPLE 30

Intermediate 30a:

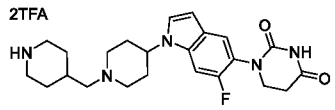
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluoro-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1903] A solution of Intermediate 5e (250 mg, 0.76 mmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (242 mg, 1.14 mmol), NaOAc (310 mg, 3.78 mmol) and THF (7.5 mL) was stirred at 60 °C for 16 h. After cooling to r.t., $NaBH(OAc)_3$ (481 mg, 2.27 mmol) was added. Upon completion, the reaction mixture was quenched with water and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (131 mg, 33%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.89 - 1.07 (2H, m), 1.40 (9H, s), 1.62 - 1.77 (3H, m), 1.84 - 2.02 (5H, m), 2.08 - 2.26 (4H, m), 2.74 (3H, s), 2.91 - 3.06 (2H, m), 3.64 - 3.76 (2H, m), 3.88 - 4.06 (2H, m), 4.26 - 4.43 (1H, m), 6.43 - 6.56 (1H, m), 7.46 - 7.64 (3H, m), 10.31 - 10.47 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 528.3.

Intermediate 30b:

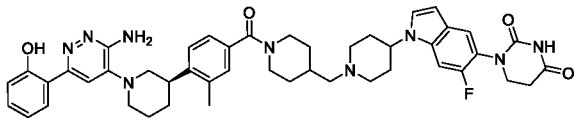
1-(6-Fluoro-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1904] Prepared in an analogous method to Intermediate 1i starting from Intermediate 30a (131 mg, 0.25 mmol) to give the title compound (155 mg, 96%) in the form of a *bis*(trifluoroacetic acid) salt as an pink solid; *m/z* (ES^+) $[M+H]^+$ = 428.3.

EXAMPLE 30:

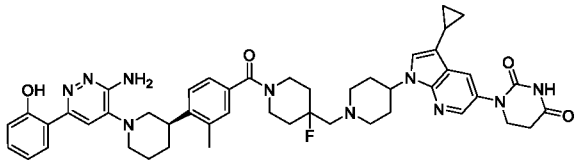
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1905] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 30b (19.5 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (8.8 mg, 44%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.01 - 1.19 (2H, m), 1.58 - 1.77 (2H, m), 1.81 - 2.08 (9H, m), 2.21 - 2.37 (2H, m), 2.40 (3H, s), 2.55 - 2.65 (1H, m), 2.70 - 2.76 (3H, m), 2.82 - 2.88 (1H, m), 3.00 - 3.15 (3H, m), 3.17 - 3.26 (4H, m), 3.47 - 3.50 (1H, m), 3.56 - 3.61 (1H, m), 3.68 - 3.75 (2H, m), 4.32 - 4.57 (2H, m), 6.20 - 6.32 (2H, m), 6.47 - 6.54 (1H, m), 6.83 - 6.91 (2H, m), 7.16 - 7.21 (2H, m), 7.21 - 7.28 (1H, m), 7.35 - 7.42 (1H, m), 7.51 - 7.62 (4H, m), 7.90 - 7.98 (1H, m), 10.36 - 10.41 (1H, m), 13.49 - 15.05 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 814.5.

EXAMPLE 31:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

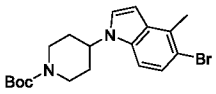


[1906] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (15 mg, 0.04 mmol) and Intermediate 20g (31 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (17.8 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.82 - 0.92 (2H, m), 1.20 - 1.33 (2H, m), 1.61 - 2.20 (13H, m), 2.41 (4H, s), 2.77 (4H, s), 2.84 - 2.97 (2H, m), 2.98 - 3.21 (3H, m), 3.22 - 3.28 (2H, m), 3.49 - 3.69 (3H, m), 3.78 - 3.88 (2H, m), 3.98 - 4.39 (1H, m), 4.48 - 4.98 (1H, m), 6.20 - 6.65 (2H, m), 6.85 - 6.96 (2H, m), 7.21 - 7.30 (3H, m), 7.34 - 7.46 (2H, m), 7.52 - 7.59 (1H, m), 7.81 - 7.91 (1H, m), 7.94 - 7.99 (1H, m), 8.16 - 8.21 (1H, m), 10.31 - 10.49 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 855.4.

EXAMPLE 32

Intermediate 32a:

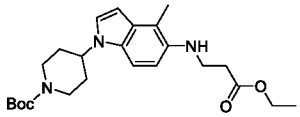
tert-Butyl 4-(5-bromo-4-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1907] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-4-methyl-1*H*-indole (2.00 g, 9.52 mmol). Purification by FSC (elution gradient: 0 to 25% EtOAc in hexanes) gave the title compound (1.69 g, 45%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.76 - 1.87 (2H, m), 1.89 - 1.95 (2H, m), 2.50 (3H, s), 2.84 - 3.10 (2H, m), 4.08 - 4.18 (2H, m), 4.50 - 4.61 (1H, m), 6.51 - 6.58 (1H, m), 7.25 - 7.31 (1H, m), 7.36 - 7.41 (1H, m), 7.52 - 7.57 (1H, m); *m/z* (ES$^+$) $[M–Boc+2H]^+$ = 293.0.

Intermediate 32b:

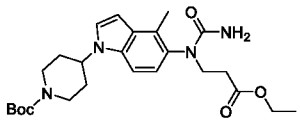
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1908] A solution of Intermediate 32a (1.69 g, 4.30 mmol), ethyl 3-aminopropanoate HCl (0.852 g, 5.59 mmol), $Pd_2(dba)_3$ (0.197 g, 0.21 mmol), CPhos (0.225 g, 0.52 mmol), Cs_2CO_3 (4.62 g, 14.18 mmol) and 1,4-dioxane (28.6 ml) was heated to 100 °C for 16 hours. Upon completion, the reaction mixture was cooled to r.t., filtered through a pad of Celite with, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.60 g, 87%) as an orange oil. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.72 - 1.83 (2H, m), 1.87 - 1.96 (2H, m), 2.21 (3H, s), 2.59 (2H, s), 2.87 - 3.07 (2H, m), 3.35 (2H, br d), 4.05 - 4.18 (4H, m), 4.22 - 4.30 (1H, m), 4.34 - 4.46 (1H, m), 6.23 - 6.35 (1H, m), 6.60 - 6.69 (1H, m), 7.17 - 7.26 (1H, m), 7.29 - 7.37 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 430.4.

Intermediate 32c:

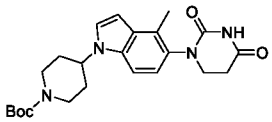
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[1909] Prepared in an analogous method to Intermediate 3c starting from Intermediate 32b (1.60 g, 3.72 mmol) to give title compound (1.43 g, 81%) as a white foam, which was carried forward without additional purification. *m/z* (ES$^+$) $[M+H]^+$ = 473.4.

Intermediate 32d:

tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate

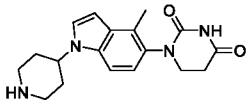


[1910] Prepared in an analogous method to Intermediate 3d starting from Intermediate 32c (1.43 mg, 3.03 mmol). Filtration of the precipitate (washing with EtOH) gave the title compound (986 mg, 76%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.76 - 1.88 (2H, m), 1.89 - 1.97 (2H, m), 2.29 (3H, s),

2.53 - 2.67 (2H, m), 2.86 - 3.10 (2H, m), 3.40 - 3.48 (1H, m), 3.58 - 3.68 (1H, m), 4.07 - 4.19 (2H, m), 4.50 - 4.61 (1H, m), 6.44 - 6.52 (1H, m), 6.92 - 7.00 (1H, m), 7.37 (1H, s), 7.51 (1H, d), 10.16 - 10.31 (1H, m); *m/z* (ES^+) $[M–tBu+2H]^+$ = 371.2.

Intermediate 32e:

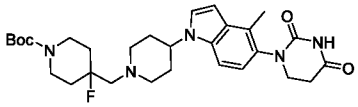
1-(4-Methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1911] Prepared in an analogous method to Intermediate 6e starting from Intermediate 32d (962 mg, 2.26 mmol). Upon completion, the reaction mixture was cooled to r.t and concentrated under reduced pressure. The crude product as suspended in 3:1 $CHCl_3$/IPA, washed with sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (531 mg, 72%) as a brown solid. *m/z* (ES^+) $[M+H]^+$ = 327.2.

Intermediate 32f:

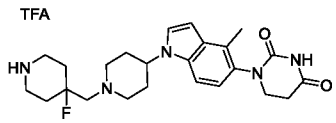
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1912] Prepared in an analogous method to Intermediate 6g starting from Intermediate 32e (200 mg, 0.61 mmol) and Intermediate 6f (403 mg, 1.10 mmol) Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (192 mg, 58%) as a yellow foam. ^1H NMR (DMSO-*d6*): δ 1.38 - 1.46 (9H, m), 1.53 - 1.71 (2H, m), 1.80 - 1.92 (4H, m), 1.94 - 2.06 (2H, m), 2.29 - 2.35 (3H, m), 2.36 - 2.45 (2H, m), 2.57 - 2.60 (1H, m), 2.61 - 2.67 (1H, m), 2.67 - 2.83 (2H, m), 3.00 - 3.07 (3H, m), 3.40 - 3.49 (1H, m), 3.50 - 3.59 (1H, m), 3.68 - 3.81 (3H, m), 4.27 - 4.33 (1H, m), 6.47 - 6.59 (1H, m), 6.96 - 7.05 (1H, m), 7.31 - 7.42 (1H, m), 7.48 - 7.58 (1H, m), 10.04 - 10.29 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 542.3.

Intermediate 32g:

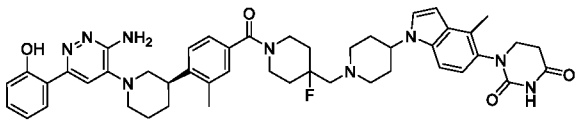
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1913] Prepared in an analogous method to Intermediate 1i starting from Intermediate 32f (192 mg, 0.35 mmol) to give the title compound (315 mg, 100%) in the form of a *tetra*(trifluoroacetic acid) salt as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 442.3.

EXAMPLE 32:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

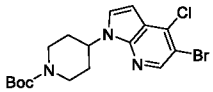


[1914] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 32g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (14 mg, 67%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.82 (2H, m), 1.83 - 2.10 (7H, m), 2.29 - 2.33 (2H, m), 2.34 - 2.38 (1H, m), 2.39 - 2.44 (4H, m), 2.54 - 2.56 (5H, m), 2.62 - 2.68 (3H, m), 2.68 - 2.82 (4H, m), 2.84 - 2.91 (1H, m), 3.00 - 3.08 (2H, m), 3.46 - 3.64 (4H, m), 3.71 - 3.79 (1H, m), 4.21 - 4.40 (2H, m), 6.22 - 6.32 (2H, m), 6.49 - 6.55 (1H, m), 6.83 - 6.91 (2H, m), 6.98 - 7.04 (1H, m), 7.20 - 7.27 (3H, m), 7.36 - 7.43 (2H, m), 7.50 - 7.55 (1H, m), 7.55 - 7.59 (1H, m), 7.89 - 7.97 (1H, m), 10.19 - 10.25 (1H, m), 14.13 - 14.39 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 828.6.

EXAMPLE 33

Intermediate 33a:

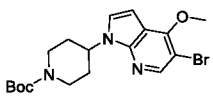
tert-Butyl 4-(5-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1915] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (3.0 g, 12.96 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (3.61g, 67%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.47 - 1.50 (1H, m), 1.52 (9H, s), 1.84 - 2.00 (2H, m), 2.08 - 2.17 (1H, m), 2.77 - 3.06 (2H, m), 4.21 - 4.46 (2H, m), 4.82 - 4.99 (1H, m), 6.49 - 6.66 (1H, m), 7.31 - 7.37 (1H, m), 8.31 - 8.46 (1H, m); *m/z* (ES$^+$) $[M–Boc+2H]^+$ = 358.0.

Intermediate 33b:

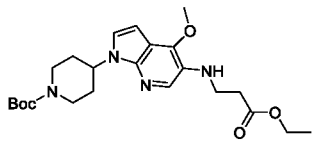
tert-Butyl 4-(5-bromo-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1916] Intermediate 33a (100 mg, 0.24 mmol) in MeOH (4.27 mL) was charged with sodium methoxide (25 wt% in MeOH, 548 µl, 2.41 mmol) and stirred at 80 °C for 24 h. After cooling to r.t., the reaction mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (35 mg, 35%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.52 (9H, s), 1.81 - 1.97 (2H, m), 2.02 - 2.21 (2H, m), 2.93 - 3.12 (2H, m), 4.23 - 4.39 (2H, m), 4.40 (3H, s), 4.87 - 5.10 (1H, m), 6.68 - 6.80 (1H, m), 7.15 - 7.23 (1H, m), 8.23 - 8.35 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 410.1.

Intermediate 33c:

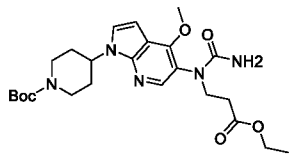
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1917] Prepared in an analogous method to Intermediate 3b starting from Intermediate 33b (1.25 g, 3.04 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.20 g, 88%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 1.17 - 1.20 (3H, m), 1.44 (9H, s), 1.85 - 1.91 (4H, m), 2.57 - 2.62 (2H, m), 2.84 - 3.01 (2H, m), 3.33 - 3.39 (2H, m), 4.04 - 4.11 (3H, m), 4.11 - 4.14 (1H, m), 4.15 - 4.18 (3H, m), 4.33 - 4.40 (1H, m), 4.68 - 4.83 (1H, m), 6.57 - 6.61 (1H, m), 7.44 - 7.49 (1H, m), 7.72 - 7.78 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 447.5.

Intermediate 33d:

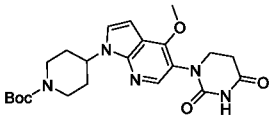
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1918] Prepared in an analogous method to Intermediate 3c starting from Intermediate 33c (1.23 g, 2.75 mmol) to give the title compound (1.35 g, 100%) as a brown foam, which was carried forward without intermediate purification. *m/z* (ES$^+$) $[M+H]^+$ = 490.6.

Intermediate 33e:

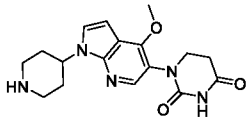
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1919] Prepared in an analogous method to Intermediate 3d starting from Intermediate 33d (1.35 g, 2.76 mmol) to give the title compound (763 mg, 62%) as an tan solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.90 (4H, br s), 2.33 - 2.47 (2H, m), 2.82 - 3.10 (2H, m), 3.36 - 3.56 (2H, m), 4.04 - 4.16 (2H, m), 4.18 (3H, s), 4.78 - 4.90 (1H, m), 6.72 - 6.85 (1H, m), 7.54 - 7.65 (1H, m), 7.88 - 7.97 (1H, m), 10.23 - 10.41 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 444.3.

Intermediate 33f:

1-(4-Methoxy-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

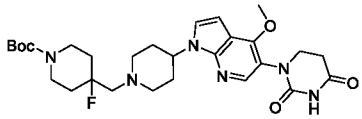


[1920] Prepared in an analogous method to Intermediate 1i starting from Intermediate 33e (250 mg, 0.56 mmol). Water, 3:1 $CHCl_3$/IPA and $NaHCO_3$ (237 mg, 2.82 mmol) were added and the mixture was

stirred vigorously. The layers were separated and the aqueous layer was extracted with 3:1 $CHCl_3$/IPA (3x). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (158 mg, 82%) as an tan solid. *m/z* (ES^+) $[M+H]^+$ = 344.2.

Intermediate 33g:

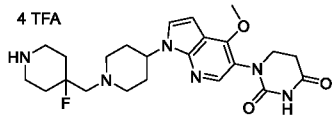
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1921] Prepared in an analogous method to Intermediate 6g starting from Intermediate 33f (100 mg, 0.29 mmol) and Intermediate 6f (192 mg, 0.52 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (79 mg, 49%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.52 - 1.70 (2H, m), 1.80 - 1.90 (4H, m), 2.01 - 2.12 (2H, m), 2.32 - 2.40 (2H, m), 2.55 - 2.58 (1H, m), 2.60 - 2.63 (1H, m), 2.66 - 2.83 (2H, m), 3.01 - 3.08 (3H, m), 3.53 - 3.68 (2H, m), 3.69 - 3.81 (2H, m), 3.96 - 4.08 (1H, m), 4.19 - 4.32 (3H, m), 4.56 - 4.75 (1H, m), 6.78 - 6.95 (1H, m), 7.51 - 7.72 (1H, m), 7.93 - 8.09 (1H, m), 10.24 - 10.38 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 559.7.

Intermediate 33h:

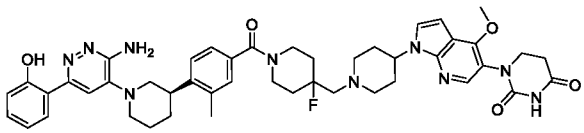
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1922] Prepared in an analogous method to Intermediate 1i starting from Intermediate 33g (75 mg, 0.13 mmol). Trituration with Et_2O gave the title compound (122 mg, 99%) in the form of a *tetra*(trifluoroacetic) acid as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 459.3.

EXAMPLE 33:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



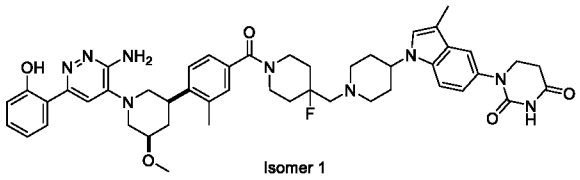
[1923] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 33h (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (11.9 mg, 56%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.60 - 1.80 (3H, m), 1.82 - 2.15 (9H, m), 2.31 - 2.38 (1H, m), 2.41 (3H, s), 2.58 - 2.70 (3H, m), 2.70 - 2.80 (2H, m), 2.84 - 2.94 (1H, m), 3.00 - 3.22 (3H, m), 3.23 - 3.28 (1H, m), 3.35 - 3.40 (1H, m), 3.45 - 3.54 (2H,

m), 3.55 - 3.72 (4H, m), 4.15 - 4.32 (4H, m), 4.58 - 4.75 (1H, m), 6.17 - 6.46 (2H, m), 6.90 (3H, br d), 7.24 (3H, br s), 7.39 - 7.47 (1H, m), 7.53 - 7.59 (1H, m), 7.60 - 7.69 (1H, m), 7.84 - 7.96 (1H, m), 8.02 (1H, s), 10.33 (1H, s), 14.08 - 14.46 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 34:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione) (Isomer 1)

((*absolute configuration not yet confirmed))

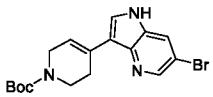


[1924] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (10 mg, 0.02 mmol) and Intermediate 1k (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (16.4 mg, 81%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.47 - 1.59 (1H, m), 1.63 - 1.79 (2H, m), 1.83 - 1.89 (3H, m), 1.90 - 2.03 (3H, m), 2.23 (3H, s), 2.26 - 2.32 (1H, m), 2.36 - 2.41 (2H, m), 2.42 (3H, s), 2.45 - 2.48 (1H, m), 2.58 - 2.67 (2H, m), 2.70 - 2.74 (2H, m), 2.77 - 2.83 (1H, m), 3.00 - 3.07 (2H, m), 3.08 - 3.20 (1H, m), 3.22 - 3.28 (1H, m), 3.29 - 3.32 (1H, m), 3.38 (3H, s), 3.42 - 3.47 (1H, m), 3.49 - 3.60 (1H, m), 3.72 - 3.79 (3H, m), 3.81 - 3.90 (1H, m), 4.22 - 4.34 (2H, m), 6.27 - 6.43 (2H, m), 6.84 - 6.94 (2H, m), 7.03 - 7.10 (1H, m), 7.21 - 7.27 (3H, m), 7.31 - 7.34 (1H, m), 7.38 - 7.40 (1H, m), 7.41 - 7.44 (1H, m), 7.44 - 7.51 (1H, m), 7.56 - 7.63 (1H, m), 7.90 - 8.01 (1H, m), 10.09 - 10.51 (1H, m), 13.97 - 14.52 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 858.7.

EXAMPLE 35

Intermediate 35a:

tert-Butyl 4-(6-bromo-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate

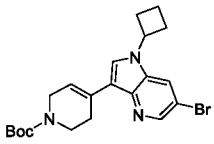


[1925] A mixture of potassium hydroxide (3.20 g, 57.10 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (11.38 g, 57.10 mmol), and 6-bromo-1*H*-pyrrolo[3,2-*b*]pyridine (7.5 g, 38.06 mmol) in methanol (100 mL) was warmed to 60 °C for 21.5 h. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was diluted with sat. aq. NH_4Cl (200 mL) and ethyl acetate (100 mL). The layers were separated. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting orange solid was triturated with EtOAc and dried *in vacuo* to give the title compound (7.44 g, 51%) as an off white solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 2.46 - 2.51 (2H, m), 3.57 (2H, br

t), 4.04 (2H, br s), 7.06 (1H, br s), 7.69 (1H, s), 8.01 (1H, d), 8.43 (1H, d), 11.46 (1H, br s). *m/z* (ES^+) $[M+H]^+$ = 380.1.

Intermediate 35b:

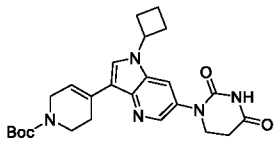
tert-Butyl 4-(6-bromo-1-cyclobutyl-pyrrolo[3,2-*b*]pyridin-3-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate



[1926] Bromocyclobutane (1.021 mL, 10.82 mmol) was added to a mixture of cesium carbonate (4.70 g, 14.42 mmol) and Intermediate 35a (2.728 g, 7.21 mmol) in DMF (36 ml) at r.t. The mixture was warmed to 100 °C with stirring. After 3h, the mixture was cooled to r.t and quenched with water (200 mL). A yellow precipitate formed which was collected by filtration and washed with water (3 x 60 mL). The crude solid was taken up in EtOAc. The mixture was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.913 g, 61%) as a yellow solid. ^1H NMR (DMSO-*d6*): δ 1.42 (9H, s), 1.74 - 1.88 (2H, m), 2.41 - 2.47 (4H, m), 2.54 (2H, br s), 3.55 (2H, br t), 4.03 (2H, br s), 5.01 (1H, quin), 7.03 (1H, br s), 7.94 (1H, s), 8.24 (1H, d), 8.42 (1H, d); *m/z* (ES^+) $[M+Na]^+$ = 456.1.

Intermediate 35c:

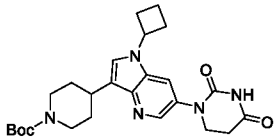
tert-Butyl 4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1927] A vial was charged with Intermediate 35b (1.913 g, 4.43 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.010 g, 8.85 mmol), *t*-BuBrettPhos Pd G3 (0.378 g, 0.44 mmol), K_3PO_4 (1.879 g, 8.85 mmol), and 1,4-dioxane (20 mL). The reaction was degassed and stirred at 100 °C for 17 h. The reaction was cooled to r.t., filtered through celite with DCM and concentrate under reduced pressure. Purification by FSC (elution gradient: 20 to 100% EtOAc in hexanes, then 0 to 20% MeOH in EtOAc) gave the title compound (1.376 g, 67%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.44 (9H, s), 1.76 - 1.89 (2H, m), 2.42 - 2.50 (4H, m), 2.54 - 2.60 (2H, m), 2.78 (2H, t), 3.58 (2H, br t), 3.86 (2H, t), 4.04 - 4.08 (2H, m), 4.97 (1H, quin), 7.10 (1H, br s), 7.94 (2H, s), 8.37 (1H, d), 10.44 (1H, s; *m/z* (ES^+) $[M+H]^+$ = 466.3.

Intermediate 35d:

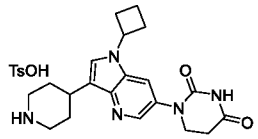
tert-Butyl 4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-yl)piperidine-1-carboxylate



[1928] Dichloromethane (15 mL) and methanol (3 mL) were added to a mixture of Intermediate 35c (1376 mg, 2.96 mmol) and platinum(IV) oxide (67.1 mg, 0.30 mmol) under a nitrogen atmosphere. The mixture was sparged with hydrogen for ten minutes. The mixture was stirred under an atmosphere of hydrogen at r.t. Upon completion, the mixture was purged with nitrogen and filtered through celite with methanol. The filtrate was concentrated under reduced pressure. The remaining solid was triturated with EtOAc and dried *in vacuo* to give the title compound (965 mg, 69%) as a grey solid. ^{1}H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.59 - 1.70 (2H, m), 1.75 - 1.86 (2H, m), 1.95 - 2.01 (2H, m), 2.37 - 2.47 (4H, m), 2.72 - 2.78 (2H, m), 2.78 - 2.98 (2H, m), 3.07 (1H, br t), 3.81 (2H, t), 3.96 - 4.13 (2H, m), 4.91 (1H, quin), 7.72 (1H, s), 7.84 - 7.88 (1H, m), 8.24 - 8.28 (1H, m), 10.40 (1H, s) ; *m/z* (ES$^+$) [M+H]$^+$ = 468.5.

Intermediate 35e:

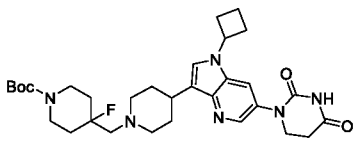
1-(1-Cyclobutyl-3-(piperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1929] A mixture of Intermediate 35d (965 mg, 2.06 mmol) and *p*-toluenesulfonic acid monohydrate (471 mg, 2.48 mmol) in acetonitrile (16 mL) was stirred at 70 °C for 18 hours. After cooling to r.t., the suspension was concentrated under reduced pressure to half of the initial volume. Trituration with Et_2O gave the title compound (1290 mg, 88%) as a grey solid in the form of a *p*-toluenesulfonic acid salt. ^{1}H NMR (DMSO-*d*6): δ 1.75 – 1.96 (5H, m), 2.18 (2H, br d), 2.50 – 2.57 (2H, m), 2.79 (2H, t), 2.98 – 3.11 (2H, m), 3.23 (1H, br t), 3.39 – 3.48 (2H, m), 3.89 (2H, t), 5.05 – 5.17 (2H, m), 8.14 (1H, br s), 8.33 (1H, br d), 8.53 – 8.65 (2H, m), 10.59 (1H, s); *m/z* (ES$^+$) [M+H]$^+$ = 368.2.

Intermediate 35f:

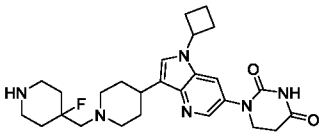
tert-Butyl 4-((4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[1930] A mixture of Intermediate 35e (300 mg, 0.42 mmol), Intermediate 6f (231 mg, 0.63 mmol), 1,4-dioxane (3 mL) and DIPEA (0.368 mL, 2.11 mmol) stirred at 85 °C for 20 h. Reaction was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (37.7 mg, 15%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.47 (9H, s), 1.54 - 1.71 (2H, m), 1.76 - 1.99 (6H, m), 2.09 (2H, br d), 2.38 - 2.64 (8H, m), 2.89 (2H, br t), 2.98 - 3.18 (5H, m), 3.80 - 3.98 (4H, m), 4.77 (1H, quin), 7.33 (1H, s), 7.58 (1H, d), 7.67 - 7.86 (1H, m), 8.35 (1H, d); *m/z* (ES$^+$) [M+H]$^+$ = 583.3.

Intermediate 35g:

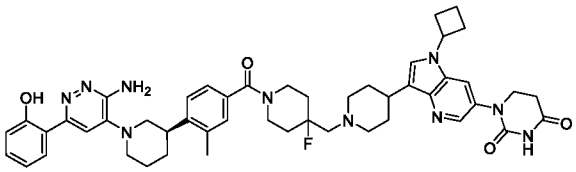
1-(1-Cyclobutyl-3-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1931] Intermediate 35f (420 mg, 0.72 mmol) was dissolved in DCM (5 mL) and TFA (1 mL). The reaction was stirred at r.t. for 2h. The reaction was concentrated under reduced pressure. The resulting residue was taken up in water, neutralized with sat. aq. $NaHCO_3$, extracted with $CHCl_3$–IPA (3:1, 3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solid was suspended in MeCN/H_2O and dried on the gave the title compound (347 mg, 100%) as a brown sticky residue.^{1}H NMR (DMSO-*d*6): δ 1.72 - 2.05 (5H, m), 2.24 (6H, br s), 2.79 (2H, t), 3.01 - 3.42 (10H, m), 3.55 - 3.72 (5H, m), 3.86 (2H, t), 5.01 (1H, quin), 7.85 (1H, s), 8.09 (1H, br s), 8.20 - 8.32 (1H, m), 8.39 (1H, br s), 8.63 (1H, br d), 8.73 - 8.84 (1H, m), 10.48 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 483.3.

EXAMPLE 35:

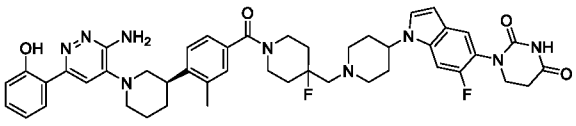
(*R*)-1-(3-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1932] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 35g (28 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (10.6 mg, 49%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.78 (3H, m), 1.78 - 1.90 (6H, m), 1.91 - 2.05 (5H, m), 2.24 - 2.32 (2H, m), 2.41 (3H, s), 2.41 - 2.47 (4H, m), 2.54 - 2.58 (1H, m), 2.58 - 2.62 (1H, m), 2.68 - 2.73 (1H, m), 2.74 - 2.79 (2H, m), 2.82 - 2.91 (2H, m), 2.96 - 3.04 (2H, m), 3.06 - 3.20 (1H, m), 3.22 - 3.29 (2H, m), 3.42 - 3.64 (3H, m), 3.78 - 3.86 (2H, m), 4.10 - 4.37 (1H, m), 4.81 - 4.99 (1H, m), 6.21 - 6.31 (2H, m), 6.82 - 6.93 (2H, m), 7.18 - 7.28 (3H, m), 7.35 - 7.44 (1H, m), 7.51 - 7.59 (1H, m), 7.65 - 7.73 (1H, m), 7.81 - 7.88 (1H, m), 7.89 - 8.00 (1H, m), 8.21 - 8.30 (1H, m), 10.36 - 10.43 (1H, m), 14.05 - 14.33 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 869.5.

EXAMPLE 36:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

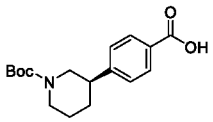


[1933] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 5g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.8 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.80 (3H, m), 1.81 - 1.91 (4H, m), 1.92 - 2.04 (5H, m), 2.35 - 2.39 (1H, m), 2.41 (3H, s), 2.42 - 2.45 (1H, m), 2.59 - 2.63 (1H, m), 2.63 - 2.68 (1H, m), 2.69 - 2.77 (3H, m), 2.83 - 2.92 (1H, m), 3.00 - 3.07 (2H, m), 3.09 - 3.21 (1H, m), 3.23 - 3.29 (2H, m), 3.43 - 3.64 (3H, m), 3.67 - 3.74 (2H, m), 4.13 - 4.27 (1H, m), 4.29 - 4.39 (1H, m), 6.19 - 6.36 (2H, m), 6.43 - 6.53 (1H, m), 6.79 - 6.93 (2H, m), 7.24 (3H, s), 7.34 - 7.45 (1H, m), 7.56 (4H, s), 7.87 - 7.97 (1H, m), 10.31 - 10.45 (1H, m) (-OH not observed); *m/z* (ES$^+$) $[M+H]^+$ = 832.5.

EXAMPLE 37

Intermediate 37a:

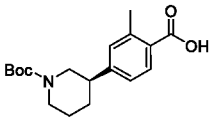
4-(1-(*tert*-Butoxycarbonyl)piperidin-3-yl)benzoic acid



[1934] A solution of (*R*)-4-(piperidin-3-yl)benzoic acid, HCl salt (1.0 g, 4.15 mmol), DCM (18.54 ml) and Et_3N (1.216 ml, 8.72 mmol) was charged with Boc_2O (1.013 ml, 4.36 mmol) and stirred at r.t. for 3 days. Upon completion, the reaction mixture was quenched with N,N-ethylenediamine (0.52 mL) and washed with 10% citric acid. The aqueous layer was extracted with DCM, and the organic extracts were dried with Na_2SO_4, filtered, and concentrated to afford the title compound (1.25 g, 99%). ^{1}H NMR (DMSO-*d*6): δ 1.41 (11H, s), 1.63 - 1.76 (2H, m), 1.85 - 1.95 (1H, m), 2.58 - 2.76 (2H, m), 3.86 - 4.09 (2H, m), 7.39 - 7.44 (2H, m), 7.86 - 7.93 (2H, m) (-OH not observed) ; *m/z* (ES$^+$) $[M–Boc+2H]^+$ = 206.1.

Intermediate 37b:

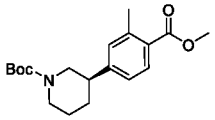
4-(1-(*tert*-Butoxycarbonyl)piperidin-3-yl)-2-methylbenzoic acid



[1935] A solution of TMEDA (0.332 mL, 2.20 mmol) and THF (2.2 mL) was cooled to –90°C and treated with 1.4M *sec*-BuLi in cyclohexane (1.570 mL, 2.20 mmol) and Intermediate 37a (305 mg, 1.00 mmol) in THF (1.0 mL). The reaction was stirred at –90 °C for one hour, then warmed to –78 °C and charged with MeI (0.187 mL, 3.00 mmol). The reaction was stirred for 1h then quenched with water and warmed to r.t. The reaction was extracted with ether then the aqueous layer was acidified with HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were then washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 80% EtOAc in Hexanes) gave the title compound (44 mg, 14%), as a white solid. *m/z* (ES$^-$) $[M–H]^-$ = 318.3.

Intermediate 37c:

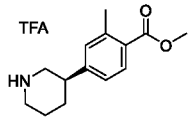
tert-Butyl 3-(4-(methoxycarbonyl)-3-methylphenyl)piperidine-1-carboxylate



[1936] Intermediate 37b (118 mg, 0.37 mmol) in DMF (1339 µl) was charged with K_2CO_3 (306 mg, 2.22 mmol) and MeI (139 µl, 2.22 mmol) then stirred at r.t. for 16h. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were then washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 14% EtOAc in hexanes) gave the title compound, (105 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.49 (9H, s), 1.56 - 1.71 (2H, m), 1.74 - 1.82 (1H, m), 1.99 - 2.05 (1H, m), 2.57 - 2.64 (3H, m), 2.66 - 2.93 (3H, m), 3.87 - 3.92 (3H, m), 4.09 - 4.37 (2H, m), 7.08 - 7.16 (2H, m), 7.86 - 7.92 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 233.9.

Intermediate 37d:

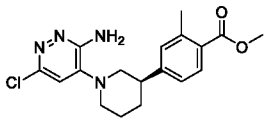
Methyl (*R*)-2-methyl-4-(piperidin-3-yl)benzoate



[1937] Prepared in an analogous method to Intermediate 1i starting from Intermediate 37c (100 mg, 0.30 mmol) to give the title compound (105 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil, which was carried forward without further purification. *m/z* (ES^+) $[M+H]^+$ = 234.4.

Intermediate 37e:

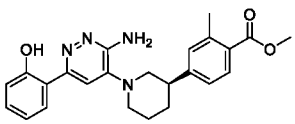
Methyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2-methylbenzoate



[1938] Prepared in an analogous method to Intermediate 1d starting from Intermediate 37d (105 mg, 0.30 mmol) and 4-bromo-6-chloropyridazin-3-amine (62.5 mg, 0.30 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (55 mg, 51%) as a light yellow solid. ^{1}H NMR (DMSO-*d6*): δ 1.50 - 1.69 (1H, m), 1.78 - 1.89 (2H, m), 1.89 - 1.97 (1H, m), 2.51 - 2.51 (3H, m), 2.61 - 2.70 (2H, m), 2.99 - 3.11 (1H, m), 3.39 - 3.49 (2H, m), 3.81 (3H, s), 6.00 - 6.21 (2H, m), 6.88 - 7.02 (1H, m), 7.21 - 7.33 (2H, m), 7.70 - 7.83 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 361.7.

Intermediate 37f:

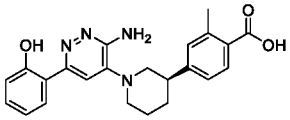
Methyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoate



[1939] Prepared in an analogous method to Intermediate 1e starting from Intermediate 37e (55 mg, 0.15 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (54 mg, 85%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.75–(1H, m), 1.78 - 1.94 (2H, m), 2.52–(3H, s), 2.65 - 2.72–(1H, m), 2.73 - 2.82–(1H, m), 3.06 - 3.17 (1H, m), 3.44 (1H– br dd), 3.49 - 3.56 (2H, m), 3.81–(3H, s), 6.20 - 6.34 (2H, m), 6.87–(2H, d), 7.19 - 7.25–(1H, m), 7.26 - 7.34 (2H, m), 7.54 (1H, s), 7.80–(1H, d), 7.88 - 8.00 –1H, m), 14.19 - 14.34 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 419.8.

Intermediate 37g:

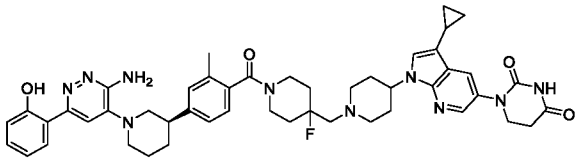
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoic acid



[1940] A solution of Intermediate 37f (55 mg, 0.13 mmol) in MeOH (2 mL) and 1 M aq. NaOH (2 ml, 2.00 mmol) was stirred at 50 °C for 1h. Upon completion, the reaction mixture was partially concentrated under reduced pressure and acidified with 1 M aq. HCl. A precipitate formed which was collected by filtration and dried in vacuo to give the title compound, (32 mg, 61%) as a light yellow solid; *m/z* (ES$^+$) [M+H]$^+$ = 403.2.

EXAMPLE 37:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

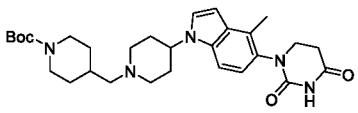


[1941] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 37g (16 mg, 0.04 mmol) and Intermediate 20g (33.1 mg, 0.05 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (18 mg, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.69 (2H, m), 0.76 - 0.91 (3H, m), 1.70 (2H, br s), 1.81 (4H, br s), 1.91 (2H, br d), 1.98 (3H, br d), 2.03 - 2.13 (2H, m), 2.23 (3H, br s), 2.30 - 2.42 (3H, m), 2.67 (1H, s), 2.74 (2H, s), 3.06 (4H, br d), 3.17 - 3.24 (2H, m), 3.55 (2H, br s), 3.78 - 3.84 (2H, m), 6.06 - 6.44 (2H, m), 6.89 (2H, d), 7.11 - 7.18 (1H, m), 7.20 - 7.27 (3H, m), 7.29 - 7.39 (2H, m), 7.40 - 7.47 (1H, m), 7.54 (1H, s), 7.87 - 7.93 (1H, m), 7.94 (1H, d), 8.11 - 8.15 (1H, m), 8.15 - 8.20 (1H, m), 10.34 - 10.42 (1H, m) (-OH not observed); *m/z* (ES$^+$) [M+H]$^+$ = 855.4.

EXAMPLE 38:

Intermediate 38a:

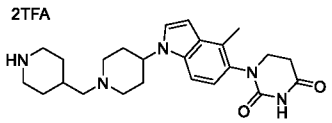
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[1942] A solution of Intermediate 32e (100 mg, 0.31 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (98 mg, 0.46 mmol) in DCM (4596 µl) and IPA (1532 µl) was charged with NaOAc (126 mg, 1.53 mmol) and $NaBH(OAc)_3$ (130 mg, 0.61 mmol) then stirred at r.t. for 30 minutes. Upon completion, the reaction mixture was diluted with DCM and water, then quenched with sat. $NaHCO_3$ solution. The reaction mixture was extracted with DCM (3 x 20 mL) before the combined organic extracts were then washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) afforded the title compound, (145 mg, 90%) as a white solid. ^1H NMR ($CHCl_3$): δ 1.06 - 1.23 (2H, m), 1.26 - 1.32 (2H, m), 1.49 (9H, s), 1.63 - 1.72 (1H, m), 1.74 - 1.83 (2H, m), 2.07 (2H, s), 2.06 - 2.09 (1H, m), 2.13 - 2.22 (2H, m), 2.24 - 2.28 (1H, m), 2.47 (3H, s), 2.68 - 2.81 (2H, m), 2.86 - 2.93 (2H, m), 2.98 - 3.10 (2H, m), 3.67 - 3.79 (2H, m), 3.80 - 3.90 (1H, m), 4.07 - 4.15 (1H, m), 4.18 - 4.26 (1H, m), 6.57 - 6.68 (1H, m), 7.00 - 7.11 (1H, m), 7.29 - 7.32 (1H, m), 7.41 - 7.47 (1H, m) (-NH not observed); *m/z* (ES^+) $[M+H]^+$ = 524.5.

Intermediate 38b:

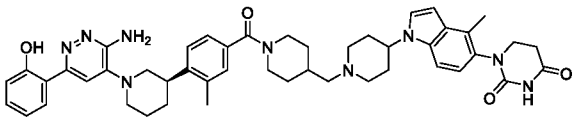
1-(4-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1943] Prepared in an analogous method to Intermediate 1i starting from Intermediate 38a (145 mg, 0.28 mmol) to give the title compound (178 mg, 99%) as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 424.4.

EXAMPLE 38:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

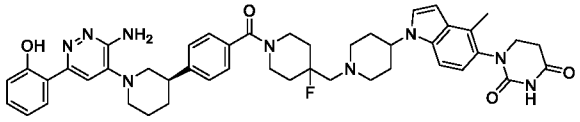


[1944] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 38b (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (16 mg, 77%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.01 - 1.23 (2H, m), 1.60 - 1.79 (2H, m), 1.82 - 2.05 (7H, m), 2.04 - 2.08 (1H, m), 2.09 - 2.28 (3H, m), 2.32 (3H, s), 2.41 (3H, s), 2.69 - 2.91 (6H, m), 2.93 - 3.16 (3H, m), 3.21 - 3.23 (1H, m), 3.23 - 3.28 (1H, m), 3.47 - 3.51 (1H, m), 3.52 - 3.56 (1H, m), 3.57 - 3.62 (1H, m), 3.63 - 3.70 (1H, m), 3.71 - 3.79 (1H, m), 4.22 - 4.57 (2H, m), 6.21 - 6.34 (2H, m), 6.52 - 6.60 (1H, m), 6.85 - 6.91 (2H, m), 6.99 - 7.07 (1H, m), 7.17 - 7.21

(2H, m), 7.21 - 7.27 (1H, m), 7.37 - 7.44 (2H, m), 7.44 - 7.53 (1H, m), 7.55 - 7.59 (1H, m), 7.90 - 7.98 (1H, m), 10.21 - 10.30 (1H, m), 13.96 - 14.63 (1H, m) ; *m/z* (ES^+) $[M+H]^+$ = 810.6.

EXAMPLE 39:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

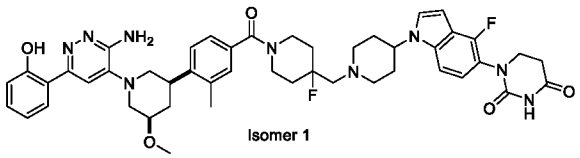


[1945] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (10 mg, 0.03 mmol) and Intermediate 32g (28 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (16.8 mg, 72%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.81 (3H, m), 1.85 - 2.05 (9H, m), 2.31 (3H, s), 2.35 - 2.38 (1H, m), 2.39 - 2.44 (4H, m), 2.63 - 2.68 (2H, m), 2.69 - 2.85 (4H, m), 3.01 - 3.09 (2H, m), 3.11 - 3.21 (2H, m), 3.52 - 3.60 (3H, m), 3.69 - 3.78 (1H, m), 4.28 - 4.39 (1H, m), 6.21 - 6.34 (2H, m), 6.46 - 6.57 (1H, m), 6.83 - 6.91 (2H, m), 6.96 - 7.05 (1H, m), 7.17 - 7.29 (1H, m), 7.37 - 7.48 (5H, m), 7.51 - 7.59 (2H, m), 7.88 - 7.97 (1H, m), 10.24 (1H, s) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 814.6.

EXAMPLE 40:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

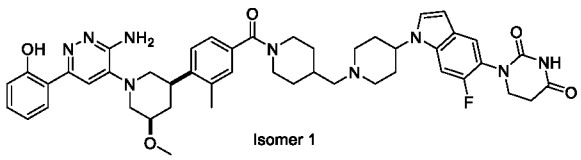


[1946] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (10 mg, 0.02 mmol) and Intermediate 3g (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.3 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 11.50 - 1.60 (1H, m), 1.65 - 1.80 (2H, m), 1.82 - 1.94 (3H, m), 1.96 - 2.07 (3H, m), 2.25 - 2.32 (1H, m), 2.36 - 2.41 (1H, m), 2.42 (3H, s), 2.44 - 2.47 (1H, m), 2.59 - 2.63 (1H, m), 2.64 - 2.68 (1H, m), 2.72 - 2.76 (2H, m), 2.77 - 2.83 (1H, m), 3.02 - 3.09 (2H, m), 3.10 - 3.25 (2H, m), 3.39 (3H, s), 3.42 - 3.48 (2H, m), 3.49 - 3.63 (2H, m), 3.68 - 3.74 (2H, m), 3.75 - 3.81 (1H, m), 3.83 - 3.89 (1H, m), 4.16 - 4.32 (1H, m), 4.33 - 4.41 (1H, m), 6.33 (2H, br s), 6.56 (1H, d), 6.89 (2H, br d), 7.12 (1H, s), 7.25 (3H, br s), 7.43 (2H, br d), 7.56 - 7.67 (2H, m), 7.96 (1H, br d), 10.29 - 10.61 (1H, m), 13.80 - 14.41 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 862.6.

EXAMPLE 41:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

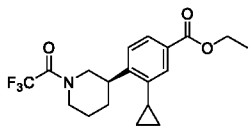


[1947] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (10 mg, 0.02 mmol) and Intermediate 30b (20.3 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (2.3 mg, 12%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.81 - 0.90 (1H, m), 1.03 - 1.14 (2H, m), 1.24 (4H, br s), 1.49 - 1.61 (1H, m), 1.62 - 1.76 (1H, m), 1.78 - 1.87 (2H, m), 1.89 - 2.05 (5H, m), 2.12 - 2.21 (2H, m), 2.22 - 2.31 (3H, m), 2.72 - 2.76 (2H, m), 2.93 - 3.13 (3H, m), 3.34 - 3.37 (1H, m), 3.39 (3H, s), 3.43 - 3.48 (1H, m), 3.59 - 3.68 (1H, m), 3.68 - 3.73 (2H, m), 3.75 - 3.81 (1H, m), 3.83 - 3.89 (1H, m), 4.28 - 4.38 (1H, m), 4.39 - 4.57 (1H, m), 6.28 - 6.38 (2H, m), 6.46 - 6.52 (1H, m), 6.86 - 6.92 (2H, m), 7.21 (2H, s), 7.22 - 7.27 (1H, m), 7.36 - 7.45 (1H, m), 7.52 - 7.58 (3H, m), 7.58 - 7.63 (1H, m), 7.92 - 8.00 (1H, m), 10.34 - 10.43 (1H, m), 14.00 - 14.37 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 844.6.

EXAMPLE 42:

Intermediate 42a:

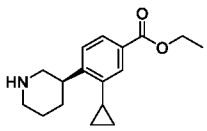
Ethyl 3-cyclopropyl-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1948] A solution of Intermediate 12b (150 mg, 0.37 mmol), THF (1.35 mL) and [(*t*-Bu)$_3$P]$_2$Pd (18.78 mg, 0.04 mmol) under N_2 atmosphere was cooled to 0 °C and charged with cyclopropylzinc(II) bromide (0.5M in THF) (0.808 mL, 0.40 mmol). The reaction mixture was warmed to r.t. over 1.5 hours, then quenched with 1 M aq. HCl and extracted with EtOAc (3 x 15mL). The combined organic extracts were then washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (97 mg, 71%), as a light brown oil. ^{1}H NMR ($CHCl_3$): δ 0.64 - 0.86 (2H, m), 0.98 - 1.14 (2H, m), 1.41 (3H, t), 1.69 - 1.90 (2H, m), 1.91 - 2.14 (3H, m), 2.71 - 2.90 (1H, m), 3.18 - 3.27 (1H, m), 3.40 - 3.60 (1H, m), 4.01 - 4.22 (1H, m), 4.39 (2H, dd), 4.67 - 4.80 (1H, m), 7.28 (1H, s), 7.77 (1H, d), 7.89 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 370.1.

Intermediate 42b:

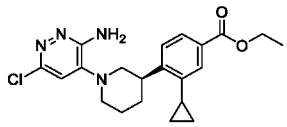
Ethyl (*R*)-3-cyclopropyl-4-(piperidin-3-yl)benzoate



[1949] Prepared in an analogous method to Intermediate 12d starting from Intermediate 42a (125 mg, 0.34 mmol) to give the title compound (93 mg, 100%) as a colorless oil, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 274.4.

Intermediate 42c:

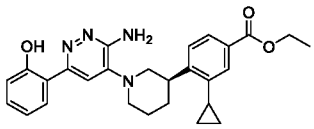
Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoate



[1950] Prepared in an analogous method to Intermediate 1d starting from Intermediate 42b (93 mg, 0.34 mmol) and 4-bromo-6-chloropyridazin-3-amine (71 mg, 0.34 mmol). Trituration with Et_2O gave the title compound (136 mg, 100%) as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 400.3.

Intermediate 42d:

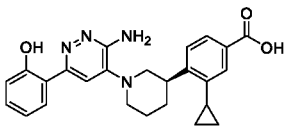
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoate



[1951] Prepared in an analogous method to Intermediate 1e starting from Intermediate 42c (174 mg, 0.43 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (38 mg, 19%) as a yellow solid. ^1H NMR ($CHCl_3$): δ 0.78 (2H, d), 0.98 - 1.08 (2H, m), 1.26 - 1.34 (1H, m), 1.41 (3H, s), 1.71 - 1.86 (1H, m), 1.91 - 2.06 (2H, m), 2.09 - 2.20 (1H, m), 2.74 - 2.88 (2H, m), 3.57 - 3.64 (1H, m), 3.68 - 3.77 (2H, m), 4.34 - 4.46 (2H, m), 4.79 - 4.97 (2H, m), 6.86 - 6.97 (1H, m), 7.05 - 7.09 (1H, m), 7.29 - 7.31 (1H, m), 7.33 - 7.40 (2H, m), 7.56 - 7.63 (1H, m), 7.76 - 7.82 (1H, m), 7.88 - 7.96 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 457.3.

Intermediate 42e:

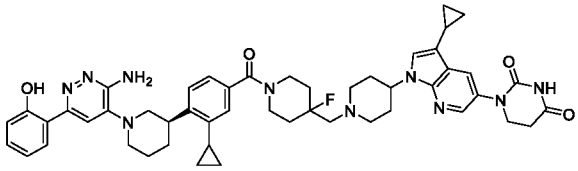
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoic acid



[1952] Prepared in an analogous method to Intermediate 20f starting from Intermediate 42d (38 mg, 0.08 mmol). The reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq. HCl, sonicated, centrifuged, decanted to afford the title compound (36 mg, 100%). *m/z* (ES^+) $[M+H]^+$ = 431.4.

EXAMPLE 42:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

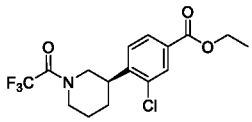


[1953] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 42e (18 mg, 0.04 mmol) and Intermediate 20g (39 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (15.5 mg, 42%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.74 (2H, m), 0.90 - 1.01 (2H, m), 1.62 - 1.78 (4H, m), 1.79 - 2.03 (9H, m), 2.13 - 2.19 (1H, m), 2.22 (3H, s), 2.35 - 2.47 (3H, m), 2.59 - 2.68 (2H, m), 2.70 - 2.76 (3H, m), 2.76 - 2.83 (2H, m), 2.87 - 2.92 (1H, m), 3.02 - 3.07 (2H, m), 3.74 - 3.78 (3H, m), 3.83 (2H, s), 4.22 - 4.32 (2H, m), 6.17 - 6.30 (2H, m), 6.85 - 6.91 (2H, m), 6.98 - 7.01 (1H, m), 7.02 - 7.07 (1H, m), 7.20 - 7.27 (2H, m), 7.28 - 7.32 (1H, m), 7.37 - 7.40 (1H, m), 7.40 - 7.44 (1H, m), 7.44 - 7.48 (1H, m), 7.51 - 7.60 (1H, m), 7.87 - 7.98 (1H, m), 10.13 - 10.30 (1H, m) (-OH not observed); *m/z* (ES$^+$) $[M+H]^+$ = 881.5.

EXAMPLE 43:

Intermediate 43a:

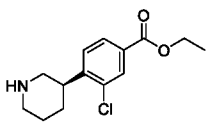
Ethyl (*R*)-3-chloro-4-(1-(2,2,2-trifluoroacetyl)piperidin-3-yl)benzoate



[1954] A solution of Intermediate 12b (250 mg, 0.61 mmol), $NiCl_2$ (159 mg, 1.22 mmol) and NMP (1.2 mL) as stirred at 200 °C in a microwave reactor for 3 hours. Upon completion, the reaction mixture was diluted with EtOAc and water, then extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (80 mg, 36%), as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, s), 1.68 - 1.85 (2H, m), 1.94 - 2.03 (1H, m), 2.10 - 2.21 (1H, m), 2.74 - 2.90 (1H, m), 3.08 - 3.25 (1H, m), 3.27 - 3.46 (1H, m), 4.09 - 4.13 (1H, m), 4.41 (2H, dd), 4.67 - 4.78 (1H, m), 7.32 (1H, br d), 7.91 - 7.98 (1H, m), 8.09 (1H, dd); *m/z* (ES$^+$) $[M+H]^+$ = 364.0.

Intermediate 43b:

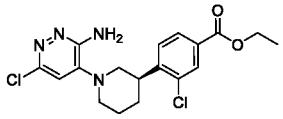
Ethyl (*R*)-3-chloro-4-(piperidin-3-yl)benzoate



[1955] Prepared in an analogous method to Intermediate 12d starting from Intermediate 43a (120 mg, 0.33 mmol) to give the title compound (88 mg, 100%) as a colorless oil, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 267.6.

Intermediate 43c:

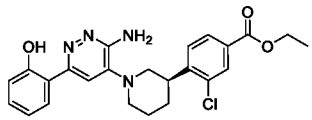
Ethyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoate



[1956] Prepared in an analogous method to Intermediate 1d starting from Intermediate 43b (88 mg, 0.33 mmol) and 4-bromo-6-chloropyridazin-3-amine (137 mg, 0.66 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (57 mg, 44%) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.33 (3H, s), 1.59 - 1.70 (1H, m), 1.79 - 1.87 (1H, m), 1.90 - 1.99 (2H, m), 2.59 - 2.68 (1H, m), 2.81 - 2.92 (1H, m), 3.40 - 3.45 (2H, m), 3.50 - 3.55 (1H, m), 4.28 - 4.37 (2H, m), 6.22 - 6.38 (2H, m), 7.01 - 7.06 (1H, m), 7.62 - 7.68 (1H, m), 7.87 - 7.92 (1H, m), 7.93 - 7.97 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 395.1.

Intermediate 43d:

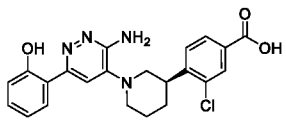
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoate



[1957] A solution of Intermediate 43c (55 mg, 0.14 mmol), (2-hydroxyphenyl)boronic acid (29 mg, 0.21 mmol), $Pd(Ph_3P)_4$ (16 mg, 0.01 mmol) and K_2CO_3 (39 mg, 0.28 mmol) 1,4-dioxane (1160 µl) and water (232 µl) was sparged with N_2 for 5 minutes then heated to 100 °C for 2 hours. Upon completion, the reaction mixture was cooled with water, diluted with water, and extracted with EtOAc. The combined organic extracts were then washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound, (22 mg, 35%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.31 - 1.37 (3H, m), 1.63 - 1.77 (1H, m), 1.83 - 1.92 (1H, m), 2.01 (2H, br s), 2.62 - 2.72 (1H, m), 2.92 - 3.02 (1H, m), 3.48 - 3.55 (2H, m), 3.58 - 3.66 (1H, m), 4.28 - 4.39 (2H, m), 6.25 - 6.34 (2H, m), 6.84 - 6.91 (2H, m), 7.21 - 7.26 (1H, m), 7.58 (1H, s), 7.69 - 7.74 (1H, m), 7.92 (2H, br dd), 7.96 (1H, s), 14.17 - 14.31 (1H, m) ; *m/z* (ES^+) $[M+H]^+$ = 453.2.

Intermediate 43e:

(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoic acid

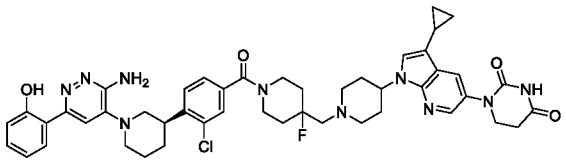


[1958] Prepared in an analogous method to Intermediate 20f starting from Intermediate 43d (38 mg, 0.08 mmol). The reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq.

HCl, sonicated, centrifuged, and decanted to afford the title compound (36 mg, 100%). *m/z* (ES^+) $[M+H]^+$ = 425.0.

EXAMPLE 43:

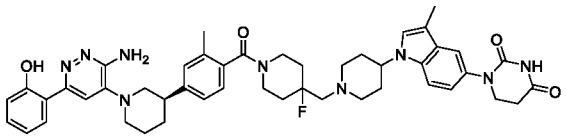
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1959] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 43e (18 mg, 0.04 mmol) and Intermediate 20g (37 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (14 mg, 38%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.70 (2H, m), 0.82 - 0.93 (2H, m), 1.70 - 2.05 (10H, m), 2.08 (2H, s), 2.15 - 2.29 (1H, m), 2.72 - 2.81 (3H, m), 2.96 - 3.06 (1H, m), 3.08 - 3.22 (2H, m), 3.23 - 3.27 (1H, m), 3.44 - 3.51 (4H, m), 3.54 - 3.60 (2H, m), 3.65 - 3.75 (2H, m), 3.82 (2H, s), 4.13 - 4.42 (2H, m), 4.56 - 4.84 (1H, m), 6.30 - 6.70 (2H, m), 6.88 - 6.97 (2H, m), 7.26 - 7.32 (1H, m), 7.34 - 7.45 (2H, m), 7.51 - 7.55 (1H, m), 7.56 - 7.59 (1H, m), 7.59 - 7.66 (1H, m), 7.78 - 7.89 (1H, m), 7.94 - 8.02 (1H, m), 8.17 - 8.23 (1H, m), 10.33 - 10.44 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 875.3.

EXAMPLE 44:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

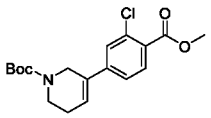


[1960] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 37g (16 mg, 0.04 mmol) and Intermediate 1k (32 mg, 0.05 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (22 mg, 63%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 1.74 (2H, m), 1.76 - 2.05 (10H, m), 2.22 (6H, s), 2.34 - 2.44 (2H, m), 2.61 - 2.70 (3H, m), 2.70 - 2.75 (3H, m), 2.97 - 3.09 (3H, m), 3.18 - 3.25 (2H, m), 3.49 - 3.59 (2H, m), 3.72 - 3.81 (2H, m), 4.20 - 4.41 (2H, m), 6.20 - 6.34 (2H, m), 6.83 - 6.92 (2H, m), 7.00 - 7.07 (1H, m), 7.12 - 7.18 (1H, m), 7.19 - 7.27 (3H, m), 7.29 - 7.32 (1H, m), 7.34 - 7.41 (2H, m), 7.42 - 7.48 (1H, m), 7.51 - 7.59 (1H, m), 7.86 - 7.96 (1H, m), 10.20 - 10.27 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 828.3.

EXAMPLE 45

Intermediate 45a:

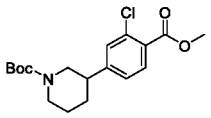
tert-Butyl 5-(3-chloro-4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1961] A solution of *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (907 mg, 2.93 mmol), methyl 4-bromo-2-chloro benzoate (732 mg, 2.93 mmol), $PdCl_2$(dppf) (107 mg, 0.15 mmol) and K_2CO_3 (1216 mg, 8.80 mmol), 1,4-dioxane (13.336 mL), and water (1.334 mL) was sparged with N_2 gas for five minutes and stirred at 100 °C for 2 hours. Upon completion, the reaction mixture was partially concentrated under reduced pressure, diluted with water, and extracted with DCM. The combined organic extracts were then washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.00 g, 97%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.51 (9H, s), 2.30 - 2.44 (2H, m), 3.53 - 3.61 (2H, m), 3.94 (3H, s), 4.22 - 4.32 (2H, m), 6.21 - 6.43 (1H, m), 7.29 - 7.37 (1H, m), 7.42 - 7.53 (1H, m), 7.77 - 7.88 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 252.1.

Intermediate 45b:

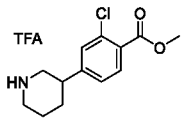
tert-Butyl 3-(3-chloro-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[1962] Intermediate 45a (820 mg, 2.33 mmol), 5% Rh/C (240 mg, 0.12 mmol) and MeOH (11.65 mL) was charged with H_2 and stirred at r.t. for 1 hour. Upon completion, the reaction mixture was filtered through Celite (washing with MeOH) and concentrated to give the title compound (800 mg, 97%), which was carried forward without additional purification. ^{1}H NMR (DMSO-*d6*): δ 1.49 (9H, s), 1.56 - 1.69 (2H, m), 1.74 - 1.82 (1H, m), 2.00 - 2.06 (1H, m), 2.65 - 2.87 (3H, m), 3.94 (3H, s), 4.10 - 4.23 (2H, m), 7.18 - 7.24 (1H, m), 7.33 - 7.39 (1H, m), 7.79 - 7.87 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 266.0.

Intermediate 45c:

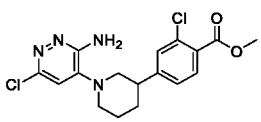
rac-Methyl 2-chloro-4-(piperidin-3-yl)benzoate



[1963] Prepared in an analogous method to Intermediate 1i starting from Intermediate 45b (800 mg, 2.26 mmol) to give the title compound (829 mg, 100%) as a colorless oil. *m/z* (ES^+) $[M+H]^+$ = 254.1.

Intermediate 45d:

rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoate

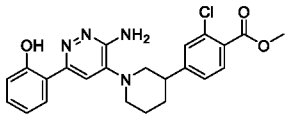


[1964] Prepared in an analogous method to Intermediate 1d starting from Intermediate 45c (829 mg, 2.26 mmol) and 4-bromo-6-chloropyridazin-3-amine (943 mg, 4.52 mmol). Purification by FSC (elution

gradient: 0 to 100% EtOAc in hexanes) gave the title compound (363 mg, 42%) as a brown solid. ^{1}H NMR ($CDCl_3$): δ 1.63 - 1.76 (1H, m), 1.79 - 1.95 (1H, m), 1.99 - 2.07 (1H, m), 2.10 - 2.22 (1H, m), 2.59 - 2.75 (2H, m), 2.92 - 3.08 (1H, m), 3.46 - 3.66 (2H, m), 3.95 (3H, s), 4.89 - 5.11 (2H, m), 6.78 (1H, s), 7.16 - 7.25 (1H, m), 7.37 (1H, s), 7.79 - 7.91 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 381.5.

Intermediate 45e:

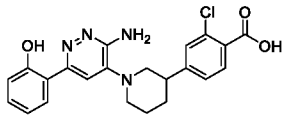
rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoate



[1965] Prepared in an analogous method to Intermediate 43d starting from Intermediate 45d (363 mg, 0.95 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOH/EtOAc] in hexanes) gave the title compound (188 mg, 45%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.75 (1H, m), 1.83 - 1.95 (2H, m), 1.96 - 2.04 (1H, m), 2.68 - 2.76 (1H, m), 2.77 - 2.84 (1H, m), 3.12 - 3.24 (1H, m), 3.48 - 3.58 (2H, m), 3.86 (3H, s), 6.30 (2H, s), 6.89 (2H, d), 7.18 - 7.31 (1H, m), 7.42 - 7.49 (1H, m), 7.57 (2H, d), 7.74 - 7.82 (1H, m), 7.88 - 7.97 (1H, m), 14.07 - 14.38 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 439.2.

Intermediate 45f:

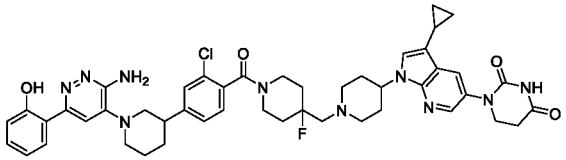
4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoic acid



[1966] Prepared in an analogous method to Intermediate 26j starting from Intermediate 45e (50 mg, 0.11 mmol). The reaction mixture was partially concentrated under reduced pressure and acidified with 1 M aq. HCl (1.1 mL), forming a white precipitate. The suspension was sonicated, centrifuged, and decanted to afford the title compound (48 mg, 99%), which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 425.2.

EXAMPLE 45:

rac-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

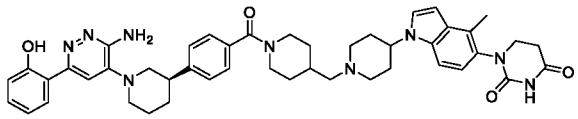


[1967] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 45f (10 mg, 0.02 mmol) and Intermediate 20g (26 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.5 mg, 61%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.73 (2H, m), 0.79 - 0.94 (2H, m), 1.64 - 1.96 (10H, m), 1.97 - 2.13 (4H, m), 2.29 - 2.36 (1H, m),

2.39 - 2.46 (1H, m), 2.73 - 2.79 (3H, m), 2.79 - 2.88 (1H, m), 2.98 - 3.09 (2H, m), 3.10 - 3.26 (5H, m), 3.50 - 3.64 (2H, m), 3.77 - 3.86 (2H, m), 4.25 - 4.39 (1H, m), 4.53 - 4.71 (1H, m), 6.15 - 6.55 (2H, m), 6.83 - 6.95 (2H, m), 7.18 - 7.30 (1H, m), 7.34 - 7.48 (3H, m), 7.52 - 7.59 (2H, m), 7.88 - 7.94 (1H, m), 7.94 - 7.98 (1H, m), 8.16 - 8.20 (1H, m), 10.32 - 10.42 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 875.5.

EXAMPLE 46:

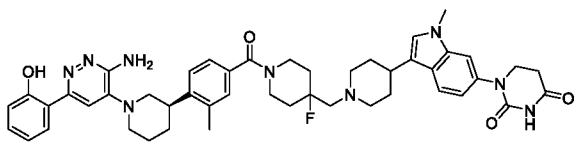
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1968] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (10 mg, 0.03 mmol) and Intermediate 38b (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.0 mg, 57%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.03 - 1.20 (2H, m), 1.61 - 1.76 (2H, m), 1.77 - 1.85 (1H, m), 1.86 - 2.04 (7H, m), 2.11 - 2.28 (3H, m), 2.32 (3H, s), 2.73 (5H, s), 2.68 - 2.84 (1H, m), 2.92 - 3.10 (3H, m), 3.11 - 3.18 (2H, m), 3.49 - 3.58 (3H, m), 3.61 - 3.69 (1H, m), 3.71 - 3.79 (1H, m), 4.23 - 4.61 (2H, m), 6.25 - 6.33 (2H, m), 6.53 - 6.59 (1H, m), 6.85 - 6.92 (2H, m), 7.00 - 7.06 (1H, m), 7.21 - 7.26 (1H, m), 7.33 - 7.37 (2H, m), 7.39 - 7.43 (2H, m), 7.43 - 7.45 (1H, m), 7.46 - 7.54 (1H, m), 7.55 - 7.57 (1H, m), 7.87 - 8.01 (1H, m), 10.16 - 10.30 (1H, m), 13.99 - 14.40 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 796.6.

EXAMPLE 47:

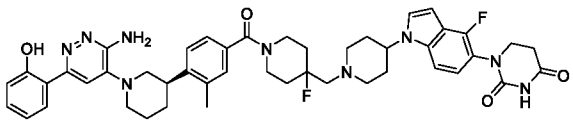
(*R*)-1-(3-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1969] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 9f (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.0 mg, 59%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.89 (13H, br s), 2.24 - 2.36 (2H, m), 2.41 (3H, s), 2.54 - 2.59 (1H, m), 2.59 - 2.65 (1H, m), 2.74 (4H, br t), 2.82 - 2.91 (1H, m), 2.94 - 3.05 (2H, m), 3.07 - 3.20 (1H, m), 3.21 - 3.29 (2H, m), 3.45 - 3.52 (1H, m), 3.56 - 3.63 (1H, m), 3.71 (3H, s), 3.80 (2H, s), 4.05 - 4.34 (1H, m), 6.18 - 6.33 (2H, m), 6.88 (2H, s), 6.93 - 6.97 (1H, m), 7.12 (1H, s), 7.24 (3H, s), 7.31 - 7.36 (1H, m), 7.38 - 7.43 (1H, m), 7.51 - 7.58 (2H, m), 7.88 - 8.00 (1H, m), 10.18 - 10.39 (1H, m), 13.67 - 14.57 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 828.5.

EXAMPLE 48:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

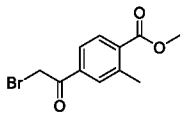


[1970] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (15 mg, 0.04 mmol) and Intermediate 3g (30 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (18 mg, 59%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 2.26 (12H, m), 2.40 (3H, s), 2.75 (2H, s), 2.77 - 2.85 (1H, m), 2.85 - 2.98 (2H, m), 3.00 - 3.22 (3H, m), 3.23 - 3.29 (3H, m), 3.35 - 3.48 (2H, m), 3.50 - 3.68 (3H, m), 3.72 (2H, s), 4.06 - 4.64 (2H, m), 6.39 - 6.72 (3H, m), 6.88 - 6.96 (2H, m), 7.11 - 7.18 (1H, m), 7.22 - 7.26 (2H, m), 7.26 - 7.32 (1H, m), 7.38 - 7.43 (1H, m), 7.43 - 7.48 (1H, m), 7.52 - 7.55 (1H, m), 7.56 - 7.63 (1H, m), 7.74 - 7.90 (1H, m), 10.31 - 10.48 (1H, m) (-OH was not observed); *m/z* (ES$^+$) $[M+H]^+$ = 832.0.

EXAMPLE 49

Intermediate 49a:

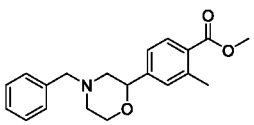
Methyl 4-(2-bromoacetyl)-2-methylbenzoate



[1971] 1-Ethoxyvinyltri-*n*-butyltin (8.44 mL, 24.97 mmol) was added to methyl 4-bromo-2-methylbenzoate (5.2 g, 22.70 mmol) and *bis*(triphenylphosphine)palladium(II) chloride (1.593 g, 2.27 mmol) in 1,4-dioxane (100 mL) under nitrogen. The resulting mixture was stirred at 90 °C for 16 h. The mixture was cooled to 0 °C, then added NBS (4.85 g, 27.24 mmol) and water (10.00 mL), stirred at 0 °C for 1 h. The reaction mixture was poured into water (500 mL), extracted with EtOAc (3 x 100 mL), the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (4.21 g, 68%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 2.51 (3 H, s), 3.81 (3 H, s), 4.92 (2 H, s), 7.82 – 7.86 (2 H, m), 7.89 (1 H, d); *m/z* (ES$^+$) $[M+H]^+$ =271.0.

Intermediate 49b:

rac-Methyl 4-(4-benzylmorpholin-2-yl)-2-methylbenzoate



[1972] Intermediate 49a (2.05 g, 7.56 mmol) was added to *N*-benzylethanolamine (1.143 g, 7.56 mmol) and K_2CO_3 (1.150 g, 8.32 mmol) in MeCN (40 mL). The resulting mixture was stirred at rt for 8h. The reaction mixture was filtered and evaporated. The crude product was used in the next step directly without further purification. TFA (11.65 mL, 151.23 mmol) and triethylsilane (1.758 g, 15.12 mmol) were added to the crude product in DCE (40.0 mL). The resulting mixture was stirred at 60 °C for 2h. The reaction mixture cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100%

EtOAc in petroleum ether) gave the title compound (2.80 g, 57%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.92 – 1.98 (1 H, m), 2.12 – 2.19 (1 H, m), 2.49 (3 H, s), 2.66 – 2.71 (1 H, m), 2.84 – 2.88 (1 H, m), 3.46 – 3.56 (2 H, m), 3.63 – 3.70 (1 H, m), 3.80 (3 H, s), 3.90 – 3.96 (1 H, m), 4.51 – 4.55 (1 H, m), 7.23 – 7.29 (3 H, m), 7.30 – 7.35 (4 H, m), 7.78 (1 H, d); *m/z* (ES^+) $[M+H]^+$ =326.3.

Intermediate 49c:

Methyl (*R**)-4-(4-benzylmorpholin-2-yl)-2-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

and

Intermediate 49d:

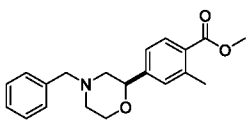
Methyl (*R**)-4-(4-benzylmorpholin-2-yl)-2-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

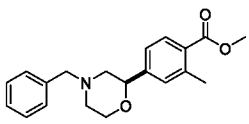
Methyl (*R*)-4-(4-benzylmorpholin-2-yl)-2-methylbenzoate

and

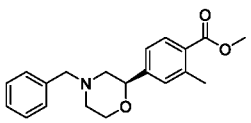
Methyl (*S*)-4-(4-benzylmorpholin-2-yl)-2-methylbenzoate



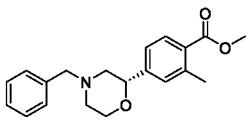
Isomer 1 (**Intermediate 49c**)



Isomer 2 (**Intermediate 49d**)



Isomer 1 or 2



Isomer 2 or 1

[1973] Intermediate 49b (2.80 g, 8.6 mmol) was dissolved in MeOH. The resulting solution was purified by preparative chiral-HPLC on a Column: CHIRALPAK AD-H, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MEOH; Flow rate: 200 mL/min; Gradient: isocratic 50% B; Column Temperature: 35 °C; Back Pressure: 100 bar; Wave Length: 220 nm; RT1: 4.87 min; RT2: 7.49 min; Sample Solvent: MEOH; Injection Volume: 9 mL). The fractions were concentrated to afford Intermediate 49c (1.10 g, 22%) as a green oil and Intermediate 49d (1.10 g, 22%) as a yellow oil.

Intermediate 49e:

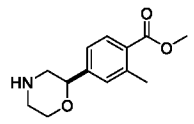
Methyl (*R**)-2-methyl-4-(morpholin-2-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

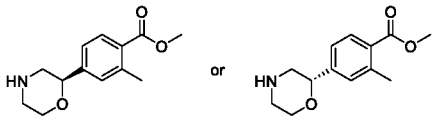
Methyl (*R*)-2-methyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-2-methyl-4-(morpholin-2-yl)benzoate



Isomer 1



[1974] Pd-C (0.327 g, 0.31 mmol, 10 wt% Pd) was added to Intermediate 49c (1 g, 3.07 mmol) in MeOH (30 mL). The mixture was sparged with hydrogen for 5 minutes and stirred under an atmosphere of hydrogen for 2.5 h. The catalyst was filtered through celite and filtrate was concentrated under reduced pressure to give the title compound (0.670 g, 67%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.42 – 2.48 (1 H, m), 2.48 – 2.53 (4 H, m), 2.69 – 2.77 (2 H, m), 2.91 – 2.96 (1 H, m), 3.54 – 3.62 (1 H, m), 3.80 (3 H, s), 3.85 – 3.91 (1 H, m), 4.36 – 4.43 (1 H, m), 7.21 – 7.34 (2 H, m), 7.78 (1 H, d); *m/z* (ES$^+$) [M+H]$^+$ =236.3.

Intermediate 49f:

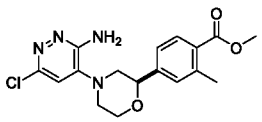
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

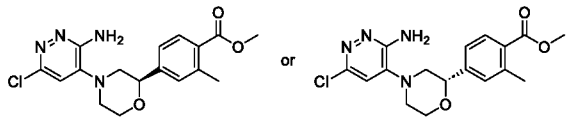
Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate



Isomer 1



[1975] Prepared in an analogous method to Intermediate 1d starting from Intermediate 49e (660 mg, 2.81 mmol. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (0.800 g, 80%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 2.49 (3H, s), 2.73 – 2.80 (1 H, m), 3.26 – 3.36 (2 H, m), 3.47 (1 H, d), 3.78 (3 H, s), 3.87 – 3.95 (1 H, m), 3.98 – 4.04 (1 H, m), 4.76 – 4.81 (1 H, m), 6.31 (2 H, s), 6.91 (1 H, s), 7.29 – 7.36 (2 H, m), 7.78 (1 H, d); *m/z* (ES$^+$) [M–H]+ =363.0.

Intermediate 49g:

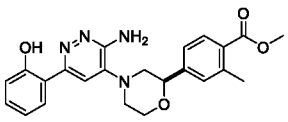
Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

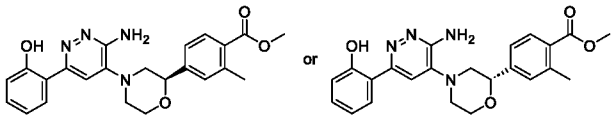
Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate



Isomer 1



[1976] Prepared in an analogous method to Intermediate 1e starting from Intermediate 49f (800 mg, 2.20 mmol). The reaction mixture was poured into water (75 mL) and filtered through filter paper to afford the title compound (700 mg, 76%) as yellow solid. The product was used in the next step directly without further purification. ^{1}H NMR ($CDCl_3$): δ 2.63 (3 H, s), 2.80 – 2.87 (1 H, m), 2.91 – 3.01 (1 H, m), 3.47 – 3.54 (2 H, m), 3.89 – 3.92 (3 H, m), 3.97 – 4.06 (1 H, m), 4.26 (1 H, d), 4.75 (1 H, d), 6.81 – 6.95 (3 H, m), 7.03 – 7.07 (1 H, m), 7.21 – 7.24 (1 H, m), 7.27 – 7.34 (4 H, m), 7.56 (1 H, d), 7.95 (1 H, d); *m/z* (ES$^+$) $[M+H]^+$ = 421.3.

Intermediate 49h:

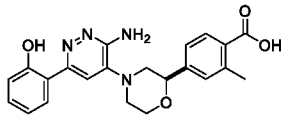
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

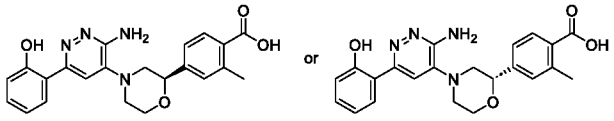
(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid



Isomer 1



[1977] Prepared in an analogous method to Intermediate 1f starting from Intermediate 49g (600 mg, 1.43 mmol). The reaction mixture was acidified with 1 M aq. HCl, solids were filtered and dried by lyophilization to afford the title compound (450 mg, 78%) as yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.54 (3 H, s), 2.71 – 2.83 (1 H, m), 2.88 – 3.01 (1 H, m), 3.48 – 3.65 (2 H, m), 3.97 – 4.15 (2 H, m), 4.86 (1 H, d), 6.69 – 7.00 (4 H, m), 7.03 – 7.20 (1 H, m), 7.23 – 7.31 (1 H, m), 7.32 – 7.41 (1 H, m), 7.55 (1 H, s), 7.79 – 7.88 (2 H, m), 2 oxygen-bound protons not observed; *m/z* (ES+) [M+H]+ = 407.3.

EXAMPLE 49:

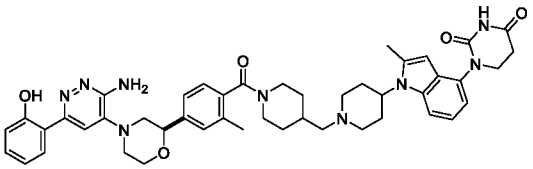
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

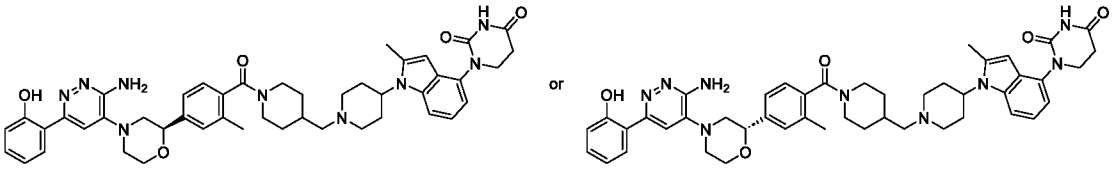
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



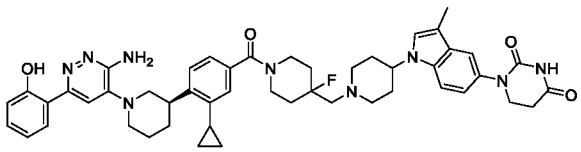
Isomer 1



[1978] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 49h (40 mg, 0.10 mmol) and Intermediate 22d (41.7 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 60% water in MeCN with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (20.0 mg, 25%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.91 – 1.17 (2H, m), 1.63 – 1.80 (3H, m), 1.80 – 1.94 (2H, m), 2.06 – 2.16 (2H, m), 2.17 – 2.31 (5H, m), 2.34 – 2.46 (5H, m), 2.70 – 2.92 (5H, m), 2.95 – 3.05 (3H, m), 3.33 – 3.37 (1H, m), 3.44 – 3.58 (2H, m), 3.70 – 3.76 (2H, m), 4.00 – 4.12 (2H, m), 4.17 – 4.28 (1H, m), 4.51 – 4.61 (1H, m), 4.82 (1H, d), 6.15 (1H, s), 6.48 (2H, s), 6.84 – 6.91 (3H, m), 7.00 – 7.06 (1H, m), 7.10 – 7.26 (2H, m), 7.29 – 7.39 (2H, m), 7.45 (1H, d), 7.57 (1H, s), 7.93 – 7.98 (1H, m), 10.30 (1H, s), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 812.5.

EXAMPLE 50:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



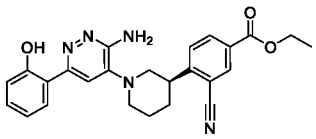
[1979] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 42e (18 mg, 0.04 mmol) and Intermediate 1k (38 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (20 mg, 52%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.74 (2H, m), 0.90 - 1.01 (2H, m), 1.62 - 1.78 (3H, m), 1.79 - 2.03 (9H, m), 2.13 - 2.19 (1H, m), 2.22 (3H, s), 2.35 - 2.47 (3H, m), 2.59 - 2.68 (2H, m), 2.70 - 2.76 (3H, m), 2.76 - 2.83 (2H, m), 2.87 - 2.92 (1H,

m), 3.02 - 3.07 (2H, m), 3.74 - 3.78 (3H, m), 3.83 (2H, s), 4.22 - 4.32 (2H, m), 6.17 - 6.30 (2H, m), 6.85 - 6.91 (2H, m), 6.98 - 7.01 (1H, m), 7.02 - 7.07 (1H, m), 7.20 - 7.27 (2H, m), 7.28 - 7.32 (1H, m), 7.37 - 7.40 (1H, m), 7.40 - 7.44 (1H, m), 7.44 - 7.48 (1H, m), 7.51 - 7.60 (1H, m), 7.87 - 7.98 (1H, m), 10.13 - 10.30 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 854.4.

EXAMPLE 51

Intermediate 51a:

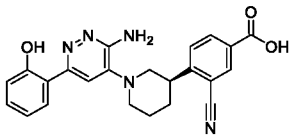
Ethyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyanobenzoate



[1980] A solution of Intermediate 43d (27 mg, 0.06 mmol), XPhos Pd G3 (5.05 mg, 5.96 µmol), XPhos (2.84 mg, 5.96 µmol), potassium hexacyanoferrate(II) trihydrate (25.2 mg, 0.06 mmol), KOAc (1.463 mg, 0.01 mmol), 1,4-dioxane (298 µl) and water (298 µl) was heated to 100 °C for 1 hour. The reaction mixture was then quenched with water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (23 mg, 87%). *m/z* (ES^+) $[M+H]^+$ = 444.2.

Intermediate 51b:

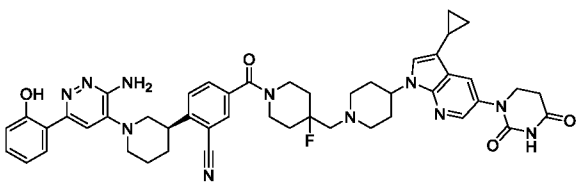
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyanobenzoic acid



[1981] Prepared in an analogous method to Intermediate 1f starting from Intermediate 51a (22 mg, 0.05 mmol). The reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq. HCl, centrifuged, decanted, and dried to the desired product (21 mg, 100%) which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 416.2.

EXAMPLE 51:

(*R*)-2-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile



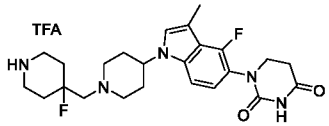
[1982] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 51b (10 mg, 0.02 mmol) and Intermediate 20g (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN

in water with 0.1% FA) gave the title compound (9.1 mg, 42%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.70 (2H, m), 0.82 - 0.91 (2H, m), 1.67 - 1.77 (2H, m), 1.78 - 1.84 (3H, m), 1.85 - 1.96 (3H, m), 1.97 - 2.14 (5H, m), 2.32 - 2.42 (3H, m), 2.58 - 2.62 (1H, m), 2.62 - 2.67 (2H, m), 2.74 - 2.79 (2H, m), 3.00 - 3.07 (2H, m), 3.08 - 3.18 (2H, m), 3.40 - 3.48 (2H, m), 3.50 - 3.58 (1H, m), 3.61 - 3.69 (1H, m), 3.79 - 3.85 (2H, m), 4.22 - 4.35 (1H, m), 4.55 - 4.65 (1H, m), 6.24 - 6.38 (2H, m), 6.85 - 6.92 (2H, m), 7.20 - 7.27 (1H, m), 7.42 - 7.47 (1H, m), 7.57 - 7.62 (1H, m), 7.77 (2H, s), 7.90 - 7.93 (1H, m), 7.93 - 7.98 (2H, m), 8.26 - 8.34 (1H, m), 10.36 - 10.42 (1H, m), 14.11 - 14.40 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 866.5.

EXAMPLE 52

Intermediate 52a:

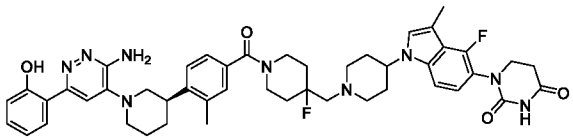
1-(4-Fluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1983] Prepared in an analogous method to Intermediate 1i starting from Intermediate 4g (224 mg, 0.40 mmol). Trituration with Et_2O gave the title compound (252 mg, 92%) in the form of a *bis*(trifluoroacetic acid) salt as an brown solid. *m/z* (ES$^+$) [M+H]$^+$ = 460.3.

EXAMPLE 52:

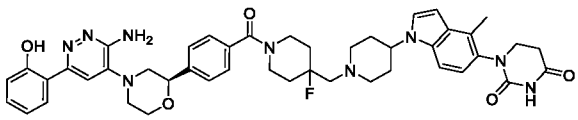
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[1984] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (15 mg, 0.04 mmol) and Intermediate 52a (31 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (17.5 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.82 (3H, m), 2.08 (9H, s), 2.36 (3H, s), 2.41 (3H, s), 2.74 (4H, s), 2.86 - 2.95 (1H, m), 2.98 - 3.21 (3H, m), 3.22 - 3.28 (2H, m), 3.33 - 3.39 (2H, m), 3.43 - 3.66 (3H, m), 3.70 (2H, s), 4.02 - 4.58 (2H, m), 6.33 - 6.55 (2H, m), 6.85 - 6.94 (2H, m), 7.02 - 7.13 (1H, m), 7.24 (4H, br s), 7.26 - 7.32 (1H, m), 7.33 - 7.37 (1H, m), 7.38 - 7.44 (1H, m), 7.53 - 7.59 (1H, m), 7.81 - 7.92 (1H, m), 10.24 - 10.49 (1H, m) (-OH not observed); *m/z* (ES$^+$) [M+H]$^+$ = 846.0.

EXAMPLE 53:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

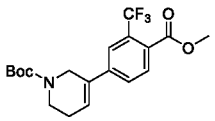


[1985] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (10 mg, 0.03 mmol) and Intermediate 32g (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (21.0 mg, 100%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.28 - 1.36 (1H, m), 1.52 - 1.62 (1H, m), 1.66 - 1.84 (2H, m), 1.87 - 1.93 (2H, m), 1.96 - 2.04 (2H, m), 2.31 (3H, s), 2.38 - 2.46 (3H, m), 2.59 - 2.63 (1H, m), 2.65 - 2.67 (1H, m), 2.68 - 2.83 (3H, m), 2.85 - 2.95 (1H, m), 3.01 - 3.09 (2H, m), 3.15 - 3.20 (1H, m), 3.45 - 3.60 (4H, m), 3.70 - 3.80 (1H, m), 4.00 - 4.13 (2H, m), 4.19 - 4.39 (2H, m), 4.83 - 4.94 (1H, m), 6.46 - 6.49 (1H, m), 6.51 - 6.55 (1H, m), 6.81 - 6.92 (2H, m), 6.96 - 7.06 (1H, m), 7.19 - 7.27 (1H, m), 7.37 - 7.41 (1H, m), 7.42 - 7.47 (2H, m), 7.50 - 7.56 (3H, m), 7.56 - 7.59 (1H, m), 7.95 (1H, d), 8.27 (1H, br s), 10.24 (1H, s), 13.92 - 14.46 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 816.6.

EXAMPLE 54

Intermediate 54a:

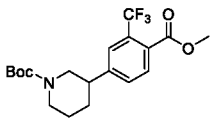
tert-Butyl 5-(4-(methoxycarbonyl)-3-(trifluoromethyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[1986] Prepared in an analogous method to Intermediate 45a starting from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (640 mg, 2.07 mmol) and methyl 4-bromo-2-(trifluoromethyl)benzoate (961 mg, 3.40 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (746 mg, 94%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s), 2.29 - 2.43 (2H, m), 3.53 - 3.63 (2H, m), 3.95 (3H, s), 4.23 - 4.39 (2H, m), 6.34 - 6.43 (1H, m), 7.54 - 7.65 (1H, m), 7.70 - 7.78 (1H, m), 7.78 - 7.85 (1H, m); *m/z* (ES$^+$) $[M–tBu+2H]^+$ = 330.0.

Intermediate 54b:

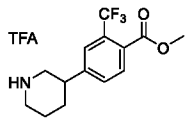
rac-tert-Butyl 3-(4-(methoxycarbonyl)-3-(trifluoromethyl)phenyl)piperidine-1-carboxylate



[1987] To a solution of Intermediate 54a (746 mg, 1.94 mmol) in MeOH (9679 µl) was added 10% Pd/C (206 mg, 0.19 mmol) under N_2. The flask was charged with H_2 and stirred at r.t. for 16h. Upon completion, the reaction mixture was filtered through celite, washed with MeOH, and concentrated under reduced pressure to afford the title compound (750 mg, 100%) as a colorless oil. *m/z* (ES$^+$) $[M–Boc+2H]^+$ = 288.1.

Intermediate 54c:

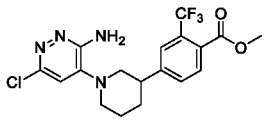
rac-Methyl 4-(piperidin-3-yl)-2-(trifluoromethyl)benzoate



[1988] Prepared in an analogous method to Intermediate 1i starting from Intermediate 54b (750 mg, 1.76 mmol) to give the title compound (778 mg, 100%) as a colorless oil, which was carried forward without purification. *m/z* (ES^+) $[M+H]^+$ = 288.3.

Intermediate 54d:

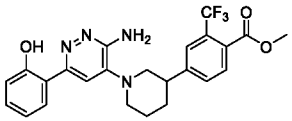
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoate



[1989] Prepared in an analogous method to Intermediate 1d starting from Intermediate 54c (778 mg, 1.72 mmol). Trituration with Et_2O gave the title compound (715 mg, 100%) as an brown solid, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 414.0.

Intermediate 54e:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoate

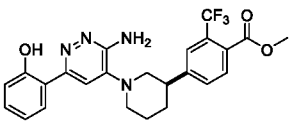


[1990] Prepared in an analogous method to Intermediate 1e starting from Intermediate 54d (715 mg, 1.72 mmol). Purification by FSC (elution gradient: 1 to 10% MeOH in DCM) gave the title compound (406 mg, 50%) as a colorless white solid. ^{1}H NMR (DMSO-*d*6): δ 1.68 - 1.81 (1H, m), 1.87 - 1.97 (2H, m), 1.98 - 2.05 (1H, m), 2.73 - 2.86 (2H, m), 3.50 - 3.56 (1H, m), 3.57 (2H, s), 3.87 (3H, s), 6.08 - 6.35 (2H, m), 6.88 (2H, s), 7.18 - 7.27 (1H, m), 7.52 - 7.59 (1H, m), 7.77 - 7.81 (1H, m), 7.82 - 7.87 (2H, m), 7.89 - 7.96 (1H, m), 13.87 - 14.52 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 473.0.

Intermediate 54f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))



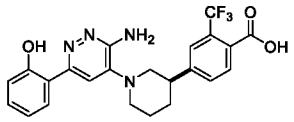
Isomer 2

[1991] Intermediate 54e (406 mg, 0.86 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak IG 21 x 250 mm; mobile phase: 45% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 75.0 mL/min; BPR: 100 bar; Column temperature: 40°C to give the title compound that eluted second from the column (37 mg, 9% yield, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 473.0.

Intermediate 54g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

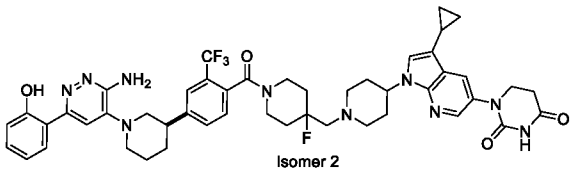


[1992] Prepared in an analogous method to Intermediate 26j starting from Intermediate 54f (37 mg, 0.08 mmol). The reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq. HCl, and filtered to give the title compound (14 mg, 39% yield) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 459.1.

EXAMPLE 54:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

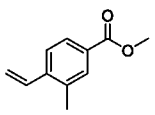


[1993] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 54g (10 mg, 0.02 mmol) and Intermediate 20g (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 in 50% MeCN in water with 0.1% FA) gave the title compound (7.3 mg, 37%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.58 - 0.71 (2H, m), 0.79 - 0.91 (2H, m), 1.69 - 1.96 (9H, m), 1.97 - 2.14 (5H, m), 2.29 - 2.36 (1H, m), 2.39 - 2.44 (1H, m), 2.59 - 2.69 (2H, m), 2.73 - 2.78 (2H, m), 2.79 - 2.89 (2H, m), 2.99 - 3.22 (5H, m), 3.50 - 3.67 (2H, m), 3.75 - 3.87 (2H, m), 4.22 - 4.38 (1H, m), 4.49 - 4.65 (1H, m), 6.17 - 6.58 (2H, m), 6.84 - 6.97 (2H, m), 7.21 - 7.30 (1H, m), 7.36 - 7.45 (1H, m), 7.46 - 7.53 (1H, m), 7.54 - 7.60 (1H, m), 7.71 - 7.77 (1H, m), 7.78 - 7.82 (1H, m), 7.85 - 7.93 (1H, m), 7.94 - 7.98 (1H, m), 8.16 - 8.20 (1H, m), 10.32 - 10.42 (1H, m) (-OH not observed); *m/z* (ES^+) $[M+H]^+$ = 909.5.

EXAMPLE 55

Intermediate 55a:

Methyl 3-methyl-4-vinylbenzoate

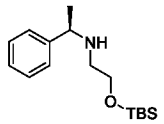


[1994] 1,4-Dioxane (100 mL) and H_2O (20 mL) were added to a mixture of methyl 4-bromo-3-methylbenzoate (5.00 g, 21.8 mmol), potassium vinyltrifluoroborate (5.85 g, 43.7 mmol), Pd

(dppf)Cl_2·DCM adduct (1.78 g, 2.18 mmol) and K_2CO_3 (6.03 g, 43.7 mmol) under nitrogen. The flash was evacuated and backfilled with nitrogen (5x). The mixture was stirred at 100 °C for 3h. After cooling to r.t., the mixture was concentrated under reduced pressure. EtOAc (50 mL), DCM (100 mL), 1 M NaOH (25 mL) and brine (50 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (3.56 g, 93%) as a colorless liquid. ^{1}H NMR (DMSO-*d*6): δ 2.35 (3H, s), 3.83 (3H, s), 5.45 (1H, dd), 5.84 (1H, dd), 6.98 (1H, dd), 7.64 (1H, d), 7.72 - 7.80 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 177.1.

Intermediate 55b:

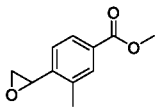
(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-N-(1-phenylethyl)ethan-1-amine



[1995] K_2CO_3 (14.9 g, 108 mmol) and (2-bromoethoxy)(*tert*-butyl)dimethylsilane (4.63 mL, 21.6 mmol) were added to a solution of (*R*)-1-phenylethan-1-amine (2.75 mL,. 21.6 mmol) in MeCN (65 mL). The mixture was stirred at 75 °C for 16h. After cooling to r.t., the mixture was filtered and the filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 80% [3:1 EtOAc/EtOH] in hexanes and 0 to 100% EtOAc in hexanes) gave the title compound (2.79 g, 46%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ -0.01 (6H, d), 0.83 (9H, s), 1.21 (3H, d), 1.90 (1H, br s), 2.33 - 2.41 (1H, m), 2.42 - 2.48 (1H, m), 3.56 (2H, t), 3.69 (1H, q), 7.16 - 7.22 (1H, m), 7.24 - 7.33 (4H, m); *m/z* (ES^+) $[M+H]^+$ = 280.2.

Intermediate 55c:

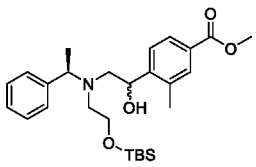
rac-Methyl 3-methyl-4-(oxiran-2-yl)benzoate



[1996] *m*-CPBA (6.97 g, 40.4 mmol) was added to a solution of Intermediate 55a (3.56 g, 20.2 mmol) in DCM (81 mL). The mixture was stirred at r.t. for 15h, washed with 3 M aq. NaOH/brine/H_2O (200 mL, 1:1:2) and 3 M aq. NaOH (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound as a colorless liquid (3.52 g, 91%). ^{1}H NMR (DMSO-*d*6): δ 2.43 (3H, s), 2.67 (1H, dd), 3.17 (1H, dd), 3.83 (3H, s), 4.08 - 4.18 (1H, m), 7.22 (1H, d), 7.71 - 7.83 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 193.1.

Intermediate 55d:

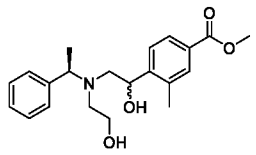
Methyl 4-(2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)((*R*)-1-phenylethyl)amino)-1-hydroxyethyl)-3-methylbenzoate



[1997] A mixture of Intermediate 55b (6.92 g, 24.8 mmol) and Intermediate 55c (2.47 g, 12.9 mmol) was stirred at 120 °C for 16 h, at 140 °C for 5 h, and at 150 °C for 42 h. After cooling to r.t., the mixture was purified by FSC (elution gradient: 0 to 100% DCM in hexanes, then EtOAc) to give the title compound (6.30 g, 104%) as a yellow oil, 1:1 mixture of diastereomers and containing minor impurities. The product was used for the next step without further purification. ^{1}H NMR (DMSO-*d*6): δ -0.06 - 0.03 (6H, m), 0.80 - 0.86 (9H, m), 1.29 (3H, dd), 2.10 - 2.31 (3H, m), 2.52 - 2.74 (4H, m), 3.39 - 3.61 (2H, m), 3.79 - 3.86 (3H, m), 3.94 - 4.03 (1H, m), 4.72 - 4.85 (1H, m), 4.91 - 5.06 (1H, m), 7.18 - 7.25 (1H, m), 7.26 - 7.39 (4H, m), 7.49 - 7.56 (1H, m), 7.65 - 7.72 (1H, m), 7.72 - 7.78 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 472.0.

Intermediate 55e:

Methyl 4-(1-hydroxy-2-((2-hydroxyethyl)((*R*)-1-phenylethyl)amino)ethyl)-3-methylbenzoate



[1998] TBAF (26.7 mL, 26.7 mmol, 1 M in THF) was added to Intermediate 55d (6.29 g, 13.3 mmol) in THF (18 mL). The mixture was stirred at r.t. for 30 minutes, diluted with EtOAc (100 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% [0.07 M NH_3 in MeOH] in DCM) to give the title compound (3.35 g, 70%) as a yellow oil and 1:1 mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 1.27 - 1.33 (3H, m), 2.11 - 2.29 (3H, m), 2.41 - 2.77 (4H, m), 3.37 - 3.52 (2H, m), 3.81 - 3.87 (3H, m), 3.93 - 4.05 (1H, m), 4.47 - 4.59 (1H, m), 4.71 - 4.88 (1H, m), 5.08 - 5.25 (1H, m), 7.19 - 7.25 (1H, m), 7.27 - 7.40 (4H, m), 7.49 - 7.56 (1H, m), 7.64 - 7.72 (1H, m), 7.73 - 7.79 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 358.4.

Intermediate 55f:

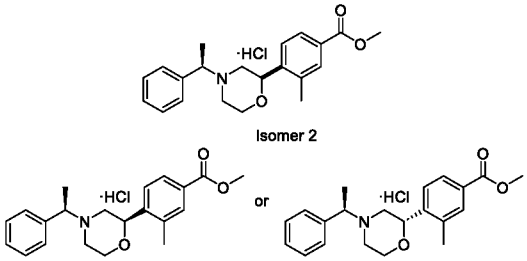
Methyl 3-methyl-4-((*R**)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate (Isomer 2)

((*relative configuration not yet confirmed))

Methyl 3-methyl-4-((*R*)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate

or

Methyl 3-methyl-4-((*S*)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate



[1999] DIAD (2.51 mL, 12.9 mmol) was added dropwise to a solution of Intermediate 55e (3.29 g, 9.21 mmol) and tri-*n*-butylphosphine (3.34 mL, 13.4 mmol) in THF (65 mL) at 0 °C. The mixture was stirred at 0 °C for 3 minutes and at r.t. for 15 minutes. The mixture was diluted with EtOAc (100 mL), washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% [3:1 EtOAc/EtOH] in hexanes). Product fractions were concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane and acidified with 4 M HCl in 1,4-dioxane. The mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) to give the title compound that eluted second from the column (1.07 g, 31%) as a white solid and hydrochloride salt. ^{1}H NMR (DMSO-*d*6): δ 1.72 (3H, br d), 2.23 (3H, s), 2.70 - 2.82 (1H, m), 2.98 - 3.14 (2H, m), 3.73 (1H, br d), 3.81 (3H, s), 4.13 - 4.26 (2H, m), 4.48 - 4.61 (1H, m), 5.24 (1H, br d), 7.39 - 7.49 (4H, m), 7.61 (2H, br d), 7.74 (1H, s), 7.78 (1H, br d), 11.64 (1H, br d); *m/z* (ES$^+$) $[M+H]^+$ = 340.2.

Intermediate 55g:

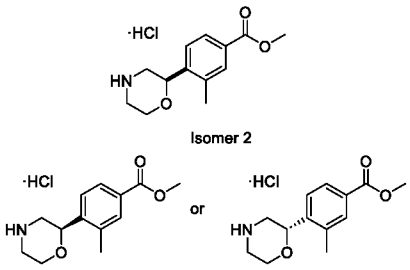
Methyl (*R**)-3-methyl-4-(morpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-3-methyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-3-methyl-4-(morpholin-2-yl)benzoate



[2000] EtOH (34 mL) was added to a mixture of Intermediate 55f (951 mg, 2.53 mmol) and Pd/C (269 mg, 0.25 mmol, 10 wt% Pd). The mixture was sparged with H_2 for 3 minutes and stirred under an atmosphere of H_2 for 3 h. After cooling to r.t., the mixture was sparged with nitrogen for 5 minutes and filtered through a pad of Celite with EtOH. The filtrate was concentrated under reduced pressure to give the title compound (653 mg, 95%) as a white solid and hydrochloride salt. ^{1}H NMR (DMSO-*d*6): δ 2.38 (3H, s), 2.86 (1H, t), 3.11 (1H, td), 3.21 - 3.39 (2H, m), 3.83 (3H, s), 3.99 (1H, td), 4.12 (1H, dd), 5.09 (1H, br d), 7.54 (1H, d), 7.77 - 7.85 (2H, m), 9.63 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 236.1.

Intermediate 55h:

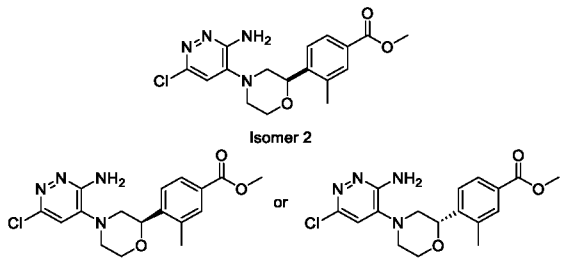
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate



[2001] Prepared in an analogous method to Intermediate 1d starting from Intermediate 55g (708 mg, 2.61 mmol) using DMSO as a solvent. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (738 mg, 78%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.40 (3H, s), 2.56 - 2.66 (1H, m), 2.81 (1H, td), 3.38 (1H, br d), 3.48 (1H, br d), 3.83 (3H, s), 3.95 - 4.09 (2H, m), 4.95 (1H, br d), 6.26 (2H, s), 6.95 (1H, s), 7.58 (1H, d), 7.74 - 7.83 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 363.1.

Intermediate 55i:

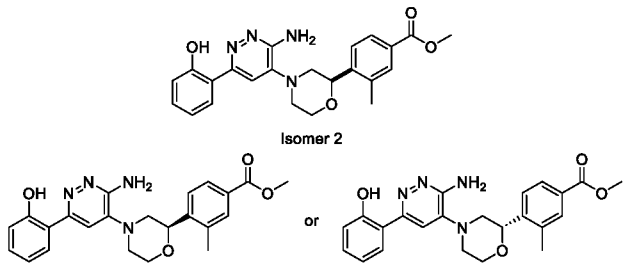
Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate



[2002] Prepared in an analogous method to Intermediate 1e starting from Intermediate 55h (732 mg, 2.02 mmol). Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (731 mg, 86%) as an orange solid. ^{1}H NMR (DMSO-*d*6): δ 2.43 (3H, s), 2.72 - 2.81 (1H, m), 2.89 (1H, ddd), 3.47 - 3.58 (2H, m), 3.84 (3H, s), 4.05 - 4.13 (2H, m), 5.00 (1H, br d), 6.42 (2H, s), 6.81 - 6.89 (2H, m), 7.21 (1H, t), 7.55 (1H, s), 7.63 (1H, d), 7.79 (1H, s), 7.82 (1H, d), 7.91 (1H, d), 14.16 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.2.

Intermediate 55j:

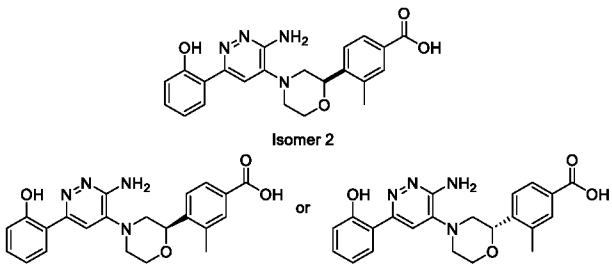
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid



[2003] Prepared in an analogous method to Intermediate 1f starting from Intermediate 55i (726 mg, 1.73 mmol). The mixture was acidified to pH 3, diluted with brine, and extracted with DCM–IPA (3:1, 3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with DCM–hexanes (1:1) to give the title compound (568 mg, 81%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 2.41 (3H, s), 2.78 (1H, br t), 2.86 - 2.95 (1H, m), 3.53 (2H, br t), 4.08 (2H, br d), 4.99 (1H, br d), 6.47 (2H, br s), 6.81 - 6.94 (2H, m), 7.22 (1H, t), 7.55 (1H, s), 7.60 (1H, d), 7.77 (1H, s), 7.80 (1H, d), 7.90 (1H, d), 12.68 - 14.16 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 407.2.

EXAMPLE 55:

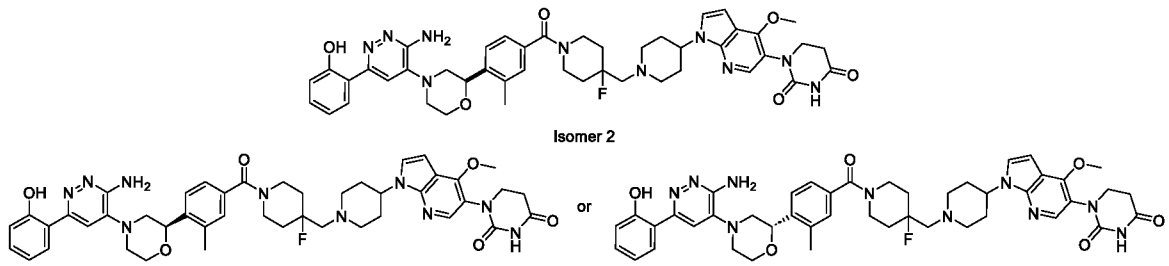
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



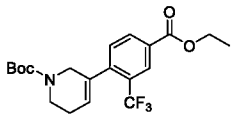
[2004] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (10 mg, 0.02 mmol) and Intermediate 33h (23 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (22.5 mg, 61%) as a white solid.^{1}H NMR (DMSO-*d*6): δ 1.65 - 1.80 (2H, m), 1.82 - 1.92 (3H, m), 1.92 - 2.02 (1H, m), 2.03 - 2.14 (2H, m), 2.33 - 2.39 (2H, m), 2.42 (3H, s), 2.59 - 2.79 (4H, m), 2.82 - 2.95 (2H, m), 3.01 - 3.12 (2H, m), 3.12 - 3.23 (1H, m), 3.23 - 3.28 (1H, m), 3.45 - 3.59 (4H, m), 3.60 - 3.79 (2H, m), 4.05 - 4.17 (2H, m), 4.25 (3H, s), 4.59 - 4.71 (1H, m), 4.92 -

5.03 (1H, m), 6.33 - 6.58 (2H, m), 6.80 - 6.91 (3H, m), 7.20 - 7.32 (3H, m), 7.54 - 7.59 (2H, m), 7.60 - 7.67 (1H, m), 7.88 - 7.97 (1H, m), 7.99 - 8.07 (1H, m), 10.26 - 10.39 (1H, m), 13.89 - 14.53 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 847.4.

EXAMPLE 56

Intermediate 56a:

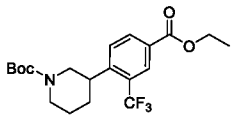
tert-Butyl 5-(4-(ethoxycarbonyl)-2-(trifluoromethyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2005] Prepared in an analogous method to Intermediate 45a starting from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.00 g, 3.23 mmol) and ethyl 4-bromo-3-(trifluoromethyl)benzoate (0.961 g, 3.23 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.10 g, 85%) as a white solid. ^1H NMR ($CDCl_3$): δ 1.44 (3H, s), 1.50 (9H, br s), 2.23 - 2.40 (2H, m), 3.54 - 3.67 (2H, m), 4.02 - 4.12 (2H, m), 4.44 (2H, d), 5.70 - 5.85 (1H, m), 7.30 - 7.46 (1H, m), 8.12 - 8.23 (1H, m), 8.36 (1H, s); *m/z* (ES^+) $[M–tBu+2H]^+$ = 344.0

Intermediate 56b:

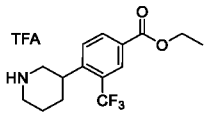
rac-tert-Butyl 3-(4-(ethoxycarbonyl)-2-(trifluoromethyl)phenyl)piperidine-1-carboxylate



[2006] Prepared in an analogous method to Intermediate 54b starting from Intermediate 56a (1.11 g, 2.78 mmol) to give the title compound (1.12 mg, 100%) as a colorless oil, which was carried forward without intermediate purification. *m/z* (ES^+) $[M–tBu+2H]^+$ = 344.6.

Intermediate 56c:

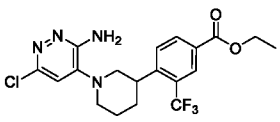
rac-Ethyl 4-(piperidin-3-yl)-3-(trifluoromethyl)benzoate



[2007] Prepared in an analogous method to Intermediate 1i starting from Intermediate 56b (1.12 g, 2.79 mmol) to give the title compound (1.16 g, 100%) in the form of a trifluoroacetic acid salt as a colorless oil. *m/z* (ES^+) $[M+H]^+$ = 301.0.

Intermediate 56d:

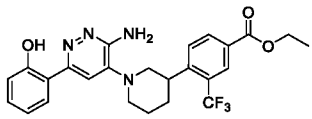
rac-Ethyl 4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoate



[2008] Prepared in an analogous method to Intermediate 1d starting from Intermediate 56c (1.16 g, 2.79 mmol) and 4-bromo-6-chloropyridazin-3-amine (582 mg, 2.79 mmol). Trituration with Et_2O gave the title compound (1.20 g, 100%) as an brown solid. *m/z* (ES^+) $[M+H]^+$ = 429.0.

Intermediate 56e:

rac-Ethyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoate



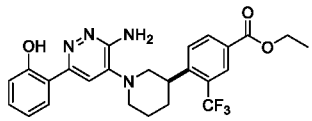
[2009] Prepared in an analogous method to Intermediate 1e starting from Intermediate 56d (210 mg, 0.49 mmol). Purification by FSC (elution gradient: 10 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (195 mg, 82%) as a brown solid. ^1H NMR ($CDCl_3$): δ 1.43 (3H, s), 1.72 - 1.87 (1H, m), 1.89 - 2.02 (1H, m), 2.06 - 2.10 (1H, m), 2.08 - 2.17 (1H, m), 2.70 - 2.81 (1H, m), 2.84 - 2.95 (1H, m), 3.41 - 3.54 (1H, m), 3.59 - 3.68 (2H, m), 4.37 - 4.51 (2H, m), 4.75 - 4.93 (2H, m), 6.83 - 6.96 (1H, m), 7.04 - 7.11 (1H, m), 7.28 (2H, s), 7.53 - 7.66 (2H, m), 8.16 - 8.28 (1H, m), 8.33 - 8.43 (1H, m), 13.42 - 14.02 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 487.5.

Intermediate 56f:

Ethyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoate

(Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

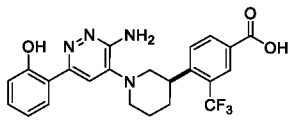
[2010] Intermediate 56e (195 mg, 0.40 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak ID 21 mm x 250 mm x 5 mm; mobile phase: 25% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 70 ; BPR: 120 bar ; Column temperature: 40°C to afford the title compound that eluted second from the column (63 mg, 32% yield, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 487.0.

Intermediate 56g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoic acid

(Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

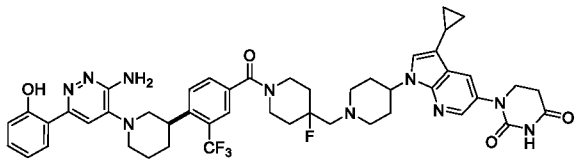
[2011] Prepared in an analogous method to Intermediate 1f starting from Intermediate 56f (63 mg, 0.13 mmol). The reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq. HCl.

The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated to give the title compound (56 mg, 94%) as an brown solid. *m/z* (ES^-) $[M–H]^-$ = 457.2.

EXAMPLE 56:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



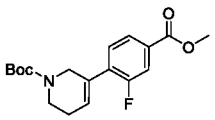
Isomer 2

[2012] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 56g (10 mg, 0.02 mmol) and Intermediate 20g (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (6.1 mg, 31%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.61 - 0.70 (2H, m), 0.82 - 0.90 (2H, m), 1.68 - 1.86 (6H, m), 1.87 - 1.97 (3H, m), 1.97 - 2.13 (4H, m), 2.33 - 2.40 (2H, m), 2.47 - 2.49 (1H, m), 2.53 - 2.57 (1H, m), 2.58 - 2.62 (1H, m), 2.63 - 2.68 (2H, m), 2.73 - 2.80 (2H, m), 3.01 - 3.08 (2H, m), 3.10 - 3.26 (2H, m), 3.37 - 3.43 (1H, m), 3.44 - 3.59 (1H, m), 3.65 - 3.73 (1H, m), 3.78 - 3.87 (2H, m), 4.22 - 4.41 (1H, m), 4.55 - 4.66 (1H, m), 6.18 - 6.33 (2H, m), 6.82 - 6.96 (2H, m), 7.14 - 7.31 (1H, m), 7.38 - 7.48 (1H, m), 7.50 - 7.59 (1H, m), 7.70 - 7.82 (2H, m), 7.85 - 7.99 (3H, m), 8.10 - 8.24 (1H, m), 10.33 - 10.43 (1H, m), 14.06 - 14.43 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 909.4.

EXAMPLE 57

Intermediate 57a:

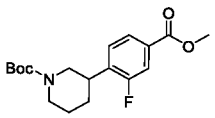
tert-Butyl 5-(2-fluoro-4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2013] Prepared in an analogous method to Intermediate 45a starting from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.00 g, 3.23 mmol) and methyl 4-bromo-3-fluorobenzoate (0.754 g, 3.23 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (964 mg, 89%) as a light brown oil. ^1H NMR ($CDCl_3$): δ 1.42 (9H, s), 2.26 - 2.32 (2H, m), 3.44 - 3.53 (2H, m), 3.87 (3H, s), 4.12 - 4.22 (2H, m), 6.06 - 6.32 (1H, m), 7.49 - 7.58 (1H, m), 7.66 - 7.73 (1H, m), 7.76 - 7.83 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 236.1.

Intermediate 57b:

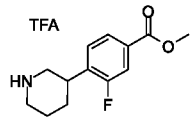
rac-tert-Butyl 3-(2-fluoro-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2014] Prepared in an analogous method To Intermediate 54b starting from Intermediate 57a (857 mg, 2.54 mmol). to give the title compound (857 mg, 88%), as a colorless oil which was carried forward without an intermediate purification. ^{1}H NMR ($CDCl_3$): δ 1.49 (9H, s), 1.58 - 1.73 (2H, m), 1.75 - 1.84 (1H, m), 1.96 - 2.06 (1H, m), 2.69 - 2.82 (1H, m), 2.82 - 2.92 (1H, m), 3.00 - 3.10 (1H, m), 3.93 (3H, s), 4.06 - 4.31 (2H, m), 7.26 - 7.35 (1H, m), 7.66 - 7.74 (1H, m), 7.77 - 7.85 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 338.1.

Intermediate 57c:

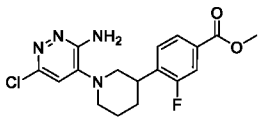
rac-Methyl 3-fluoro-4-(piperidin-3-yl)benzoate



[2015] Prepared in an analogous method to Intermediate 1i starting from Intermediate 57b (857 mg, 2.54 mmol) to give the title compound (892 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil; *m/z* (ES^+) $[M+H]^+$ = 238.2.

Intermediate 57d:

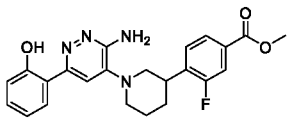
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoate



[01000] Prepared in an analogous method to Intermediate 1d starting from Intermediate 57c (892 mg, 2.54 mmol) and 4-bromo-6-chloropyridazin-3-amine (1059 mg, 5.08 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (474 mg, 51%) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.59 - 1.72 (1H, m), 1.80 - 1.86 (1H, m), 1.87 - 1.98 (2H, m), 2.58 - 2.70 (1H, m), 2.77 - 2.87 (1H, m), 3.34 - 3.41 (1H, m), 3.42 - 3.51 (2H, m), 3.87 (3H, s), 6.14 (2H, s), 6.97 (1H, s), 7.55 - 7.62 (1H, m), 7.65 - 7.71 (1H, m), 7.76 - 7.82 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 365.3.

Intermediate 57e:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoate



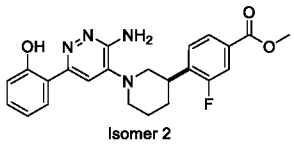
[01001] Prepared in an analogous method to Intermediate 1e starting from Intermediate 57d (474 mg, 1.30 mmol). Purification by FSC (elution gradient: 1 to 7% MeOH in DCM) gave the title compound (281 mg, 51%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.64 - 1.78 (1H, m), 1.82 - 1.91 (1H, m), 1.93 - 2.02 (2H, m), 2.64 - 2.75 (1H, m), 2.86 - 3.01 (1H, m), 3.38 - 3.47 (1H, m), 3.49 - 3.54 (1H, m), 3.56 - 3.61 (1H, m), 3.84 - 3.89 (3H, m), 6.19 - 6.42 (2H, m), 6.85 - 6.91 (2H, m), 7.20 - 7.27 (1H, m), 7.54 - 7.58 (1H, m),

7.60 - 7.66 (1H, m), 7.66 - 7.73 (1H, m), 7.76 - 7.84 (1H, m), 7.88 - 7.95 (1H, m), 14.11 - 14.31 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 423.5.

Intermediate 57f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoate (Isomer 2)

((*absolute configuration not yet confirmed))



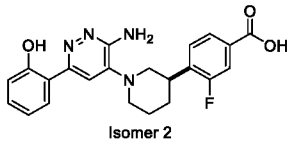
Isomer 2

[2016] Intermediate 57e (200 mg, 0.49 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak OJ 21 mm x 250 mm x 5 mm; mobile phase: 20% MeOH in $scCO_2$; Flow rate: 75 mL/min; BPR: 100 bar; Column temperature: 40°C to give the title compound that eluted second from the column (57 mg, 28% yield, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 423.1.

Intermediate 57g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



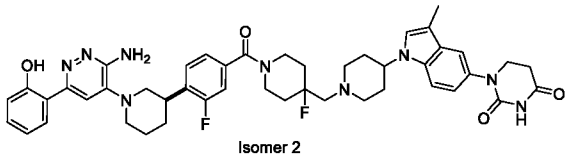
Isomer 2

[2017] Prepared in an analogous method to Intermediate 26j starting from Intermediate 57f (56 mg, 0.13 mmol). Upon completion, the reaction mixture was partially concentrated under reduced pressure, acidified with 1 M aq. HCl, and filtered to afford the title compound (54 mg, 100%) as a white solid. *m/z* (ES^-) $[M-H]^-$ = 407.1.

EXAMPLE 57:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

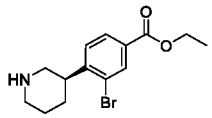
[2018] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 57g (10 mg, 0.02 mmol) and Intermediate 1k (26 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (8.4 mg, 41%) as a white solid. ^1H NMR (DMSO-*d*6): δ

1.61 - 1.82 (4H, m), 1.83 - 2.07 (10H, m), 2.23 (3H, s), 2.40 (3H, br t), 2.59 (1H, br s), 2.66 (2H, br d), 2.72 (3H, t), 2.90 - 2.98 (1H, m), 3.03 (2H, br d), 3.51 (1H, br d), 3.60 (1H, br d), 3.76 (2H, t), 4.27 (2H, br s), 6.28 (2H, s), 6.84 - 6.88 (1H, m), 6.89 (1H, s), 7.05 (1H, dd), 7.20 - 7.29 (3H, m), 7.30 (1H, s), 7.39 (1H, d), 7.46 (1H, d), 7.51 - 7.56 (1H, m), 7.57 (1H, s), 7.93 (1H, d), 10.23 (1H, s), 14.06 - 14.51 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 832.4.

EXAMPLE 58

Intermediate 58a:

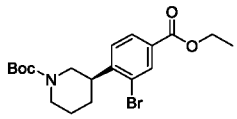
Ethyl (*R*)-3-bromo-4-(piperidin-3-yl)benzoate



[2019] A solution of Intermediate 12b (500 mg, 1.22 mmol) in EtOH (3.1 mL) was charged with K_2CO_3 (846 mg, 6.12 mmol) and stirred at 80 °C for 4 h. Upon completion, the reaction mixture was filtered through a pad of celite and concentrated to give the title compound (382 mg, 100%) as an orange solid, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 314.3.

Intermediate 58b:

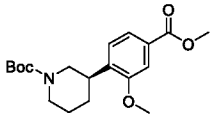
tert-Butyl (*R*)-3-(2-bromo-4-(ethoxycarbonyl)phenyl)piperidine-1-carboxylate



[2020] To a solution of Intermediate 58a (382 mg, 1.22 mmol) in DCM (11.7 mL) was added Boc_2O (312 µl, 1.35 mmol) and Et_3N (205 µl, 1.47 mmol) in dropwise fashion. The reaction mixture was stirred for 15 minutes, then concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) afforded the title compound (396 mg, 78%) as a colorless oil. *m/z* (ES^+) $[M–Boc+2H]^+$ = 309.9.

Intermediate 58c:

tert-Butyl (*R*)-3-(2-methoxy-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

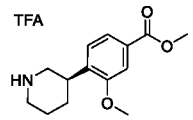


[2021] A solution of Intermediate 58b (280mg, 0.68 mmol), *t*-BuXPhos Pd G3 (53.9 mg, 0.07 mmol), *t*-BuXPhos (28.8 mg, 0.07 mmol), Cs_2CO_3 (266 mg, 0.81 mmol), PhMe (1698 µl) and MeOH (1698 µl) was heated to 110 °C for 2 h. The reaction mixture was cooled to r.t., filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound, (140 mg, 59%) as a light brown oil. ^1H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.44 - 1.51 (1H, m), 1.61 - 1.76 (2H, m), 1.78 - 1.87 (1H, m), 2.68 - 2.87 (2H, m), 2.96 - 3.06 (1H, m), 3.86 (3H, s), 3.86 - 3.91 (3H, m), 3.94 -

4.03 (2H, m), 7.33 - 7.41 (1H, m), 7.46 - 7.50 (1H, m), 7.53 - 7.61 (1H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 250.1.

Intermediate 58d:

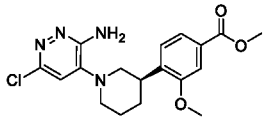
Methyl (*R*)-3-methoxy-4-(piperidin-3-yl)benzoate



[2022] Prepared in an analogous method to Intermediate 1i starting from Intermediate 58c (150 mg, 0.43 mmol) to give the title compound (199 mg, 100%) as a purple oil, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 250.6.

Intermediate 58e:

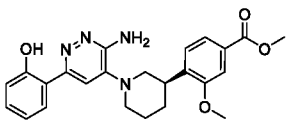
Methyl (*R*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoate



[2023] Prepared in an analogous method to Intermediate 1d starting from Intermediate 58d (199 mg, 0.43 mmol) and 4-bromo-6-chloropyridazin-3-amine (89 mg, 0.43 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (80 mg, 50%) as an yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.64 - 1.74 (1H, m), 1.76 - 1.87 (2H, m), 1.87 - 1.94 (1H, m), 2.60 - 2.75 (2H, m), 3.34 - 3.40 (1H, m), 3.41 - 3.47 (1H, m), 3.53 - 3.63 (1H, m), 3.84 - 3.88 (3H, m), 3.88 - 3.93 (3H, m), 6.03 - 6.12 (2H, m), 6.96 - 7.00 (1H, m), 7.40 - 7.44 (1H, m), 7.48 - 7.51 (1H, m), 7.56 - 7.60 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 377.1.

Intermediate 58f:

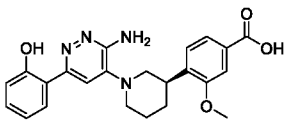
Methyl (*R*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoate



[2024] Prepared in an analogous method to Intermediate 1e starting from Intermediate 58e (70 mg, 0.21 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (70 mg, 76%) as an yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.66 - 1.78 (1H, m), 1.81 - 1.88 (1H, m), 1.89 - 1.98 (2H, m), 2.65 - 2.73 (1H, m), 2.78 - 2.87 (1H, m), 3.40 - 3.47 (1H, m), 3.48 - 3.57 (1H, m), 3.59 - 3.66 (1H, m), 3.87 (3H, s), 3.89 (3H, s), 6.19 - 6.30 (2H, m), 6.82 - 6.90 (2H, m), 7.20 - 7.26 (1H, m), 7.45 - 7.51 (2H, m), 7.52 - 7.56 (1H, m), 7.58 - 7.62 (1H, m), 7.88 - 7.94 (1H, m), 14.21 - 14.29 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 435.3.

Intermediate 58g:

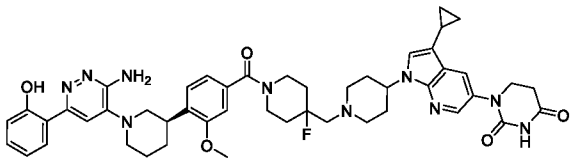
(*R*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoic acid



[2025] Prepared in an analogous method to Intermediate 26j starting from Intermediate 58f (70 mg, 0.16 mmol). The reaction mixture was concentrated under reduced pressure partially, acidified with 1 M aq. HCl, filtered, and dried to afford the title compound (67 mg, 99%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 421.3.

EXAMPLE 58:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

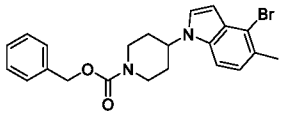


[2026] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 58g (10 mg, 0.02 mmol) and Intermediate 20g (26 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (11 mg, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.70 (2H, m), 0.81 - 0.89 (2H, m), 1.63 - 1.77 (3H, m), 1.78 - 1.88 (4H, m), 1.89 - 2.01 (4H, m), 2.01 - 2.12 (3H, m), 2.33 - 2.41 (2H, m), 2.58 - 2.62 (1H, m), 2.62 - 2.69 (2H, m), 2.77 (2H, s), 2.81 - 2.88 (1H, m), 2.99 - 3.07 (2H, m), 3.10 - 3.23 (1H, m), 3.37 - 3.44 (1H, m), 3.45 - 3.58 (2H, m), 3.61 - 3.68 (1H, m), 3.82 (2H, s), 3.86 (3H, s), 4.10 - 4.39 (1H, m), 4.54 - 4.66 (1H, m), 6.19 - 6.32 (2H, m), 6.85 - 6.91 (2H, m), 6.98 - 7.04 (2H, m), 7.21 - 7.27 (1H, m), 7.36 - 7.41 (1H, m), 7.43 - 7.46 (1H, m), 7.49 - 7.59 (1H, m), 7.91 - 7.94 (1H, m), 7.94 - 7.96 (1H, m), 8.16 - 8.18 (1H, m), 10.28 - 10.42 (1H, m), 12.52 - 12.98 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 871.5.

EXAMPLE 59

Intermediate 59a:

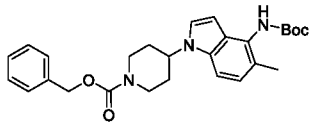
Benzyl 4-(4-bromo-5-methyl-indol-1-yl)piperidine-1-carboxylate



[2027] Prepared in an analogous method to Intermediate 1g starting from benzyl 4-methylsulfonyloxypiperidine-1-carboxylate (4.48 g, 14.28 mmol) and 4-bromo-5-methyl-1*H*-indole (1.0 g, 4.76 mmol) in DMF (19 mL). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.992 g, 49%) as a light peach solid. ^{1}H NMR (DMSO-*d*6): δ 1.82-2.02 (4H, m), 2.43 (3H, s), 3.07 (2H, br s), 4.20 (2H, br d), 4.61 (1H, br t), 5.12 (2H, br s), 6.37 (1H, br s), 7.11 (1H, br d), 7.27-7.37 (1H, m), 7.40 (4H, br d), 7.53 (1H, br d), 7.58 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 429.1.

Intermediate 59b:

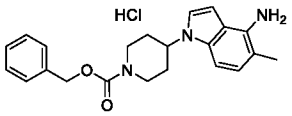
Benzyl 4-(4-((*tert*-butoxycarbonyl)amino)-5-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2028] 1,4-Dioxane (4 mL) was added to a mixture of Intermediate 59a (0.299 g, 0.7 mmol), *tert*-butyl carbamate (0.246 g, 2.10 mmol), XPhos Pd G3 (0.059 g, 0.07 mmol) and Cs_2CO_3 (0.570 g, 1.75 mmol) under N_2. The mixture was sparged with N_2. The resulting slurry was stirred at 100 °C for 16 h then cooled to r.t. The mixture was filtered and then the filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.323 g, 99%) as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 464.3.

Intermediate 59c:

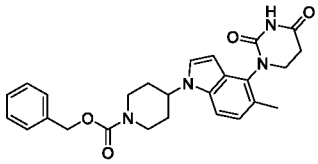
Benzyl 4-(4-amino-5-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2029] A solution of Intermediate 59b (322.6 mg, 0.70 mmol) and 4 M HCl in 1,4-dioxane (1.740 mL, 6.96 mmol was stirred at r.t for 1 h then concentrated under reduced pressure to give the title compound in the form of a hydrochloride salt (0.253 g, 100%) as a pink solid. *m/z* (ES^+) $[M+H]^+$ = 365.4.

Intermediate 59d:

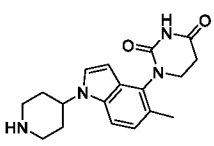
Benzyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2030] Acrylic acid (0.137 mL, 2.00 mmol) and Intermediate 59c (0.182 g, 0.5 mmol) were added to a scintillation vial. The mixture was allowed to stir at 100 °C for 3 h. The mixture was then cooled to r.t. and AcOH (3 mL) was then added. The mixture was stirred at 120 °C for 10 min. Urea (0.180 g, 3.00 mmol) was then added. The resulting solution was stirred at 120 °C for 16 h. The mixture was cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.141 g, 61%) as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 461.2.

Intermediate 59e:

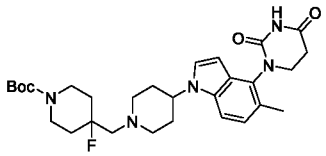
1-(5-Methyl-1-(piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2031] A solution of Intermediate 59d (141.4 mg, 0.31 mmol), Pd/C (32.7 mg, 0.03 mmol), and MeOH (3 mL) was charged with H_2. The resulting suspension was stirred at 40 °C for 16 h then cooled to r.t. The mixture was purged with N_2, filtered through celite, and concentrated to give the title compound (0.100 g, 100%) as a colourless oil, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 327.1.

Intermediate 59f:

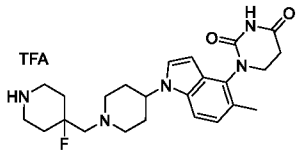
tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2032] Prepared in an analogous method to Intermediate 6g starting from Intermediate 59e (17 mg, 0.05 mmol) and Intermediate 6f (21 mg, 0.06 mmol). Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (24 mg, 85%) as a sticky reddish brown solid. *m/z* (ES^+) $[M+H]^+$ = 542.3.

Intermediate 59g:

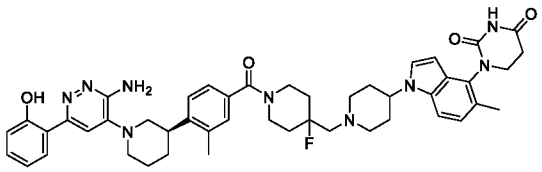
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2033] Prepared in an analogous method to Intermediate 1i starting from Intermediate 59f (23 mg, 0.04 mmol). Trituration with Et_2O gave the title compound in the form of a bis-trifluoroacetate salt (25 mg, 88%) as a light brown solid after trituration with diethyl ether. *m/z* (ES^+) $[M+H]^+$ = 442.3.

EXAMPLE 59:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2034] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (10 mg, 0.02 mmol) and Intermediate 59g (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (6.7 mg, 32%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.63 - 1.80 (2H, m), 1.86 - 1.94 (4H, m), 1.95 - 2.06 (3H, m), 2.23 (2H, s), 2.37 (1H, s), 2.41 (3H, s), 2.57 - 2.58 (1H, m), 2.58 - 2.68 (5H, m), 2.69 - 2.78 (3H, m), 2.80 - 2.89 (2H, m), 3.01 - 3.07 (2H, m), 3.08 - 3.20 (1H, m), 3.47 - 3.52 (2H, m), 3.55 - 3.63 (3H, m), 3.72 - 3.79 (1H, m), 4.12 - 4.27 (1H, m), 4.28 - 4.37

(1H, m), 6.22 - 6.31 (2H, m), 6.37 - 6.45 (1H, m), 6.84 - 6.92 (2H, m), 7.00 - 7.07 (1H, m), 7.21 - 7.27 (3H, m), 7.39 - 7.46 (2H, m), 7.47 - 7.50 (1H, m), 7.54 - 7.60 (1H, m), 7.91 - 7.97 (1H, m), 8.23 - 8.31 (1H, m), 10.25 - 10.33 (1H, m), 14.12 - 14.44 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 828.6.

EXAMPLE 60:

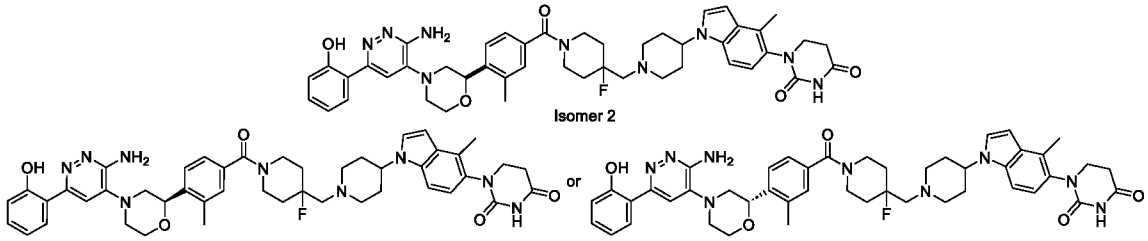
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

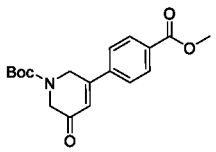


[2035] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (10 mg, 0.02 mmol) and Intermediate 32g (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (16.4 mg, 76%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.91 (8H, br d), 2.32 (3H, s), 2.35 - 2.40 (1H, m), 2.42 (3H, s), 2.43 - 2.47 (1H, m), 2.58 - 2.78 (4H, m), 2.80 - 2.94 (3H, m), 2.98 - 3.20 (3H, m), 3.39 - 3.63 (5H, m), 3.70 - 3.80 (1H, m), 4.03 - 4.15 (2H, m), 4.18 - 4.41 (2H, m), 4.93 - 5.05 (1H, m), 6.41 - 6.51 (1H, m), 6.52 - 6.57 (1H, m), 6.85 - 6.93 (2H, m), 6.98 - 7.05 (1H, m), 7.25 (2H, s), 7.27 - 7.30 (1H, m), 7.37 - 7.44 (1H, m), 7.49 - 7.54 (1H, m), 7.55 - 7.60 (2H, m), 7.88 - 7.97 (1H, m), 10.17 - 10.29 (1H, m), 12.42 - 14.03 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 830.5.

EXAMPLE 61

Intermediate 61a:

tert-Butyl 5-(4-(methoxycarbonyl)phenyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

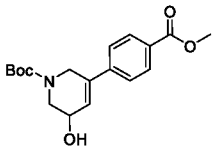


[2036] Prepared in an analogous method to Intermediate 26b starting from Intermediate 26a (9.30 g, 36.43 mmol) and (4-(methoxycarbonyl)phenyl)boronic acid (9.83g, 54.65 mmol). Purification by FSC (elution gradient: 15 to 50% EtOAc in hexanes) gave the title compound (10.5 g, 87%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.50 - 1.54 (9H, m), 3.96 (3H, s), 4.19 (2H, s), 4.66 (2H, br s), 6.57 (1H, s), 7.63 (2H, br d), 8.12 (2H, d); *m/z* (ES^+) $[M–Boc+2H]^+$ = 232.1.

Intermediate 61b:

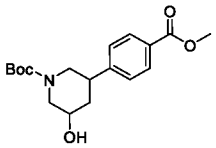
rac-tert-Butyl 3-hydroxy-5-(4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2037] Prepared in an analogous method to Intermediate 26c starting from Intermediate 61a (5.96 g, 18.00 mmol). The reaction was quenched with sat. NH_4Cl solution and partially concentrated under reduced pressure. The reaction was partitioned between EtOAc and water, and the organic phase was washed with 1N HCl, dried with MgSO4, filtered, and concentrated to give the title compound (6.02 g, 100%) as a white gum, which was carried forward without additional purification. ^{1}H NMR (CD_2Cl_2): δ 1.44 - 1.49 (9H, m), 1.73 - 1.91 (1H, m), 3.53 (1H, dd), 3.67 (1H, dd), 4.15 - 4.25 (1H, m), 4.30 - 4.41 (2H, m), 6.32 - 6.35 (1H, m), 7.50 (2H, br d), 8.01 (2H, d); *m/z* (ES^+) $[M–t\text{BuO}]^+$ = 260.1.

Intermediate 61c:

tert-Butyl 3-hydroxy-5-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2038] A solution of Intermediate 61b (6.00 g, 18 mmol), Pd/C (1.91, 1.80 mmol), and MeOH (180 mL) was charged with H_2 and stirred at r.t. for 30 minutes. Upon completion, the reaction mixture was filtered through Celite and concentrated under reduced pressure to give the title compound (5.83g, 97%) as a 3:2 mixture of isomers as a white gum, which was carried forward without intermediate purification. ^{1}H NMR (CD_2Cl_2): δ 1.38 - 1.51 (m, 9H), 1.56 - 1.67 (m, 1H), 1.76 - 1.89 (m, 1H), 2.27 (br d, J = 11.9 Hz, 1H), 2.43 - 3.06 (m, 3H), 3.75 (td, J = 10.3, 5.0 Hz, 1H), 3.88 (s, 3H), 4.03 - 4.45 (m, 2H), 7.33 (br d, J = 8.2 Hz, 2H), 7.92 - 8.05 (m, 2H). $[M–t\text{Bu}+2H]^+$ = 280.0.

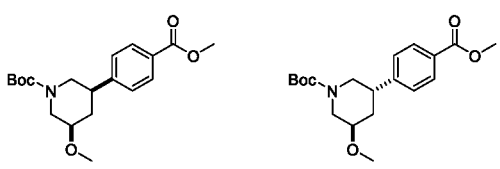
Intermediate 61d:

rac-tert-Butyl (3*R*,5*R*)-3-methoxy-5-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

and

Intermediate 61e:

rac-tert-Butyl (3*R*,5*S*)-3-methoxy-5-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

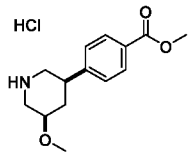


Intermediate 61d **Intermediate 61e**

[2039] A solution of Intermediate 61c (1.25 g, 3.73 mmol) in DMF (14.63 mL) was added NaH (0.298 g, 7.45 mmol). The reaction was stirred at r.t. for 30 minutes before MeI (0.280 ml, 4.47 mmol) was added and the reaction was stirred at r.t. for 1 hour. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc, dried, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 5 to 35% EtOAc in hexanes) gave the title compound *cis* isomer (0.560 g, 43%)and *trans* isomer (0.110 g, 8%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.41 - 1.49 (9H, m), 1.70 - 1.85 (1H, m), 2.14 (1H, br dd), 2.61 - 2.90 (2H, m), 3.07 - 3.18 (1H, m), 3.37 (3H, s), 3.41 - 3.56 (1H, m), 3.87 - 3.93 (3H, m), 4.01 - 4.29 (1H, m), 4.29 - 4.41 (1H, m), 7.32 (2H, d), 7.96 (2H, d); *m/z* (ES^+) $[M–tBu+2H]^+$ = 294.1.

Intermediate 61f:

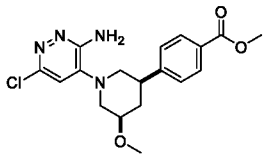
rac-Methyl 4-((3*R*,5*R*)-5-methoxypiperidin-3-yl)benzoate



[2040] Prepared in an analogous method to Intermediate 2e starting from Intermediate 61d (510 mg, 1.46 mmol) to give the title compound (415 mg, 100%) in the form of a hydrochloric acid salt as an off-white solid, which was carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 250.9.

Intermediate 61g:

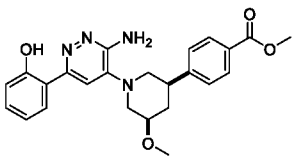
rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-chloropyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate



[2041] Prepared in an analogous method to Intermediate 1d starting from Intermediate 61f (416 mg, 1.46 mmol). Purification by FSC (elution gradient: 1 to 5% MeOH in EtOAc) gave the title compound (490 mg, 89%) as a brown gum. ^{1}H NMR (CD_2Cl_2): δ 1.59 - 1.67 (1H, m), 2.42 - 2.54 (2H, m), 2.66 (1H, t), 3.01 - 3.09 (1H, m), 3.41 (3H, s), 3.49 - 3.60 (2H, m), 3.74 (1H, br dd), 3.88 (3H, s), 4.79 (2H, s), 6.80 (1H, s), 7.36 (2H, d), 7.99 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 377.1.

Intermediate 61h:

rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate



[2042] Prepared in an analogous method to Intermediate 1e starting from Intermediate 61g (410 mg, 1.09 mmol). Purification by FSC (elution gradient: 1 in 4% MeOH in EtOAc) gave the title compound (151 mg, 32%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.63 - 1.72 (1H, m), 2.49 (1H, br d), 2.61 (1H, t), 2.76 (1H,

t), 3.40 - 3.50 (4H, m), 3.58 - 3.66 (2H, m), 3.82 (1H, br dd), 3.89 (3H, s), 4.88 (2H, s), 6.90 (1H, t), 6.98 (1H, d), 7.27 (1H, t), 7.37 - 7.41 (3H, m), 7.63 (1H, d), 8.01 (2H, d), 13.75 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 435.2.

Intermediate 61i:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate (Isomer 1)

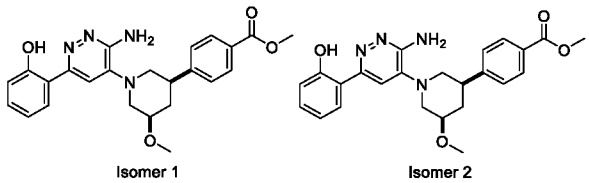
((*absolute configuration not yet confirmed))

and

Intermediate 61j:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

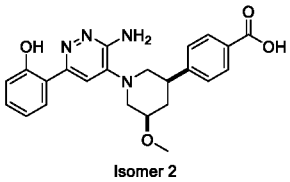


[2043] Intermediate 61h (151 mg, 0.35 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak IA 4.6 mm x 100 mm x 5 mm; mobile phase: 10 to 60% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 4.0 mL/min; BPR: 357 bar ; Column temperature: 40°C to afford Intermediate 61i that eluted first from the column (72 mg, 99% ee) and Intermediate 61j that eluted second from the column (70 mg, 99% ee) as off-white solids. *m/z* (ES^+) $[M+H]^+$ = 435.2.

Intermediate 61k:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

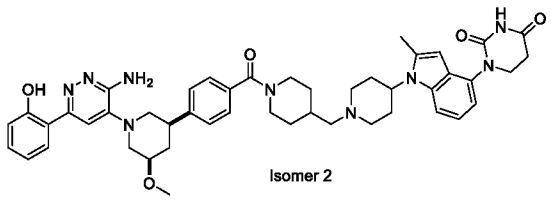


[2044] A solution of Intermediate 61j (70 mg, 0.16 mmol) and LiOH (23.15 mg, 0.97 mmol), water (537 µl), MeOH (537 µl), and THF (537 µl) were stirred at room temperature overnight. The reaction mixture was partially concentrated under reduced pressure, acidified with 1N HCl to pH 4-5 and filtered to afford the title compound (69.0 mg, 87%) as a white solid, which was carried forward without purification. *m/z* (ES^+) $[M+H]^+$ = 421.2.

EXAMPLE 61:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

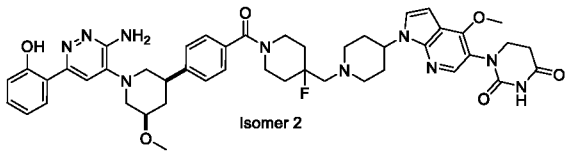


[2045] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (11 mg, 0.03 mmol) and Intermediate 22d (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (10.8 mg, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.82 (3H, m), 2.08 (9H, s), 2.36 (3H, s), 2.41 (3H, s), 2.74 (4H, s), 2.86 - 2.95 (1H, m), 2.98 - 3.21 (3H, m), 3.22 - 3.28 (2H, m), 3.33 - 3.39 (2H, m), 3.43 - 3.66 (3H, m), 3.70 (2H, s), 4.02 - 4.58 (2H, m), 6.33 - 6.55 (2H, m), 6.85 - 6.94 (2H, m), 7.02 - 7.13 (1H, m), 7.24 (4H, br s), 7.26 - 7.32 (1H, m), 7.33 - 7.37 (1H, m), 7.38 - 7.44 (1H, m), 7.53 - 7.59 (1H, m), 7.81 - 7.92 (1H, m), 10.24 - 10.49 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 847.5

EXAMPLE 62:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

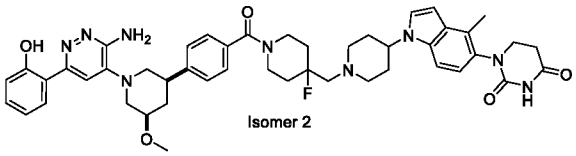


[2046] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (11 mg, 0.03 mmol) and Intermediate 33h (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (10.5 mg, 47%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.49 - 1.62 (1H, m), 1.64 - 1.80 (2H, m), 1.81 - 1.92 (3H, m), 1.94 - 2.13 (3H, m), 2.31 - 2.41 (3H, m), 2.53 - 2.56 (1H, m), 2.58 - 2.70 (3H, m), 2.71 - 2.84 (2H, m), 3.01 - 3.10 (2H, m), 3.11 - 3.17 (1H, m), 3.18 - 3.27 (2H, m), 3.39 (3H, s), 3.49 - 3.55 (2H, m), 3.55 - 3.69 (2H, m), 3.70 - 3.78 (1H, m), 3.80 - 3.88 (1H, m), 4.25 (4H, s), 4.56 - 4.74 (1H, m), 6.31 - 6.53 (2H, m), 6.82 - 6.87 (1H, m), 6.87 - 6.95 (2H, m), 7.20 - 7.29 (1H, m), 7.37 - 7.42 (2H, m), 7.43 - 7.49 (2H, m), 7.57 - 7.61 (1H, m), 7.62 - 7.67 (1H, m), 7.92 - 7.98 (1H, m), 7.98 - 8.04 (1H, m), 10.29 - 10.39 (1H, m), 13.77 - 14.56 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 861.6.

EXAMPLE 63:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

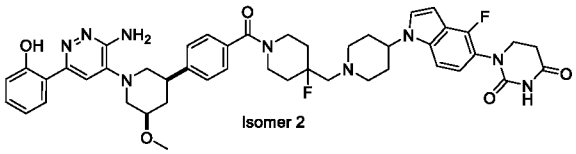


[2047] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (11 mg, 0.02 mmol) and Intermediate 32g (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (11.0 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.50 - 1.62 (1H, m), 1.64 - 1.82 (2H, m), 1.82 - 1.94 (3H, m), 1.95 - 2.11 (3H, m), 2.29 - 2.33 (3H, m), 2.33 - 2.38 (1H, m), 2.39 - 2.48 (2H, m), 2.53 - 2.57 (1H, m), 2.58 - 2.69 (2H, m), 2.70 - 2.84 (4H, m), 2.98 - 3.07 (1H, m), 3.10 - 3.18 (1H, m), 3.18 - 3.29 (2H, m), 3.38 - 3.40 (3H, m), 3.47 - 3.57 (3H, m), 3.69 - 3.78 (2H, m), 3.80 - 3.87 (1H, m), 4.15 - 4.41 (2H, m), 6.25 - 6.49 (2H, m), 6.50 - 6.63 (1H, m), 6.84 - 6.94 (2H, m), 6.98 - 7.10 (1H, m), 7.20 - 7.31 (1H, m), 7.37 - 7.43 (3H, m), 7.44 - 7.48 (2H, m), 7.49 - 7.57 (1H, m), 7.58 - 7.64 (1H, m), 7.90 - 8.06 (1H, m), 10.20 - 10.30 (1H, m), 13.79 - 14.54 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 844.7.

EXAMPLE 64:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

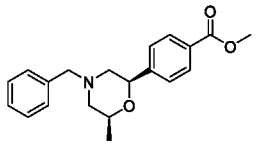


[2048] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (11 mg, 0.02 mmol) and Intermediate 3g (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.4 mg, 62%) as a white solid following lyophilization.^{1}H NMR (DMSO-*d*6): δ 1.53 - 1.64 (1H, m), 1.65 - 1.83 (2H, m), 1.83 - 1.95 (3H, m), 1.95 - 2.11 (3H, m), 2.31 - 2.37 (1H, m), 2.38 - 2.47 (2H, m), 2.53 - 2.58 (1H, m), 2.58 - 2.69 (2H, m), 2.72 - 2.82 (3H, m), 2.99 - 3.10 (2H, m), 3.17 - 3.26 (2H, m), 3.38 - 3.40 (3H, m), 3.44 - 3.64 (3H, m), 3.67 - 3.78 (4H, m), 3.80 - 3.90 (1H, m), 4.21 - 4.32 (1H, m), 4.32 - 4.47 (1H, m), 6.31 - 6.50 (1H, m), 6.52 - 6.63 (1H, m), 6.83 - 6.96 (2H, m), 7.07 - 7.19 (1H, m), 7.22 - 7.32 (1H, m), 7.41 (2H, s), 7.46 (3H, s), 7.55 - 7.68 (2H, m), 7.84 - 8.02 (1H, m), 10.38 - 10.47 (1H, m), 14.03 - 14.40 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 848.7.

EXAMPLE 65

Intermediate 65a:

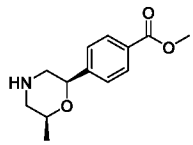
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)benzoate



[2049] (*S*)-1-(Benzylamino)propan-2-ol (0.86 g, 5.20 mmol) was added to a suspension of methyl 4-(2-bromoacetyl)benzoate (1.34 g, 5.20 mmol) and K_2CO_3 (0.79 g, 5.73 mmol) in MeCN (7.7 mL). The mixture was stirred at r.t. for 14h and filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. DCM (8.0 mL) and TFA (8.0 mL, 104 mmol) were added and the mixture was heated to 60 °C. Triethylsilane (0.83 mL, 5.20 mmol) was added and the mixture was stirred at 60 °C for 1h. More triethylsilane (0.83 mL, 5.20 mmol) was added and stirring was continued at 60 °C for 2h. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM (30 mL) and sat. aq. K_2CO_3/H_2O (50 mL, 1:3) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (1.22 g, 72%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.12 (3H, d), 1.78 (1H, t), 1.85 (1H, t), 2.75 (1H, br d), 2.86 (1H, br d), 3.42 - 3.49 (1H, m), 3.49 - 3.55 (1H, m), 3.72 - 3.80 (1H, m), 3.83 (3H, s), 4.64 (1H, dd), 7.21 - 7.35 (5H, m), 7.45 (2H, d), 7.91 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 326.2.

Intermediate 65b:

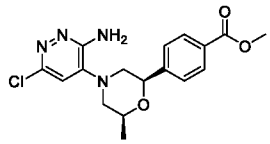
Methyl 4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2050] Pd/C (0.38 g, 0.36 mmol, 10 wt% palladium) was added to a solution of Intermediate 65a (1.17 g, 3.60 mmol) in MeOH (14 mL). The mixture was sparged with hydrogen for 5 minutes and stirred under an atmosphere of hydrogen for 2.5h. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR (DMSO-*d*6): δ 1–10 (3H, d), 2.26 - 2.40 (2H, m), 2.55 - 3.00 (1H, m), 2.80 (1H, dd), 2.92 (1H, dd), 3.58 - 3.68 (1H, m), 3.83 (3H, s), 4.50 (1H, dd), 7.46 (2H, d), 7.91 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 236.2.

Intermediate 65c:

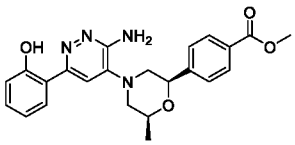
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate



[2051] Prepared in an analogous method to Intermediate 1d starting from Intermediate 65b (847 mg, 3.60 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (863 mg, 66%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.22 (3H, d), 2.42 - 2.48 (2H, m), 3.38 (1H, br d), 3.54 (1H, br d), 3.84 (3H, s), 3.98 - 4.07 (1H, m), 4.87 - 5.00 (1H, m), 6.32 (2H, s), 6.94 (1H, s), 7.56 (2H, d), 7.96 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 363.1.

Intermediate 65d:

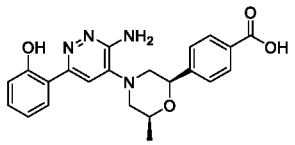
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate



[2052] Prepared in an analogous method to Intermediate 1e starting from Intermediate 65c (859 mg, 2.37 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (774 mg, 78%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.28 (3H, d), 2.54 - 2.67 (2H, m), 3.50 (1H, br d), 3.60 (1H, br d), 3.86 (3H, s), 4.12 (1H, ddd), 5.02 (1H, dd), 6.51 (2H, s), 6.83 - 6.91 (2H, m), 7.20 - 7.26 (1H, m), 7.56 (1H, s), 7.62 (2H, d), 7.92 - 7.97 (1H, m), 7.99 (2H, d), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.2.

Intermediate 65e:

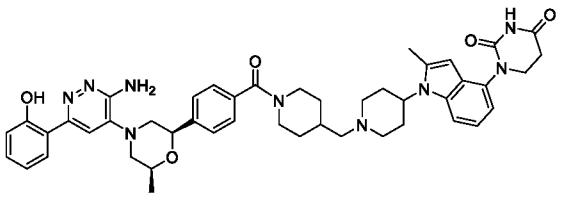
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoic acid



[2053] Prepared in an analogous method to Intermediate 1f starting from Intermediate 65d (770 mg, 1.83 mmol). DCM–IPA (3:1) and pH 3 phosphate buffer were added and the mixture was acidified to pH 3. The phases were separated and the aqueous layer was extracted with DCM–IPA (3:1, 2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (720 mg, 97%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 2.64 - 2.77 (2H, m), 3.60 (1H, br d), 3.71 (1H, br d), 4.07 - 4.16 (1H, m), 5.00 (1H, dd), 6.93 (1H, t), 6.99 (1H, d), 7.12 (2H, br d), 7.30 - 7.37 (1H, m), 7.53 - 7.63 (3H, m), 7.74 (1H, br d), 7.97 (2H, d), 11.24 - 15.25 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 407.2.

EXAMPLE 65:

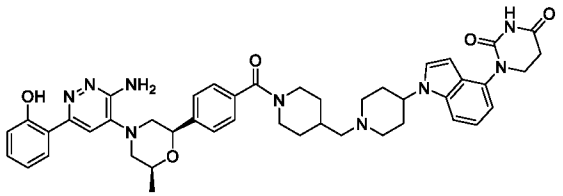
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2054] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 22d (39 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (19.4 mg, 53%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br s), 1.27 (3H, d), 1.69 - 1.94 (5H, m), 2.08 - 2.17 (2H, m), 2.24 (2H, br s), 2.35 - 2.46 (5H, m), 2.52 - 2.58 (1H, m), 2.67 - 2.88 (4H, m), 2.97 - 3.15 (3H, m), 3.47 - 3.67 (3H, m), 3.74 (2H, t), 4.07 - 4.17 (1H, m), 4.23 (1H, br t), 4.50 (1H, br d), 4.96 (1H, br d), 6.16 (1H, s), 6.51 (2H, s), 6.84 - 6.93 (3H, m), 7.04 (1H, t), 7.21 - 7.28 (1H, m), 7.41 (2H, d), 7.46 (1H, d), 7.53 (2H, d), 7.57 (1H, s), 7.94 - 8.00 (1H, m), 10.33 (1H, br s), 14.25 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 66:

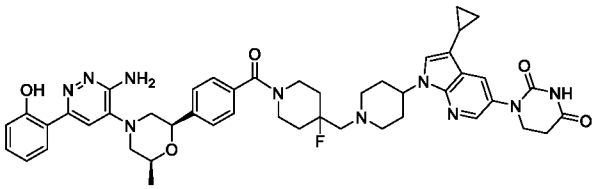
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2055] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (15 mg, 0.04 mmol) and Intermediate 10e (16 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (8.0 mg, 30%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.01 - 1.18 (2H, m), 1.27 (3H, d), 1.63 - 2.06 (7H, m), 2.11 - 2.33 (4H, m), 2.53 - 2.58 (1H, m), 2.65 - 2.87 (4H, m), 2.92 - 3.11 (3H, m), 3.46 - 3.66 (3H, m), 3.78 (2H, t), 4.07 - 4.17 (1H, m), 4.30 - 4.59 (2H, m), 4.95 (1H, br d), 6.42 (1H, d), 6.50 (2H, s), 6.84 - 6.91 (2H, m), 6.96 (1H, d), 7.15 (1H, t), 7.24 (1H, t), 7.40 (2H, d), 7.47 - 7.62 (5H, m), 7.96 (1H, d), 10.34 (1H, br s), 14.24 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 798.6.

EXAMPLE 67:

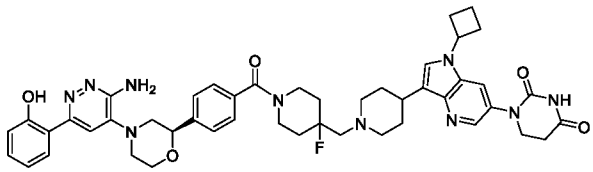
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2056] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 20g (27 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.3 mg, 69%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.68 (2H, m), 0.80 - 0.87 (2H, m), 1.25 (3H, d), 1.64 - 1.95 (7H, m), 2.00 - 2.09 (2H, m), 2.34 (2H, br t), 2.52 - 2.71 (4H, m), 2.75 (2H, t), 2.98 - 3.28 (4H, m), 3.40 - 3.62 (3H, m), 3.80 (2H, t), 4.07 - 4.38 (2H, m), 4.53 - 4.63 (1H, m), 4.94 (1H, br d), 6.48 (2H, s), 6.81 - 6.92 (2H, m), 7.18 - 7.26 (1H, m), 7.40 - 7.46 (3H, m), 7.49 - 7.58 (3H, m), 7.91 - 7.97 (2H, m), 8.15 (1H, d), 10.38 (1H, br s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 857.6.

EXAMPLE 68:

(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



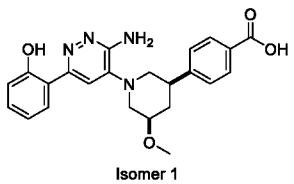
[2057] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20mg, 0.05 mmol) and Intermediate 35g (39 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (7.0 mg, 18%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 2.01 (10H, m), .26 (2H, br t), 2.38 - 2.47 (4H, m), 2.53 - 2.64 (2H, m), 2.72 - 2.92 (5H, m), 2.98 (2H, br d),3.04 - 3.28 (2H, m), 3.39 - 3.62 (3H, m), 3.81 (2H, t), 4.01 - 4.13 (2H, m), 4.25 (1H, br d), 4.84 - 4.97 (2H, m), 6.46 (2H, s), 6.82 - 6.91 (2H, m), 7.21 (1H, t),7.42 (2H, d), 7.49 - 7.57 (3H, m), 7.68 (1H, s), 7.84 (1H, s), 7.93 (1H, d), 8.25 (1H, s), 10.39 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 857.6.

EXAMPLE 69

Intermediate 69a:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

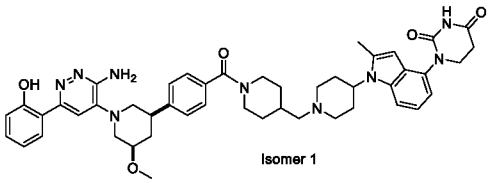
[2058] A solution of Intermediate 61i (70 mg, 0.16 mmol) and LiOH (23.15 mg, 0.97 mmol), water (537 µl), MeOH (537 µl), and THF (537 µl) were stirred at room temperature overnight. The reaction mixture was partially concentrated under reduced pressure, acidified with 1N HCl to pH 4-5 and filtered to

afford the title compound (69.0 mg, 87%) as a white solid, which was carried forward without purification. ^{1}H NMR (DMSO-*d*6): δ 1.50 (1H, q), 2.29 (1H, br d), 2.69 (1H, t), 3.19 - 3.23 (1H, m), 3.31 - 3.35 (3H, m), 3.59 - 3.80 (4H, m), 6.33 (2H, s), 6.81 - 6.88 (2H, m), 7.20 (1H, t), 7.34 (2H, br d), 7.56 (1H, s), 7.86 (2H, d), 7.92 (1H, d)*m/z* (ES$^+$) $[M+H]^+$ = 421.2.

EXAMPLE 69:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

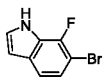


[2059] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 69a(15 mg, 0.04 mmol) and Intermediate 22d (29 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (10.8 mg, 40%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br d), 1.56 (1H, q), 1.67 - 1.97 (5H, m), 2.12 (2H, br t), 2.24 (2H, br s), 2.33 - 2.47 (6H, m), 2.52 (1H, br s), 2.71 - 2.87 (4H, m), 3.01 (3H, br d), 3.18 - 3.26 (1H, m), 3.39 (3H, s), 3.52 (2H, br d), 3.71 - 3.79 (3H, m), 3.79 - 3.86 (1H, m), 4.17 - 4.29 (1H, m), 4.49 (1H, br s), 6.16 (1H, s), 6.38 (2H, s), 6.82 - 6.94 (3H, m), 7.04 (1H, t), 7.20 - 7.29 (1H, m), 7.37 (2H, d), 7.42 - 7.51 (3H, m), 7.61 (1H, s), 7.93 - 8.03 (1H, m), 10.32 (1H, br s), 14.23 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 826.7.

EXAMPLE 70

Intermediate 70a:

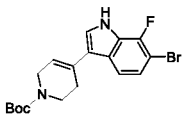
6-Bromo-7-fluoro-1*H*-indole



[2060] Vinylmagnesium bromide in THF (170 mL, 170.46 mmol) was added slowly to 1-bromo-2-fluoro-3-nitrobenzene (12.5 g, 56.82 mmol). The resulting mixture was stirred at –50 °C for 2h. The reaction mixture was quenched with sat. aq. NH_4Cl (50 mL), and washed sequentially with DCM (100 mL), saturated $NaHCO_3$ (100 mL), and saturated brine (100 mL). The layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 80% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (1.000 g, 8%) as a brown oil. ^{1}H NMR (DMSO-*d*6): δ 6.50 – 6.55 (1H, m), 7.14 (1H, dd), 7.32 (1H, dd), 7.43 (1H, t), 11.81 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 213.2

Intermediate 70b:

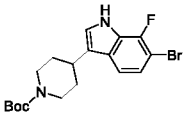
tert-Butyl 4-(6-bromo-7-fluoro-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2061] Prepared in an analogous method to Intermediate 35a starting from Intermediate 70a (2, 2 g, 9.34 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (1.000 g, 27%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.90 – 2.06 (2H, m), 2.31 – 2.39 (4H, m), 5.44 – 5.48 (1H, m), 6.10 (1H, s), 7.21 (1H, dd), 7.50 – 7.66 (2H, m). *m/z* (ES$^+$) $[M+H]^+$ =395.0.

Intermediate 70c:

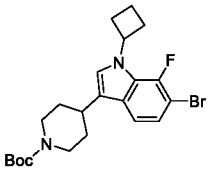
tert-Butyl 4-(6-bromo-7-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylate



[2062] Prepared in an analogous method to Intermediate 35d starting from Intermediate 70b (1.00 g, 2.53 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (0.80 g, 80%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.85 – 1.96 (2H, m), 2.81 – 2.89 (1H, m), 3.58 – 3.63 (4H, m), 3.95 – 4.04 (2H, m), 7.14 (1H, dd), 7.21 – 7.24 (1H, m), 7.36 (1H, d), 11.40 – 11.78 (1H, m). *m/z* (ES$^+$) $[M+H]^+$ =397.0.

Intermediate 70d:

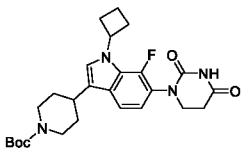
tert-Butyl 4-(6-bromo-1-cyclobutyl-7-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylate



[2063] Prepared in an analogous method to Intermediate 35b starting from Intermediate 70c (0.408 g, 3.02 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound (0.750 g, 83%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.88 – 1.95 (2H, m), 2.89 – 3.05 (4H, m), 3.39 – 3.50 (6H, m), 3.99 – 4.14 (3H, m), 5.48 (1H, p), 7.18 (1H, dd), 7.36 (1H, d), 7.51 (1H, s). *m/z* (ES$^+$) $[M–Boc+2H]^+$ =351.0.

Intermediate 70e:

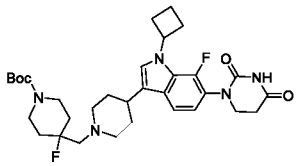
tert-Butyl 4-(6-bromo-1-cyclobutyl-7-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylate



[2064] Prepared in an analogous method to Intermediate 35c starting from Intermediate 70d (300 mg, 0.66 mmol). Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (100 mg, 37%) as a white solid. *m/z* (ES$^+$) $[M+Na]^+$ = 507.2.

Intermediate 70f:

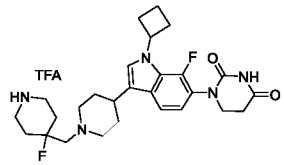
tert-Butyl 4-((4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-7-fluoro-1*H*-indol-3-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2065] *p*-Toluenesulfonic acid (0.078 g, 0.45 mmol) was added to Intermediate 70e (0.11 g, 0.23 mmol) in MeCN (5 mL). The resulting mixture was stirred at 80 °C for 16 h. The solution was concentrated under reduced pressure. The crude product was used for next step without further purification. To the crude product was added to Intermediate 6f (0.166 g, 0.45 mmol) and DIEA (0.089 g, 0.68 mmol) and 1,4-dioxane (5.0 mL). The resulting mixture was stirred at 80 °C for 16 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (0.060 g, 44%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.19 – 1.26 (2H, m), 1.40 (9H, s), 1.65 – 1.82 (10H, m), 2.20 – 2.32 (2H, m), 2.38 – 2.49 (4H, m), 2.56 – 2.79 (3H, m), 2.97 – 3.10 (4H, m), 3.65 – 3.82 (4H, m), 5.01 – 5.10 (1H, m), 6.96 (1H, t), 7.36 (1H, d), 7.50 (1H, s), 10.43 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 600.3.

Intermediate 70g:

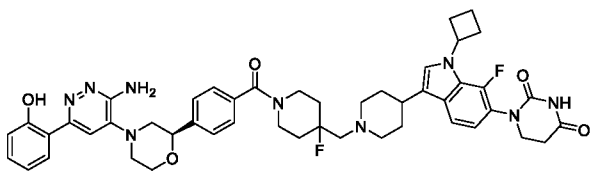
1-(1-Cyclobutyl-7-fluoro-3-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2066] Prepared in an analogous method to Intermediate 1i starting from Intermediate 70f (0.6 g, 1.00 mmol). Purification by RPC (elution gradient: 0 to 80% MeOH in water with 0.04% TFA) gave the title compound (0.400 g, 49%) as a pale yellow solid.

EXAMPLE 70:

(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



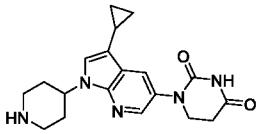
[2067] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (15 mg, 0.04 mmol) and Intermediate 70g (29 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN

in water with 0.1% NH_4OH) gave the title compound (17.7 mg, 58%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.59 - 2.03 (10H, m), 2.28 (2H, br t), 2.34 - 2.46 (4H, m), 2.53 - 2.64 (2H, m), 2.67 - 2.82 (4H, m), 2.87 (1H, td), 2.99(2H, br d), 3.04 - 3.28 (2H, m), 3.36 - 3.63 (3H, m), 3.70 (2H, br t), 4.00 - 4.13 (2H, m), 4.15 - 4.38 (1H, m), 4.87 (1H, br d), 5.04 (1H, quin), 6.46 (2H, s),6.81 - 6.89 (2H, m), 6.95 (1H, dd), 7.18 - 7.24 (1H, m), 7.35 (1H, d), 7.42 (2H, d), 7.48 (1H, s), 7.49 - 7.58 (3H, m), 7.93 (1H, d), 10.39 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 874.5.

EXAMPLE 71:

Intermediate 71a:

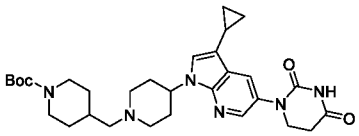
1-(3-Cyclopropyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2068] *p*-Toluenesulfonic acid (2.01 g, 10.6 mmol) was added to a solution of Intermediate 7d (4.00 g, 8.82 mmol) in MeCN (220 mL). The mixture was stirred at 70 °C for 320 minutes. More *p*-toluenesulfonic acid (0.67 g, 3.53 mmol) was added and stirring was continued at 70 °C for 1 hour. More *p*-toluenesulfonic acid (1.00 g, 5.29 mmol) was added and stirring was continued at 70 °C for 1 hour. The mixture was partially concentrated under reduced pressure to ~100 mL. MTBE (50 mL) was added and the mixture was stirred at r.t. for 5 minutes. The resulting precipitate was collected by filtration and washed with hexanes. The solids were stirred in a mixture of DCM and sat. aq. NaHCO3 until all solids dissolved. The phases were separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure to give the title compound (2.42 g, 78%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.59 - 0.69 (2H, m), 0.79 - 0.90 (2H, m), 1.74 - 1.96 (5H, m), 1.99 - 2.26 (1H, m), 2.63 (2H, br t), 2.75 (2H, t), 3.05 (2H, br d), 3.80 (2H, t), 4.65 (1H, tt), 7.38 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.36 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 354.1.

Intermediate 71b:

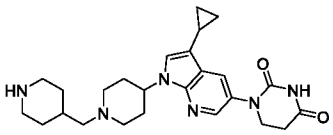
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2069] Prepared in an analogous method to Intermediate 10d starting from Intermediate 71a (500 mg, 1.41 mmol) using DCM as a solvent. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (678 mg, 87%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.68 (2H, m), 0.78 - 0.89 (4H, m), 1.38 (9H, s), 1.69 (3H, br d), 1.82 (2H, br d), 1.88 - 1.95 (1H, m), 1.98 - 2.12 (4H, m), 2.17 (2H, br d), 2.57 - 2.80 (4H, m), 2.95 (2H, br d), 3.80 (2H, t), 3.92 (2H, br d), 4.54 - 4.63 (1H, m), 7.43 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.36 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 551.5.

Intermediate 71c:

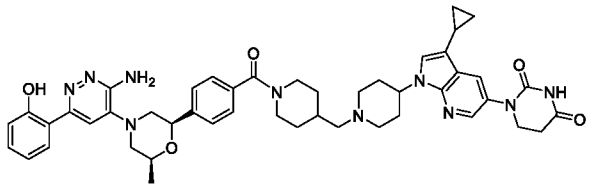
1-(3-Cyclopropyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2070] TFA (1.86 mL, 24.2 mmol) was added to a solution of Intermediate 71b (666 mg, 1.21 mmol) in DCM (7.4 mL). The mixture was stirred at r.t. for 50 minutes and concentrated under reduced pressure. The residue was dissolved in water and lyophilized. The residue was dissolved in DCM/IPA (25 mL, 3:1). Sat. aq. K_2CO_3 (20 mL) was added and the phases were separated. The aqueous layer was extracted with DCM/IPA (2 x 20 mL, 3:1). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (834 mg, 78%) as a white solid and 0.9 IPA and 2.5 potassium trifluoroacetate adduct. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.67 (2H, m), 0.80 - 0.87 (2H, m), 0.90 - 1.00 (2H, m), 1.51 - 1.58 (1H, m), 1.62 (2H, br d), 1.77 - 1.86 (2H, m), 1.87 - 1.94 (1H, m), 1.97 - 2.09 (4H, m), 2.14 (2H, br d), 2.41 (2H, br t), 2.75 (2H, t), 2.84 - 2.99 (4H, m), 3.80 (2H, t), 4.53 - 4.63 (1H, m), 7.43 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.32 (1H, s), 1 heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 451.3.

EXAMPLE 71:

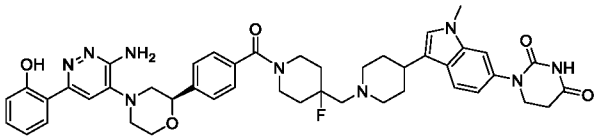
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine2,4(1*H*,3*H*)-dione



[2071] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 71c (40 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (20.5 mg, 55%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.70 (2H, m), 0.81 - 0.88 (2H, m), 1.01 - 1.18 (2H, m), 1.26 (3H, d), 1.61 - 1.96 (6H, m), 1.97 - 2.14 (4H, m), 2.16 - 2.30 (2H, m), 2.52 - 2.58 (1H, m), 2.69 (1H, br t), 2.76 (3H, br t), 2.92 - 3.11 (3H, m), 3.48 - 3.67 (3H, m), 3.82 (2H, t), 4.04 - 4.22 (1H, m), 4.34 - 4.72 (2H, m), 4.95 (1H, br d), 6.49 (2H, s), 6.80 - 6.97 (2H, m), 7.18 - 7.28 (1H, m), 7.40 (2H, d), 7.45 (1H, s), 7.50 - 7.61 (3H, m), 7.89 - 8.01 (2H, m), 8.17 (1H, d), 10.38 (1H, br s), 14.11 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 839.7.

EXAMPLE 72:

(*R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2072] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 9f (36 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.3 mg, 56%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.59 - 2.03 (8H, m), 2.28 (2H, br t), 2.51 - 2.61 (2H, m), 2.66 - 2.81 (4H, m), 2.83 - 2.91 (1H, m), 2.98 (2H, br d), 3.03- 3.27 (2H, m), 3.37 - 3.60 (3H, m), 3.69 (3H, s), 3.78 (2H, t), 4.00 - 4.13 (2H, m), 4.25 (1H, br d), 4.87 (1H, br d), 6.46 (2H, s), 6.83 - 6.90 (2H, m), 6.93 (1H, d), 7.10 (1H, s), 7.21 (1H, t), 7.32 (1H, s), 7.42 (2H, d), 7.48 - 7.58 (4H, m), 7.93 (1H, d), 10.27 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 816.5.

EXAMPLE 73:

(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

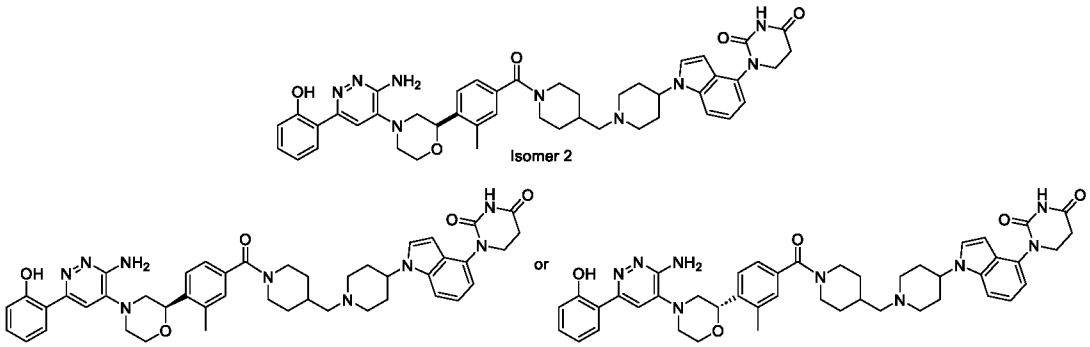
(Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



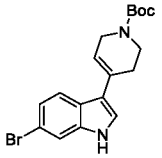
[2073] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15 mg, 0.04 mmol) and Intermediate 10e (29 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (16.2 mg, 61%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.57 - 2.06 (7H, m), 2.12 - 2.31 (4H, m), 2.41 (3H, s), 2.71 - 2.94 (5H, m), 3.00 (3H, br d), 3.49 - 3.71(3H, m), 3.78 (2H, t), 4.09 (2H, br d), 4.32 - 4.59 (2H,

m), 4.97 (1H, br d), 6.34 - 6.49 (3H, m), 6.83 - 6.92 (2H, m), 6.96 (1H, d), 7.15 (1H, t), 7.19 - 7.28 (3H,m), 7.46 - 7.62 (4H, m), 7.95 (1H, d), 10.32 (1H, br s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 798.5.

EXAMPLE 74

Intermediate 74a:

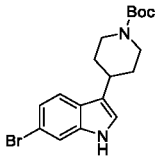
tert-Butyl 4-(6-bromo-1*H*-indol-3-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate



[2074] Prepared in an analogous method to Intermediate 35a starting from 6-bromo-1*H*-indole (3 g, 15.30 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (5.70 g, 99%) as a yellow solid. ^1H NMR (DMSO-*d*6): δ 1.39 – 1.41 (2H, m), 1.44 (9H, s), 3.56 (2H, t), 4.04 (2H, q), 6.11 (1H, s), 7.11 – 7.19 (1H, m), 7.46 (1H, d), 7.57 (1H, d), 7.77 (1H, d), 11.30 (1H, d). *m/z* (ES^+) $[M+H]^+$ = 377.1.

Intermediate 74b:

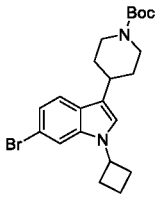
tert-Butyl 4-(6-bromo-1*H*-indol-3-yl)piperidine-1-carboxylate



[2075] Prepared in an analogous method to Intermediate 35d starting from Intermediate 74a (3.0 g, 7.95 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in DCM) gave the title compound (2.230 g, 74%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.45 – 1.57 (2H, m), 1.86 – 1.97 (2H, m), 2.79 – 3.00 (3H, m), 3.99 – 4.12 (2H, m), 7.02 – 7.22 (2H, m), 7.45 – 7.60 (2H, m), 10.97 (1H, s). *m/z* (ES^+) $[M+H]^+$ = 379.0.

Intermediate 74c:

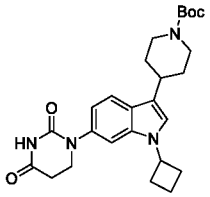
tert-Butyl 4-(6-bromo-1-cyclobutyl-1*H*-indol-3-yl)piperidine-1-carboxylate



[2076] Prepared in an analogous method to Intermediate 35b starting from Intermediate 74b (1.08 g, 2.85 mmol). Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (0.890 g, 72%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.45 - 1.56 (2H, m), 1.74 - 1.84 (2H, m), 1.87 - 1.93 (2H, m), 2.33 - 2.44 (4H, m), 2.76 - 2.98 (3H, m), 3.98 - 4.12 (2H, m), 4.87 - 4.98 (1H, m), 7.10 (1H, dd), 7.42 (1H, s), 7.51 (1H, d), 7.65 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 433.2.

Intermediate 74d:

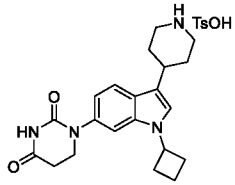
tert-Butyl 4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-3-yl)piperidine-1-carboxylate



[2077] Prepared in an analogous method to Intermediate 35c starting from Intermediate 74c (700 mg, 1.62 mmol). Purification by FSC (elution gradient: 0 to 60% EtOAc in petroleum ether) gave the title compound (460 mg, 61%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.48 – 1.67 (2H, m), 1.70 – 2.04 (4H, m), 2.35 – 2.48 (4H, m), 2.73 (2H, t), 2.82 – 3.04 (3H, m), 3.79 (2H, t), 4.01 – 4.13 (2H, m), 4.83 – 4.95 (1H, m), 6.96 (1H, dd), 7.37 – 7.45 (2H, m), 7.55 (1H, d), 10.30 (1H, s); *m/z* (ES$^+$) [M–Boc+2H]$^+$ = 367.2.

Intermediate 74e:

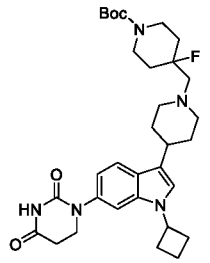
1-(1-Cyclobutyl-3-(piperidin-4-yl)-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2078] Prepared in an analogous method to Intermediate 35e starting from Intermediate 74d (460 mg, 0.99 mmol). MTBE (10 mL) was added and the resulting mixture was stirred at r.t for 15 min. The solid was collected by filtration and dried to give the title compound in the form of a *p*-toluenesulfonic acid salt (480 mg, 90%) as a yellow solid. *m/z* (ES$^+$) [M+H]$^+$ = 367.2.

Intermediate 74f:

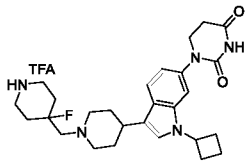
tert-Butyl 4-((4-(1-cyclobutyl-6-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-3-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2079] Prepared in an analogous method to Intermediate 35f starting from Intermediate 74e (480 mg, 1.31 mmol). Purification by FSC (elution gradient: 0 to 5% EtOH in DCM) gave the title compound (330 mg, 43%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.39 (9H, s), 1.52 - 1.91 (10H, m), 2.22 - 2.31 (2H, m), 2.36 - 2.45 (4H, m), 2.51 - 2.58 (2H, m), 2.66 - 2.76 (3H, m), 2.92 - 3.09 (4H, m), 3.68 - 3.74 (2H, m), 3.77 (2H, t), 4.87 (1H, quin), 6.93 (1H, d), 7.38 (2H, s), 7.51 (1H, d), 10.26 (1H, s); *m/z* (ES$^+$) [M+H]$^+$ = 582.3.

Intermediate 74g:

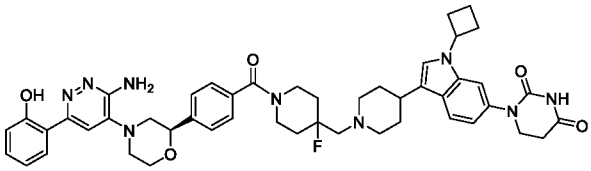
1-(1-Cyclobutyl-3-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2080] Prepared in an analogous method to Intermediate 1i starting from Intermediate 74f (1.6g, 2.75 mmol). The solvent was removed and triturated with diethyl ether, solids were filtered off, dried gave the title compound (2.000 g, 99%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 482.3.

EXAMPLE 74:

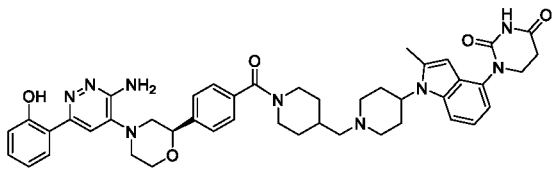
(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2081] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 74g (43 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (28.0 mg, 71%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.63 - 2.06 (10H, m), 2.30 (2H, br t), 2.36 - 2.47 (4H, m), 2.54 - 2.66 (2H, m), 2.68 - 2.84 (4H, m), 2.86 - 2.94 (1H, m), 3.01 (2H, br d), 3.14 (2H, br d), 3.38 - 3.63 (3H, m), 3.79 (2H, t), 4.01 - 4.14 (2H, m), 4.26 (1H, br s), 4.83 - 4.94 (2H, m), 6.47 (2H, s), 6.83 - 6.91 (2H, m), 6.95 (1H, d), 7.23 (1H, t), 7.35 - 7.46 (4H, m), 7.48 - 7.60 (4H, m), 7.95 (1H, d), 10.28 (1H, br s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 856.6.

EXAMPLE 75:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



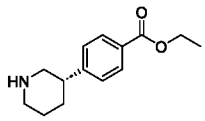
[2082] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 22d (37 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (20.3 mg, 55%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.01 - 1.19 (2H, m), 1.66 - 1.94 (5H, m), 2.11 (2H, br t), 2.23 (2H,

br s), 2.34 - 2.46 (5H, m), 2.70 - 2.92 (5H, m), 2.99 (3H, br d), 3.42 - 3.66 (3H, m), 3.72 (2H, t), 3.99 - 4.13 (2H, m), 4.22 (1H, br t), 4.49 (1H, br d), 4.87 (1H, br d), 6.14 (1H, s), 6.46 (2H, s), 6.82 - 6.91 (3H, m), 7.02 (1H, t), 7.22 (1H, t), 7.39 (2H, d), 7.44 (1H, d), 7.52 (2H, d), 7.56 (1H, s), 7.94 (1H, d), 10.28 (1H, br s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 798.6.

EXAMPLE 76

Intermediate 76a:

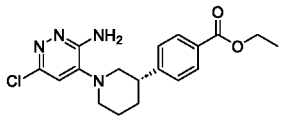
Ethyl (*S*)-4-(piperidin-3-yl)benzoate



[2083] Intermediate 1b (2.00 g, 8.57 mmol) was purified by chiral SFC (Column: IG 30mm × 250 5µm, MeOH/0.2% NH_4OH) to give the title compound (944 mg, 47% yield, >99% ee) as a light brown oil, which solidified upon standing in the refrigerator at 0°C. Absolute configuration was assigned by VCD.

Intermediate 76b:

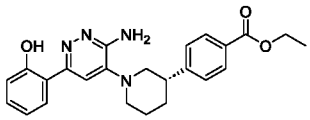
Ethyl (*S*)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)benzoate



[2084] Prepared in an analogous method to Intermediate 1d starting from Intermediate 76a (0.500 g, 2.14 mmol). Trituration with diethyl ether affords the title compound (0.394 g, 51%) as a light white solid. ^1H NMR (DMSO-*d6*): δ 1.32 (3H, t), 1.57 - 1.71 (1H, m), 1.79 - 1.91 (2H, m), 1.92 - 2.02 (1H, m), 2.60 - 2.71 (2H, m), 3.07 - 3.21 (1H, m), 3.39 - 3.53 (2H, m), 4.24 - 4.36 (2H, m), 6.12 - 6.24 (2H, m), 6.87 - 7.01 (1H, m), 7.39 - 7.53 (2H, m), 7.82 - 7.98 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 361.7.

Intermediate 76c:

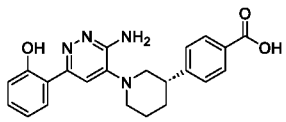
Ethyl (*S*)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoate



[2085] Prepared in an analogous method to Intermediate 1e starting from Intermediate 76b (0.394 g, 1.09 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.349 g, 76%) as an , off-white solid. ^1H NMR (DMSO-*d6*): δ 1.32 (3H, s), 1.61 - 1.74 (1H, m), 1.86 - 2.03 (3H, m), 2.71 - 2.84 (2H, m), 3.12 - 3.25 (1H, m), 3.46 - 3.63 (2H, m), 4.22 - 4.40 (2H, m), 6.22 - 6.44 (2H, m), 6.82 - 6.96 (2H, m), 7.17 - 7.32 (1H, m), 7.46 - 7.61 (3H, m), 7.88 - 8.02 (3H, m), 14.14 - 14.44 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 419.2.

Intermediate 76d:

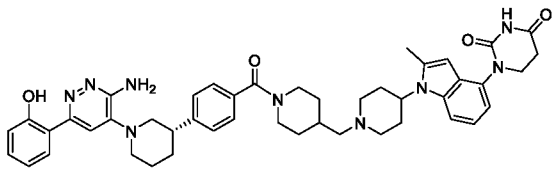
(*S*)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoic acid



[2086] Prepared in an analogous method to Intermediate 1f starting from Intermediate 76c (0.349 g, 0.83 mmol) to afford the title compound (0.310 g, 95%) as a light brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.72 - 1.82 (1H, m), 1.85 - 1.93 (2H, m), 1.95 - 2.05 (1H, m), 2.90 - 3.08 (2H, m), 3.12 - 3.22 (1H, m), 3.37 - 3.47 (2H, m), 3.67 - 3.88 (2H, m), 6.93 - 7.01 (1H, m), 7.04 - 7.10 (1H, m), 7.36 - 7.42 (1H, m), 7.45 - 7.50 (2H, m), 7.50 - 7.56 (1H, m), 7.57 - 7.62 (1H, m), 7.91 (2H, s), 12.53 - 13.45 (1H, m), 14.16 - 15.58 (1H, m). *m/z* (ES$^-$) [M-H$^+$] = 391.3.

EXAMPLE 76:

(*S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

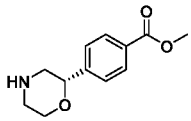


[2087] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 76d (15 mg, 0.04 mmol) and Intermediate 22d (31 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (18.7 mg, 67%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.08 (2H, br d), 1.62 - 2.03 (9H, m), 2.10 (2H, br t), 2.16 - 2.28 (2H, m), 2.33 - 2.46 (5H, m), 2.64 - 2.84 (5H, m), 2.93 - 3.17 (4H, m), 3.47 - 3.78 (5H, m), 4.21 (1H, br t), 4.48 (1H, br d), 6.14 (1H, s), 6.30 (2H, s), 6.81 - 6.91 (3H, m), 7.02 (1H, t), 7.19 - 7.26 (1H, m), 7.34 (2H, d), 7.37 - 7.47 (3H, m), 7.55 (1H, s), 7.93 (1H, dd), 10.31 (1H, br s), 14.28 (1H, br s); *m/z* (ES$^+$) [M+H]$^+$ = 796.7.

EXAMPLE 77

Intermediate 77a:

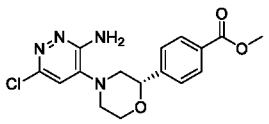
Methyl (*S*)-4-(morpholin-2-yl)benzoate



[2088] Prepared using the method described for Intermediate 16f isolating the compound that eluted first from the column (0.14 g, 32% yield, >98% ee) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 2.47 (1H, dd), 2.60 - 2.81 (3H, m), 2.97 (1H, dd), 3.62 (1H, td), 3.85 (3H, s), 3.88 - 3.95 (1H, m), 4.47 (1H, dd), 7.48 (2H, d), 7.93 (2H, d); *m/z* (ES$^+$) [M+H]$^+$ = 222.1.

Intermediate 77b:

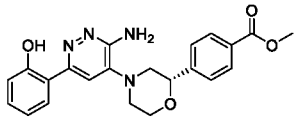
Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)benzoate



[2089] Prepared in an analogous method to Intermediate 1d starting from Intermediate 77a (40 mg, 0.18 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR (DMSO-*d*6): δ 2.57 (1H, t), 2.84 (1H, td), 3.36 (1H, br d), 3.55 (1H, br d), 3.86 (3H, s), 3.94 - 4.01 (1H, m), 4.06 - 4.11 (1H, m), 4.90 (1H, br d), 6.34 (2H, s), 6.96 (1H, s), 7.58 (2H, d), 7.97 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 349.2.

Intermediate 77c:

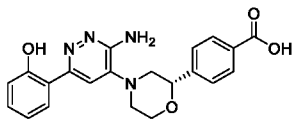
Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoate



[2090] Prepared in an analogous method to Intermediate 1e starting from Intermediate 77b (63 mg, 0.18 mmol). Purification by FSC (elution gradient: 30 to 100% EtOAc in hexanes) gave the title compound (30 mg, 40%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.84 (1H, dd), 2.96 - 3.05 (1H, m), 3.48 - 3.58 (2H, m), 3.95 (3H, s), 4.04 (1H, td), 4.28 (1H, dd), 4.82 (1H, dd), 5.01 (2H, s), 6.87 - 6.93 (1H, m), 7.06 (1H, dd), 7.28 - 7.31 (1H, m), 7.32 (1H, s), 7.52 (2H, d), 7.57 (1H, dd), 8.09 (2H, d), 11.22 - 13.94 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 407.3.

Intermediate 77d:

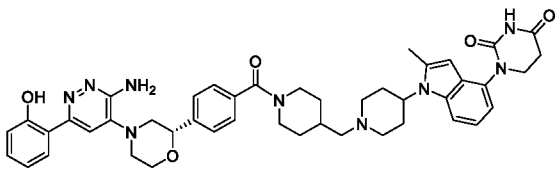
(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoic acid



[2091] Prepared in an analogous method to Intermediate 1f starting from Intermediate 77c (30 mg, 0.07 mmol). The mixture was acidified to pH 1. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give the title compound (19 mg, 65%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.73 (1H, t), 2.89 (1H, td), 3.46 (1H, br d), 3.57 (1H, br d), 3.98 - 4.14 (2H, m), 4.91 (1H, br d), 6.46 (2H, s), 6.81 - 6.91 (2H, m), 7.22 (1H, t), 7.50 - 7.63 (3H, m), 7.87 - 8.01 (3H, m), 12.19 - 15.08 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 393.2.

EXAMPLE 77:

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2092] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 77d (20 mg, 0.05 mmol) and Intermediate 22d (41 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (25.1 mg, 68%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br d), 1.61 - 1.92 (5H, m), 2.12 (2H, br t), 2.19 - 2.30 (2H, m), 2.35 - 2.48 (5H, m), 2.69 - 2.93 (5H, m), 2.95 – 3.13 (3H, m), 3.45 - 3.68 (3H, m), 3.74 (2H, t), 4.00 - 4.14 (2H, m), 4.23 (1H, br t), 4.50 (1H, br s), 4.79 - 4.98 (1H, m), 6.16 (1H, s), 6.50 (2H, s), 6.80 - 6.93 (3H, m), 7.04 (1H, t), 7.19 - 7.28 (1H, m), 7.41 (2H, d), 7.46 (1H, d), 7.53 (2H, d), 7.58 (1H, s), 7.96 (1H, dd), 10.32 (1H, br s), 14.23 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 798.6.

EXAMPLE 78:

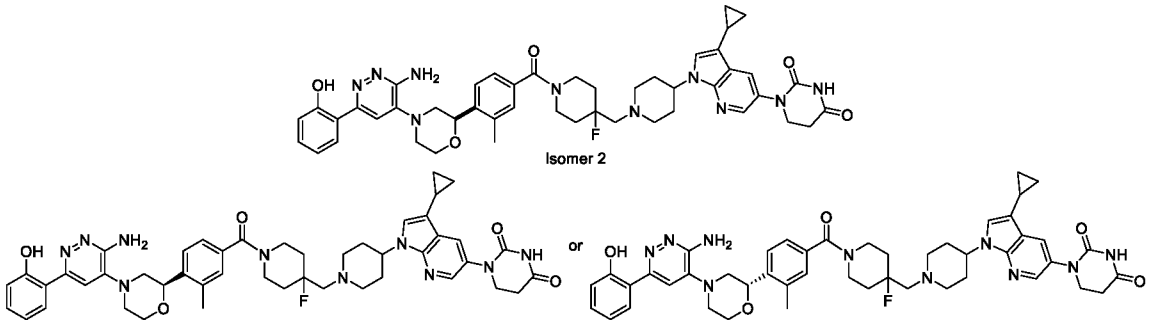
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2093] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 20g (27 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (24.5 mg, 64%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.65 (2H, q), 0.79 - 0.89 (2H, m), 1.62 - 2.12 (9H, m), 2.34 (2H, br t), 2.40 (3H, s), 2.56 - 2.66 (2H, m), 2.75 (2H, t), 2.79 - 2.91 (2H, m), 3.02 (2H, br d), 3.07 - 3.28 (2H, m), 3.52 (3H, br t), 3.80 (2H, t), 4.08 (2H, br d), 4.16 - 4.33 (1H, m), 4.58 (1H, br t), 4.96 (1H, br d), 6.41 (2H, s), 6.81 - 6.91 (2H, m), 7.19 - 7.29 (3H, m), 7.43 (1H, s), 7.52 - 7.59 (2H, m), 7.93 (2H, br d), 8.15 (1H, s), 10.36 (1H, br s), 14.18 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 857.5.

EXAMPLE 79:

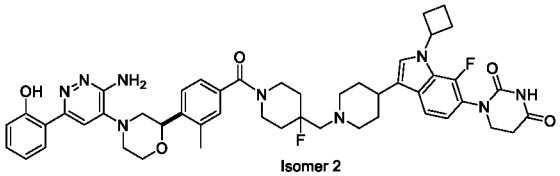
(*R**)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

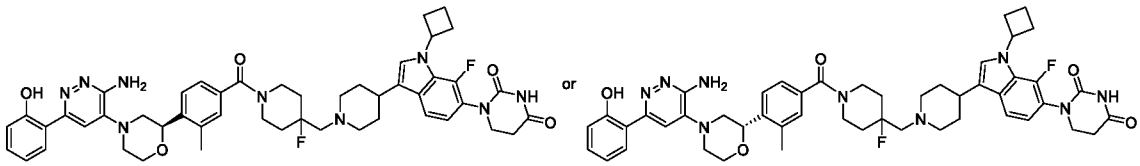
(*R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 2



[2094] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15 mg, 0.04 mmol) and Intermediate 70g (28 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (15.6 mg, 52%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.57 - 2.05 (10H, m), 2.28 (2H, br t), 2.35 - 2.47 (7H, m), 2.52 - 2.65 (2H, m), 2.66 - 2.77 (3H, m), 2.78 - 2.91 (2H, m), 2.99 (2H, br d), 3.04 - 3.27 (2H, m), 3.52 (3H, br t), 3.70 (2H, br t), 4.07 (2H, br d), 4.14 - 4.38 (1H, m), 4.96 (1H, br d), 4.99 - 5.10 (1H, m), 6.41 (2H, s), 6.80 - 6.91 (2H, m), 6.95 (1H, t), 7.18 - 7.28 (3H, m), 7.35 (1H, d), 7.48 (1H, s), 7.52 - 7.59 (2H, m), 7.93 (1H, d), 10.39 (1H, br s), 14.16 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 888.5.

EXAMPLE 80

Intermediate 80a:

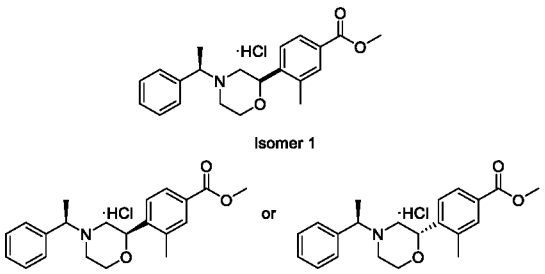
Methyl 3-methyl-4-((*R**)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate (Isomer 1)

((*relative configuration not yet confirmed))

Methyl 3-methyl-4-((*R*)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate

or

Methyl 3-methyl-4-((*S*)-4-((*R*)-1-phenylethyl)morpholin-2-yl)benzoate



[2095] Prepared using the method described for Intermediate 55f isolating the compound that eluted first from the column (1.03 g, 29% yield) as a white solid and hydrochloride salt. ^{1}H NMR (DMSO-*d*6): δ 1.71 (3H, br d), 2.44 (3H, s), 2.80 (1H, q), 2.91 - 3.05 (2H, m), 3.77 (1H, br d), 3.84 (3H, s), 3.99 - 4.14 (2H, m), 4.42 - 4.55 (1H, m), 5.40 (1H, br d), 7.42 - 7.54 (4H, m), 7.63 (2H, br d), 7.79 - 7.86 (2H, m), 11.90 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 340.2.

Intermediate 80b:

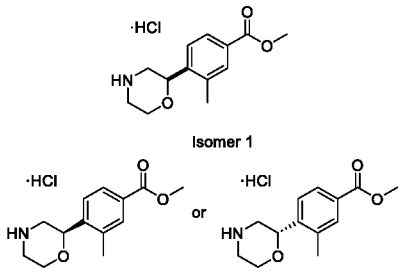
Methyl (*R**)-3-methyl-4-(morpholin-2-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

Methyl (*R*)-3-methyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-3-methyl-4-(morpholin-2-yl)benzoate



[2096] Prepared in an analogous method to Intermediate 55g using Intermediate 80a (1.00 g, 2.67 mmol) to give the title compound (693 mg, 95%) as a white solid and hydrochloride salt. ^{1}H NMR (DMSO-*d*6): δ 2.38 (3H, s), 2.87 (1H, t), 3.12 (1H, td), 3.27 (1H, br d), 3.35 (1H, br d), 3.83 (3H, s), 3.99 (1H, br t), 4.12 (1H, dd), 5.09 (1H, br d), 7.54 (1H, d), 7.77 - 7.87 (2H, m), 9.68 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 236.1.

Intermediate 80c:

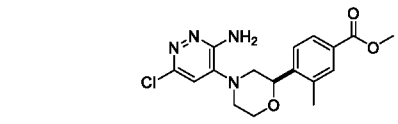
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

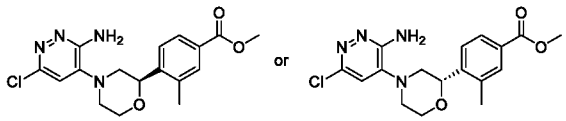
Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate



Isomer 1



[2097] Prepared in an analogous method to Intermediate 1d starting from Intermediate 80b (684 mg, 2.52 mmol) using DMSO as a solvent. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (688 mg, 75%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 2.40 (3H, s), 2.60 (1H, t), 2.81 (1H, td), 3.38 (1H, br d), 3.48 (1H, br d), 3.83 (3H, s), 3.96 - 4.10 (2H, m), 4.95 (1H, br d), 6.26 (2H, s), 6.95 (1H, s), 7.58 (1H, d), 7.74 - 7.84 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 363.1.

Intermediate 80d:

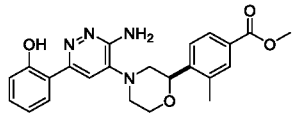
Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

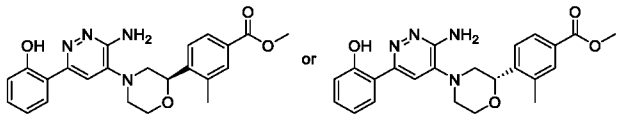
Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoate



Isomer 1



[2098] Prepared in an analogous method to Intermediate 1e starting from Intermediate 80c (684 mg, 1.89 mmol). Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (592 mg, 74%) as an orange solid. ^{1}H NMR (DMSO-*d*6): δ 2.43 (3H, s), 2.76 (1H, t), 2.89 (1H, ddd), 3.46 - 3.58 (2H, m), 3.84 (3H, s), 4.02 - 4.15 (2H, m), 5.00 (1H, br d), 6.42 (2H, s), 6.80 - 6.90 (2H, m), 7.21 (1H, t), 7.55 (1H, s), 7.63 (1H, d), 7.79 (1H, s), 7.82 (1H, d), 7.91 (1H, d), 14.16 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.2.

Intermediate 80e:

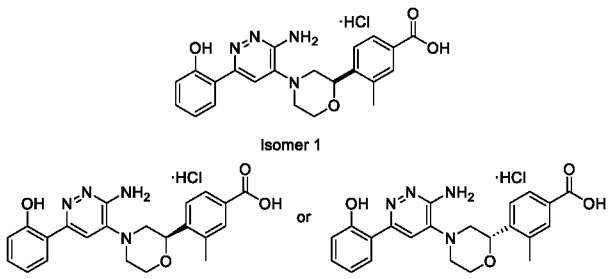
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoic acid



[2099] Prepared in an analogous method to Intermediate 1f starting from Intermediate 80d (589 mg, 1.40 mmol). The mixture was acidified to pH 1, diluted with brine, and extracted with DCM–IPA (3:1, 3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with DCM to give the title compound(544 mg, 96%) as an off-white solid and hydrochloride salt. ^{1}H NMR (DMSO-*d*6): δ 2.43 (3H, s), 2.94 (1H, br t), 3.08 (1H, br t), 3.67 - 3.78 (2H, m), 4.05 - 4.16 (2H, m), 5.02 (1H, br d), 6.97 (1H, t), 7.08 (1H, br d), 7.23 - 7.76 (6H, m), 7.77 - 7.85 (2H, m), 12.34 - 13.42 (1H, m), two heteroatom-bound protons not observed; *m/z* (ES$^+$) $[M+H]^+$ = 407.2.

EXAMPLE 80:

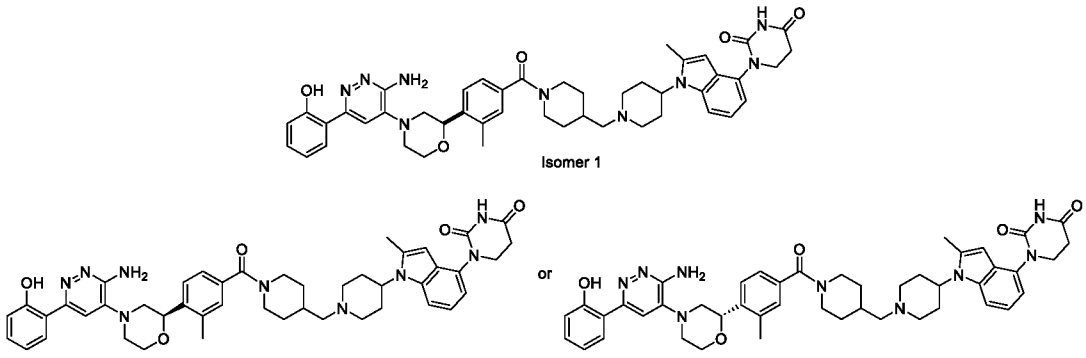
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

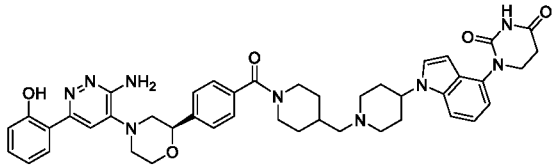


[2100] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 80e (20 mg, 0.05 mmol) and Intermediate 22d (35 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN/water with 0.1% NH_4OH) gave the title compound (16.9 mg, 47%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.64 - 1.98 (5H, m), 2.11 (2H, br t), 2.23 (2H, br

d), 2.41 (8H, br d), 2.70 - 2.92 (5H, m), 3.00 (3H, br d), 3.52 (3H, br t), 3.72 (2H, t), 4.08 (2H, br d), 4.22 (1H, br t), 4.48 (1H, br s), 4.96 (1H, br d), 6.14 (1H, s), 6.42 (2H, s), 6.82 - 6.92 (3H, m), 7.03 (1H, t), 7.17 - 7.29 (3H, m), 7.45 (1H, d), 7.51 - 7.61 (2H, m), 7.94 (1H, d), 10.28 (1H, br s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 81:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

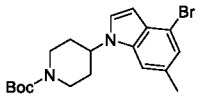


[2101] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 10e (30 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (16.4 mg, 45%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.63 - 2.05 (7H, m), 2.08 - 2.33 (4H, m), 2.71 - 3.12 (8H, m), 3.43 - 3.65 (3H, m), 3.76 (2H, t), 3.99 - 4.13 (2H, m), 4.28 - 4.59 (2H, m), 4.87 (1H, br d), 6.40 (1H, d), 6.46 (2H, s), 6.82 - 6.90 (2H, m), 6.95 (1H, d), 7.13 (1H, t), 7.22 (1H, t), 7.38 (2H, d), 7.47 - 7.58 (5H, m), 7.93 (1H, d), 10.30 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 784.5.

EXAMPLE 82

Intermediate 82a:

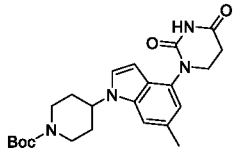
tert-Butyl 4-(4-bromo-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2102] 4-Bromo-6-methyl-1*H*-indole (252 mg, 1.20 mmol) was added to a mixture of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (670 mg, 2.40 mmol) and KOH (471 mg, 8.49 mmol) in DMF (3 mL). The mixture was stirred at 80 °C for 16h. After cooling to r.t., the mixture was diluted with H_2O (25 mL) and EtOAc (15 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 80% DCM in hexanes) gave the title compound (344 mg, 72%) as a yellow oil. ^1H NMR (DMSO-*d*6): δ 1.50 (9H, s), 1.89 (2H, qd), 2.06 (2H, d), 2.46 (3H, s), 2.92 (2H, s), 4.29 (3H, tt), 6.48 – 6.54 (1H, m), 7.10 (1H, s), 7.15 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 393.1.

Intermediate 82b:

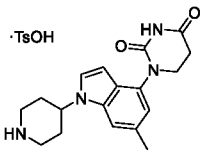
tert-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2103] Prepared in an analogous method to Intermediate 8b starting from Intermediate 82a (0.94 g, 2.26 mmol). Trituration with MTBE/heptane (1:1) gave the title compound (0.63 g, 65%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.50 (9H, s), 1.84 – 1.95 (2H, m), 2.07 (2H, d), 2.50 (3H, s), 2.87 (2H, t), 2.92 (2H, s), 3.91 (2H, t), 4.33 (3H, ddq), 6.31 – 6.35 (1H, m), 6.86 – 6.91 (1H, m), 7.15 (2H, d), 7.57 (1H, s); *m/z* (ES$^+$) $[M+Na]^+$ = 449.6.

Intermediate 82c:

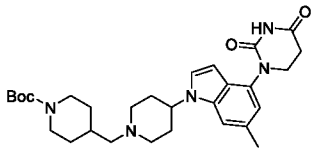
1-(6-Methyl-1-(piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2104] Prepared in an analogous method to Intermediate 6e using Intermediate 82b (0.98 g, 2.07 mmol). Trituration with MTBE gave the title compound (1.05 g, quant.) as a pale brown solid in the form of a *p*-toluenesulfonic acid salt. ^{1}H NMR (DMSO-*d*6): δ 2.06 – 2.17 (4H, m), 2.29 (3H, s), 2.43 (3H, s), 2.75 (2H, t), 3.16 (2H, s), 3.47 (2H, d), 3.76 (2H, t), 4.71 (1H, p), 6.40 (1H, d), 6.84 (1H, s), 7.11 (2H, d), 7.32 (1H, d), 7.36 (1H, s), 7.48 (2H, d), 8.33 (1H, d), 8.59 (1H, d), 10.32 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 327.5.

Intermediate 82d:

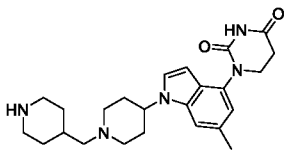
tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2105] Prepared in an analogous method to Intermediate 10d starting from Intermediate 82c (300 mg, 0.60 mmol) using DMF as a solvent. Purification by FSC (elution gradient: 0 to 100% ethyl acetate in hexanes, then 0 to 10% MeOH in EtOAc) gave the title compound (270 mg, 86%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.91 - 1.01 (2H, m), 1.38 (9H, s), 1.70 (3H, br d), 1.87 - 2.02 (4H, m), 2.09 - 2.22 (4H, m), 2.41 (3H, s), 2.63 - 2.78 (4H, m), 2.96 (2H, br d), 3.74 (2H, t), 3.92 (2H, br d), 4.25 - 4.35 (1H, m), 6.33 (1H, d), 6.78 (1H, s), 7.29 (1H, s), 7.42 (1H, d), 10.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 524.4.

Intermediate 82e:

1-(6-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

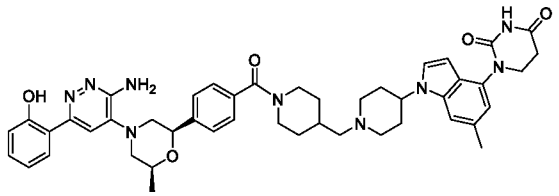


[2106] Prepared in an analogous method to Intermediate 71c using Intermediate 82d (264 mg, 0.50 mmol). After extraction, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated

under reduced pressure to ~1 mL. Hexanes (20 mL) were added and the resulting precipitate was collected by filtration, washed with hexanes, and dried in vacuo to give the title compound (201 mg, 94%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.89 - 1.00 (2H, m), 1.50 - 1.68 (3H, m), 1.85 - 1.98 (4H, m), 2.08 - 2.19 (4H, m), 2.41 (5H, s), 2.73 (2H, t), 2.83 - 3.02 (4H, m), 3.74 (2H, t), 4.25 - 4.33 (1H, m), 6.32 (1H, d), 6.78 (1H, s), 7.29 (1H, s), 7.42 (1H, d), 9.95 - 10.52 (1H, m), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 424.3.

EXAMPLE 82:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2107] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 82e (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (19.2 mg, 53%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br s), 1.26 (3H, d), 1.66 - 2.01 (7H, m), 2.11 - 2.26 (4H, m), 2.42 (3H, s), 2.52 - 2.59 (1H, m), 2.63 - 2.85 (4H, m), 2.93 - 3.09 (3H, m), 3.47 - 3.67 (3H, m), 3.76 (2H, t), 4.07 - 4.17 (1H, m), 4.27 - 4.38 (1H, m), 4.40 - 4.64 (1H, m), 4.87 - 5.03 (1H, m), 6.34 (1H, d), 6.50 (2H, s), 6.80 (1H, s), 6.84 - 6.92 (2H, m), 7.20 - 7.26 (1H, m), 7.31 (1H, s), 7.37 - 7.46 (3H, m), 7.49 - 7.59 (3H, m), 7.84 - 8.10 (1H, m), 10.31 (1H, br s), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 812.7.

EXAMPLE 83:

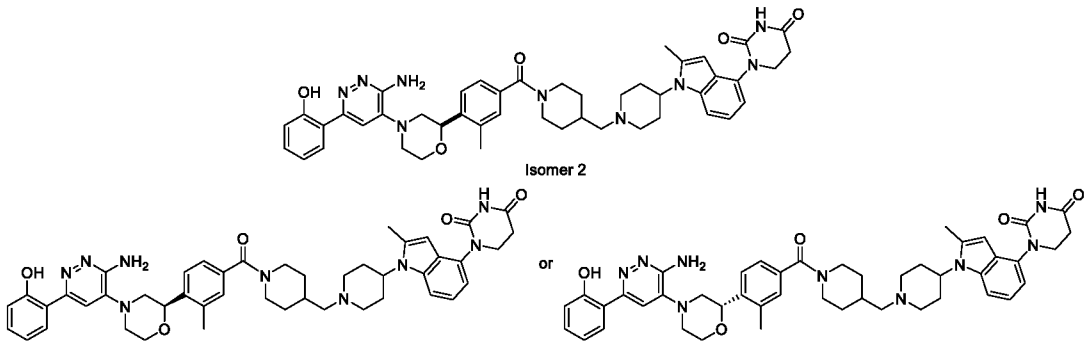
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

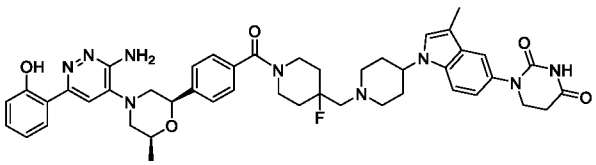
(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2108] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 22d (35 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (20.5 mg, 56%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.03 - 1.17 (2H, m), 1.67 - 1.95 (5H, m), 2.13 (2H, br d), 2.20 - 2.29 (2H, m), 2.34 - 2.45 (8H, m), 2.69 - 2.91 (5H, m), 2.94 - 3.10 (3H, m), 3.47 - 3.68 (3H, m), 3.72 (2H, t), 4.08 (2H, br d), 4.22 (1H, br t), 4.48 (1H, br s), 4.96 (1H, br d), 6.14 (1H, s), 6.41 (2H, s), 6.82 - 6.91 (3H, m), 7.03 (1H, t), 7.18 - 7.27 (3H, m), 7.45 (1H, br d), 7.51 - 7.62 (2H, m), 7.94 (1H, d), 10.28 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 84:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



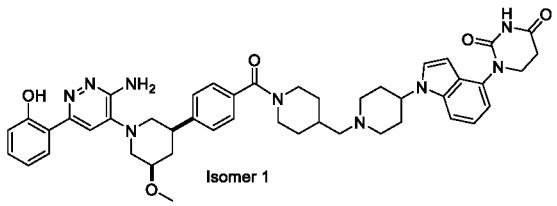
[2109] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 1k (40 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (17.1 mg, 46%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.61 - 2.06 (8H, m), 2.23 (3H, s), 2.37 - 2.45 (2H, m), 2.52 - 2.77 (6H, m), 2.99 - 3.33 (4H, m), 3.39 - 3.63 (3H, m), 3.77 (2H, t), 4.06 - 4.17 (1H, m), 4.18 - 4.44 (2H, m), 4.86 - 5.05 (1H, m), 6.50 (2H, s), 6.82 - 6.94 (2H, m), 7.05 (1H, dd), 7.20 - 7.27 (1H, m), 7.32 (1H, s), 7.40 (1H, d), 7.42 - 7.50 (3H, m), 7.51 - 7.60 (3H, m), 7.96 (1H, dd), 10.27 (1H, br s), 14.24 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 830.6.

EXAMPLE 85:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(Isomer 1)

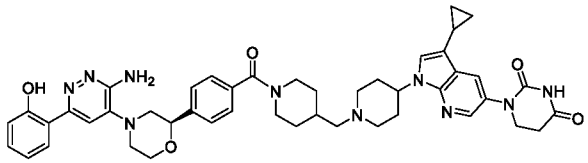
((*absolute configuration not yet confirmed))



[2110] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 69a 15 mg, 0.04 mmol) and Intermediate 10e (16 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (8.0 mg, 30%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.50 - 2.07 (8H, m), 2.11 - 2.31 (4H, m), 2.36 (1H, br d), 2.51 (2H, s), 2.69 - 3.16 (6H, m), 3.18 - 3.26 (1H, m), 3.39 (3H, s), 3.47 - 3.89 (6H, m), 4.25 - 4.69 (2H, m), 6.35 (2H, s), 6.41 (1H, d), 6.85 - 6.92 (2H, m), 6.96 (1H, d), 7.14 (1H, t), 7.21 - 7.28 (1H, m), 7.36 (2H, d), 7.44 (2H, d), 7.47 - 7.56 (2H, m), 7.60 (1H, s), 7.96 (1H, d), 10.32 (1H, br s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 86:

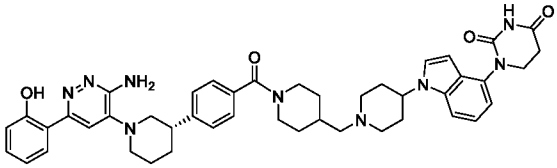
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2111] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05 mmol) and Intermediate 71c (41 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (19.1 mg, 50%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.64 (2H, br d), 0.85 (2H, br d), 0.99 - 1.36 (2H, m), 1.57 - 2.32 (10H, m), 2.55 - 3.25 (9H, m), 3.33 - 3.76 (4H, m), 3.80 (2H, br t), 3.99 - 4.14 (2H, m), 4.31 - 5.10 (3H, m), 6.46 (2H, br s), 6.78 - 6.93 (2H, m), 7.17 - 7.63 (6H, m), 7.22 (1H, br t), 7.93 (2H, br d), 8.17 (1H, br s), 10.36 (1H, br s), 14.17 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 825.5.

EXAMPLE 87:

(*S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2112] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 76d (15 mg, 0.04 mmol) and Intermediate 10e (17 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (10.4 mg, 38%) as a white solid, following

lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.58 - 2.05 (11H, m), 2.10 - 2.30 (4H, m), 2.63 - 2.86 (5H, m), 2.92 - 3.18 (4H, m), 3.49 - 3.72 (3H, m), 3.78 (2H, t), 4.22 - 4.68 (2H, m), 6.31 (2H, s), 6.42 (1H, d), 6.85 - 6.91 (2H, m), 6.96 (1H, d), 7.14 (1H, t), 7.20 - 7.27 (1H, m), 7.35 (2H, d), 7.39 - 7.45 (2H, m), 7.48 - 7.60 (3H, m), 7.91 - 7.98 (1H, m), 10.34 (1H, br s), 14.28 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 782.6.

EXAMPLE 88:

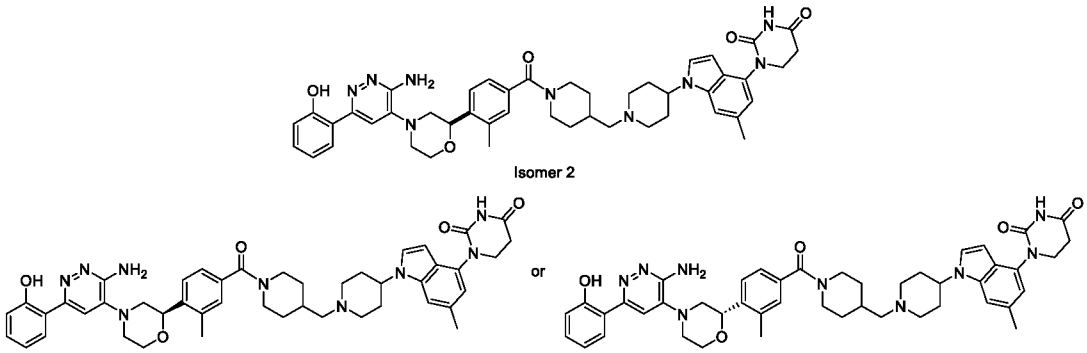
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

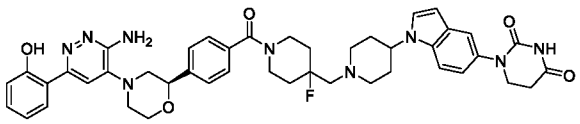
(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2113] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 82e (19 mg, 19 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (16.2 mg, 44%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.08 (2H, br d), 1.59 - 2.03 (7H, m), 2.09 - 2.30 (4H, m), 2.40 (6H, d), 2.68 - 2.91 (5H, m), 2.93 - 3.11 (3H, m), 3.43 - 3.68 (3H, m), 3.74 (2H, t), 4.07 (2H, br d), 4.26 - 4.36 (1H, m), 4.46 (1H, br d), 4.96 (1H, br d), 6.33 (1H, d), 6.41 (2H, s), 6.79 (1H, s), 6.82 - 6.90 (2H, m), 7.18 - 7.25 (3H, m), 7.29 (1H, s), 7.41 (1H, d), 7.51 - 7.60 (2H, m), 7.93 (1H, d), 10.28 (1H, br s), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 812.5.

EXAMPLE 89:

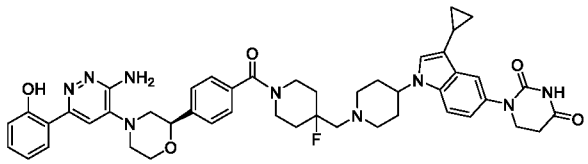
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2114] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (16 mg, 0.04 mmol) and Intermediate 2e (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (15.0 mg, 45%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.59 - 2.07 (8H, m), 2.40 (2H, br t), 2.56 - 2.67 (2H, m), 2.71 (2H, t), 2.78 (1H, br t), 2.83 - 2.92 (1H, m), 3.03 (2H, br d), 3.07 - 3.29 (2H, m), 3.37 - 3.63 (3H, m), 3.75 (2H, t), 4.00 - 4.13 (2H, m), 4.15 - 4.40 (2H, m), 4.87 (1H, br d), 6.38 - 6.51 (3H, m), 6.81 - 6.91 (2H, m), 7.06 (1H, dd), 7.18 - 7.25 (1H, m), 7.39 - 7.46 (3H, m), 7.47 - 7.58 (5H, m), 7.93 (1H, d), 10.24 (1H, br s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 802.5.

EXAMPLE 90:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2115] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (20 mg, 0.05mmol) and Intermediate 6h (32 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (18.0 mg, 46%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.59 (2H, q), 0.76 - 0.87 (2H, m), 1.60 - 2.03 (9H, m), 2.38 (2H, br t), 2.53 - 2.66 (2H, m), 2.72 (2H, t), 2.78 (1H, br t), 2.84 - 2.92 (1H, m), 3.01 (2H, br d), 3.06 - 3.27 (2H, m), 3.39 - 3.64 (3H, m), 3.76 (2H, t), 3.99 - 4.13 (2H, m), 4.24 (2H, br t), 4.87 (1H, br d), 6.46 (2H, s), 6.81 - 6.91 (2H, m), 7.03 (1H, br d), 7.17 - 7.25 (2H, m), 7.39 - 7.60 (7H, m), 7.93 (1H, d), 10.23 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 842.6.

EXAMPLE 91:

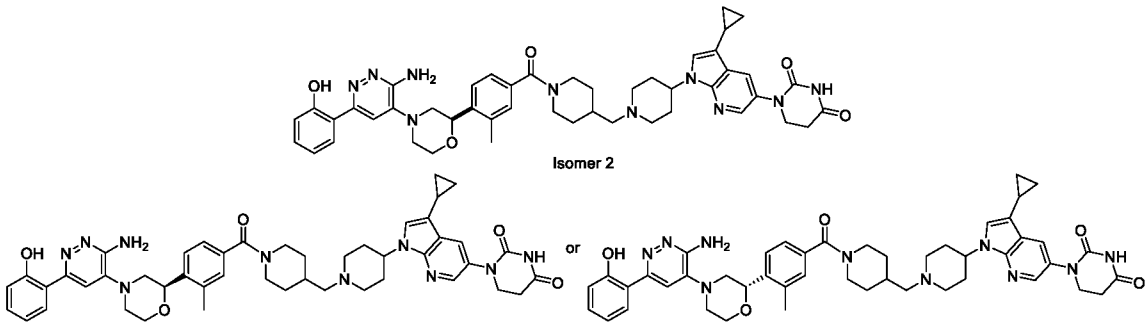
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2116] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 71c (40 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (25.2 mg, 67%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.67 (2H, m), 0.80 - 0.87 (2H, m), 1.07 (2H, br d), 1.57 - 1.94 (6H, m), 1.98 - 2.14 (4H, m), 2.21 (2H, br d), 2.39 (3H, s), 2.70 - 2.91 (5H, m), 2.97 (3H, br d), 3.48 - 3.68 (3H, m), 3.80 (2H, t), 4.07 (2H, br d), 4.46 (1H, br d), 4.55 - 4.66 (1H, m), 4.95 (1H, br d), 6.41 (2H, s), 6.81 - 6.92 (2H, m), 7.14 - 7.27 (3H, m), 7.43 (1H, s), 7.48 - 7.61 (2H, m), 7.88 - 7.97 (2H, m), 8.15 (1H, d), 10.21 (1H, br s), 14.08 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 839.6.

EXAMPLE 92:

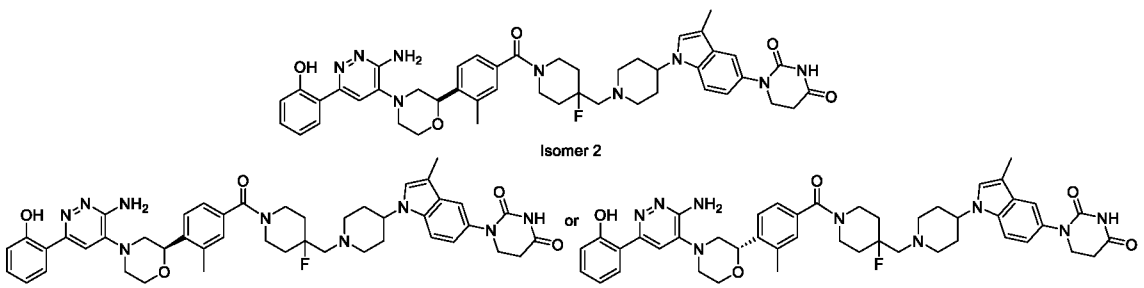
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



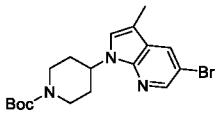
[2117] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 1k (40 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (23.5 mg, 63%) as a white solid, following

lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.65 - 2.04 (8H, m), 2.23 (3H, s), 2.42 (5H, s), 2.57 - 2.68 (2H, m), 2.73 (2H, t), 2.81 - 2.94 (2H, m), 2.99 - 3.28 (4H, m), 3.41 – 3.61 (3H, m), 3.77 (2H, t), 4.09 (2H, br d), 4.19 - 4.38 (2H, m), 4.98 (1H, d), 6.43 (2H, s), 6.84 - 6.93 (2H, m), 7.05 (1H, br d), 7.20 - 7.34 (4H, m), 7.40 (1H, s), 7.47 (1H, d), 7.54 - 7.62 (2H, m), 7.95 (1H, d), 10.24 (1H, br s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 830.6.

EXAMPLE 93

Intermediate 93a:

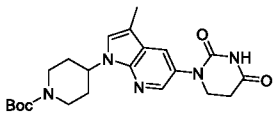
tert-Butyl 4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2118] *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.59 g, 23.59 mmol) and Cs_2CO_3 (11.5 g, 35.4 mmol) were added to a solution of 5-bromo-3-methyl-1H-pyrrolo[2,3-b]pyridine (4.98 g, 23.6 mmol) in DMF (79 mL) and the mixture was heated to 75 °C. More *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.59 g, 23.59 mmol) and Cs_2CO_3 (7.69 g, 23.6 mmol) were added after 4 and 7 h. After the final addition. Stirring was continued at 75 °C for 16 h. The mixture was partially concentrated under reduced pressure, diluted with EtOAc (100 mL), washed with brine (2 x 150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (7.27 g, 78%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.80 - 1.94 (4H, m), 2.23 (3H, s), 2.93 (2H, br s), 4.10 (2H, br s), 4.69 - 4.92 (1H, m), 7.51 (1H, s), 8.16 (1H, d), 8.26 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 394.2.

Intermediate 93b:

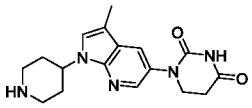
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2119] 1,4-Dioxane (82 mL) was added to a mixture of Intermediate 93a (5.48 g, 13.9 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (3.17 g, 27.8 mmol), K_3PO_4 (5.90 g, 27.8 mmol), $[Pd(cinnamyl)Cl]_2$ (0.36 g, 0.69 mmol) and *t*-BuBrettPhos (0.67 g, 1.39 mmol). The flask was evacuated and backfilled with nitrogen (5x). The mixture was stirred at 90 °C for 15 hours. After cooling to r.t., sat. aq. NH_4Cl (150 mL) was added and the mixture was extracted with DCM (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with hexanes/DCM (5:1), H_2O, and hexanes to give the title compound (4.61 g, 78%) as a grey solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.77 - 1.98 (4H, m), 2.23 (3H, s), 2.75 (2H, t), 2.94 (2H, br d), 3.79 (2H, t), 4.10 (2H, br d), 4.71 - 4.87 (1H, m), 7.49 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.36 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 428.4.

Intermediate 93c:

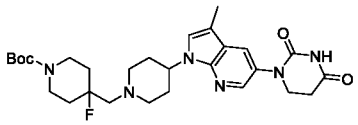
1-(3-Methyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2120] TFA (5.41 mL, 70.2 mmol) was added to a solution of Intermediate 93b (1.50 g, 3.51 mmol) in DCM (17 mL). The mixture was stirred at r.t. for 30 minutes and concentrated under reduced pressure. DCM (100 mL), IPA (30 mL) and sat. aq. K_2CO_3 (100 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (1.17 g, 102%, 92% purity) as a yellowish salt which was used for the next step without further purification. ^{1}H NMR (DMSO-*d*6): δ 1.72 - 1.93 (4H, m), 2.26 (3H, s), 2.61 - 2.71 (2H, m), 2.76 (2H, t), 3.07 (2H, br d), 3.81 (2H, t), 4.63 - 4.72 (1H, m), 7.45 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.38 (1H, br s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 328.2.

Intermediate 93d:

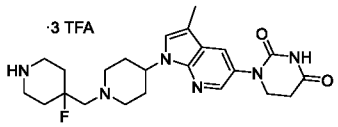
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1H-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2121] Prepared in an analogous method to Intermediate 6g using Intermediate 6f (3.71 g, 10.2 mmol) and Intermediate 93c (1.66 g, 5.08 mmol), stirring at 85 °C for 23 hours. Purification by FSC (elution gradient: 0 to 15% MeOH in DCM) gave the title compound (1.42 g, 51%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.40 (9H, s), 1.51 - 1.69 (2H, m), 1.77 - 1.89 (4H, m), 1.98 - 2.10 (2H, m), 2.24 (3H, s), 2.34 (2H, br t), 2.52 - 2.64 (2H, m), 2.74 (2H, t), 3.02 (4H, br d), 3.68 - 3.76 (2H, m), 3.79 (2H, t), 4.58 (1H, tt), 7.48 (1H, s), 7.86 (1H, d), 8.16 (1H, d), 10.36 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 543.5.

Intermediate 93e:

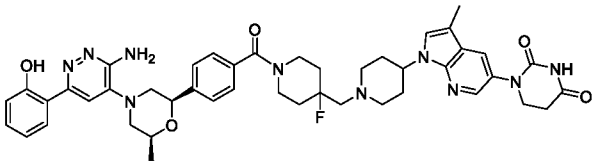
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2122] Prepared in an analogous method to Intermediate 1k starting from Intermediate 93d (160 mg, 0.29 mmol). The mixture was concentrated under reduced pressure. The residue was suspended in H_2O/MeCN and lyophilized to give the title compound (220 mg, 96%) as a brown solid and 3 TFA salt. ^{1}H NMR (DMSO-*d*6): δ 1.88 – 2.17 (4H, m), 2.28 (5H, s), 2.46 (2H, s), 2.56 (1H, t), 2.77 (2H, t), 3.08 (2H, d), 3.35 (3H, d), 3.64 (4H, m), 3.82 (2H, t), 4.94 (1H, s), 7.32 (1H, d), 7.94 (1H, d), 8.21 (1H, d), 8.90 (2H, s), 10.42 (1H, s), one TFA proton observed; *m/z* (ES$^+$) $[M+H]^+$ = 443.3.

EXAMPLE 93:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

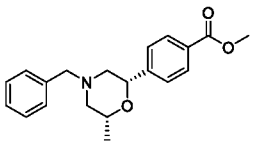


[2123] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (15 mg, 0.04 mmol) and Intermediate 93e (30 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (12.4 mg, 44%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.62 - 2.11 (8H, m), 2.25 (3H, s), 2.36 (2H, br t), 2.52 - 2.73 (4H, m), 2.76 (2H, t), 3.00 - 3.32 (4H, m), 3.40 - 3.65 (3H, m), 3.81 (2H, t), 4.06 - 4.17 (1H, m), 4.28 (1H, br d), 4.54 - 4.67 (1H, m), 4.96 (1H, br d), 6.50 (2H, s), 6.81 - 6.93 (2H, m), 7.20 - 7.28 (1H, m), 7.44 (2H, d), 7.50 (1H, s), 7.52 - 7.61 (3H, m), 7.88 (1H, d), 7.96 (1H, d), 8.18 (1H, d), 10.41 (1H, br s), 14.24 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 831.6.

EXAMPLE 94:

Intermediate 94a:

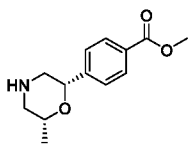
Methyl 4-((2*S*,6*R*)-4-benzyl-6-methylmorpholin-2-yl)benzoate



[2124] Prepared in an analogous procedure to Intermediate 65a using (*R*)-1-(benzylamino)propan-2-ol (1.30 g, 7.87 mmol) and methyl 4-(2-bromoacetyl)benzoate (2.02 g, 7.87 mmol) to give the title compound (1.66 g, 64%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.14 (3H, d), 1.79 (1H, t), 1.87 (1H, t), 2.77 (1H, br d), 2.88 (1H, br d), 3.44 - 3.50 (1H, m), 3.52 - 3.57 (1H, m), 3.73 - 3.81 (1H, m), 3.84 (3H, s), 4.66 (1H, dd), 7.24 - 7.29 (1H, m), 7.30 - 7.36 (4H, m), 7.48 (2H, d), 7.92 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 326.4.

Intermediate 94b:

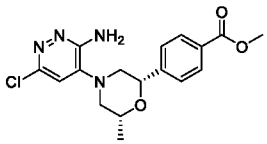
Methyl 4-((2*S*,6*R*)-6-methylmorpholin-2-yl)benzoate



[2125] Prepared in an analogous method to Intermediate 65b using Intermediate 94a (1.64 g, 5.04 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. *m/z* (ES$^+$) $[M+H]^+$ = 236.2.

Intermediate 94c:

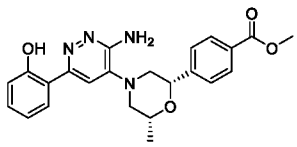
Methyl 4-((2*S*,6*R*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate



[2126] Prepared in an analogous method to Intermediate 1d starting from Intermediate 94b (1.19 g, 5.04 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (1.32 g, 72%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.23 (3H, d), 2.44 - 2.50 (2H, m), 3.40 (1H, br d), 3.55 (1H, br d), 3.86 (3H, s), 3.97 - 4.11 (1H, m), 4.96 (1H, dd), 6.37 (2H, s), 6.96 (1H, s), 7.58 (2H, d), 7.97 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 363.3.

Intermediate 94d:

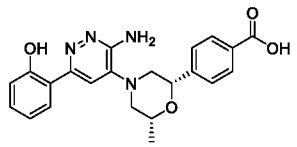
Methyl 4-((2*S*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate



[2127] Prepared in an analogous method to Intermediate 1e starting from Intermediate 94c (1.31 g, 3.60 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (1.22 g, 81%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 2.52 - 2.67 (2H, m), 3.48 (1H, br d), 3.59 (1H, br d), 3.85 (3H, s), 4.06 - 4.16 (1H, m), 4.88 - 5.12 (1H, m), 6.47 (2H, s), 6.82 - 6.89 (2H, m), 7.19 - 7.26 (1H, m), 7.54 (1H, s), 7.60 (2H, d), 7.92 (1H, dd), 7.97 (2H, d), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.4.

Intermediate 94e:

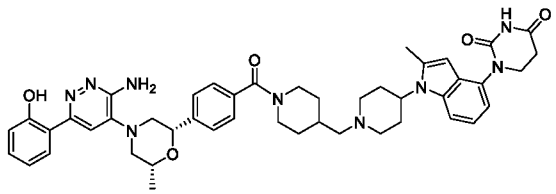
4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoic acid



[2128] Prepared in an analogous method to Intermediate 1f starting from Intermediate 94d (1.21 g, 2.88 mmol). The mixture was diluted with pH3 phosphate buffer and acidified to pH 3. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give the title compound (1.04 g, 89%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 2.55 - 2.72 (2H, m), 3.53 (1H, br d), 3.62 (1H, br d), 4.04 - 4.16 (1H, m), 4.99 (1H, br d), 6.70 (2H, br s), 6.85 - 6.95 (2H, m), 7.25 (1H, t), 7.50 - 7.63 (3H, m), 7.85 (1H, br d), 7.95 (2H, d), 11.22 - 14.74 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 407.4.

EXAMPLE 94:

1-(1-(1-((1-(4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2129] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 94e (20 mg, 0.05 mmol) and Intermediate 22d (39 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (16.4 mg, 45%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 - 1.19 (2H, m), 1.27 (3H, d), 1.69 - 1.96 (5H, m), 2.09 - 2.19 (2H, m), 2.22 - 2.31 (2H, m), 2.35 - 2.46 (5H, m), 2.54 - 2.59 (1H, m), 2.67 - 2.85 (4H, m), 2.95 - 3.18 (3H, m), 3.42 - 3.69 (3H, m), 3.74 (2H, t), 4.08 - 4.18 (1H, m), 4.19 - 4.31 (1H, m), 4.38 - 4.60 (1H, m), 4.88 - 5.05 (1H, m), 6.16 (1H, s), 6.48 (2H, s), 6.81 - 6.93 (3H, m), 7.04 (1H, t), 7.20 - 7.28 (1H, m), 7.41 (2H, d), 7.46 (1H, d), 7.53 (2H, d), 7.57 (1H, s), 7.96 (1H, d), 10.29 (1H, br s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 95:

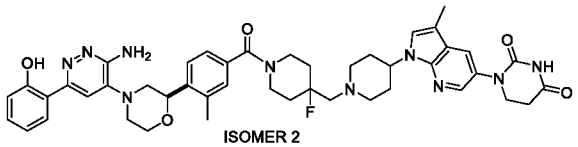
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

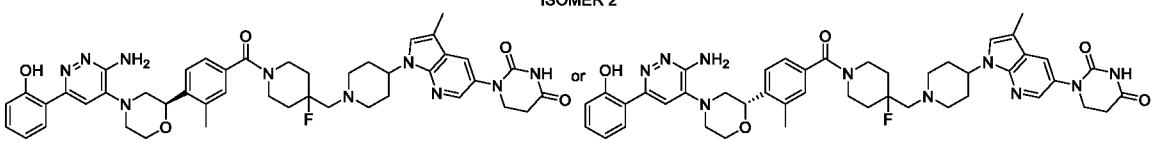
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



ISOMER 2



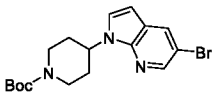
[2130] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15 mg, 0.04 mmol) and Intermediate 93e (30 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (18.8 mg, 67%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 2.10 (8H, m), 2.23 (3H, s), 2.31 - 2.42 (5H, m), 2.55 - 2.66 (2H, m), 2.74 (2H, t), 2.80 - 2.90 (2H, m), 2.98 - 3.29 (4H, m), 3.52 (3H, br t), 3.79 (2H, t), 4.08 (2H, br d),

4.25 (1H, br d), 4.52 - 4.67 (1H, m), 4.96 (1H, br d), 6.44 (2H, br s), 6.82 - 6.91 (2H, m), 7.19 - 7.30 (3H, m), 7.48 (1H, s), 7.51 - 7.59 (2H, m), 7.87 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.39 (1H, br s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 831.7.

EXAMPLE 96

Intermediate 96a:

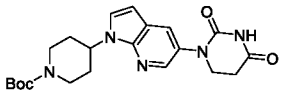
tert-Butyl 4-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2131] Prepared in an analogous method to Intermediate 93a using 5-bromo-1H-pyrrolo[2,3-b]pyridine (1.00 g, 5.08 mmol), *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (2.13 g, 7.61 mmol) and Cs_2CO_3 (2.48 g, 7.61 mmol) in DMF (25 mL) at 70 °C. Purification by FSC (elution gradient: 0 to 20% EtOAc in hexanes) gave the title compound (1.67 g, 87%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.85 - 1.99 (4H, m), 2.94 (2H, br s), 4.00 - 4.24 (2H, m), 4.78 - 4.88 (1H, m), 6.47 (1H, d), 7.76 (1H, d), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 380.1.

Intermediate 96b:

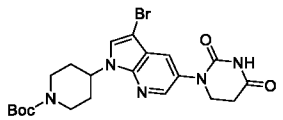
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2132] Prepared in an analogous method to Intermediate 93b using Intermediate 96a (1.62 g, 4.25 mmol). Trituration with DCM/hexanes afforded the title compound (1.41 g, 80%) as a grey solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.86 - 2.04 (4H, m), 2.76 (2H, t), 2.83 - 3.12 (2H, m), 3.81 (2H, t), 4.14 (2H, br d), 4.81 - 4.95 (1H, m), 6.51 (1H, d), 7.75 (1H, d), 7.93 (1H, d), 8.21 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 414.2.

Intermediate 96c:

tert-Butyl 4-(3-bromo-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate

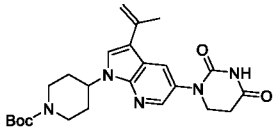


[2133] NBS (136 mg, 0.76 mmol) was added to a suspension of Intermediate 96b (300 mg, 0.73 mmol) in DMF (7.3 mL) at 0 °C. The mixture was stirred at 0 °C for 1h. The mixture was diluted with DCM (40 mL), washed with sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (2 x 50 mL, 1:1), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (321 mg, 90%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s),

1.88 - 2.02 (4H, m), 2.76 (2H, t), 2.94 (2H, br s), 3.83 (2H, t), 4.04 - 4.23 (2H, m), 4.84 - 4.95 (1H, m), 7.83 (1H, d), 8.02 (1H, s), 8.29 (1H, d), 10.41 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 492.2.

Intermediate 96d:

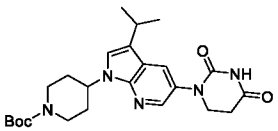
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-(prop-1-en-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2134] Intermediate 96c (0.65 g, 1.32 mmol) was added to a mixture of 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.67 g, 3.97 mmol), Cs_2CO_3 (1.29 g, 3.97 mmol) and XPhos Pd G3 (0.11 g, 0.13 mmol) in 1,4-dioxane (15 mL) and H_2O (1.5 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was filtered. The filtrate was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.49 g, 82%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.88 (2H, d), 1.94 – 2.03 (2H, m), 2.12 (3H, s), 2.75 (2H, t), 3.05 (2H, s), 3.82 (2H, t), 4.11 (2H, dd), 4.81 – 4.93 (1H, m), 4.96 – 5.02 (1H, m), 5.41 (1H, s), 7.89 (1H, s), 8.22 (2H, q), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 454.2.

Intermediate 96e:

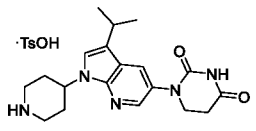
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2135] A mixture of Intermediate 96d (270 mg, 0.60 mmol) and Pd-C (32 mg, 0.03 mmol, 10 wt% Pd) in DCM (50 mL) was stirred under an atmosphere of hydrogen for 5 hours. The mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound (200 mg, 73%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.18 (1H, t), 1.24 (1H, s), 1.30 (6H, d), 1.44 (9H, s), 1.82 – 1.96 (3H, m), 2.77 (2H, t), 3.11 (1H, p), 3.82 (2H, t), 4.04 (1H, q), 4.13 (2H, d), 4.75 – 4.91 (1H, m), 7.51 (1H, s), 7.98 (1H, d), 8.17 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 456.2.

Intermediate 96f:

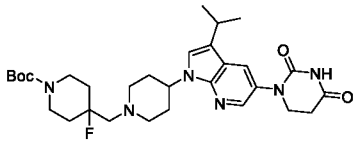
1-(3-Isopropyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2136] *p*-Toluenesulfonic acid (113 mg, 0.66 mmol) was added to a solution of Intermediate 96e (200 mg, 0.44 mmol). The mixture was stirred at 80 °C for 3h and concentrated under reduced pressure to give the title compound (150 mg, 100%) solid. *m/z* (ES^+) $[M+H]^+$ = 356.2.

Intermediate 96g:

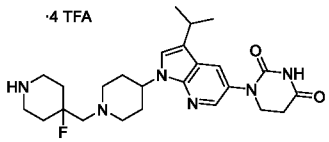
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2137] Prepared in an analogous method to Intermediate 6g using Intermediate 6f (308 mg, 0.84 mmol) and Intermediate 96f (200 mg, 0.56 mmol), stirring the mixture at 80 °C for 16h. Purification by RPC (elution gradient: 0 to 70% MeCN in water with 0.04% NH_4HCO_3) gave the title compound (150 mg, 46%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.16 (2H, t), 1.29 (6H, d), 1.40 (9H, s), 1.81 (4H, d), 2.03 – 2.15 (2H, m), 2.27 – 2.40 (2H, m), 2.62 (1H, s), 2.75 (2H, t), 2.95 – 3.16 (5H, m), 3.67 – 3.86 (4H, m), 4.02 (1H, q), 4.59 (1H, t), 7.46 (1H, s), 7.94 (1H, d), 8.15 (1H, d), 10.37 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 571.3.

Intermediate 96h:

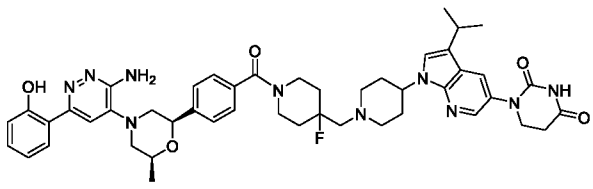
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2138] TFA (3 mL) was added to a solution of Intermediate 96g (200 mg, 0.35 mmol) in DCM (3 mL). The mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure to give the title compound (200 mg, 59%) as a pale yellow solid and 4 TFA salt. ^{1}H NMR (DMSO-*d*6): δ 1.24 (1H, d), 1.31 (6H, d), 1.91 – 2.18 (4H, m), 2.20 – 2.31 (2H, m), 2.57 (1H, d), 2.77 (2H, t), 3.12 (3H, td), 3.29 – 3.50 (4H, m), 3.69 (4H, s), 3.82 (2H, t), 4.90 (1H, s), 7.32 (1H, s), 8.02 (1H, d), 8.21 (1H, d), 8.83 – 9.12 (2H, m), 10.41 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 471.3.

EXAMPLE 96:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2139] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (15 mg, 0.04 mmol) and Intermediate 96h (31 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (6.5 mg, 22%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.30 (6H, d), 1.63 - 2.15 (8H, m), 2.37 (2H, t), 2.53 - 2.80 (6H, m), 3.01 - 3.32 (5H, m), 3.43 - 3.64 (3H, m), 3.81 (2H, t), 4.07 - 4.17 (1H, m), 4.28 (1H, br s),

4.62 (1H, br t), 4.96 (1H, br d), 6.51 (2H, br s), 6.83 - 6.94 (2H, m), 7.24 (1H, t), 7.41 - 7.50 (3H, m), 7.51 - 7.60 (3H, m), 7.93 - 8.00 (2H, m), 8.17 (1H, d), 10.40 (1H, br s), 14.24 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 859.7.

EXAMPLE 97:

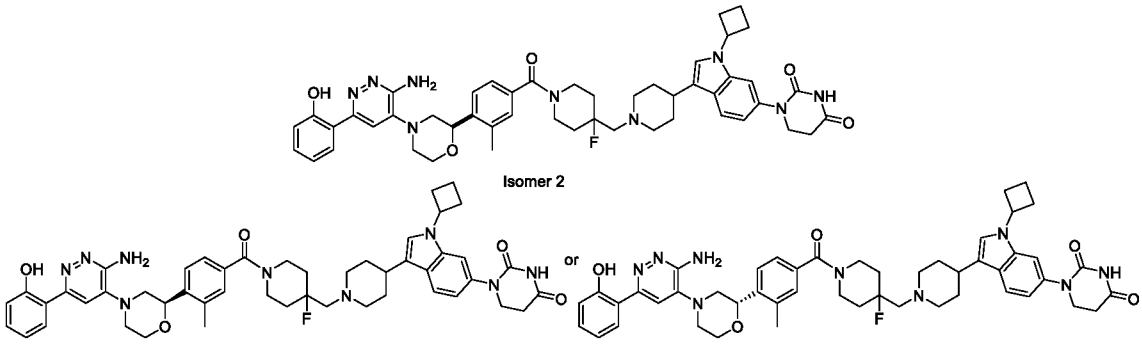
(*R**)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

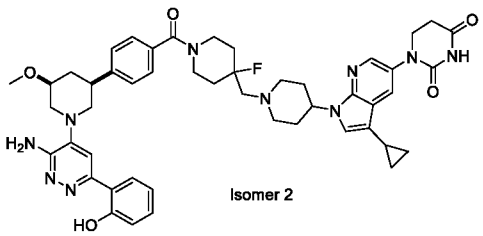


[2140] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 74g (37 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (25.6 mg, 65%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.65 - 2.03 (10H, m), 2.30 (2H, t), 2.35 - 2.47 (8H, m), 2.56 - 2.66 (2H, m), 2.69 - 2.77 (3H, m), 2.80 - 2.92 (2H, m), 2.97 - 3.21 (3H, m), 3.38 - 3.62 (3H, m), 3.79 (2H, t), 4.09 (2H, m), 4.16 - 4.36 (1H, m), 4.89 (1H, quin), 4.97 (1H, d), 6.43 (2H, br s), 6.82 - 6.90 (2H, m), 6.91 - 6.98 (1H, m), 7.18 - 7.31 (3H, m), 7.39 (2H, s), 7.50 - 7.64 (3H, m), 7.94 (1H, d), 10.28 (1H, br s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 870.7.

EXAMPLE 98:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

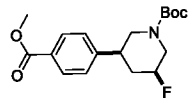


[2141] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (13 mg, 0.03 mmol) and Intermediate 20g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (14mg, 56%) as a white solid. ^{1}H NMR (DMSO-d6): δ 0.61 - 0.66 (2H, m), 0.78 - 0.88 (2H, m), 1.22 - 1.32 (2H, m), 1.49 - 1.60 (1H, m), 1.61 - 1.77 (2H, m), 1.77 - 1.83 (2H, m), 1.86 - 1.97 (2H, m), 1.98 - 2.10 (2H, m), 2.30 - 2.40 (3H, m), 2.56 - 2.66 (2H, m), 2.68 - 2.78 (3H, m), 2.96 - 3.04 (2H, m), 3.07 - 3.14 (1H, m), 3.16 - 3.30 (4H, m), 3.37 - 3.42 (3H, m), 3.48 - 3.53 (1H, m), 3.67 - 3.76 (1H, m), 3.79 - 3.84 (2H, m), 4.16 - 4.39 (1H, m), 4.52 - 4.64 (1H, m), 6.36 (2H, s), 6.83 - 6.92 (2H, m), 7.18 - 7.26 (1H, m), 7.38 (2H, d), 7.42 - 7.46 (3H, m), 7.58 (1H, s), 7.89 - 7.98 (2H, m), 8.12 - 8.18 (1H, m), 10.38 (1H, s), 13.97 - 14.41 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 871.5.

EXAMPLE 99

Intermediate 99a:

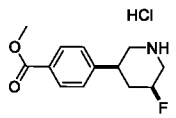
rac-tert-Butyl (3*R*,5*R*)-3-fluoro-5-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2142] Intermediate 61c (0.516 g, 1.54 mmol) in CH_2Cl_2 (7 mL) was stirred at 0 °C. DAST (0.610 ml, 4.62 mmol) was added in dropwise. The reaction was allowed to warm to r.t. and was stirred for 30 min. The reaction was quenched by addition of $NaHCO_3$ solution. Organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 10 to 35% EtOAc in hexanes) gave the title compound (0.251 g, 48%) as a white solid. Structure was confirmed by 2D NMR. ^{1}H NMR (CD_2Cl_2): δ 1.40 (9H, s), 1.87 (1H, br t), 2.29 (1H, br s), 2.87 (3H, br s), 3.79 - 3.98 (4H, m), 4.19 (1H, br s), 4.53 - 4.75 (1H, m), 7.47 (2H, d), 7.92 (2H, d).

Intermediate 99b:

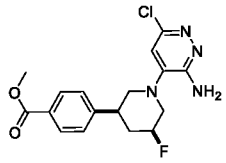
rac-Methyl 4-((3*R*,5*R*)-5-fluoropiperidin-3-yl)benzoate



[2143] HCl, 4 M in 1,4-dioxane (3.5 mL, 14 mmol) was added to Intermediate 99a (440 mg, 1.30 mmol). The reaction was stirred at r.t. for 2 h. Solvent was removed to obtain the title compound as an off-white solid in the form of HCl salt. assumed quantitative yield. *m/z* (ES$^+$) $[M+H]^+$ = 238.1.

Intermediate 99c:

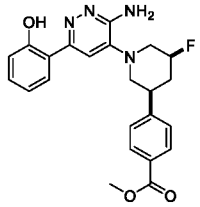
rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-chloropyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoate)



[2144] Prepared in an analogous method to Intermediate 1d starting from Intermediate 99b (356 mg, 1.3 mmol), and 4-bromo-6-chloropyridazin-3-amine (406 mg, 1.95 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in EtOAc) gave the title compound (306 mg, 64%) as a brown solid. ^{1}H NMR (CD_2Cl_2): δ 1.85 - 2.00 (1H, m), 2.55 (1H, br dd), 2.66 - 2.81 (2H, m), 3.10 (1H, br t), 3.53 (1H, br d), 3.72 - 3.82 (1H, m), 3.89 (3H, s), 4.71 - 4.96 (3H, m), 6.75 - 6.94 (1H, m), 7.37 (2H, d), 8.01 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 365.1.

Intermediate 99d:

rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoate



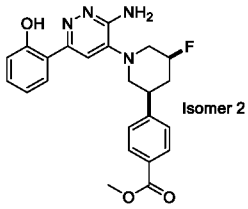
[2145] Prepared in an analogous method to Intermediate 1e starting from Intermediate 99c (306 mg, 0.84 mmol), and (2-hydroxyphenyl)boronic acid (127 mg, 0.92 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in EtOAc) gave the title compound (260 mg, 73%) as an off-white solid. ^{1}H NMR (CD_2Cl_2): δ 1.98 (1H, quin), 2.58 (1H, br d), 2.79 (1H, t), 2.84 - 2.92 (1H, m), 3.16 (1H, br t), 3.42 (1H, br s), 3.61 (1H, br d), 3.89 - 3.91 (3H, m), 4.84 - 5.01 (3H, m), 6.91 (1H, t), 6.99 (1H, d), 7.28 (1H, t), 7.38 - 7.42 (3H, m), 7.63 (1H, d), 8.02 (2H, d), 13.66 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 423.2.

Intermediate 99e:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoate

(Isomer 2)

((*absolute configuration not yet confirmed))



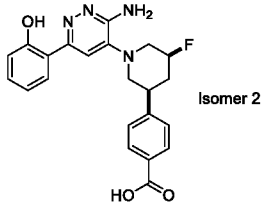
[2146] Intermediate 99d (240 mg, 0.57 mmol) was purified by chiral SFC (Column: IA 21mm × 250 5μm, MeOH/0.2% NH_4OH) to give the title compound that eluted second from the column (100 mg, 83% yield, >99% ee) as a light brown oil, which solidified upon standing in the refrigerator at 0 °C.

Intermediate 99f:

4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoic acid

(Isomer 2)

((*absolute configuration not yet confirmed))

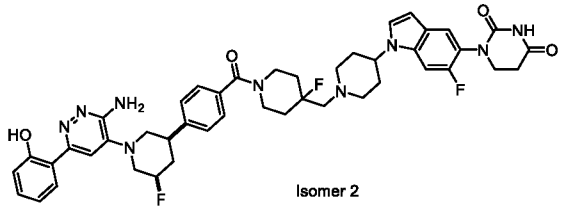


[2147] Intermediate 99e (100 mg, 0.24 mmol) and LiOH (47.9 mg, 2mmol) in a mixture of H_2O (0.5 ml), MeOH (0.5 ml), and THF (0.5 ml) were stirred at r.t. overnight. Solvent was removed and the residue was acidified using 1 M aq. HCl to pH 4-5. The mixture was centrifuged. The liquid was decanted off and the solids were dried *in vacuo* to give the title compound (95 mg, 90%) as a white solid in the form of HCl salt. *m/z* (ES^+) $[M+H]^+$ = 409.2.

EXAMPLE 99:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

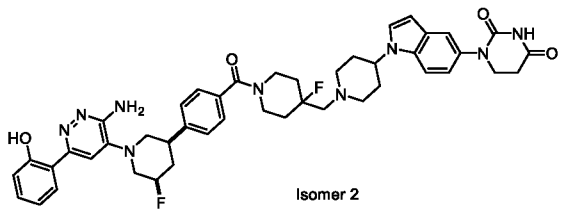


[2148] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 99f (13 mg, 0.03 mmol) and Intermediate 5g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (14 mg, 56%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.68 - 2.10 (8H, m), 2.36 - 2.43 (1H, m), 2.71 - 2.75 (2H, m), 2.82 - 2.91 (2H, m), 3.00 - 3.19 (2H, m), 3.19 - 3.27 (4H, m), 3.36 - 3.50 (4H, m), 3.51 - 3.59 (2H, m), 3.68 - 3.73 (2H, m), 3.89 - 3.96 (1H, m), 4.28 - 4.47 (1H, m), 5.03 - 5.19 (1H, m), 6.42 - 6.61 (2H, m), 6.87 - 6.96 (2H, m), 7.23 - 7.32 (1H, m), 7.34 - 7.54 (6H, m), 7.56 - 7.68 (3H, m), 7.82 - 7.94 (1H, m), 10.38 (1H, s), OH (not observed); *m/z* (ES^+) $[M+H]^+$ = 836.5.

EXAMPLE 100:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

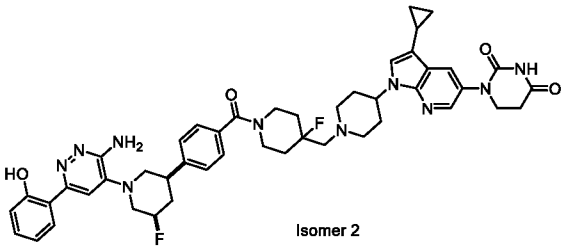


[2149] Prepared in an analogous method to EXAMPLE 1starting from Intermediate 99f (14 mg, 0.03 mmol) and Intermediate 2e (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% HCOOH) gave the title compound (5 mg, 21%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.22 - 1.29 (1H, m), 1.66 - 2.10 (8H, m), 2.11 - 2.30 (2H, m), 2.38 - 2.43 (1H, m), 2.70 - 2.74 (2H, m), 2.77 - 2.96 (4H, m), 3.02 - 3.24 (6H, m), 3.50 - 3.63 (2H, m), 3.72 - 3.78 (2H, m), 3.85 - 3.95 (1H, m), 4.17 - 4.49 (1H, m), 5.01 - 5.21 (1H, m), 6.42 - 6.67 (2H, m), 6.87 - 6.96 (2H, m), 7.06 - 7.14 (1H, m), 7.23 - 7.31 (1H, m), 7.33 - 7.55 (7H, m), 7.53 - 7.62 (2H, m), 7.78 - 7.96 (1H, m), 10.20 - 10.28 (1H, m), OH (not observed); *m/z* (ES$^+$) $[M+H]^+$ = 818.5.

EXAMPLE 101:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

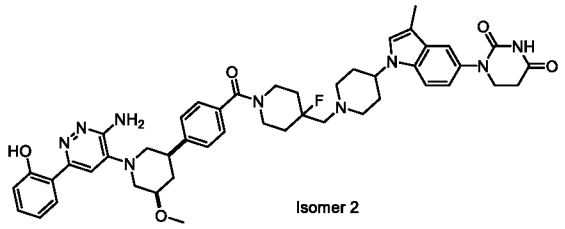


[2150] Prepared in an analogous method to EXAMPLE 1starting from Intermediate 99f (14 mg, 0.03 mmol) and Intermediate 20g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (16 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.58 - 0.68 (2H, m), 0.79 - 0.87 (2H, m), 1.61 - 1.76 (2H, m), 1.78 - 1.83 (2H, m), 1.86 - 1.92 (2H, m), 2.00 - 2.09 (2H, m), 2.29 - 2.39 (2H, m), 2.53 - 2.67 (2H, m), 2.70 - 2.81 (4H, m), 3.00 - 3.06 (2H, m), 3.06 - 3.28 (6H, m), 3.42 - 3.54 (2H, m), 3.76 - 3.82 (2H, m), 3.83 - 3.92 (1H, m), 4.19 - 4.35 (1H, m), 4.52 - 4.65 (1H, m), 4.98 - 5.23 (1H, m), 6.35 - 6.49 (2H, m), 6.83 - 6.91 (2H, m), 7.17 - 7.27 (1H, m), 7.36 - 7.51 (5H, m), 7.59 - 7.65 (1H, m), 7.88 - 8.18 (3H, m), 10.29 - 10.46 (1H, m), 14.01 - 14.31 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 859.6.

EXAMPLE 102:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

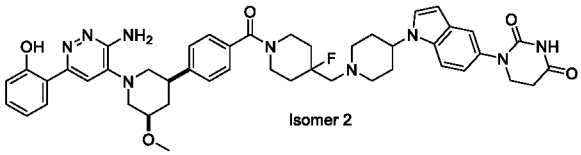


[2151] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (14 mg, 0.03 mmol) and Intermediate 1k (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (16.5 mg, 65%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.52 - 1.66 (1H, m), 1.67 - 2.13 (6H, m), 2.20 - 2.26 (3H, m), 2.34 - 2.38 (1H, m), 2.52 - 2.67 (2H, m), 2.68 - 2.74 (2H, m), 2.75 - 2.97 (2H, m), 3.03 - 3.29 (10H, m), 3.37 - 3.39 (3H, m), 3.54 - 3.67 (2H, m), 3.69 - 3.74 (1H, m), 3.74 - 3.80 (2H, m), 3.80 - 3.94 (1H, m), 4.21 - 4.68 (1H, m), NH2 (not observed) 6.85 - 7.00 (2H, m), 7.04 - 7.12 (1H, m), 7.13 - 7.24 (1H, m), 7.26 - 7.35 (1H, m), 7.37 - 7.44 (3H, m), 7.44 - 7.48 (2H, m), 7.48 - 7.55 (1H, m), 7.55 - 7.62 (1H, m), 7.68 - 7.89 (1H, m), 10.19 - 10.29 (1H, m), OH (not observed); *m/z* (ES$^+$) $[M+H]^+$ = 844.5.

EXAMPLE 103:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

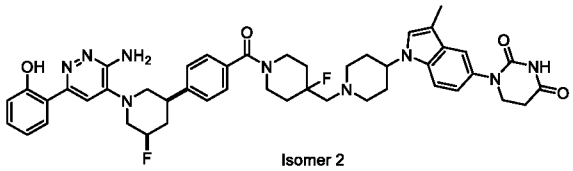


[2152] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 29a (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (10 mg, 46%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.49 - 1.60 (1H, m), 1.61 - 1.80 (2H, m), 1.80 - 2.01 (6H, m), 2.32 - 2.38 (1H, m), 2.38 - 2.45 (2H, m), 2.57 - 2.67 (2H, m), 2.71 - 2.79 (2H, m), 3.00 - 3.07 (2H, m), 3.09 - 3.28 (4H, m), 3.37 - 3.40 (3H, m), 3.44 - 3.54 (2H, m), 3.54 - 3.78 (4H, m), 3.78 - 3.85 (1H, m), 4.17 - 4.30 (1H, m), 4.30 - 4.38 (1H, m), 6.33 (2H, s), 6.44 (1H, d), 6.87 (2H, d), 7.04 - 7.07 (1H, m), 7.22 (1H, s), 7.36 - 7.41 (2H, m), 7.42 - 7.47 (3H, m), 7.49 - 7.55 (2H, m), 7.58 (1H, s), 7.94 (1H, d), 10.23 (1H, s), 14.12 - 14.26 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 830.4.

EXAMPLE 104:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



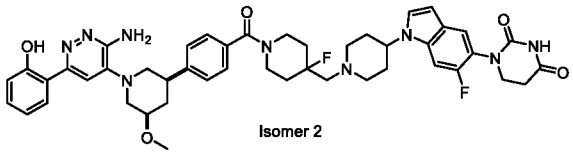
Isomer 2

[2153] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 99f (14 mg, 0.03 mmol) and Intermediate 1k (26 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (16 mg, 65%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.66 - 2.18 (8H, m), 2.21 - 2.27 (3H, m), 2.36 - 2.47 (2H, m), 2.70 - 2.75 (2H, m), 2.83 - 3.07 (3H, m), 3.08 - 3.22 (4H, m), 3.56 - 3.66 (4H, m), 3.75 - 3.79 (2H, m), 3.88 - 4.03 (2H, m), 4.26 - 4.44 (1H, m), 4.51 - 4.67 (1H, m), 5.02 - 5.20 (1H, m), NH2 (not observed). 6.92 - 7.00 (2H, m), 7.03 - 7.12 (1H, m), 7.03 - 7.03 (1H, m), 7.13 - 7.20 (1H, m), 7.30 - 7.36 (1H, m), 7.39 - 7.43 (3H, m), 7.46 - 7.51 (2H, m), 7.51 - 7.55 (1H, m), 7.59 - 7.66 (1H, m), 7.68 - 7.78 (1H, m), 10.24 (1H, s), OH (not observed); *m/z* (ES$^+$) [M+H]$^+$ = 832.5.

EXAMPLE 105:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



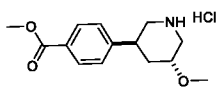
Isomer 2

[2154] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 5g (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (8 mg, 36%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.48 - 1.61 (1H, m), 1.62 - 1.81 (2H, m), 1.82 - 2.02 (6H, m), 2.30 - 2.45 (3H, m), 2.57 - 2.68 (2H, m), 2.68 - 2.77 (3H, m), 2.97 - 3.06 (2H, m), 3.14 - 3.20 (2H, m), 3.20 - 3.26 (2H, m), 3.37 - 3.39 (3H, m), 3.47 - 3.53 (2H, m), 3.67 - 3.85 (4H, m), 4.20 - 4.37 (2H, m), 6.36 (2H, s), 6.47 (1H, d), 6.80 - 6.89 (2H, m), 7.20 - 7.24 (1H, m), 7.33 - 7.41 (2H, m), 7.41 - 7.48 (2H, m), 7.51 - 7.61 (4H, m), 7.96 (1H, s), 10.39 (1H, s), 14.06 - 14.41 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 848.5.

EXAMPLE 106

Intermediate 106a:

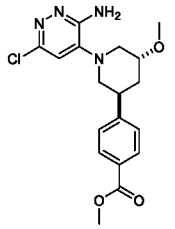
rac-Methyl 4-((3*S*,5*R*)-5-methoxypiperidin-3-yl)benzoate



[2155] HCl, 4 M in 1,4-dioxane (787 µl, 3.15 mmol) was added to Intermediate 61e (110 mg, 0.31 mmol). The reaction was stirred at room temperature for 2 h. Solvent was removed to afford the title compound as a white solid in the form of HCl salt. Quantitative yield assumed. *m/z* (ES^+) $[M+H]^+$ = 250.1.

Intermediate 106b:

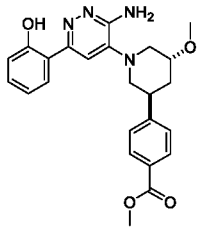
rac-Methyl 4-((3*S*,5*R*)-1-(3-amino-6-chloropyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate



[2156] Prepared in an analogous method to Intermediate 1d starting from Intermediate 106a (89 mg, 0.31 mmol). Purification by FSC (elution gradient: 10 to 50% EtOAc in hexanes and 0 to 10% methanol in EtOAc) afforded the title compound (99 mg, 85 %) as a brown solid. ^1H NMR (CD_2Cl_2): δ 1.72 - 1.80 (1H, m), 2.36 (1H, br d), 2.66 (1H, d), 2.94 - 3.03 (1H, m), 3.35 - 3.40 (2H, m), 3.45 (3H, s), 3.69 (1H, br s), 3.88 - 3.90 (3H, m), 3.90 - 3.96 (1H, m), 5.18 (2H, br s), 6.65 (1H, s), 7.36 (2H, d), 8.00 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 377.1.

Intermediate 106c:

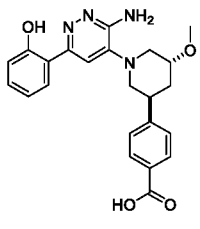
rac-Methyl 4-((3*S*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoate



[2157] Prepared in an analogous method to Intermediate 1e starting from Intermediate 106b (41 mg, 0.11 mmol). Purification by FSC (elution gradient: 10 to 40% [10% MeOH in EtOAc] in hexanes) afforded the title compound (24.0 mg, 50%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.77 - 1.87 (1H, m), 2.40 (1H, br d), 2.74 (1H, d), 3.09 - 3.15 (1H, m), 3.38 - 3.46 (1H, m), 3.47 - 3.49 (3H, m), 3.49 - 3.53 (1H, m), 3.72 - 3.77 (1H, m), 3.87 - 3.92 (3H, m), 3.93 - 4.01 (1H, m), 6.85 (1H, t), 6.95 (1H, d), 7.21 - 7.27 (2H, m), 7.41 (2H, d), 7.57 (1H, d), 8.02 (2H, d), 13.70 - 13.97 (1H, m), NH2 not observed; *m/z* (ES^+) $[M+H]^+$ = 435.2.

Intermediate 106d:

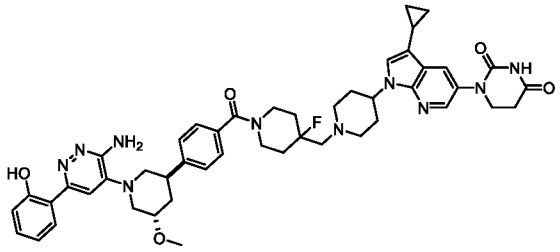
rac-4-((3*S*,5*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoic acid



[2158] Prepared in an analogous method to Intermediate 1f starting from Intermediate 106c (24 mg, 0.06 mmol). Solvent was removed and the residue was acidified with 1N HCl to pH 4. Solids were filtered, dried to give the title compound. Quantitative yield assumed. *m/z* (ES^+) $[M+H]^+$ = 421.2.

EXAMPLE 106:

rac-1-(1-(1-((1-(4-((3*R*,5*S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



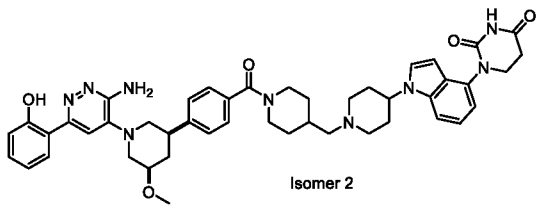
[2159] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 106d (13 mg, 0.03 mmol) and Intermediate 20g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (13 mg, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.64 (2H, br d), 0.85 (2H, br d), 1.11 - 1.27 (2H, m), 1.57 - 1.96 (9H, m), 2.02 - 2.16 (2H, m), 2.14 - 2.27 (2H, m), 2.74 - 2.77 (2H, m), 2.84 - 2.99 (2H, m), 2.99 - 3.24 (6H, m), 3.36 - 3.38 (3H, m), 3.54 - 3.62 (1H, m), 3.70 - 3.76 (1H, m), 3.77 - 3.88 (3H, m), 4.03 - 4.41 (1H, m), 4.46 - 4.75 (1H, m), 6.13 - 6.47 (2H, m), 6.82 - 6.95 (2H, m), 7.16 - 7.29 (1H, m), 7.34 - 7.43 (3H, m), 7.43 - 7.50 (2H, m), 7.53 (1H, s), 7.79 - 7.89 (1H, m), 7.94 (1H, s), 8.13 - 8.19 (1H, m), 10.36 (1H, s), OH (not observed); *m/z* (ES^+) $[M+H]^+$ = 871.4.

EXAMPLE 107:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(Isomer 2)

((*absolute configuration not yet confirmed))



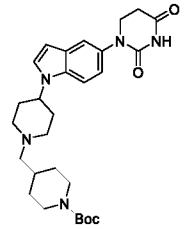
[2160] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 10e (16 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (11 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.02 - 1.16 (2H, m), 1.49 - 1.61 (1H, m), 1.61 - 1.76 (1H, m), 1.76 - 1.87 (2H, m), 1.87 - 2.01 (4H, m), 2.10 - 2.19 (2H, m), 2.19 - 2.29 (2H, m), 2.31 - 2.36 (1H, m), 2.67 - 2.77 (4H, m), 2.93 - 2.99 (2H, m), 3.12 - 3.19 (3H, m), 3.50 - 3.67 (4H, m), 3.69 - 3.85 (5H, m), 4.31 - 4.43 (1H, m), 4.43 - 4.54 (1H, m), 6.32 - 6.44

(3H, m), 6.80 - 6.91 (2H, m), 6.94 (1H, d), 7.13 (1H, t), 7.22 (1H, t), 7.34 (2H, d), 7.43 (2H, d), 7.46 - 7.55 (2H, m), 7.58 (1H, s), 7.95 (1H, d), 10.32 (1H, s), 13.94 - 14.53 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 108

Intermediate 108a:

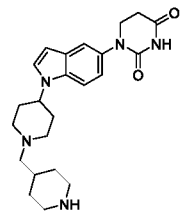
1-(1-(1-(Piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2161] Sodium triacetoxyborohydride (339 mg, 1.60 mmol) was added to *tert*-butyl 4-formylpiperidine-1-carboxylate (137 mg, 0.64 mmol) and Intermediate 2c (200 mg, 0.64 mmol) in mixture DCM (2 mL) and NMP (2 mL). The reaction was stirred at r.t for 2h. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% FA) gave the title compound (0.170 g, 48%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.91-1.06 (2H, m), 1.40 (9H, s), 1.67 – 1.79 (3H, m), 1.89-2.06 (3H, m), 2.32 (4H, d), 2.72 (4H, t), 3.07 (2H, d), 3.76 (2H, t), 3.94 (2H, d), 4.40 (1H, t), 6.46 (1H, d), 7.04-7.10 (1H, m), 7.46 (1H, d), 7.51 – 7.57 (2H, m), 8.14 (1H, s), 10.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 510.4.

Intermediate 108b:

1-(1-(1-(Piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



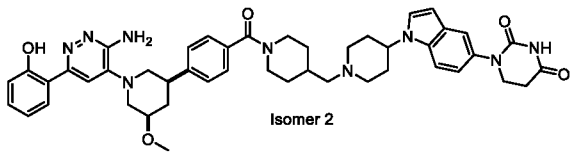
[2162] TFA (2 mL) was added to a stirred solution of Intermediate 108a (499 mg, 0.98 mmol) in DCM (8 mL) and stirred at r.t. for 30 min. Solvent was removed. The crude residue was basified by dissolving in MeOH (3 mL), passing through a RxnCX 5g column, and was washing with MeOH (40 mL) and eluted with 1.4 M NH_3 in MeOH (80 mL). The solvent was removed under reduced pressure to give title compound (312 mg, 78 %) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.98 (2H, qd), 1.54 - 1.69 (3H, m), 1.89 - 2.05 (4H, m), 2.10 - 2.21 (4H, m), 2.41 - 2.49 (2H, m), 2.72 (2H, t), 2.88 - 3.00 (4H, m), 3.06 - 3.52 (1H, m), 3.77 (2H, t), 4.29 - 4.39 (1H, m), 6.46 (1H, d), 7.07 (1H, dd), 7.46 (1H, d), 7.54 (1H, d), 7.56 (1H, d), 9.83 - 10.97 (1H, m);); *m/z* (ES^+) $[M+H]^+$ = 410.4.

EXAMPLE 108:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(Isomer 2)

((*absolute configuration not yet confirmed))

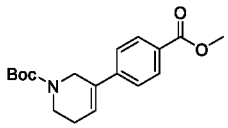


[2163] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 108b (16 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (12 mg, 56%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.03 - 1.16 (2H, m), 1.50 - 1.59 (1H, m), 1.62 - 1.73 (1H, m), 1.76 - 1.85 (2H, m), 1.88 - 1.96 (4H, m), 2.07 - 2.16 (2H, m), 2.18 - 2.24 (2H, m), 2.30 - 2.36 (1H, m), 2.70 - 2.73 (2H, m), 2.93 - 2.98 (2H, m), 3.13 - 3.20 (3H, m), 3.49 - 3.53 (2H, m), 3.56 - 3.67 (2H, m), 3.68 - 3.77 (4H, m), 3.79 - 3.84 (1H, m), 4.33 - 4.40 (1H, m), 4.40 - 4.54 (1H, m), 6.36 (2H, s), 6.44 (1H, d), 6.84 - 6.90 (3H, m), 7.05 (1H, dd), 7.20 - 7.24 (1H, m), 7.34 (2H, d), 7.42 - 7.45 (3H, m), 7.49 - 7.56 (2H, m), 7.58 (1H, s), 7.95 (1H, d), 10.26 (1H, s), 13.97 - 14.45 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 812.6.

EXAMPLE 109

Intermediate 109a:

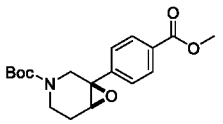
tert-Butyl 5-(4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2164] Prepared in an analogous method to Intermediate 45a starting from methyl 4-bromobenzoate (10.00 g, 46.5 mmol) and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14.38 g, 46.5 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) affords the title compound (13.52 g, 92 %) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s), 2.27 - 2.49 (2H, m), 3.48 - 3.66 (2H, m), 3.94 (3H, s), 4.23 - 4.38 (2H, m), 6.27 - 6.42 (1H, m), 7.37 - 7.55 (2H, m), 7.94 - 8.10 (2H, m); *m/z* (ES$^+$) $[M-t\text{Bu}+2H]^+$ = 262.3.

Intermediate 109b:

rac-tert-Butyl (1*R*,6*S*)-1-(4-(methoxycarbonyl)phenyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

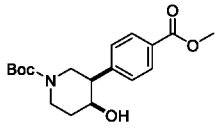


[2165] A solution of Intermediate 109a (9.00 g, 28.36 mmol) in DCM (95 ml) was charged with *m*CPBA (13.98 g, 56.71 mmol) at 0 °C. The reaction mixture was warmed up to r.t. over 2 hours. Upon completion, the reaction mixture was subsequently diluted with filtered through a pad of celite (washing with DCM). The layer was subsequently washed with sat. $NaHCO_3$ and brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) afforded a mixture of the title compound. The compound was dissolved in DCM, washed with sat. K_2CO_3, dried, filtered and concentrated to afford the title compound, (6.45 g, 68%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.50 (9H, s), 1.94 - 2.09 (1H, m), 2.10 - 2.27 (1H, m), 3.06 - 3.27 (1H, m), 3.29 - 3.51 (2H, m), 3.82 - 3.91 (1H, m), 3.93 (3H, s), 4.11 - 4.40 (1H, m), 7.41 - 7.59 (2H, m), 7.94 - 8.15 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 234.1.

Intermediate 109c:

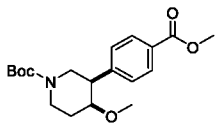
rac-tert-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2166] Intermediate 109b (6.25 g, 18.75 mmol) and 10% Pd-C (1.995 g, 1.87 mmol) in EtOAc (187 ml) was charged with hydrogen and stirred at r.t. for 3h. The reaction mixture was subsequently filtered through a pad of Celite and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) afforded the title compound (4.02 g, 64%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 1.40 (9H, br s), 1.62 - 1.74 (2H, m), 2.78 - 2.89 (1H, m), 3.08 - 3.27 (1H, m), 3.37 - 3.56 (1H, m), 3.70 - 3.81 (2H, m), 3.85 (3H, s), 3.95 - 4.02 (1H, m), 4.77 (1H, d), 7.43 (2H, d), 7.89 (2H, d); *m/z* (ES^+) $[M-t\text{BuO}]^+$ = 262.2.

Intermediate 109d:

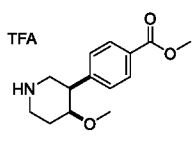
rac-tert-Butyl (3*R*,4*S*)-4-methoxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2167] A solution of Intermediate 109c (1.50 g, 4.47 mmol) in DMF (17.47 ml) was cooled to 0 °C and charged with NaH (0.224 g, 5.59 mmol). The reaction was stirred at 0°C for 30 min. before MeI (0.419 ml, 6.71 mmol) was added in a slow dropwise fashion. The reaction mixture was stirred at 0 °C for 3h. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (3 x 30mL). The combined organic extracts were then washed with 10% LiCl solution and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) afforded the title compound (0.503 g, 32%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 1.39 (9H, br s), 1.53 - 1.63 (1H, m), 1.93 - 1.99 (1H, m), 2.91 - 2.98 (1H, m), 2.99 - 3.06 (1H, m), 3.08 (3H, s), 3.36 - 3.56 (1H, m), 3.60 - 3.65 (1H, m), 3.71 - 3.78 (1H, m), 3.85 (4H, s), 7.44 (2H, d), 7.90 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 294.2.

Intermediate 109e:

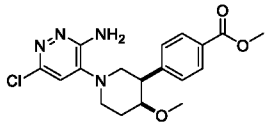
rac-Methyl 4-((3*R*,4*S*)-4-hydroxypiperidin-3-yl)benzoate



[2168] Prepared in an analogous method to Intermediate 1i starting from Intermediate 109d (503 mg, 1.50 mmol) to give the title compound (525 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil. *m/z* (ES^+) $[M+H]^+$ = 250.4.

Intermediate 109f:

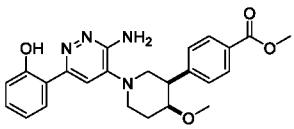
rac-Methyl 4-((3*R*,4*S*)-1-(3-amino-6-chloropyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate



[2169] Prepared in an analogous method to Intermediate 1d starting from Intermediate 109e (525 mg, 2.13 mmol) and 4-bromo-6-chloropyridazin-3-amine (443 mg, 2.13 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (568 mg, 71%) as an brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.76 (1H, m), 2.20 - 2.32 (1H, m), 2.69 - 2.86 (2H, m), 3.11 (3H, s), 3.13 - 3.18 (1H, m), 3.37 - 3.42 (1H, m), 3.46 - 3.53 (1H, m), 3.58 - 3.67 (1H, m), 3.85 (3H, s), 6.05 - 6.35 (2H, m), 6.84 - 7.04 (1H, m), 7.28 - 7.62 (2H, m), 7.82 - 8.07 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 377.4.

Intermediate 109g:

rac-Methyl 4-((3*R*,4*S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate

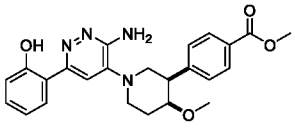


[2170] Prepared in an analogous method to Intermediate 1e starting from Intermediate 109f (343 mg, 0.91 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (186 mg, 47%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 2.00 - 2.08 (1H, m), 2.12 - 2.23 (1H, m), 2.96 - 3.06 (1H, m), 3.12 (3H, s), 3.22 - 3.30 (1H, m), 3.38 (3H, s), 3.68 - 3.76 (1H, m), 3.85 (3H, s), 6.31 (2H, s), 6.83 - 6.97 (2H, m), 7.16 - 7.27 (1H, m), 7.53 (2H, d), 7.66 (1H, s), 7.92 (2H, d), 7.96 - 8.05 (1H, m), 14.00 - 14.50 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 435.7.

Intermediate 109h:

Methyl 4-((3*R**,4*S**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

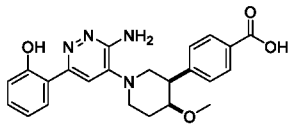
[2171] Intermediate 109g (180 mg, 0.41 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak IB 4.6 x 150mm, 5um; mobile phase: 10 to 60% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 70 mL/min; BPR: 120 bar; Column temperature:

40°C to afford the title compound that eluted second from the column (85 mg, 47% yield, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 435.7.

Intermediate 109i:

4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



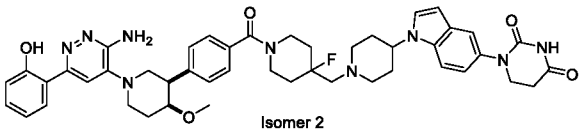
Isomer 2

[2172] Prepared in an analogous method to Intermediate 26j starting from Intermediate 109h (75 mg, 0.17 mmol) to give the title compound (73 mg, 100%) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 421.5.

EXAMPLE 109:

1-(1-(1-((1-(4-((3*R**,*4*S*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

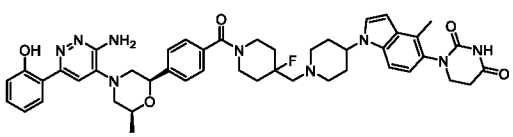


Isomer 2

[2173] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 109i (10 mg, 0.02 mmol) and Intermediate 29a (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (12.6 mg, 62%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.66 - 1.86 (m, 3H), 1.87 - 2.14 (7H, m), 2.14 - 2.23 (2H, m), 2.73 (3H, s), 2.99 - 3.12 (3H, m), 3.17 (4H, s), 3.19 - 3.26 (3H, m), 3.36 - 3.48 (5H, m), 3.72 - 3.81 (3H, m), 4.05 - 4.66 (1H, m), 6.40 - 6.62 (3H, m), 6.86 - 6.98 (2H, m), 7.06 - 7.13 (1H, m), 7.25 - 7.32 (1H, m), 7.35 - 7.41 (2H, m), 7.43 - 7.48 (3H, m), 7.49 - 7.54 (1H, m), 7.54 - 7.58 (1H, m), 7.60 - 7.67 (1H, m), 7.83 - 7.97 (1H, m), 10.07 - 10.45 (1H, m) (-OH was not observed); *m/z* (ES^+) $[M+H]^+$ = 830.6.

EXAMPLE 110:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

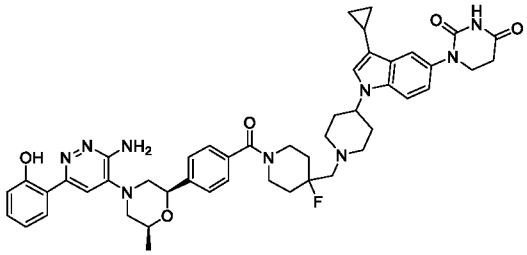


[2174] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (17 mg, 0.04 mmol) and Intermediate 32g (36mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN

in water with 0.1% FA) gave the title compound (15 mg, 45%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 1.57 - 1.80 (2H, m), 1.82 - 2.03 (6H, m), 2.29 (3H, s), 2.34 - 2.46 (2H, m), 2.53 - 2.83 (6H, m), 3.01 - 3.06 (2H, m), 3.06 - 3.18 (2H, m), 3.49 - 3.60 (4H, m), 3.68 - 3.77 (1H, m), 4.05 - 4.17 (1H, m), 4.17 - 4.40 (2H, m), 4.93 (1H, br d), 6.45 - 6.54 (3H, m), 6.84 - 6.89 (2H, m), 6.99 (1H, d), 7.19 - 7.24 (1H, m), 7.33 - 7.45 (3H, m), 7.49 - 7.56 (4H, m), 7.94 (1H, d), 10.25 (1H, s), 13.95 - 14.51 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 830.6.

EXAMPLE 111:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

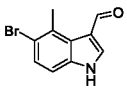


[2175] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (17.72 mg, 0.04 mmol) and Intermediate 6h (36mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (14 mg, 41%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.56 - 0.62 (2H, m), 0.78 - 0.84 (2H, m), 1.25 (3H, d), 1.58 - 1.77 (2H, m), 1.77 - 1.89 (4H, m), 1.89 - 1.96 (2H, m), 2.33 - 2.41 (2H, m), 2.51 - 2.60 (2H, m), 2.60 - 2.70 (2H, m), 2.70 - 2.75 (2H, m), 2.93 - 3.03 (2H, m), 3.06 - 3.23 (2H, m), 3.41 - 3.48 (2H, m), 3.50 - 3.55 (1H, m), 3.55 - 3.61 (1H, m), 3.76 (2H, t), 4.06 - 4.14 (1H, m), 4.24 (2H, br t), 4.94 (1H, br d), 6.48 (2H, br s), 6.84 - 6.89 (2H, m), 7.03 (1H, dd), 7.19 - 7.25 (2H, m), 7.40 - 7.56 (7H, m), 7.94 (1H, br d), 10.25 (1H, s), 13.97 - 14.46 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 856.6.

EXAMPLE 112

Intermediate 112a:

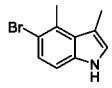
5-Bromo-4-methyl-1*H*-indole-3-carbaldehyde



[2176] Phosphoryl trichloride (2.92 g, 19.04 mmol) was added to 5-bromo-4-methyl-1*H*-indole (2 g, 9.52 mmol) in DMF (20 mL) at 0°C under nitrogen. The reaction was stirred at 25 °C for 2 h. The reaction mixture was quenched by aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 10 mL). Organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether) gave the title compound (1.1 g, 4.62 mmol, 48%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.92 (3H, s), 7.30 (1H, dd), 7.45 (1H, d), 8.35 (1H, d), 9.87 (1H, s), 12.47 (1H, s).

Intermediate 112b:

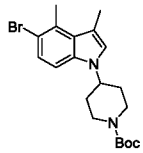
5-Bromo-3,4-dimethyl-1*H*-indole



[2177] Intermediate 112a (1.00 g, 4.20 mmol) was added to $NaBH_4$ (0.795 g, 21.00 mmol) in THF (20 mL) and AcOH (2.0 mL) at 0°C under nitrogen. The reaction was stirred at r.t for 2 h. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether) gave the title compound (600 mg, 2.68 mmol, 64%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.43 (3H, d), 2.69 (3H, s), 7.02 – 7.21 (3H, m), 10.88 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 224.2.

Intermediate 112c:

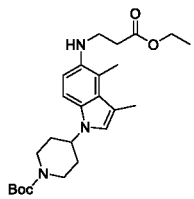
tert-Butyl 4-(5-bromo-3,4-dimethyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2178] Prepared in an analogous method to Intermediate 1g starting from Intermediate 112b (1.00 g, 4.46 mmol). Purification by FSC (elution gradient: 30 to 50% EtOAc in petroleum ether in) gave the title compound (0.700 g, 38%) as a pale yellow gum. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.67 – 1.89 (4H, m), 2.42 (3H, d), 2.68 (3H, s), 2.85-3.01 (2H, m), 4.07 (2H, dd), 4.41 – 4.56 (1H, m), 7.23 (1H, d), 7.31 (2H, d).

Intermediate 112d:

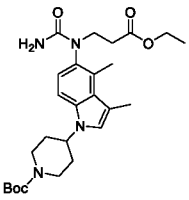
tert-Butyl 4-(4-((3-ethoxy-3-oxopropyl)amino)-5-fluoro-1*H*-indol-1-yl)piperidine-1-carboxylate



[2179] Prepared in an analogous method to Intermediate 3b starting from Intermediate 112c (200 mg, 0.50 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.4% NH_4HCO_3) gave the title compound (150 mg, 69%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.70 (2H, dd), 1.86 (2H, d), 2.35 – 2.40 (6H, m), 2.58 (2H, t), 2.94 (2H, s), 4.08 (4H, q), 4.20 (1H, s), 4.28 – 4.37(1H, m), 6.62 (1H, d), 7.06 (1H, s), 7.15 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 434.2.

Intermediate 112e:

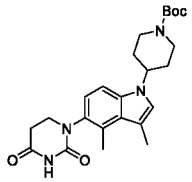
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-3,4-dimethyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2180] Prepared in an analogous method to Intermediate 3c starting from Intermediate 112d (10.0 mg, 0.02 mmol). The reaction was diluted with EtOAc 10 mL). Organic layer was washed with water and aq. $NaHCO_3$ solution, dried over NaSO4, and was concentrated to afford the title compound as a yellow solid, assumed quantitative conversion assumed. *m/z* (ES^+) $[M+H]^+ = 487.3$.

Intermediate 112f:

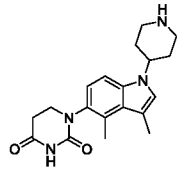
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3,4-dimethyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2181] Prepared in an analogous method to Intermediate 3d starting from Intermediate 112e (125 mg, 0.26 mmol). Purification by FSC (elution gradient: 10 to 50% EtOAc in hexanes) gave the title compound (110 mg, 97%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.44 (9H, s), 1.72 – 1.92 (4H, m), 2.44 (6H, d), 2.75 (2H, q), 2.96 (2H, s), 3.50 (1H, dd), 3.72 (1H, ddd), 4.11 (2H, d), 4.46 (1H, d), 6.97 (1H, d), 7.22 – 7.40 (2H, m), 10.26 (1H, s); *m/z* (ES^+) $[M+H]^+ = 441.2$.

Intermediate 112g:

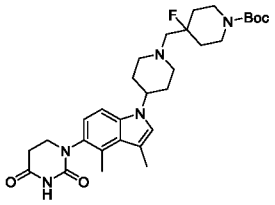
1-(3,4-Dimethyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2182] Prepared in an analogous method to Intermediate 6e starting from Intermediate 112f (160.00 mg, 0.36 mmol). The reaction mixture was diluted with DCM:IPA (3:1, 5 mL), and was washed with sat. aq. $NaHCO_3$. Organic layer was dried over Na_2SO_4, filtered, and was concentrated down to afford the title compound (60 mg, 48%) as an off white solid. *m/z* (ES^+) $[M+H]^+ = 341.1$.

Intermediate 112h:

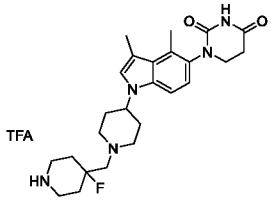
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3,4-dimethyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2183] Prepared in an analogous method to Intermediate 6g starting from Intermediate 112g (60.00 mg, 0.18 mmol) The reaction mixture was diluted with DCM:IPA(3:1) (5 mL), and was washed sequentially with saturated $NaHCO_3$ solution and brine. Organic layer was dried over Na_2SO_4, filtered, and evaporated to afford the title compound (98 mg, 100%) as a brown solid. The crude material was used for the next step. *m/z* (ES^+) $[M+H]^+$ = 556.3.

Intermediate 112i:

1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

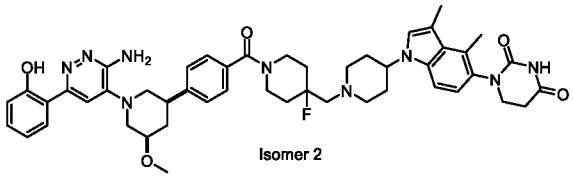


[2184] Prepared in an analogous method to Intermediate 1i starting from Intermediate 112h (60.0 mg, 0.11 mmol). Purification by RPC (elution gradient: 10 to 30% MeCN in water with 0.1% TFA) gave the title compound (30 mg, 0.026 mmol, 24%) as a white solid in the form of TFA salt. *m/z* (ES^+) $[M+H]^+$ = 456.3.

EXAMPLE 112:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



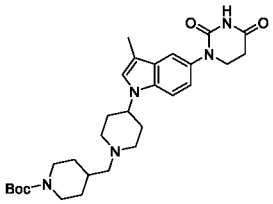
[2185] Prepared in an analogous method to EXAMPLE 1starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 112i (30 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (7.5 mg, 33%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.54 (1H, br d), 1.62 - 1.78 (2H, m), 1.78 - 2.02 (6H, m), 2.29 - 2.40 (3H, m), 2.39 - 2.44 (6H, m), 2.44 - 2.46 (1H, m), 2.56 - 2.60 (1H, m), 2.61 - 2.65 (1H, m), 2.68 - 2.82 (3H, m), 2.95 - 3.04 (2H, m), 3.05 - 3.24 (4H, m), 3.38 - 3.44 (3H, m), 3.48 - 3.53 (2H, m), 3.64 - 3.77 (2H, m), 3.76 - 3.84 (1H, m), 4.10 - 4.33 (2H,

m), 6.36 (2H, s), 6.84 - 6.89 (2H, m), 6.93 (1H, d), 7.20 - 7.31 (3H, m), 7.35 - 7.41 (2H, m), 7.42 - 7.46 (2H, m), 7.58 (1H, s), 7.95 (1H, d), 10.24 (1H, s), 14.08 - 14.40 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 858.6.

EXAMPLE 113

Intermediate 113a:

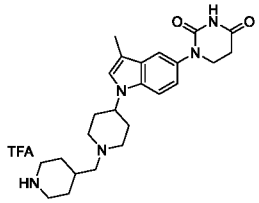
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2186] Prepared in an analogous method to Intermediate 10d starting from Intermediate 1i (0.051 g, 0.09 mmol). Purification by FSC (elution gradient: 0 to 100% ethyl acetate in hexanes and 0 to 15% methanol in DCM) gave the title compound (0.042 g, 87%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.89 - 1.02 (2H, m), 1.38 (9H, s), 1.63 - 1.74 (3H, m), 1.82 - 1.96 (4H, m), 2.09 - 2.20 (4H, m), 2.22 (3H, d), 2.63 - 2.78 (4H, m), 2.90 - 2.99 (2H, m), 3.75 (2H, t), 3.86 - 3.96 (2H, m), 4.22 - 4.30 (1H, m), 7.03 (1H, dd), 7.30 (1H, s), 7.38 (1H, d), 7.45 (1H, d), 10.22 (1H, s); *m/z* ES^+ $[M+H]^+$ = 524.1.

Intermediate 113b:

1-(3-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

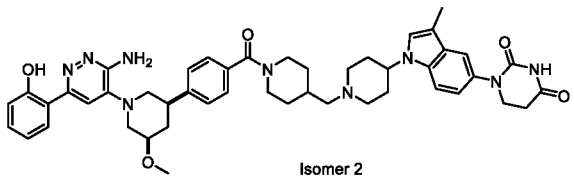


[2187] Prepared in an analogous method to Intermediate 1i starting from Intermediate 113a (0.040 g, 0.08 mmol). The reaction was concentrated under reduced pressure, then triturated with diethyl ether and sonication to generate a solid. Solvent was carefully removed by pipette, then the resulting material was dried under reduced pressure to provide the title compound (0.050 g, 100%) as a trifluoroacetic acid salt. *m/z* (ES^+) $[M+H]^+$= 424.0.

EXAMPLE 113:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

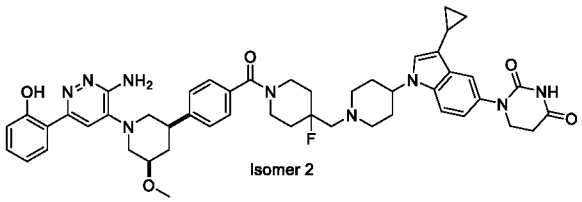


[2188] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 113b (23 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (10 mg, 46%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.98 - 1.13 (2H, m), 1.12 - 1.22 (1H, m), 1.54 (1H, br d), 1.60 - 1.72 (1H, m), 1.75 - 1.94 (6H, m), 2.08 - 2.16 (2H, m), 2.18 - 2.21 (3H, m), 2.24 - 2.37 (2H, m), 2.67 - 2.72 (2H, m), 2.91 - 2.98 (2H, m), 3.12 - 3.19 (2H, m), 3.19 - 3.23 (2H, m), 3.47 - 3.50 (3H, m), 3.50 - 3.62 (4H, m), 3.73 - 3.77 (2H, m), 3.77 - 3.83 (1H, m), 4.20 - 4.34 (1H, m), 4.38 - 4.57 (1H, m), 6.36 (2H, br s), 6.83 - 6.90 (2H, m), 7.03 (1H, d), 7.18 - 7.26 (1H, m), 7.29 (1H, s), 7.34 (2H, d), 7.38 (1H, d), 7.45 (3H, br s), 7.55 - 7.62 (1H, m), 7.91 - 7.98 (1H, m), 10.21 - 10.26 (1H, m), OH (not observed); *m/z* (ES$^+$) $[M+H]^+$ = 826.6.

EXAMPLE 114:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

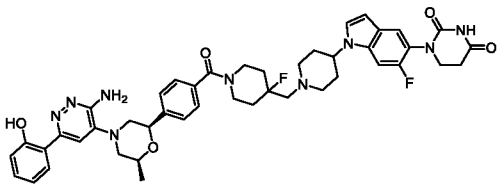
((*absolute configuration not yet confirmed))



[2189] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 6h (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (8mg, 35%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.56 - 0.61 (2H, m), 0.80 - 0.85 (2H, m), 1.49 - 1.59 (1H, m), 1.65 - 1.78 (2H, m), 1.81 - 1.90 (4H, m), 1.94 - 1.99 (2H, m), 2.26 - 2.43 (3H, m), 2.58 - 2.65 (2H, m), 2.68 - 2.80 (4H, m), 2.96 - 3.02 (2H, m), 3.09 - 3.19 (3H, m), 3.19 - 3.23 (2H, m), 3.49 - 3.55 (2H, m), 3.66 - 3.86 (6H, m), 4.24 (2H, br t), 6.36 (2H, s), 6.82 - 6.89 (2H, m), 7.03 (1H, dd), 7.19 - 7.25 (2H, m), 7.37 - 7.40 (2H, m), 7.43 - 7.47 (3H, m), 7.48 - 7.50 (1H, m), 7.58 (1H, s), 7.92 - 7.98 (1H, m), 10.25 (1H, s), 14.02 - 14.39 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 870.7.

EXAMPLE 115:

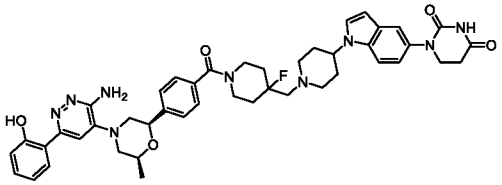
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2190] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (18 mg, 0.04 mmol) and Intermediate 5g (36 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (13mg, 39%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 1.63 - 1.78 (2H, m), 1.80 - 2.04 (6H, m), 2.35 - 2.44 (2H, m), 2.51 - 2.61 (2H, m), 2.61 - 2.69 (2H, m), 2.69 - 2.76 (2H, m), 3.00 - 3.05 (2H, m), 3.06 - 3.17 (2H, m), 3.48 - 3.52 (2H, m), 3.52 - 3.61 (2H, m), 3.67 - 3.72 (2H, m), 4.08 - 4.14 (1H, m), 4.28 - 4.36 (1H, m), 4.94 (1H, br d), 6.43 - 6.51 (3H, m), 6.83 - 6.88 (2H, m), 7.20 - 7.24 (1H, m), 7.42 (2H, d), 7.51 - 7.57 (6H, m), 7.94 (1H, d), 10.39 (1H, s), 14.06 - 14.39 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 834.5.

EXAMPLE 116:

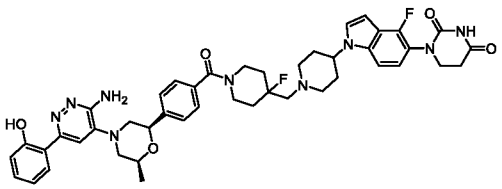
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2191] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (18 mg, 0.04 mmol) and Intermediate 29a (35 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (9 mg, 28%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 1.63 - 1.80 (2H, m), 1.83 - 2.03 (6H, m), 2.37 - 2.45 (2H, m), 2.53 - 2.63 (2H, m), 2.63 - 2.69 (2H, m), 2.69 - 2.73 (2H, m), 2.97 - 3.04 (2H, m), 3.06 - 3.13 (1H, m), 3.13 - 3.23 (2H, m), 3.48 - 3.53 (1H, m), 3.54 - 3.60 (1H, m), 3.75 (2H, t), 4.07 - 4.15 (1H, m), 4.18 - 4.38 (2H, m), 4.93 (1H, br d), 6.35 - 6.54 (3H, m), 6.83 - 6.89 (2H, m), 7.05 (1H, dd), 7.20 - 7.23 (1H, m), 7.39 - 7.47 (3H, m), 7.50 - 7.56 (5H, m), 7.94 (1H, d), 10.26 (1H, s), 13.93 - 14.38 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 816.6.

EXAMPLE 117:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

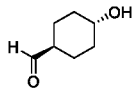


[2192] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (17 mg, 0.04 mmol) and Intermediate 3g (36 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (10 mg, 29%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 1.64 - 1.79 (2H, m), 1.84 - 2.03 (6H, m), 2.36 - 2.43 (2H, m), 2.53 - 2.63 (2H, m), 2.63 - 2.70 (2H, m), 2.70 - 2.76 (2H, m), 2.98 - 3.05 (2H, m), 3.06 - 3.12 (1H, m), 3.13 - 3.21 (2H, m), 3.50 - 3.60 (2H, m), 3.69 (2H, t), 4.06 - 4.15 (1H, m), 4.21 - 4.32 (1H, m), 4.32 - 4.41 (1H, m), 4.89 - 4.97 (1H, m), 6.44 - 6.52 (2H, m), 6.54 (1H, d), 6.84 - 6.89 (2H, m), 7.07 - 7.15 (1H, m), 7.19 - 7.25 (1H, m), 7.38 - 7.45 (3H, m), 7.49 - 7.57 (3H, m), 7.60 (1H, d), 7.94 (1H, d), 10.39 (1H, s), 13.99 - 14.48 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 834.6.

EXAMPLE 118

Intermediate 118a:

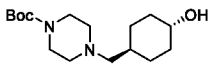
(1*s*,4*s*)-4-Hydroxycyclohexane-1-carbaldehyde



[2193] Ethyl (1*s*,4*s*)-4-hydroxycyclohexane-1-carboxylate (6.00 g, 34.84 mmol) in DCM (20 mL) was cooled to –78°C. Diisobutylaluminum hydride (105 mL, 1 M in DCM, 105 mmol) was added dropwise. The resulting mixture was stirred at –78 °C for 2 h, and was quenched by potassium sodium tartrate solution, and extracted with DCM (200 mL). Organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product, assumed quantitative yields.

Intermediate 118b:

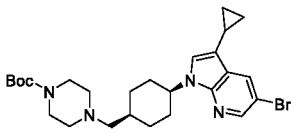
tert-Butyl 4-(((1*s*,4*s*)-4-hydroxycyclohexyl)methyl)piperazine-1-carboxylate



[2194] Intermediate 118a and *tert*-butyl piperazine-1-carboxylate (7.79 g, 41.81 mmol) in a mixture of DCE (20.0 mL) and NMP (20.0 mL) were stirred at 40°C for 40 min. Sodium triacetoxyborohydride (29.5 g, 103 mmol) was added, and the reaction was stirred at r.t for 1h. The reaction was diluted with DCM (150 mL), and washed with saturated $NaHCO_3$ solution. Organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in DCM) gave the title compound as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 0.78 – 0.87 (2H, m), 1.02 – 1.14 (2H, m), 1.39 (9H, d), 1.68 – 1.86 (4H, m), 1.99 – 2.07 (3H, m), 2.21 – 2.26 (4H, m), 3.25 – 3.30 (5H, m), 4.47 (1H, d); mass not observed.

Intermediate 118c:

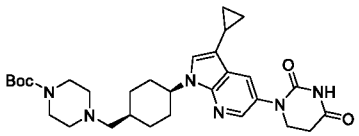
tert-Butyl 4-(((1*r*,4*r*)-4-(5-bromo-3-cyclopropyl-1H-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2195] Intermediate 118b (690 mg, 2.31 mmol), 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (548 mg, 2.31 mmol), and 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (1116 mg, 4.62 mmol) in *m*-xylene (15 mL) were stirred at 110 °C for 4 hours. Solvent was removed. Purification on RPC (elution gradient: 0 to 90% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (330 mg, 28%) as a brown oil. ^{1}H NMR (DMSO-*d*6): δ 0.59 – 0.68 (2H, m), 0.80 – 0.88 (3H, m), 1.38 (9H, s), 1.62 (3H, d), 1.75 (2H, d), 1.85 – 2.03 (6H, m), 2.34 (5H, d), 2.40 (3H, d), 4.57 (1H, s), 7.52 (1H, s), 8.17 (1H, d), 8.24 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 517.2.

Intermediate 118d:

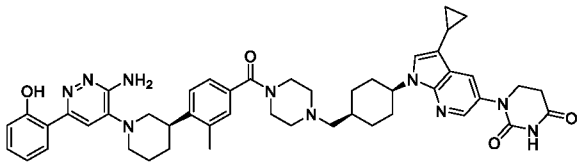
tert-Butyl 4-(((1*r*,4*r*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2196] Dihydropyrimidine-2,4(1*H*,3*H*)-dione (331 mg, 2.90 mmol), Intermediate 118c (300 mg, 0.58 mmol), Cs_2CO_3 (756 mg, 2.32 mmol), $[Pd(cinnamyl)Cl]_2$ (193 mg, 0.35 mmol) and *t*-BuBrettPhos (169 mg, 0.35 mmol) in 1,4-dioxane (20 mL) were stirred at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, and was filtered through filter celite. The solvent was removed. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (255 mg, 80%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.64 – 0.68 (2H, m), 0.84 – 0.87 (2H, m), 1.24 (2H, s), 1.40 (9H, s), 1.59 –1.81 (8H, m), 1.84 – 2.03 (6H, m), 2.35 (4H, t), 2.43 (2H, d), 3.81 (2H, t), 4.61 (1H, d), 7.52 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 551.3.

EXAMPLE 118:

1-(1-((1*S*,4*s*)-4-((4-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



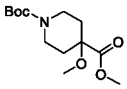
[2197] TFA (1.5 mL) was added to stirred solution of Intermediate 118d (60 mg, 0.11 mmol) in DCM (1.5 mL). The mixture was stirred at r.t for 30 min. The solvent was removed to afford the crude amine as a beige solid in the form of TFA salt. The residue was dissolved in DMF (1.0 mL) and added DIPEA (0.114 mL, 0.65 mmol), Intermediate 12g (26.4 mg, 0.07 mmol) and HATU (24.86 mg, 0.07 mmol). The reaction mixture was stirred at r.t. for 1h. Purification by RPC (elution gradient: 18 to 32% MeCN in water with 0.1% FA) gave the title compound (21.4 mg, 23%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 – 0.71 (2H, m), 0.81 – 0.91 (2H, m), 1.66 (5H, d), 1.79 (2H, d), 1.84 – 2.04 (7H, m), 2.41 (4H, s), 2.47 (3H, d), 2.67 – 2.80 (3H, m), 2.86 (1H, t), 3.25 (4H, s), 3.49 (2H, d), 3.59 (3H, d), 3.82 (2H, t), 4.62 (1H, d), 6.29

(2H, s), 6.88 (2H, t), 7.19 – 7.27 (3H, m), 7.40 (1H, d), 7.51 (1H, s), 7.57 (1H, s), 7.91 – 7.97 (2H, m), 8.16 (1H, d), 10.39 (1H, s), 14.27 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 837.5

EXAMPLE 119

Intermediate 119a:

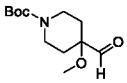
1-(*tert*-Butyl) 4-methyl 4-methoxypiperidine-1,4-dicarboxylate



[2198] Sodium hydride (63.9 mg, 2.66 mmol) was added to a solution of 1-(tert-butyl) 4-methyl 4-hydroxypiperidine-1,4-dicarboxylate (300 mg, 1.16 mmol) and Iodomethane (197 mg, 1.39 mmol) in DMF (4 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EtOAc (75 mL), washed sequentially with saturated $NaHCO_3$ (75 mL x 2) and saturated brine (75 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 3 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (210 mg, 66%) as a colorless oil. ^1H NMR (DMSO-*d*6): δ 1.40 (9H, s), 1.67 – 1.76 (2H, m), 1.78 – 1.86 (2H, m), 2.97 (2H, s), 3.15 (3H, s), 3.59 – 3.67 (2H, m), 3.69 (3H, s).

Intermediate 119b:

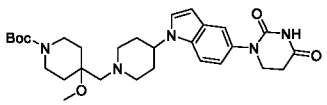
tert-Butyl 4-formyl-4-methoxypiperidine-1-carboxylate



[2199] Diisobutylaluminum hydride (78 mg, 0.55 mmol) in DCM (2 mL) was stirred at -80 °C under nitrogen. Intermediate 119a (50 mg, 0.18 mmol) was added to the reaction. The resulting mixture was stirred for 1h. The reaction was quenched by water, and was diluted with DCM (50 mL), washed sequentially with saturated NH_4Cl (25 mL x 2) and saturated brine (25 mL x 2), dried over $MgSO_4$, filtered, and evaporated to afford crude title compound. The product was used in the next step without further purification and quantitative yield was assumed.

Intermediate 119c:

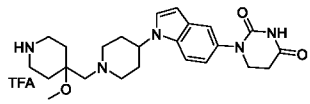
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-methoxypiperidine-1-carboxylate



[2200] Intermediate 2c (183 mg, 0.59 mmol) and Intermediate 119b (160 mg, 0.59 mmol) in DCE (2 mL) and NMP (2.0 mL) were stirred at 40 °C for 1h. Sodium triacetoxyborohydride (124 mg, 0.59 mmol) was added, and the reaction was stirred at r.t. for 30 min. The reaction was diluted with DCM (50 mL), washed aqueous $NaHCO_3$ solution, dried over MgSO4, filtered, and concentrated to afford the crude product. Quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 540.3.

Intermediate 119d:

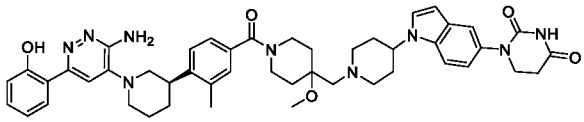
1-(1-(1-((4-Methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2201] Intermediate 119c (10 mg, 0.02 mmol) in DCM (1 mL) was added TFA (0.250 mL). The resulting mixture was stirred at RT for 1h. After removing solvent, the title compound was obtained as a white solid in the form of TFA salt, assumed quantitative yield. *m/z* (ES^+) $[M+H]^+$ = 440.4.

EXAMPLE 119:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

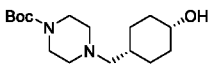


[2202] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 119d (46 mg, 0.11 mmol) and Intermediate 12g (50 mg, 0.11 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (22.8mg, 24%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.39 – 1.59 (2H, s), 1.60 – 1.67 (1H, m), 1.68 – 1.79 (1H, m), 1.81 – 2.06 (8H, m), 2.32 – 2.43 (5H, m), 2.43 – 2.47 (2H, m), 2.66 – 2.76 (3H, m), 2.80 – 2.90 (1H, t), 3.01 – 3011 (2H, d), 3.14 – 3.18 (3H, s), 3.21 – 3.28 (2H, m), 3.43 – 3.51 (2H, m), 3.53 – 3.63 (1H, m), 3.70 – 3.81 (2H, t), 4.13 (1H, s), 4.25 – 4.39 (2H, m), 6.29 (2H, s), 6.45 (1H, d), 6.87 (2H, t), 7.06 (1H, dd), 7.18 – 7.27 (3H, m), 7.39 (1H, d), 7.45 (1H, d), 7.49 – 7.58 (3H, m), 7.94 (1H, dd), 10.27 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 826.6.

EXAMPLE 120

Intermediate 120a:

tert-Butyl 4-(((1*s*,4*s*)-4-hydroxycyclohexyl)methyl)piperazine-1-carboxylate

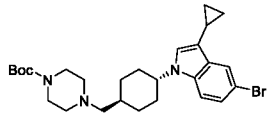


[2203] Ethyl (1*s*,4*s*)-4-hydroxycyclohexane-1-carboxylate (6 g, 34.84 mmol) was added to diisobutylaluminum hydride (14.86 g, 104.52 mmol) in DCM (40mL) under air. The resulting mixture was stirred at –50 °C for 1 hour. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with sat. aq. NH_4Cl (2 x 50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product. To the crude mixture was added *tert*-butyl 1-piperazinecarboxylate (7.79 g, 41.81 mmol) in NMP (40.0 mL) and DCE (40.0 mL) under air. The resulting mixture was stirred at 50° C for 1 h. The reaction mixture cooled to r.t. then added Sodium triacetoxyborohydride (29.5 g, 139.35 mmol) under air. The resulting mixture was stirred at r.t for 2 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat. aq. $NaHCO_3$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (1.500 g, 14%) as a

yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.39 (9H, s), 1.47 – 1.61 (2H, m), 1.84 – 1.97 (3H, m), 2.15 – 2.27 (6H, m), 2.70 (3H, d), 3.27 – 3.32 (5H, m), 3.73 (1H, s), 4.20 – 4.26 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 299.2.

Intermediate 120b:

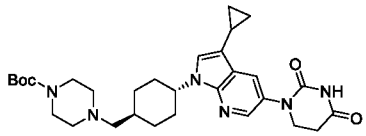
tert-Butyl 4-(((1*r*,4r)-4-(5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2204] 2-(Tributyl-λ^5-phosphaneylidene)acetonitrile (2.103 g, 8.71 mmol) was added to 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.413 g, 1.74 mmol) and Intermediate 120a (1.3 g, 4.36 mmol) in m-xylene (20 mL) under nitrogen. The resulting mixture was stirred at 110 °C for 16h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 1% NH_4HCO_3) gave the title compound (0.500 g, 22%) as a brown oil. ^{1}H NMR (DMSO-*d*6): δ 0.61 – 0.68 (2H, m), 0.81 – 0.91 (2H, m), 1.00 – 1.27 (2H, m), 1.40 (9H, d), 1.64 (3H, d), 1.76 (2H, d), 1.82 – 2.00 (5H, m), 2.10 – 2.46 (6H, m), 3.26 – 3.32 (2H, m), 4.48 – 4.65 (1H, m), 7.48 (1H, d), 8.15 – 8.29 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 519.1.

Intermediate 120c:

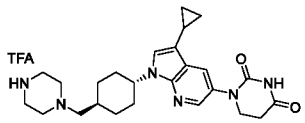
tert-Butyl 4-(((1*r*,4*r*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2205] Cs_2CO_3 (1259 mg, 3.86 mmol) was added to $[Pd(cinnamyl)Cl]_2$ (321 mg, 0.58 mmol), Intermediate 120b (500 mg, 0.97 mmol), *t*-BuBrettPhos (281 mg, 0.58 mmol) and dihydropyrimidine-2,4(1H,3H)-dione (1102 mg, 9.66 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered and filtrate was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (280 mg, 52%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.60 – 0.71 (2H, m), 0.80 – 0.91 (2H, m), 1.41 (9H, s), 1.56 – 1.81 (6H, m), 1.84 – 2.00 (4H, m), 2.21 – 2.48 (7H, m), 2.77 (2H, t), 3.30 – 3.32 (1H, m), 3.73 – 3.91 (4H, m), 4.65 (1H, d), 7.51 (1H, s), 7.94 (1H, d), 8.16 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 551.4.

Intermediate 120d:

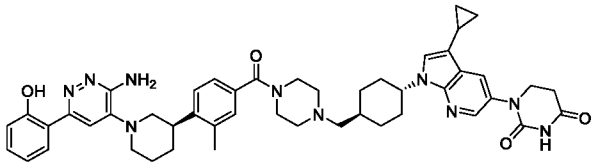
1-(3-Cyclopropyl-1-((1*r*,4*r*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2206] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 120c (130 mg, 0.24 mmol). The solvent was removed under reduced pressure to give title compound (100 mg, 94%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 0.57 – 0.68 (2H, m), 0.82 – 0.94 (2H, m), 1.61 – 1.84 (7H, m), 1.85 – 2.04 (4H, m), 2.27 (1H, s), 2.77 (2H, t), 3.43 (8H, d), 3.82 (3H, t), 4.60 – 4.76 (1H, m), 7.46 (1H, s), 7.97 (1H, d), 8.18 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 451.2.

EXAMPLE 120:

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

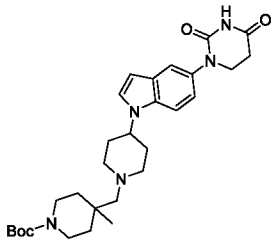


[2207] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 120d (49 mg, 0.12 mmol) and Intermediate 12g (55 mg, 0.12 mmol). Purification by RPC (elution gradient: 50 to 70% MeCN in water with 0.1% NH_4OH) gave the title compound (16.7 mg, 16%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.63 – 0.73 (2H, m), 0.83 – 0.95 (2H, m), 1.21 (1H, d), 1.69 (4H, t), 1.83 – 2.09 (10H, m), 2.41 (4H, d), 2.76 (4H, d), 2.86 (2H, t), 3.15 – 3.33 (3H, m), 3.44 – 3.75 (6H, m), 3.82 (2H, t), 4.59 – 4.78 (1H, m), 6.34 (2H, s), 6.90 (2H, d), 7.19 – 7.34 (3H, m), 7.35 – 7.49 (2H, m), 7.59 (2H, d), 7.89 – 8.03 (2H, m), 8.19 (1H, s), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 837.4.

EXAMPLE 121

Intermediate 121a:

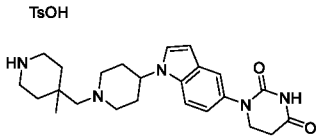
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-methylpiperidine-1-carboxylate



[2208] Sodium triacetoxyborohydride (509 mg, 2.40 mmol) was added to *tert*-butyl 4-formyl-4-methylpiperidine-1-carboxylate (364 mg, 1.60 mmol) and Intermediate 2c (250 mg, 0.80 mmol) in DCM (10 mL) . The resulting mixture was stirred at r.t for 1 h. The reaction was diluted with EtOAc (30 mL) and washed with sat. aq.$NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 25% EtOAc in petroleum ether) gave the title compound (300 mg, 71%) as a pale yellow solid. *m/z* (ES$^+$) $[M+H]^+$ = 524.5.

Intermediate 121b:

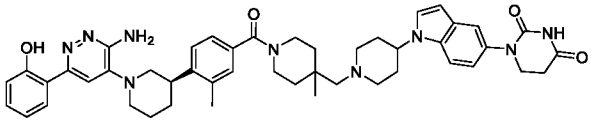
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-methylpiperidine-1-carboxylate



[2209] Intermediate 121a (100 mg, 0.19 mmol) and *p*-toluenesulfonic acid (49.3 mg, 0.29 mmol) in MeCN (1.0 mL) were stirred at 80 °C for 1 h. Solvent was removed under reduced pressure to afford the title compound as a white solid in the form of *p*-toluenesulfonic acid salt, assumed quantitative yield. *m/z* (ES^+) $[M+H]^+$ = 424.6.

EXAMPLE 121:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

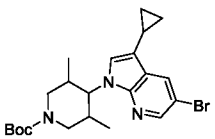


[2210] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (93 mg, 0.23 mmol) and Intermediate 121b (100 mg, 0.19 mmol). Purification by RPC (elution gradient: 21 to 29% MeCN in water with 0.1% FA) gave the title compound (24 mg, 15%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, s), 1.19–1.29 (1H, m), 1.39–1.47 (1H, m), 1.47–1.56 (2H, m),1.64–1.69 (1H, m), 1.89 (4H, s), 1.93–2.06 (3H, m), 2.27 (2H, s), 2.40 (3H, s), 2.52 (2H, s), 2.73 (3H, t), 2.8–2.94 (3H, m), 3.27 (3H, s), 3.48 (2H, d), 3.59 (1H, d), 3.77 (2H, t), 3.98 (1H, s), 4.33 (1H, s), 6.28 (2H, s), 6.46 (1H, d), 6.87 (2H, t), 7.07 (1H, dd), 7.17–7.28 (3H, m), 7.39 (1H, d), 7.46 (1H, d), 7.5–7.58 (3H, m), 7.93 (1H, d), 10.27 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 810.3

EXAMPLE 122

Intermediate 122a:

tert-Butyl 4-(5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidine-1-carboxylate

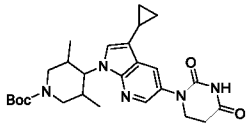


[2211] 2-(Tributyl-λ^5-phosphaneylidene)acetonitrile (2.53 g, 10.47 mmol) was added to *tert*-butyl 4-hydroxy-3,5-dimethylpiperidine-1-carboxylate (1.2 g, 5.23 mmol, mixture of isomers) and 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.241 g, 5.23 mmol) in xylenes (10 mL) under nitrogen. The resulting mixture was stirred at 120 °C for 2 h. Purification by FSC (elution gradient: 5 to 100% EtOAc in petroleum ether) afforded the title compound (0.160 g, 7%) as a yellow solid as a mixture of *cis* and *trans* isomers. ^{1}H NMR (DMSO-*d*6): δ 0.42 (6H, t), 0.60 – 0.69 (1H, m), 0.75 – 0.79 (1H, m), 0.83 – 0.91 (2H,

m), 1.44 (9H, s), 1.88 – 2.06 (2H, m), 2.10 – 2.25 (1H, m), 2.57 – 2.77 (1H, m), 2.91 – 3.12 (1H, m), 3.84 (1H, s), 4.03 (1H, s), 5.28 (1H, s), 7.62 (1H, s), 8.22 (1H, d), 8.27 (1H, dd); *m/z* (ES^+) $[M+H]^+$ = 448.1

Intermediate 122b:

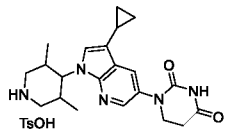
tert-Butyl 4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1H-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidine-1-carboxylate



[2212] [Pd(cinnamyl)Cl]$_2$ (19.16 mg, 0.03 mmol), *t*-BuBrettPhos (16.75 mg, 0.03 mmol), Cs_2CO_3 (338 mg, 1.04 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (118 mg, 1.04 mmol) and Intermediate 122a (155 mg, 0.35 mmol) in 1,4-dioxane (2 mL) was stirred at 100 °C for 5h. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (121 mg, 73%) as a yellow solid as a mixture of *cis* and *trans* isomers. ^{1}H NMR (DMSO-*d*6): δ 0.83 – 0.53 (6H, m), 0.61 – 0.72 (1H, m), 0.75 – 0.94 (3H, m), 1.04 – 1.30 (2H, m), 1.45 (9H, s), 1.89 – 2.05 (1H, m), 2.10 – 2.25(1H, m), 2.58 – 2.71 (1H, m), 2.76 (2H, t), 2.90 – 3.11 (1H, m), 3.15 – 3.24 (1H, m), 3.73 – 3.96 (2H, m), 4.02 – 4.14 (1H, m), 7.61 (1H, s), 7.95 – 7.99 (1H, m), 8.14 – 8.23 (1H, m), 10.41 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 482.1

Intermediate 122c:

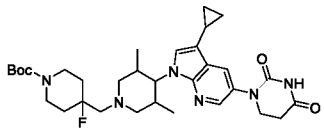
1-(3-Cyclopropyl-1-(3,5-dimethylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2213] *p*-Toluenesulfonic acid (92 mg, 0.48 mmol) was added to Intermediate 122b (116 mg, 0.24 mmol) in CH_3CN (1 mL). The reaction was stirred at 80 °C for 4 h. Solvent was removed under reduced pressure to give the title compound (130 mg, 74%) as a yellow solid in the form of TSOH salt as a mixture of *cis* and *trans* isomers. Quantitative yield assumed. *m/z* (ES^+) $[M+H]^+$ = 382.2.

Intermediate 122d:

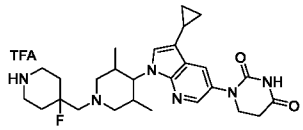
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2214] DIPEA (0.172 mL, 0.98 mmol), Intermediate 6f (349 mg, 0.49 mmol), and Intermediate 122c(125 mg, 0.33 mmol) in MeCN (2 mL) were stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 5 to 20% MeOH in DCM) gave the title compound (105 mg, 53%) as a white solid as a mixture of *cis* and *trans* isomers. *m/z* (ES^+) $[M+H]^+$ = 597.3.

Intermediate 122e:

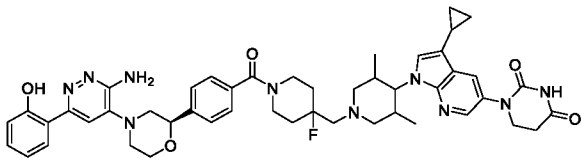
1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2215] Intermediate 122d (100 mg, 0.17 mmol) in DCM (2ml) was added TFA (0.5 ml). The reaction was stirred at r.t. for 1 hour. Solvent was removed to afford the title compound (75 mg, 90%) was obtained as a yellow solid in the form of TFA salt as a mixture of *cis* and *trans* isomers. *m/z* (ES^+) $[M+H]^+$ = 497.5.

EXAMPLE 122:

1-(1-(1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

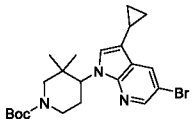


[2216] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (28 mg, 0.07 mmol) and Intermediate 122e (35mg, 0.07 mmol). Purification by RPC (elution gradient: 17 to 32% MeCN in water with 0.1% FA) gave the title compound (12.4 mg, 20%) as a white solid as a mixture of *cis* and *trans* isomers. ^{1}H NMR (DMSO-*d*6): δ 0.43 (6H, d), 0.65 – 0.76 (2H, m), 0.69 – 0.77 (2H, m), 0.83 – 0.94 (2H, m), 1.62 – 1.84 (2H, s), 1.87 – 2.05 (3H, d), 2.06 – 2.21 (2H, m), 2.26 – 2.40 (2H, m), 2.60 (1H, s),2.44 – 2.48 (1H, m), 2.54 – 2.69 (1H, m), 2.70 – 2.83 (5H, m), 2.85 – 2.94 (1H, m), 2.97 – 3.06 (1H, m), 3.07 – 3.24 (1H, d), 3.50 (1H, d), 3.58 (1H, d), 3.80 – 3.88 (1H, m), 3.99 – 4.15 (2H, m), 4.20 – 4.36 (1H, m), 4.89 (1H, d), 6.51 (2H, s), 6.83 – 6.93 (2H, m), 7.20 – 7.28 (1H, m), 7.45 (2H, d), 7.51 – 7.60 (4H, m), 7.92 – 7.99 (2H, m), 8.13 – 8.22 (1H, dd), 10.41 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 871.6.

EXAMPLE 123

Intermediate 123a:

rac-tert-Butyl 4-(5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-dimethylpiperidine-1-carboxylate

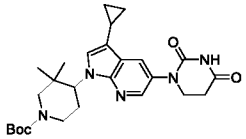


[2217] 5-Bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (3 g, 12.65 mmol), *tert*-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (4.35 g, 18.98 mmol) and 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (6.11 g, 25.31 mmol) in toluene (20 mL) were stirred at 100 °C for 16 h. Solvent was removed under reduced pressure. Purification RPC (elution gradient: 0 to 90% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (1.20 g, 21%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ

0.63 (4H, d), 0.80 – 0.92 (6H, m), 1.18 (1H, t), 1.24 (2H, s), 1.43 (9H, s), 2.39 (1H, s), 3.71 (1H, d), 4.04 (1H, q), 4.16 (1H, s), 4.76 (1H, dd), 7.42 (1H, s), 8.21 (1H, d), 8.27 (1H, d).

Intermediate 123b:

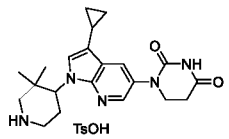
rac-tert-Butyl 4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-dimethylpiperidine-1-carboxylate



[2218] Intermediate 123a (1 g, 2.23 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.018 g, 8.92 mmol), Cs_2CO_3 (2.180 g, 6.69 mmol), $[Pd(cinnamyl)Cl]_2$ (0.114 g, 0.22 mmol) and *t*-BuBrettPhos (0.108 g, 0.22 mmol) in 1,4-dioxane (20 mL) were stirred at 100 °C for 16h. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (0.250 g, 23%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.59 – 0.70 (5H, m), 0.78 – 0.94 (6H, m), 1.22 (1H, s), 1.42 (9H, s), 1.85 – 2.02 (1H, m), 2.27 – 2.44 (1H, m), 2.74 (2H, t), 2.87 (1H, s), 3.81 (3H, t), 4.12 (1H, d), 4.78 (1H, dd), 7.37 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.38 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 482.3.

Intermediate 123c:

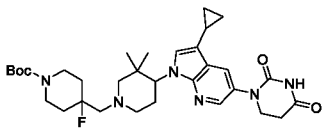
rac-1-(3-Cyclopropyl-1-(3,3-dimethylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2219] 4-Methylbenzenesulfonic acid (0.215 g, 1.25 mmol) and Intermediate 123b (0.3 g, 0.62 mmol) in MeCN (6 mL) were stirred at 80 °C for 3h. Solvent was removed under reduced pressure to afford the title compound as a yellow solid in the form of TSOH salt assumed Quantitative yield. *m/z* (ES$^+$) $[M+H]^+$ = 382.2.

Intermediate 123d:

rac-tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

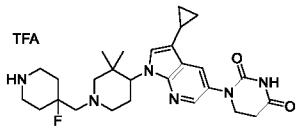


[2220] DIPEA (0.549 mL, 3.15 mmol), Intermediate 6f (0.575 g, 1.57 mmol), and Intermediate 123c (0.3 g, 0.79 mmol) in 1,4-dioxane (15 mL) were stirred at 80 °C for 16h. The reaction was diluted with DCM, and was washed with aq. $NaHCO_3$ solution. Organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.04% NH_4HCO_3) gave the title compound (0.300 g, 64%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.59 –

0.69 (4H, m), 0.81 – 0.89 (2H, m), 1.05 (3H, s), 1.16 (2H, t), 1.22 (2H, s), 1.39 (9H, d), 1.49 (1H, s), 1.86 (3H, d), 2.21 (2H, dt), 2.52 – 2.68 (2H, m), 2.74 (2H, t), 3.02 (3H, t), 3.71 (2H, d), 3.80 (2H, t), 4.02 (1H, q), 4.55 (1H, dd), 7.33 (1H, s), 7.92 (1H, d), 8.14 (1H, d), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 597.3.

Intermediate 123e:

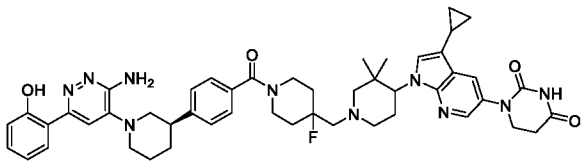
rac-1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)-3,3-dimethylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2221] Intermediate 123d (0.3 g, 0.50 mmol) in DCM (2 mL) and TFA (2.0 mL) were stirred at r.t for 1 h. Solvent was removed under reduced pressure gave the title compound (0.230 g, 92%) as a pale yellow solid in the form of TFA salt. *m/z* (ES^+) $[M+H]^+$ = 497.3.

EXAMPLE 123:

1-(1-(1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

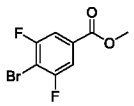


[2222] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (19 mg, 0.05 mmol) and Intermediate 123e (40 mg, 0.08 mmol). Purification by RPC (elution gradient: 16 to 26% MeCN in water with 0.1% FA) gave the title compound (13 mg, 18%) as a white solid as a mixture of diastereomers. ^1H NMR (DMSO-*d*6): δ 0.65 (5H, d), 0.79 – 0.91 (2H, m), 1.08 (3H, s), 1.49 (1H, d), 1.61 – 2.05 (10H, m), 2.21 (1H, d), 2.26 – 2.36 (1H, m), 2.54 (1H, d), 2.58 – 2.86 (7H, m), 3.07 (1H, d), 3.15 (2H, t), 3.49 – 3.62 (3H, m), 3.82 (2H, t), 4.24 (1H, d), 4.58 (1H, dd), 6.31 (2H, s), 6.88 (2H, t), 7.24 (1H, ddd), 7.35 (1H, s), 7.39 (2H, d), 7.44 (2H, d), 7.56 (1H, s), 7.94 (2H, q), 8.17 (1H, d), 10.40 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 869.5.

EXAMPLE 124

Intermediate 124a:

Methyl 4-bromo-3,5-difluorobenzoate

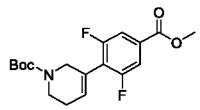


[2223] 4-Bromo-3,5-difluorobenzoic acid (2 g, 8.44 mmol) in MeOH (20 mL) was added H_2SO_4 (0.450 mL, 8.44 mmol) , and the reaction was stirred at 60 °C for 16 h. Solvent was removed, solid participated

out, washed with water (20 mL) and dried under vacuum to afford the title compound (1.70 g, 80%) as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 3.89 (3H, s), 7.73 (1H, q), 7.75–7.78 (1H, m).

Intermediate 124b:

tert-Butyl 5-(2,6-difluoro-4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

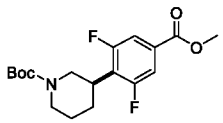


[2224] Intermediate 124a (1.00 g, 3.98 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.232 g, 3.98 mmol), K_2CO_3 (1.652 g, 11.95 mmol), and [Pd(dppf)Cl_2]·DCM (0.325 g, 0.40 mmol) in a mixture 1,4-Dioxane (12 mL) and water (3 mL) was stirred at 100 °C for 2 h. The reaction mixture was cooled to r.t. and was partitioned between water (20 mL) and EtOAc (60 mL). Organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound. (1.10 g, 78%) as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 2.25–2.33 (2H, m), 3.51 (2H, t), 3.89 (3H, s), 4.03 (2H, d), 6.06 (1H, s), 7.63 (1H, d), 7.65 (1H, s).

Intermediate 124c:

tert-Butyl (*R**)-3-(2,6-difluoro-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (Isomer 2)

((*absolute configuration not yet confirmed))



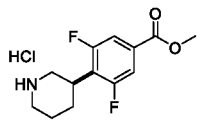
Isomer 2

[2225] Intermediate 124b (1 g, 2.83 mmol) and Pd-C (0.301 g, 2.83 mmol) in MeOH (13 mL) were degassed. The reaction was stirred under an atmosphere of H_2 at r.t for 2 h. Catalyst was filtered off, washed with methanol. The combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound. The racemic compound was purified by chiral SFC ((R, R)-WHELK-O1-Kromasil 5*25 cm, 5 μm Mobile Phase A: CO2, Mobile Phase B: IPA; Flow rate: 150 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.5; RT2(min): 6.4; Sample Solvent: DCM: ACN=1: 1) to give the title compound that eluted second from the column (0.40 g, 41%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.41 (9H, s), 1.61–2.05 (4H, m), 2.77 (1H, s), 3.05 (2H, s), 3.88 (3H, d), 3.99 (2H, s), 7.58 (2H, d).

Intermediate 124d:

Methyl (*R**)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoate (Isomer 2)

((*absolute configuration not yet confirmed))



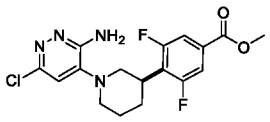
Isomer 2

[2226] HCl (4 M in 1,4-dioxane) was added to Intermediate 124c (340 mg, 0.96 mmol), and the reaction was stirred at r.t for 1 h. Solvent was removed to afford the title compound as a white solid in the form of HCl salt. *m/z* (ES^+) $[M+H]^+$ = 256.1.

Intermediate 124e:

Methyl (*R**)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoate (Isomer 2)

((*absolute configuration not yet confirmed))



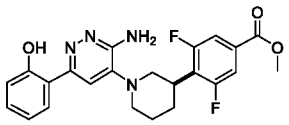
Isomer 2

[2227] Intermediate 124d (340 mg, 0.96 mmol), 4-bromo-6-chloropyridazin-3-amine (199 mg, 0.96 mmol), and DIPEA (371 mg, 2.87 mmol) in DMSO (5 mL) were stirred at 80 °C for 16 h. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether) gave the title compound (200 mg, 55%) as a yellow solid. ^1H NMR (DMSO-*d*6): δ 1.85 (4H, d, J=35.7 Hz), 2.55 – 2.65 (1H, m), 3.00-3.09 (1H, m), 3.37-3.56 (3H, m), 3.88 (3H, s), 6.15 (2H, s), 6.94 (1H, s), 7.59 (2H, d, J=8.9 Hz); *m/z* (ES^+) $[M+H]^+$ = 383.0.

Intermediate 124f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoate (Isomer 2)

((*absolute configuration not yet confirmed))



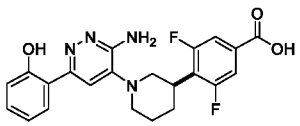
Isomer 2

[2228] Prepared in an analogous method to Intermediate 1e using Intermediate 124e (190 mg, 0.50 mmol). Purification by (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (110 mg, 50%) as a yellow solid. ^1H NMR (DMSO-*d*6): δ 1.79 – 1.99 (4H, m), 2.64-2.72 (1H, m), 3.16-3.24 (1H, m), 3.43 – 3.68 (3H, m), 3.89 (3H, s), 6.30 (2H, s), 6.85-6.89 (2H, m), 7.20-3.25 (1H, m), 7.54 – 7.66 (3H, m), 7.93 (1H, d, *J*=7.5 Hz), (OH proton not observed); *m/z* (ES^+) $[M+H]^+$ = 441.1.

Intermediate 124g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



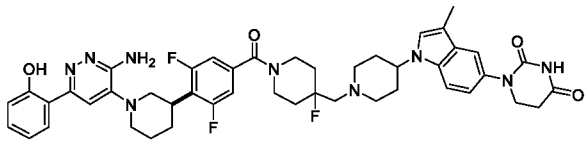
Isomer 2

[2229] Prepared in an analogous method to 1f starting from Intermediate 124f (100 mg, 0.23 mmol. The reaction mixture was acidified to pH 4 with HCl (2.0 M), and extracted with ethyl acetate (20 mL). Organic layer was dried over sodium sulfate., filtered and concentrated down to afford the title compound (60.0 mg, 62%) as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 427.1.

EXAMPLE 124:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



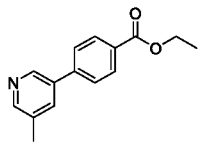
Isomer 2

[2230] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 124g (50 mg, 0.12 mmol) and Intermediate 1k (52 mg, 0.12 mmol). Purification by RPC (elution gradient: 10 to 30% MeCN in water with 0.1% FA) gave the title compound (7 mg, 7%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.69-1.74 (2 H, m), 1.85 – 2.07 (12H, m), 2.23 (3H, d, *J*=1.0 Hz), 2.27-2.31 (2 H, m), 2.70-2.75 (3H, m), 3.05 (3H, s), 3.40 – 3.57 (4H, m), 3.65 (2H, d, *J*=13.0 Hz), 3.77 (2H, t, *J*=6.7 Hz), 4.28 (2H, s), 6.31 (2H, s), 6.85-6.90 (2H, m), 7.01 – 7.10 (1H, m), 7.22-7.26 (3H, m), 7.31 (1H, s), 7.40 (1H, d, *J*=2.0 Hz), 7.47 (1H, d, *J*=8.8 Hz), 7.55 (1H, s), 7.93 (1H, d, *J*=7.8 Hz), 10.25 (1H, s). (OH proton not observed); *m/z* (ES^+) $[M+H]^+$ = 850.5.

EXAMPLE 125

Intermediate 125a:

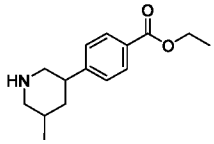
Ethyl 4-(5-methylpyridin-3-yl)benzoate



[2231] Prepared in an analogous method to Intermediate 1a from (5-methylpyridin-3-yl)boronic acid (750 mg, 5.48 mmol) and ethyl 4-bromobenzoate (0.890 mL, 5.48 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (652 mg, 49%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.44 (3H, t), 2.44 (3H, s), 4.43 (2H, q), 7.63 - 7.69 (2H, m), 7.73 (1H, s), 8.14 - 8.18 (2H, m), 8.49 (1H, s), 8.70 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 242.4.

Intermediate 125b:

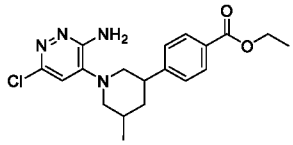
Ethyl 4-(5-methylpiperidin-3-yl)benzoate



[2232] Prepared in an analogous method to Intermediate 1b from Intermediate 125a (590 mg, 2.45 mmol) at 105 °C. The title compound (526 mg, 87%) was obtained as a colorless oil and mixture of isomers. *m/z* (ES^+) $[M+H]^+$ =248.6.

Intermediate 125c:

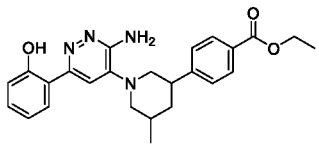
Ethyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-5-methylpiperidin-3-yl)benzoate



[2233] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 125b (525.7 mg, 2.13 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (486 mg, 61%) as a white solid and 2:1 mixture of diastereomers. ^1H NMR (DMSO-*d*6): δ 0.85 - 1.18 (3H, m), 1.24 - 1.37 (4H, m), 1.65 - 2.06 (2H, m), 2.12 - 2.35 (1H, m), 2.52 - 2.70 (1H, m), 2.85 - 3.23 (1H, m), 3.33 - 3.53 (2H, m), 4.29 (2H, q), 6.00 - 6.24 (2H, m), 6.92 (1H, s), 7.46 (2H, s), 7.86 - 7.94 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 375.2.

Intermediate 125d:

Ethyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoate

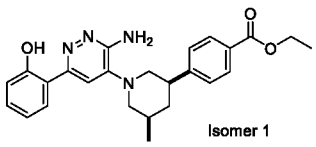


[2234] Prepared in an analogous manner to Intermediate 1e starting from Intermediate 125c (486 mg, 1.30 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (359 mg, 64%) as an off-white solid and mixture of isomers. ^1H NMR (DMSO-*d*6): δ 0.94 - 1.21 (3H, m), 1.26 - 1.37 (4H, m), 1.97 (2H, s), 2.15 - 2.42 (1H, m), 2.58 - 2.83 (1H, m), 2.90 - 3.27 (1H, m), 3.41 - 3.61 (2H, m), 4.24 - 4.34 (2H, m), 6.10 - 6.33 (2H, m), 6.82 - 6.93 (2H, m), 7.18 - 7.26 (1H, m), 7.44 - 7.59 (3H, m), 7.87 - 7.95 (3H, m), 14.14 - 14.31 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 433.5.

Intermediate 125e:

Ethyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

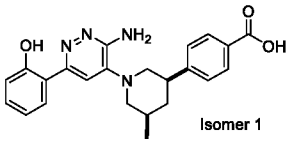


[2235] Intermediate 125d (359 mg, 0.83 mmol) was dissolved in MeOH and purified by SFC conditions detailed below: Column: ChromegaChiral CC4 from ES Industries, 2.0 x 25.0 cm; mobile phase: 75% MeOH with 0.25% isopropylamine in $scCO_2$; Flow rate: 80 mL/min; BPR: 125 bar; Column temperature: 25°C to afford the title compound that eluted first from the column (82 mg, 23% yield) as a white solid. Relative stereochemistry assigned by ROSEY NMR. ^{1}H NMR (DMSO-*d*6): δ 0.99 (3H, d), 1.29 - 1.46 (4H, m), 1.98 (1H, br d), 2.04 - 2.14 (1H, m), 2.35 - 2.44 (1H, m), 2.69 (1H, br t), 3.20 - 3.29 (1H, m), 3.44 - 3.52 (1H, m), 3.56 (1H, br d), 4.31 (2H, q), 6.30 (2H, s), 6.84 - 6.92 (2H, m), 7.23 (1H, t), 7.49 (2H, d), 7.55 (1H, s), 7.93 (3H, br d), 14.24 (1H, br s).

Intermediate 125f:

4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

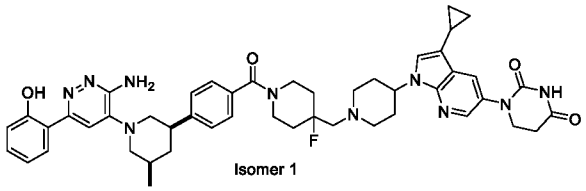


[2236] Prepared in an analogous manner to Intermediate 1f starting from Intermediate 125e (76.6 mg, 0.18 mmol). The title compound (63.6 mg, 89%) was obtained as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.97 (3H, d), 1.45 (1H, q), 1.97 (1H, br d), 2.05 (1H, br d), 2.58 (1H, br t), 2.89 (1H, br t), 3.12 - 3.22 (1H, m), 3.66 (1H, br d), 3.75 (1H, br d), 6.95 (1H, t), 7.06 (1H, br d), 7.14 - 7.29 (1H, m), 7.35 (1H, br t), 7.43 - 7.49 (2H, m), 7.53 (1H, br s), 7.62 (1H, br d), 7.88 - 7.92 (2H, m), 12.34 - 13.11 (1H, m).; *m/z* (ES^+) $[M+H]^+$ =405.2.

EXAMPLE 125:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



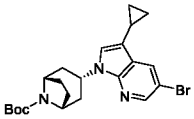
[2237] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 125f (10.11 mg, 0.025 mmol) and Intermediate 7g (23.12 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (13.40 mg, 63%) as a white solid. ^{1}H NMR

(DMSO-*d*6): δ 0.66 (2H, br d), 0.85 (2H, br d), 1.00 (3H, br d), 1.37 (1H, q), 1.65 - 2.13 (11H, m), 2.31 - 2.43 (3H, m), 2.58 - 2.67 (2H, m), 2.67 - 2.81 (3H, m), 3.04 (2H, br d), 3.12 - 3.28 (3H, m), 3.46 - 3.61 (3H, m), 3.82 (2H, br t), 4.25 (1H, br s), 4.59 (1H, br t), 6.29 (2H, br s), 6.86 - 6.91 (2H, m), 7.24 (1H, br t), 7.36 - 7.47 (5H, m), 7.56 (1H, s), 7.91 - 7.98 (2H, m), 8.17 (1H, s), 10.37 (1H, s), 14.26 (1H, br s).; *m/z* (ES^+) $[M+H]^+$ =855.6.

EXAMPLE 126

Intermediate 126a:

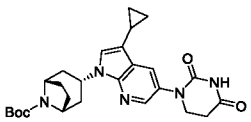
tert-Butyl (1*R*,3*s*,5*S*)-3-(5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



[2238] To a stirred solution of 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (330 mg, 1.39 mmol), *tert*-butyl (1*R*,3*r*,5*S*)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (475 mg, 2.09 mmol), and toluene (10 mL) was added 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (0.547 mL, 2.09 mmol). The reaction was heated to 100 °C for 6 h. After cooling the reaction was concentrated *in vacuo*. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (372 mg, 60%) as an off white solid.^{1}H NMR ($CDCl_3$): δ 0.57 - 0.66 (2H, m), 0.90 (2H, dd), 1.55 (9H, s), 1.80 - 1.91 (1H, m), 1.90 - 2.05 (5H, m), 2.05 - 2.28 (3H, m), 4.24 - 4.51 (2H, m), 5.26 - 5.34 (1H, m), 6.93 (1H, s), 8.09 (1H, d), 8.30 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 448.2.

Intermediate 126b:

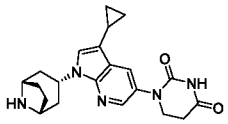
tert-Butyl (1*R*,3*s*,5*S*)-3-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



[2239] A vial was charged with Intermediate 126a (372 mg, 0.83 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (190 mg, 1.67 mmol), *t*-BuBrettPhos Pd G3 (71.2 mg, 0.08 mmol), K_3PO_4 (354 mg, 1.67 mmol) and 1,4-dioxane (5 mL). The reaction was degassed and heated to 100 °C for 6 h. After cooling the reaction was concentrated *in vacuo*. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0-30% MeOH in EtOAc) gave the title compound (248 mg, 62%) as a brown solid.^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.67 (2H, m), 0.81 - 0.91 (2H, m), 1.48 (9H, s), 1.78 - 2.04 (7H, m), 2.20 - 2.33 (2H, m), 2.77 (2H, t), 3.82 (2H, t), 4.22 (2H, br s), 5.04 - 5.15 (1H, m), 7.28 (1H, s), 7.94 (1H, d), 8.15 (1H, d), 10.37 (1H, s); *m/z* (ES^+) $[M+H]^+$ =480.5.

Intermediate 126c:

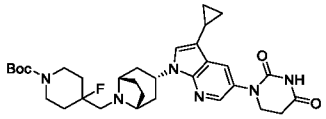
1-(1-((1*R*,3*s*,5*S*)-8-Azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2240] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 126b (248 mg, 62%). Purification by ion exchange chromatography (Porpak Rxn CX 5g cartridge) eluting with 2 N NH_3 in MeOH gave the title compound (180 mg, 91%) as a white solid.^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.69 (2H, m), 0.81 - 0.91 (2H, m), 1.71 - 1.84 (6H, m), 1.85 - 2.02 (3H, m), 2.16 (1H, br s), 2.77 (2H, t), 3.48 - 3.57 (2H, m), 3.81 (2H, t), 5.05 (1H, tt), 7.39 (1H, s), 7.93 (1H, d), 8.18 (1H, d), 10.38 (1H, br s); *m/z* (ES^+) $[M+H]^+$ =380.5.

Intermediate 126d:

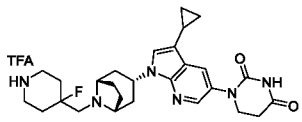
tert-Butyl 4-(((1*R*,3*s*,5*S*)-3-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2241] Prepared in an analogous manner to Intermediate 7f starting from Intermediate 126c (170 mg, 0.45 mmol) and Intermediate 6f (327 mg, 0.90 mmol). Purification by FSC (elution gradient: 0 to 3% MeOH in EtOAc) gave the title compound (128 mg, 48%) as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.72 (2H, m), 0.82 - 0.89 (2H, m), 1.42 (9H, s), 1.59 - 1.76 (6H, m), 1.83 - 1.98 (5H, m), 2.12 (2H, br t), 2.62 - 2.71 (2H, m), 2.77 (2H, t), 3.04 (2H, br s), 3.71 - 3.86 (4H, m), 4.97 (1H, td), 7.39 (1H, s), 7.94 (1H, d), 8.18 (1H, d), 10.38 (1H, s) (2H under H_2O peak); *m/z* (ES^+) $[M+H]^+$ = 595.6.

Intermediate 126e:

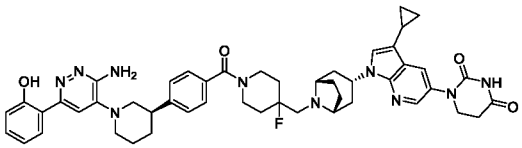
1-(3-Cyclopropyl-1-((1*R*,3*s*,5*S*)-8-((4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2242] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 126d (128 mg, 0.22 mmol). Concentration *in vacuo* gave the title compound in the form of a trifluoroacetate salt (208 mg, 100%). ^{1}H NMR (DMSO-*d*6): δ 0.54 - 0.68 (2H, m), 0.86 - 0.95 (2H, m), 1.88 - 2.42 (11H, m), 2.65 (1H, br t), 2.78 (2H, t), 2.83 - 2.96 (1H, m), 3.04 - 3.16 (2H, m), 3.33 - 3.43 (2H, m), 3.53 - 3.67 (1H, m), 3.83 (2H, t), 4.16 - 4.26 (2H, m), 4.97 - 5.32 (1H, m), 7.31 - 7.45 (1H, m), 8.01 (1H, s), 8.24 (1H, br s), 8.74 - 8.94 (1H, m), 8.98 - 9.12 (1H, m), 9.93 - 10.38 (1H, m), 10.40 (1H, s), 12.54 - 13.89 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 495.4.

EXAMPLE 126:

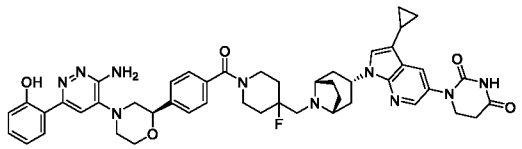
1-(1-((1*R*,3*s*,5*S*)-8-((1-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2243] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 1f (16 mg, 0.04 mmol) and Intermediate 126e (38 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (16.10 mg, 46%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.71 (2H, m), 0.81 - 0.88 (2H, m), 1.64 - 1.85 (8H, m), 1.86 - 2.05 (8H, m), 2.14 (2H, br t), 2.64 - 2.88 (6H, m), 3.10 - 3.19 (2H, m), 3.32 - 3.36 (2H, m), 3.46 - 3.62 (3H, m), 3.81 (2H, t), 4.19 - 4.46 (1H, m), 4.94 - 5.02 (1H, m), 6.28 (2H, s), 6.85 - 6.93 (2H, m), 7.20 - 7.26 (1H, m), 7.40 (3H, d), 7.42 - 7.47 (2H, m), 7.56 (1H, s), 7.92 - 7.95 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 867.7.

EXAMPLE 127:

1-(1-((1*R*,3*s*,5*S*)-8-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



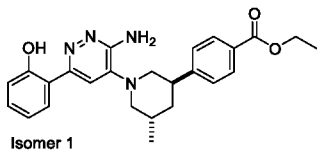
[2244] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 16i (19.6 mg, 0.05 mmol) and Intermediate 126e (47.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (31.4 mg, 72%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.63 - 0.70 (2H, m), 0.82 - 0.88 (2H, m), 1.65 - 1.85 (6H, m), 1.87 - 2.07 (5H, m), 2.14 (2H, br t), 2.64 - 2.84 (5H, m), 2.89 (1H, td), 3.05 - 3.30 (2H, m), 3.32 - 3.36 (2H, m), 3.44 - 3.55 (2H, m), 3.58 (1H, br d), 3.81 (2H, t), 4.02 - 4.14 (2H, m), 4.19 - 4.39 (1H, m), 4.89 (1H, br d), 4.98 (1H, dt), 6.47 (2H, s), 6.85 - 6.91 (2H, m), 7.20 - 7.26 (1H, m), 7.40 (1H, s), 7.45 (2H, d), 7.51 - 7.60 (3H, m), 7.91 - 7.97 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 869.6.

EXAMPLE 128

Intermediate 128a:

Ethyl 4-((3*R**,5*S**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

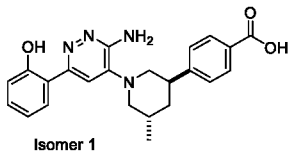


[2245] Intermediate 125d (359 mg, 0.83 mmol) was purified in an analogous manner to Intermediate 125e afford the title compound that eluted second from the column (29.6 mg, 8% yield) as a white solid. Relative stereochemistry assigned by ROSEY NMR. ^{1}H NMR (DMSO-*d*6): δ 1.20 (3H, d), 1.30 (3H, t), 1.69 - 1.76 (1H, m), 1.87 - 1.99 (1H, m), 2.17 - 2.26 (1H, m), 2.77 (1H, br t), 3.02 (1H, br d), 3.16 (1H, br dd), 3.48 - 3.58 (2H, m), 4.29 (2H, q), 6.17 (2H, s), 6.85 - 6.90 (2H, m), 7.23 (1H, t), 7.51 (2H, d), 7.54 (1H, s), 7.87 - 7.95 (3H, m), 14.15 (1H, br s).

Intermediate 128b:

4-((3*R**,5*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

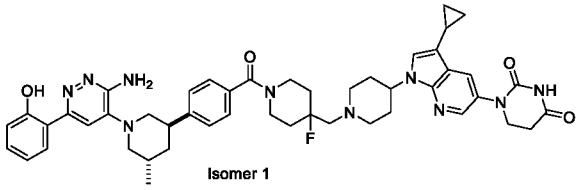


[2246] Prepared in an analogous manner to Intermediate 1f starting from Intermediate 128a (25.6 mg, 0.06 mmol). The title compound (22.3 mg, 93%) was obtained as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 1.11 (3H, d), 1.74 (1H, br d), 1.94 - 2.04 (1H, m), 2.20 - 2.31 (1H, m), 2.97 (1H, br t), 3.21 - 3.29 (1H, m), 3.37 (2H, br d), 3.58 (1H, br t), 3.77 (1H, br d), 6.95 (1H, t), 7.11 (1H, d), 7.21 - 7.32 (1H, m), 7.36 (1H, br t), 7.48 (3H, br d), 7.57 (1H, br d), 7.88 (2H, d), 12.23 - 13.22 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 405.3.

EXAMPLE 128:

1-(1-(1-((1-(4-((3*R**,5*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



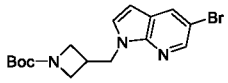
[2247] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 128b (10.1 mg, 0.025 mmol) and Intermediate 7g (23.1 mg, 0.03 mmol) Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (12.9 mg, 60%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.85 (2H, br d), 1.23 (3H, br d), 1.65 - 1.85 (5H, m), 1.87 - 1.99 (3H, m), 2.00 - 2.13 (2H, m), 2.26 (1H, br s), 2.31 - 2.40 (2H, m), 2.57 - 2.68 (2H, m), 2.70 - 2.85 (3H, m), 2.98 -

3.11 (3H, m), 3.16 (2H, br d), 3.25 - 3.30 (1H, m), 3.34 - 3.39 (1H, m), 3.49 (1H, br s), 3.55 (2H, br d), 3.82 (2H, t), 4.25 (1H, br s), 4.59 (1H, br t), 6.17 (2H, br s), 6.86 - 6.92 (2H, m), 7.24 (1H, br t), 7.38 (2H, br d), 7.42 - 7.48 (3H, m), 7.56 (1H, s), 7.91 - 7.96 (2H, m), 8.17 (1H, s), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 855.6.

EXAMPLE 129

Intermediate 129a:

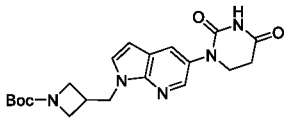
tert-Butyl 3-((5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)azetidine-1-carboxylate



[2248] Prepared in an analogous manner to Intermediate 126a starting from 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.788 g, 4 mmol), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (1.498 g, 8.00 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.247 g, 85%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.36 (9H, s), 2.97 - 3.07 (1H, m), 3.69 (2H, br s), 3.85 (2H, br s), 4.46 (2H, d), 6.47 (1H, d), 7.71 (1H, d), 8.21 (1H, s), 8.31 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 368.1.

Intermediate 129b:

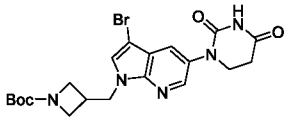
tert-Butyl 3-((5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)azetidine-1-carboxylate



[2249] Prepared in an analogous manner to Intermediate 126b starting from Intermediate 129a (1.247g, 3.40 mmol). Trituration of the crude residue with hexanes gave the title compound (1.212 g, 89%) as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 1.35 (9H, s), 2.73 (2H, t), 2.99 - 3.08 (1H, m), 3.70 (2H, br s), 3.76 - 3.87 (4H, m), 4.46 (2H, br d), 6.47 (1H, d), 7.67 (1H, d), 7.91 (1H, s), 8.21 (1H, s), 10.05 - 10.30 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 400.2.

Intermediate 129c:

tert-Butyl 3-((3-bromo-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)azetidine-1-carboxylate

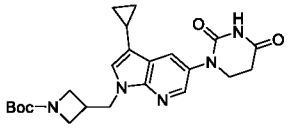


[2250] To a stirred solution of Intermediate 129b (1.212 g, 3.03 mmol) in DCM (30 mL) at 0 °C was added *N*-bromosuccinimide (0.567 g, 3.18 mmol). The reaction was stirred at 0 °C for 30 min. The reaction mixture was washed with sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (1:1, 200 mL). The aqueous layer was extracted with DCM (50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (1.334 g, 92%) as a brown solid. ^{1}H NMR

(DMSO-*d*6): δ 1.37 (9H, s), 2.77 (2H, t), 3.00 - 3.09 (1H, m), 3.68 - 3.74 (2H, m), 3.83 - 3.92 (4H, m), 4.49 (2H, br d), 7.86 (1H, s), 7.97 (1H, s), 8.33 (1H, s), 10.44 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 480.1.

Intermediate 129d:

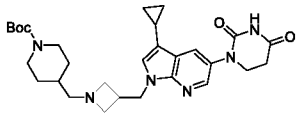
tert-Butyl 3-((3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)azetidine-1-carboxylate



[2251] A flask was charged with Intermediate 129c (1.186 g, 2.48 mmol), cyclopropylboronic acid (0.426 g, 4.96 mmol), $PdCl_2$(dtbpf) (0.081 g, 0.12 mmol), K_3PO_4 (1.579 g, 7.44 mmol), toluene (24 ml), and water (2.4 ml). The reaction was degassed and was stirred at 70 °C for 1h. After cooling to r.t. the reaction mixture was poured into sat. aq. NH_4Cl (100 mL) and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes then 0-15% MeOH in EtOAc) gave the title compound (0.746 g, 68%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.58 - 0.65 (2H, m), 0.82 - 0.90 (2H, m), 1.35 (9H, s), 1.87 - 1.94 (1H, m), 2.75 (2H, t), 2.93 - 3.03 (1H, m), 3.62 - 3.72 (2H, m), 3.77 - 3.88 (4H, m), 4.36 (2H, br d), 7.38 (1H, s), 7.94 - 7.96 (1H, m), 8.17 - 8.20 (1H, m), 10.37 (1H, s); *m/z* (ES^+) $[M+H]^+$ =440.2.

Intermediate 129e:

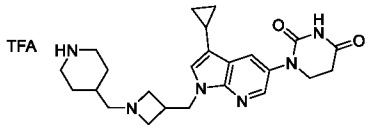
tert-Butyl 4-((3-((3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)azetidin-1-yl)methyl)piperidine-1-carboxylate



[2252] A vial was charged with Intermediate 129d (50 mg, 0.11 mmol), DCM (1 mL) and trifluoroacetic acid (0.2 mL, 2.60 mmol). The reaction was stirred at r.t. for 20 min. then concentrated under reduced pressure. DCM (1 mL) and IPA (0.200 mL) and *tert*-butyl 4-formylpiperidine-1-carboxylate (72.8 mg, 0.34 mmol) were added and the mixture was stirred at r.t. for 15 min. Sodium triacetoxyborohydride (72.3 mg, 0.34 mmol) was added and the reaction was stirred at r.t for 20 min. then concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (40.2 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.67 (2H, m), 0.84 - 0.91 (2H, m), 0.92 - 1.02 (2H, m), 1.37 - 1.39 (9H, m), 1.42 - 1.49 (1H, m), 1.60 (2H, br d), 1.89 - 1.95 (1H, m), 2.38 (2H, br d), 2.59 - 2.70 (2H, m), 2.77 (2H, t), 2.86 - 2.94 (1H, m), 3.14 (2H, br t), 3.33 - 3.39 (2H, m), 3.82 (2H, t), 3.86 - 3.92 (2H, m), 4.36 (2H, br d), 7.32 (1H, s), 7.96 (1H, d), 8.18 - 8.20 (1H, m), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 537.4.

Intermediate 129f:

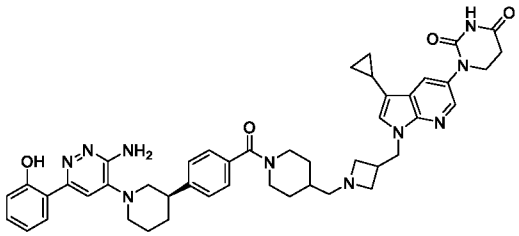
1-(3-Cyclopropyl-1-((1-(piperidin-4-ylmethyl)azetidin-3-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2253] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 129e (25.0 mg, 0.04 mmol). Concentration *in vacuo* gave the title compound (35.7 mg, 100% yield) as a brown film in the form of a trifluoroacetate salt. *m/z* (ES^+) $[M+H]^+$ =473.3.

EXAMPLE 129:

(*R*)-1-(1-((1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

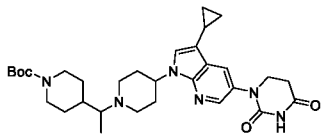


[2254] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 129f (35.7 mg, 0.04 mmol) and Intermediate 1f (15.6 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% FA) gave the title compound (11.0 mg, 31%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.61 (2H, br d), 0.82 - 0.88 (2H, m), 1.45 - 1.55 (1H, m), 1.55 - 1.75 (3H, m), 1.82 - 2.01 (4H, m), 2.20 - 2.30 (2H, m), 2.66 - 2.85 (7H, m), 2.91 - 2.99 (3H, m), 3.07 - 3.14 (1H, m), 3.21 (2H, br t), 3.53 (2H, br d), 3.80 (2H, br t), 4.28 - 4.50 (4H, m), 6.26 (2H, br s), 6.82 - 6.90 (2H, m), 7.22 (1H, br t), 7.31 (3H, br d), 7.39 (2H, br d), 7.53 (1H, s), 7.88 - 7.97 (2H, m), 8.17 (1H, s), 8.25 (2H, s), 10.36 (1H, s); *m/z* (ES^+) $[M+H]^+$ =809.5.

EXAMPLE 130

Intermediate 130a:

rac-tert-Butyl 4-(1-(4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate

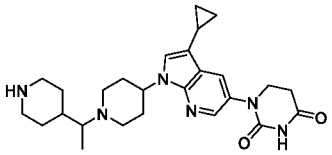


[2255] A vial was charged Intermediate 7e (1.0 g, 2.83 mmol), *tert*-butyl 4-acetylpiperidine-1-carboxylate (1.929 g, 8.49 mmol), THF (12 mL) and titanium(IV) isopropoxide (2.51 ml, 8.49 mmol). The reaction was stirred at 65 °C for 20 h. Sodium triacetoxyborohydride (1.649 g, 7.78 mmol) was added and the reaction was stirred at 65 °C for 20 min. The reaction was quenched with MeOH (5 mL) and

concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 40% MeOH in EtOAc) gave the title compound (853 mg, 53%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.67 (2H, br d), 0.79 - 0.89 (2H, m), 0.92 (3H, d), 0.95 - 1.03 (2H, m), 1.18 (1H, t), 1.40 (9H, s), 1.45 - 1.53 (1H, m), 1.65 (1H, br d), 1.81 - 1.89 (2H, m), 1.93 - 1.97 (1H, m), 2.00 - 2.07 (2H, m), 2.19 - 2.37 (2H, m), 2.60 - 2.82 (7H, m), 3.82 (2H, t), 3.96 (2H, br d), 4.56 (1H, br t), 7.44 (1H, s), 7.95 (1H, s), 8.17 (1H, s), 10.37 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 565.4.

Intermediate 130b:

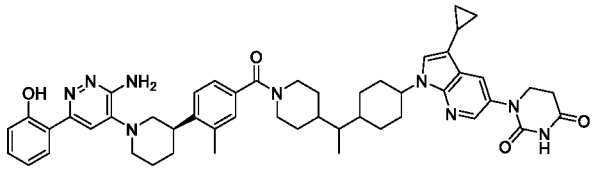
rac-1-(3-Cyclopropyl-1-(1-(1-(piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2256] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 130a (838 mg, 1.48 mmol). Purification by ion exchange chromatography (Porpak Rxn CX 5g cartridge) eluting with 2N NH_3 in MeOH gave the title compound (0.579 g, 84%) as a light brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.72 (2H, m), 0.80 - 0.88 (2H, m), 0.88 - 1.03 (5H, m), 1.31 - 1.42 (1H, m), 1.59 (1H, br d), 1.82 - 2.05 (6H, m), 2.15 - 2.34 (2H, m), 2.37 - 2.49 (2H, m), 2.61 - 2.68 (1H, m), 2.69 - 2.74 (1H, m), 2.77 (3H, br t), 2.94 (2H, br d), 3.24 - 3.44 (1H, m), 3.82 (2H, t), 4.52 - 4.60 (1H, m), 7.45 (1H, s), 7.94 (1H, d), 8.15 - 8.19 (1H, m), 9.75 - 10.97 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 465.4.

EXAMPLE 130:

1-(1-(1-(-1-(1-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

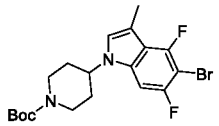


[2257] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 130b (12.2 mg, 0.03 mmol) and Intermediate 12g (12.19 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (9.92 mg, 39%) as a white solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.65 (2H, br s), 0.85 (2H, br s), 0.93 (3H, br s), 1.02 - 1.12 (2H, m), 1.52 - 1.77 (3H, m), 1.78 - 2.05 (9H, m), 2.17 - 2.29 (1H, m), 2.33 - 2.38 (1H, m), 2.41 (3H, s), 2.63 - 3.05 (9H, m), 3.20 - 3.29 (1H, m), 3.45 - 3.53 (1H, m), 3.54 - 3.73 (2H, m), 3.81 (2H, br t), 4.39 - 4.64 (2H, m), 6.28 (2H, br s), 6.84 - 6.93 (2H, m), 7.15 - 7.27 (3H, m), 7.33 - 7.49 (2H, m), 7.57 (1H, s), 7.88 - 8.00 (2H, m), 8.17 (1H, br s), 10.38 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 851.6.

EXAMPLE 131

Intermediate 131a:

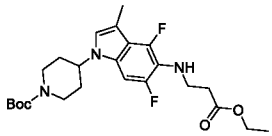
tert-Butyl 4-(5-bromo-4,6-difluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2258] Prepared in an analogous manner to Intermediate 1g starting from 5-bromo-4,6-difluoro-3-methyl-1*H*-indole (936 mg, 3.80 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in hexanes) gave the title compound (722 mg, 44%) yellow film. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.70 - 1.83 (2H, m), 1.86 (2H, br d), 2.31 (3H, s), 2.91 (2H, br s), 3.99 - 4.14 (2H, m), 4.44 - 4.52 (1H, m), 7.36 (1H, s), 7.56 (1H, d; *m/z* (ES$^+$) $[M–tBu+2H]^+$ = 372.9.

Intermediate 131b:

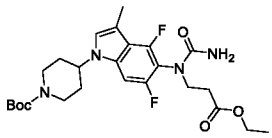
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-4,6-difluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2259] Prepared in an analogous manner to Intermediate 3b starting from Intermediate 131a (0.722 g, 1.68 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.445 g, 57%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, t), 1.50 (9H, s), 1.83 (2H, qd), 1.95 - 2.07 (2H, m), 2.39 (3H, s), 2.57 (2H, t), 2.79 - 2.97 (2H, m), 3.46 - 3.55 (2H, m), 3.69 - 3.76 (1H, m), 4.04 - 4.13 (1H, m), 4.17 (2H, q), 4.23 - 4.39 (2H, m), 6.76 - 6.82 (2H, m); *m/z* (ES$^+$) $[M+Na]^+$ = 488.2.

Intermediate 131c:

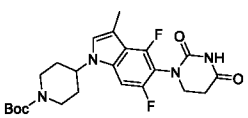
tert-Butyl 4-(5-(1-(3-ethoxy-3-oxopropyl)ureido)-4,6-difluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2260] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 131b (445 mg, 0.96 mmol). The title compound (488 mg, 100%) was obtained as a white solid. *m/z* (ES$^+$) $[M+Na]^+$ = 531.1.

Intermediate 131d:

tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4,6-difluoro-3-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate

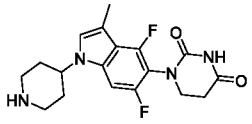


[2261] Prepared in an analogous manner to Intermediate 3d starting from Intermediate 131c (488 mg, 0.96 mmol). Trituration of the crude solid with MeOH gave the title compound (211 mg, 47%) as a white

solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.70 - 1.81 (2H, m), 1.84 - 1.91 (2H, m), 2.32 (3H, s), 2.66 - 2.78 (2H, m), 2.92 (2H, br s), 3.62 - 3.73 (2H, m), 3.98 - 4.21 (2H, m), 4.47 (1H, ddt), 7.35 (1H, s), 7.46 (1H, d), 10.51 (1H, s); *m/z* (ES$^+$) [M+Na]$^+$ = 485.2.

Intermediate 131e:

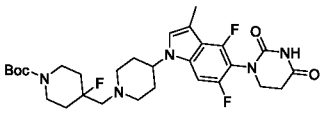
1-(4,6-Difluoro-3-methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2262] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 131d (210 mg, 0.45 mmol). The crude residue was suspended in water and neutralized with sat. aq. $NaHCO_3$ solution. The resulting precipitate was collected by vacuum filtration, wash with water, and dried *in vacuo*. The title compound (107 mg, 65%) was obtained as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.68 - 1.88 (4H, m), 2.33 (3H, s), 2.62 - 2.77 (4H, m), 3.04 (2H, br d), 3.11 - 3.29 (1H, m), 3.63 - 3.72 (2H, m), 4.26 - 4.37 (1H, m), 7.27 (1H, s), 7.43 (1H, d), 10.15 - 10.80 (1H, m); *m/z* (ES$^-$) [M–H]$^-$ = 361.1.

Intermediate 131f:

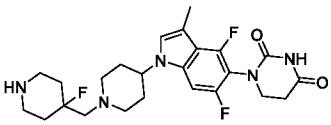
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4,6-difluoro-3-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2263] Prepared in an analogous manner to Intermediate 6g starting from Intermediate 131e (92 mg, 0.25 mmol) and Intermediate 6f (139 mg, 0.38 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (105 mg, 71%) as a white solid. Product contained impurity from Intermediate 6f. *m/z* (ES$^+$) [M+Na]$^+$ = 600.1.

Intermediate 131g:

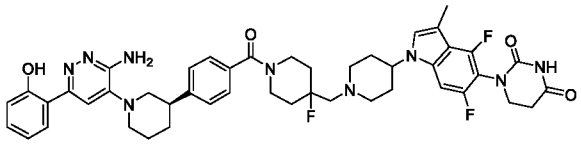
1-(4,6-Difluoro-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2264] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 131f (104.8 mg, 0.18 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (86 mg, 100%) as a white solid. *m/z* (ES$^+$) [M+H]$^+$ = 478.5.

EXAMPLE 131:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

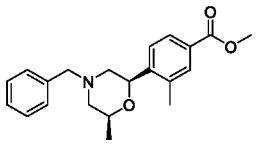


[2265] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 131g (23.88 mg, 0.05 mmol) and Intermediate 1f (19.52 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% FA) gave the title compound (10.10 mg, 24%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.79 (3H, m), 1.80 - 2.04 (9H, m), 2.34 (3H, s), 2.40 (2H, br t), 2.58 - 2.66 (2H, m), 2.67 - 2.85 (5H, m), 3.02 (2H, br d), 3.09 - 3.19 (2H, m), 3.45 - 3.60 (3H, m), 3.69 (2H, br t), 4.21 - 4.32 (2H, m), 6.29 (2H, s), 6.86 - 6.91 (2H, m), 7.23 (1H, t), 7.33 - 7.48 (6H, m), 7.56 (1H, s), 7.94 (1H, br d), 10.52 (1H, s), 13.90 - 14.44 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 850.4.

EXAMPLE 132

Intermediate 132a:

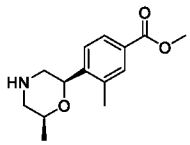
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-3-methylbenzoate



[2266] Prepared in an analogous manner to Intermediate 65a starting from (*S*)-1-(benzylamino)propan-2-ol (6.36 g, 38.50 mmol) and methyl 4-(2-bromoacetyl)-3-methylbenzoate (9.49 g, 35 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (5.18 g, 44%) as a yellow oil. Relative stereochemistry assigned by ROSEY. ^{1}H NMR (DMSO-*d*6): δ 1.14 (3H, d), 1.82 (2H, td), 2.29 (3H, s), 2.75 - 2.88 (2H, m), 3.46 - 3.57 (2H, m), 3.77 - 3.86 (4H, m), 4.76 (1H, br d), 7.22 - 7.28 (1H, m), 7.29 - 7.36 (4H, m), 7.51 (1H, d), 7.71 - 7.76 (1H, m), 7.78 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ =340.5.

Intermediate 132b:

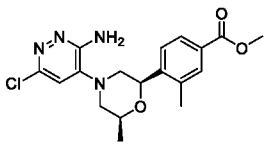
Methyl 3-methyl-4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2267] Prepared in an analogous manner to Intermediate 65b starting from Intermediate 132a (5.2 g, 15.32 mmol). Filtration through celite and concentration *in vacuo* gave the title compound (3.8 g, 100%) as a yellow residue. ^{1}H NMR (DMSO-*d*6): δ 1.11 (3H, d), 2.28 - 2.41 (5H, m), 2.82 - 2.87 (1H, m), 2.90 - 2.95 (1H, m), 3.65 - 3.74 (1H, m), 3.84 (3H, s), 4.66 (1H, dd), 7.52 (1H, d), 7.75 (1H, s), 7.79 (1H, d) (N-H not observed); *m/z* (ES$^+$) $[M+H]^+$ = 250.4.

Intermediate 132c:

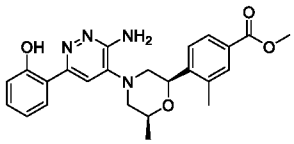
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2268] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 132b (3.82 g, 15.32 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave the title compound (4.00 g, 69%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.20 (3H, d), 2.40 (3H, s), 2.42 - 2.48 (1H, m), 2.50 - 2.56 (1H, m), 3.42 (1H, br d), 3.49 (1H, br d), 3.83 (3H, s), 4.04 - 4.11 (1H, m), 5.01 (1H, br d), 6.26 (2H, s), 6.95 (1H, s), 7.58 (1H, d), 7.77 (1H, s), 7.80 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 379.1.

Intermediate 132d:

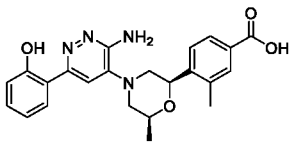
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2269] Prepared in an analogous manner to Intermediate 1e starting from Intermediate 132c (4.0 g, 10.61 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 50% MeOH in EtOAc) gave the title compound (3.65 g, 79%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 2.44 (3H, s), 2.52 - 2.58 (1H, m), 2.67 (1H, br t), 3.51 - 3.60 (2H, m), 3.85 (3H, s), 4.11 - 4.19 (1H, m), 5.09 (1H, br d), 6.46 (2H, s), 6.80 - 6.94 (2H, m), 7.23 (1H, t), 7.56 (1H, s), 7.64 (1H, d), 7.80 (1H, s), 7.84 (1H, br d), 7.94 (1H, d), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 435.3.

Intermediate 132e:

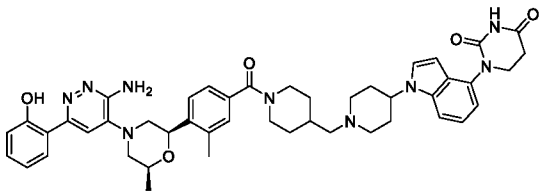
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoic acid



[2270] A vial was charged with Intermediate 132d (3.65 g, 8.40 mmol), LiOH (2.012 g, 84.01 mmol), MeOH (40 mL), and water (20 mL). The reaction was stirred at 50 °C for 1h then concentrated under reduced pressure. The crude residue was dissolved in water and acidified to pH 2 with 1 M aq. HCl forming a brown precipitate. The solid was collected by vacuum filtration, washed with water, and dried *in vacuo*. The title compound (3.16 g, 89%) was obtained as brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.41 (3H, s), 2.56 - 2.64 (1H, m), 2.71 (1H, br t), 3.54 - 3.62 (2H, m), 4.10 - 4.18 (1H, m), 5.06 (1H, br d), 6.70 (2H, br s), 6.87 (1H, t), 6.91 (1H, br d), 7.25 (1H, br t), 7.54 (1H, s), 7.59 (1H, d), 7.76 (1H, s), 7.80 (1H, br d), 7.84 (1H, br d), 12.56 - 13.75 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 421.5.

EXAMPLE 132:

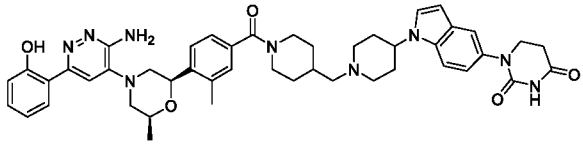
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2271] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (21.0 mg, 0.05 mmol) and Intermediate 10e (24.1 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (14.88 mg, 37%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.03 - 1.17 (2H, m), 1.25 (3H, d), 1.64 - 1.75 (1H, m), 1.84 (2H, br s), 1.90 - 2.03 (4H, m), 2.12 - 2.20 (2H, m), 2.22 - 2.29 (2H, m), 2.41 (3H, s), 2.52 - 2.56 (1H, m), 2.71 - 2.81 (4H, m), 3.00 (3H, br d), 3.51 - 3.66 (3H, m), 3.75 - 3.80 (2H, m), 4.11 - 4.20 (1H, m), 4.33 - 4.42 (1H, m), 4.43 - 4.53 (1H, m), 5.03 (1H, br d), 6.42 (1H, d), 6.45 (2H, s), 6.85 - 6.91 (2H, m), 6.96 (1H, d), 7.14 (1H, t), 7.19 - 7.26 (3H, m), 7.50 - 7.58 (4H, m), 7.96 (1H, d), 10.34 (1H, s), 14.24 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 812.5.

EXAMPLE 133:

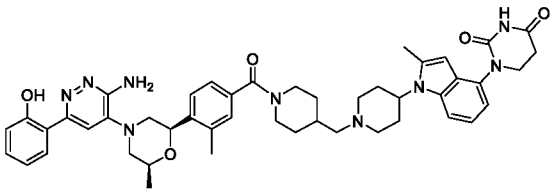
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2272] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (21.0 mg, 0.05 mmol) and Intermediate 108b (20.48 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (13.06 mg, 32). ^1H NMR (DMSO-*d*6): δ 1.03 - 1.16 (2H, m), 1.25 (3H, d), 1.63 - 1.76 (1H, m), 1.77 - 1.89 (2H, m), 1.90 - 2.05 (4H, m), 2.12 - 2.30 (4H, m), 2.41 (3H, s), 2.53 - 2.58 (1H, m), 2.68 - 2.81 (4H, m), 2.94 - 3.12 (3H, m), 3.52 - 3.66 (3H, m), 3.77 (2H, t), 4.08 - 4.23 (1H, m), 4.30 - 4.41 (1H, m), 4.43 - 4.54 (1H, m), 5.04 (1H, br d), 6.42 - 6.51 (3H, m), 6.88 (2H, s), 7.07 (1H, dd), 7.19 - 7.26 (3H, m), 7.46 (1H, d), 7.52 - 7.60 (4H, m), 7.92 - 8.00 (1H, m), 10.28 (1H, s), 13.84 - 14.63 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 812.7.

EXAMPLE 134:

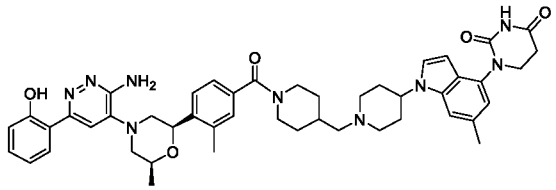
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2273] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (21.0 mg, 0.05 mmol) and Intermediate 22d (44.9 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (14.16 mg, 34%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.03 - 1.19 (2H, m), 1.25 (3H, d), 1.76 (3H, br d), 1.82 - 1.94 (2H, m), 2.08 - 2.17 (2H, m), 2.21 - 2.30 (2H, m), 2.37 - 2.46 (8H, m), 2.52 - 2.57 (1H, m), 2.69 - 2.80 (4H, m), 3.01 (3H, br d), 3.56 (2H, br t), 3.60 - 3.68 (1H, m), 3.74 (2H, t), 4.12 - 4.19 (1H, m), 4.20 - 4.31 (1H, m), 4.44 - 4.59 (1H, m), 5.04 (1H, br d), 6.16 (1H, s), 6.46 (2H, br s), 6.85 - 6.92 (3H, m), 7.04 (1H, t), 7.20 - 7.27 (3H, m), 7.46 (1H, d), 7.55 (1H, d), 7.58 (1H, s), 7.97 (1H, d), 10.32 (1H, s), 14.24 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 826.6.

EXAMPLE 135:

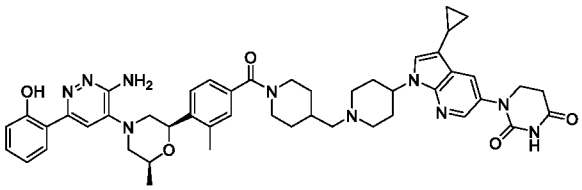
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2274] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (10.51 mg, 0.025 mmol) and Intermediate 82e (10.59 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (5.09 mg, 25%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.64 - 2.06 (9H, m), 2.11 - 2.20 (2H, m), 2.20 - 2.31 (2H, m), 2.36 - 2.45 (7H, m), 2.53 - 2.59 (1H, m), 2.75 (5H, br t), 2.89 - 3.12 (4H, m), 3.50 - 3.66 (3H, m), 3.76 (2H, t), 4.10 - 4.20 (1H, m), 4.28 - 4.40 (1H, m), 4.42 - 4.58 (1H, m), 5.04 (1H, br d), 6.34 (1H, d), 6.45 (2H, s), 6.80 (1H, s), 6.83 - 6.92 (2H, m), 7.18 - 7.28 (3H, m), 7.31 (1H, s), 7.44 (1H, d), 7.52 - 7.60 (2H, m), 7.92 - 8.00 (1H, m), 10.33 (1H, s), 14.24 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 826.7.

EXAMPLE 136:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

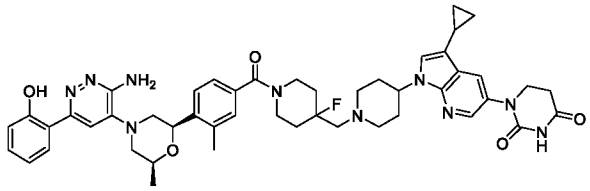


[2275] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (21.02 mg, 0.05 mmol) and Intermediate 71c (39.6 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (16.43 mg, 38%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.64 - 0.70 (2H, m), 0.82 - 0.88 (2H, m), 1.02 - 1.17 (2H, m), 1.25 (3H, d), 1.61 - 1.73 (1H,

m), 1.79 - 1.96 (5H, m), 2.00 - 2.12 (4H, m), 2.17 - 2.30 (2H, m), 2.41 (3H, s), 2.52 - 2.58 (1H, m), 2.69 - 2.83 (4H, m), 2.92 - 3.12 (3H, m), 3.51 - 3.67 (3H, m), 3.82 (2H, t), 4.12 - 4.19 (1H, m), 4.41 - 4.54 (1H, m), 4.55 - 4.64 (1H, m), 5.04 (1H, br d), 6.45 (2H, s), 6.85 - 6.91 (2H, m), 7.19 - 7.26 (3H, m), 7.45 (1H, s), 7.55 (1H, d), 7.58 (1H, s), 7.93 - 7.97 (2H, m), 8.17 (1H, d), 10.40 (1H, br s), 14.24 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 853.7.

EXAMPLE 137:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

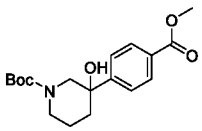


[2276] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (42.0 mg, 0.1 mmol) and Intermediate 20g (92 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (53.8 mg, 62%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.82 - 0.89 (2H, m), 1.25 (3H, d), 1.81 (5H, br d), 1.89 - 2.00 (2H, m), 2.02 - 2.09 (2H, m), 2.35 (2H, br t), 2.42 (3H, s), 2.53 - 2.58 (1H, m), 2.58 - 2.67 (2H, m), 2.70 - 2.82 (3H, m), 2.97 - 3.30 (4H, m), 3.44 - 3.65 (3H, m), 3.82 (2H, t), 4.13 - 4.20 (1H, m), 4.21 - 4.41 (1H, m), 4.60 (1H, br t), 5.04 (1H, br d), 6.45 (2H, br s), 6.84 - 6.92 (2H, m), 7.21 - 7.30 (3H, m), 7.45 (1H, s), 7.52 - 7.61 (2H, m), 7.92 - 7.98 (2H, m), 8.17 (1H, d), 10.40 (1H, s), 14.23 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 871.6.

EXAMPLE 138

Intermediate 138a:

rac-tert-Butyl 3-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

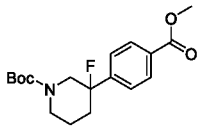


[2277] 1.3 M isopropylmagnesium chloride–lithium chloride complex solution in THF (20.4 mL, 26.50 mmol) was added to a solution of methyl 4-iodobenzoate (6.40 g, 24.42 mmol) in tetrahydrofuran (40 mL) at – 40 °C. The mixture was stirred at this temperature for 1h then a solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (4.4 g, 22.08 mmol) in THF (40 mL) was slowly added. After stirring for 2 h the mixture was warmed to r.t., quenched with saturated aqueous NH_4Cl solution (20 mL), and extracted with ethyl acetate (2 x 75 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 90% EtOAc in hexanes) gave the title compound (5.36 g, 68%) as colorless oil. ^1H NMR ($CDCl_3$): δ 1.48 (9H, s), 1.57 - 1.67 (1H,

m), 1.85 - 2.00 (3H, m), 2.37 - 2.58 (1H, m), 2.80 - 2.93 (1H, m), 3.09 - 3.26 (1H, m), 3.92 (3H, s), 3.94 - 4.04 (1H, m), 4.08 - 4.16 (1H, m), 7.60 (2H, d), 8.04 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 336.1.

Intermediate 138b:

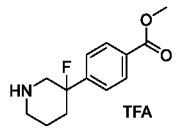
rac-tert-Butyl 3-fluoro-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2278] DAST (2.19 mL, 16.59 mmol) was slowly added to solution of Intermediate 138a (3.71 g, 11.06 mmol) in dichloromethane (50 mL) at –78 °C After stirring for 30 min. the mixture was warmed to r.t., and after stirring for an additional 30 min. the mixture was carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with DCM (2 x 20 mL), then the combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (1.21 g, 32%) as a pale yellow liquid. ^1H NMR ($CDCl_3$): δ 1.48 (9H, br s), 1.61 - 1.71 (1H, m), 1.90 - 2.04 (2H, m), 2.09 - 2.20 (1H, m), 2.75 - 2.93 (1H, m), 2.95 - 3.26 (1H, m), 3.93 (3H, s), 4.08 - 4.41 (2H, m), 7.49 (2H, d), 8.06 (2H, br d); ^{19}F NMR ($CDCl_3$): -162.04 (1F, br s); *m/z* (ES^+) $[M+Na]^+$ = 360.1.

Intermediate 138c:

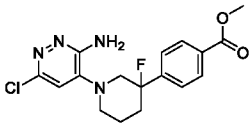
rac-Methyl 4-(3-fluoropiperidin-3-yl)benzoate



[2279] A mixture of Intermediate 138b (1.21 g, 3.58 mmol) and TFA (1.93 mL, 25.08 mmol) in DCM (10 mL) was stirred at r.t. for 45 min. then concentrated under reduced pressure to give the title compound in the form of a trifluoroacetate salt (1.26 g, 100%) as a yellow oil. *m/z* (ES^+) $[M+H]^+$ = 238.2.

Intermediate 138d:

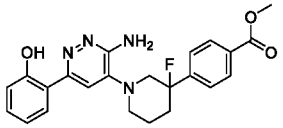
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoate



[2280] A mixture of Intermediate 138c (1.26 g, 3.58 mmol), 4-bromo-6-chloropyridazin-3-amine (0.821 g, 3.94 mmol), and DIPEA (3.13 mL, 17.91 mmol) in DMA (6 mL) was stirred at 120 °C for 14.5h then cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) and washing with ice-cold EtOH gave the title compound (0.650 g, 50%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.66 - 1.81 (1H, m), 2.02 - 2.30 (3H, m), 2.88 - 2.98 (1H, m), 3.32 - 3.39 (1H, m), 3.52 - 3.64 (2H, m), 3.87 (3H, s), 5.95 (2H, s), 7.00 (1H, s), 7.66 (2H, d), 8.01 (2H, d); ^{19}F NMR (DMSO-*d*6): δ -157.32 (1F, s); *m/z* (ES^+) $[M+H]^+$ = 365.1.

Intermediate 138e:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoate

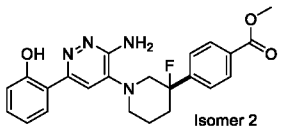


[2281] Prepared in an analogous method to Intermediate 1e starting from Intermediate 138d (0.611 g, 1.67 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.415 g, 59%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.71 - 1.82 (1H, m), 2.03 - 2.13 (1H, m), 2.13 - 2.30 (2H, m), 2.89 - 2.99 (1H, m), 3.34 - 3.46 (1H, m), 3.59 - 3.71 (2H, m), 3.86 (3H, s), 6.10 (2H, s), 6.82 - 6.91 (2H, m), 7.18 - 7.26 (1H, m), 7.57 (1H, s), 7.68 (2H, d), 7.91 (1H, d), 8.02 (2H, d), 14.20 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -157.22 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 423.2.

Intermediate 138f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

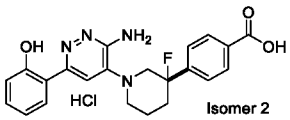


[2282] Intermediate 138e (0.415 g, 0.98 mmol) was purified using the SFC conditions detailed below: Column: Chiralpak IJ, 21 × 250 mm, 5μm; mobile phase: 25% 1:1 MeOH:MeCN with 0.2% NH_4OH in $scCO_2$; Flow rate: 70 mL/min; BPR: 120 bar; Column temperature: 40 °C to afford the title compound Isomer 1 (200 mg) and isomer 2 (205 mg) that eluted second from the column as an off-white solid.

Intermediate 138g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

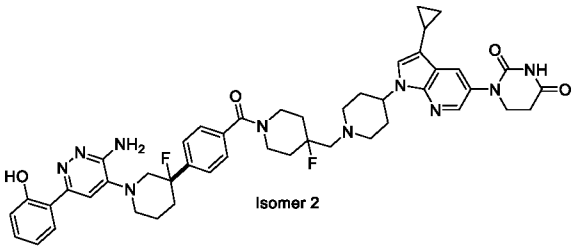


[2283] A mixture of lithium hydroxide hydrate (0.411 g, 9.80 mmol) and Intermediate 138f (0.207 g, 0.49 mmol) in water (2.0 mL), MeOH (2.0 mL) and THF (2.0 mL) was stirred at 60 °C for 24h then cooled to r.t. and concentrated under reduced pressure. The resulting solid was resuspended in water (2 mL) and acidified with 2M aqueous HCl. The resulting solid was collected by filtration, washed with water, and dried to provide the title compound in the form of a hydrochloride salt (0.150 g, 69%) as a pale yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.71 - 1.83 (1H, m), 2.04 - 2.13 (1H, m), 2.15 - 2.39 (2H, m), 3.11 - 3.22 (1H, m), 3.52 - 3.68 (1H, m), 3.74 - 3.99 (2H, m), 6.46 - 6.91 (2H, m), 6.92 - 7.02 (2H, m), 7.28 - 7.38 (1H, m), 7.56 (1H, s), 7.65 (2H, d), 7.68 - 7.77 (1H, m), 8.01 (2H, d) (-OH and -CO_2H not observed); ^{19}F NMR (DMSO-*d*6): δ -156.97 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 409.2.

EXAMPLE 138:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

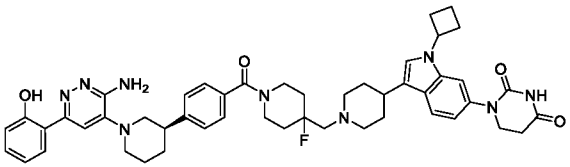
((*absolute configuration not yet confirmed))



[2284] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 138g (18 mg, 0.04 mmol) and Intermediate 20g (30 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 40% MeCN in water with 0.1% FA) gave the title compound (19 mg, 55%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.68 (2H, m), 0.80 - 0.88 (2H, m), 1.62 - 2.14 (11H, m), 2.15 - 2.28 (2H, m), 2.30 - 2.39 (2H, m), 2.55 - 2.66 (2H, m), 2.75 (2H, t), 2.90 - 2.98 (1H, m), 2.99 - 3.06 (2H, m), 3.09 - 3.18 (1H, m), 3.23 - 3.30 (1H, m), 3.34 - 3.42 (2H, m), 3.61 - 3.70 (2H, m), 3.80 (2H, t), 4.19 - 4.34 (1H, m), 4.52 - 4.63 (1H, m), 6.10 (2H, s), 6.84 - 6.91 (2H, m), 7.19 - 7.26 (1H, m), 7.43 (1H, s), 7.48 (2H, d), 7.56 - 7.62 (3H, m), 7.91 - 7.95 (2H, m), 8.15 (1H, s), 10.36 (1H, s), 14.18 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.93 (1F, s), -156.43 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 859.5.

EXAMPLE 139:

(*R*)-1-(3-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

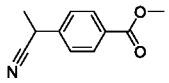


[2285] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 1f (15 mg, 0.04 mmol) and Intermediate 74g (37 mg, 0.04 mmol). Purification by RPC (5-35% MeCN in water with 0.1% HCOOH) gave the title compound (11 mg, 33 %) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 2.00 (14H, m), 2.20 - 2.32 (2H, m), 2.36 - 2.45 (4H, m), 2.53 - 2.61 (2H, m), 2.67 - 2.75 (4H, m), 2.76 - 2.83 (1H, m), 2.94 - 3.02 (2H, m), 3.09 - 3.16 (2H, m), 3.40 - 3.58 (4H, m), 3.77 (2H, t), 4.11 - 4.35 (1H, m), 4.87 (1H, quin), 6.27 (2H, s), 6.82 - 6.89 (2H, m), 6.93 (1H, d), 7.17 - 7.24 (1H, m), 7.34 - 7.39 (4H, m), 7.40 - 7.44 (2H, m), 7.51 (1H, d), 7.54 (1H, s), 7.92 (1H, d), 10.26 (1H, s), 14.22 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.42 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 854.6.

EXAMPLE 140

Intermediate 140a:

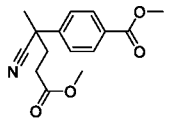
rac-Methyl 4-(1-cyanoethyl)benzoate



[2286] 1 M KHMDS in THF (31.4 mL, 31.4 mmol) was added to a solution of methyl 4-(cyanomethyl)benzoate (5.00 g, 28.54 mmol) in THF (30 mL) at 0 °C. After stirring for 35 minutes iodomethane (1.96 mL, 31.4 mmol) was added and the mixture was warmed to r.t. After stirring for 3.75h the mixture was filtered and the filter cake was washed with hexanes (50 mL). The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 25% EtOAc in hexanes) gave the title compound (2.420 g, 45%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.69 (3H, d), 3.95 (3H, s), 3.96 - 4.01 (1H, m), 7.47 (2H, d), 8.09 (2H, d).

Intermediate 140b:

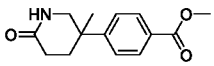
rac-Methyl 4-(2-cyano-5-methoxy-5-oxopentan-2-yl)benzoate



[2287] 40 w/w% benzyltrimethylammonium hydroxide in MeOH (1.15 mL, 2.54 mmol) was added to a mixture of methyl acrylate (2.30 mL, 25.4 mmol) and Intermediate 140a (2.40 g, 12.7 mmol) in 1,4-dioxane (20 mL) then the mixture was warmed to 90 °C. After stirring for 5h the mixture was cooled to r.t. and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (2.98 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.79 (3H, s), 2.17 - 2.26 (1H, m), 2.27 - 2.42 (2H, m), 2.47 - 2.57 (1H, m), 3.65 (3H, s), 3.95 (3H, s), 7.55 (2H, d), 8.09 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 276.1.

Intermediate 140c:

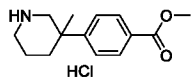
rac-Methyl 4-(3-methyl-6-oxopiperidin-3-yl)benzoate



[2288] A mixture of Intermediate 140b (2.98 g, 10.8 mmol) and platinum(IV) oxide (0.247 g, 1.09 mmol) in acetic acid (20 mL) was stirred under H_2 atmosphere for 24h. The mixture was then purged with N_2 and filtered through Celite. The Celite was washed with DCM (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 20% MeOH in EtOAc) gave the title compound (1.69 g, 63%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, s), 2.01 - 2.10 (1H, m), 2.13 - 2.23 (1H, m), 2.25 - 2.32 (1H, m), 2.40 - 2.48 (1H, m), 3.39 - 3.49 (1H, m), 3.74 - 3.82 (1H, m), 3.94 (3H, s), 6.30 (1H, br s), 7.46 (2H, d), 8.05 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 248.1.

Intermediate 140d:

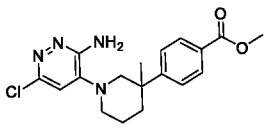
rac-Methyl 4-(3-methylpiperidin-3-yl)benzoate



[2289] 1 M borane-tetrahydrofuran complex solution in THF (20.50 mL, 20.50 mmol) was added to a solution of Intermediate 140c (1.69 g, 6.83 mmol) in THF (20 mL) at r.t. then the mixture was warmed to 50 °C. After stirring for 17.5h the mixture was cooled to r.t., quenched with MeOH (5 mL) and concentrated under reduced pressure. 4 M HCl in 1,4-dioxane (12 mL, 48.0 mmol) was added to the residue. After stirring for 15 min. the mixture was concentrated under reduced pressure. The resulting residue was washed with diethyl ether (50 mL) and dried under reduced pressure to give the title compound in the form of a hydrochloride salt (1.90 g, 103%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 234.1.

Intermediate 140e:

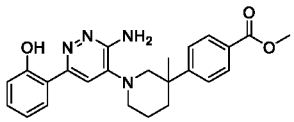
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-3-methylpiperidin-3-yl)benzoate



[2290] A mixture of Intermediate 140d (1.90 g, 7.04 mmol), 4-bromo-6-chloropyridazin-3-amine (1.44 g, 6.91 mmol), and DIPEA (3.69 mL, 21.13 mmol) in DMA (15 mL) was stirred at 120 °C for 24 h then cooled to r.t. Water (100 mL) was added and the resulting solid was collected by filtration, washed with water and dried. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.920 g, 36%) as a tan foam. ^{1}H NMR (DMSO-*d*6): δ 1.35 (3H, s), 1.59 - 1.68 (1H, m), 1.79 - 1.87 (1H, m), 1.88 - 1.99 (2H, m), 2.67 - 2.76 (1H, m), 3.12 - 3.25 (3H, m), 3.85 (3H, s), 5.97 (2H, s), 7.03 (1H, s), 7.59 (2H, d), 7.91 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 361.2.

Intermediate 140f:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoate

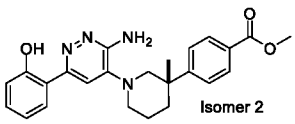


[2291] Prepared in an analogous method to Intermediate 1e starting from Intermediate 140e (0.920 g, 2.55 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.580 g, 59%) as a tan foam. ^{1}H NMR (DMSO-*d*6): δ 1.38 (3H, s), 1.60 - 1.71 (1H, m), 1.78 - 1.87 (1H, m), 1.95 - 2.03 (2H, m), 2.77 - 2.86 (1H, m), 3.13 - 3.22 (1H, m), 3.22 - 3.28 (1H, m), 3.34 - 3.41 (1H, m), 3.83 (3H, s), 6.06 (2H, s), 6.82 - 6.94 (2H, m), 7.20 - 7.27 (1H, m), 7.57 - 7.66 (3H, m), 7.88 - 7.98 (3H, m), 14.20 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 419.3.

Intermediate 140g:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

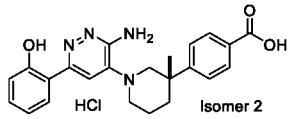


[2292] Intermediate 140f (0.577 g, 1.37 mmol) was dissolved in 1:1 DCM:MeOH (40 mL) and purified using the SFC conditions detailed below: Column: Unichiral AS-5H, 21 × 250 mm, 5μm; mobile phase: 40% IPA with 0.25% diethylamine in $scCO_2$; Flow rate: 70 mL/min to afford the title compound that eluted second from the column (0.250 g, 43% yield, >99% ee) as an off-white solid.

Intermediate 140h:

(R)*-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

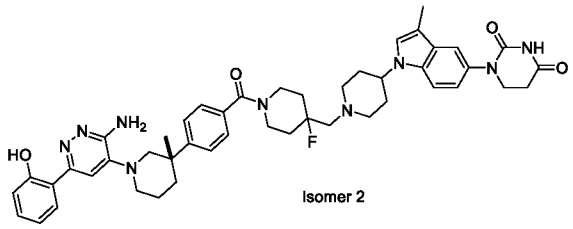


[2293] A mixture of lithium hydroxide hydrate (0.501 g, 11.95 mmol) and Intermediate 140g (0.250 g, 0.60 mmol) in water (2.5 mL) and MeOH (2.0 mL) was stirred at 50 °C for 2h then cooled to r.t. and concentrated under reduced pressure. The resulting solid was resuspended in water (2 mL) and acidified with 2M aqueous HCl. The resulting solid was collected by filtration, washed with water, and dried to provide the title compound in the form of a hydrochloride salt (0.204 g, 77%) as a tan solid. ^{1}H NMR (DMSO-*d*6): δ 1.31 (3H, s), 1.69 - 1.78 (1H, m), 1.81 - 1.89 (1H, m), 1.96 - 2.11 (2H, m), 2.99 - 3.15 (1H, m), 3.57 - 3.68 (1H, m), 6.83 - 7.17 (4H, m), 7.32 - 7.40 (1H, m), 7.44 - 7.59 (4H, m), 7.87 (2H, d) (-OH, -CO_2H and -CH_2- not observed); *m/z* (ES$^+$) $[M+H]^+$ = 405.3.

EXAMPLE 140:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



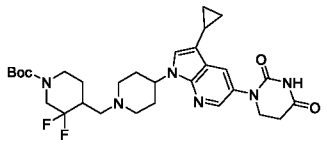
[2294] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 140h (16 mg, 0.04 mmol) and Intermediate 1k (34 mg, 0.04 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% FA) gave the title compound (10 mg, 33%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.41 (3H, s), 1.63 - 2.07 (13H, m), 2.23 (3H, s), 2.36 - 2.45 (2H, m), 2.59 - 2.68 (2H, m), 2.73 (2H, t), 2.77 - 2.85 (1H, m), 2.99 - 3.05 (2H, m), 3.10 - 3.18 (1H, m), 3.25 - 3.30 (2H, m), 3.40 - 3.51 (2H, m), 3.77 (2H, t), 4.19 - 4.32 (2H, m), 6.12 (2H, br s), 6.86 - 6.92 (2H, m), 7.05 (1H, br d), 7.22 -

7.27 (1H, m), 7.31 (1H, s), 7.36 - 7.41 (3H, m), 7.47 (1H, d), 7.55 (2H, br d), 7.60 (1H, s), 7.96 (1H, br d), 10.24 (1H, s), 14.21 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.91 (1F, br s); *m/z* (ES$^+$) $[M+H]^+$ = 828.5.

EXAMPLE 141

Intermediate 141a:

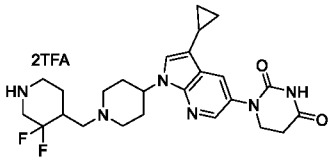
rac-tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate



[2295] Dess-Martin periodinane (304 mg, 0.72 mmol) was added to a stirred solution of *tert*-butyl 3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (120 mg, 0.48 mmol) in DCM (3 mL) at 0 °C. The resulting solution was stirred at r.t. for 1h. The solids were filtered off, washed with DCM. The filtrate was washed with saturated sodium bicarbonate and water. The organic layer was separated, dried over sodium sulfate, filtered and concentrated to give the title compound. The crude material was used for the next step. Sodium triacetoxyborohydride (48.0 mg, 0.23 mmol) was added to a stirred solution of Intermediate 7e (40mg, 0.11 mmol), and aldehyde intermediate (42.3 mg, 0.17 mmol) in DCM (2.0 mL) and isopropanol (0.5 mL) mixture. The resulting solution was stirred at r.t. for 2h. The reaction mixture was diluted with DCM (10 mL) and water (2 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (42.0 mg, 63%) as an orange gum. *m/z* (ES$^+$) $[M+H]^+$ = 587.4.

Intermediate 141b:

rac-1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2296] Prepared in an analogous method to 1i starting from Intermediate 141a (50 mg, 0.09 mmol). The reaction mixture concentrated under reduced pressure to give the title compound (45.0 mg, 74%) as a gum. *m/z* (ES$^+$) $[M+H]^+$ = 487.3.

EXAMPLE 141:

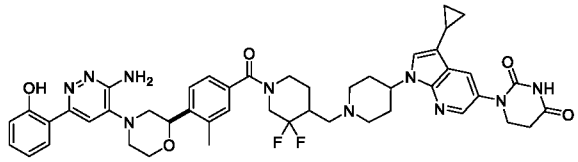
1-(1-(1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

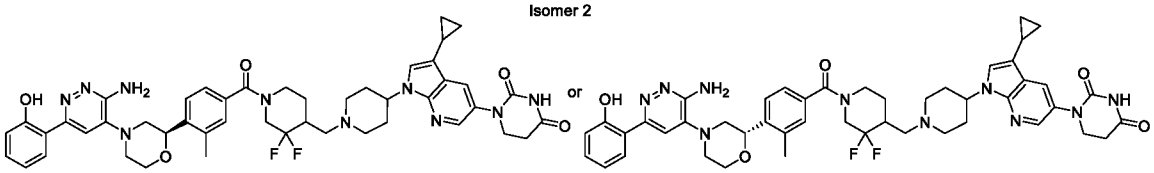
1-(1-(1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 2

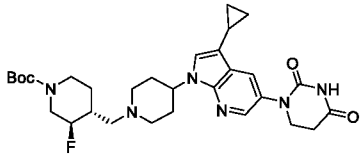


[2297] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15mg, 0.04 mmol) and the mixture Intermediate 141b (34.6 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% formic acid) gave the title compound (10.00 mg, 31%) as a white solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.85 (2H, br d), 1.36 - 1.50 (1H, m), 1.86 (2H, br s), 1.92 (1H, br s), 2.01 (4H, br s), 2.30 (1H, br s), 2.42 (4H, s), 2.56 - 2.67 (1H, m), 2.77 (2H, t), 2.85 (2H, br d), 2.94 (1H, br d), 3.05 (1H, br s), 3.12 - 3.32 (3H, m), 3.41 - 3.48 (1H, m), 3.50 - 3.59 (2H, m), 3.58 - 3.72 (1H, m), 3.82 (2H, t), 4.10 (2H, br d), 4.62 (1H, br s), 4.98 (1H, br d), 6.46 (2H, br s), 6.88 (2H, t), 7.21 - 7.30 (3H, m), 7.40 - 7.50 (1H, m), 7.58 (2H, t), 7.94 - 7.98 (2H, m), 8.17 (1H, d), 10.41 (1H, s), 13.91 - 14.61 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 875.5.

EXAMPLE 142

Intermediate 142a:

tert-Butyl (3*R*,4*R*)-4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

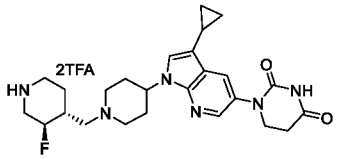


[2298] Dess-Martin periodinane (327 mg, 0.77 mmol) was added to a stirred solution of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (120mg, 0.51 mmol) in DCM (3 mL) at 0 °C. The resulting solution was stirred at r. t. for 1h. The solids were filtered off, washed with DCM. The filtrate was washed with saturated sodium bicarbonate (3.0 mL) and water (3.0 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was used for the next step. sodium triacetoxyborohydride (60.0 mg, 0.28 mmol) was added to a stirred

solution of Intermediate 7e (50mg, 0.14 mmol), and *tert*-butyl (3R,4R)-3-fluoro-4-formylpiperidine-1-carboxylate (49.1 mg, 0.21 mmol) in DCM (2.0 mL) and isopropanol (0.5 mL) mixture. The resulting solution was stirred at r. t. for overnight. The reaction mixture diluted with DCM (5 mL), washed with water (3.0 mL). The organic layer separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave title compound (35.0 mg, 43%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 569.6.

Intermediate 142b:

1-(3-Cyclopropyl-1-(1-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2299] Prepared in an analogous method to 1i starting from Intermediate 142a (35mg, 0.06 mmol). The reaction mixture concentrated to give title compound (35.0 mg, 70%) as a gum. *m/z* (ES^+) $[M+H]^+$ = 469.4.

EXAMPLE 142:

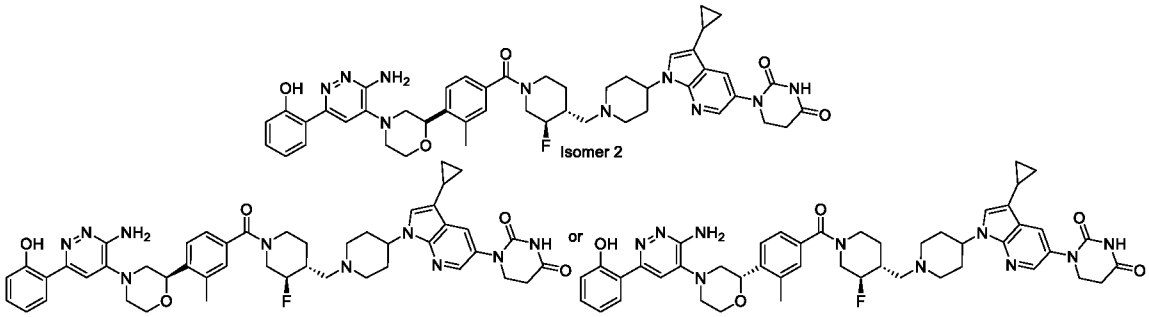
1-(1-(1-(((3*R*,4*R*)-1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*relative configuration not yet confirmed))

1-(1-(1-(((3*R*,4*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((3*R*,4*R*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



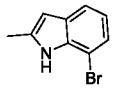
[2300] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15mg, 0.04 mmol) and the mixture Intermediate 142b (34.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0

to 50% MeCN/water with 0.1% formic acid) gave the title compound (12.00 mg, 38%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.88 (2H, br d), 1.29 - 1.52 (1H, m), 1.94 (7H, br s), 2.42 (4H, s), 2.77 (2H, br t), 2.82 - 2.94 (2H, m), 3.01 - 3.31 (5H, m), 3.42 (2H, br s), 3.55 (3H, br s), 3.65 - 3.76 (1H, m), 3.82 (2H, br t), 4.10 (2H, br d), 4.46 - 4.64 (1H, m), 4.68 - 4.91 (1H, m), 4.99 (1H, br d), 6.45 (2H, br s), 6.89 (2H, t), 7.25 (3H, br s), 7.32 - 7.49 (1H, m), 7.54 - 7.65 (2H, m), 7.90 - 8.00 (2H, m), 8.20 (1H, br s), 10.39 (1H, s), 13.94 - 14.65 (1H, m)); *m/z* (ES$^+$) $[M+H]^+$ = 857.5.

EXAMPLE 143

Intermediate 143a:

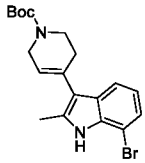
7-Bromo-2-methyl-1*H*-indole



[2301] 1-Bromo-2-nitrobenzene (5 g, 24.75 mmol) was added to prop-1-en-2-ylmagnesium bromide (3.60 g, 24.75 mmol) in THF (1 mL) under nitrogen at –50 °C. The resulting mixture was stirred at –50 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with saturated NH_4Cl (75 mL x 2) and saturated brine (100 mL x 2). The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification by RPC (elution gradient: 3 to 80% MeCN in water (0.1%NH_4HCO_3) gave the title compound (2.150 g, 41%) as a brown oil. ^{1}H NMR (DMSO-*d*6): δ 2.39 (3H, d), 6.15 – 6.29 (1H, m), 6.75 – 6.96 (1H, m), 7.06 – 7.23 (1H, m), 7.39 (1H, d), 11.05 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 209.3.

Intermediate 143b:

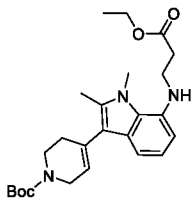
tert-Butyl 4-(7-bromo-2-methyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2302] Intermediate 143a (1.5 g, 7.14 mmol) was added to 1-iodopyrrolidine-2,5-dione (1.606 g, 7.14 mmol) in MeCN (15 mL) under nitrogen. The resulting mixture was stirred at r.t. for 2h. Above crude product was added to 3,6-Dihydro-2H-pyridine-1-*tert*-butoxycarbonyl-4-boronic acid, pinacol ester (2.208 g, 7.14 mmol), potassium phosphate (4.55 g, 21.42 mmol) and pd(dppf)Cl2 (5.83 g, 7.14 mmol) in toluene (15 mL) and water (1.5 mL) under nitrogen. The resulting mixture was stirred at 60 °C for 4h. The reaction mixture was filtered through silica. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with saturated NH_4Cl (100 mL x 3) and saturated brine (50 mL x 3). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. Purification by FSC (elution gradient: 0 to 10% EtOAc in petroleum ether) gave the title compound (1.100 g, 39%) as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 391.5.

Intermediate 143c:

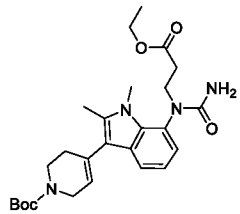
tert-Butyl 4-(7-((3-ethoxy-3-oxopropyl)amino)-1,2-dimethyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2303] Intermediate 143b (500 mg, 1.28 mmol) was added to sodium hydride (30.7 mg, 1.28 mmol) and iodomethane (181 mg, 1.28 mmol) in 1,4-dioxane (3 mL) cooled to 0 °C over a period of 30 min. under nitrogen. The resulting mixture was stirred at r.t. for 2h. Above crude prpduct was added to ethyl 3-aminopropanoate (239 mg, 2.04 mmol), cesium carbonate (1249 mg, 3.83 mmol), GPhos Pd G6 (121 mg, 0.13 mmol) and GPhos (68.6 mg, 0.13 mmol) in 1,4-dioxane (3 mL) under nitrogen. The resulting mixture was stirred at 100 °C for overnight. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with sat. aq. NH_4Cl (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (130 mg, 23%) as a brown oil. *m/z* (ES^+) $[M+H]^+$ = 442.5.

Intermediate 143d:

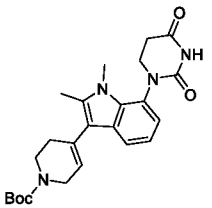
tert-Butyl 4-(7-(1-(3-ethoxy-3-oxopropyl)ureido)-1,2-dimethyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2304] Prepared in an analogous method to 3c starting from Intermediate 143c (230 mg, 0.52 mmol). After work up and removal of the solvent to afford the title compound (230 mg, 91%) as a brown oil. *m/z* (ES^+), $[M+H]^+$ = 485.2.

Intermediate 143e:

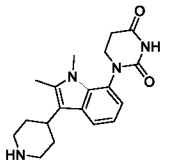
tert-Butyl 4-(7-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1,2-dimethyl-1*H*-indol-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2305] Prepared in an analogous method to 3d starting from Intermediate 143d (230 mg, 0.47 mmol). Purification by RPC (elution gradient: 3 to 30% MeCN in water with 0.1%NH_4HCO_3) gave the title compound (120 mg, 58%) as a yellow oil. *m/z* (ES^+) $[M+H]^+$ = 439.2.

Intermediate 143f:

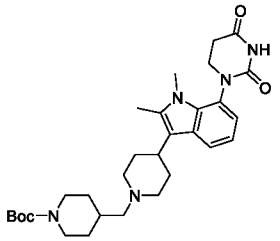
1-(1,2-Dimethyl-3-(piperidin-4-yl)-1*H*-indol-7-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2306] Prepared in an analogous method to 6e starting from Intermediate 143e (120 mg, 0.27 mmol). The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 40%, acetonitrile in water with 0.1% formic acid) gave the title compound (61.0 mg, 50%) as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 341.3.

Intermediate 143g:

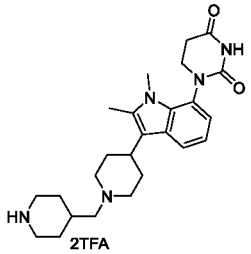
tert-Butyl 4-((4-(7-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1,2-dimethyl-1*H*-indol-3-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2307] Sodium triacetoxyborohydride (49.6 mg, 0.23 mmol) was added to a stirred solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (37.4 mg, 0.18 mmol), and Intermediate 143f (60 mg, 0.12 mmol) in DCM (2.0 mL) and isopropanol (0.5 mL) mixture. The resulting solution was stirred at r.t. for 2h. The reaction mixture was diluted with DCM (10 mL) and water (2 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in EtOAc) gave title compound (48.0 mg, 76%) as an orange gum. *m/z* (ES^+) $[M+H]^+$ = 538.4.

Intermediate 143h:

1-(1,2-Dimethyl-3-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-7-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2308] Prepared in an analogous method to 1i starting from Intermediate 143g (40mg, 0.07 mmol). The solvent was removed under reduced pressure to give title compound (40.0 mg, 81%) as an orange gum. *m/z* (ES^+) $[M+H]^+$ = 438.3.

EXAMPLE 143:

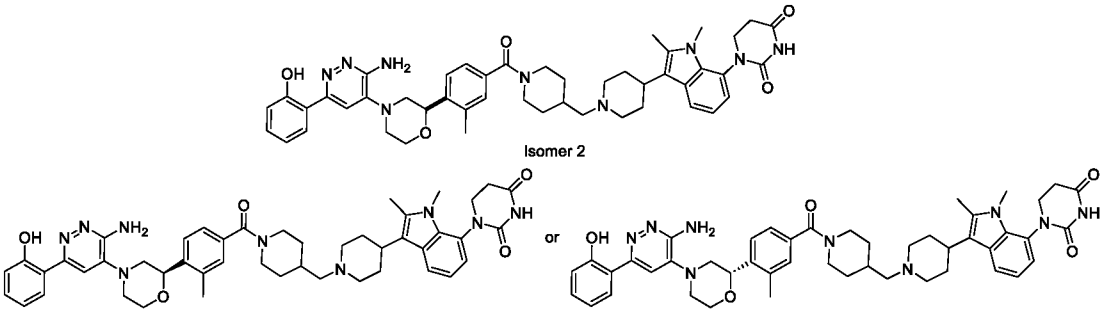
(*R**)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1*H*-indol-7-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1*H*-indol-7-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1*H*-indol-7-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

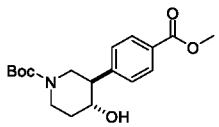


[2309] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (15mg, 0.04 mmol) and Intermediate 143h (34.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% formic acid) gave the title compound (12.00 mg, 38%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.07 - 1.22 (2H, m), 1.59 - 1.77 (3H, m), 1.84 - 1.98 (2H, m), 2.14 - 2.26 (3H, m), 2.34 (4H, s), 2.42 (3H, s), 2.76 (1H, s), 2.80 - 2.92 (5H, m), 3.04 - 3.16 (3H, m), 3.36 - 3.44 (2H, m), 3.54 (2H, br t), 3.62 - 3.71 (5H, m), 3.89 (1H, ddd), 4.10 (2H, br d), 4.39 - 4.61 (1H, m), 4.98 (1H, br d), 6.43 (2H, s), 6.83 - 6.91 (2H, m), 6.97 (2H, d), 7.19 - 7.29 (3H, m), 7.53 - 7.63 (3H, m), 7.95 (1H, d), 10.44 (1H, s), 13.86 - 14.50 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ =826.6.

EXAMPLE 144

Intermediate 144a:

rac-tert-Butyl (3*R*,4*R*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

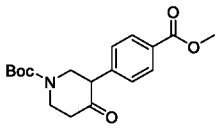


[2310] 1 M Borane-tetrahydrofuran complex in THF (18.5 mL, 18.5 mmol) was added slowly to a solution of Intermediate 109a (5.34 g, 16.82 mmol) in THF (45 mL) at 0 °C. The mixture was warmed to r.t. and stirred at this temperature for 14h prior to cooling to 0 °C. 1 M aq. NaOH solution (3.36 mL, 3.36 mmol) was added and after stirring for 10 minutes 35 w/w% H_2O_2 in water (3.44 mL, 33.65 mmol) was added. The mixture was warmed to r.t., stirred for 1.5h, then quenched with saturated aqueous $Na_2S_2O_3$

solution (5 mL) and diluted with EtOAc (200 mL) and water (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and brine (2 x 50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 70% EtOAc in hexanes) gave the title (1.73 g, 31%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.49 (9H, s), 1.57 - 1.65 (2H, m), 2.07 - 2.11 (1H, m), 2.64 - 2.74 (1H, m), 2.75 - 2.96 (2H, m), 3.88 - 3.98 (4H, m), 4.11 - 4.32 (2H, m), 7.37 (2H, d), 8.05 (2H, d); *m/z* (ES^+) $[M+Na]^+$ = 358.1.

Intermediate 144b:

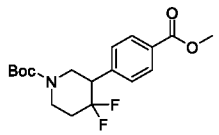
rac-tert-Butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate



[2311] Dess-Martin periodinane (2.40 g, 5.65 mmol) was added to a solution of Intermediate 144a (1.73 g, 5.14 mmol) in DCM (50 mL) at 0 °C, then the mixture was warmed to r.t. After stirring for 40 minutes the mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (5 mL), then diluted with DCM (30 mL). The organic layer was separated, washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.50 g, 88%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.53 (9H, s), 2.52 - 2.68 (2H, m), 3.47 - 3.68 (2H, m), 3.73 - 3.82 (1H, m), 3.93 (3H, s), 4.18 - 4.25 (1H, m), 4.25 - 4.42 (1H, m), 7.29 (2H, br d), 8.04 (2H, d); *m/z* (ES^+) $[M+Na]^+$ = 356.1.

Intermediate 144c:

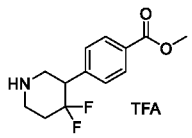
rac-tert-Butyl 4,4-difluoro-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2312] DAST (1.19 mL, 8.99 mmol) was slowly added to solution of Intermediate 144b (1.50 g, 4.51 mmol) in DCM (25 mL) at 0 °C then the mixture was warmed to r.t. After stirring 2h minutes the mixture was carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with DCM (50 mL), then the organic layer was washed with water (2 x 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.893 g, 56%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.48 (9H, s), 1.90 - 2.08 (1H, m), 2.12 - 2.18 (1H, m), 3.05 - 3.21 (2H, m), 3.22 - 3.42 (1H, m), 3.93 (3H, s), 4.09 - 4.41 (2H, m), 7.40 (2H, d), 8.03 (2H, br d); ^{19}F NMR ($CDCl_3$): δ -114.55 - -113.06 (1F, m), -95.69 (1F, br d); *m/z* (ES^+) $[M–tBu+2H]^+$ = 300.1.

Intermediate 144d:

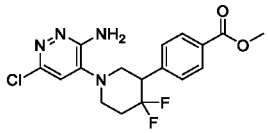
rac-Methyl 4-(4,4-difluoropiperidin-3-yl)benzoate



[2313] A mixture of Intermediate 144c (0.890 g, 2.50 mmol) and TFA (0.960 mL, 12.5 mmol) in DCM (4 mL) was stirred at r.t. for 80 minutes then concentrated under reduced pressure to give the title compound in the form of a trifluoroacetate salt (0.924 g, 100%) as a yellow oil. *m/z* (ES^+) $[M+H]^+$ = 256.8.

Intermediate 144e:

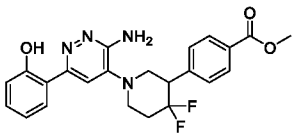
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoate



[2314] A mixture of Intermediate 144d (0.924 g, 2.50 mmol), 4-bromo-6-chloropyridazin-3-amine (0.548 g, 2.63 mmol), and DIPEA (2.19 mL, 12.5 mmol) in DMA (4 mL) was stirred at 120 °C for 15.5h then cooled to r.t. Water (30 mL) was added and the resulting solid was collected by filtration, washed with water and dried. The solid was suspended in EtOH (5 mL) and the resulting mixture was cooled to -20 °C for 1h. The solid was collected by filtration, washed with cold EtOH, and dried to give the title compound (0.457 g, 48%) as a tan solid. ^{1}H NMR (DMSO-*d*6): δ 2.21 - 2.31 (1H, m), 2.36 - 2.49 (1H, m), 2.91 - 3.00 (1H, m), 3.21 - 3.29 (1H, m), 3.48 - 3.58 (2H, m), 3.74 - 3.84 (1H, m), 3.86 (3H, s), 6.33 (2H, s), 7.11 (1H, s), 7.53 (2H, d), 7.96 (2H, d); ^{19}F NMR (DMSO-*d*6): δ -111.56 (1F, br d), -95.28 (1F, br d); *m/z* (ES^+) $[M+H]^+$ = 383.2.

Intermediate 144f:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoate



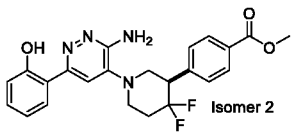
[2315] Prepared in an analogous method to Intermediate 1e starting from Intermediate 144e (0.457 g, 1.19 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.330 g, 63%) as a tan foam. ^{1}H NMR (DMSO-*d*6): δ 2.23 - 2.32 (1H, m), 2.51 - 2.59 (1H, m), 3.01 - 3.11 (1H, m), 3.33 - 3.42 (1H, m), 3.53 - 3.65 (2H, m), 3.75 - 3.89 (4H, m), 6.46 (2H, s), 6.84 - 6.91 (2H, m), 7.20 - 7.27 (1H, m), 7.55 (2H, d), 7.69 (1H, s), 7.92 - 7.99 (3H, m), 14.13 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -111.43 (1F, br d), -95.22 (1F, br d); *m/z* (ES^+) $[M+H]^+$ = 441.3.

Intermediate 144g:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoate

(Isomer 2)

((*absolute configuration not yet confirmed))

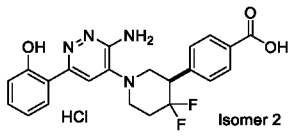


[2316] Intermediate 144f (0.330 g, 0.75 mmol) was dissolved purified using the SFC conditions detailed below: Column: Chiralpak IJ, 30 × 250 mm, 5μm; mobile phase: 15% 1:1 MeOH:MeCN in $scCO_2$; Flow rate: 70 mL/min; BPR: 120 bar; Column temperature: 40°C to afford the title compound that eluted second from the column (0.124 g, 37% yield, 90% ee) as an off-white solid.

Intermediate 144h:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

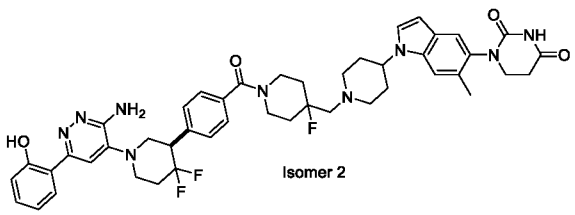


[2317] A mixture of lithium hydroxide hydrate (0.236 g, 5.63 mmol) and Intermediate 144g (0.124 g, 0.28 mmol) in water (1.0 mL) and MeOH (1.5 mL) was stirred at 50 °C for 1.75h then cooled to r.t. and concentrated under reduced pressure. The resulting solid was resuspended in water (2 mL) and acidified with 2M aqueous HCl. The resulting solid was collected by filtration, washed with water, and dried to provide the title compound in the form of a hydrochloride salt (0.092 g, 71%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 2.25 - 2.36 (1H, m), 3.06 - 3.20 (1H, m), 3.41 - 3.51 (2H, m), 3.68 - 3.89 (3H, m), 6.87 - 7.18 (4H, m), 7.29 - 7.40 (1H, m), 7.53 (2H, d), 7.70 (1H, s), 7.74 - 7.83 (1H, m), 7.96 (2H, d), (-OH and -CO_2H and not observed); ^{19}F NMR (DMSO-*d*6): δ -111.68 (1F, br d), -95.23 (1F, br d); *m/z* (ES^+) $[M+H]^+$ = 427.3.

EXAMPLE 144:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



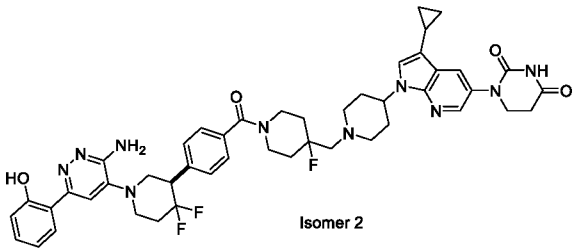
[2318] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 144h (13 mg, 0.03 mmol) and Intermediate 24b (24 mg, 0.03 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% FA) gave the title compound (13 mg, 54%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.65 - 1.81 (2H, m), 1.83 - 2.06 (6H, m), 2.24 - 2.34 (4H, m), 2.38 - 2.46 (2H, m),

2.59 - 2.67 (2H, m), 2.68 - 2.80 (2H, m), 3.00 - 3.10 (3H, m), 3.11 - 3.20 (1H, m), 3.37 - 3.43 (3H, m), 3.52 - 3.68 (4H, m), 3.72 - 3.84 (2H, m), 4.18 - 4.37 (2H, m), 6.40 (1H, d), 6.48 (2H, s), 6.88 - 6.93 (2H, m), 7.22 - 7.28 (1H, m), 7.40 - 7.45 (4H, m), 7.46 - 7.51 (3H, m), 7.71 (1H, s), 7.95 - 8.02 (1H, m), 10.25 (1H, s), 14.16 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -158.00 (1F, br s), -111.55 (1F, br d), -95.24 (1F, br d); *m/z* (ES$^+$) $[M+H]^+$ = 850.5.

EXAMPLE 145:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

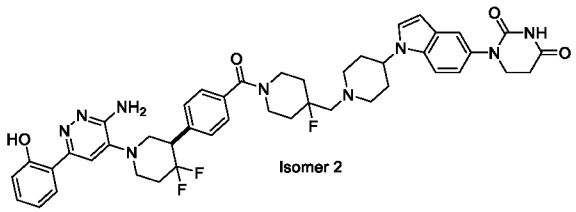


[2319] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 144h (18 mg, 0.04 mmol) and Intermediate 20g (28 mg, 0.04 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% FA) gave the title compound (21 mg, 62%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.69 (2H, m), 0.79 - 0.87 (2H, m), 1.62 - 2.11 (9H, m), 2.23 - 2.39 (3H, m), 2.56 - 2.66 (2H, m), 2.75 (2H, t), 2.99 - 3.16 (4H, m), 3.36 - 3.51 (4H, m), 3.55 - 3.66 (2H, m), 3.70 - 3.83 (3H, m), 4.14 - 4.35 (1H, m), 4.53 - 4.63 (1H, m), 6.46 (2H, s), 6.85 - 6.91 (2H, m), 7.20 - 7.27 (1H, m), 7.39 - 7.44 (3H, m), 7.46 - 7.50 (2H, m), 7.69 (1H, s), 7.93 (1H, s), 7.96 (1H, br d), 8.15 (1H, s), 10.36 (1H, s), 14.14 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.89 (1F, br s), -111.54 (1F, br d), -95.24 (1F, br d); *m/z* (ES$^+$) $[M+H]^+$ = 877.5.

EXAMPLE 146:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



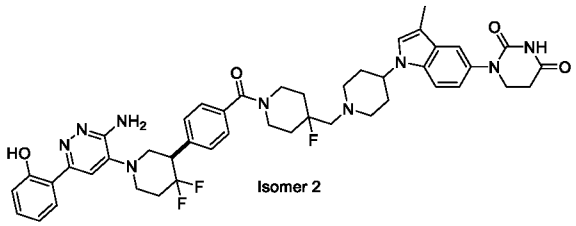
[2320] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 144h (18 mg, 0.04 mmol) and Intermediate 29a (32 mg, 0.04 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN

in water with 0.1% FA) gave the title compound (18 mg, 55%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.65 - 1.80 (2H, m), 1.83 - 2.06 (6H, m), 2.25 - 2.35 (1H, m), 2.38 - 2.46 (2H, m), 2.60 - 2.68 (2H, m), 2.73 (2H, t), 2.99 - 3.09 (3H, m), 3.11 - 3.19 (1H, m), 3.25 - 3.33 (1H, m), 3.37 - 3.43 (2H, m), 3.46 - 3.52 (1H, m), 3.57 - 3.68 (2H, m), 3.72 - 3.84 (3H, m), 4.19 - 4.40 (2H, m), 6.46 (1H, d), 6.48 (2H, s), 6.87 - 6.94 (2H, m), 7.05 - 7.10 (1H, m), 7.22 - 7.27 (1H, m), 7.41 - 7.58 (7H, m), 7.71 (1H, s), 7.98 (1H, dd), 10.25 (1H, s), 14.15 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.99 (1F, br s), -111.54 (1F, br d), -95.24 (1F, br d); *m/z* (ES$^+$) $[M+H]^+$ = 836.5.

EXAMPLE 147:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

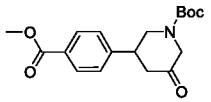


[2321] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 144h (18 mg, 0.04 mmol) and Intermediate 1k (37 mg, 0.04 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% FA) gave the title compound (22 mg, 67%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.79 (2H, m), 1.81 - 2.02 (6H, m), 2.21 (3H, s), 2.24 - 2.32 (1H, m), 2.34 - 2.42 (2H, m), 2.51 - 2.66 (3H, m), 2.71 (2H, t), 2.95 - 3.15 (4H, m), 3.24 - 3.30 (1H, m), 3.37 - 3.41 (1H, m), 3.45 - 3.53 (1H, m), 3.54 - 3.66 (2H, m), 3.70 - 3.82 (3H, m), 4.16 - 4.38 (2H, m), 6.49 (2H, s), 6.86 - 6.91 (2H, m), 7.01 - 7.05 (1H, m), 7.20 - 7.26 (1H, m), 7.30 (1H, s), 7.38 (1H, s), 7.40 - 7.49 (5H, m), 7.70 (1H, s), 7.97 (1H, d), 10.25 (1H, s), 14.16 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -158.07 (1F, br s), -111.60 (1F, br d), -95.25 (1F, br d); *m/z* (ES$^+$) $[M+H]^+$ = 850.5.

EXAMPLE 148

Intermediate 148a:

rac-*tert*-Butyl 3-(4-(methoxycarbonyl)phenyl)-5-oxopiperidine-1-carboxylate

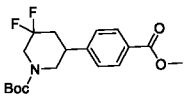


[2322] To Intermediate 61c (900 mg, 2.68 mmol) in CH_2Cl_2 (30 ml) was added Dess-Martin periodinane (1366 mg, 3.22 mmol) portion wise. The reaction was stirred at r.t. for 1 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and sat. aq. $Na_2S_2O_3$. Organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 15 to 50% EtOAc in hexanes) to obtain the title compound (612 mg, 68%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 1.34 - 1.51

(9H, m), 2.60 - 2.74 (1H, m), 2.74 - 2.82 (1H, m), 3.29 - 3.59 (2H, m), 3.68 - 3.89 (3H, m), 3.90 - 4.25 (3H, m), 7.32 (2H, br d), 8.00 (2H, d); *m/z* (ES^-) $[M–H]^-$ = 332.1.

Intermediate 148b:

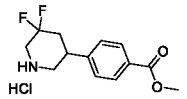
rac-tert-Butyl 3,3-difluoro-5-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2323] Intermediate 148a (0.49 g, 1.47 mmol) in CH_2Cl_2 (15 ml) was added DAST (0.388 ml, 2.94 mmol) dropwise. The reaction was stirred at r.t. for 30 min. The reaction was quenched by addition of sat. aq. $NaHCO_3$. Organic phase was separated and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (410 mg, 78%) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.33 - 1.49 (9H, m), 1.98 - 2.17 (1H, m), 2.35 - 2.56 (1H, m), 2.62 - 2.92 (1H, m), 2.92 - 3.17 (2H, m), 3.82 - 3.94 (3H, m), 4.11 - 4.65 (2H, m), 7.23 - 7.48 (2H, m), 7.74 - 8.29 (2H, m); *m/z* (ES^+) $[M–t\text{Bu}+2H]^+$ = 300.1.

Intermediate 148c:

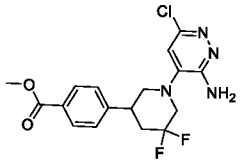
rac-Methyl 4-(5,5-difluoropiperidin-3-yl)benzoate



[2324] HCl, 4 M in 1,4-dioxane (4 mL) was added to Intermediate 148b (460 mg, 1.29 mmol). The reaction was stirred at r.t. for 2 h. Solvent was removed to obtain the title compound as an off-white solid in the form of HCl salt. Quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 256.1.

Intermediate 148d:

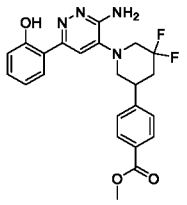
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoate



[2325] Prepared in an analogous method to Intermediate 1d starting from Intermediate 148c (376 mg, 1.29 mmol). Purification by FSC (elution gradient: 10 to 30% EtOAc in hexanes, then 0 to 10% methanol in EtOAc) gave the title compound (181 mg, 37%) as a brown solid. ^1H NMR (CD_2Cl_2): δ 2.11 - 2.26 (1H, m), 2.52 - 2.62 (1H, m), 2.82 - 2.98 (2H, m), 3.31 - 3.42 (1H, m), 3.50 - 3.57 (1H, m), 3.89 - 3.92 (3H, m), 3.92 - 3.99 (1H, m), 4.85 (2H, br s), 6.81 (1H, s), 7.36 (2H, d), 8.03 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 383.1.

Intermediate 148e:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoate

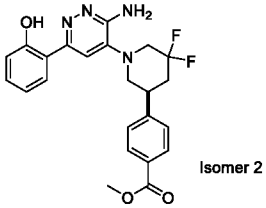


[2326] Prepared in an analogous method to Intermediate 1e starting from Intermediate 148d (181 mg, 0.47 mmol). Purification by FSC (elution gradient: 10 to 40% EtOAc in hexanes, then10% MeOH in EtOAc) gave the title compound (150 mg, 72%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 2.15 - 2.29 (m, 1H), 2.57 - 2.63 (m, 1H), 2.90 - 3.11 (m, 2H), 3.41 (br t, *J* = 12.1 Hz, 1H), 3.62 (br d, *J* = 11.6 Hz, 1H), 3.90 (s, 3H), 4.00 (br t, *J* = 10.8 Hz, 1H), 5.18 (br s, 2H), 6.82 - 6.96 (m, 1H), 6.98 (br d, *J* = 8.1 Hz, 1H), 7.21 - 7.33 (m, 1H), 7.37 - 7.42 (m, 3H), 7.59 (br d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 2H), OH (not observed); *m/z* (ES^+) $[M+H]^+$ = 441.2.

Intermediate 148f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

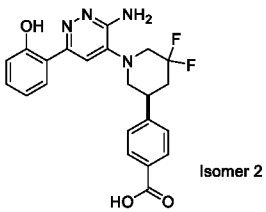


[2327] Intermediate 148e (130 mg, 0.34 mmol) was purified by chiral SFC (Column: IJ 4.6X150mm 5μm, 40% MeOH with 0.2% NH_4OH in $scCO_2$, Flow rate: 70 mL/min, Colum temperature: 40 °C) to give the title compound that eluted second from the column (45 mg, 69% yield, >99% ee) as a light brown solid.

Intermediate 148g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

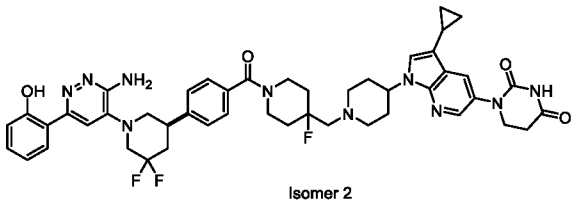


[2328] Prepared in an analogous method to Intermediate 1f starting from Intermediate 148f (45 mg, 0.10 mmol). Filtration gave the title compound (41.0 mg, 87%) as a white solid in the form of HCl salt. *m/z* (ES^+) $[M+H]^+$ = 427.2

EXAMPLE 148:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



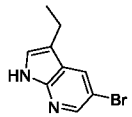
Isomer 2

[2329] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 148g (14 mg, 0.03 mmol) and Intermediate 20g (28 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (14 mg, 53%) as a white solid. 1H NMR (DMSO-*d*6): δ 0.61 - 0.67 (2H, m), 0.77 - 0.91 (2H, m), 1.67 - 1.78 (2H, m), 1.79 - 1.86 (2H, m), 1.87 - 1.97 (2H, m), 2.00 - 2.10 (2H, m), 2.29 - 2.36 (2H, m), 2.36 - 2.44 (2H, m), 2.55 - 2.65 (2H, m), 2.71 - 2.77 (2H, m), 2.78 - 2.84 (1H, m), 2.98 - 3.06 (2H, m), 3.05 - 3.18 (2H, m), 3.37 - 3.50 (4H, m), 3.56 - 3.65 (1H, m), 3.66 - 3.74 (1H, m), 3.78 - 3.84 (2H, m), 4.15 - 4.34 (1H, m), 4.52 - 4.62 (1H, m), 6.25 - 6.37 (2H, m), 6.85 - 6.92 (2H, m), 7.17 - 7.28 (1H, m), 7.36 - 7.47 (3H, m), 7.47 - 7.53 (2H, m), 7.61 - 7.67 (1H, m), 7.91 - 7.96 (1H, m), 7.96 - 8.01 (1H, m), 8.11 - 8.18 (1H, m), 10.36 - 10.43 (1H, m), 14.00 - 14.22 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 877.0.

EXAMPLE 149

Intermediate 149a:

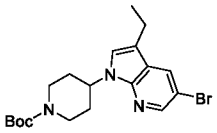
5-Bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine



[2330] Triethylsilane (11.67 g, 100 mmol) was added to a solution of 1-(5-bromo-1*H*-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-one (2.00 g, 8.37 mmol) in TFA (15 mL). The resulting mixture was stirred at 60 °C for 2 days. The mixture was concentrated under reduced pressure. The residue was diluted with DCM (200 mL), washed sequentially with sat. aq. $NaHCO_3$ (2 x 150 mL) and brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound (1.40 g, 74%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.19-1.28 (3H, m), 2.60-2.74 (2H, m), 7.31 (1H, d), 8.17 (1H, d), 8.23 (1H, d), 11.55 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 225.0.

Intermediate 149b:

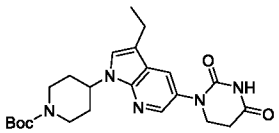
tert-Butyl 4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2331] *tert*-Butyl 4-hydroxypiperidine-1-carboxylate (2.50 g, 12.4 mmol) was added to 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (3.00 g, 12.4 mmol) and Intermediate 149a (1.40 g, 6.22 mmol) in *m*-xylene (20 mL) under nitrogen. The resulting mixture was stirred at 110 °C for 16 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.90 g, 35%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.18-1.28 (3H, m), 1.43 (9H, d), 1.83-1.99 (4H, m), 2.62-2.70 (2H, m), 2.81 (2H, s), 4.12 (2H, s), 4.75-4.84 (1H, m), 7.56 (1H, d), 8.18-8.21 (1H, m), 8.27 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 408.1.

Intermediate 149c:

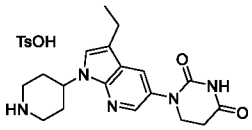
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2332] Prepared in an analogous manner to Intermediate 8b starting from Intermediate 149b (0.90 g, 2.20 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.60 g, 61%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.23-1.28 (3H, m), 1.44 (9H, s), 1.83-1.98 (4H, m), 2.65-2.72 (2H, m), 2.74-2.80 (2H, m), 2.96 (2H, m), 3.78-3.84 (2H, m), 4.13 (2H, s), 4.78-4.91 (1H, m), 7.53 (1H, s), 7.93 (1H, d), 8.18 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 442.2.

Intermediate 149d:

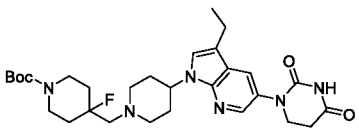
1-(3-Ethyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2333] Prepared in an analogous manner to Intermediate 6e starting from Intermediate 149c (600 mg, 1.36 mmol). The resulting mixture was filtered. The solids were dried *in vacuo* to give the title compound (400 mg, 57%) as a white solid and *p*-toluenesulfonic acid salt. *m/z* (ES$^+$) $[M+H]^+$ = 342.2.

Intermediate 149e:

tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

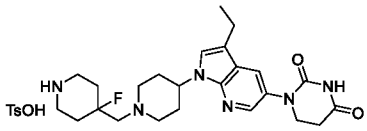


[2334] Prepared in an analogous manner to Intermediate 6g starting from Intermediate 6f (770 mg, 2.11 mmol) and Intermediate 149d (400 mg, 1.17 mmol). Purification by RPC (elution gradient: 5 to 100%

MeCN in water with 0.1% NH_4HCO_3) gave the title compound (400 mg, 61%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 – 1.30 (3H, m), 1.41 (9H, s), 1.54 – 1.66 (2H, m), 1.83 (4H, d), 2.01 – 2.07 (1H, m), 2.10 (1H, d), 2.32 – 2.39 (2H, m), 2.59 (2H, d), 2.66 – 2.72 (2H, m), 2.74 – 2.79 (2H, m), 3.04 (4H, d), 3.74 (2H, d), 3.79 – 2.83 (2H, m), 4.55 – 4.64 (1H, m), 7.51 (1H, s), 7.92 (1H, d), 8.17 (1H, d), 10.38 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 557.3.

Intermediate 149f:

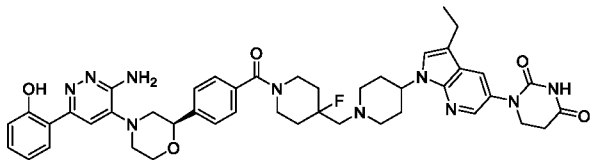
1-(3-Ethyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2335] Prepared in an analogous manner to Intermediate 6e using Intermediate 149e (400 mg, 0.72 mmol) to give the title compound (320 mg, 70%) as a white solid and *p*-toluenesulfonic acid salt. *m/z* (ES$^+$) $[M+H]^+$ = 457.1.

EXAMPLE 149:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2336] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 16i (40 mg, 0.10 mmol) and Intermediate 149f (47 mg, 0.10 mmol). Purification by RPC (elution gradient: 16 to 36% MeCN in water with 0.08% NH_4HCO_3 and 0.1%NH_4OH) gave the title compound (11.3 mg, 13%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.18 – 1.32 (3H, m), 1.60 – 2.00 (6H, m), 2.01 – 2.15 (2H, m), 2.28 – 2.41 (2H, m), 2.60 (1H, s), 2.62 – 2.70 (3H, m), 2.73 – 2.84 (3H, m), 2.86 – 2.98 (1H, m), 3.05 (2H, d), 3.08 – 3.23 (2H, m), 3.49 (2H, d), 3.53 – 3.62 (1H, m), 3.75 – 3.90 (2H, m), 4.01 – 4.12 (2H, m), 4.13 – 4.39 (1H, m), 4.55 – 4.70 (1H, m), 4.72 – 4.95 (1H, m), 6.50 (2H, s), 6.70 – 6.98 (2H, m), 7.13 – 7.32 (1H, m), 7.40 (2H, d), 7.46 – 7.68 (4H, m), 7.80 – 8.02 (2H ,m), 8.17 (1H, d), 10.40 (1H, s), O*H* not observed; *m/z* (ES$^+$) $[M+H]^+$ = 831.6.

EXAMPLE 150:

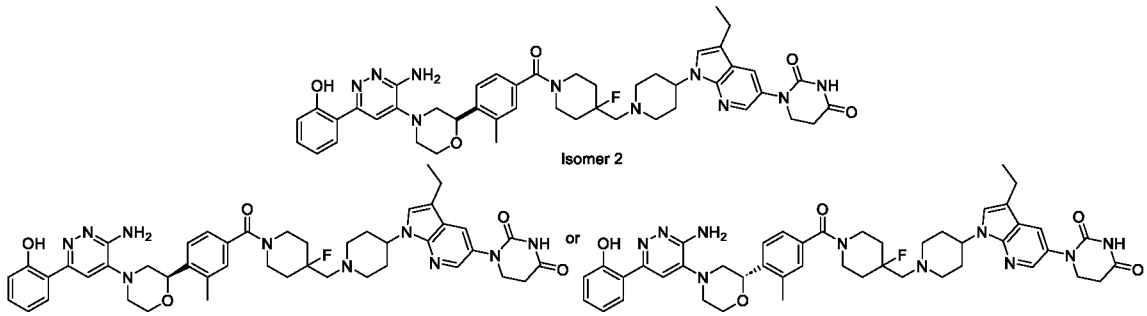
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



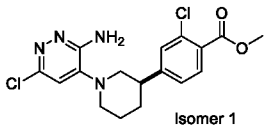
[2337] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 55j (50 mg, 0.12 mmol) and Intermediate 149f (77 mg, 0.12 mmol) in DMF (4mL). Purification by preparative HPLC (elution gradient: 40 to 68% MeCN in water with 0.08% NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (42.2 mg, 40%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, t), 1.59 – 1.85 (2H, m), 1.86 – 1.91 (2H, m), 1.98 (1H, s), 2.02 – 2.17 (2H, m), 2.27 – 2.39 (2H, m), 2.45 (3H, s), 2.54 – 2.58 (1H, m), 2.60 (1H, s), 2.62 – 2.73 (3H, m), 2.74 –2.81 (2H, m), 2.82 – 2.95 (2H, m), 3.05 (2H, d), 3.10 – 3.30 (2H, m), 3.45 – 3.61 (3H, m), 3.81 (2H, t), 4.05 – 4.20 (2H, m), 4.30 (1H, s), 4.49 – 4.75 (1H, m), 4.89 – 5.12 (1H, m), 6.46 (2H, s), 6.72 – 7.02 (2H, m), 7.09 – 7.39 (3H, m), 7.41 – 7.55 (1H, m), 7.56 – 7.65 (2H, m), 7.75 – 8.05 (2H, m), 8.18 (1H, d), 10.40 (1H, s), 14.22 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -157.9; *m/z* (ES^+) $[M+H]^+$ = 845.4.

EXAMPLE 151

Intermediate 151a:

Methyl (*R**)-4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

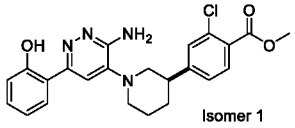


[2338] Intermediate 45d (3.00 g, 7.87 mmol) was dissolved in MeOH–DCM (16:1). The resulting solution was purified using the following SFC conditions: Column: CHIRAL ART Cellulose-SB 3*25 cm , 5 μm; mobile phase: 50% [IPA:MeCN 1:1] in CO_2; Flow rate: 90 mL/min; BPR: 100 bar; Column temperature: 35 °C to afford the title compound that eluted first from the column (900 mg, 30%, 100% ee) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 381.2.

Intermediate 151b:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

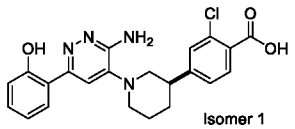


[2339] $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (64 mg, 0.08 mmol) was added to a mixture of K_2CO_3 (181 mg, 1.31 mmol), (2-hydroxyphenyl)boronic acid (87 mg, 0.63 mmol) and Intermediate 151a (200 mg, 0.52 mmol) in THF–H_2O (10:1, 1 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 3 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (150 mg, 65%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.68 (1H, d), 1.85–2.04 (3H, m), 2.66–2.84 (2H, m), 3.19 (1H, s), 3.54 (2H, d), 3.86 (3H, s), 6.32 (2H, s), 6.89 (2H, d), 7.24 (1H, t), 7.46 (1H, d), 7.54–7.63 (2H, m), 7.80 (1H, d), 7.94 (1H, d), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ =438.8.

Intermediate 151c:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

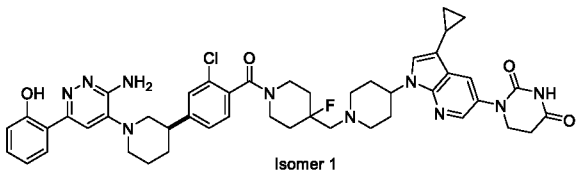


[2340] Prepared in an analogous manner to Intermediate 1f starting from Intermediate 151b (80 mg, 0.18 mmol) to give the title compound (70 mg, 90%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.6–1.72 (1H, m), 1.84–2.05 (3H, m), 2.65–2.89 (2H, m), 3.15 (1H, d), 3.54 (2H, d), 6.32 (2H, s), 6.89 (2H, d), 7.24 (1H, t), 7.39–7.45 (1H, m), 7.53–7.58 (2H, m), 7.78 (1H, d), 7.89–7.97 (1H, m), 13.65 (1H, s), one exchangeable proton not observed; *m/z* (ES^+) $[M+H]^+$ =424.90.

EXAMPLE 151:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



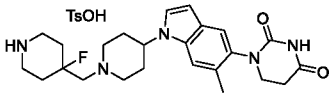
[2341] Prepared in an analogous manner to EXAMPLE 1 using Intermediate 151c (100 mg, 0.24 mmol), Intermediate 20g (110 mg, 0.24 mmol) and PyBOP (122 mg, 0.24 mmol). After stirring at r.t. for 1 hour, the mixture was poured into sat. aq. Na_2CO_3 (25 mL) and extracted with DCM–IPA (3:1, 3 x 25 mL).

The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: MeCN in water with 0.1% formic acid) gave the title compound (49 mg, 23%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62–0.7 (2H, m), 0.81–0.9 (2H, m), 1.70 (3H, d), 1.81 (3H, d), 1.88–1.97 (3H, m), 1.97–2.09 (5H, m), 2.37 (2H, d), 2.62 (2H, d), 2.7–2.87 (3H, m), 3.03 (2H, s), 3.12–3.26 (4H, m), 3.55 (2H, d), 3.82 (2H, t), 4.31 (1H, d), 4.59 (1H, s), 6.32 (2H, s), 6.84–6.92 (2H, m), 7.18–7.47 (4H, m), 7.52–7.59 (2H, m), 7.91–7.98 (2H, m), 8.17 (1H, d), 10.39 (1H, s), 14.27 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -158.102, -158.471; *m/z* (ES$^+$) $[M+H]^+$ = 875.3.

EXAMPLE 152

Intermediate 152a:

1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2342] Prepared in an analogous manner to Intermediate 6e using Intermediate 24a (220 mg, 0.41 mmol) to give the title compound (200 mg, 80%) as a red solid in the form of a *p*-toluenesulfonic acid salt. *m/z* (ES$^+$) $[M+H]^+$ = 442.2.

EXAMPLE 152:

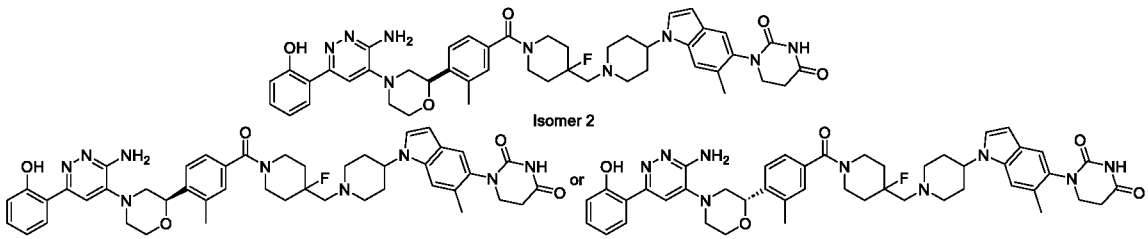
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



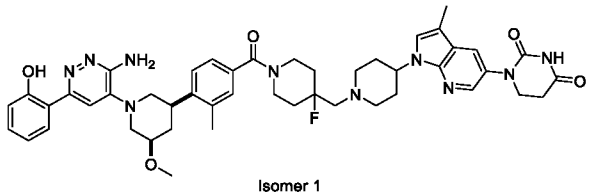
[2343] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 152a (60 mg, 0.08 mmol) and Intermediate 55j (33 mg, 0.08 mmol. Purification by preparative HPLC (elution gradient: 11 to 28% MeCN in water with 0.1% formic acid) gave the title compound (25.0 mg, 22%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.72 (2H, d), 1.91 (3H, s), 1.99 (3H, t), 2.28 (3H, s), 2.41 (5H, s), 2.61 (1H, s), 2.67 (1H, s), 2.70 – 2.78 (2H, m), 2.81 – 2.92 (2H, m), 3.05 (3H, d), 3.50 – 3.58 (4H, m), 3.70 – 3.82 (2H, m),

4.09 (2H, d), 4.31 (2H, s), 4.98 (1H, d), 6.40 (1H, d), 6.45 (2H, s), 6.84 – 6.91 (2H, m), 7.21 – 7.30 (3H, m), 7.42 (2H, d), 7.47 (1H, d), 7.54 – 7.60 (2H, m), 7.94 – 7.99 (1H, m), 10.27 (1H, s), 14.19 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -158.0; *m/z* (ES$^+$) $[M+H]^+$ = 830.4.

EXAMPLE 153:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



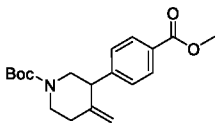
Isomer 1

[2344] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (15.6 mg, 0.04 mmol) and Intermediate 93e (17.7 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (16.1 mg, 52%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.94 (1H, d), 1.53 (1H, q), 1.64 - 1.77 (2H, m), 1.83 (2H, br d), 1.88 - 1.98 (1H, m), 2.04 (2H, td), 2.20 - 2.28 (4H, m), 2.35 (2H, br t), 2.40 (3H, s), 2.51 - 2.57 (1H, m), 2.58 - 2.66 (2H, m), 2.71 - 2.82 (3H, m), 3.03 (2H, br d), 3.09 - 3.18 (1H, m), 3.21 - 3.28 (1H, m), 3.32-3.34 (1H, m), 3.34 - 3.38 (3H, m), 3.44 (1H, br d), 3.48 - 3.61 (1H, m), 3.73 - 3.86 (4H, m), 4.15 - 4.30 (1H, m), 4.55 - 4.62 (1H, m), 6.32 (2H, br s), 6.83 - 6.90 (2H, m), 7.19 - 7.26 (3H, m), 7.38 - 7.44 (1H, m), 7.47 (1H, s), 7.59 (1H, s), 7.86 (1H, d), 7.94 (1H, br d), 8.16 (1H, d), 10.36 (1H, s), 14.18 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 859.6.

EXAMPLE 154

Intermediate 154a:

tert-Butyl 3-(4-(methoxycarbonyl)phenyl)-4-methylenepiperidine-1-carboxylate

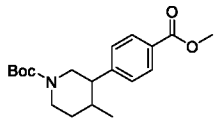


[2345] A solution of $MePPh_3Br$ (2.049 g, 5.74 mmol) in THF (9.18 mL) was cooled to 0 °C and charged with KO*t*-Bu (0.644 g, 5.74 mmol). The reaction mixture was warmed to r.t. for 1h, cooled to 0 °C and charged with Intermediate 144b (1.53 g, 4.59 mmol) in THF (2.30 ml) then warmed to r.t. over 16h. The reaction mixture was quenched with sat. NH_4Cl and water and extracted with EtOAc (3 X 30 mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.13 g, 74%). ^{1}H NMR (DMSO-*d*6): δ 1.38 (9H, br s), 2.14 - 2.36 (2H, m), 3.33 (1H, s), 3.54

(2H, br s), 3.61 - 3.81 (2H, m), 3.85 (3H, s), 4.24 - 4.53 (1H, m), 4.81 - 5.00 (1H, m), 7.43 (2H, d), 7.79 - 8.04 (2H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 232.1.

Intermediate 154b:

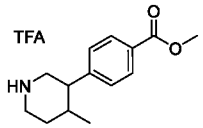
tert-Butyl 3-(4-(methoxycarbonyl)phenyl)-4-methylpiperidine-1-carboxylate



[2346] A solution of Intermediate 154a (1.03 g, 3.11 mmol) and Pd/C (10% w/w) (0.331 g, 0.31 mmol) in EtOAc (31.1 ml) was charged with H_2 and stirred at r.t. for 2h. The reaction mixture was then filtered through a pad of Celite (washing with EtOAc) and concentrated to afford the title compound (1.03 g, 100%) as a mixture of isomers, which was then carried forward without further purification. *m/z* (ES^+) $[M–Boc+2H]^+$ = 234.1.

Intermediate 154c:

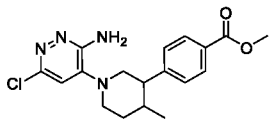
3-(4-(Methoxycarbonyl)phenyl)-4-methylpiperidine



[2347] Prepared in an analogous method to Intermediate 1i starting from Intermediate 154b (1.05 g, 3.15 mmol) to afford the title compound (1.09 g, 100%) in the form of a trifluoroacetic acid salt as a mixture of isomers, which was then carried forward without further purification. *m/z* (ES^+) $[M+H]^+$ = 234.1.

Intermediate 154d:

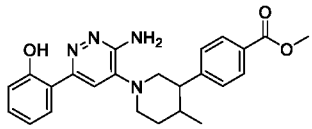
Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-4-methylpiperidin-3-yl)benzoate



[2348] Prepared in an analogous method to Intermediate 1d starting from Intermediate 154c (1.04 g, 2.73 mmol) and 4-bromo-6-chloropyridazin-3-amine (570 mg, 2.73 mmol). Trituration with diethyl ether gave the title compound (987 mg, 99%) as a mixture of isomers, which was then carried forward without intermediate purification. *m/z* (ES^+) $[M+H]^+$ = 361.4.

Intermediate 154e:

Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoate



[2349] Prepared in an analogous method to Intermediate 1e starting from Intermediate 154d (1.14 g, 2.74 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (788 mg, 69%) as a mixture of isomers. ^1H NMR (DMSO-*d*6): δ 1.64 - 1.85 (2H, m), 1.88 - 2.13 (5H, m),

2.23 - 2.34 (1H, m), 2.43 (3H, s), 2.54 - 2.70 (3H, m), 2.74 (4H, s), 2.90 (3H, s), 3.00 - 3.10 (2H, m), 3.43 - 3.57 (3H, m), 3.64 - 3.71 (1H, m), 3.77 (2H, s), 3.90 - 4.02 (1H, m), 4.18 - 4.44 (2H, m), 6.44 - 6.48 (1H, m), 6.49 - 6.58 (2H, m), 6.88 - 6.95 (2H, m), 7.04 - 7.12 (1H, m), 7.23 - 7.28 (2H, m), 7.29 - 7.32 (1H, m), 7.44 - 7.48 (1H, m), 7.48 - 7.52 (1H, m), 7.52 - 7.58 (2H, m), 7.71 (1H, s), 7.96 (2H, s), 10.21 - 10.30 (1H, m), 13.42 - 14.43 (1H, m); *m/z* (ES^+) $[M+H]^+ = 419.5$.

Intermediate 154f and 154g:

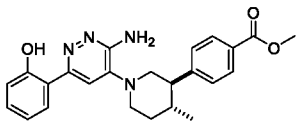
Methyl 4-((3*R**,4*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoate ((*absolute configurations not yet confirmed))

and

Intermediate: 154h and 154i:

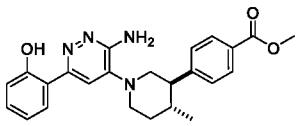
Methyl 4-((3*R**,4*S**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoate ((*absolute configurations not yet confirmed))

Trans isomers



Isomer 1

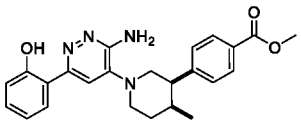
Intermediate 154f



Isomer 2

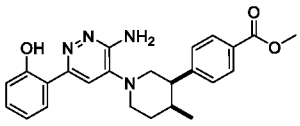
Intermediate 154g

Cis isomers



Isomer 1

Intermediate 154h



Isomer 2

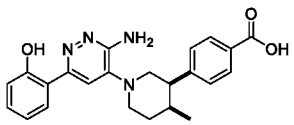
Intermediate 154i

[2350] Intermediate 154e (788 mg, 1.18 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: OJ-H 30 x 250 mm, 5 mm; mobile phase: 10 to 60% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 2.5 mL/min; BPR: 120 bar; Column temperature: 40°C to afford the title compounds Intermediate 154f (156 mg, 20% yield, 99% ee), Intermediate 154g (131 mg, 17% yield, 99% ee), Intermediate 154h (107 mg, 13% yield, 99% ee) and Intermediate 154i (109 mg, 14% yield, 99% ee) that eluted in this order from the column as off-white solids. *Trans* isomers: Intermediate 154f and 154g: ^1H NMR (DMSO-*d*6): δ 0.68 - 0.78 (3H, m), 1.59 - 1.73 (1H, m), 1.84 - 1.97 (2H, m), 2.78 - 2.84 (2H, m), 2.85 - 2.90 (1H, m), 3.39 - 3.49 (1H, m), 3.53 - 3.62 (1H, m), 3.85 (3H, s), 6.24 - 6.32 (2H, m), 6.83 - 6.91 (2H, m), 7.18 - 7.27 (1H, m), 7.45 - 7.51 (2H, m), 7.51 - 7.56 (1H, m), 7.88 - 7.92 (1H, m), 7.93 - 7.98 (2H, m), 13.81 - 14.46 (1H, m); *m/z* (ES^+) $[M+H]^+ = 419.5$. *Cis* isomers: Intermediate 154h and 154i : ^1H NMR (DMSO-*d*6): δ 0.65 - 0.78 (3H, m), 1.71 - 1.82 (1H, m), 2.08 - 2.19 (1H, m), 2.22 - 2.31 (1H, m), 3.11 - 3.20 (2H, m), 3.35 - 3.44 (3H, m), 3.81 - 3.90 (3H, m), 6.14 - 6.26 (2H, m), 6.82 - 6.96 (2H, m), 7.21 - 7.29 (1H, m), 7.47 - 7.54 (2H, m), 7.66 - 7.71 (1H, m), 7.89 - 7.95 (2H, m), 7.96 - 8.00 (1H, m), 13.99 - 14.44 (1H, m); *m/z* (ES^+) $[M+H]^+ = 419.5$.

Intermediate 154j:

4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



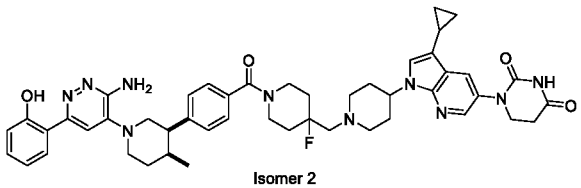
Isomer 2

[2351] Prepared in an analogous manner to Intermediate 26j starting from Intermediate 154i (50.0 mg, 0.12 mmol). To give the title compound (48 mg, 100%) as a white solid, which was carried forward without further. ^{1}H NMR (DMSO-*d*6): δ 0.72 (3H, d), 1.71 - 1.80 (1H, m), 2.07 - 2.16 (1H, m), 2.21 - 2.30 (1H, m), 2.53 - 2.58 (2H, m), 3.17 - 3.26 (2H, m), 3.38 - 3.54 (4H, m), 6.93 (1H, br t), 6.97 - 7.03 (1H, m), 7.25 - 7.35 (1H, m), 7.43 (2H, d), 7.58 - 7.67 (1H, m), 7.70 - 7.83 (1H, m), 7.88 (2H, d), 12.84 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 405.4.

EXAMPLE 154:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



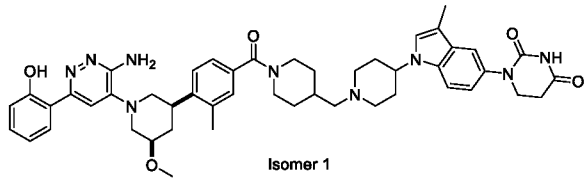
Isomer 2

[2352] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 154j (20 mg, 0.02 mmol) and Intermediate 20g (22.39 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (15.8 mg, 76%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 – 0.66 (2H, m), 0.75 (3H, d), 0.80 – 0.86 (2H, m), 1.60 – 1.70 (1H, m), 1.73 – 1.83 (4H, m), 1.90 (2H, ddd), 1.96 – 2.15 (4H, m), 2.19 – 2.26 (1H, m), 2.33 (2H, t), 2.51 – 2.56 (1H, m), 2.57 – 2.65 (2H, m), 2.75 (2H, t), 3.02 (2H, br d), 3.10 – 3.17 (2H, m), 3.25 – 3.31 (1H, m), 3.34 – 3.41 (3H, m), 3.43 – 3.56 (1H, m), 3.80 (2H, t), 4.18 – 4.35 (1H, m), 4.53- 4.62 (1H, m), 6.23 (2H, br s), 6.85- 6.93 (2H, m), 7.21 – 7.26 (1H, m), 7.34 – 7.38 (2H, m), 7.39 – 7.47 (3H, m), 7.67 (1H, s), 7.93 (1H, d), 7.96- 8.00 (1H, m), 8.15 (1H, d), 10.39 (1H, s), 14.29 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 855.5.

EXAMPLE 155:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



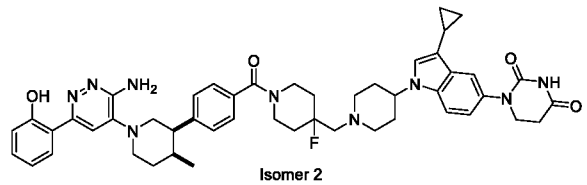
Isomer 1

[2353] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (16.3 mg, 0.04 mmol) and Intermediate 113b (28.7 mg, 0.04 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (11.6 mg, 36%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.01 - 1.14 (2H, m), 1.19 - 1.29 (1H, m), 1.48 - 1.58 (1H, m), 1.62 - 1.75 (1H, m), 1.75 - 1.85 (2H, m), 1.86 - 1.96 (4H, m), 2.06 - 2.17 (2H, m), 2.20 - 2.29 (6H, m), 2.40 (3H, s), 2.51 - 2.54 (1H, m), 2.69 - 2.80 (4H, m), 2.94 - 3.04 (2H, m), 3.31 - 3.34 (1H, m), 3.37 (3H, s), 3.41 - 3.47 (1H, m), 3.53 - 3.67 (1H, m), 3.73 - 3.79 (3H, m), 3.80 - 3.86 (1H, m), 4.23 - 4.32 (1H, m), 4.37 - 4.52 (1H, m), 6.31 (2H, br s), 6.84 -6.90 (2H, m), 7.04 (1H, dd), 7.16 - 7.25 (3H, m), 7.29 (1H, s), 7.37 - 7.41 (2H, m), 7.44 - 7.47 (1H, m), 7.59 (1H, s), 7.79 - 8.03 (1H, m), 10.23 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 840.6.

EXAMPLE 156:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

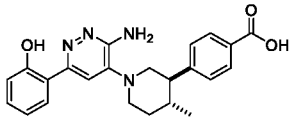
[2354] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 154j (23.7 mg, 0.03 mmol) and Intermediate 6h (20.0 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (13.3 mg, 54%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.55 - 0.61 (2H, m), 0.75 (3H, br d), 0.78 - 0.84 (2H, m), 1.64 - 1.78 (3H, m), 1.79 - 2.00 (8H, m), 2.05 - 2.14 (1H, m), 2.18 - 2.27 (1H, m), 2.33 - 2.40 (2H, m), 2.55 - 2.63 (2H, m), 2.72 (2H, br t), 2.97 - 3.04 (2H, m), 3.08 - 3.19 (3H, m), 3.34 - 3.40 (3H, m), 3.43 - 3.55 (1H, m), 3.76 (2H, t), 4.18 - 4.30 (2H, m), 6.23 (2H, br s), 6.85 - 6.93 (2H, m), 6.99 - 7.06 (1H, m), 7.21 - 7.28 (2H, m), 7.34 - 7.46 (5H, m), 7.47 - 7.52 (1H, m), 7.67 (1H, s), 7.94 - 8.01 (1H, m), 10.25 (1H, br s), 14.23 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 854.5.

EXAMPLE 157

Intermediate 157a:

4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



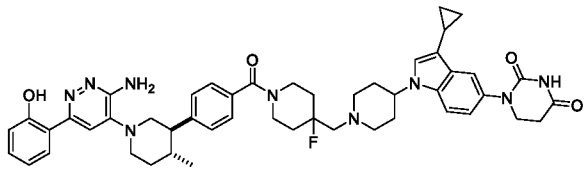
Isomer 2

[2355] Prepared in an analogous method to Intermediate 26j starting from Intermediate 154g (100 mg, 0.24 mmol). To give the title compound (98 mg, 100%) as a white solid, which was carried forward without further purification. ^{1}H NMR (DMSO-*d*6): δ 0.71 (3H, d), 1.55 - 1.67 (1H, m), 1.84 - 1.90 (1H, m), 1.93 - 2.01 (1H, m), 2.54 - 2.65 (1H, m), 2.78 (1H, td), 2.90 - 3.06 (2H, m), 3.37 - 3.48 (2H, m), 3.49 - 3.61 (1H, m), 3.65 - 3.79 (1H, m), 6.91 (1H, t), 7.03 - 7.09 (1H, m), 7.30 (1H, br t), 7.44 (2H, d), 7.48 - 7.56 (1H, m), 7.62 - 7.72 (1H, m), 7.90 (2H, d), 12.85 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 405.4.

EXAMPLE 157:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



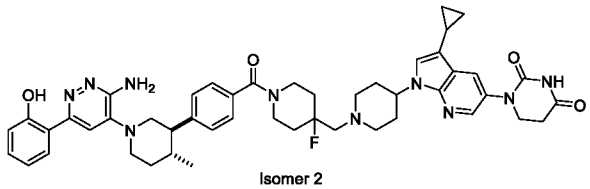
Isomer 2

[2356] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate157a (23.7 mg, 0.03 mmol) and Intermediate 6h (20.0 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (8.6mg, 34%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.53 - 0.61 (2H, m), 0.75 (3H, br d), 0.78 - 0.84 (2H, m), 1.61 - 1.77 (3H, m), 1.80 - 1.99 (8H, m), 2.37 (2H, br t), 2.56 - 2.65 (2H, m), 2.69 - 2.85 (5H, m), 3.00 (2H, br d), 3.07 - 3.16 (1H, m), 3.37 - 3.60 (5H, m), 3.76 (2H, t), 4.16 - 4.29 (2H, m), 6.27 (2H, br s), 6.82- 6.89 (2H, m), 6.99 - 7.06 (1H, m), 7.15 - 7.24 (2H, m), 7.32 - 7.41 (4H, m), 7.43 - 7.47 (1H, m), 7.47 - 7.53 (2H, m), 7.91 (1H, br d), 10.25 (1H, s), 14.26 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 854.5.

EXAMPLE 158:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



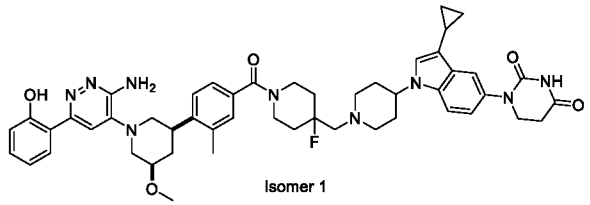
Isomer 2

[2357] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 157a (20.0 mg, 0.02 mmol) and Intermediate 20g (22.4 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (7.5 mg, 36%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.63 - 0.69 (2H, m), 0.75 (3H, d), 0.83 - 0.88 (2H, m), 1.65 - 1.84 (5H, m), 1.85 - 2.01 (5H, m), 2.02 - 2.11 (2H, m), 2.36 (2H, br t), 2.58 - 2.68 (2H, m), 2.74 - 2.89 (5H, m), 3.04 (2H, br d), 3.09 - 3.23 (1H, m), 3.40 - 3.62 (4H, m), 3.80 (2H, t), 4.26 (1H, br s), 4.54 - 4.66 (1H, m), 6.27 (2H, br s), 6.83 - 6.92 (2H, m), 7.19 - 7.27 (1H, m), 7.35-7.40 (4H, m), 7.45 (1H, s), 7.53 (1H, s), 7.89 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, br s), 14.23 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 855.5.

EXAMPLE 159:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



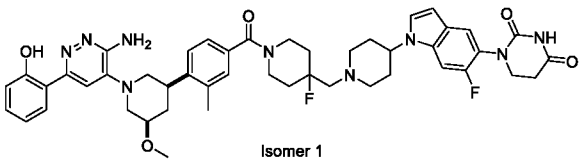
Isomer 1

[2358] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (27.9 mg, 0.06 mmol) and Intermediate 6h (44.5 mg, 0.06 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (41 mg, 72%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.54 - 0.63 (2H, m), 0.78 - 0.86 (2H, m), 1.44 - 1.57 (1H, m), 1.62 - 1.77 (2H, m), 1.78 - 1.89 (4H, m), 1.90 - 2.03 (3H, m), 2.19 - 2.30 (1H, m), 2.33 - 2.42 (5H, m), 2.41 - 2.47 (1H, m), 2.51 - 2.55 (1H, m), 2.56 - 2.65 (2H, m), 2.72 (2H, t), 2.78 (1H, t), 2.96 - 3.04 (2H, m), 3.06 - 3.15 (1H, m), 3.30 (1H, br s), 3.37 (3H, s), 3.40 - 3.55 (2H, m), 3.70 - 3.79 (3H, m), 3.81 - 3.86 (1H, m), 4.24 (2H, br t), 6.34 (2H, br s), 6.78 - 6.92 (2H, m), 7.03 (1H, dd), 7.18 - 7.26 (4H, m), 7.39 - 7.50 (3H, m), 7.59 (1H, s), 7.95 (1H, d), 10.25 (1H, s), 14.21 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 884.7.

EXAMPLE 160:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



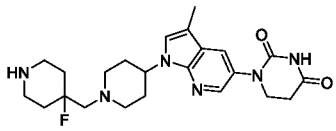
Isomer 1

[2359] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (22.2 mg, 0.05 mmol) and Intermediate 5g (46 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (21.5 mg, 48%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.45 - 1.58 (1H, m), 1.63 - 1.79 (2H, m), 1.81 - 2.02 (6H, m), 2.22 - 2.30 (1H, m), 2.34 - 2.43 (5H, m), 2.56 - 2.65 (2H, m), 2.72 (2H, br t), 2.75 - 2.81 (1H, m), 3.02 (2H, br d), 3.07 - 3.16 (1H, m), 3.20-3.26 (1H, m), 3.26 - 3.31 (1H, m), 3.37 (3H, s), 3.41 - 3.47 (1H, m), 3.47 - 3.57 (1H, m), 3.69 (2H, br t), 3.73 - 3.79 (1H, m), 3.81 - 3.87 (1H, m), 4.15 - 4.35 (2H, m), 6.34 (2H, br s), 6.47 (1H, d), 6.46 - 6.46 (1H, m), 6.82 - 6.91 (2H, m), 7.19 - 7.25 (3H, m), 7.38 - 7.43 (1H, m), 7.51 - 7.60 (4H, m), 7.73 - 8.08 (1H, m), 10.40 (1H, s), 14.21 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 862.6.

EXAMPLE 161

Intermediate 161a:

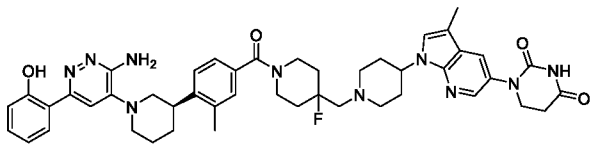
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2360] TFA (4.0 mL) was added to a solution of Intermediate 93d (1.42 g, 2.61 mmol) in DCM (12.1 mL). The resulting mixture was stirred at r.t. for 30 minutes and concentrated under reduced pressure. The residue was azeotroped with DCM (3x) and dried *in vacuo*. DCM (90 mL), IPA (30 mL), sat. aq. K_2CO_3 (50 mL) and water (20 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.01 g, 78%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.55 - 1.70 (2H, m), 1.73 - 1.88 (4H, m), 2.04 (2H, qd), 2.24 (3H, s), 2.33 (2H, br t), 2.51 - 2.58 (2H, m), 2.68 - 2.85 (6H, m), 3.02 (2H, br d), 3.79 (2H, t), 4.58 (1H, tt), 7.48 (1H, s), 7.86 (1H, d), 8.16 (1H, d), 10.36 (1H, br s), one heteroatom-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 443.4.

EXAMPLE 161:

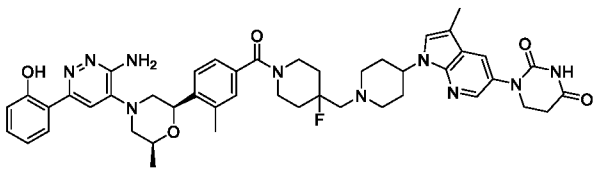
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2361] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (22 mg, 0.04 mmol) and Intermediate 12g (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (22.8 mg, 61%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.54 - 2.16 (13H, m), 2.25 (3H, s), 2.34 - 2.44 (5H, m), 2.55 - 2.67 (2H, m), 2.68 - 2.79 (3H, m), 2.86 (1H, br t), 2.99 - 3.31 (5H, m), 3.37 - 3.70 (2H, m), 3.81 (2H, t), 4.09 - 4.46 (1H, m), 4.53 - 4.66 (1H, m), 6.27 (2H, s), 6.84 - 6.92 (2H, m), 7.20 - 7.28 (3H, m), 7.40 (1H, d), 7.49 (1H, s), 7.56 (1H, s), 7.88 (1H, d), 7.94 (1H, d), 8.17 (1H, d), 10.38 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 829.6.

EXAMPLE 162:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

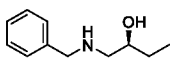


[2362] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (21 mg, 0.04 mmol) and Intermediate 132e (20 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (15.4 mg, 42%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 1.62 - 2.11 (8H, m), 2.23 (3H, s), 2.35 (2H, br t), 2.40 (3H, s), 2.50 - 2.65 (3H, m), 2.69 - 2.78 (3H, m), 2.93 - 3.27 (4H, m), 3.37 - 3.62 (3H, m), 3.79 (2H, t), 4.08 - 4.18 (1H, m), 4.19 - 4.36 (1H, m), 4.54 - 4.65 (1H, m), 5.03 (1H, br d), 6.41 (2H, s), 6.81 - 6.92 (2H, m), 7.18 - 7.31 (3H, m), 7.48 (1H, s), 7.52 - 7.58 (2H, m), 7.86 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.36 (1H, s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 163

Intermediate 163a:

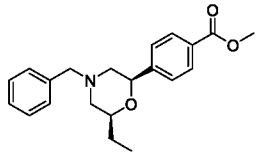
(*S*)-1-(Benzylamino)butan-2-ol



[2363] Benzyl bromide (1.06 mL, 8.94 mmol) was added to a suspension of (*S*)-1-aminobutan-2-ol (2.39 g, 26.81 mmol) and K_2CO_3 (1.48 g, 10.7 mmol) in MeCN (26 mL). The resulting mixture was stirred at r.t. for 90 minutes and filtered. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (1.19 g, 74%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 0.85 (3H, t), 1.26 - 1.36 (1H, m), 1.37 - 1.47 (1H, m), 2.46 - 2.51 (1H, m), 2.63 (1H, dd), 3.49 - 3.56 (1H, m), 3.81 - 3.91 (2H, m), 4.43 - 6.09 (2H, m), 7.26 - 7.32 (1H, m), 7.32 - 7.45 (4H, m); *m/z* (ES^+) $[M+H]^+$ = 180.2.

Intermediate 163b:

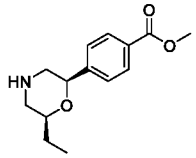
Methyl 4-((2*R*,6*S*)-4-benzyl-6-ethylmorpholin-2-yl)benzoate



[2364] Prepared in an analogous procedure to Intermediate 65a using Intermediate 163a (1.18 g, 6.60 mmol) and methyl 4-(2-bromoacetyl)benzoate (1.54 g, 6.00 mmol) to give the title compound (1.50 g, 73%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 0.88 (3H, t), 1.40 - 1.58 (2H, m), 1.74 - 1.92 (2H, m), 2.78 (1H, br d), 2.87 (1H, br d), 3.46 - 3.61 (3H, m), 3.83 (3H, s), 4.62 (1H, br d), 7.18 - 7.37 (5H, m), 7.46 (2H, br d), 7.91 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 340.2.

Intermediate 163c:

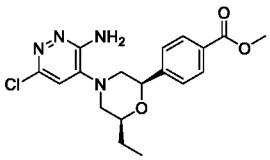
Methyl 4-((2*R*,6*S*)-6-ethylmorpholin-2-yl)benzoate



[2365] Prepared in an analogous manner to Intermediate 65b using Intermediate 163b (1.50 g, 4.42 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. *m/z* (ES$^+$) $[M+H]^+$ = 250.2.

Intermediate 163d:

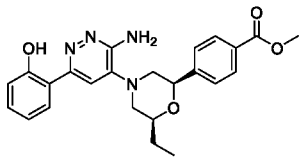
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoate



[2366] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 163c (1.11 g, 5.30 mmol). After cooling to r.t., the mixture was diluted with EtOAc (50 mL), washed with brine (2 x 50 mL) and sat. aq. NH_4Cl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (934 mg, 56%) as a brown wax. ^{1}H NMR (DMSO-*d*6): δ 0.98 (3H, t), 1.59 (2H, quin), 2.44 – 2.54 (2H, m), 3.36 – 3.42 (1H, m), 3.57 (1H, br d), 3.81 – 3.88 (4H, m), 4.91 – 5.01 (1H, m), 6.33 (2H, s), 6.97 (1H, s), 7.59 (2H, d), 7.98 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 377.3.

Intermediate 163e:

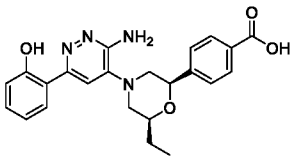
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-ethylmorpholin-2-yl)benzoate



[2367] Prepared in an analogous method to Intermediate 1e starting from Intermediate 163d (859 mg, 2.28 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. DCM–IPA (3:1, 20 mL) was added followed by sat. aq. K_2CO_3–H_2O (3:1, 20 mL). The resulting mixture was stirred vigorously for 20 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (20 mL) and sat. aq. NH_4Cl (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (732 mg, 73%) as an orange solid. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.61 (2H, quin), 2.55 - 2.64 (2H, m), 3.47 (1H, br d), 3.60 (1H, br d), 3.85 (3H, s), 3.87 - 3.94 (1H, m), 4.93 - 5.08 (1H, m), 6.46 (2H, s), 6.82 - 6.92 (2H, m), 7.18 - 7.27 (1H, m), 7.54 (1H, s), 7.60 (2H, d), 7.92 (1H, dd), 7.98 (2H, d), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 435.3.

Intermediate 163f:

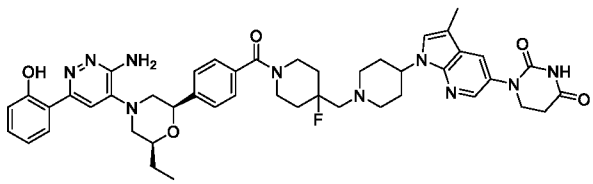
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoic acid



[2368] Prepared in an analogous manner to Intermediate 1f starting from Intermediate 163e (726 mg, 1.67 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and acidified with 6M HCl. A precipitate was formed which was collected by filtration, washed with water and dried *in vacuo* to give the title compound (684 mg, 97%) as a yellowish solid. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.61 (2H, quin), 2.58 - 2.71 (2H, m), 3.52 (1H, br d), 3.64 (1H, br d), 3.86 - 3.94 (1H, m), 4.98 (1H, br d), 6.70 (2H, br s), 6.84 - 6.94 (2H, m), 7.25 (1H, br t), 7.51 - 7.61 (3H, m), 7.85 (1H, br d), 7.95 (2H, d), 11.64 - 15.08 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 421.2.

EXAMPLE 163:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



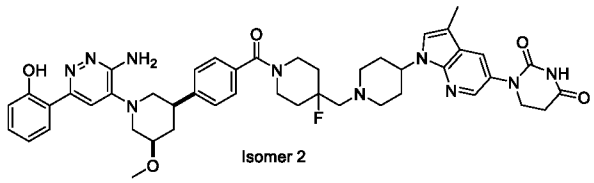
[2369] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (21 mg, 0.04 mmol) and Intermediate 163f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (24.0 mg, 65%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.57 - 2.11 (10H, m), 2.23 (3H, s), 2.35 (2H, br t), 2.52 - 2.61 (2H, m), 2.62 - 2.70 (2H, m), 2.74 (2H, t), 2.98 - 3.28 (4H, m), 3.50 (2H, br d), 3.59 (1H, br d), 3.79 (2H, t), 3.86 - 3.95 (1H, m), 4.26 (1H, br s), 4.59 (1H, tt), 4.89 - 4.99 (1H, m), 6.46 (2H, s), 6.81 - 6.92 (2H,

m), 7.18 - 7.27 (1H, m), 7.43 (2H, d), 7.47 (1H, s), 7.50 - 7.59 (3H, m), 7.86 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.20 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 164:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

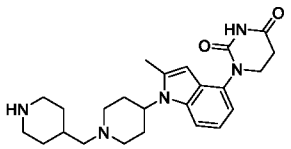


[2370] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (21 mg, 0.04 mmol) and Intermediate 61k (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (22.2 mg, 60%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.55 (1H, q), 1.63 - 1.98 (6H, m), 2.00 - 2.10 (2H, m), 2.23 (3H, s), 2.31 - 2.40 (3H, m), 2.45 - 2.52 (1H, m), 2.57 - 2.65 (2H, m), 2.70 - 2.78 (3H, m), 2.97 - 3.27 (5H, m), 3.37 (3H, s), 3.50 (2H, br d), 3.68 - 3.75 (1H, m), 3.79 (3H, br t), 4.25 (1H, br dd), 4.58 (1H, tt), 6.34 (2H, s), 6.80 - 6.92 (2H, m), 7.16 - 7.27 (1H, m), 7.36 - 7.41 (2H, m), 7.42 - 7.50 (3H, m), 7.58 (1H, s), 7.86 (1H, d), 7.95 (1H, d), 8.16 (1H, d), 10.36 (1H, s), 14.19 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 165

Intermediate 165a:

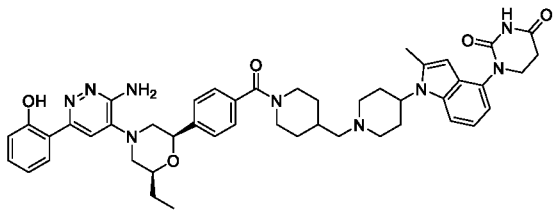
1-(2-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2371] Prepared in an analogous manner to Intermediate 161a using Intermediate 22c (1.84 g, 3.51 mmol) to give the title compound (1.28 g, 83%) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.91 - 1.04 (2H, m), 1.57 (1H, ddd), 1.66 (2H, br d), 1.74 (2H, br d), 2.08 (2H, br t), 2.16 (2H, br d), 2.34 - 2.47 (7H, m), 2.72 (2H, t), 2.91 (2H, br d), 2.97 (2H, br d), 3.72 (2H, t), 4.21 (1H, br t), 6.14 (1H, s), 6.87 (1H, d), 7.03 (1H, t), 7.44 (1H, d), 9.22 - 11.15 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 424.5.

EXAMPLE 165:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

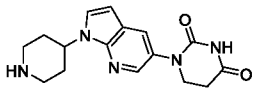


[2372] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 165a (19 mg, 0.04 mmol) and Intermediate 163f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (18.4 mg, 51%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.02 (3H, t), 1.06 - 1.20 (2H, m), 1.63 (2H, quin), 1.68 - 1.96 (5H, m), 2.13 (2H, br t), 2.25 (2H, br s), 2.37 - 2.48 (5H, m), 2.55 - 2.62 (1H, m), 2.68 (1H, br t), 2.73 - 2.91 (3H, m), 2.96 - 3.15 (3H, m), 3.52 (1H, br d), 3.60 (2H, br d), 3.74 (2H, t), 3.88 - 3.98 (1H, m), 4.24 (1H, br t), 4.39 - 4.63 (1H, m), 4.91 - 5.00 (1H, m), 6.16 (1H, s), 6.48 (2H, s), 6.84 - 6.94 (3H, m), 7.04 (1H, t), 7.20 - 7.29 (1H, m), 7.41 (2H, d), 7.46 (1H, d), 7.54 (2H, d), 7.58 (1H, s), 7.97 (1H, dd), 10.30 (1H, s), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 826.7.

EXAMPLE 166

Intermediate 166a:

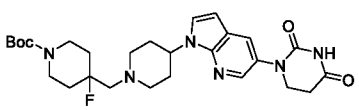
1-(1-(Piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2373] TFA (3.2 mL) was added to a solution of Intermediate 96b (1.72 g, 4.16 mmol) in DCM (8.2 mL). The resulting mixture was stirred at r.t. for 40 minutes. More TFA (1.6 mL) was added. The mixture was stirred at r.t. for 60 minutes and concentrated under reduced pressure. The residue was azeotroped with PhMe (1x). DCM (100 mL), IPA (50 mL), sat. aq. K_2CO_3 (100 mL) and water (100 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (100 mL). The combined aqueous layers were extracted with DCM–IPA (3:1, 2 x 70 mL). The combined organic layers were washed with sat. aq. K_2CO_3 (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.15 g, 88%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.78 - 1.97 (4H, m), 2.07 (1H, br s), 2.60 - 2.69 (2H, m), 2.74 (2H, t), 3.07 (2H, br d), 3.79 (2H, t), 4.64 - 4.80 (1H, m), 6.49 (1H, d), 7.68 (1H, d), 7.90 (1H, d), 8.19 (1H, d), 10.37 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 314.2.

Intermediate 166b:

tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1H-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

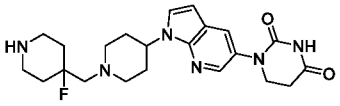


[2374] Prepared in an analogous manner to Intermediate 6g using Intermediate 6f (1.86 g, 5.11 mmol) and Intermediate 166a (0.80 g, 2.55 mmol), stirring at 85 °C for 23 h. Purification by FSC (elution gradient:

0 to15% MeOH in DCM) gave the title compound (0.91 g, 67%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.40 (9H, s), 1.52 - 1.69 (2H, m), 1.78 - 1.91 (4H, m), 2.02 - 2.14 (2H, m), 2.35 (2H, br t), 2.54 - 2.64 (2H, m), 2.74 (2H, t), 3.04 (4H, br d), 3.68 - 3.86 (4H, m), 4.64 (1H, tt), 6.49 (1H, d), 7.72 (1H, d), 7.90 (1H, d), 8.19 (1H, d), 10.37 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 529.5.

Intermediate 166c:

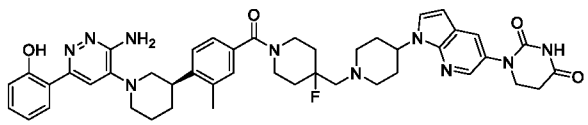
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2375] TFA (2.6 mL) was added to a solution of Intermediate 166b (900 mg, 1.70 mmol) in DCM (7.9 mL). The resulting mixture was stirred at r.t. for 45 minutes and concentrated under reduced pressure. The residue was azeotroped with DCM (3x) and dried *in vacuo*. DCM (90 mL), IPA (30 mL), sat. aq. K_2CO_3 (50 mL) and water (20 mL) were added and the phase were separated. The organic layer was washed with sat. aq. K_2CO_3 (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (632 mg) as a white solid and 0.7 IPA adduct. ^{1}H NMR (DMSO-*d*6): δ 1.53 - 1.67 (2H, m), 1.68 - 1.78 (2H, m), 1.87 (3H, br d), 2.10 (2H, qd), 2.35 (2H, br t), 2.52 - 2.59 (2H, m), 2.61 - 2.81 (6H, m), 3.06 (2H, br d), 3.80 (2H, t), 4.65 (1H, tt), 6.50 (1H, d), 7.74 (1H, d), 7.91 (1H, d), 8.21 (1H, d), 10.38 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 429.3.

EXAMPLE 166:

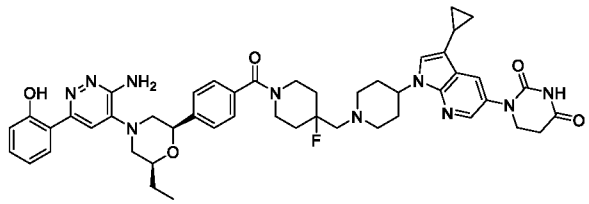
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2376] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 166c (21 mg, 0.04 mmol) and Intermediate 12g (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (22.4 mg, 61%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.57 - 2.05 (10H, m), 2.06 - 2.18 (2H, m), 2.33 - 2.45 (5H, m), 2.57 - 2.67 (2H, m), 2.68 - 2.79 (3H, m), 2.86 (1H, br t), 3.01 - 3.31 (5H, m), 3.42 - 3.65 (3H, m), 3.81 (2H, t), 4.04 - 4.47 (1H, m), 4.60 - 4.74 (1H, m), 6.27 (2H, s), 6.50 (1H, d), 6.83 - 6.93 (2H, m), 7.18 - 7.28 (3H, m), 7.40 (1H, d), 7.56 (1H, s), 7.73 (1H, d), 7.88 - 7.98 (2H, m), 8.21 (1H, d), 10.37 (1H, br s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 815.6.

EXAMPLE 167:

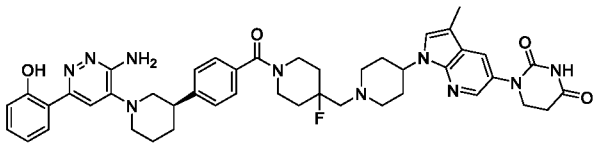
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2377] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 20g (24 mg, 0.04 mmol) and Intermediate 163f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (24.1 mg, 64%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 – 0.68 (2H, m), 0.80 – 0.87 (2H, m), 1.00 (3H, t), 1.55 – 2.11 (11H, m), 2.34 (2H, br t), 2.52 – 2.71 (4H, m), 2.75 (2H, t), 2.95 – 3.28 (4H, m), 3.50 (2H, br d), 3.59 (1H, br d), 3.80 (2H, t), 3.86 – 3.97 (1H, m), 4.07 – 4.43 (1H, m), 4.58 (1H, tt), 4.93 (1H, br d), 6.46 (2H, s), 6.80 – 6.93 (2H, m), 7.22 (1H, t), 7.40 – 7.47 (3H, m), 7.50 – 7.59 (3H, m), 7.90 – 7.98 (2H, m), 8.16 (1H, d), 10.36 (1H, br s), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 871.6.

EXAMPLE 168:

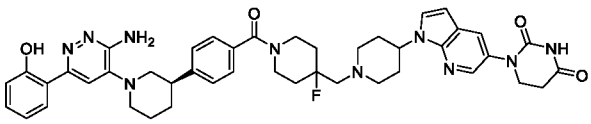
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2378] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (23 mg, 0.05 mmol) and Intermediate 1f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.5 mg, 56%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.58 - 2.11 (12H, m), 2.23 (3H, s), 2.35 (2H, br t), 2.55 - 2.66 (2H, m), 2.67 - 2.85 (4H, m), 2.95 - 3.29 (5H, m), 3.54 (3H, br d), 3.79 (2H, t), 4.06 - 4.38 (1H, m), 4.51 - 4.65 (1H, m), 6.27 (2H, s), 6.81 - 6.91 (2H, m), 7.22 (1H, t), 7.35 - 7.40 (2H, m), 7.40 - 7.45 (2H, m), 7.47 (1H, s), 7.54 (1H, s), 7.86 (1H, d), 7.92 (1H, d), 8.16 (1H, d), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 815.6.

EXAMPLE 169:

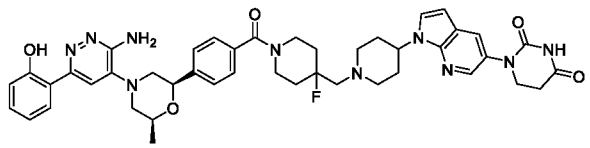
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2379] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 166c (22 mg, 0.05 mmol) and Intermediate 1f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (16.9 mg, 45%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 2.03 (10H, m), 2.05 - 2.18 (2H, m), 2.38 (2H, br t), 2.57 - 2.67 (2H, m), 2.68 - 2.84 (4H, m), 3.01 - 3.30 (5H, m), 3.55 (3H, br d), 3.81 (2H, t), 4.26 (1H, br d), 4.60 - 4.71 (1H, m), 6.29 (2H, s), 6.50 (1H, d), 6.84 - 6.91 (2H, m), 7.23 (1H, t), 7.37 - 7.41 (2H, m), 7.42 - 7.46 (2H, m), 7.56 (1H, s), 7.73 (1H, d), 7.89 - 7.96 (2H, m), 8.21 (1H, d), 10.38 (1H, br s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 801.5.

EXAMPLE 170:

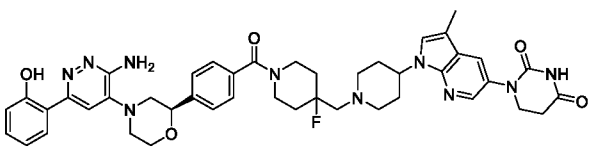
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2380] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 166c (19 mg, 0.04 mmol) and Intermediate 65e (20 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.3 mg, 65%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.64 - 2.05 (6H, m), 2.05 - 2.17 (2H, m), 2.38 (2H, br t), 2.52 - 2.73 (4H, m), 2.76 (2H, t), 3.00 - 3.31 (4H, m), 3.51 (2H, br d), 3.59 (1H, br d), 3.81 (2H, t), 4.06 - 4.16 (1H, m), 4.17 - 4.39 (1H, m), 4.61 - 4.71 (1H, m), 4.95 (1H, br d), 6.37 - 6.56 (3H, m), 6.82 - 6.96 (2H, m), 7.23 (1H, t), 7.44 (2H, d), 7.49 - 7.61 (3H, m), 7.73 (1H, d), 7.92 (1H, d), 7.95 (1H, d), 8.21 (1H, d), 10.38 (1H, s), 14.21 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 817.5.

EXAMPLE 171:

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2381] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (23 mg, 0.05 mmol) and Intermediate 16i (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.3 mg, 56%) as a white solid, following

lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.66 – 2.12 (8H, m), 2.25 (3H, s), 2.37 (2H, br t), 2.58 – 2.70 (2H, m), 2.74 – 2.84 (3H, m), 2.89 (1H, td), 2.98 – 3.30 (4H, m), 3.40 – 3.65 (3H, m), 3.81 (2H, t), 4.01 – 4.15 (2H, m), 4.19 – 4.38 (1H, m), 4.60 (1H, tt), 4.83 – 4.95 (1H, m), 6.48 (2H, s), 6.83 – 6.94 (2H, m), 7.20 – 7.27 (1H, m), 7.44 (2H, d), 7.49 (1H, s), 7.52 – 7.60 (3H, m), 7.88 (1H, d), 7.95 (1H, dd), 8.18 (1H, d), 10.38 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 817.6.

EXAMPLE 172:

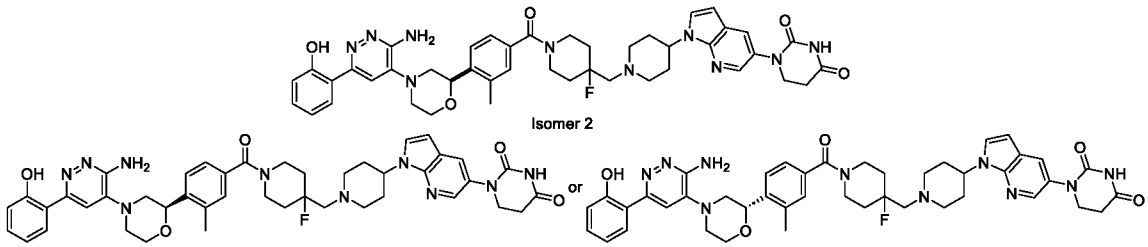
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

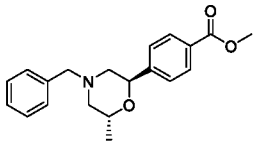


[2382] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 166c (19 mg, 0.04 mmol) and Intermediate 55j (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (22.8 mg, 68%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 2.05 (6H, m), 2.06 - 2.18 (2H, m), 2.33 - 2.46 (5H, m), 2.57 - 2.71 (2H, m), 2.76 (2H, t), 2.82 - 2.96 (2H, m), 3.00 - 3.29 (4H, m), 3.54 (3H, br t), 3.81 (2H, t), 4.09 (2H, br d), 4.18 - 4.39 (1H, m), 4.66 (1H, tt), 4.98 (1H, br d), 6.43 (2H, s), 6.50 (1H, d), 6.82 - 6.94 (2H, m), 7.19 - 7.31 (3H, m), 7.52 - 7.61 (2H, m), 7.73 (1H, d), 7.92 (1H, d), 7.95 (1H, d), 8.21 (1H, d), 10.39 (1H, br s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 817.5.

EXAMPLE 173

Intermediate 173a:

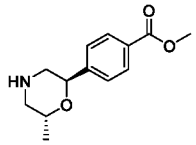
Methyl 4-((2*R*,6*R*)-4-benzyl-6-methylmorpholin-2-yl)benzoate



[2383] Prepared following the same procedure as for Intermediate 94a isolating the diastereomer that eluted first from the column (446 mg, 17%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.22 (3H, d), 2.24 (1H, dd), 2.44 (1H, dd), 2.51 - 2.56 (1H, m), 2.68 (1H, dd), 3.41 - 3.47 (1H, m), 3.49 - 3.56 (1H, m), 3.83 - 3.93 (4H, m), 4.92 (1H, dd), 7.23 - 7.29 (1H, m), 7.29 - 7.39 (4H, m), 7.52 (2H, d), 7.92 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 326.4.

Intermediate 173b:

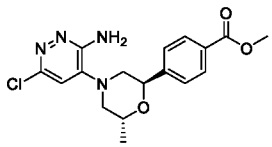
Methyl 4-((2*R*,6*R*)-6-methylmorpholin-2-yl)benzoate



[2384] Prepared in an analogous manner to Intermediate 65b using Intermediate 173a (423 mg, 1.30 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. *m/z* (ES$^+$) $[M+H]^+$ = 236.2.

Intermediate 173c:

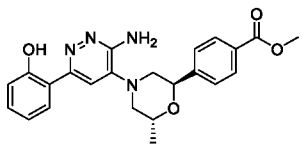
Methyl 4-((2*R*,6*R*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate



[2385] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 173b (306 mg, 1.30 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (228 mg, 48%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.39 (3H, d), 2.65 (1H, br dd), 2.90 (1H, dd), 3.21 (1H, dd), 3.58 (1H, br d), 3.85 (3H, s), 4.24 - 4.35 (1H, m), 5.33 (1H, dd), 6.25 (2H, s), 6.95 (1H, s), 7.56 (2H, d), 7.96 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 363.3.

Intermediate 173d:

Methyl 4-((2*R*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoate

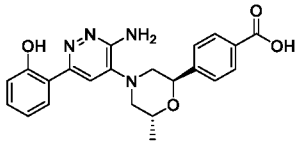


[2386] Prepared in an analogous method to Intermediate 1e starting from Intermediate 173c (1.31 g, 3.60 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. DCM–IPA (3:1, 10 mL) was added followed by sat. aq. K_2CO_3–H2O (3:1, 10 mL). The resulting mixture was stirred vigorously for 20 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (10 mL) and sat. aq. NH_4Cl (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (1.22 g, 81%)

as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.45 (3H, d), 2.80 (1H, dd), 3.04 (1H, dd), 3.33 (1H, s), 3.64 (1H, br d), 3.86 (3H, s), 4.30 - 4.42 (1H, m), 5.37 (1H, dd), 6.34 (2H, s), 6.85 - 6.94 (2H, m), 7.21 - 7.30 (1H, m), 7.53 - 7.66 (3H, m), 7.92 - 8.02 (3H, m), 14.13 (1H, br s); *m/z* (ES$^+$) [M+H]$^+$ = 421.3.

Intermediate 173e:

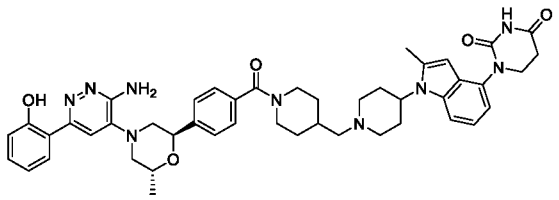
4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoic acid



[2387] Prepared in an analogous manner to Intermediate 1f starting from Intermediate 173d (198 mg, 0.47 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in water (5 mL) and acidified with 6M HCl. A precipitate was formed which was collected by filtration, washed with water and dried *in vacuo* to give the title compound (184 mg, 96%) as a yellowish solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 2.55 - 2.72 (2H, m), 3.53 (1H, br d), 3.62 (1H, br d), 4.04 - 4.16 (1H, m), 4.99 (1H, br d), 6.70 (2H, br s), 6.85 - 6.95 (2H, m), 7.25 (1H, t), 7.50 - 7.63 (3H, m), 7.85 (1H, br d), 7.95 (2H, d), 11.22 - 14.74 (2H, m); *m/z* (ES$^+$) [M+H]$^+$ = 407.4.

EXAMPLE 173:

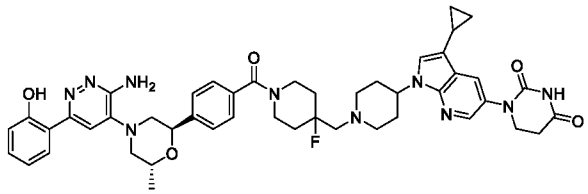
1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2388] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 165a (23 mg, 0.04 mmol) and Intermediate 173e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (14.6 mg, 40%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br d), 1.44 (3H, d), 1.64 - 1.93 (5H, m), 2.11 (2H, br t), 2.22 (2H, br s), 2.35 - 2.47 (5H, m), 2.69 - 2.89 (4H, m), 2.93 - 3.07 (4H, m), 3.31 - 3.35 (1H, m), 3.61 (2H, br d), 3.72 (2H, t), 4.22 (1H, br t), 4.30 - 4.38 (1H, m), 4.40 - 4.60 (1H, m), 5.19 - 5.39 (1H, m), 6.14 (1H, s), 6.31 (2H, s), 6.88 (3H, t), 7.02 (1H, t), 7.23 (1H, t), 7.37 (2H, d), 7.44 (1H, d), 7.50 (2H, d), 7.55 (1H, s), 7.93 (1H, d), 10.28 (1H, s), 14.14 (1H, br s); *m/z* (ES$^+$) [M+H]$^+$ = 812.6.

EXAMPLE 174:

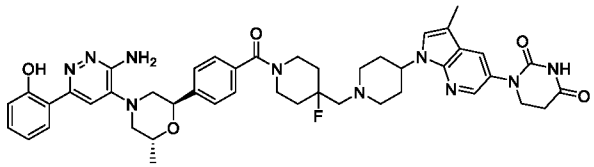
1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2389] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 20g (25 mg, 0.04 mmol) and Intermediate 173e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.2 mg, 55%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 – 0.68 (2H, m), 0.80 – 0.88 (2H, m), 1.43 (3H, d), 1.59 – 2.11 (9H, m), 2.34 (2H, br t), 2.54 – 2.66 (2H, m), 2.75 (2H, t), 2.85 (1H, br dd), 3.28 (6H, br s), 3.36 – 3.68 (2H, m), 3.80 (2H, t), 4.10 – 4.40 (2H, m), 4.52 – 4.64 (1H, m), 5.30 (1H, dd), 6.31 (2H, s), 6.83 – 6.93 (2H, m), 7.19 – 7.28 (1H, m), 7.37 – 7.45 (3H, m), 7.50 (2H, d), 7.55 (1H, s), 7.90 – 7.96 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.14 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 857.6.

EXAMPLE 175:

1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

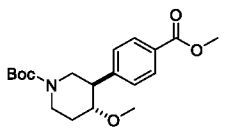


[2390] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 93e (40 mg, 0.04 mmol) and Intermediate 173e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (17.7 mg, 47%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.43 (3H, d), 1.58 - 2.11 (8H, m), 2.23 (3H, s), 2.35 (2H, br t), 2.55 - 2.66 (2H, m), 2.74 (2H, t), 2.85 (1H, br dd), 2.96 - 3.30 (6H, m), 3.38 - 3.56 (1H, m), 3.61 (1H, br d), 3.79 (2H, t), 4.11 - 4.37 (2H, m), 4.58 (1H, tt), 5.30 (1H, dd), 6.31 (2H, s), 6.82 - 6.95 (2H, m), 7.18 - 7.29 (1H, m), 7.41 (2H, d), 7.47 (1H, s), 7.50 (2H, d), 7.55 (1H, s), 7.86 (1H, d), 7.92 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.14 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 831.6.

EXAMPLE 176

Intermediate 176a:

rac-tert-Butyl (3*R*,4*R*)-4-methoxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

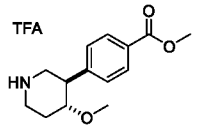


[2391] Intermediate 144a (1.17 g, 3.49 mmol) in DMF (13.67 ml) was cooled to 0 °C and charged with NaH (0.209 g, 5.23 mmol). The reaction was stirred at temperature for 30 minutes then MeI (0.284 ml, 4.53 mmol) was added. The reaction mixture was warmed to r.t. and stirred for 1h. The reaction mixture was

subsequently cooled to 0°C and quenched with water, leading to the formation of a precipitate. The solid was subsequently filtered, dried and lyophilized to give the title compound, (730 mg, 60%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.19 - 1.28 (1H, m), 1.40 (9H, br s), 2.11 - 2.23 (1H, m), 2.64 (1H, br d), 2.77 - 3.01 (2H, m), 3.06 (3H, s), 3.54 - 3.66 (1H, m), 3.85 (4H, s), 3.96 - 4.09 (1H, m), 7.45 (2H, d), 7.91 (2H, d); *m/z* (ES$^+$) [M–Boc+2H]$^+$ = 250.3

Intermediate 176b:

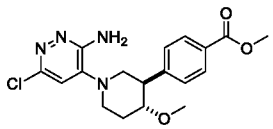
rac-Methyl 4-((3*R*,4*R*)-4-hydroxypiperidin-3-yl)benzoate



[2392] Prepared in an analogous method to Intermediate 1i starting from Intermediate 176a (755 mg, 2.25 mmol). To give the title compound (788 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil. *m/z* (ES$^+$) [M+H]$^+$ = 250.4.

Intermediate 176c:

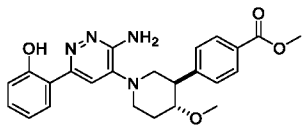
rac-Methyl 4-((3*R*,4*S*)-1-(3-amino-6-chloropyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate



[2393] Prepared in an analogous method to Intermediate 1d starting from Intermediate 176b (788 mg, 2.13 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (568 mg, 71%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.76 (1H, m), 2.20 - 2.32 (1H, m), 2.69 - 2.86 (2H, m), 3.11 (3H, s), 3.13 - 3.18 (1H, m), 3.37 - 3.42 (1H, m), 3.46 - 3.53 (1H, m), 3.58 - 3.67 (1H, m), 3.85 (3H, s), 6.05 - 6.35 (2H, m), 6.84 - 7.04 (1H, m), 7.28 - 7.62 (2H, m), 7.82 - 8.07 (2H, m); *m/z* (ES$^+$) [M+H]$^+$ = 377.4

Intermediate 176d:

rac-Methyl 4-((3*R*,4*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoate

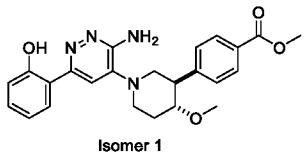


[2394] Prepared in an analogous method to Intermediate 1e starting from Intermediate 176c (568 mg, 1.51 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (198 mg, 30%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 2.00 - 2.08 (1H, m), 2.12 - 2.23 (1H, m), 2.96 - 3.06 (1H, m), 3.12 (3H, s), 3.22 - 3.30 (1H, m), 3.38 (3H, s), 3.68 - 3.76 (1H, m), 3.85 (3H, s), 6.31 (2H, s), 6.83 - 6.97 (2H, m), 7.16 - 7.27 (1H, m), 7.53 (2H, d), 7.66 (1H, s), 7.92 (2H, d), 7.96 - 8.05 (1H, m), 14.00 - 14.50 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 435.2.

Intermediate 176e:

Methyl 4-((3*R**,4*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))



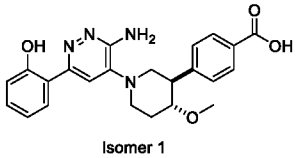
Isomer 1

[2395] Intermediate 176d (200 mg, 0.46 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: OJ 4.6x150mm, 5uM; mobile phase: 10% to 60% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 2.5 mL/min ; BPR: 120 bar ; Column temperature: 40°C to afford the title compound that eluted first from the column (61 mg, 30%, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 435.2.

Intermediate 176f:

4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))



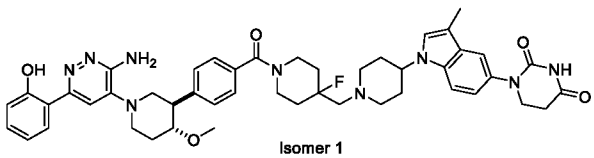
Isomer 1

[2396] Prepared in an analogous method to Intermediate 26j starting from Intermediate 176e (61 mg, 0.14 mmol). To give the title compound (59 mg, 100%) as an off-white solid, which was carried forward without further purification. *m/z* (ES^+) $[M+H]^+$ = 421.5.

EXAMPLE 176:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

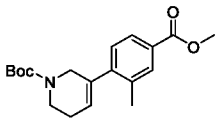
[2397] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 176f (15 mg, 0.04 mmol) and Intermediate 1k (32.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (6.6 mg, 22%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.61 - 1.81 (3H, m), 1.82 - 2.03 (6H, m), 2.22 (3H, s), 2.28 - 2.35 (1H, m), 2.36 - 2.44 (2H, m), 2.58 - 2.61 (1H, m), 2.65 - 2.68 (1H, m), 2.70 - 2.74 (2H, m), 2.83 - 2.91 (2H, m), 3.00 - 3.06 (2H, m), 3.15 (3H, s), 3.45 - 3.49 (2H, m), 3.59 - 3.68 (3H, m), 3.74 - 3.79 (3H, m), 4.19 - 4.34 (2H, m), 6.26 - 6.38 (2H, m), 6.83

- 6.91 (2H, m), 7.01 - 7.08 (1H, m), 7.19 - 7.25 (1H, m), 7.27 - 7.33 (1H, m), 7.36 - 7.40 (3H, m), 7.42 - 7.48 (3H, m), 7.50 - 7.55 (1H, m), 7.86 - 7.95 (1H, m), 8.28 - 8.38 (1H, m), 10.18 - 10.26 (1H, m), 13.92 - 14.44 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 844.4.

EXAMPLE 177

Intermediate 177a:

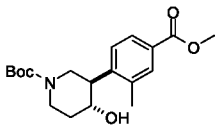
tert-Butyl 5-(4-(methoxycarbonyl)-2-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2398] Prepared in an analogous method to Intermediate 45a starting from tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (6.75 g, 21.83 mmol) and methyl 4-bromo-3-methylbenzoate (5.00 g, 21.83mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes), gave the title compound (7.68 g, 96%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.27 - 2.34 (m, 2H), 2.37 (s, 3H), 3.57 - 3.64 (m, 2H), 3.93 (s, 3H), 3.98 - 4.05 (m, 2H), 5.67 - 5.77 (m, 1H), 7.18 - 7.21 (m, 1H), 7.77 - 7.85 (m, 1H), 7.88 - 7.94 (m, 1H); *m/z* (ES^+) $[M–Boc+2H]^+$ = 232.2.

Intermediate 177b:

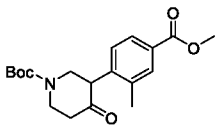
rac-tert-Butyl (3*R*,4*R*)-4-hydroxy-3-(4-(methoxycarbonyl)-2-methylphenyl)piperidine-1-carboxylate



[2399] Prepared in an analogous method to Intermediate 144a starting from Intermediate 177a (5.00 g, 15.09 mmol) Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.56 g, 30%) as a white solid. ^1H NMR ($CDCl_3$): δ 1.50 (9H, s), 1.61 - 1.70 (1H, m), 2.09 - 2.15 (1H, m), 2.43 - 2.56 (3H, m), 2.64 - 2.76 (1H, m), 2.85 - 3.00 (2H, m), 3.93 (3H, s), 4.04 - 4.13 (2H, m), 4.26 - 4.36 (1H, m), 7.31 - 7.35 (1H, m), 7.87 - 7.96 (2H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 250.2.

Intermediate 177c:

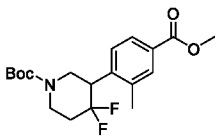
rac-tert-Butyl 3-(4-(methoxycarbonyl)-2-methylphenyl)-4-oxopiperidine-1-carboxylate



[2400] Prepared in an analogous method to Intermediate 144b starting from Intermediate 177b (1.56 g, 4.46 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.23 g, 79%) as a colorless oil, which solidifies over time. ^1H NMR ($CDCl_3$): δ 1.53 (9H, s), 2.35 (3H, s), 2.56 - 2.63 (1H, m), 2.64 - 2.74 (1H, m), 3.32 - 3.47 (2H, m), 3.88 - 3.92 (1H, m), 3.93 (3H, s), 4.21-4.61 (2H, m), 7.11 - 7.23 (1H, m), 7.80 - 8.00 (2H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ = 248.1.

Intermediate 177d:

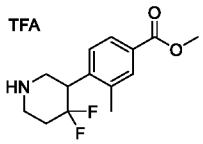
rac-tert-Butyl 4,4-difluoro-3-(4-(methoxycarbonyl)-2-methylphenyl)piperidine-1-carboxylate



[2401] Prepared in an analogous method to Intermediate 144c starting from Intermediate 177c (1.42 g, 4.09 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (830 mg, 55%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 1.49 (9H, s), 1.96 - 2.09 (1H, m), 2.13 - 2.28 (1H, m), 2.44 (3H, s), 3.09 - 3.21 (1H, m), 3.23 - 3.33 (1H, m), 3.34 - 3.46 (1H, m), 3.93 (3H, s), 4.01 - 4.18 (1H, m), 4.19 - 4.43 (1H, m), 7.40 - 7.50 (1H, m), 7.86 - 7.89 (1H, m), 7.90 - 7.93 (1H, m); *m/z* (ES$^+$) [M–tBu+2H]$^+$ = 314.2.

Intermediate 177e:

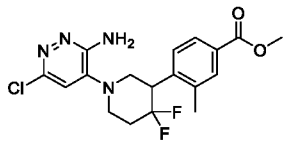
rac-Methyl 4-(4,4-difluoropiperidin-3-yl)-3-methylbenzoate



[2402] Prepared in an analogous method to Intermediate 1i starting from Intermediate 177d (867 mg, 2.35 mmol) to give the title compound (902 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil, which was carried forward without intermediate purification. *m/z* (ES$^+$) [M+H]$^+$ = 270.4.

Intermediate 177f:

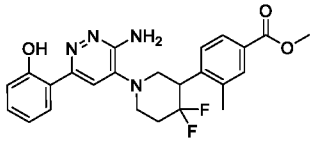
rac-Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoate



[2403] Prepared in an analogous method to Intermediate 1d starting from Intermediate 177e (902 mg, 2.35 mmol) and 4-bromo-6-chloropyridazin-3-amine (489 mg, 2.35 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (556 mg, 60%) as a white solid. *m/z* (ES$^+$) [M+H]$^+$ = 397.4.

Intermediate 177g:

rac-Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoate



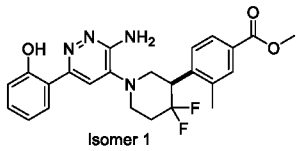
[2404] Prepared in an analogous method to Intermediate 1e starting from Intermediate 177f (556 mg, 1.40 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (411 mg, 65%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 2.23 - 2.34 (1H, m), 2.46 (3H, s), 2.54 - 2.69 (1H, m), 2.98 - 3.07 (1H, m), 3.41 - 3.54 (2H, m), 3.60 - 3.71 (1H, m), 3.86 (3H, s), 3.91 - 4.03 (1H, m), 6.46 -

6.58 (2H, m), 6.85 - 6.95 (2H, m), 7.21 - 7.28 (1H, m), 7.55 - 7.61 (1H, m), 7.69 - 7.74 (1H, m), 7.79 - 7.83 (1H, m), 7.83 - 7.87 (1H, m), 7.94 - 8.00 (1H, m), 14.17 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 455.7.

Intermediate 177h:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))



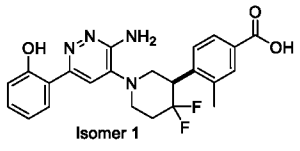
Isomer 1

[2405] Intermediate 177g (400 mg, 0.88 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: OJ 4.6x150mm, 5uM; mobile phase: 10% to 90% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 2.5 mL/min ; BPR: 120 bar ; Column temperature: 40°C to afford the title compound that eluted first from the column (134 mg, 34%, 99% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 455.7.

Intermediate 177i:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))



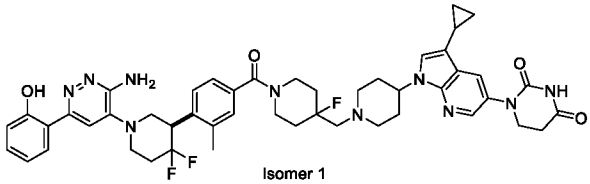
Isomer 1

[2406] Prepared in an analogous method to Intermediate 20f starting from Intermediate 177h (134 mg, 0.29 mmol). Filtration gave the title compound (130 mg, 100%) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 441.6.

EXAMPLE 177:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

[2407] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (15 mg, 0.03 mmol) and Intermediate 20g (31.5 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN

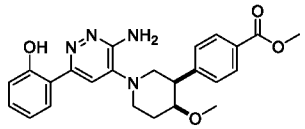
in water with 0.1% FA) gave the title compound (17 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.59 - 0.73 (2H, m), 0.79 - 0.97 (2H, m), 1.63 - 2.20 (9H, m), 2.24 - 2.34 (2H, m), 2.35 - 2.40 (1H, m), 2.43 (3H, s), 2.53 - 2.71 (3H, m), 2.77 (2H, s), 3.00 - 3.10 (2H, m), 3.11 - 3.24 (2H, m), 3.43 - 3.63 (4H, m), 3.65 - 3.73 (1H, m), 3.82 (2H, s), 3.90 - 4.02 (1H, m), 4.15 - 4.43 (1H, m), 4.54 - 4.78 (1H, m), 6.47 - 6.71 (2H, m), 6.88 - 6.95 (2H, m), 7.23 - 7.32 (3H, m), 7.47 - 7.53 (1H, m), 7.67 - 7.75 (1H, m), 7.89 - 8.01 (2H, m), 8.12 - 8.15 (1H, m), 8.16 - 8.24 (1H, m), 10.34 - 10.43 (1H, m), 13.41 - 14.72 (1H, m); *m/z* (ES$^-$) $[M-H]^-$ = 889.8.

EXAMPLE 178

Intermediate 178a:

Methyl 4-((3*R**,4*S**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))



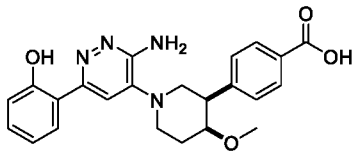
Isomer 1

[2408] Prepared following the same method as for Intermediate 109h isolating the compound that eluted first from the column (85 mg, 47%, 99% ee) as an off-white solid. *m/z* (ES$^+$) $[M+H]^+$ = 435.7.

Intermediate 178b:

4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))



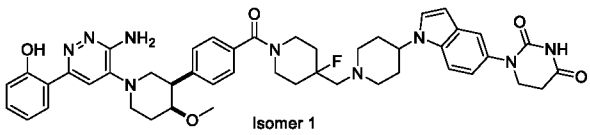
Isomer 1

[2409] Prepared in an analogous method to Intermediate 26j starting from Intermediate 178a (75 mg, 0.17 mmol). Filtration gave the title compound (72 mg, 99%) as an off-white solid, which was carried forward without further purification. *m/z* (ES$^+$) $[M+H]^+$ = 421.5.

EXAMPLE 178:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

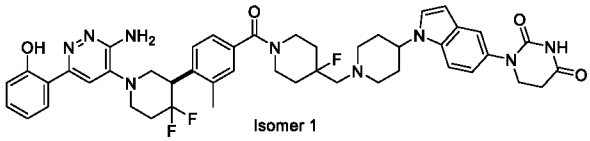


[2410] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 178b (10 mg, 0.02 mmol) and Intermediate 2e (21.0 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (7.3 mg, 37%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.82 (2H, m), 1.84 - 1.93 (3H, m), 1.94 - 2.08 (4H, m), 2.13 - 2.24 (1H, m), 2.37 - 2.47 (2H, m), 2.59 - 2.64 (1H, m), 2.65 - 2.69 (1H, m), 2.70 - 2.77 (3H, m), 3.01 - 3.09 (3H, m), 3.09 - 3.13 (1H, m), 3.16 (4H, s), 3.38 - 3.43 (1H, m), 3.42 - 3.66 (3H, m), 3.71 - 3.84 (3H, m), 4.16 - 4.30 (1H, m), 4.31 - 4.41 (1H, m), 6.25 - 6.37 (2H, m), 6.42 - 6.49 (1H, m), 6.84 - 6.94 (2H, m), 7.01 - 7.10 (1H, m), 7.19 - 7.28 (1H, m), 7.34 - 7.40 (2H, m), 7.42 - 7.48 (3H, m), 7.51 - 7.58 (2H, m), 7.62 - 7.69 (1H, m), 7.96 - 8.03 (1H, m), 10.14 - 10.30 (1H, m), 13.53 - 14.55 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 830.6.

EXAMPLE 179:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

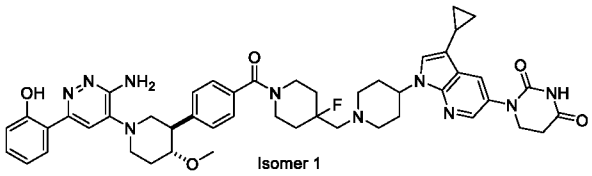


[2411] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (15.0 mg, 0.03 mmol) and Intermediate 2e (30 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (13.2 mg, 44%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 1.81 (2H, m), 1.92 (3H, br s), 1.95 - 2.06 (3H, m), 2.23 - 2.34 (1H, m), 2.43 (5H, s), 2.60 - 2.63 (1H, m), 2.64 - 2.69 (1H, m), 2.73 (2H, d), 2.99 - 3.08 (3H, m), 3.10 - 3.21 (2H, m), 3.49 (4H, br s), 3.62 - 3.71 (1H, m), 3.77 (2H, s), 3.90 - 4.01 (1H, m), 4.18 - 4.30 (1H, m), 4.30 - 4.40 (1H, m), 6.43 - 6.47 (1H, m), 6.47 - 6.54 (2H, m), 6.83 - 6.94 (2H, m), 7.03 - 7.11 (1H, m), 7.22 - 7.32 (3H, m), 7.44 - 7.48 (1H, m), 7.49 - 7.52 (1H, m), 7.52 - 7.56 (2H, m), 7.67 - 7.75 (1H, m), 7.94 - 8.00 (1H, m), 10.18 - 10.30 (1H, m), 13.34 - 14.69 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 850.6.

EXAMPLE 180:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

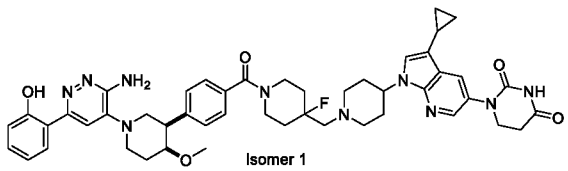


[01002] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 176f (10 mg, 0.02 mmol) and Intermediate 20g (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (9.1 mg, 44%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.56 - 0.70 (2H, m), 0.77 - 0.91 (2H, m), 1.14 - 1.30 (1H, m), 1.57 - 2.16 (11H, m), 2.28 - 2.41 (3H, m), 2.55 - 2.67 (1H, m), 2.70 - 2.78 (2H, m), 2.80 - 2.96 (2H, m), 2.96 - 3.08 (2H, m), 3.14 (5H, br s), 3.19 - 3.24 (1H, m), 3.41 - 3.57 (2H, m), 3.59 - 3.73 (2H, m), 3.74 - 3.86 (2H, m), 4.05 - 4.75 (1H, m), 6.24 - 6.57 (1H, m), 6.79 - 6.95 (2H, m), 7.18 - 7.29 (1H, m), 7.31 - 7.47 (5H, m), 7.48 - 7.56 (1H, m), 7.76 - 7.99 (2H, m), 8.09 - 8.14 (1H, m), 8.14 - 8.20 (1H, m), 10.31 - 10.40 (1H, m) (-OH not observed); *m/z* (ES$^+$) $[M+H]^+$ = 871.6.

EXAMPLE 181:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

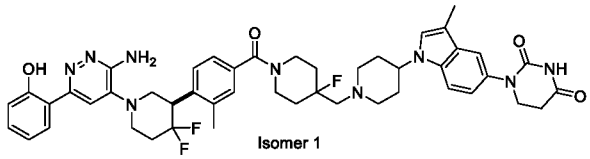


[2412] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 178b (10 mg, 0.02 mmol) and Intermediate 20g (22 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (15.1 mg, 73%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.70 (2H, m), 0.79 - 0.93 (2H, m), 1.63 - 2.25 (11H, m), 2.28 - 2.46 (1H, m), 2.54 - 2.70 (2H, m), 2.77 (2H, s), 3.00 - 3.10 (2H, m), 3.16 (4H, s), 3.20 - 3.26 (1H, m), 3.35 - 3.46 (5H, m), 3.48 - 3.68 (2H, m), 3.71 - 3.77 (1H, m), 3.82 (2H, s), 4.11 - 4.43 (1H, m), 4.51 - 4.82 (1H, m), 6.27 - 6.55 (2H, m), 6.87 - 6.96 (2H, m), 7.23 - 7.30 (1H, m), 7.35 - 7.39 (2H, m), 7.40 - 7.45 (1H, m), 7.45 - 7.50 (2H, m), 7.59 - 7.71 (1H, m), 7.88 - 8.01 (2H, m), 8.15 - 8.23 (1H, m), 10.31 - 10.50 (1H, m), 13.14 - 14.70 (1H, m); *m/z* (ES$^-$) $[M-H]^-$ = 869.7.

EXAMPLE 182:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

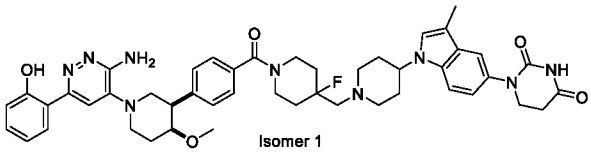


[2413] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (15.0 mg, 0.03 mmol) and Intermediate 1k (30.6 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (18.5 mg, 62%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.68 - 2.12 (7H, m), 2.25 (3H, s), 2.28 - 2.34 (1H, m), 2.43 (3H, s), 2.53 - 2.68 (2H, m), 2.74 (4H, s), 2.80 - 2.99 (2H, m), 3.01 - 3.10 (2H, m), 3.11 - 3.23 (2H, m), 3.40 - 3.50 (2H, m), 3.51 - 3.62 (2H, m), 3.66 - 3.72 (1H, m), 3.75 - 3.81 (2H, m), 3.90 - 4.03 (1H, m), 4.13 - 4.55 (2H, m), 6.46 - 6.74 (2H, m), 6.92 (2H, d), 7.03 - 7.12 (1H, m), 7.24 - 7.32 (4H, m), 7.40 - 7.44 (1H, m), 7.46 - 7.54 (2H, m), 7.68 - 7.73 (1H, m), 7.90 - 7.95 (1H, m), 10.25 (1H, s), 13.04 - 14.51 (1H, m); *m/z* (ES$^-$) $[M-H]^-$ = 862.6.

EXAMPLE 183:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

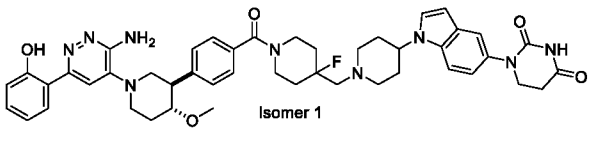


[2414] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 178b (15 mg, 0.04 mmol) and Intermediate 1k (32 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (8.0 mg, 27%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.63 – 1.84 (2H, m), 1.85 – 2.13 (7H, m), 2.15 – 2.21 (1H, m), 2.24 (3H, s), 2.56 – 2.69 (2H, m), 2.73 (3H, s), 3.00 – 3.09 (2H, m), 3.17 (4H, s), 3.21 – 3.27 (1H, m), 3.39 (4H, br s), 3.47 – 3.65 (2H, m), 3.77 (4H, s), 4.13 – 4.47 (2H, m), 6.28 – 6.48 (2H, m), 6.88 – 6.94 (2H, m), 7.03 – 7.10 (1H, m), 7.24 – 7.28 (1H, m), 7.29 – 7.33 (1H, m), 7.35 – 7.42 (3H, m), 7.44 – 7.52 (3H, m), 7.60 – 7.68 (1H, m), 7.91 – 8.00 (1H, m), 10.09 – 10.43 (1H, m), 13.59 – 14.81 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 844.4.

EXAMPLE 184:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

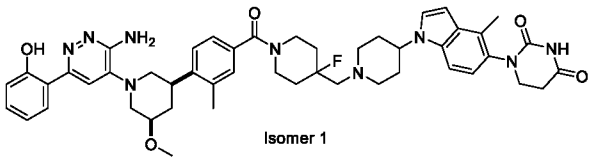


[2415] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 176f (10 mg, 0.02 mmol) and Intermediate 2e (21 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (7.1 mg, 36%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.21 - 1.30 (1H, m), 1.60 - 1.84 (4H, m), 1.85 - 2.11 (6H, m), 2.27 - 2.35 (1H, m), 2.35 - 2.46 (2H, m), 2.57 - 2.63 (1H, m), 2.64 - 2.68 (1H, m), 2.69 - 2.74 (2H, m), 2.81 - 2.91 (2H, m), 3.00 - 3.08 (2H, m), 3.09 - 3.13 (1H, m), 3.15 (4H, s), 3.24 - 3.28 (1H, m), 3.42 - 3.50 (1H, m), 3.58 - 3.71 (2H, m), 3.72 - 3.80 (2H, m), 4.26 - 4.40 (1H, m), 6.28 - 6.38 (2H, m), 6.42 - 6.48 (1H, m), 6.83 - 6.90 (2H, m), 7.02 - 7.10 (1H, m), 7.18 - 7.26 (1H, m), 7.39 (2H, s), 7.45 (3H, s), 7.54 (3H, br s), 7.88 - 7.94 (1H, m), 10.22 - 10.27 (1H, m), 13.91 - 14.48 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 830.5.

EXAMPLE 185:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

[2416] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (10 mg, 0.02 mmol) and Intermediate 32g (20.6 mg, 0.02 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (2.7 mg, 14%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (2H, br s), 1.66 - 1.80 (2H, m), 1.86 - 1.93 (3H, m), 1.96 - 2.07 (3H, m), 2.25 - 2.30 (1H, m), 2.30 - 2.33 (3H, m), 2.35 - 2.40 (1H, m), 2.41 - 2.43 (4H, m), 2.43 - 2.46 (1H, m), 2.52 - 2.56 (1H, m), 2.58 - 2.63 (1H, m), 2.63 - 2.67 (1H, m), 2.67 - 2.75 (1H, m), 2.76 - 2.83 (2H, m), 3.02 - 3.08 (2H, m), 3.38 - 3.39 (3H, m), 3.41 - 3.48 (2H, m), 3.50 - 3.58 (2H, m), 3.70 - 3.80 (2H, m), 3.81 - 3.88 (1H, m), 4.12 - 4.28 (1H, m), 4.29 - 4.39 (1H, m), 6.25 - 6.40 (2H, m), 6.47 - 6.58 (1H, m), 6.84 - 6.94 (2H, m), 6.97 - 7.05 (1H, m), 7.25 (3H, s), 7.36 - 7.46 (2H, m), 7.49 - 7.54 (1H, m), 7.57 - 7.63 (1H, m), 7.90 - 8.00 (1H, m), 10.14 - 10.27 (1H, m), 13.77 - 14.46 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 858.7.

EXAMPLE 186:

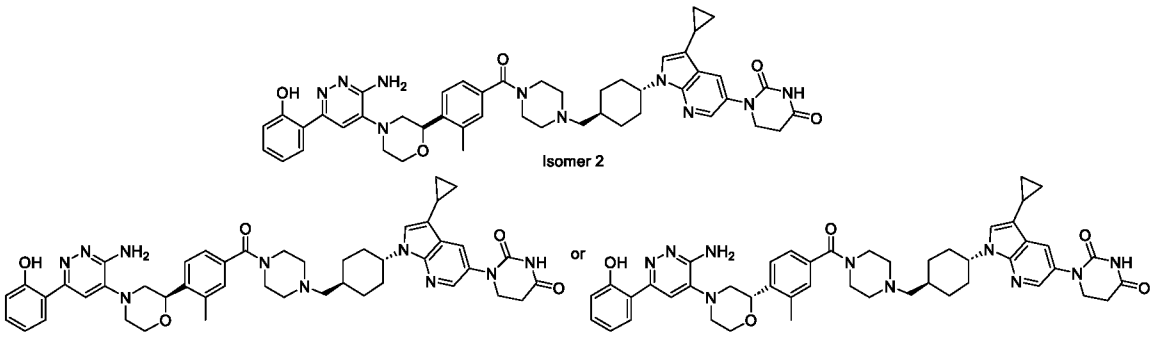
1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

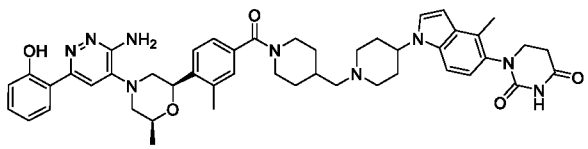
1-(1-((1*R*,4*r*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2417] HATU (0.023 g, 0.06 mmol) was added to a stirred solution of Intermediate 55j (0.024 g, 0.06 mmol) and DIPEA (0.031 mL, 0.18 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 1h, then added Intermediate 120d (0.05 g, 0.06 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 1h. Purification by RPC (elution gradient: 0 to 43% MeCN in water with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) gave the title compound (0.019 g, 37%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.61 – 0.68 (2H, m), 0.80 – 0.90 (2H, m), 1.04 – 1.19 (3H, m), 1.63 (1H, s), 1.81 – 2.01 (7H, m), 2.20 (2H, d), 2.41 (7H, s), 2.77 (2H, t), 2.82 – 2.94 (2H, m), 3.35 – 3.41 (1H, m), 3.49 – 3.71 (4H, m), 3.82 (2H, t), 4.09 (2H, d), 4.55 – 4.70 (1H, m), 4.91 – 5.01 (1H, m), 6.43 (2H, s), 6.83 – 6.94 (2H, m), 7.21 – 7.28 (3H, m), 7.40 (1H, s), 7.53 – 7.61 (2H, m), 7.91 – 7.97 (2H, m), 8.16 (1H, d), 10.37 (1H, s), 14.20 (1H, s); *m/z* (ES$^+$), $[M+H]^+$ = 839.

EXAMPLE 187:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

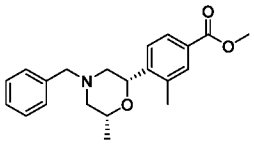


[2418] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 132e (21.02 mg, 0.05 mmol) and Intermediate 38b (38.3 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (23.00 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.09 (2H, br s), 1.25 (3H, d), 1.68 (1H, br s), 1.78 - 1.88 (2H, m), 1.89 - 2.03 (4H, m), 2.16 (2H, br t), 2.20 - 2.28 (2H, m), 2.31 (3H, s), 2.41 (3H, s), 2.52 - 2.57 (1H, m), 2.68 - 2.83 (4H, m), 2.95 - 3.10 (3H, m), 3.45 - 3.65 (4H, m), 3.74 (1H, ddd), 4.12 - 4.19 (1H, m), 4.28 - 4.38 (1H, m), 4.48 (1H, br s), 5.04 (1H, br d), 6.45 (2H, s), 6.53 (1H, d), 6.84 - 6.92 (2H, m), 7.01 (1H, d), 7.19 - 7.27 (3H, m), 7.39 (1H, d), 7.51 - 7.59 (3H, m), 7.96 (1H, d), 10.27 (1H, s), 14.23 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 826.6.

EXAMPLE 188

Intermediate 188a:

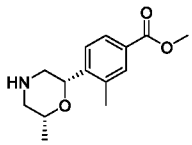
Methyl 4-((2*S*,6*R*)-4-benzyl-6-methylmorpholin-2-yl)-3-methylbenzoate



[2419] Prepared in an analogous manner to Intermediate 65a starting from (*R*)-1-(benzylamino)propan-2-ol (2.290 g, 13.86 mmol) and methyl 4-(2-bromoacetyl)-3-methylbenzoate (3.42 g, 12.6 mmol). Purification by FSC (elution gradient: 0 to 35% EtOAc in hexanes) gave the title compound that eluted second off the column (1.87 g, 43%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.12 (3H, d), 1.79 (2H, q), 2.27 (3H, s), 2.73 - 2.86 (2H, m), 3.45 - 3.55 (2H, m), 3.75 - 3.80 (1H, m), 3.81 (3H, s), 4.72 - 4.77 (1H, m), 7.21 - 7.26 (1H, m), 7.27 - 7.32 (4H, m), 7.49 (1H, d), 7.72 (1H, s), 7.77 (1H, d); *m/z* (ES$^+$) [M+H]$^+$ = 340.6.

Intermediate 188b:

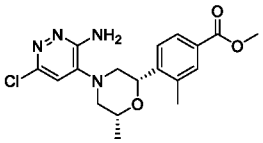
Methyl 3-methyl-4-((2*S*,6*R*)-6-methylmorpholin-2-yl)benzoate



[2420] Prepared in an analogous manner to Intermediate 65b staring from Intermediate 188a (1.8702 g, 5.51 mmol). Filtration through celite and concentration *in vacuo* gave the title compound (1.374 mg, 100%) as a yellow film. *m/z* (ES$^+$) [M+H]$^+$ = 250.4.

Intermediate 188c:

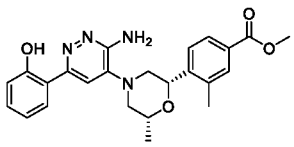
Methyl 4-((2*S*,6*R*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2421] Prepared in an analogous manner to Intermediate 1d staring from Intermediate 188b (1.374 g, 5.51 mmol). Purification by FSC (elution gradient: 0to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave the title compound (1.039 g, 50%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.20 (3H, d), 2.40 (3H, s), 2.44 (1H, br t), 2.51 - 2.56 (1H, m), 3.42 (1H, br d), 3.49 (1H, br d), 3.83 (3H, s), 4.03 - 4.13 (1H, m), 5.01 (1H, br d), 6.28 (2H, s), 6.95 (1H, s), 7.58 (1H, d), 7.77 (1H, s), 7.78 - 7.82 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 377.5.

Intermediate 188d:

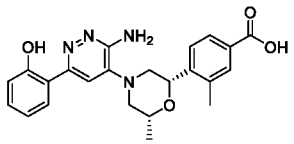
Methyl 4-((2*S*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2422] Prepared in an analogous manner to Intermediate 1e staring from Intermediate 188c (1.03 g, 2.76 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (1.033 g, 86%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, br d), 2.44 (3H, s), 2.56 (1H, br t), 2.67 (1H, br t), 3.53 (1H, br d), 3.57 - 3.60 (1H, m), 3.85 (3H, s), 4.11 - 4.21 (1H, m), 5.09 (1H, br d), 6.45 (2H, s), 6.80 - 6.95 (2H, m), 7.23 (1H, t), 7.56 (1H, s), 7.64 (1H, d), 7.79 - 7.82 (1H, m), 7.84 (1H, d), 7.94 (1H, d), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 435.7.

Intermediate 188e:

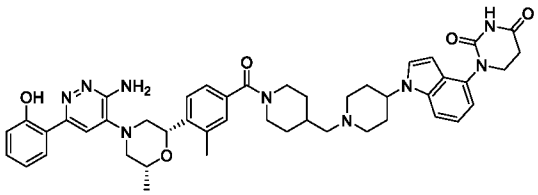
4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoic acid



[2423] Prepared in an analogous manner to Intermediate 132e staring from Intermediate 188d (1.033 g, 2.38 mmol). The title compound (0.715 g, 71%) was obtained as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 2.43 (3H, s), 2.53 - 2.65 (1H, m), 2.73 (1H, br t), 3.53 - 3.66 (2H, m), 4.11 - 4.20 (1H, m), 5.07 (1H, br d), 6.73 (2H, br s), 6.89 (1H, t), 6.93 (1H, br d), 7.27 (1H, br t), 7.56 (1H, s), 7.61 (1H, d), 7.78 (1H, s), 7.82 (1H, br d), 7.86 (1H, br d), 13.32 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.5.

EXAMPLE 188:

1-(1-(1-((1-(4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

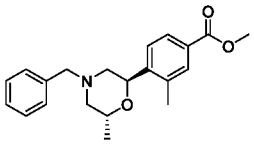


[2424] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 188e (21.02 mg, 0.05 mmol) and Intermediate 10e (24.12 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (19.8 mg, 48%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.04 - 1.16 (2H, m), 1.25 (3H, d), 1.63 - 1.74 (1H, m), 1.79 - 1.89 (2H, m), 1.90 - 2.06 (4H, m), 2.17 (2H, br t), 2.22 - 2.28 (2H, m), 2.41 (3H, s), 2.52 - 2.59 (1H, m), 2.70 - 2.81 (4H, m), 2.95 - 3.10 (3H, m), 3.51 - 3.67 (3H, m), 3.78 (2H, t), 4.10 - 4.21 (1H, m), 4.34 - 4.42 (1H, m), 4.42 - 4.56 (1H, m), 5.04 (1H, br d), 6.38 - 6.46 (3H, m), 6.85 - 6.92 (2H, m), 6.96 (1H, d), 7.15 (1H, t), 7.18 - 7.27 (3H, m), 7.48 - 7.63 (4H, m), 7.96 (1H, d), 10.32 (1H, s), 14.21 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 812.6.

EXAMPLE 189

Intermediate 189a:

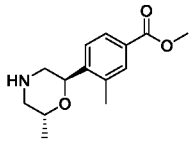
Methyl 4-((2*R*,6*R*)-4-benzyl-6-methylmorpholin-2-yl)-3-methylbenzoate



[2425] Prepared following the same procedure as for Intermediate 188a isolating the diastereomer that eluted first off the column (1.79 g, 41%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.21 (3H, d), 2.25 - 2.36 (5H, m), 2.39 - 2.46 (1H, m), 2.70 (1H, dd), 3.42 - 3.52 (2H, m), 3.80 - 3.88 (4H, m), 4.99 (1H, dd), 7.22 - 7.27 (1H, m), 7.30 - 7.35 (4H, m), 7.68 (1H, d), 7.71 - 7.76 (2H, m); *m/z* (ES$^+$) [M+H]$^+$ = 340.6.

Intermediate 189b:

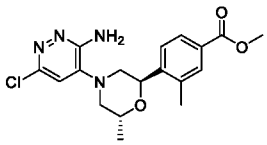
Methyl 3-methyl-4-((2*R*,6*R*)-6-methylmorpholin-2-yl)benzoate



[2426] Prepared in an analogous manner to Intermediate 65b staring from Intermediate 189a (1.7878 g, 5.27 mmol). Filtration through celite and concentration *in vacuo* gave the title compound (1.31 g, 100%) as a yellow film. *m/z* (ES$^+$) [M+H]$^+$ = 250.5.

Intermediate 189c:

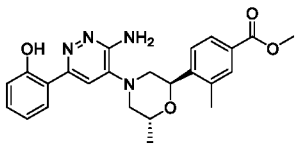
Methyl 4-((2*R*,6*R*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2427] Prepared in an analogous manner to Intermediate 1d staring from Intermediate 189b (1.314 g, 5.27 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave the title compound (1.014 g, 51%) as a light brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.46 (3H, d), 2.46 (3H, s), 2.53 - 2.59 (1H, m), 2.98 (1H, br d), 3.19 (1H, dd), 3.63 (1H, br d), 3.84 (3H, s), 4.25 - 4.32 (1H, m), 5.38 (1H, dd), 6.23 (2H, s), 6.96 (1H, s), 7.57 (1H, d), 7.74 - 7.80 (2H, m); *m/z* (ES$^+$) [M+H]$^+$ = 377.5.

Intermediate 189d:

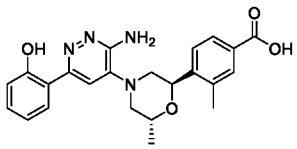
Methyl 4-((2*R*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2428] Prepared in an analogous manner to Intermediate 1e staring from Intermediate 189c (1.0141 g, 2.69 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (1.029 g, 88%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.52 (3H, d), 2.49 (3H, s), 2.66 (1H, dd), 3.14 (1H, br d), 3.30 (1H, dd), 3.69 (1H, br d), 3.83 - 3.86 (3H, m), 4.34 (1H, dt), 5.43 (1H, dd), 6.36 (2H, s), 6.85 - 6.94 (2H, m), 7.20 - 7.29 (1H, m), 7.57 (1H, s), 7.62 (1H, d), 7.77 - 7.81 (2H, m), 7.94 (1H, dd), 14.16 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 435.6.

Intermediate 189e:

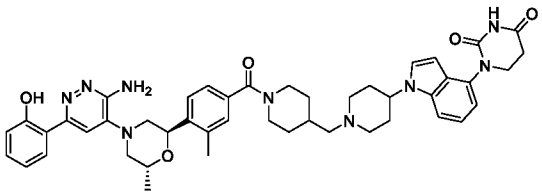
4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoic acid



[2429] Prepared in an analogous manner to Intermediate 132e staring from Intermediate 189d (1.0289 g, 2.37 mmol). The title compound (0.694 g, 69%) was obtained as a beige solid. ^{1}H NMR (DMSO-*d*6): δ 1.51 (3H, d), 2.46 - 2.49 (3H, m), 2.69 (1H, br dd), 3.14 (1H, br d), 3.28 - 3.33 (1H, m), 3.69 (1H, br d), 4.29 - 4.39 (1H, m), 5.42 (1H, dd), 6.37 (2H, br s), 6.87 - 6.92 (2H, m), 7.25 (1H, t), 7.55 - 7.62 (2H, m), 7.75 - 7.81 (2H, m), 7.94 (1H, d), 13.48 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.4.

EXAMPLE 189:

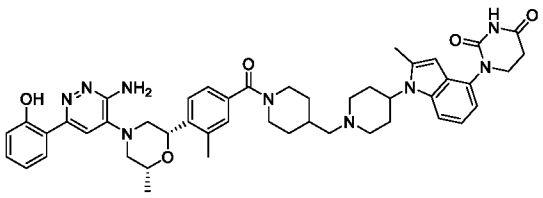
1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2430] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 189e (21.02 mg, 0.05 mmol) and Intermediate 10e (24.12 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (18.0 mg, 44%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.99 - 1.16 (2H, m), 1.50 (3H, d), 1.60 - 1.73 (1H, m), 1.77 - 1.87 (2H, m), 1.88 - 2.03 (4H, m), 2.11 - 2.18 (2H, m), 2.19 - 2.26 (2H, m), 2.44 (3H, s), 2.70 - 2.78 (3H, m), 2.90 - 3.07 (3H, m), 3.12 (1H, br d), 3.24 - 3.29 (1H, m), 3.32 - 3.38 (1H, m), 3.53 - 3.62 (1H, m), 3.66 (1H, br d), 3.76 (2H, t), 4.27 - 4.39 (2H, m), 4.40 - 4.52 (1H, m), 5.37 (1H, dd), 6.30 (2H, s), 6.40 (1H, d), 6.85 - 6.91 (2H, m), 6.94 (1H, d), 7.13 (1H, t), 7.15 - 7.20 (2H, m), 7.23 (1H, t), 7.46 - 7.53 (3H, m), 7.56 (1H, s), 7.93 (1H, d), 10.30 (1H, s), 14.14 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 812.6.

EXAMPLE 190:

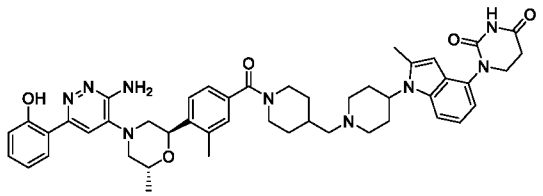
1-(1-(1-((1-(4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2431] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 188e (21.02 mg, 0.05 mmol) and Intermediate 165a (27.5 mg, 0.07 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (24.1 mg, 58%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.02 - 1.16 (2H, m), 1.24 (3H, d), 1.66 - 1.79 (3H, m), 1.79 - 1.91 (2H, m), 2.11 (2H, br t), 2.18 - 2.28 (2H, m), 2.35 - 2.46 (8H, m), 2.51 - 2.58 (1H, m), 2.68 - 2.82 (4H, m), 2.95 - 3.08 (3H, m), 3.54 (2H, br t), 3.58 - 3.67 (1H, m), 3.72 (2H, t), 4.09 - 4.17 (1H, m), 4.18 - 4.28 (1H, m), 4.38 - 4.55 (1H, m), 5.03 (1H, br d), 6.14 (1H, s), 6.41 (2H, s), 6.83 - 6.91 (3H, m), 7.03 (1H, t), 7.17 - 7.26 (3H, m), 7.44 (1H, d), 7.51 - 7.58 (2H, m), 7.94 (1H, d), 10.28 (1H, s), 14.20 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 826.6.

EXAMPLE 191:

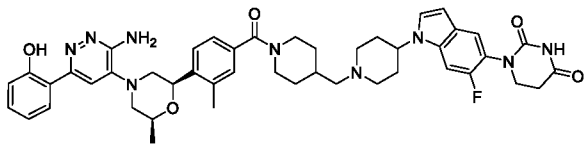
1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2432] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 189e (21.02 mg, 0.05 mmol) and Intermediate 165a (27.5 mg, 0.07 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (26.8 mg, 64%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.03 - 1.18 (2H, m), 1.52 (3H, d), 1.76 (3H, br d), 1.81 - 1.93 (2H, m), 2.13 (2H, br t), 2.24 (2H, br d), 2.36 - 2.48 (8H, m), 2.71 - 2.81 (4H, m), 2.95 - 3.11 (3H, m), 3.15 (1H, br d), 3.25 - 3.31 (1H, m), 3.55 - 3.66 (1H, m), 3.68 (1H, br d), 3.74 (2H, t), 4.18 - 4.29 (1H, m), 4.30 - 4.37 (1H, m), 4.40 - 4.62 (1H, m), 5.39 (1H, br d), 6.16 (1H, s), 6.33 (2H, s), 6.87 - 6.92 (3H, m), 7.04 (1H, t), 7.18 - 7.22 (2H, m), 7.25 (1H, t), 7.46 (1H, d), 7.51 - 7.56 (1H, m), 7.59 (1H, s), 7.95 (1H, d), 10.29 (1H, s), 14.16 (1H, s); *m/z* (ES^+) $[M+H]^+$ =826.6.

EXAMPLE 192:

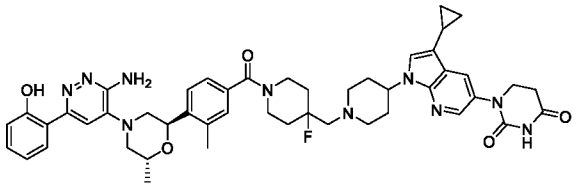
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2433] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 132e (21.02 mg, 0.05 mmol) and Intermediate 30b (32.8 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (22.1 mg, 53%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.01 - 1.15 (2H, m), 1.25 (3H, d), 1.61 - 1.75 (1H, m), 1.78 - 2.02 (6H, m), 2.11 - 2.27 (4H, m), 2.41 (3H, s), 2.52 - 2.57 (1H, m), 2.67 - 2.81 (4H, m), 2.93 - 3.08 (3H, m), 3.46 - 3.64 (3H, m), 3.70 (2H, br t), 4.09 - 4.22 (1H, m), 4.27 - 4.40 (1H, m), 4.42 - 4.56 (1H, m), 5.04 (1H, br d), 6.44 - 6.50 (3H, m), 6.84 - 6.92 (2H, m), 7.19 - 7.27 (3H, m), 7.52 - 7.60 (5H, m), 7.96 (1H, d), 10.41 (1H, s), 14.23 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 830.5.

EXAMPLE 193:

1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

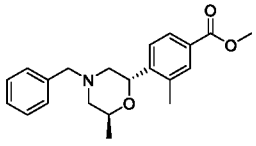


[2434] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 189e (21.02 mg, 0.05 mmol) and Intermediate 20g (46.2 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (33.3 mg, 76%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.63 - 0.70 (2H, m), 0.81 - 0.90 (2H, m), 1.52 (3H, d), 1.64 - 1.87 (5H, m), 1.88 - 2.00 (2H, m), 2.01 - 2.12 (2H, m), 2.35 (2H, br t), 2.46 (3H, s), 2.57 - 2.67 (2H, m), 2.72 - 2.81 (3H, m), 3.03 (2H, br d), 3.14 (2H, br d), 3.22 - 3.32 (2H, m), 3.41 - 3.54 (1H, m), 3.68 (1H, br d), 3.82 (2H, t), 4.19 - 4.30 (1H, m), 4.30 - 4.39 (1H, m), 4.54 - 4.65 (1H, m), 5.36 - 5.43 (1H, m), 6.32 (2H, s), 6.87 - 6.93 (2H, m), 7.22 - 7.27 (3H, m), 7.44 (1H, s), 7.52 - 7.57 (1H, m), 7.58 (1H, s), 7.95 (2H, br d), 8.17 (1H, d), 10.36 (1H, br s), 14.16 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 871.6.

EXAMPLE 194

Intermediate 194a:

Methyl 4-((2*S*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-3-methylbenzoate

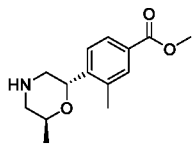


[2435] Prepared following the same procedure as for Intermediate 132a isolating the diastereomer that eluted first off the column (4.21 g, 35%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.28 - 2.40

(5H, m), 2.45 (1H, dd), 2.73 (1H, dd), 3.42 - 3.60 (2H, m), 3.80 - 3.91 (4H, m), 5.02 (1H, dd), 7.21 - 7.30 (1H, m), 7.30 - 7.42 (4H, m), 7.67 - 7.80 (3H, m); *m/z* (ES^+) $[M+H]^+$ = 340.5.

Intermediate 194b:

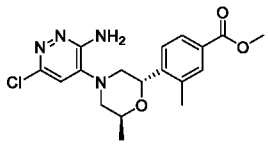
Methyl 3-methyl-4-((2*S*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2436] Prepared in an analogous manner to Intermediate 65b staring from Intermediate 194a (4.2 g, 12.37 mmol). Filtration through celite and concentration *in vacuo* gave the title compound (3.08 g, 12.37 mmol) as a yellow oil. ^1H NMR (DMSO-*d*6): δ 1.31 (3H, d), 2.37 (3H, s), 2.52 - 2.62 (2H, m), 2.94 (2H, ddd), 2.99 - 3.12 (1H, m), 3.84 (3H, s), 3.90 - 3.98 (1H, m), 4.91 (1H, dd), 7.63 (1H, d), 7.74 (1H, s), 7.77 (1H, br d); *m/z* (ES^+) $[M+H]^+$ = 250.4.

Intermediate 194c:

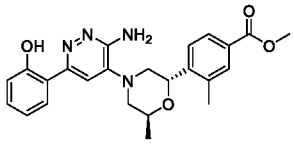
Methyl 4-((2*S*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2437] Prepared in an analogous manner to Intermediate 1d staring from Intermediate 194b (3.08 g, 12.37 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave the title compound (2.67 g, 57%) as a light brown solid. ^1H NMR (DMSO-*d*6): δ 1.46 (3H, d), 2.46 (3H, s), 2.53 - 2.60 (1H, m), 2.98 (1H, br d), 3.20 (1H, dd), 3.63 (1H, br d), 3.84 (3H, s), 4.25 - 4.32 (1H, m), 5.38 (1H, dd), 6.24 (2H, s), 6.96 (1H, s), 7.58 (1H, d), 7.78 (1H, d), 7.77 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 377.5.

Intermediate 194d:

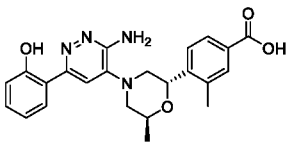
Methyl 4-((2*S*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoate



[2438] Prepared in an analogous manner to Intermediate 1e staring from Intermediate 194c (2.66 g, 7.08 mmol). Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (2.126 g, 69%) as a brown solid. ^1H NMR (DMSO-*d*6): δ 1.52 (3H, d), 2.49 (3H, s), 2.66 (1H, dd), 3.11 - 3.17 (1H, m), 3.30 (1H, br dd), 3.69 (1H, br d), 3.84 (3H, s), 4.30 - 4.39 (1H, m), 5.43 (1H, dd), 6.36 (2H, s), 6.86 - 6.93 (2H, m), 7.21 - 7.28 (1H, m), 7.57 (1H, s), 7.62 (1H, d), 7.77 - 7.82 (2H, m), 7.91 - 7.98 (1H, m), 14.17 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 435.7.

Intermediate 194e:

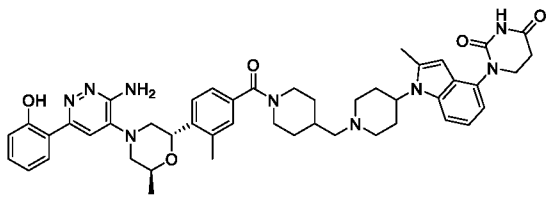
4-((2*S*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoic acid



[2439] Prepared in an analogous manner to Intermediate 132e staring from Intermediate 194d (2.126 g, 4.89 mmol). The title compound (1.699 g, 83%) was obtained as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.50 (3H, d), 2.46 (3H, s), 2.68 (1H, br dd), 3.12 (1H, br d), 3.29 (1H, br dd), 3.67 (1H, br d), 4.27 - 4.38 (1H, m), 5.40 (1H, dd), 6.36 (2H, br s), 6.82 - 6.94 (2H, m), 7.20 - 7.28 (1H, m), 7.52 - 7.62 (2H, m), 7.72 - 7.79 (2H, m), 7.91 (1H, d), 12.78 - 14.13 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 421.6.

EXAMPLE 194:

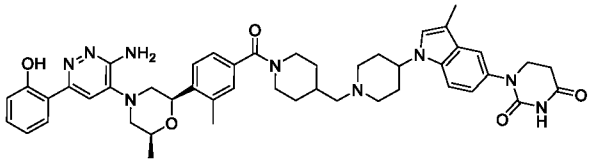
1-(1-(1-((1-(4-((2*S*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2440] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 194e (21.02 mg, 0.05 mmol) and Intermediate 165a (27.5 mg, 0.07 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (27.6 mg, 66%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.02 - 1.28 (2H, m), 1.52 (3H, d), 1.66 - 1.94 (5H, m), 2.07 - 2.17 (2H, m), 2.24 (2H, br s), 2.36 - 2.48 (7H, m), 2.70 - 2.81 (4H, m), 2.95 - 3.07 (3H, m), 3.14 (1H, br d), 3.27 - 3.32 (1H, m), 3.36 - 3.41 (1H, m), 3.53 - 3.65 (1H, m), 3.68 (1H, br d), 3.74 (2H, t), 4.23 (1H, br t), 4.29 - 4.39 (1H, m), 4.49 (1H, br d), 5.39 (1H, dd), 6.15 (1H, s), 6.35 (2H, s), 6.90 (3H, t), 7.04 (1H, t), 7.17 - 7.22 (2H, m), 7.23 - 7.28 (1H, m), 7.46 (1H, d), 7.53 (1H, d), 7.59 (1H, s), 7.96 (1H, d), 10.32 (1H, br s), 14.19 (1H, br s); *m/z* (ES$^-$) $[M-H]^-$ = 824.9.

EXAMPLE 195:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

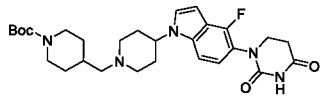


[2441] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 132e (21.02 mg, 0.05 mmol) and Intermediate 113b (38.3 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (26.8 mg, 64%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.02 - 1.15 (2H, m), 1.25 (3H, d), 1.64 - 1.73 (1H, m), 1.78 - 1.99 (6H, m), 2.14 (2H, br t), 2.23 (5H, s), 2.41 (3H, s), 2.53 - 2.58 (1H, m), 2.67 - 2.80 (4H, m), 2.93 - 3.08 (3H, m), 3.51 - 3.67 (3H, m), 3.77 (2H, t), 4.11 - 4.19 (1H, m), 4.24 - 4.33 (1H, m), 4.48 (1H, br s), 5.04 (1H, br d), 6.45 (2H, s), 6.85 - 6.91 (2H, m), 7.05 (1H, dd), 7.19 - 7.27 (3H, m), 7.31 (1H, s), 7.40 (1H, d), 7.47 (1H, d), 7.52 - 7.59 (2H, m), 7.96 (1H, dd), 10.27 (1H, s), 14.24 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 826.5.

EXAMPLE 196

Intermediate 196a:

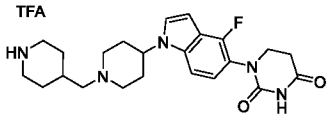
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluoro-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2442] Prepared in an analogous manner to Intermediate 10d staring from Intermediate 3e (250 mg, 0.50 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes then 0 to 30% MeOH in EtOAc) gave the title compound (201 mg, 77%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.90 - 1.02 (2H, m), 1.40 (9H, s), 1.71 (3H, br d), 1.89 - 1.95 (2H, m), 1.96 - 2.06 (2H, m), 2.12 - 2.23 (4H, m), 2.58 - 2.81 (4H, m), 2.98 (2H, br d), 3.71 (2H, t), 3.86 - 4.02 (2H, m), 4.34 - 4.42 (1H, m), 6.56 (1H, d), 7.12 (1H, t), 7.43 (1H, d), 7.63 (1H, d), 10.42 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 528.5.

Intermediate 196b:

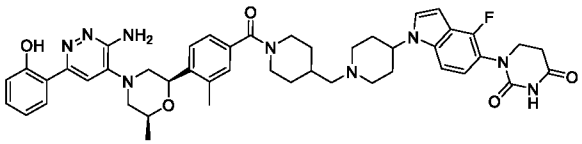
1-(4-Fluoro-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2443] Prepared in an analogous manner to Intermediate 1i staring from Intermediate 196a (201 mg, 0.38 mmol). Suspension in MeCN/H_2O and lyophilization gave the title compound (288 mg, 98%) as a white solid in the form of a *tris*(trifluoroacetic acid) salt. ^{1}H NMR (DMSO-*d*6): δ 1.35 - 1.46 (2H, m), 1.95 (2H, br d), 2.04 - 2.25 (3H, m), 2.33 - 2.43 (2H, m), 2.75 (2H, t), 2.90 (2H, q), 3.07 - 3.24 (3H, m), 3.34 (2H, br d), 3.45 - 3.55 (1H, m), 3.69 - 3.80 (4H, m), 4.73 - 4.88 (1H, m), 6.62 - 6.67 (1H, m), 7.18 (1H, t), 7.46 - 7.52 (2H, m), 8.47 (1H, br d), 8.63 - 8.81 (1H, m), 9.76 (1H, br s), 10.44 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 428.5

EXAMPLE 196:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

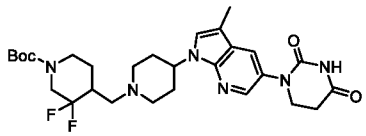


[2444] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 132e (21.02 mg, 0.05 mmol) and Intermediate 196b (38.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound(26.6 mg, 64%) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.02 - 1.16 (2H, m), 1.25 (3H, d), 1.64 - 1.73 (1H, m), 1.80 - 1.89 (2H, m), 1.90 - 2.06 (4H, m), 2.11 - 2.28 (4H, m), 2.41 (3H, s), 2.52 - 2.57 (1H, m), 2.69 - 2.81 (4H, m), 2.93 - 3.12 (3H, m), 3.49 - 3.65 (3H, m), 3.71 (2H, t), 4.11 - 4.19 (1H, m), 4.33 - 4.43 (1H, m), 4.43 - 4.56 (1H, m), 5.04 (1H, br d), 6.45 (2H, s), 6.56 (1H, d), 6.84 - 6.91 (2H, m), 7.12 (1H, t), 7.19 - 7.26 (3H, m), 7.43 (1H, d), 7.53 - 7.59 (2H, m), 7.62 (1H, d), 7.96 (1H, d), 10.41 (1H, s), 14.23 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 830.5.

EXAMPLE 197

Intermediate 197a:

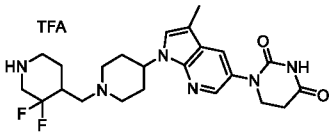
rac-tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate



[2445] Dess-Martin periodinane (306 mg, 0.72 mmol) was added to a stirred solution of *tert*-butyl 3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (121 mg, 0.48 mmol) in DCM (3 mL) at 0 °C. The resulting solution was stirred at r.t. for 1.5 h. The solids were filtered off and washed with DCM. The filtrate was filtered again and concentrated to afford crude aldehyde intermediate that was used in the next step assuming a quantitative yield. Sodium triacetoxyborohydride (97 mg, 0.46 mmol) was added to a stirred solution of Intermediate 93c (75 mg, 0.23 mmol) and aldehyde intermediate (120 mg, 0.48 mmol) in DCM-IPA (4:1, 5 mL). The resulting solution was stirred at r.t. for 2 h. The reaction mixture was diluted with DCM (25 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 10% MeOH in EtOAc) gave the title compound (98 mg, 76%) as an white solid. *m/z* (ES^+) $[M+H]^+$ = 561.6.

Intermediate 197b:

rac-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2446] Prepared in an analogous method to Intermediate 1i starting from Intermediate 197a (98 mg, 0.17 mmol), which gave the title compound (167 mg, 104%) in the form of a *tetrakis*(trifluoroacetic acid) salt as an amber solid *m/z* (ES^+) $[M+H]^+ = 461.2$.

Intermediate 197c:

(*R**)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

and

Intermediate 197d:

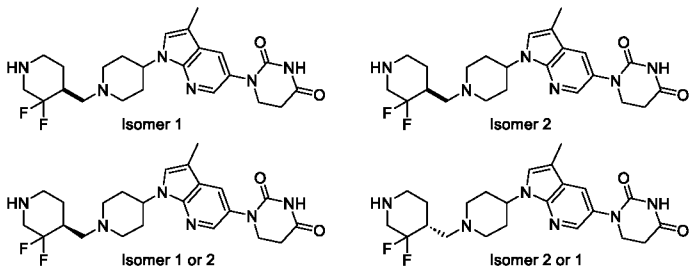
(*R**)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*S*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

and

(*R*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2447] Intermediate 197b (137 mg, 0.149 mmol) was purified using SFC (Column: Chiralpak IH 4.6 x 150 mm, 5 mm; mobile phase: 15% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 75 mL/min; Column temperature: 40°C) to afford Intermediate 197c that eluted first from the column (9.5 mg, 14%, 99% ee) as a white solid and Intermediate 197d that eluted second from the column (10.5 mg, 15%, 96% ee) as a white solid. Intermediate 197c: *m/z* (ES^+) $[M+H]^+ = 461.3$; Intermediate 197d: *m/z* (ES^+) $[M+H]^+ = 461.2$.

EXAMPLE 197:

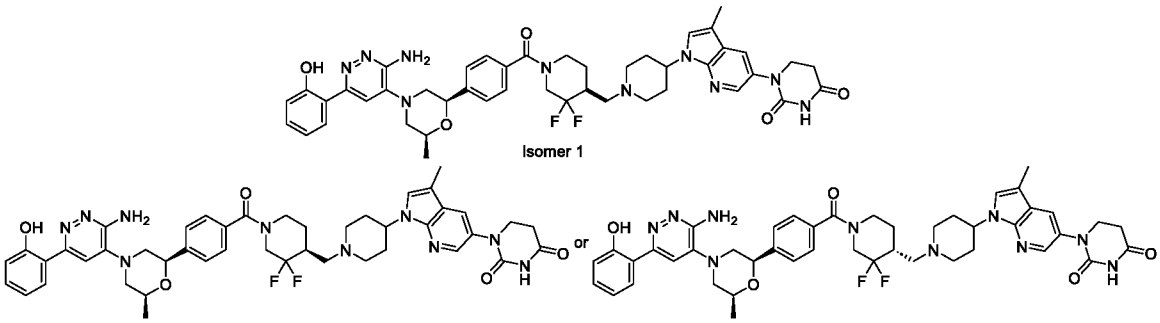
1-(1-(1-(((*R**)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

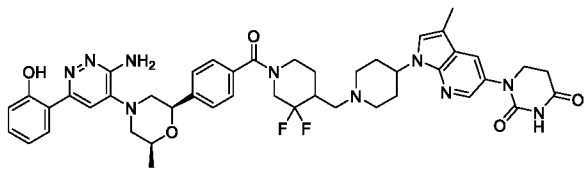
1-(1-(1-(((*R*)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2448] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (9.5 mg, 0.02 mmol) and Intermediate 197c (8 mg, 0.02 mmol). Purification by RPC (elution gradient: 25 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (16 mg, 93%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.36 - 1.51 (1H, m), 1.88 (2H, br d), 1.93 - 2.16 (4H, m), 2.25 (3H, s), 2.31 (1H, br t), 2.38 - 2.48 (2H, m), 2.52 - 2.64 (3H, m, overlaps with residual solvent), 2.70 (1H, br s), 2.76 (2H, t), 2.95 (1H, br d), 3.01 - 3.12 (1.5H, m), 3.22 (0.5H, br s), 3.51 (1H, br d), 3.56 - 3.72 (1.5H, m), 3.81 (2.5H, t), 4.08 - 4.17 (1H, m), 4.42 (0.5H, br s), 4.56 - 4.76 (1.5H, m), 4.97 (1H, br d), 6.49 (2H, s), 6.85 - 6.92 (2H, m), 7.24 (1H, t), 7.42 (2H, d), 7.49 (1H, br s), 7.53 - 7.59 (3H, m), 7.88 (1H, d), 7.96 (1H, d), 8.18 (1H, d), 10.39 (1H, s), 14.22 (1H, br s) (compound exists as a mixture of rotamers); ^{19}F NMR (DMSO-*d*6): δ -116.12 (1F, br dd), -107.40 - -103.95 (1F, m); *m/z* (ES^+) $[M+H]^+$ = 849.5.

EXAMPLE 198:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2449] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (12 mg, 0.03 mmol) and Intermediate 197b (28 mg, 0.03 mmol). Purification by RPC (elution gradient: 25 to 100% MeOH in water with 0.1% NH4OH) gave the title compound (20 mg, 77%) as a white solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 1.21 - 1.32 (3H, m), 1.43 (1H, br d), 1.81 - 1.92 (2H, m), 1.94 - 2.18 (4H, m), 2.25 (3H, s), 2.27 - 2.35 (1H, m), 2.36 - 2.47 (2H, m), 2.51 - 2.64 (m, 3H, overlaps with residual

solvent), 2.69 (1H, br t), 2.76 (2H, t), 2.95 (1H, br d), 3.06 (1.5H, br s), 3.14 - 3.29 (0.5H, m), 3.47 - 3.55 (1H, m), 3.55 - 3.69 (1.5H, m), 3.72 - 3.87 (2.5H, m), 4.08 - 4.16 (1H, m), 4.33 - 4.53 (0.5H, m), 4.55 - 4.72 (1.5H, m), 4.96 (1H, br d), 6.50 (2H, s), 6.84 - 6.92 (2H, m), 7.24 (1H, t), 7.42 (2H, d), 7.45 - 7.53 (1H, m), 7.53 - 7.60 (3H, m), 7.89 (1H, d), 7.96 (1H, d), 8.18 (1H, d), 10.41 (1H, s), 14.24 (1H, br s) (compound exists as a mixture of rotamers); ^{19}F NMR (DMSO-*d*6): δ -116.11 (1F, br dd), -107.21, 104.36 (1F, m); *m/z* (ES$^+$) $[M+H]^+$ = 849.6.

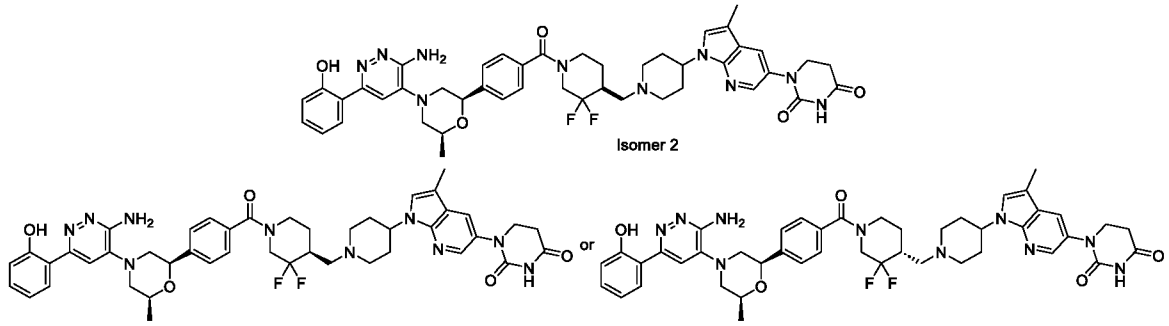
EXAMPLE 199:

1-(1-(1-(((*R**)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)((*relative stereochemistry not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((*R*)-1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

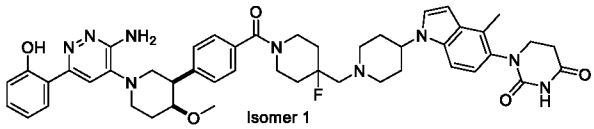


[2450] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (9 mg, 0.02 mmol) and Intermediate 197d (11 mg, 0.02 mmol). Purification by RPC (elution gradient: 25 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (14 mg, 73%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, d), 1.43 (1H, br d), 1.82 - 1.93 (2H, m), 1.94 - 2.14 (4H, m), 2.25 (3H, s), 2.28 - 2.36 (1H, m), 2.37 - 2.46 (2H, m), 2.49 - 2.63 (3H, m, overlaps with residual solvent), 2.69 (1H, br t), 2.76 (2H, t), 2.95 (1H, br d), 3.06 (1.5H, br s), 3.15 - 3.29 (0.5H, m), 3.52 (1H, br d), 3.56 - 3.70 (1.5H, m), 3.81 (2.5H, t), 4.08 - 4.17 (1H, m), 4.34 - 4.50 (0.5H, m), 4.62 (1.5H, br t), 4.96 (1H, br d), 6.49 (2H, s), 6.85 - 6.92 (2H, m), 7.24 (1H, t), 7.42 (2H, d), 7.45 - 7.53 (1H, m), 7.53 - 7.60 (3H, m), 7.88 (1H, d), 7.96 (1H, d), 8.18 (1H, d), 10.39 (1H, s), 14.22 (1H, br s) (compound exists as a mixture of rotamers); ^{19}F NMR (DMSO-*d*6): δ -117.12 - -114.94 (1F, m), -107.14 - -104.20 (1F, m); *m/z* (ES$^+$) $[M+H]^+$ = 849.6.

EXAMPLE 200:

1-(1-(1-((1-(4-((3*R**,4*S**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

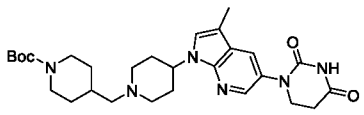


[2451] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 178b (14 mg, 0.03 mmol) and Intermediate 32g (25 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (14 mg, 50%) as a white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.63 - 1.82 (2H, m), 1.82 - 2.09 (7H, m), 2.18 (1H, br d), 2.31 (3H, s), 2.35 - 2.47 (2H, m), 2.59 - 2.67 (2H, m), 2.68 - 2.83 (2H, m), 2.99 - 3.09 (4H, m), 3.16 (4H, s), 3.26 - 3.40 (4H, m), 3.54 (2H, dt), 3.68 - 3.79 (2H, m), 4.10 - 4.38 (2H, m), 6.31 (2H, s), 6.53 (1H, d), 6.85 - 6.94 (2H, m), 7.00 (1H, d), 7.24 (1H, t), 7.35 - 7.42 (3H, m), 7.46 (2H, d), 7.52 (1H, d), 7.66 (1H, s), 8.00 (1H, d), 10.24 (1H, s), 14.29 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.98 (1F, s); *m/z* (ES^+) $[M+H]^+$ = 844.6.

EXAMPLE 201

Intermediate 201a:

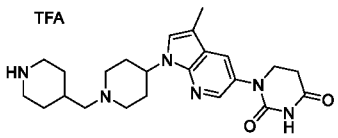
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2452] Prepared in an analogous manner to Intermediate 10d starting from Intermediate 93c (62 mg, 0.19 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (50.5 mg, 0.24 mmol. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 10% MeOH in EtOAc) gave the title compound (71 mg, 72%) as a solid. ^{1}H NMR (DMSO-*d*6): δ 0.91 - 1.01 (2H, m), 1.40 (9H, s), 1.71 (3H, br d), 1.86 (2H, br d), 1.98 - 2.13 (4H, m), 2.19 (2H, br d), 2.25 (3H, s), 2.59 - 2.82 (4H, m), 2.98 (2H, br d), 3.81 (2H, t), 3.93 (2H, br s), 4.56 - 4.65 (1H, m), 7.51 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 525.6.

Intermediate 201b:

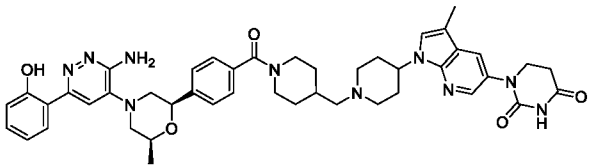
1-(3-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2453] Prepared in an analogous method to Intermediate 1i starting from Intermediate 201a (68 mg, 0.13 mmol), which gave the title compound (118 mg, 103%) in the form of a *tetrakis*(trifluoroacetic acid) salt as a white solid . *m/z* (ES^+) $[M+H]^+$ = 425.5.

EXAMPLE 201:

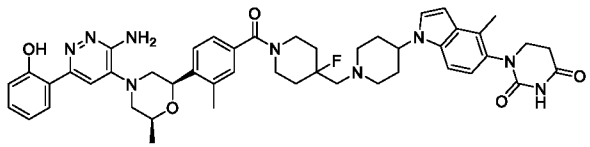
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2454] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (12 mg, 0.03 mmol) and Intermediate 201b (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (19 mg, 75%) as a white solid. ^1H NMR (DMSO-*d6*): δ 1.09 (2H, br s), 1.26 (3H, d), 1.68 (1H, br s), 1.86 (4H, br d), 1.97 - 2.17 (4H, m), 2.19 - 2.30 (2H, m), 2.20 - 2.25 (3H, m), 2.50 - 2.58 (1H, m), 2.63 - 2.73 (1H, m), 2.76 (3H, br t), 2.99 (3H, br d), 3.51 (1H, br d), 3.58 (2H, br d), 3.81 (2H, t), 4.07 - 4.16 (1H, m), 4.48 (1H, br s), 4.56 - 4.66 (1H, m), 4.95 (1H, br d), 6.50 (2H, s), 6.83 - 6.91 (2H, m), 7.24 (1H, t), 7.36 - 7.43 (2H, m), 7.49 (1H, s), 7.51 - 7.55 (2H, m), 7.57 (1H, s), 7.88 (1H, d), 7.96 (1H, d), 8.17 (1H, d), 10.41 (1H, s), 14.24 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 813.6.

EXAMPLE 202:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

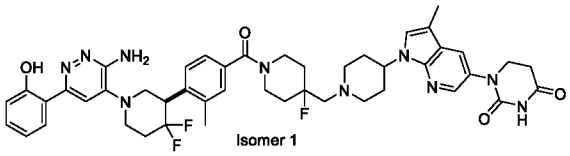


[2455] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 132e (16 mg, 0.04 mmol) and Intermediate 32g (21 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 81% MeOH in water with 0.1%) gave the title compound (14 mg, 43%) as an off-white solid. ^1H NMR (DMSO-*d6*): δ 1.25 (3H, d), 1.62 - 1.80 (2H, m), 1.81 - 2.09 (6H, m), 2.31 (3H, s), 2.37 - 2.46 (5H, m), 2.50 - 2.58 (2H, m), 2.59 - 2.83 (5H, m), 3.05 (2H, br d), 3.48 - 3.60 (5H, m), 3.69 - 3.79 (1H, m), 4.09 - 4.19 (1H, m), 4.20 - 4.37 (2H, m), 5.04 (1H, br d), 6.42 (2H, s), 6.53 (1H, d), 6.84 - 6.92 (2H, m), 7.01 (1H, d), 7.20 - 7.31 (3H, m), 7.39 (1H, d), 7.53 (1H, d), 7.54 - 7.59 (2H, m), 7.95 (1H, d), 10.24 (1H, s), 14.22 (1H, br s); ^{19}F NMR (DMSO-*d6*): δ -157.89 (1F, s); *m/z* (ES^+) $[M+H]^+$ = 844.6.

EXAMPLE 203:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

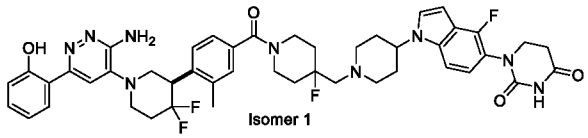


[2456] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (11 mg, 0.02 mmol) and Intermediate 161a (12 mg, 0.02 mmol). Purification by RPC (elution gradient: 20 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (14 mg, 66%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.79 (2H, m), 1.84 (3H, br d), 1.92 - 2.12 (3H, m), 2.18 - 2.33 (4H, m), 2.32 - 2.40 (2H, m), 2.43 (3H, s), 2.52 - 2.71 (4H, m), 2.76 (2H, t), 2.97 - 3.20 (4H, m), 3.38 - 3.55 (3H, m), 3.66 (1H, br d), 3.81 (2H, t), 3.88 - 4.02 (1H, m), 4.27 (1H, br s), 4.54 - 4.66 (1H, m), 6.52 (2H, s), 6.87 - 6.93 (2H, m), 7.21 - 7.31 (3H, m), 7.46 - 7.53 (2H, m), 7.71 (1H, s), 7.88 (1H, d), 7.98 (1H, dd), 8.17 (1H, d), 10.40 (1H, s), 14.19 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.98 (1F, s), -111.11 (1F, br d), -95.47 (1F, br d); *m/z* (ES$^+$) $[M+H]^+$ = 865.7.

EXAMPLE 204:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

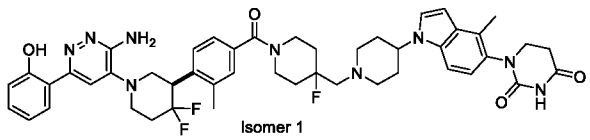


[2457] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (11 mg, 0.02 mmol) and Intermediate 3g (17 mg, 0.02 mmol). Purification by RPC (elution gradient: 20 to 100% MeOH in water with 0.1% NH_4OH) gave the title compound (11 mg, 52%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.81 (2H, m), 1.82 - 1.96 (3H, m), 2.01 (3H, br s), 2.30 (1H, br d), 2.33 - 2.49 (5H, m), 2.51 - 2.71 (4H, m), 2.74 (2H, t), 2.95 - 3.20 (4H, m), 3.39 - 3.59 (3H, m), 3.62 - 3.76 (3H, m), 3.88 - 4.02 (1H, m), 4.28 (1H, br s), 4.38 (1H, br s), 6.47 - 6.61 (3H, m), 6.86 - 6.93 (2H, m), 7.13 (1H, t), 7.21 - 7.31 (3H, m), 7.44 (1H, d), 7.49 (1H, br d), 7.61 (1H, br s), 7.71 (1H, s), 7.97 (1H, d), 10.41 (1H, s), 14.16 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -158.03 (1F, s), -130.21 (1F, s), -111.12 (1F, br d), -95.46 (1F, br d), -73.42 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 868.6.

EXAMPLE 205:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

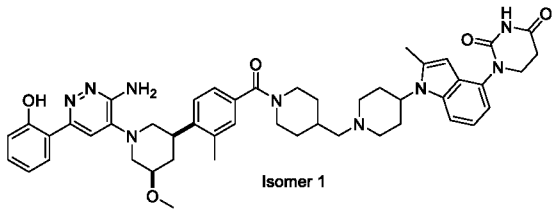


[2458] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 177i (11 mg, 0.02 mmol) and Intermediate 32g (20 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeOH/water with 0.1% NH_4OH) gave the title compound (17 mg, 79%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.62 - 1.80 (2H, m), 1.81 - 2.08 (6H, m), 2.23 - 2.34 (1H, m), 2.31 (3H, s), 2.35 - 2.46 (5H, m), 2.58 - 2.69 (3H, m), 2.69 - 2.83 (2H, m), 2.97 - 3.20 (4H, m), 3.37 - 3.58 (5H, m), 3.66 (1H, br d), 3.74 (1H, ddd), 3.87 - 4.02 (1H, m), 4.15 - 4.40 (2H, m), 6.53 (3H, br d), 6.86 - 6.93 (2H, m), 7.01 (1H, d), 7.21 - 7.32 (3H, m), 7.39 (1H, d), 7.49 (1H, br d), 7.53 (1H, d), 7.71 (1H, s), 7.98 (1H, d), 10.27 (1H, s), 14.19 (1H, br s); ^{19}F NMR (DMSO-*d*6): δ -157.97 (1F, br s), -111.12 (1F, br d), -95.47 (1F, br d); *m/z* (ES^+) $[M+H]^+$ = 864.6.

EXAMPLE 206:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

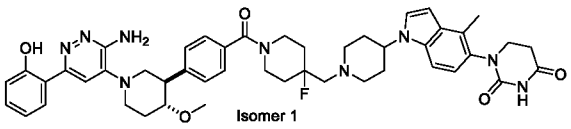


[2459] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (20 mg, 0.05 mmol) and Intermediate 165a (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 15 to 100% MeOH in water with 0.1% HCOOH) gave the title compound (27 mg, 71%) as a purple solid. ^{1}H NMR (DMSO-*d*6): δ 1.04 - 1.20 (2H, m), 1.21 - 1.30 (1H, m), 1.55 (1H, q), 1.67 - 1.98 (5H, m), 2.28 (5H, br d), 2.40 - 2.47 (6H, m), 2.46 - 2.56 (2H, m), 2.68 - 2.86 (4H, m), 3.11 (3H, br s), 3.26 - 3.41 (4H, m, overlaps with residual water), 3.43 - 3.49 (1H, m), 3.56 - 3.81 (4H, m), 3.85 (1H, br d), 4.29 (1H, br s), 4.49 (1H, br s), 6.16 (1H, s), 6.34 (2H, br s), 6.84 - 6.94 (3H, m), 7.05 (1H, t), 7.17 - 7.29 (3H, m), 7.42 (1H, br d), 7.50 (1H, br d), 7.61 (1H, s), 7.96 (1H, br d), 10.30 (1H, s), 13.28 - 14.96 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 840.6.

EXAMPLE 207:

1-(1-(1-((1-(4-((3*R**,4*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



[2460] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 176f (14 mg, 0.03 mmol) and Intermediate 32g (25 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 81% MeOH in water with 0.1% FA) gave the title compound (13 mg, 47%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 1.64 - 1.84 (3H, m), 1.85 - 2.08 (6H, m), 2.26 - 2.46 (6H, m), 2.58 - 2.68 (2H, m), 2.68 - 2.82 (2H, m), 2.83 - 2.90 (2H, m), 3.05 (2H, br d), 3.10 - 3.19 (5H, m), 3.43 - 3.59 (3H, m), 3.59 - 3.78 (3H, m), 4.32 (2H, br t), 6.33 (2H, s), 6.53 (1H, d), 6.83 - 6.91 (2H, m), 7.01 (1H, d), 7.23 (1H, t), 7.39 (3H, d), 7.41 - 7.47 (2H, m), 7.50 - 7.56 (2H, m), 7.92 (1H, d), 10.24 (1H, s), 14.22 (1H, br s) (one proton not assigned potentially due to solvent overlap); ^{19}F NMR (DMSO-*d*6): δ -157.92 (1F, s); *m/z* (ES$^+$) $[M+H]^+$ = 844.6.

EXAMPLE 208

Intermediate 208a:

tert-Butyl (*R**)-(-4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate (Isomer 1)

((*absolute configuration not yet confirmed))

and

Intermediate 208b:

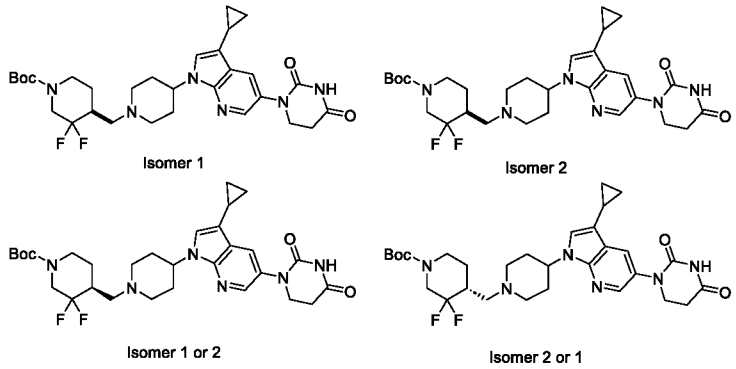
tert-Butyl (*R**)-(-4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate (Isomer 2)

((*absolute configuration not yet confirmed))

tert-Butyl (*S*)-(-4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate

and

tert-Butyl (*R*)-(-4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate



[2461] Intermediate 141a (100 mg, 0.17 mmol) was purified by chiral SFC (Column: IG 30mm × 250 5µm, mobile phase MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 75 mL/min; Column temperature: 40°C) to give the title compounds Isomer 1 (32 mg, 32%, >95% ee) and Isomer 2 (30 mg, 30%, 97% ee) as white solids.

Intermediate 208c:

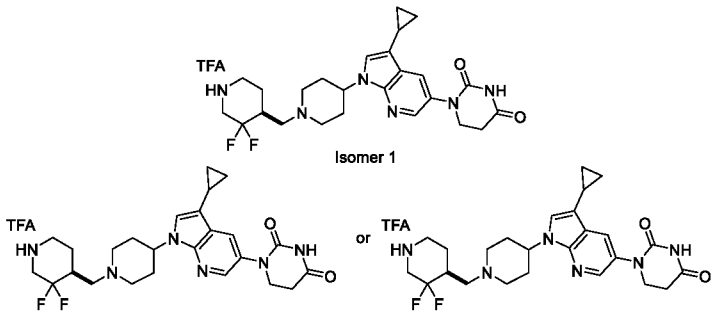
(*R**)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*S*)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*R*)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2462] Prepared in an analogous method to Intermediate 1i starting from Intermediate 208a (30mg, 0.05 mmol). The solvent was removed under reduced pressure to give the title compound (29 mg, 95%) in the form of a trifluoroacetic acid salt as an orange solid. *m/z* (ES^+) $[M+H]^+$ = 487.2.

EXAMPLE 208:

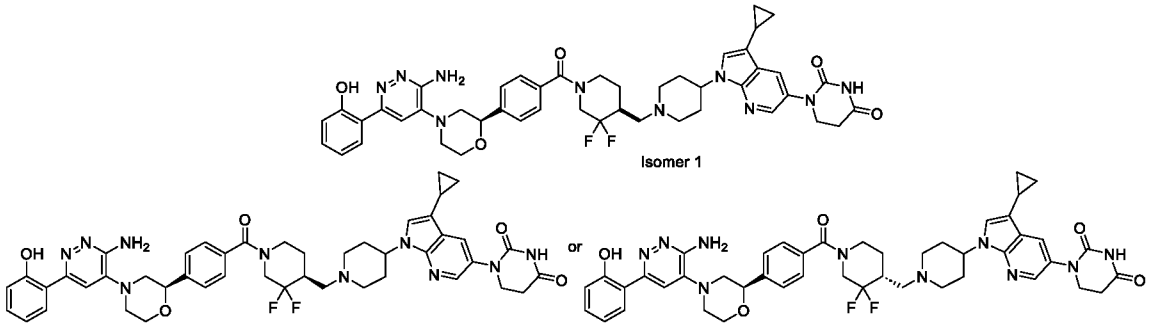
1-(1-(1-(((*R**)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*relative stereochemistry not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

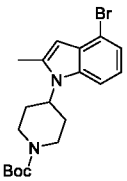


[2463] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (10mg, 0.03 mmol) and Intermediate 208c (12.40 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (4.00 mg, 18%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.59 - 0.72 (2H, m), 0.80 - 0.91 (2H, m), 1.37 - 1.49 (1H, m), 1.83 - 1.94 (3H, m), 2.00 - 2.11 (3H, m), 2.26 - 2.35 (1H, m), 2.40 - 2.45(1H, m), 2.59 - 2.66 (1H, m), 2.77 (3H, s), 2.85 - 2.97 (2H, m), 3.02 - 3.10 (2H, m), 3.48 - 3.51 (2H, m), 3.56 - 3.61 (2H, m), 3.76 - 3.85 (3H, m), 4.02 - 4.14 (3H, m), 4.57 -4.67 (2H, m), 4.84 - 4.94 (1H, m), 6.47 (2H, s), 6.89 (2H, br d), 7.15 - 7.30 (1H, m), 7.42 (3H, br d), 7.56 (3H, br d), 7.89 - 8.00 (2H, m), 8.17 (1H, d), 10.37 (1H, s), 14.00 -14.40 (1H, m); *m/z* (ES$^+$) [M+H]$^+$ = 861.4.

EXAMPLE 209

Intermediate 209a:

tert-Butyl 4-(4-bromo-2-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate

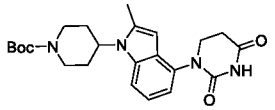


[2464] A mixture of 4-bromo-2-methyl-1*H*-indole (525 mg, 2.5 mmol), tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (1397 mg, 5.00 mmol) and cesium carbonate (2036 mg, 6.25 mmol) in DMF (8 mL) was heated at 80 °C for 20 h, then added another two equivalents each of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate and cesium carbonate and heating was continued to another 30 h. The reaction was cooled to r.t. and filtered to remove Cs_2CO_3. The filter cake was washed with EtOAc (100 mL). The filtrate was washed with brine (5 x 80 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in Hexanes) gave the title

compound (370 mg, 37%) as an orange solid. ^{1}H NMR (DMSO-*d*6): δ 1.55 (9H, s), 1.83 - 1.90 (2H, m), 2.36 - 2.48 (2H, m), 2.49 (3H, s), 2.84 - 2.92 (2H, m), 4.24 - 4.34 (1H, m), 4.37 (2H, br d), 6.34 (1H, br s), 6.97 (1H, t), 7.24 (1H, d), 7.38 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 393.2.

Intermediate 209b:

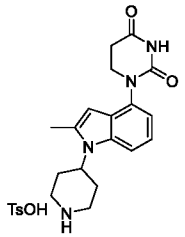
tert-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2465] Prepared in an analogous method to Intermediate 8b starting from Intermediate 209a (1 g, 2.54 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in DCM) gave the title compound (0.710 g, 65%) as a as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.47 (9H, s), 1.72 – 1.86 (2H, m), 2.16 – 2.35 (2H, m), 2.38 – 2.48 (3H, m), 2.67 – 2.78 (2H, m), 2.84 – 3.08 (2H, m), 3.67 – 3.79 (2H, m), 4.13 (2H, d), 4.47 (1H, d), 6.17 (1H, s), 6.90 (1H, d), 6.97– 7.08 (1H, m), 7.41 (1H, d), 10.32 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 427.4.

Intermediate 209c:

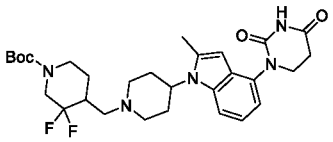
1-(2-Methyl-1-(piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2466] Prepared in an analogous method to Intermediate 35e starting from Intermediate 209b (0.5 g, 1.17 mmol). The precipitate was collected by filtration, washed with Et_2O (10 mL) and dried under vacuum to afford the title compound (0.550 g, 94%) in the form *p*-toluenesulfonic acid salt as a slaty grey solid. *m/z* (ES$^+$) $[M+H]^+$ = 327.0.

Intermediate 209d:

tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate



[2467] Prepared in an analogous manner to Intermediate 10d starting from Intermediate 209c in DCM (2 mL) and *tert*-butyl 3,3-difluoro-4-formylpiperidine-1-carboxylate (92 mg, 0.37 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (105 mg, 51%) as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 560.5.

Intermediate 209e:

tert-Butyl (*R**)-4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate (Isomer 1)

((*absolute configuration not yet confirmed))

and

Intermediate 209f:

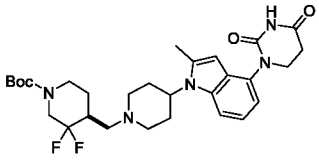
tert-Butyl (*R**)-4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate (Isomer 2)

((*absolute configuration not yet confirmed))

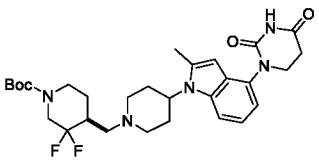
tert-Butyl (*S*)-4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate

and

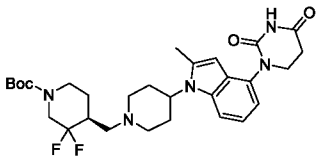
tert-Butyl (*R*)-4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate



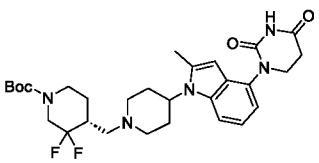
Isomer 1



Isomer 2



Isomer 1 or 2



Isomer 2 or 1

[2468] Intermediate 209d (105 mg, 0.187 mmol) was purified by chiral SFC (Column: AD-H 21 x 250 mm, 30% MeOH with 0.25% diethylamine in $scCO_2$) to give the title compounds Isomer 1, Intermediate 209e (44 mg, 44%, 100% ee) and Isomer 2, Intermediate 209f (42 mg, 42%, 99%ee) as white solids.

Intermediate 209g:

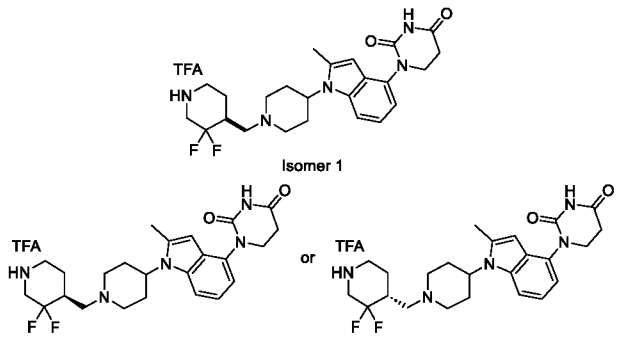
(*R**)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*S*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*R*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2469] Prepared in an analogous method to Intermediate 1i starting from Intermediate 209e (40mg, 0.07 mmol) to give the title compound (40mg, 98%) in the form of a trifluoroacetic acid salt as an orange solid. *m/z* (ES^+) $[M+H]^+$ = 460.2.

EXAMPLE 209:

1-(1-(1-(((*S**)-1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute and relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

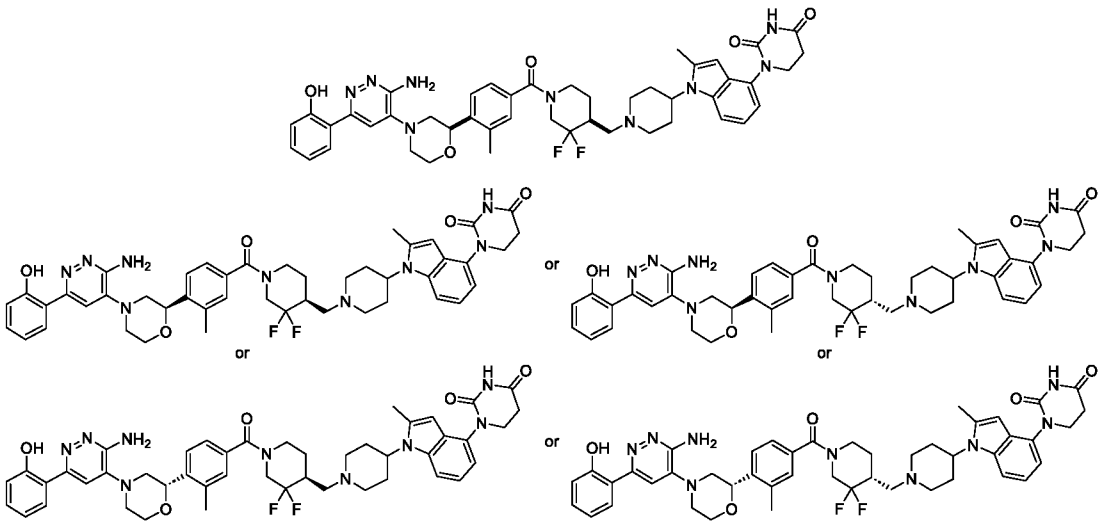
1-(1-(1-(((*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

1-(1-(1-(((*S*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

1-(1-(1-(((*R*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

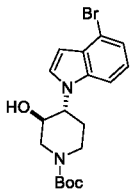


[2470] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 80e (9 mg, 0.02 mmol) and Intermediate 209g (10 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (5.0 mg, 26%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 - 1.53 (1H, m), 1.73 - 1.86 (3H, m), 2.02 - 2.15 (2H, m), 2.34 - 2.38 (1H, m), 2.44 (8H, br d), 2.57 - 2.65 (2H, m),2.68 - 2.78 (3H, m), 2.83 - 3.17 (6H, m), 3.55 (2H, br t), 3.74 (2H, br t), 4.10 (2H, br d), 4.26 (1H, br t), 4.41 - 4.75 (1H, m), 4.99 (1H, br d), 6.16 (1H, s), 6.44 (2H, s), 6.83 - 6.94 (3H, m), 7.00 - 7.11 (1H, m), 7.21 - 7.29 (3H, m), 7.43 - 7.51 (1H, m), 7.57 - 7.64 (2H, m), 7.96 (1H, d), 10.29 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 848.5.

EXAMPLE 210

Intermediate 210a:

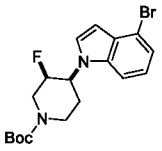
rac-tert-Butyl (3*R*,4*R*)-4-(4-bromo-1*H*-indol-1-yl)-3-hydroxypiperidine-1-carboxylate



[2471] *tert*-Butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (1.00 g, 5.02 mmol) was dissolved in DMF (30 mL) and then 4-bromo-1*H*-indole (0.772 mL, 6.02 mmol) and cesium carbonate (4.91 g, 15.06 mmol) were added. Then the reaction mixture was stirred at 100 °C overnight. The reaction was concentrated under reduced pressure and then it was taken into DCM (100 mL) and washed with ammonium chloride, water and brine. The organic layer was dried, Na_2SO_4 concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (0.880 g, 44%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.53 (9H, s), 1.70 - 1.83 (1H, m), 2.03 - 2.09 (2H, m), 2.80 (1H, br t), 2.87 - 2.97 (1H, m), 3.92 - 4.01 (1H, m), 4.16 - 4.24 (1H, m), 4.29 - 4.39 (1H, m), 4.45 - 4.58 (1H, m), 6.70 (1H, d), 7.11 (1H, t), 7.27 (1H, d), 7.33 (1H, d), 7.44 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 395.2.

Intermediate 210b:

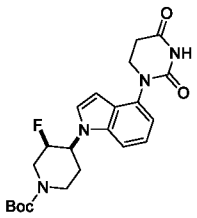
rac-tert-Butyl (3*R*,4*S*)-4-(4-bromo-1*H*-indol-1-yl)-3-fluoropiperidine-1-carboxylate



[2472] Intermediate 210a (880 mg, 2.23 mmol) was dissolved in THF (55 mL). Then DAST (0.382 mL, 2.89 mmol) was added to the solution and stirred at r.t for 3h. The reaction was then quenched with ammonium chloride and then the solvent was removed and then taken up in DCM (50 mL) and washed with water and brine. The organic layers was separated, dried over Na_2SO_4, filtered and then concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) to afford the title compound (461 mg, 52%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 397.3.

Intermediate 210c:

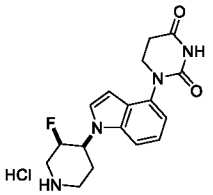
*rac-ter*t-Butyl (3*R*,4*S*)-4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1H-indol-1-yl)-3-fluoropiperidine-1-carboxylate



[2473] Prepared in an analogous method to Intermediate 2b starting from Intermediate 210b (461 mg, 1.16 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% formic acid) gave the title compound (141 mg, 28%) as a white solid. *m/z* (ES^+) $[M–tBu+2H]^+$ = 375.3.

Intermediate 210d:

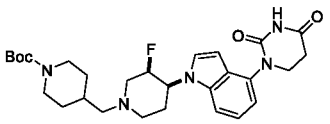
rac-1-(1-(-3-Fluoropiperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2474] HCl, 4 M in 1,4-dioxane (5 mL, 20 mmol) was added to a stirred solution of Intermediate 210c (141 mg, 0.33 mmol) in DCM (2 mL). The reaction mixture was stirred for 1h. The reaction solution was concentrated under reduced pressure to afford (130 mg, 60%) the title compound as a white solid. *m/z* (ES^+) $[M+H]^+$ = 331.3.

Intermediate 210e:

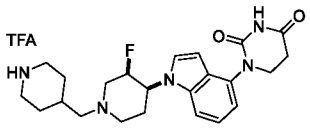
rac-tert-Butyl 4-(-4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2475] Prepared in an analogous manner to Intermediate 10d starting from Intermediate 210d (21 mg, 0.06 mmol), and *tert*-butyl 4-formylpiperidine-1-carboxylate (13.56 mg, 0.06 mmol). The reaction mixture was diluted with DCM (10 mL) and water (2 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated to give the title compound (28.0 mg, 83%) as an orange gum. The crude material was used for the next step without further purification. *m/z* (ES^+) $[M+H]^+$ = 528.3.

Intermediate 210f:

rac-1-(1-(-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2476] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 210e (20mg, 0.04 mmol). The solvent was removed to give the title compound (20.0 mg, 81%) form of TFA salt as a yellow solid. *m/z* (ES^+) $[M+H]^+$ = 428.3.

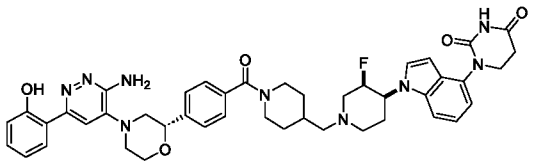
EXAMPLE 210:

1-(1-(-1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

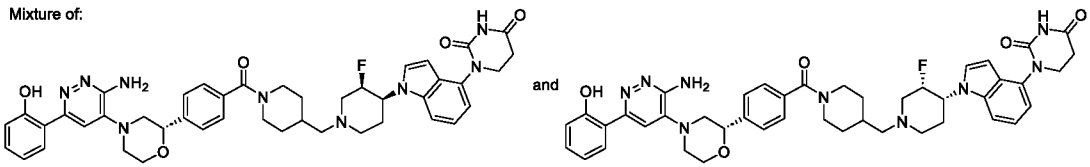
1-(1-((3*R*,4*S*)-1-((1-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

and

1-(1-((3*S*,4*R*)-1-((1-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Mixture of:



[2477] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 77d (9 mg, 0.02 mmol) and Intermediate 210f (14.99 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (12.0 mg, 65%) as a white solid and mixture

of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 1.06 - 1.19 (2H, m), 1.65 - 1.78 (1H, m), 1.83 - 1.94 (2H, m), 1.94 - 2.02 (1H, m), 2.04 - 2.16 (1H, m), 2.21 - 2.31 (2H,m), 2.31 - 2.41 (2H, m), 2.74 - 2.85 (4H, m), 2.87 - 2.97 (2H, m), 3.02 - 3.11 (1H, m), 3.36 - 3.42 (1H, m), 3.46 - 3.67 (3H, m), 3.79 (2H, t), 4.01 - 4.15 (2H,m), 4.44 - 4.54 (1H, m), 4.55 - 4.65 (1H, m), 4.86 - 5.03 (2H, m), 6.45 - 6.52 (3H, m), 6.85 - 6.91 (2H, m), 6.97 (1H, d), 7.12 - 7.19 (1H, m), 7.21 - 7.26 (1H,m), 7.40 (2H, d), 7.51 - 7.56 (3H, m), 7.57 (1H, s), 7.67 (1H, d), 7.93 - 7.97 (1H, m), 10.33 (1H, s), 14.10 - 14.31 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 802.5.

EXAMPLE 211:

1-(1-(1-(((*R**)-1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute and relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

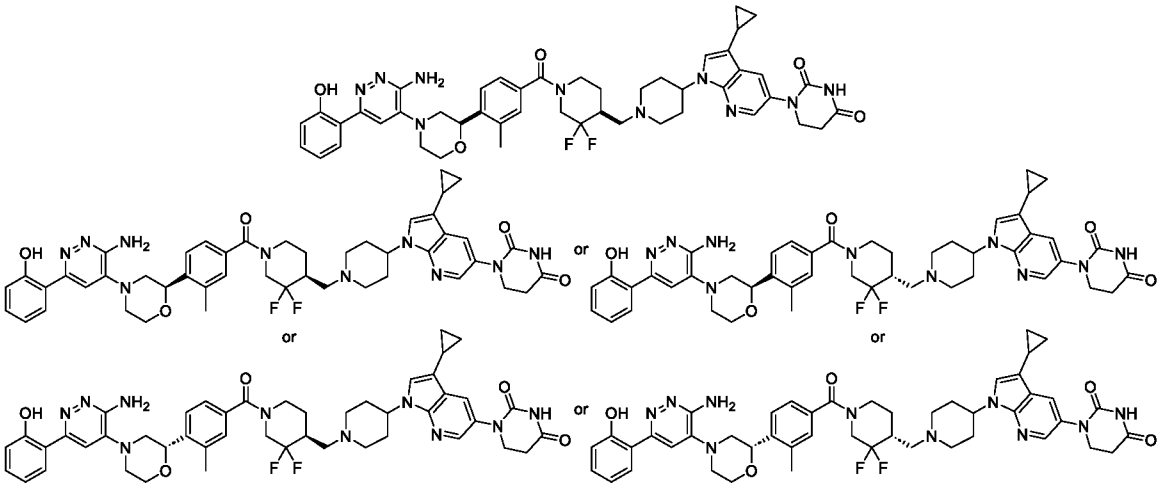
1-(1-(1-(((*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

1-(1-(1-(((*S*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

1-(1-(1-(((*R*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2478] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (9mg, 0.02 mmol) and Intermediate 208c (10.77 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (4.10 mg, 21%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.83 - 0.88 (2H, m), 1.44 (1H, br d), 1.82 - 1.95 (3H, m), 1.96 - 2.16 (4H, m), 2.28 - 2.35 (1H, m), 2.42 (5H, s), 2.53 -2.62 (2H, m), 2.77 (2H, t), 2.83 - 2.97 (3H, m), 3.06 (2H, br d), 3.37 - 3.41 (1H, m), 3.50 - 3.58 (3H, m), 3.82 (2H, s), 4.10 (2H, br d), 4.56 - 4.68 (1H, m), 4.99 (1H, br d), 6.43 (2H, s), 6.78 - 6.97 (2H, m), 7.22 - 7.31 (3H, m), 7.44 (1H, br s), 7.58 (2H, t), 7.90 - 8.01 (2H, m), 8.17 (1H, d), 10.37 (1H, s), 14.09 - 14.53 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 875.5.

EXAMPLE 212

Intermediate 212a:

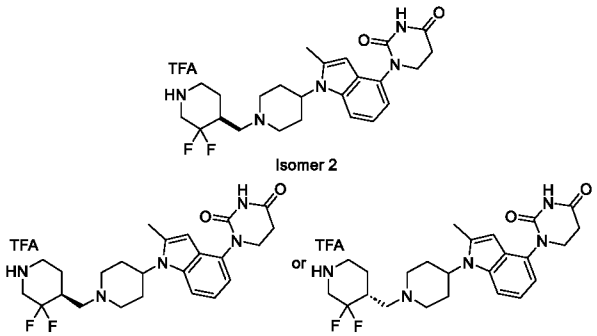
(*R**)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*S*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

Or

(*R*)-1-(1-(1-((3,3-Difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2479] Prepared in an analogous method to Intermediate 1i starting from Intermediate 209f (40mg, 0.07 mmol) to give the title compound (38 mg, 93%) in the form of a trifluoroacetic acid salt as an orange solid. *m/z* (ES$^+$) $[M+H]^+$ = 460.2.

EXAMPLE 212:

1-(1-(1-(((*R**)-1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute and relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

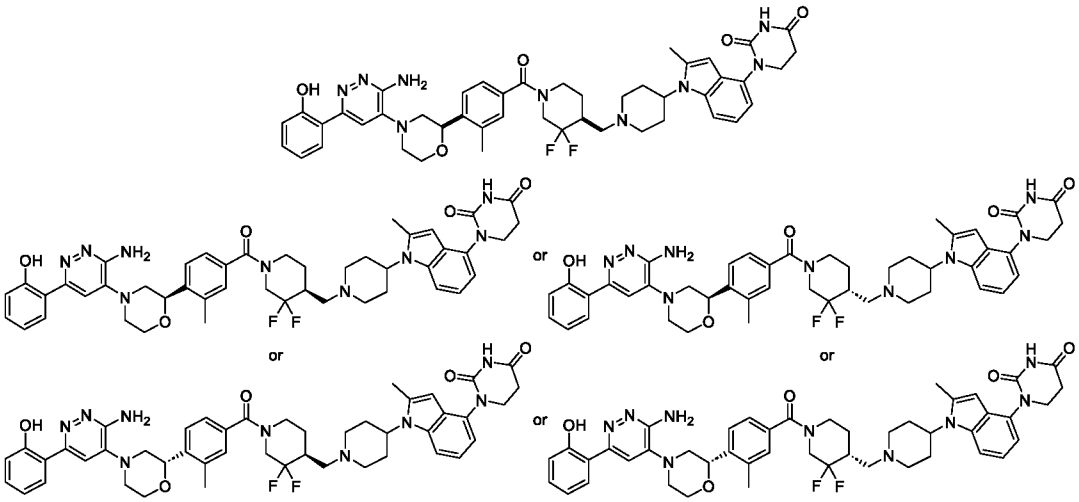
1-(1-(1-(((*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((*S*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((*R*)-1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2480] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 80e (9 mg, 0.02 mmol) and Intermediate 212a (10.18 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (10.0 mg, 53%) as a white solid. ^{1}H NMR (DMSO-*d6*): δ 1.40 – 1.56 (1H, m), 1.79 (2H, br d), 2.00 – 2.18 (2H, m), 2.30 – 2.38 (2H, m), 2.39 – 2.48 (10H, m), 2.55 – 2.62 (1H,m), 2.75 (2H, t), 2.83 – 3.10 (5H, m), 3.55 (3H, br t), 3.74 (2H, t), 4.10 (2H, br d), 4.26 (1H, br t), 4.40 – 4.80 (1H, m), 4.99 (1H, br d), 6.16 (1H, s), 6.44 (2H,s), 6.82 – 6.92 (3H, m), 7.04 (1H, br s), 7.21 – 7.34 (3H, m), 7.42 – 7.53 (1H, m), 7.56 – 7.65 (2H, m), 7.96 (1H, d), 10.29 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 848.5.

EXAMPLE 213:

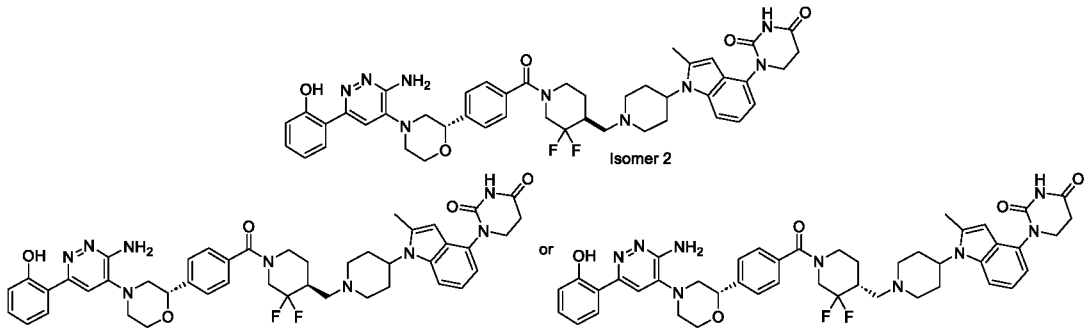
1-(1-(1-(((*R**)-1-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-(((*R*)-1-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2481] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 77d (9 mg, 0.02 mmol) and Intermediate 209h (10.54 mg, 0.02 mmol. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (14 mg, 73%) as a white solid.^{1}H NMR (DMSO-*d*6): δ 1.43 - 1.53 (1H, m), 1.79 (2H, br d), 1.99 - 2.24 (2H, m), 2.29 - 2.39 (2H, m), 2.39 - 2.48 (6H, m), 2.52 (3H, br s), 2.52- 2.69 (1H, m), 2.70 - 2.75 (2H, m), 2.81 (1H, br s), 2.86 - 3.00 (2H, m), 3.09 (1H, br d), 3.50 (1H, br d), 3.59 (1H, br d), 3.74 (2H, t), 4.02 - 4.15 (2H, m),4.20 - 4.31 (1H, m), 4.37 - 4.75 (1H, m), 4.91 (1H, br d), 6.16 (1H, s), 6.49 (2H, s), 6.82 - 6.93 (3H, m), 7.01 - 7.09 (1H, m), 7.20 - 7.30 (1H, m), 7.43 (3H, d), 7.57 (3H, d), 7.96 (1H, dd), 10.29 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 834.5.

EXAMPLE 214

Intermediate 214a:

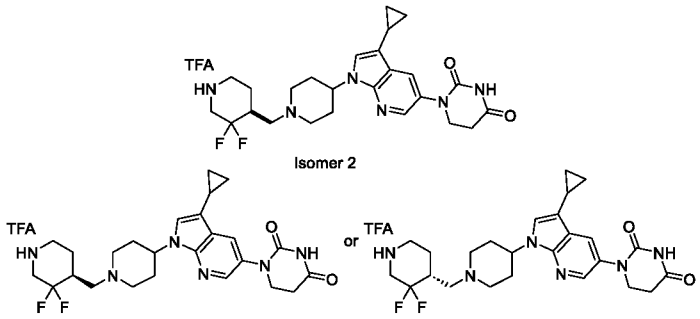
(*R**)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*S*)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*R*)-(1-(3-Cyclopropyl-1-(1-((3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2482] Prepared in an analogous method to Intermediate 1i starting from Intermediate 208b (30mg, 0.05 mmol). The solvent was removed under reduced pressure to give the title compound (28 mg, 91%) in the form of a trifluoroacetic acid salt as an orange solid. *m/z* (ES^+) $[M+H]^+$ = 487.2.

EXAMPLE 214:

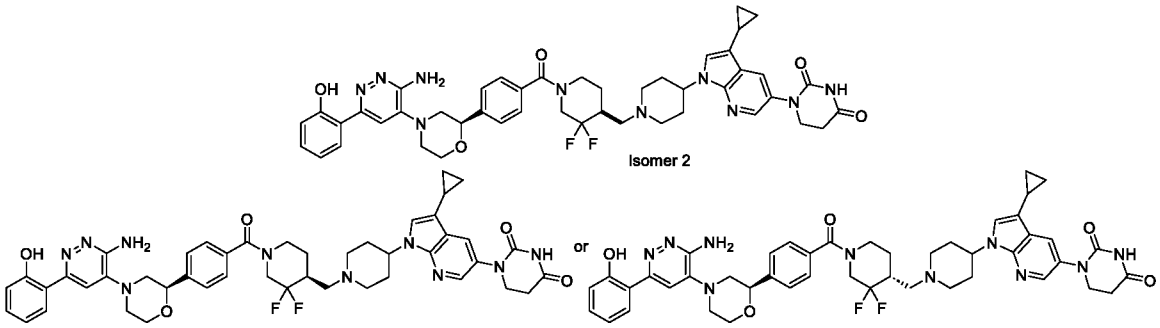
1-(1-(1-(((*R**)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*relative configuration not yet confirmed))

1-(1-(1-(((*S*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

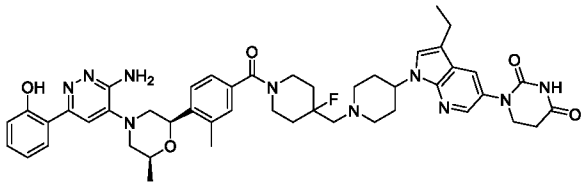
1-(1-(1-(((*R*)-1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2483] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 16i (10 mg, 0.03 mmol) and Intermediate 214a (12.40 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (4.20 mg, 19%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.66 (2H, br d), 0.80 - 0.91 (2H, m), 1.39 - 1.51 (1H, m), 1.83 - 1.95 (3H, m), 1.99 - 2.10 (3H, m), 2.31 (1H, br t), 2.37 - 2.47 (2H, m), 2.57 - 2.62 (1H, m), 2.73 - 2.83 (4H, m), 2.87 - 2.98 (3H, m), 3.04 - 3.13 (2H, m), 3.47 - 3.52 (2H, m), 3.56 - 3.62 (2H, m), 3.82 (2H, t), 4.03 - 4.12 (2H, m), 4.62 (1H, br s), 4.90 (1H, br d), 6.48 (2H, s), 6.83 - 6.93 (2H, m), 7.17 - 7.29 (1H, m), 7.40 - 7.47 (3H, m), 7.56 (3H, br d), 7.91 - 7.99 (2H, m), 8.17 (1H, d), 10.37 (1H, s), 13.97 - 14.55 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 861.5.

EXAMPLE 215:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

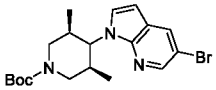


[2484] Prepared in an analogous manner to EXAMPLE 1 using Intermediate 149f (60 mg, 0.10 mmol) and Intermediate 132e (40 mg, 0.10 mmol). Purification by preparative HPLC (elution gradient: 16 to 36% MeCN in water with 0.08% NH_4CO_3 and 0.1% NH_4OH) gave the title compound (28.0 mg, 34%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.18 – 1.30 (6H, m), 1.61 – 1.79 (2H, m), 1.81 – 1.88 (3H, m), 1.98 (1H, s), 2.02 – 2.14 (2H, m), 2.31 – 2.40 (2H, m), 2.42 (3H, s), 2.55 – 2.57 (1H, m), 2.62 (1H, s), 2.63 – 2.72 (3H, m), 2.74 – 2.82 (3H, m), 3.05 (2H, d), 3.15 (1H, s), 3.21 – 3.30 (1H, m), 3.42 – 3.60 (3H, m), 3.75 – 3.90 (2H, m), 4.08 – 4.20 (1H, m), 4.35 (1H, s), 4.50 – 4.80 (1H, m), 4.92 – 5.11 (1H, m), 6.45 (2H, s), 6.80 – 6.99 (2H, m), 7.12 – 7.38 (3H, m), 7.39 – 7.72 (3H, m), 7.85 – 8.02 (2H, m), 8.17 (1H, d), 10.39 (1H, s), 14.23 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -157.91; *m/z* (ES$^+$) $[M+H]^+$ = 859.4.

EXAMPLE 216

Intermediate 216a:

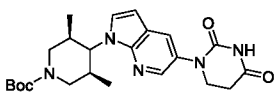
tert-Butyl (3*S*,5*R*)-4-(5-bromo-1*H*-indol-1-yl)-3,5-dimethylpiperidine-1-carboxylate



[2485] Prepared in an analogous manner to Intermediate 126a using *tert*-butyl (3*S*,5*R*)-4-hydroxy-3,5-dimethylpiperidine-1-carboxylate (2.30 g, 10.0 mmol, mixture of diastereomers) and 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (3.95 g, 20.1 mmol) in xylenes (20 mL). The mixture was stirred at 120 °C for 16 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeOH in water with 0.4% NH_4HCO_3) gave the title compound (2.00 g, 48%) as a yellow solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.45 (6H, dd), 1.44 (9H, s), 2.22 (1H, dt), 2.69 (1H, d), 2.99 (1H, d), 3.35 (1H, s), 3.87 (1H, s), 3.97 – 4.37 (1H, m), 5.34 (1H, s), 6.53 (1H, d), 8.01 (1H, d), 8.24 (1H, dd), 8.32 (1H, d). *m/z* (ES$^+$); $[M+H]^+$ = 408.1.

Intermediate 216b:

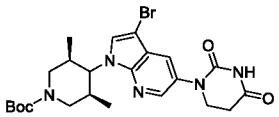
tert-Butyl (3*S*,5*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidine-1-carboxylate



[2486] Prepared in an analogous manner to Intermediate 126b using Intermediate 216a (1.30 g, 3.18 mmol), stirring at 100 °C for 5 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (1.25 g, 89%) as a yellow solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.47 (6H, dd), 1.44 (9H, s), 2.21 (1H, dt), 2.75 (2H, t), 2.88 – 3.16 (1H, m), 3.33 (4H, m), 3.83 (3H, td), 3.98 – 4.16 (1H, m), 6.55 (1H, d), 7.95 (1H, td), 8.24 (1H, d), 10.41 (1H, d); *m/z* (ES$^+$), $[M+H]^+$ = 442.2.

Intermediate 216c:

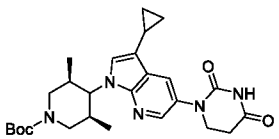
tert-Butyl (3*S*,5*R*)-4-(3-bromo-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidine-1-carboxylate



[2487] NBS (0.524 g, 2.94 mmol) was added to Intermediate 216b (1.30 g, 2.94 mmol) in DCM (10 mL) . The resulting mixture was stirred at 0 °C for 1 hour and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (1.25 g, 82%) as a yellow solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.49 (6H, t), 1.45 (9H, s), 2.12 – 2.32 (2H, m), 2.77 (2H, t), 3.02 (2H, m), 3.87 (2H, dd), 4.04 (2H, q), 5.43 (1H, s), 7.87 (1H, dd), 8.23 (1H, s), 8.34 (1H, d), 10.46 (1H, d); *m/z* (ES$^+$), $[M+H]^+$ = 519.8.

Intermediate 216d:

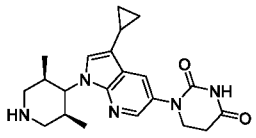
tert-Butyl (3*S*,5*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidine-1-carboxylate



[2488] K_3PO_4 (1.53 g, 7.21 mmol) was added to Pd(dppf)Cl_2 (0.157 g, 0.24 mmol), cyclopropylboronic acid (0.413 g, 4.80 mmol) and Intermediate 216c (1.25 g, 2.40 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 2 hours. After cooling to r.t., the mixture was concentrated under reduced pressure Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (1.00 g, 86%) as a yellow solid and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.46 (6H, t), 0.61 – 0.72 (1H, m), 0.73 – 0.92 (4H, m), 1.09 – 1.29 (1H, m), 1.45 (9H, s), 1.96 (1H, td), 2.18 (1H, dd), 2.76 (2H, t), 3.01 (1H, m), 3.84 (3H, dd), 4.10 (1H, q), 5.33 (1H, s), 7.60 (1H, s), 7.97 (1H, dd), 8.18 (1H, dd), 10.40 (1H, s); *m/z* (ES$^+$), $[M+H]^+$ = 481.9.

Intermediate 216e:

1-(3-Cyclopropyl-1-((3*S*,5*R*)-3,5-dimethylpiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2489] TFA (1.5 mL) was added to a solution of Intermediate 216d (840 mg) in DCM (4.5 mL). The resulting mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure. The residue was triturated with MTBE to give the title compound (800 mg, 93%) as a red solid, TFA salt and mixture of diastereomers. ^{1}H NMR (DMSO-*d*6): δ 0.43 – 0.59 (6H, m), 0.77 (2H, d), 0.86 – 0.95 (2H, m), 1.11 (1H, s), 2.77 (2H, t), 3.14 (4H, d), 3.40 (1H, d), 3.85 (2H, t), 4.54 (1H, m), 5.42 (1H, s), 7.60 (1H, s), 8.01 (1H, t), 8.23 (1H, d), 8.79 (1H, s), 10.42 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 382.1.

Intermediate 216f:

tert-Butyl 4-(((3*S*,4*s**,5*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate (Isomer 1)

((*relative configuration not yet confirmed))

and

Intermediate 216g:

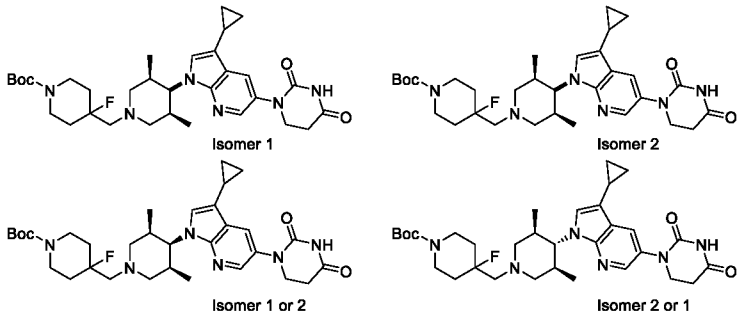
tert-Butyl 4-(((3*S*,4*s**,5*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate (Isomer 2)

((*relative configuration not yet confirmed))

tert-Butyl 4-(((3*S*,4*s*,5*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

and

tert-Butyl 4-(((3*S*,4*r*,5*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,5-dimethylpiperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2490] Prepared in an analogous manner to Intermediate 6g using Intermediate 6f (1.53 g, 4.19 mmol) and Intermediate 216e (0.80 g, 2.10 mmol), stirring at 80 °C for 6 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) and preparative HPLC (Column: CHIRALPAKIG3; isocratic: 60% hexanes, 20% DCM, 20% EtOH with 0.1% diethylamine; Flow rate: 1.0 mL/min) gave Intermediate 216f (50 mg, 4%) which eluted first from the column and Intermediate 216g (125 mg, 10%) which eluted second from the column as yellow solids. Intermediate 216f: ^{1}H NMR (DMSO-*d*6): δ 0.37 – 0.51 (6H, m), 0.69 (2H, s), 0.80 – 0.91 (4H, m), 1.23 –

1.28 (1H, m), 1.42 (9H, s), 1.58 – 1.69 (2H, m), 1.79 – 1.89 (2H, m), 1.95 (1H, s), 2.03 – 2.20 (3H, m), 2.59 (2H, d), 2.76 (2H, t), 2.99 – 3.04 (2H, m), 3.69 – 3.79 (2H, m), 3.84 (2H, t), 4.03 (1H, s), 7.39 – 7.48 (1H, m), 7.95 (1H, d), 8.15 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 597.2. Intermediate 216g: ^1H NMR (DMSO-*d*6): δ 0.39 – 0.53 (6H, m), 0.70 – 0.75 (2H, m), 0.83 – 0.96 (4H, m), 1.24 – 1.28 (1H, m), 1.41 (9H, s), 1.56 – 1.69 (2H, m), 1.80 – 1.90 (2H, m), 1.94 – 2.04 (1H, m), 2.26 – 2.38 (2H, m), 2.46 (1H, d), 2.70 (1H, d), 2.73 – 2.78(3H, m), 3.05 (2H, s), 3.75 (2H, d), 3.84 (2H, t), 5.29 (1H, t), 7.54 (1H, s), 7.96 (1H, d), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 597.2.

EXAMPLE 216:

1-(1-((3*S*,4*S**,5*R*)-1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute and relative configuration not yet confirmed))

1-(1-((3*S*,4*S*,5*R*)-1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

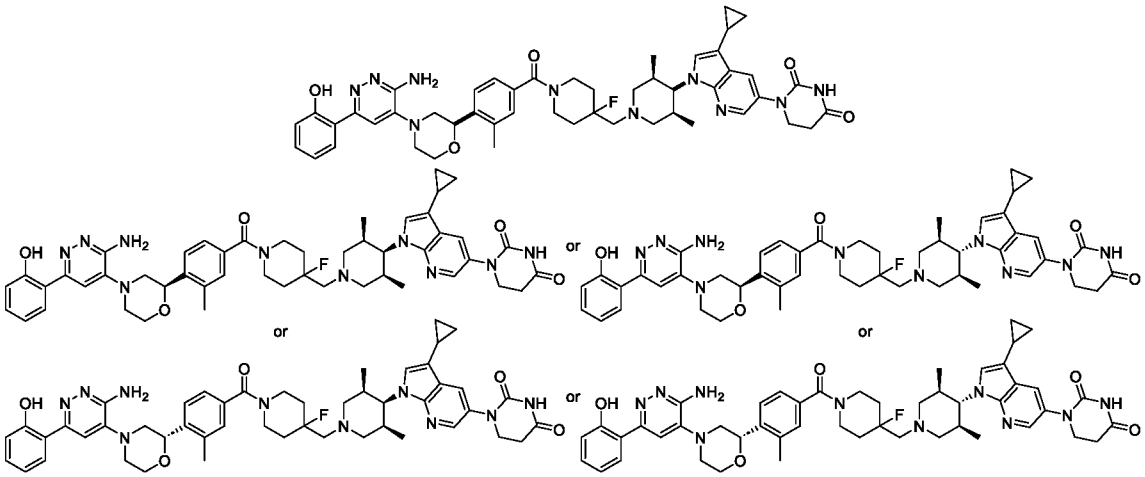
1-(1-((3*S*,4*R*,5*R*)-1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*,5*R*)-1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*,5*R*)-1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

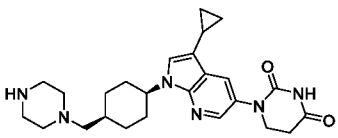


[2491] TFA (1 mL) was added to a solution of Intermediate 216f (40 mg, 0.07 mmol) in DCM (1 mL). The resulting mixture was stirred at r.t. for 1h and concentrated under reduced pressure. A mixture of Intermediate 55j (27 mg, 0.07 mmol), HATU (26 mg, 0.07 mmol) and DIPEA (0.035 mL) in DMF (1 mL) was stirred at 40 °C for 1 h. The mixture was added to the residue of the first reaction and the resulting mixture was stirred at r.t. for 1 hour. Purification by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; elution gradient: 41 to 60% MeCN in water with 0.08% NH_4HCO_3 and 0.05% NH_4OH, Flow rate: 60 mL/min) gave the title compound (13.2 mg, 22%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.43 (6H, d), 0.69 – 0.79 (2H, m), 0.83 – 0.97 (2H, m), 1.73 (2H, d), 1.99 (3H, tt), 2.27 – 2.38 (2H, m), 2.42 (3H, s), 2.47 (2H, d), 2.68 – 2.80 (6H, m), 2.87 (2H, tt), 3.13 (2H, s), 3.54 (3H, t), 3.84 (2H, t), 4.10 (2H, d), 4.27 (1H, s), 4.94 – 5.04 (1H, m), 5.29 (1H, t), 6.45 (2H, s), 6.88 (2H, ddd), 7.18 – 7.32 (3H, m), 7.52 – 7.61 (3H, m), 7.95 (2H, dd), 8.20 (1H, d), 10.40 (1H, s), 14.21 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -157.485. *m/z* (ES$^+$), $[M+H]^+$ = 885.6.

EXAMPLE 217

Intermediate 217a:

1-(3-Cyclopropyl-1-((1*s*,4*s*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2492] TFA (1 mL) was added to a solution of Intermediate 118d (130 mg, 0.24 mmol) in DCM (4 mL). The resulting mixture was stirred at r.t. for 1h and concentrated under reduced pressure to give the title compound (100 mg) as a yellow solid and TFA salt. *m/z* (ES$^+$) $[M+H]^+$ = 451.2.

EXAMPLE 217:

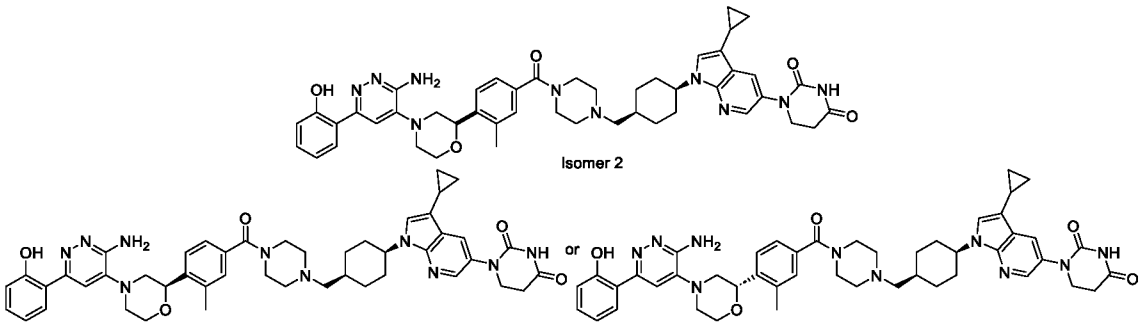
1-(1-((1*S*,4*s*)-4-((4-(4-((*R**)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((1*S*,4*s*)-4-((4-(4-((*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*S*,4*s*)-4-((4-(4-((*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

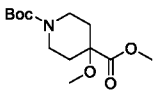


[2493] Prepared in an analogous manner to EXAMPLE 1 using Intermediate 55j (22 mg, 0.05 mmol) and Intermediate 217a (40 mg, 0.09 mmol). The mixture was diluted with DCM (15 mL), washed with 2% aq. NH_4OH (3 x 10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: 41 to 60% MeCN in water with 0.08% NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (21 mg, 27%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 – 0.70 (2H, m), 0.81 – 0.91 (2H, m), 1.03 – 1.31 (1H, m), 1.66 (4H, d), 1.73 – 1.84 (2H, m), 1.85 – 2.02 (4H, m), 2.41 (5H, s), 2.47 (3H, d), 2.77 (2H, t), 2.80 – 2.92 (2H, m), 3.26 (1H, s), 3.53 (3H, t), 3.64 (2H, s), 3.81 (2H, t), 4.09 (2H, d), 4.57 – 4.70 (1H, m), 4.97 (1H, dd), 6.45 (2H, s), 6.87 (2H, ddd), 7.20 – 7.29 (3H, m), 7.51 (1H, s), 7.56 (1H, d), 7.58 (1H, s), 7.90 – 7.99 (2H, m), 8.16 (1H, d), 10.40 (1H, s), 14.22 (1H, s); *m/z* (ES^+), $[M+H]^+$ = 839.6.

EXAMPLE 218

Intermediate 218a:

1-(*tert*-Butyl) 4-methyl 4-methoxypiperidine-1,4-dicarboxylate

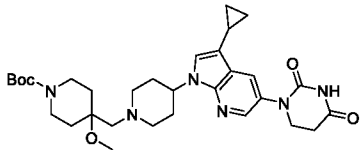


[2494] 1-(*tert*-Butyl) 4-methyl 4-methoxypiperidine-1,4-dicarboxylate (500 mg, 2.04 mmol) was added to a mixture of sodium hydride (408 mg, 10.2 mmol) and iodomethane (1.01 g, 7.13 mmol) in DMF (4 mL). The resulting mixture was stirred at r.t. for 2h. The mixture was diluted with DCM (50 mL), washed with sat. aq. NH_4Cl (2 x 25 mL) and brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (400 mg, 81%) as a colorless oil. ^{1}H NMR (DMSO-*d*6): δ 1.38

(9H, s), 1.63 – 1.85 (4H, m), 2.96 – 3.06 (2H, m), 3.14 (3H, s), 3.59 – 3.67 (5H, m); *m/z* (ES^+) $[M–Boc+2H]^+$ =174.

Intermediate 218b:

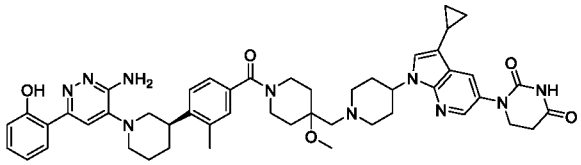
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-methoxypiperidine-1-carboxylate



[2495] Intermediate 218a (150 mg, 0.55 mmol) was added to DIBAL-H (1.65 mL, 1.65 mmol) in DCM (5 mL) under nitrogen at –60 °C. The resulting mixture was stirred at –60 °C for 1 hour. The mixture was diluted with DCM (50 mL), sequentially washed with sat. aq. NH_4Cl (2 x 5 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. DCM (2 mL), Intermediate 71a (131 mg, 0.37 mmol) and sodium triacetoxyborohydride (118 mg, 0.55 mmol) were added and the mixture was stirred at r.t. for 3 hours. Sat. aq. Na_2CO_3 (15 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: 14 to 30% MeCN in water with 0.1% formic acid) gave the title compound (80 mg, 37%) as a white solid. ^1H NMR (DMSO-*d6*): δ 0.65 (2H, d), 0.83 (2H, d), 1.39 (9H, s), 1.59 (6H, d), 1.67 – 1.80 (6H, m), 2.22 – 2.43 (7H, m), 2.75 (4H, t), 3.79 (2H, d), 4.56 (2H, d), 7.43 (1H, s), 7.93 (1H, d), 8.15 (1H, s), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ =581.0.

EXAMPLE 218:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2496] *p*-Toluenesulfonic acid (25 mg, 0.14 mmol) was added to a solution of Intermediate 218b (55 mg, 0.09 mmol) in MeCN (2 mL). The resulting mixture was stirred at 60 °C for 1 h and concentrated under reduced pressure. DMF (2 mL), Intermediate 12g (60 mg, 0.15 mmol), HATU (68 mg, 0.18 mmol) and DIPEA (0.077 mL, 0.045 mmol) were added and the mixture was stirred at r.t. for 1 h. The mixture was diluted with DCM (50 mL), washed with sat. aq. $NaHCO_3$ (2 x 25 mL) and brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: 25 to 33% MeCN in water with 0.1% formic acid) gave the title compound (10.0 mg, 7%) as a white solid. ^1H NMR (DMSO-*d6*): δ 0.61 – 0.71 (2H, m), 0.77 – 0.90 (2H, m), 1.53 – 1.61 (2H, s), 1.79 – 1.85 (5H, d), 1.86 – 1.95 (4H, m), 1.99 – 2.13 (3H, m), 2.34 (2H, t), 2.45 – 2.51 (3H, s), 2.71 (2H, s), 2.76

(3H, t), 2.86 (1H, t), 3.06 (3H, d), 3.16 (3H, s), 3.25 (2H, d), 3.48 (1H, d), 3.59 (1H, d), 3.81 (2H, t), 4.14 (1H, s), 4.58 (1H, s), 6.30 (2H, s), 6.88 (2H, t), 7.18 – 7.28 (3H, m), 7.36 – 7.50 (1H, m), 7.45 (1H, S) 7.57 (1H, s), 7.94 (2H, dd), 8.17 (1H, d), 10.40 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 867.4.

EXAMPLE 219

Intermediate 219a:

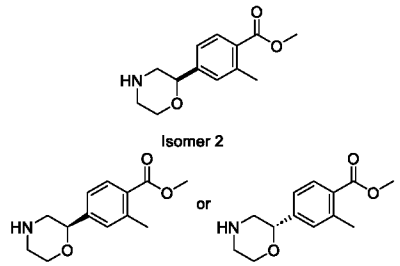
Methyl (*R**)-2-methyl-4-(morpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-2-methyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-2-methyl-4-(morpholin-2-yl)benzoate



[2497] Prepared in an analogous manner to Intermediate 49e starting from Intermediate 49d (1.1 g, 3.38 mmol). The reaction mixture was filtered and filtrate was concentrated to afford the title compound (0.750 g, 94 %) as a yellow solid. The product was used in the next step directly without further purification. ^{1}H NMR (DMSO-*d*6): δ 2.40 – 2.46 (1 H, m), 2.48 – 2.50 (4 H, m), 2.67 – 2.74 (2 H, m), 2.89 – 2.94 (1 H, m), 3.53 – 3.60 (1 H, m), 3.78 (3 H, s), 3.83 – 3.88 (1 H, m), 4.35 – 4.40 (1 H, m), 7.21 – 7.27 (2 H, m), 7.74 – 7.79 (1 H, m); *m/z* (ES^+) $[M+H]^+$ = 236.0.

Intermediate 219b:

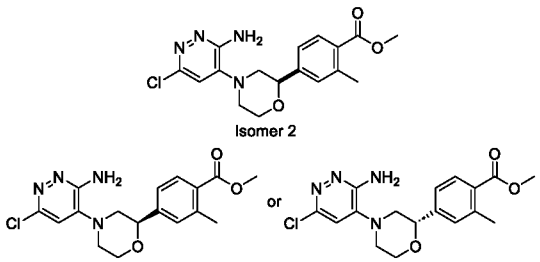
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate



[2498] Prepared in an analogous method to Intermediate 1d starting from Intermediate 219a (750 mg, 3.19 mmol) and 4-bromo-6-chloropyridazin-3-amine (731 mg, 3.51 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (1000 mg, 86 %) as a yellow oil.

^{1}H NMR (DMSO-*d*6): δ 2.52 (3 H, s), 2.77 – 2.85 (1 H, m), 3.33 – 3.37 (2 H, m), 3.48 – 3.53 (1 H, m), 3.82 (3 H, s), 3.92 – 3.98 (1 H, m), 4.03 – 4.08 (1 H, m), 4.80 – 4.85 (1 H, m), 6.35 (2 H, s), 6.95 (1 H, s), 7.32 – 7.41 (2 H, m), 7.82 (1 H, d); *m/z* (ES$^+$) $[M+H]^+$ = 363.3.

Intermediate 219c:

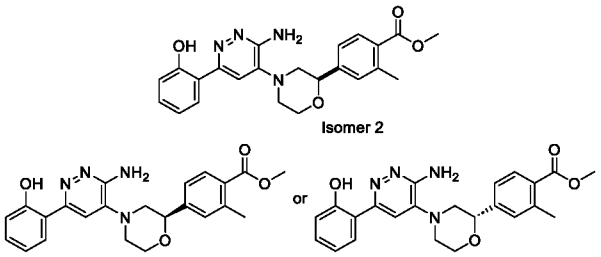
Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoate



[2499] Prepared in an analogous method to Intermediate 1e starting from Intermediate 219b (990 mg, 2.73 mmol). The reaction mixture was poured into water (75 mL). A precipitate formed which was collected by filtration and dried *in vacuo* to give the title compound (800 mg, 69.7 %) as yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.54 (3 H, s), 2.70 – 2.77 (1 H, m), 2.84 – 2.93 (1 H, m), 3.46 (1 H, d), 3.53 – 3.59 (1 H, m), 3.82 (3 H, s), 4.00 – 4.13 (2 H, m), 4.84 – 4.89 (1 H, m), 6.49 (2 H, s), 6.82 – 6.90 (2 H, m), 7.20 – 7.25 (1 H, m), 7.36 – 7.43 (2 H, m), 7.55 (1 H, s), 7.84 (1 H, d), 7.91 – 7.96 (1 H, m), 14.20 (1 H, s); *m/z* (ES$^+$) $[M+H]^+$ =421.0.

Intermediate 219d:

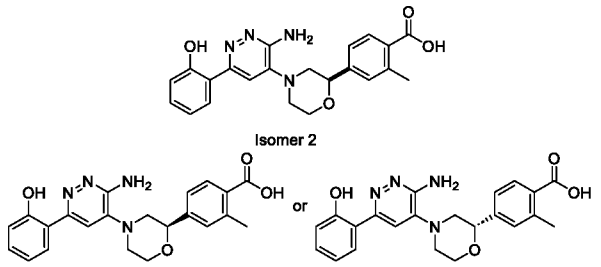
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoic acid



[2500] Prepared in an analogous method to Intermediate 1f starting from Intermediate 219c (800 mg, 1.90 mmol). The reaction mixture was acidified with 1 M aq. HCl. A precipitate formed which was collected by filtration and dried by lyophilization to afford the title compound (560 mg, 72.4 %) as yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.54 (3 H, s), 2.75 – 2.84 (1 H, m), 2.91 – 3.01 (1 H, m), 3.49 – 3.68 (2 H, m), 3.97 – 4.16 (2 H, m), 4.83 – 4.89 (1 H, m), 6.71 – 6.98 (4 H, m), 7.25 – 7.32 (1 H, m), 7.33 – 7.41 (2 H, m), 7.55 (1 H, s), 7.77 – 7.87 (2 H, m), (two exchangeable protons not observed); *m/z* (ES$^+$) $[M+H]^+$ =407.1.

EXAMPLE 219:

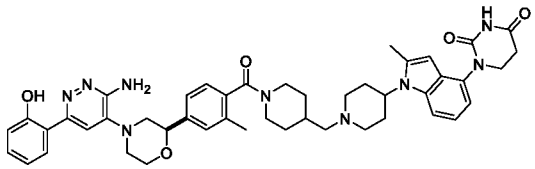
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

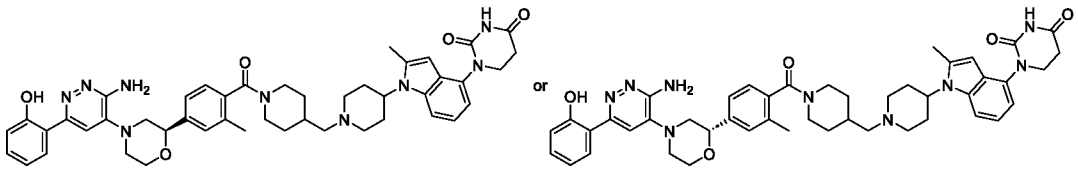
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 2

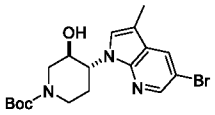


[2501] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 219d (40 mg, 0.10 mmol) and Intermediate 22d (41.7 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 60% water in MeCN with 10mmol/L NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (28.0 mg, 35%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.93 – 1.16 (2 H, m), 1.65 – 1.79 (3 H, m), 1.80 – 1.95 (2 H, m), 2.07 – 2.16 (2 H, m), 2.18 – 2.31 (5 H, m), 2.38 – 2.47 (5 H, m), 2.71 – 2.91 (5 H, m), 2.95 – 3.05 (3 H, m), 3.34 – 3.35 (1 H, m),3.44 – 3.59 (2 H, m), 3.70 – 3.76 (2 H, m), 4.00 – 4.12 (2 H, m), 4.18 – 4.28 (1 H, m), 4.52 – 4.61 (1 H, m), 4.82 (1 H, d), 6.15 (1 H, s), 6.48 (2 H, s), 6.83 – 6.92 (3 H, m), 7.00 – 7.06 (1 H, m), 7.10 – 7.26 (2 H, m), 7.29 – 7.38 (2 H, m), 7.45 (1 H, d), 7.57 (1 H, s), 7.95 (1 H, d), 10.30 (1 H, s), 14.22 (1 H, s); *m/z* (ES$^+$) $[M+H]^+$ = 812.

EXAMPLE 220

Intermediate 220a:

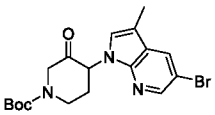
rac-tert-Butyl (3*R*,4*R*)-4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-hydroxypiperidine-1-carboxylate



[2502] Prepared in an analogous manner to Intermediate 210a using *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (4.91 g, 24.6 mmol), 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4.00 g, 19.0 mmol) and Cs_2CO_3 (9.26 g, 28.4 mmol), stirring at 100 °C for 90 minutes. After cooling to r.t., the mixture was filtered. The filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% acetone in hexanes and 0 to 70% EtOAc in hexanes) gave the title compound (4.35 g, 55%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 1.42 (9H, s), 1.77 – 1.84 (1H, m), 1.90 – 1.98 (1H, m), 2.22 (3H, d), 2.53 – 2.77 (1H, m), 2.78 – 3.01 (1H, m), 3.88 (1H, tt), 3.95 – 4.07 (1H, m), 4.16 (1H, br s), 4.50 (1H, ddd), 5.08 (1H, d), 7.51 (1H, s), 8.13 (1H, d), 8.22 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 410.3.

Intermediate 220b:

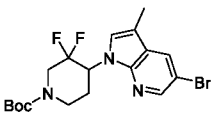
rac-tert-Butyl 4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-1-yl)-3-oxopiperidine-1-carboxylate



[2503] DMP (5.38 g, 12.7 mmol) was added to a solution of Intermediate 220a (4.34 g, 10.6 mmol) in DCM (53 mL). The resulting mixture was stirred at r.t. for 6 hours. Sat. aq. $Na_2S_2O_3$–sat. aq. $NaHCO_3$ (1:1, 80 mL) was added and the mixture was stirred vigorously for 15 minutes. The phases were separated and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR (DMSO-*d*6): δ 1.45 (9H, s), 2.23 - 2.32 (4H, m), 2.55 - 2.68 (1H, m), 3.56 (1H, br d), 4.03 - 4.17 (2H, m), 4.29 (1H, br d), 5.69 (1H, dd), 7.39 (1H, s), 8.20 (1H, d), 8.23 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 408.2.

Intermediate 220c:

rac-tert-Butyl 4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidine-1-carboxylate

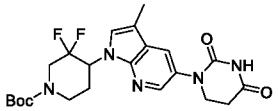


[2504] DAST (6.99 mL, 52.9 mmol) was added to a solution of Intermediate 220b (4.32 g, 10.6 mmol) in DCM (81 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes and at r.t. for 3 hours. The mixture was washed with sat. aq. $NaHCO_3$ (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (2.29 g, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.45 (9H, s), 1.93 – 2.05 (1H, m), 2.23

– 2.40 (4H, m), 3.07 – 3.30 (1H, m), 3.39 – 3.73 (1H, m), 4.06 – 4.44 (2H, m), 5.38 – 5.54 (1H, m), 7.53 (1H, s), 8.23 (1H, d), 8.31 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 430.3.

Intermediate 220d:

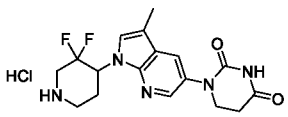
rac-tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-1-yl)-3,3-difluoropiperidine-1-carboxylate



[2505] Prepared in an analogous manner to Intermediate 93b using Intermediate 220c (2.29 g, 5.32 mmol), stirring at 95 °C for 24 hours. After cooling to r.t., the mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc–EtOH] in hexanes) gave impure product. Trituration with DCM–hexanes (1:2) and drying *in vacuo* gave the title compound (0.64 g, 25%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.96 (1H, br dd), 2.24 - 2.38 (4H, m), 2.75 (2H, t), 3.05 - 3.28 (1H, m), 3.38 - 3.73 (1H, m), 3.81 (2H, t), 4.06 - 4.44 (2H, m), 5.39 - 5.56 (1H, m), 7.48 (1H, s), 7.93 (1H, d), 8.20 (1H, d), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 464.4.

Intermediate 220e:

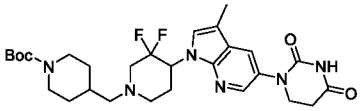
rac-1-(1-(3,3-Difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2506] HCl, 4 M in 1,4-dioxane (6.80 mL, 27.2 mmol) was added to a solution of Intermediate 220d (0.63 g, 1.36 mmol) in 1,4-dioxane (10.2 mL). The resulting mixture was stirred at 40 °C for 150 minutes and concentrated under reduced pressure to give the title compound as an off-white solid and HCl salt. The product was used for the next step without further purification and quantitative yield was assumed. ^{1}H NMR (DMSO-*d*6): δ 2.17 – 2.33 (4H, m), 2.52 – 2.64 (1H, m), 2.75 (2H, t), 3.32 – 3.48 (2H, m), 3.82 (3H, t), 3.87 – 3.95 (1H, m), 5.56 – 5.81 (1H, m), 7.36 (1H, s), 7.96 (1H, d), 8.23 (1H, d), 9.65 (1H, br s), 10.39 (1H, s), 10.48 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 364.2.

Intermediate 220f:

rac-tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

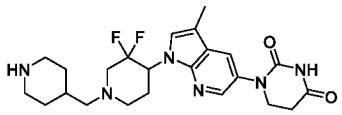


[2507] Prepared in an analogous manner to Intermediate 10d using Intermediate 220e (544 mg, 1.36 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (348 mg, 1.63 mmol) in DMF (9.1 mL). Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (748 mg, 98%) as an off-

white solid. ^{1}H NMR (DMSO-*d*6): δ 0.93 – 1.05 (2H, m), 1.41 (9H, s), 1.64 – 1.80 (3H, m), 1.93 (1H, br d), 2.27 (3H, d), 2.29 – 2.44 (4H, m), 2.53 – 2.63 (1H, m), 2.64 – 2.81 (4H, m), 3.01 (1H, br d), 3.19 – 3.29 (1H, m), 3.83 (2H, t), 3.94 (2H, br d), 5.13 – 5.31 (1H, m), 7.49 (1H, s), 7.94 (1H, d), 8.21 (1H, d), 10.39 (1H, s).; *m/z* (ES$^+$) $[M+H]^+$ = 561.3.

Intermediate 220g:

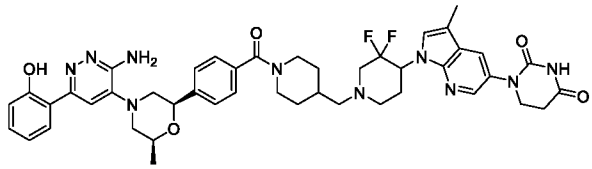
rac-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2508] 2 M aq. H_2SO_4 (3.6 mL) was added to a solution of Intermediate 220f (200 mg, 0.36 mmol) in THF (3.6 mL). The resulting mixture was stirred at 40 °C for 4h. DCM–IPA (3:1, 20 mL) was added followed by sat. aq. K_2CO_3 (20 mL). The phases were separated and the aqueous layer was extracted with DCM–IPA (3:1, 3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (136 mg, 83%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.99 - 1.11 (2H, m), 1.62 - 1.75 (3H, m), 1.90 - 1.97 (1H, m), 2.26 - 2.34 (5H, m), 2.38 (2H, br t), 2.47 - 2.61 (3H, m), 2.77 (2H, t), 2.98 (3H, br d), 3.22 (1H, br t), 3.83 (2H, t), 5.12 - 5.33 (1H, m), 7.49 (1H, s), 7.94 (1H, d), 8.20 (1H, d), 9.85 - 10.83 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 461.4.

EXAMPLE 220:

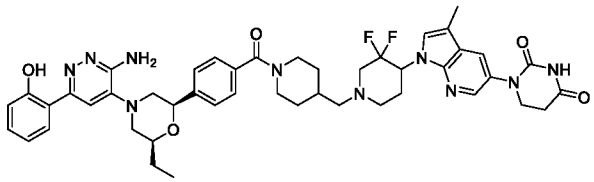
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2509] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 220g (31 mg, 0.07 mmol) and Intermediate 65e (30 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (45.7 mg, 80%) as a white solid and mixture of diastereomers, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br d), 1.27 (3H, d), 1.60 - 2.00 (4H, m), 2.27 (3H, d), 2.33 - 2.46 (4H, m), 2.53 - 2.65 (2H, m), 2.70 (1H, br t), 2.77 (3H, t), 2.97 - 3.15 (2H, m), 3.20 - 3.30 (1H, m), 3.47 - 3.72 (3H, m), 3.83 (2H, t), 4.08 - 4.19 (1H, m), 4.36 - 4.63 (1H, m), 4.95 (1H, dd), 5.13 - 5.34 (1H, m), 6.48 (2H, s), 6.80 - 6.94 (2H, m), 7.19 - 7.27 (1H, m), 7.40 (2H, d), 7.48 (1H, s), 7.53 (2H, d), 7.57 (1H, s), 7.91 - 7.99 (2H, m), 8.21 (1H, d), 10.40 (1H, s), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 849.6.

EXAMPLE 221:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

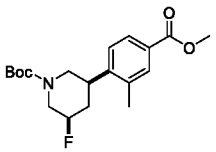


[2510] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 220g (30 mg, 0.07 mmol) and Intermediate 163f (30 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (37.6 mg, 67%) as a white solid and mixture of diastereomers, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.04 - 1.17 (2H, m), 1.55 - 1.94 (6H, m), 2.25 (3H, d), 2.29 - 2.42 (4H, m), 2.52 - 2.70 (3H, m), 2.71 - 2.86 (3H, m), 2.93 - 3.13 (2H, m), 3.18 - 3.27 (1H, m), 3.43 - 3.69 (3H, m), 3.81 (2H, t), 3.86 - 3.94 (1H, m), 4.44 (1H, br s), 4.93 (1H, dd), 5.12 - 5.29 (1H, m), 6.46 (2H, s), 6.81 - 6.94 (2H, m), 7.19 - 7.26 (1H, m), 7.39 (2H, d), 7.46 (1H, s), 7.52 (2H, d), 7.56 (1H, s), 7.92 (1H, d), 7.95 (1H, dd), 8.19 (1H, d), 10.38 (1H, s), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 863.6.

EXAMPLE 222

Intermediate 222a:

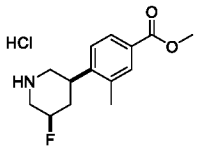
rac-tert-Butyl (3*R*,5*R*)-3-fluoro-5-(4-(methoxycarbonyl)-2-methylphenyl)piperidine-1-carboxylate



[2511] Intermediate 61c (776 mg, 2.22 mmol) stirring in DCM (10.2 mL) at 0 °C was added DAST (0.88 mL, 6.66 mmol) and the reaction mixture was allowed to come to r.t. and stirred for 1 h. The reaction mixture was then poured into a saturated solution of sodium bicarbonate (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAC in hexanes) gave the title compound (407 mg, 52%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.43 (9H, s), 1.89 - 2.06 (1H, m), 2.24 (1H, br d), 2.37 - 2.43 (3H, m), 2.66 - 2.94 (2H, m), 3.01 (1H, br t), 3.78 - 3.92 (4H, m), 4.16 - 4.33 (1H, m), 4.56 - 4.76 (1H, m), 7.44 - 7.51 (1H, m), 7.77 - 7.82 (2H, m); *m/z* (ES$^+$) $[M+Na]^+$ = 374.1.

Intermediate 222b:

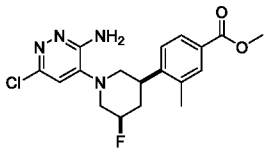
rac-Methyl 4-((3*R*,5*R*)-5-fluoropiperidin-3-yl)-3-methylbenzoate



[2512] To Intermediate 222a (407 mg, 1.16 mmol) was added 4M HCl in 1,4-dioxane (2.90 mL, 11.58 mmol). The reaction mixture was allowed to stir at r.t for 2 h. The reaction mixture was then concentrated *in vacuo* to afford the title compound (326 mg, 98%) as an HCl salt which was used without further purification. *m/z* (ES^+) $[M+H]^+$ = 252.1.

Intermediate 222c:

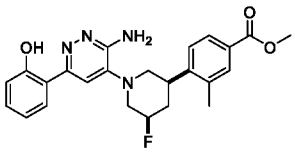
rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-chloropyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoate



[2513] To Intermediate 222b (326 mg, 1.14 mmol) and 4-bromo-6-chloropyridazin-3-amine (355 mg, 1.70 mmol) were added butan-1-ol (0.34 mL) and DIPEA (0.79 mL). The reaction mixture was allowed to stir overnight at 125 °C. Upon completion the crude mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (347 mg, 81%). ^{1}H NMR (DMSO-*d*6): δ 1.78 - 1.88 (1H, m), 2.28 - 2.36 (1H, m), 2.40 - 2.43 (3H, m), 2.66 - 2.72 (1H, m), 2.72 - 2.78 (1H, m), 3.33 - 3.38 (2H, m), 3.76 - 3.81 (1H, m), 3.84 (3H, s), 4.95 - 5.17 (1H, m), 6.19 - 6.34 (2H, m), 7.02 - 7.09 (1H, m), 7.50 - 7.55 (1H, m), 7.74 - 7.82 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 379.1.

Intermediate 222d:

rac-Methyl 4-((3*R*,5*R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoate

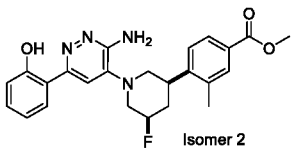


[2514] Prepared in an analogous method to Intermediate 1e starting from Intermediate 222c (352 mg, 0.93 mmol) and (2-hydroxyphenyl)boronic acid (192 mg, 1.39 mmol). Purification FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (314 mg, 77%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.81 - 1.94 (1H, m), 2.30 - 2.39 (1H, m), 2.43 (3H, s), 2.72 - 2.90 (2H, m), 3.34 - 3.47 (2H, m), 3.83 (3H, s), 3.85 - 3.90 (1H, m), 5.02 - 5.22 (1H, m), 6.34 - 6.45 (2H, m), 6.82 - 6.90 (2H, m), 7.18 - 7.25 (1H, m), 7.51 - 7.57 (1H, m), 7.62 (1H, s), 7.73 - 7.82 (2H, m), 7.89 -7.97 (1H, m), 13.77 - 14.24 (1H, m); *m/z* (ES^+) $[M+H]^+$= 437.7.

Intermediate 222e:

Methyl 4-((3*R**,5*R**)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

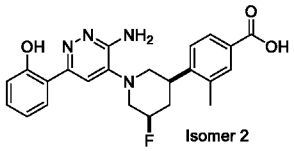


[2515] Intermediate 222d (314 mg, 0.72 mmol) was dissolved in dichloromethane. The resulting solution was purified using the following SFC conditions: Column: ChiralPak IA 21 x 250 mm, 5 µm; mobile phase A: 100% CO_2, mobile phase B: MeOH with 0.2% NH_4OH; Isocratic 60% mobile phase B; Flow rate: 75 mL/minute; BPR: 120 bar ; Column temperature: 40°C to afford the title compound that eluted second from the column (122 mg, 30%, 99% ee) as a white solid. *m/z* (ES^+) $[M+H]^+$= 437.7.

Intermediate 222f:

4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

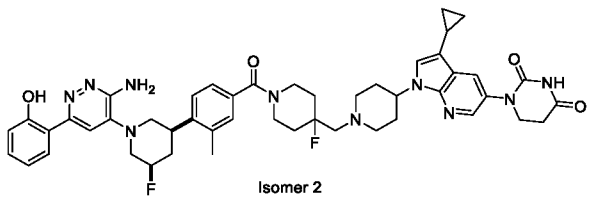


[2516] Prepared in an analogous method to Intermediate 1f starting from Intermediate 222e (122 mg, 0.28 mmol). The crude reaction mixture was concentrated under reduced pressure and acidified using 4 M HCl in 1,4-dioxane to pH ~3 when a precipitate formed. The precipitate was collected by filtration and dried to yield the title compound (116 mg, 98%) as a yellow solid. *m/z* (ES^-) $[M-H]^-$ = 421.1.

EXAMPLE 222:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



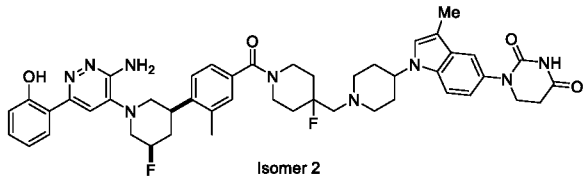
[2517] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10.0 mg, 0.02 mmol) and Intermediate 20g (13.1 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (20.2 mg, 98%) as a white solid following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.61 - 0.67 (2H, m), 0.80 - 0.86 (2H, m), 0.92 - 0.94 (3H, m), 1.66 - 1.74 (1H, m), 1.80 (2H, br d), 1.83 - 1.87 (1H, m), 1.87 - 1.93 (2H, m), 1.93 - 2.00 (1H, m), 2.00 - 2.09 (2H, m), 2.29 - 2.38 (3H, m), 2.39 - 2.41 (3H, m), 2.56 - 2.65 (2H, m), 2.73 - 2.77 (2H, m), 2.84 - 2.89 (1H, m), 2.99 - 3.06 (2H, m), 3.08 - 3.22 (1H, m), 3.33 - 3.44 (2H, m), 3.44 - 3.60 (1H, m), 3.76 - 3.83 (2H, m),

3.84 - 3.92 (1H, m), 4.11 - 4.30 (1H, m), 4.51- 4.63 (1H, m), 5.00 - 5.24 (1H, m), 6.39 (2H, s), 6.83 - 6.89 (2H, m), 7.19 - 7.27 (3H, m), 7.41 - 7.48 (2H, m), 7.62 (1H, s), 7.91 - 7.98 (2H, m), 8.13 - 8.18 (1H, m), 10.37 (1H, br s), 14.1 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 873.5.

EXAMPLE 223:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



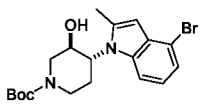
Isomer 2

[2518] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10 mg, 0.02 mmol) and Intermediate 1k (21.2 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (13.2 mg, 66%) as a white solid following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.93 (1H, d), 1.63 - 1.79 (2H, m), 1.83 - 1.89 (3H, m), 1.90 - 1.99 (3H, m), 2.19 - 2.24 (3H, m), 2.32 - 2.42 (6H, m), 2.56 - 2.65 (2H, m), 2.69 - 2.73 (2H, m), 2.75 - 2.80 (1H, m), 2.82 - 2.89 (1H, m), 2.98 - 3.05 (2H, m), 3.08 - 3.21 (1H, m), 3.21 - 3.29 (1H, m), 3.33 - 3.44 (2H, m), 3.45 - 3.60 (1H, m), 3.75 (2H, t), 3.85 - 3.93 (1H, m), 4.19 - 4.30 (2H, m), 5.04 - 5.22 (1H, m), 6.39 (2H, s), 6.83 - 6.90 (2H, m), 7.00 - 7.09 (1H, m), 7.17 - 7.27 (3H, m), 7.29 (1H, s), 7.36 - 7.41 (1H, m), 7.42 - 7.51 (2H, m), 7.62 (1H, s), 7.89 - 8.00 (1H, m), 10.22 (1H, s), 14.13 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 846.4.

EXAMPLE 224

Intermediate 224a:

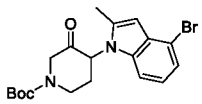
rac-tert-Butyl (3*R*,4*R*)-4-(4-bromo-2-methyl-1*H*-indol-1-yl)-3-hydroxypiperidine-1-carboxylate



[2519] Prepared in an analogous manner to Intermediate 210a using *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (13.3 g, 66.6 mmol), 4-bromo-2-methyl-1*H*-indole (7.00 g, 33.3 mmol) and Cs_2CO_3 (21.7 g, 66.6 mmol), stirring at 100 °C for 20 h. After cooling to r.t., the mixture was partially concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), washed with brine (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave impure title compound (8.505 g) which was used for the next step without further purification. *m/z* (ES^+) $[M+H]^+$ = 409.3.

Intermediate 224b:

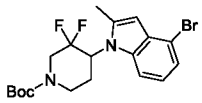
rac-tert-Butyl 4-(4-bromo-2-methyl-1*H*-indol-1-yl)-3-oxopiperidine-1-carboxylate



[2520] Prepared in an analogous manner to Intermediate 220b using Intermediate 224a (8.50 g) and DMP (8.51 g, 20.8 mmol), stirring at r.t. for 6h. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes and 0 to 100% DCM in hexanes, then 0 to 30% EtOAc in DCM) gave the title compound (3.57 g, 26% over 2 steps) as a yellowish foam. ^{1}H NMR ($CDCl_3$): δ 1.54 (9H, s), 2.27 - 2.35 (1H, m), 2.37 (3H, s), 2.56 - 2.70 (1H, m), 3.48 (1H, br s), 4.04 (1H, d), 4.18 - 4.42 (1H, m), 4.62 (1H, br d), 4.94 (1H, dd), 6.39 (1H, s), 6.85 (1H, br d), 6.95 (1H, t), 7.24 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 407.3.

Intermediate 224c:

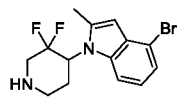
rac-tert-Butyl 4-(4-bromo-2-methyl-1*H*-indol-1-yl)-3,3-difluoropiperidine-1-carboxylate



[2521] Prepared in an analogous manner to Intermediate 220c using Intermediate 224b (2.50 g, 6.14 mmol) and DAST (3.24 mL, 24.6 mmol), stirring at 0 °C for 1 hour and at r.t. for 3h. Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (1.82 g, 69%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.54 (9H, s), 1.87 - 1.98 (1H, m), 2.45 (3H, s), 2.84 - 2.97 (1H, m), 3.00 - 3.10 (1H, m), 3.10 - 3.28 (1H, m), 4.34 - 4.65 (3H, m), 6.40 (1H, s), 6.97 (1H, t), 7.23 - 7.26 (1H, m), 7.43 - 7.52 (1H, m), product is present as mixture of rotamers by NMR (~3:1), ^{1}H NMR data represents major rotamer; *m/z* (ES^+) $[M+H]^+$ = 429.1.

Intermediate 224d:

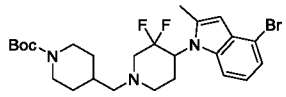
rac-4-Bromo-1-(3,3-difluoropiperidin-4-yl)-2-methyl-1*H*-indole



[2522] HCl, 4 M in 1,4-dioxane (10.5 mL, 42.1 mmol) was added to a solution of Intermediate 224c (1.81 g, 4.22 mmol) in 1,4-dioxane (10.5 mL). The resulting mixture was stirred at r.t. for 5h and concentrated under reduced pressure. The residue was dissolved in water (50 mL) and washed with EtOAc (50 mL). The aqueous layer was basified with sat. aq. K_2CO_3 (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.16 g, 84%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.83 - 1.90 (1H, m), 2.42 (3H, s), 2.68 (1H, br s), 2.74 - 2.86 (2H, m), 2.95 - 3.07 (2H, m), 3.17 - 3.24 (1H, m), 4.69 - 4.84 (1H, m), 6.25 (1H, s), 6.95 (1H, t), 7.18 - 7.20 (1H, m), 7.63 (1H, dd), product is present as mixture of rotamers by NMR (~4:1), ^{1}H NMR data represents major rotamer; *m/z* (ES^+) $[M+H]^+$ = 329.0.

Intermediate 224e:

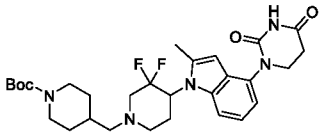
rac-tert-Butyl 4-((4-(4-bromo-2-methyl-1*H*-indol-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2523] Prepared in an analogous manner to Intermediate 10d using Intermediate 224d (1.15 g, 3.50 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.27 g, 5.94 mmol) in DMF (21 mL). Purification by FSC (elution gradient: 0 to 80% EtOAc in hexanes) gave the title compound (1.60 g, 87%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.97 - 1.05 (2H, m), 1.41 (9H, s), 1.72 - 1.78 (3H, m), 1.87 - 1.97 (1H, m), 2.34 (2H, br dd), 2.44 (4H, s), 2.61 - 2.78 (3H, m), 2.83 - 2.94 (1H, m), 3.03 (1H, br d), 3.20 - 3.28 (1H, m), 3.96 (2H, br d), 4.53 - 4.80 (1H, m), 6.28 (1H, s), 6.96 - 7.01 (1H, m), 7.21 (1H, d), 7.54 (1H, dd), product is present as mixture of rotamers by NMR (~3:1), ^{1}H NMR data represents major rotamer; *m/z* (ES$^+$) $[M+H]^+$ = 526.4.

Intermediate 224f:

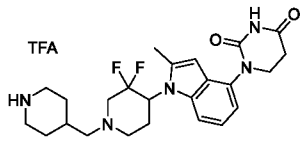
rac-tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2524] Prepared in an analogous manner to Intermediate 93b using Intermediate 224e (500 mg, 0.95 mmol), stirring at 95 °C for 17h. After cooling to r.t., the mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc–EtOH] in hexanes) gave the title compound (212 mg, 40%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.96 - 1.05 (2H, m), 1.41 (9H, s), 1.71 - 1.79 (3H, m), 1.87 - 1.96 (1H, m), 2.30 - 2.36 (2H, m), 2.38 - 2.44 (4H, m), 2.53 - 2.82 (5H, m), 2.92 (1H, qd), 3.04 (1H, br d), 3.20 - 3.27 (1H, m), 3.75 (2H, td), 3.96 (2H, br d), 4.56 - 4.74 (1H, m), 6.24 (1H, s), 6.93 (1H, d), 7.06 (1H, t), 7.44 - 7.50 (1H, m), 10.31 (1H, s), product is present as mixture of rotamers by NMR (~3:1), ^{1}H NMR data represents major rotamer; *m/z* (ES$^+$) $[M+H]^+$ = 560.5.

Intermediate 224g:

rac-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2525] Prepared in an analogous manner to Intermediate 1i using Intermediate 224f (205 mg, 0.37 mmol) to give the title compound (276 mg, 94%) as a brown solid and *tris*(trifluoroacetic acid) salt. *m/z* (ES$^+$) $[M+H]^+$ = 460.5.

EXAMPLE 224:

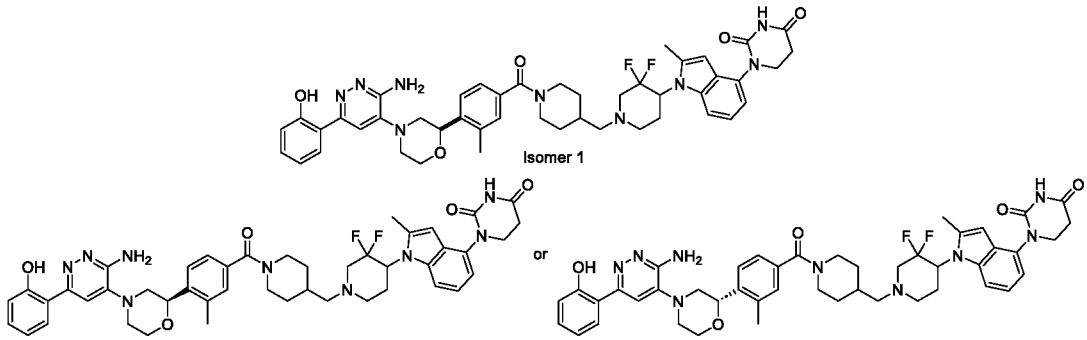
1-(1-(1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

1-(1-(1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

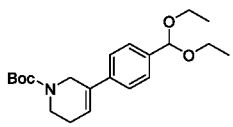


[2526] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 224g (54 mg, 0.07 mmol) and Intermediate 80e (30 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (33.9 mg, 59%) as a white solid and mixture of diastereomers, following lyophilization. ^{1}H NMR (DMSO-*d*6, 80 °C): δ 1.06 - 1.23 (2H, m), 1.72 - 2.02 (4H, m), 2.23 - 2.48 (9H, m), 2.60 - 2.80 (3H, m), 2.82 - 3.01 (5H, m), 3.06 (2H, br s), 3.24 (1H, br t), 3.43 - 3.64 (2H, m), 3.75 (2H, t), 3.86 - 4.37 (3H, m), 4.40 - 4.88 (1H, m), 4.99 (1H, br d), 6.14 (2H, s), 6.23 (1H, s), 6.81 - 6.97 (3H, m), 7.04 (1H, br t), 7.16 - 7.32 (3H, m), 7.42 - 7.51 (1H, m), 7.52 - 7.63 (2H, m), 7.89 (1H, d), 9.56 - 10.36 (1H, m), 13.47 - 14.33 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 848.6.

EXAMPLE 225

Intermediate 225a:

tert-Butyl 5-(4-(diethoxymethyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

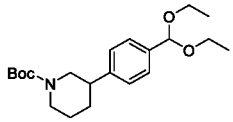


[2527] 1-Bromo-4-(diethoxymethyl)benzene (3 g, 11.58 mmol) was added to 1(2*H*)-pyridinecarboxylic acid, 3,6-dihydro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-,1,1-dimethylethyl ester (3.94 g, 12.73 mmol), potassium carbonate (4.80 g, 34.73 mmol) and $Pd(dppf)Cl_2$ (0.945 g, 1.16 mmol) in THF (30 mL) and water (3.00 mL) under nitrogen. The resulting mixture was stirred at 60 °C for

overnight. The reaction mixture was filtered and diluted with EtOAc (75 mL), washed with sat. aq. NH_4Cl (2 x 50 mL) and brine (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% EtOAc in petroleum ether) gave the title compound (3.50 g, 84%) as a yellow oil. ^1H NMR (DMSO-*d*6): δ 1.14 (6H, t), 1.43 (9H, s), 2.21 – 2.29 (2H, m), 3.43 – 3.58 (6H, m), 4.20 (2H, q), 5.48 (1H, s), 6.22 – 6.36 (1H, m), 7.34 – 7.43 (4H, m).

Intermediate 225b:

rac-tert-Butyl -3-(4-(diethoxymethyl)phenyl)piperidine-1-carboxylate



[2528] Platinum(IV) oxide (0.110 g, 0.48 mmol) was added to Intermediate 225a (3.5 g, 9.68 mmol) in ethanol (100 mL). The resulting mixture was stirred at r.t. for overnight under hydrogen. The catalyst was filtered off through celite, filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% EtOAc in petroleum ether) gave the title compound (2.90 g, 82%) as an oil. ^1H NMR (DMSO-*d*6): δ 1.12 (6H, t), 1.38 (9H, s), 1.64 – 1.77 (2H, m), 1.78 – 1.91 (1H, m), 2.53 – 2.90 (4H, m), 3.44 – 3.53 (4H, m), 3.88 – 4.01 (2H, m), 5.43 (1H, s), 7.24 (2H, d), 7.32 (2H, d). *m/z* (ES^+) $[M+H]^+$ = 364.1.

Intermediate 225c:

(*R**)-4-(1-(3-Amino-6-chloropyridazin-4-yl)piperidin-3-yl)benzaldehyde (Isomer 1)

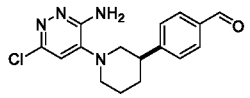
((*absolute configuration not yet confirmed))

and

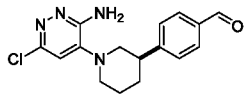
Intermediate 225d:

(*R**)-4-(1-(3-Amino-6-chloropyridazin-4-yl)piperidin-3-yl)benzaldehyde (Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 1



Isomer 2

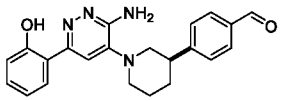
[2529] HCl, 4 M in 1,4-dioxane (20 mL, 80.00 mmol) was added to Intermediate 225b (2.9 g, 7.98 mmol). The resulting mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure. To the residue was added N,N-Diisopropylethylamine (3.09 g, 23.93 mmol) and 3-Amino-4-bromo-6-chloropyridazine (1.663 g, 7.98 mmol) in MeCN (30 mL). The resulting mixture was stirred at 80 °C for 24h. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with saturated NH_4Cl (50 mL) and saturated brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 5% MeOH in DCM) gave racemic title compound (1.5 g). The racemic mixture was separated by preparative SFC (Column: CHIRALPAK IH, 3.0*50mm, 3μm; Mobile Phase B: MeOH (0.1%DEA; Flow rate: 2 mL/min; Gradient: isocratic 10% B; Wave Length: 220 nm). The fractions containing were concentrated to dryness to afford Intermediate 225c

(Isomer 1, 0.300 g, 12%, 97.1% ee) and Intermediate 225d (Isomer 2, 0.27g, 11%, 98.5% ee). Isomer 1: ^{1}H NMR (DMSO-*d*6): δ 1.56 – 1.70 (1H, m), 1.79 – 1.83 (2H, m), 1.91 – 1.99 (1H, m), 2.58 – 2.72 (2H, m), 3.05 – 3.23 (1H, m), 3.38 – 3.51 (2H, m), 6.15 (2H, s), 6.93 (1H, s), 7.55 (2H, d), 7.86 (2H, d), 9.97 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 317.2. Isomer 2: ^{1}H NMR (DMSO-*d*6): δ 1.56 – 1.70 (1H, m), 1.79 – 1.83 (2H, m), 1.91 – 1.99 (1H, m), 2.58 – 2.72 (2H, m), 3.05 – 3.23 (1H, m), 3.38 – 3.51 (2H, m), 6.15 (2H, s), 6.93 (1H, s), 7.55 (2H, d), 7.86 (2H, d), 9.97 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 317.3.

Intermediate 225e:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzaldehyde (Isomer 1)

((*absolute configuration not yet confirmed))



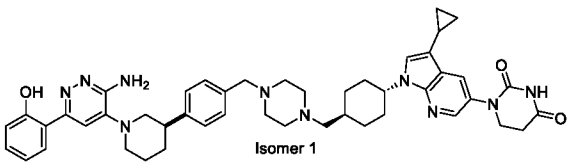
Isomer 1

[2530] Prepared in an analogous method to Intermediate 1e starting from Intermediate 225c (270 mg, 0.85 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (110 mg, 34%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.64 – 1.79 (1H, m), 1.83 – 2.05 (3H, m), 2.66 – 2.90 (2H, m), 3.16 – 3.26 (1H, m), 3.50 – 3.57 (2H, m), 6.30 (2H, s), 6.82 – 6.91 (2H, m), 7.18 – 7.27 (1H, m), 7.52 – 7.63 (3H, m), 7.83 – 7.96 (3H, m), 9.98 (1H, s), 14.24 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 375.1.

EXAMPLE 225:

1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



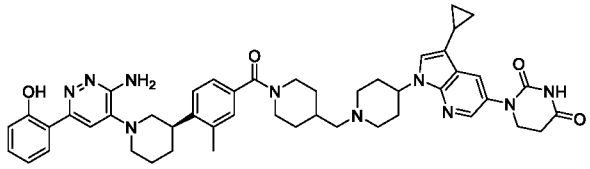
Isomer 1

[2531] Intermediate 225e (66.5 mg, 0.18 mmol) was added to Intermediate 120d (80 mg, 0.18 mmol) in NMP (2 mL) and DCE (2 mL). The resulting mixture was stirred at r.t. for 1h. Then Sodium triacetoxyborohydride (564 mg, 2.66 mmol) was added. The resulting mixture was stirred at r.t for 1h. The reaction mixture was diluted with DCM (10 mL), and washed sequentially with saturated $NaHCO_3$ (5 mL x 2) and saturated brine (5 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 74% MeCN in water with 0.1% NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (6.94 mg, 5%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.60 – 0.70 (2H, m), 0.81 – 0.90 (2H, m), 1.00 – 1.15 (2H, m), 1.52 – 1.70 (2H, m), 1.76 – 2.09 (11H, m), 2.10 – 2.19 (2H, m), 2.37 (7H, s), 2.64 – 2.85 (4H, m), 3.01 – 3.15 (1H, m), 3.40 – 3.48 (2H, m), 3.49 – 3.60 (2H, m), 3.76 – 3.90 (2H, m), 4.55 – 4.70 (1H, m), 6.29 (2H, s), 6.79 – 6.98 (2H, m), 7.15

– 7.35 (5H, m), 7.39 (1H, s), 7.54 (1H, s), 7.86 – 7.99 (2H, m), 8.16 (1H, d), 10.40 (1H, s), 14.29 (1H, s). *m/z* (ES^+) $[M+H]^+$ = 809.5.

EXAMPLE 226:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2532] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 71c (22 mg, 0.04 mmol) and Intermediate 12g (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.9 mg, 71%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.59 - 0.71 (2H, m), 0.80 - 0.90 (2H, m), 1.08 (2H, br d), 1.60 - 2.15 (14H, m), 2.23 (2H, br d), 2.40 (3H, s), 2.69 - 2.91 (5H, m), 2.98 (3H, br d), 3.23 - 3.30 (1H, m), 3.49 (1H, br d), 3.54 - 3.74 (2H, m), 3.82 (2H, t), 4.36 - 4.56 (1H, m), 4.57 - 4.64 (1H, m), 6.27 (2H, s), 6.82 - 6.95 (2H, m), 7.15 - 7.27 (3H, m), 7.39 (1H, d), 7.44 (1H, s), 7.57 (1H, s), 7.90 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 837.7.

EXAMPLE 227

Intermediate 227a:

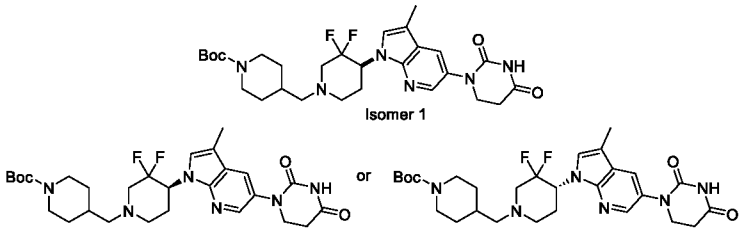
tert-Butyl (*S**)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate (Isomer 1)

((*absolute configuration not yet confirmed))

tert-Butyl (*S*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl (*R*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2533] Intermediate 220f (540 mg, 0.96 mmol) was purified by using SFC (Column: ChiralPak AD 21 x 250 mm, ; mobile phase: 40% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 75 mL/min; Column temperature: 40 °C) to give the title compound that eluted first from the column (180 mg, 33%, 100% ee) as a white solid.

Intermediate 227b:

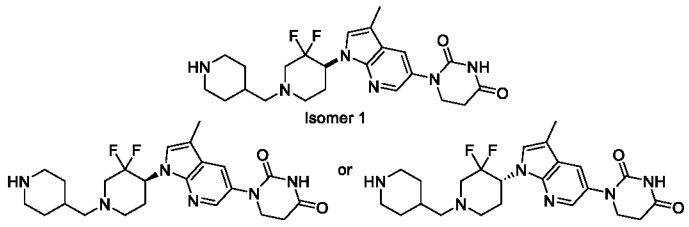
(*S**)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*S*)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*R*)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2534] Prepared in an analogous manner to Intermediate 220g using Intermediate 227a (180 mg, 0.32 mmol) to give the title compound (138 mg, 95%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.92 - 1.04 (2H, m), 1.53 - 1.71 (3H, m), 1.88 - 1.97 (1H, m), 2.23 - 2.41 (7H, m), 2.42 - 2.49 (2H, m), 2.52 - 2.60 (1H, m), 2.77 (2H, t), 2.87 - 3.06 (3H, m), 3.17 - 3.25 (1H, m), 3.83 (2H, t), 5.12 - 5.30 (1H, m), 7.49 (1H, s), 7.94 (1H, d), 8.21 (1H, d), 9.41 - 11.45 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES$^+$) [M+H]$^+$ = 461.5.

EXAMPLE 227:

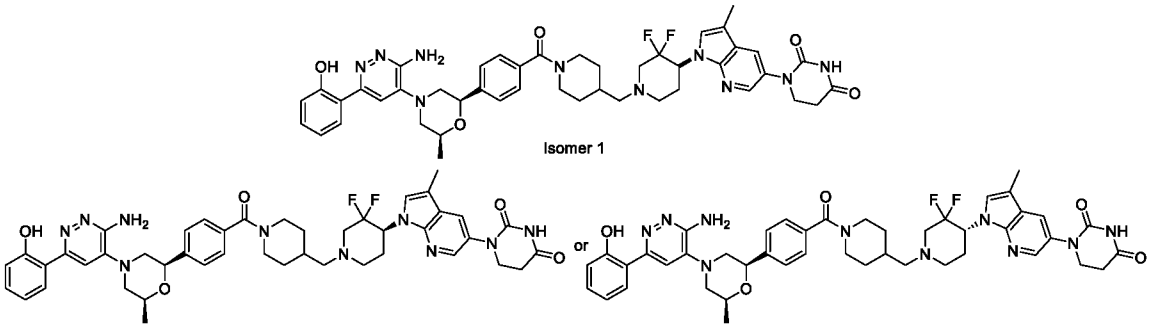
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*relative configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

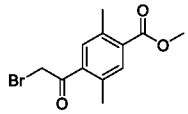


[2535] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 227b (21 mg, 0.04 mmol) and Intermediate 65e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.1 mg, 69%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br s), 1.27 (3H, d), 1.58 - 1.99 (4H, m), 2.27 (3H, s), 2.31 - 2.47 (4H, m), 2.53 - 2.65 (2H, m), 2.70 (1H, br t), 2.74 - 2.88 (3H, m), 3.02 (2H, br d), 3.20 - 3.28 (1H, m), 3.45 - 3.73 (3H, m), 3.83 (2H, t), 4.07 - 4.19 (1H, m), 4.48 (1H, br d), 4.95 (1H, dd), 5.14 - 5.31 (1H, m), 6.48 (2H, s), 6.84 - 6.94 (2H, m), 7.20 - 7.28 (1H, m), 7.40 (2H, d), 7.48 (1H, s), 7.53 (2H, d), 7.57 (1H, s), 7.92 - 7.99 (2H, m), 8.21 (1H, d), 10.40 (1H, br s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 849.5.

EXAMPLE 228

Intermediate 228a:

Methyl 4-(2-bromoacetyl)-2,5-dimethylbenzoate



[2536] $Pd(PPh_3)Cl_2$ (1.44 g, 2.06 mmol) was added to a solution of methyl 4-bromo-2,5-dimethylbenzoate (5.00 g, 20.6 mmol) and tributyl(1-ethoxyvinyl)stannane (7.64 mL, 22.6 mmol) in 1,4-dioxane (100 mL). The flask was evacuated and back-filled with nitrogen (3x). The mixture was stirred at 90 °C for 16 hours. The mixture was cooled to 0 °C. Water (10 mL) was added followed by slow addition of NBS (4.39 g, 24.7 mmol). The mixture was stirred at 0 °C for 30 minutes. EtOAc (100 mL) and 1 M aq. KF (100 mL) were added and the mixture was stirred at r.t. for 5 minutes. The resulting suspension was filtered. The filtrate was washed with 1 M aq. KF (2 x 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% ethyl acetate in petroleum ether) gave the title compound (3.80 g, 65%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.49 (3H, s), 2.60 (3H, s), 3.92 (3H, s), 4.40 (2H, s), 7.47 (1H, s), 7.80 (1H, s); mass not observed

Intermediate 228b:

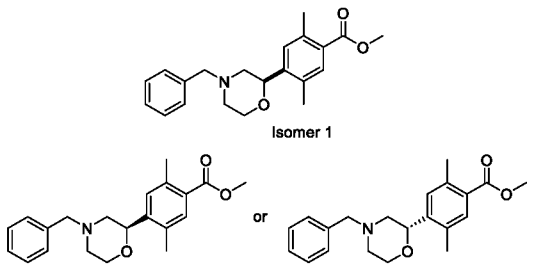
Methyl (*R**)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate



[2537] Prepared in an analogous manner to Intermediate 65a using Intermediate 228a (3.80 g, 13.3 mmol) and *N*-benzylethanolamine (2.02 g, 13.3 mmol). Purification by FSC (elution gradient: 0 to 20% ethyl acetate in petroleum ether) followed by preparative HPLC (Column: ChiralPak IG 34.6 x 50 mm, 3 μm; mobile phase: 15% MeOH in $scCO_2$, Flow rate: 4 mL/min) gave the title compound which eluted first from the column (0.69 g, 15%, >99% ee) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.84–1.94 (1H, m), 2.22 (4H, s), 2.46 (3H, s), 2.67–2.88 (2H, m), 3.53 (2H, d), 3.66–3.77 (1H, m), 3.80 (3H, s), 3.91–3.99 (1H, m), 4.62–4.69 (1H, m), 7.21–7.29 (1H, m), 7.29–7.38 (5H, m), 7.59 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 340.2.

Intermediate 228c:

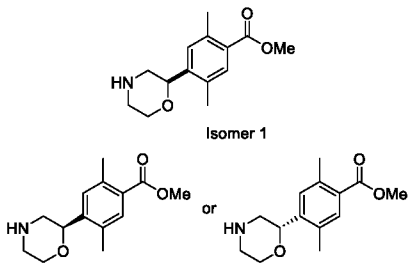
Methyl (*R**)-2,5-dimethyl-4-(morpholin-2-yl)benzoate (Isomer 1)

((*absolute configuration not yet confirmed))

Methyl (*R*)-2,5-dimethyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-2,5-dimethyl-4-(morpholin-2-yl)benzoate



[2538] Prepared in an analogous manner to Intermediate 65b starting from Intermediate 228b (687 mg, 2.01 mmol) to give the title compound (380 mg, 75%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.29 (3H, s), 2.47 (3H, s), 2.57 (1H, s), 2.65–2.84 (2H, m), 2.89 (1H, dd), 3.33 (1H, s), 3.58-3.70 (1H, m), 3.81 (3H, s), 4.49–4.68 (1H, m), 7.31 (1H, s), 7.61 (1H, s), nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 250.1.

Intermediate 228d:

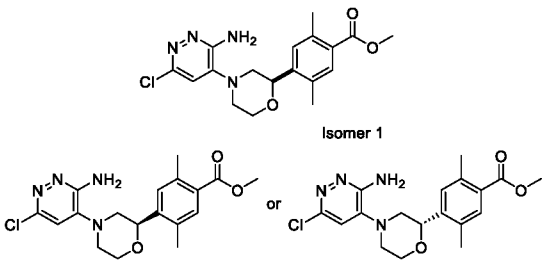
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate



[2539] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 228c (380 mg, 1.52 mmol). Purification by FSC (elution gradient: 0 to 90% ethyl acetate in petroleum ether) gave the title compound (470 mg, 82%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 2.35 (3H, s), 2.49 (3H, s), 2.77-2.85 (2H, m), 3.38-3.48 (2H, m), 3.82 (3H, s), 4.03 (2H, dd), 4.6–5 (1H, m), 6.29 (2H, s), 6.97 (1H, s), 7.39 (1H, s), 7.64 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 377.2.

Intermediate 228e:

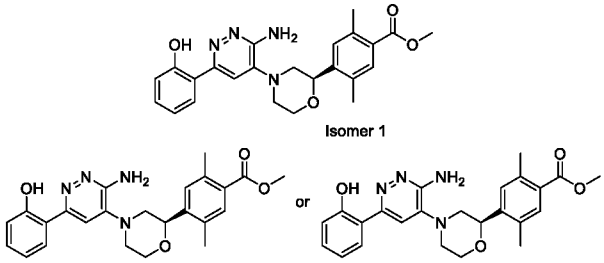
Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate (Isomer 1)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate



[2540] Prepared in an analogous manner to Intermediate 1e starting from Intermediate 228d (470 mg, 1.25 mmol) stirring at 80 °C for 6h. After cooling to r.t. the mixture was poured into water (150 mL). A precipitate formed which was collected by filtration and dried *in vacuo* to give the title compound (497 mg, 92%) as a yellow solid, which was used for the next step without further purification. ^{1}H NMR (DMSO-*d*6): δ 2.36 (3H, d), 2.50 (3H, s), 2.75–2.83 (1H, m), 2.88 (1H, d), 3.51 (2H, d), 3.58 (2H, s), 3.82 (3H, d), 4.90-4.98 (1H, m), 6.45 (2H, s), 6.81–6.95 (2H, m), 7.12–7.28 (1H, m), 7.44 (1H, s), 7.57 (1H, s), 7.65 (1H, d), 7.93-7.95 (1H, m), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 435.1.

Intermediate 228f:

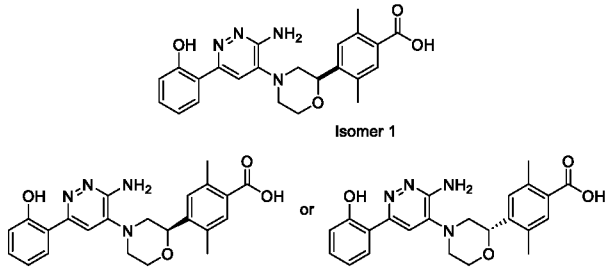
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid



[2541] Prepared in an analogous manner to Intermediate 132e using Intermediate 228e (497 mg, 1.14 mmol) stirring at 60 °C for 1h to give the title compound (350 mg, 73%) as a yellow solid, which was used for the next step without further purification. ^{1}H NMR (DMSO-*d*6): δ 2.35 (3H, s), 2.43 (3H, s), 2.69 – 2.98 (2H, m), 3.35 – 3.44 (1H, m), 3.50 (2H, d), 4.08 (2H, d), 4.95 (1H, d), 6.42 (2H, s), 6.80 – 6.91 (2H, m), 7.22 (1H, td), 7.37 (1H, d), 7.55 (1H, s), 7.64 (1H, d), 7.93 (1H, d), NH proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 421.2.

EXAMPLE 228:

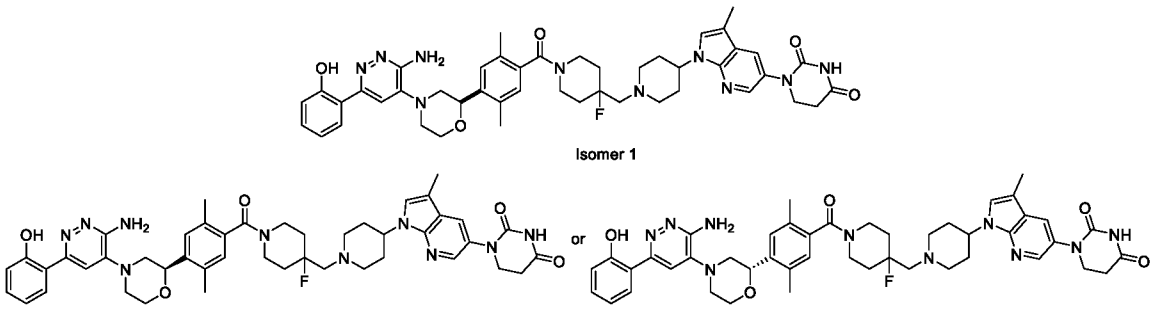
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2542] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (22 mg, 0.05 mmol) and Intermediate 228f (25 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (27.3 mg, 70%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.42 – 1.89 (5H, m), 1.93 – 2.09 (3H, m), 2.14 – 2.28 (6H, m), 2.33 (5H, s), 2.56 – 2.69 (2H, m), 2.74 (2H, t), 2.78 – 2.92 (2H, m), 2.99 – 3.26 (5H, m), 3.50 (2H, br d), 3.79

(2H, t), 4.07 (2H, br d), 4.21 – 4.43 (1H, m), 4.52 – 4.66 (1H, m), 4.92 (1H, br d)– 6.41 (2H, s), 6.81 – 6.92 (2H, m), 6.95 – 7.08 (1H, m), 7.18 – 7.26 (1H, m), 7.37 (1H, s), 7.46 (1H, s), 7.56 (1H, s), 7.86 (1H, d), 7.90 – 7.97 (1H, m), 8.16 (1H, d), 10.36 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 229:

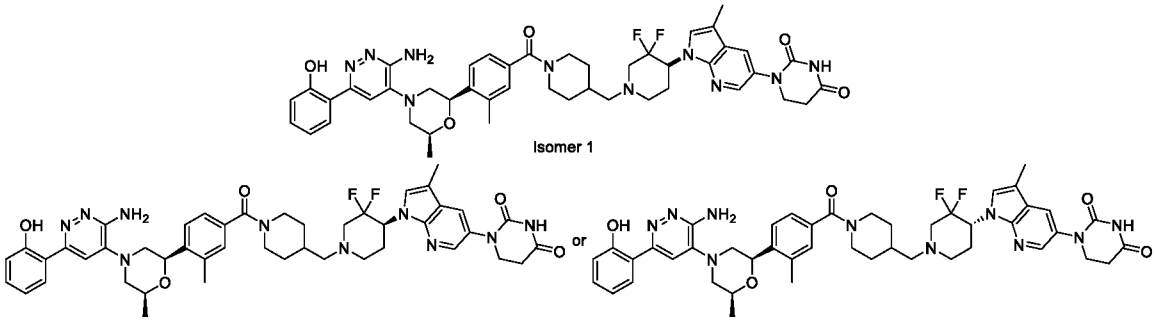
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*relative configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2543] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 227b (22 mg, 0.05 mmol) and Intermediate 132e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: water with 0.1% formic acid, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (32.0 mg, 78%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.02 – 1.18 (2H, m), 1.22 – 1.28 (3H, m), 1.56 – 2.00 (4H, m), 2.27 (3H, d), 2.30 – 2.49 (7H, m), 2.53 – 2.66 (2H, m), 2.70 – 2.91 (4H, m), 2.93 – 3.13 (2H, m), 3.20 – 3.29 (1H, m), 3.47 – 3.73 (3H, m), 3.83 (2H, t), 4.10 – 4.23 (1H, m), 4.48 (1H, br s), 5.04 (1H, dd), 5.14 – 5.33 (1H, m), 6.43 (2H, s), 6.83 – 6.93 (2H, m), 7.18 – 7.29 (3H, m), 7.48 (1H, br s), 7.53 – 7.62 (2H, m), 7.91 – 8.00 (2H, m), 8.21 (1H, d), 10.40 (1H, s), 14.21 (1H,–br s); *m/z* (ES^+) $[M+H]^+$ = 863.6.

EXAMPLE 230:

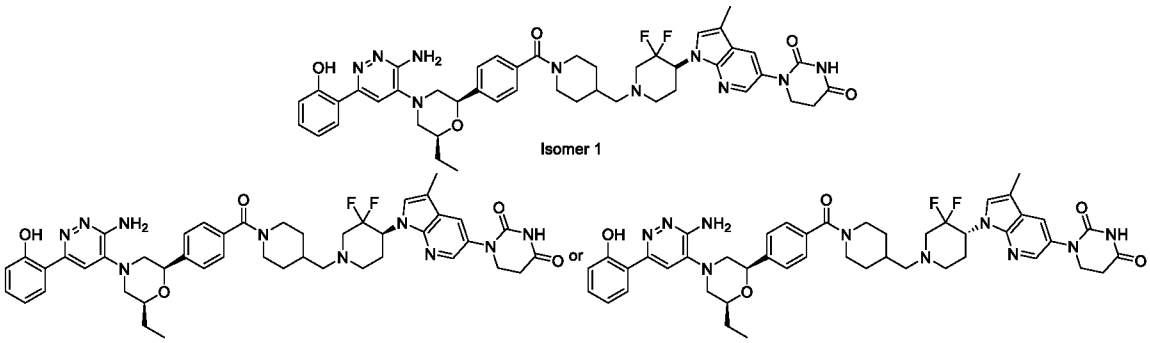
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*relative configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

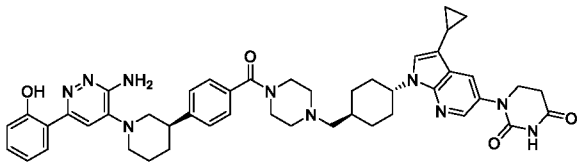
1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2544] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 227b (22 mg, 0.05 mmol) and Intermediate 163f (20 mg, 0.05 mmol). Purification by RPC (elution gradient: water with 0.1% formic acid, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (33.3 mg, 81%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.04 – 1.17 (2H, m), 1.53 – 1.99 (6H, m), 2.25 (3H, s), 2.28 – 2.44 (4H, m), 2.52 – 2.69 (3H, m), 2.75 (3H, t), 3.01 (2H, br d), 3.18 – 3.27 (1H, m), 3.44 – 3.69 (3H, m), 3.81 (2H, t), 3.86 – 3.94 (1H, m), 4.47 (1H, br s), 4.93 (1H, dd), 5.14 – 5.27 (1H, m), 6.46 (2H, s), 6.81 – 6.92 (2H, m), 7.18 – 7.26 (1H, m), 7.39 (2H, d), 7.47 (1H, s), 7.49 – 7.60 (3H, m), 7.88 – 8.00 (2H, m), 8.19 (1H, d), 10.38 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 863.6.

EXAMPLE 231:

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

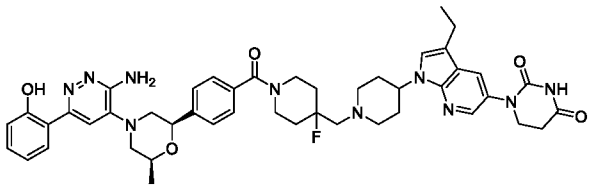


[2545] HATU (9.02 mg, 0.02 mmol) was added to a stirred solution of Intermediate 1f (9.26 mg, 0.02 mmol) and DIPEA (0.012 mL, 0.07 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 1h. Then added DIPEA (0.012 mL, 0.07 mmol) and Intermediate 120d (0.020 g, 0.02 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 1 h. Purification by RPC (elution gradient: 0 to 40% MeCN in water with 0.1% formic acid) gave the title compound (9.90 mg, 50%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.62 – 0.68 (2H, m), 0.81 – 0.90 (2H, m), 1.06 – 1.18 (2H, m), 1.68 (2H, qd), 1.80 – 1.97 (9H, m), 1.97 – 2.04 (1H, m), 2.19 (2H, m), 2.29 (1H, s), 2.41 (4H, s), 2.66 – 2.85 (4H, m), 3.09 – 3.28 (2H, m), 3.55

(3H, d), 3.63 (1H, s), 3.82 (2H, t), 4.61 (1H, tt), 6.30 (2H, s), 6.88 (2H, t), 7.24 (1H, ddd), 7.35 – 7.41 (3H, m), 7.43 (2H, d), 7.56 (1H, s), 7.94 (2H, q), 8.16 (1H, d), 10.38 (1H, s), 14.21 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 823.

EXAMPLE 232:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2546] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 149f (36 mg, 0.04 mmol) and Intermediate 65e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.5 mg, 70%) as a white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.22 – 1.29 (6H, m), 1.60 – 2.02 (6H, m), 2.03 – 2.12 (2H, m), 2.32 – 2.39 (2H, m), 2.50 – 2.56 (1H, m), 2.57 – 2.65 (2H, m), 2.65 – 2.71 (3H, m), 2.74 (2H, t), 3.00 – 3.06 (2H, m), 3.07 – 3.30 (2H, m), 3.35 – 3.61 (3H, m), 3.79 (2H, t), 4.06 – 4.14 (1H, m), 4.16 – 4.36 (1H, m), 4.60 (1H, tt), 4.94 (1H, dd), 6.47 (2H, s), 6.81 – 6.92 (2H, m), 7.18 – 7.28 (1H, m), 7.42 (2H, d), 7.49 (1H, s), 7.50 – 7.57 (3H, m), 7.90 (1H, d), 7.94 (1H, dd), 8.15 (1H, d), 10.37 (1H, s), 14.21 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 233:

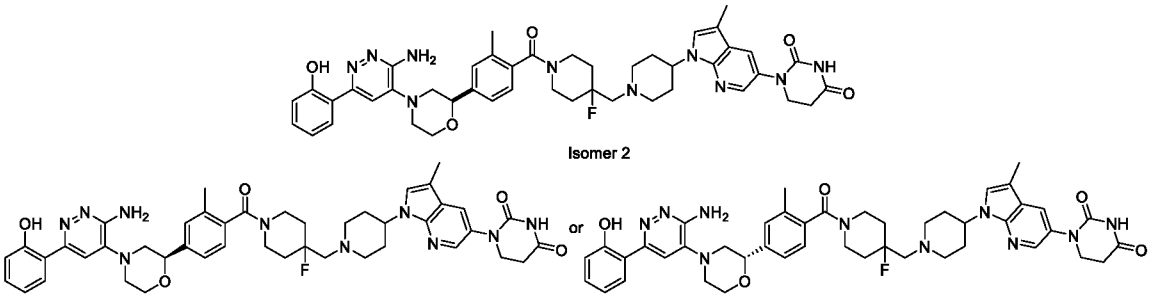
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

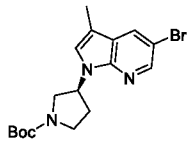


[2547] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (21 mg, 0.04 mmol) and Intermediate 219d (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (23.8 mg, 64%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.47 - 1.90 (5H, m), 1.92 - 2.09 (3H, m), 2.16 - 2.30 (6H, m), 2.31 - 2.38 (2H, m), 2.56 - 2.66 (2H, m), 2.71 - 2.82 (3H, m), 2.87 (1H, td), 2.98 - 3.26 (5H, m), 3.41 - 3.58 (2H, m), 3.79 (2H, t), 3.99 - 4.11 (2H, m), 4.19 - 4.40 (1H, m), 4.52 - 4.63 (1H, m), 4.72 - 4.90 (1H, m), 6.46 (2H, s), 6.82 - 6.91 (2H, m), 7.13 - 7.26 (2H, m), 7.31 (1H, br d), 7.36 (1H, s), 7.47 (1H, br s), 7.55 (1H, s), 7.86 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.37 (1H, br s), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 831.6.

EXAMPLE 234

Intermediate 234a:

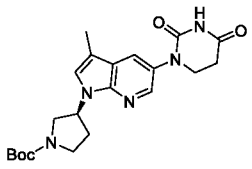
tert-Butyl (S)-3-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate



[2548] 5-Bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 4.74 mmol) was added to *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (0.887 g, 4.74 mmol) and 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (1.372 g, 5.69 mmol) in toluene (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water (0.1% NH_4HCO_3) gave the title compound (1.0 g, 56%) as a brown gum. ^{1}H NMR (DMSO-d_6) δ 1.38 – 1.42 (9H, s), 2.24 (3H, s), 2.29 – 2.33 (2H, m), 3.40 – 3.49 (2H, m), 3.50 – 3.54 (1H, m), 3.75 – 3.79 (1H, m), 5.28 – 5.35 (1H, m), 7.44 (1H, d), 8.20 (1H, d), 8.30 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 380.1.

Intermediate 234b:

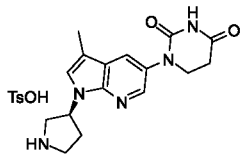
tert-Butyl (*S*)-3-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate



[2549] Prepared in an analogous method to Intermediate 2b starting from Intermediate 234a (900 mg, 2.37 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (600 mg, 61%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, d), 2.26 (3H, d), 2.29 – 2.35 (2H, m), 2.76 (2H, t), 3.38 – 3.50 (2H, m), 3.52 – 3.57 (1H, m), 3.76 – 3.81 (1H, m), 3.83 (2H, t), 5.31 – 5.39 (1H, m), 7.42 (1H, d), 7.92 (1H, d), 8.21 (1H, d), 10.41 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 414.2.

Intermediate 234c:

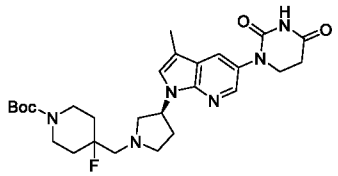
(*S*)-1-(3-Methyl-1-(pyrrolidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2550] Prepared in an analogous method to Intermediate 6e starting from Intermediate 234b (600 mg, 1.45 mmol). The mixture was concentrated under reduced pressure. MTBE was added (3 mL). The solids were collected by filtration, washed with MTBE (1 mL), and dried *in vacuo* to give title compound (690 mg, 98%) as a yellow solid and TsOH salt, which was used without further purification. *m/z* (ES$^+$) $[M+H]^+$ = 314.1.

Intermediate 234d:

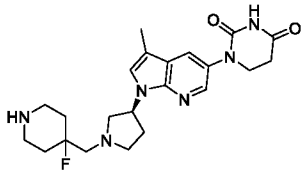
tert-Butyl (*S*)-4-((3-(5-(2,4-dioxotetrahydropyrimidin-1(*2H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2551] Prepared in an analogous method to Intermediate 6g starting from Intermediate 6f (1224 mg, 3.35 mmol) and Intermediate 234c (700 mg, 2.23 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (580 mg, 49%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, s), 1.56 – 1.68 (3H, m), 1.80 – 1.92 (3H, m), 2.27 (3H, s), 2.38 – 2.42 (1H, m), 2.53 – 2.57 (1H, m), 2.69 – 2.72 (1H, m), 2.74 – 2.78 (3H, m), 2.86 (1H, d), 2.99 – 3.10 (3H, m), 3.72 – 3.77 (2H, m), 3.81 (2H, t), 5.37 – 5.41 (1H, m), 7.47 (1H, s), 7.89 (1H, d), 8.16 (1H, s), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 529.3.

Intermediate 234e:

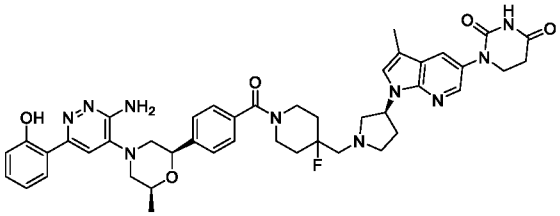
(*S*)-1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)pyrrolidin-3-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2552] Prepared in an analogous method to Intermediate 1i starting from Intermediate 234d (570 mg, 1.08 mmol). The crude residue was triturated with MTBE (5 mL) and dried *in vacuo* to give the title compound (300 mg, 65%) as a white solid and TFA salt. m/z (ES^+) $[M+H]^+$ = 429.2.

EXAMPLE 234:

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)pyrrolidin-3-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

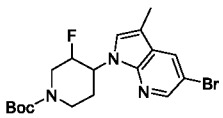


[2553] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (26.1 mg, 0.06 mmol) and Intermediate 234e (25 mg, 0.06 mmol). Purification by preparative HPLC (Column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; Mobile Phase A: Water with 0.1% FA, Mobile Phase B: MeCN; Flow rate: 60 mL/min, elution gradient: 13 to 31% B in 8 min) gave the title compound (27.0 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.24 – 1.28 (3H, m), 1.69 –1.79 (2H, m), 1.85 –1.96 (3H, m), 2.26 (3H, s), 2.38 –2.43 (1H, m), 2.53 – 2.60 (2H, m), 2.69 – 2.79 (5H, m), 2.85 –2.91 (2H, m), 3.08 – 3.14 (2H, m), 3.51 (2H, d), 3.58 (2H, d), 3.81 (2H, t), 4.09 – 4.14 (1H, m), 4.23 –4.31 (1H, m), 4.93 – 4.97 (1H, m), 5.36 – 5.43 (1H, m), 6.49 (2H, s), 6.85 – 6.90 (2H, m), 7.22 – 7.26 (1H, m), 7.44 (2H, d), 7.49 (1H, s), 7.52–7.57 (3H, m), 7.88 (1H, d), 7.94 – 7.97 (1H, m), 8.18 (1H, s), 10.39 (1H, s), 13.88 – 14.43 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 817.4.

EXAMPLE 235

Intermediate 235a:

tert-Butyl 4-(4-hydroxycyclohexane-1-carbonyl)piperazine-1-carboxylate



[2554] Prepared in an analogous method to Intermediate 126a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.6 g, 7.58 mmol) and *tert*-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (2.327 g, 10.61 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (1.500 g, 48%) as a white solid and racemic mixture of *cis*- and *trans*-isomers. ^{1}H NMR (DMSO-*d6*) δ 1.44 (9H, d), 1.86 – 2.16 (2H, m), 2.24 (3H, d), 2.92- – 3.09 (2H, m), 3.98 – 4.09 (1H, m), 4.29 – 4.43 (1H, m), 4.86 – 5.22 (2H, m), 7.42 – 7.68 (1H, m), 8.20 (1H, dd), 8.28 (1H, dd); *m/z* (ES^+) $[M+H]^+$ = 412.2.

Intermediate 235b:

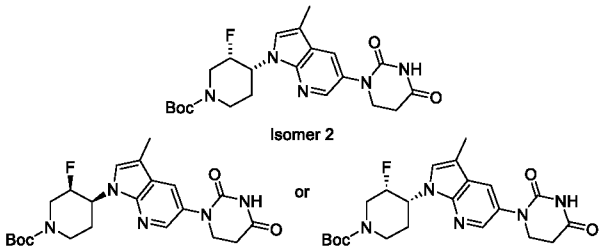
tert-Butyl (3*S**,4*R**)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

((*absolute configuration not yet confirmed))

tert-Butyl (3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

or

tert-Butyl (3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2555] Prepared in an analogous method to Intermediate 2b starting from Intermediate 235a (1.5 g, 3.64 mmol). The crude product was purified by FSC (elution gradient 0 to 10% MeOH in DCM) gave a mixture of *cis*- and *trans*-isomers as a yellow solid. Purification by preparative SFC (Column: CHIRAL ART Cellulose-SZ, 3*25 cm, 5 μm; Flow rate: 100 mL/min; isocratic 35% [MeOH with 0.1% 2 M NH_3 in MeOH] in $scCO_2$; RT1(min): 12; RT2(min): 16) isolating the isomers that eluted second from the column (0.400 g, 25%, 99% ee). ^{1}H NMR (DMSO-*d6*) δ 1.45 (9H, s), 1.88 – 1.92 (1H,m), 2.01 – 2.19 (1H, m), 2.26 (3H, d), 2.76 (2H, t), 2.93 – 3.10 (2H, m), 3.81 (2H, t), 3.97 – 4.08 (1H, m), 4.30 – 4.40 (1H, m), 4.89 – 5.16 (2H, m), 7.64 (1H, d), 7.91 (1H, d), 8.18 (1H, d); nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 446.1.

Intermediate 235c:

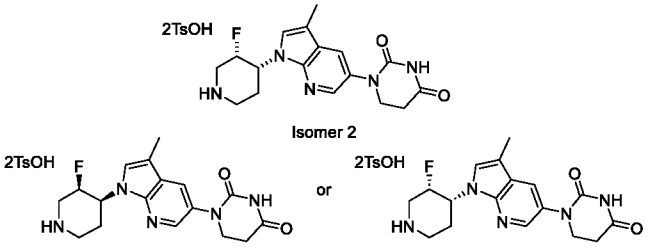
1-(1-((3*S**,4*R**)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

1-(1-((3*R*,4*S*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2556] TsOH (139 mg, 0.81 mmol) was added to Intermediate 235b (180 mg, 0.40 mmol) in MeCN (3 mL). The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was poured into MTBE (20 mL). A precipitate formed which was collected by filtration and dried *in vacuo* to give the title compound (120 mg, 43%) as a white solid and *bis*-TsOH salt. *m/z* (ES^+) $[M+H]^+$ =346.1.

Intermediate 235d:

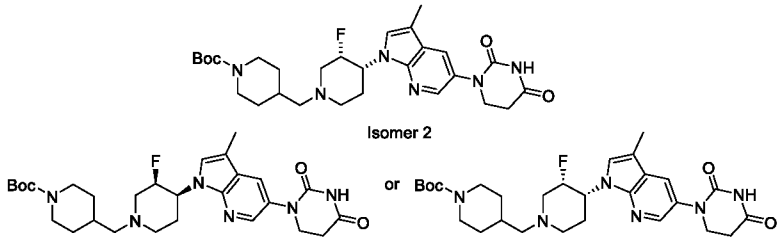
tert-Butyl 4-(((3*S**,4*R**)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

((*absolute configuration not yet confirmed))

tert-Butyl 4-(((3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl 4-(((3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2557] Intermediate 235c (110 mg, 0.32 mmol) was added to *tert*-butyl 4-formylpiperidine-1-carboxylate (67.9 mg, 0.32 mmol) in DCE (2 mL) and NMP (2 mL). The resulting mixture was stirred at 40 °C for 30 min. Sodium triacetoxyborohydride (270 mg, 1.27 mmol) was added. The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (100 mg, 58%) as a yellow solid. ^1H NMR (DMSO-d_6) δ 1.38 (9H, s), 1.63–1.8 (4H, m), 1.86–1.94 (1H, m), 2.13–2.22 (2H, m), 2.23–2.28 (4H, m), 2.29–2.32 (1H, m), 2.41 (1H, d), 2.64–2.79 (5H, m), 3.00 (1H, d), 3.16 (1H, d), 3.73–3.84 (2H, m), 3.92 (2H, d), 4.79 (1H, d), 4.87–5 (1H, m), 7.43 (1H, s), 7.91 (1H, d), 8.18 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 543.4.

Intermediate 235e:

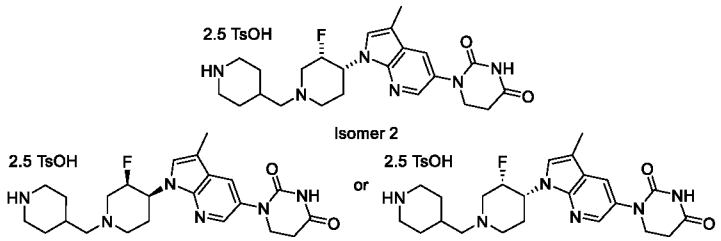
1-(1-((3*R**,4*S**)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

((*absolute configuration not yet confirmed))

1-(1-((3*R*,4*S*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2558] TsOH (87 mg, 0.51 mmol) was added to Intermediate 235d (110 mg, 0.20 mmol) in MeCN (2 mL). The resulting mixture was stirred at 80 °C for 16 h. After cooling to r.t., the mixture was filtered. The solids were dried *in vacuo* to give the title compound (100 mg, 56%) as a pale yellow solid and 2.5 TsOH salt. The product was used in the next step without further purification. *m/z* (ES^+) $[M+H]^+$ = 443.2.

EXAMPLE 235:

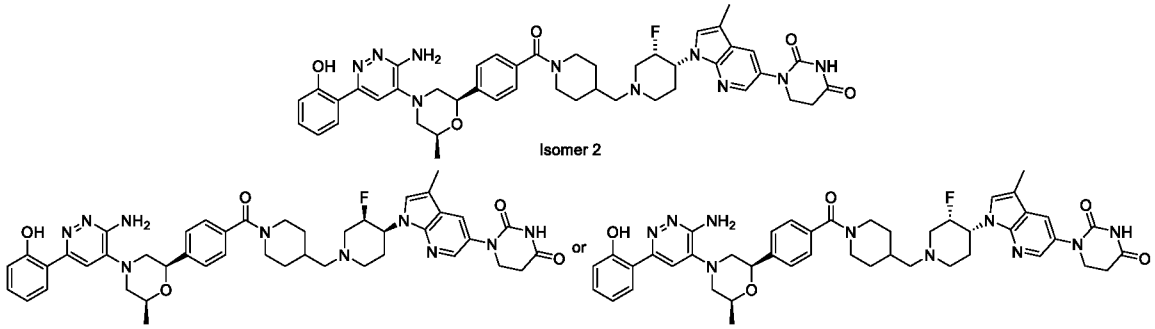
1-(1-((3*S**,4*R**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



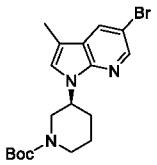
[2559] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (27.6 mg, 0.07 mmol) and Intermediate 235e (50 mg, 0.11 mmol). Purification by preparative HPLC (Mobile Phase A: Water with 10 mmol/L NH_4HCO_3 and 0.05% NH_3H_2O); Mobile Phase B: MeCN; Flow rate: 60 mL/min; elution gradient: 40 to 50% B) gave title compound (30.4 mg, 32%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.10 (2H, s), 1.27 (3H, d), 1.69 (1H, s), 1.74–1.96 (3H, m), 2.27 (5H, d), 2.32 (1H, d), 2.35–2.48 (2H, m), 2.56 (1H, d), 2.66–2.73 (1H, m), 2.76 (2H, d), 3.04 (2H, d), 3.22 (2H, s), 3.51 (1H, d), 3.58 (2H, d), 3.77–

3.86 (2H, m), 4.06–4.17 (1H, m), 4.48 (1H, s), 4.78–4.97 (3H, m), 6.48 (2H, s), 6.83–6.91 (2H, m), 7.21–7.27 (1H, m), 7.36–7.46 (3H, m), 7.48–7.58 (3H, m), 7.93 (1H, d), 7.95–8.01 (1H, m), 8.20 (1H, d), 10.40 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 831.4.

EXAMPLE 236

Intermediate 236a:

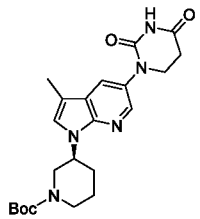
tert-Butyl (*S*)-3-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate



[2560] Prepared in an analogous method to Intermediate 234a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.00 g, 4.74 mmol) and *tert*-butyl (*R*)-3-hydroxypiperidine-1-carboxylate (0.954 g, 4.74 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.680 g, 36%) as a brown solid. ^{1}H NMR (DMSO-*d6*) δ 1.32 – 1.44 (9H, m), 1.53 – 1.63 (2H, m), 1.77 – 1.82 (1H, m), 1.98 – 2.03 (1H, m), 2.24 (3H, s), 2.84 – 2.93 (1H, t), 3.06 – 3.32 (1H, m), 3.86 – 4.07 (2H, m), 4.57 – 4.63 (1H, m), 7.51 (1H, s), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 394.2.

Intermediate 236b:

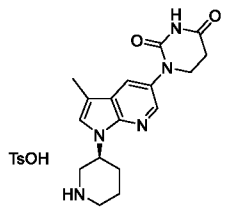
tert-Butyl (*S*)-3-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2561] Prepared in an analogous method to Intermediate 2b starting from Intermediate 236a (660 mg, 1.67 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (330 mg, 46%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.40 (9H, s), 1.53 – 1.59 (2H, m), 1.79 – 1.83 (1H, m), 1.99 – 2.04 (1H, m), 2.06 – 2.13 (1H, m), 2.26 (3H, s), 2.77 (2H, t), 2.84– 2.91 (1H, m), 3.82 (2H, t), 3.91– 3.95 (1H, d), 4.01– 4.09 (1H, m), 4.61 – 4.67 (1H, m), 7.49 (1H, s), 7.91 (1H, d), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 428.3.

Intermediate 236c:

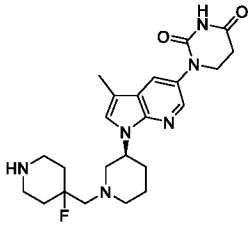
(*S*)-1-(3-Methyl-1-(piperidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2562] Prepared in an analogous method to Intermediate 6e starting from Intermediate 236b (320mg, 0.75 mmol. After cooling to r.t., MTBE (3 mL) was added. The solids were collected by filtration, washed with MTBE (1 mL), and dried *in vacuo* to give the title compound (420 mg, 84%) as a yellow solid and 2.5 TsOH salt, which was used without further purification.; *m/z* (ES^+) $[M+H]^+$ = 328.3.

Intermediate 236d:

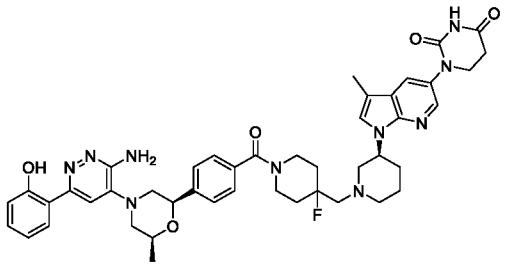
(*S*)-1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-3-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2563] Intermediate 236c (400 mg, 1.22 mmol) was added to Intermediate 6f (670 mg, 1.83 mmol) and DIPEA (316 mg, 2.44 mmol) in 1,4-dioxane (4 mL). The resulting mixture was stirred at 80 °C for 35 h. The solvent was removed under reduced pressure. To the residue was added DCM (3 mL) and TFA (1 mL) (3:1) mixture. The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (150 mg, 28%) as a brown solid. ^{1}H NMR (DMSO-*d6*) δ 1.60 – 1.69 (3H, m), 1.72 – 1.78 (3H, m), 1.82 – 1.86 (1H, m), 1.88 – 1.93 (1H, m), 2.21 –2.30 (4H, m), 2.47– 2.49 (1H, m),2.53 – 2.62 (3H, m), 2.70 – 2.80 (6H, m), 2.87 (1H, d), 2.97 – 3.01 (1H, m), 3.81 (2H, t), 4.78 – 4.84 (1H, m), 7.54 (1H, s), 7.89 (1H, d), 8.19 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 443.2.

EXAMPLE 236:

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-3-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



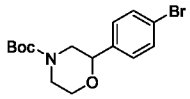
[2564] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (25.3 mg, 0.06 mmol) and Intermediate 236d (25 mg, 0.06 mmol). Purification by preparative HPLC (Column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; Mobile Phase A: Water with 0.1% FA, Mobile Phase B: MeCN; Flow rate: 60 mL/min; elution gradient: 10 to 30% B in 10 min) gave the title compound (10.0 mg, 21%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.24 – 1.26 (3H, m), 1.64 – 1.71 (2H, m), 1.73 – 1.79 (2H, m), 1.81 – 1.93 (4H, m), 2.25 (4H, s), 2.54 – 2.72 (5H, m), 2.76 (2H, t), 2.87 – 2.91 (1H, m), 2.99 – 3.03

(1H, d), 3.08 – 3.14 (1H, m), 3.49 – 3.53 (2H, m), 3.58 (2H, d), 3.78 – 3.82 (2H, t), 4.09 – 4.15 (1H, m), 4.20 – 4.31 (1H, s), 4.78 – 4.83 (1H, m), 4.93 – 4.96 (1H, m), 6.48 (2H, s), 6.85 – 6.90 (2H, m), 7.21 – 7.25 (1H, m), 7.43 (2H, d), 7.52 – 7.57 (4H, m), 7.89 (1H, d), 7.94 – 7.97 (1H, m), 8.18 (1H, d), 10.39 (1H, s),13.93 – 14.50 (1H, br s); *m/z* (ES+) $[M+H]^+$ = 831.4.

EXAMPLE 237

Intermediate 237a:

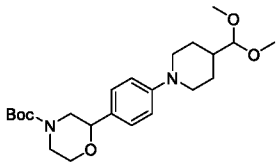
tert-Butyl-2-(4-bromophenyl)morpholine-4-carboxylate



[2565] Di-*tert*-butyl dicarbonate (2.70 g, 12.39 mmol was added to a stirred solution of Et_3N (3.45 mL, 24.78 mmol) and 2-(4-bromophenyl)morpholine (2 g, 8.26 mmol) in DCM (30 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with DCM (200 mL), washed with saturated aq. citric acid (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (2.70 g, 96%) as a colorless oil. ^{1}H NMR (DMSO-*d6*) δ 1.40 (9H, s), 2.72 (1H, s), 2.95 (1H, s), 3.47 – 3.62 (1H, m), 3.78 (1H, d), 3.82 – 3.98 (2H, m), 4.39 (1H, dd), 7.29 – 7.36 (2H, m), 7.51 – 7.58 (2H, m); *m/z* (ES+) $[M\text{-}tBu+2H]^+$ = 286.0.

Intermediate 237b:

tert-Butyl-2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholine-4-carboxylate



[2566] RuPhos Pd G3 (0.495 g, 0.58 mmol) was added to 4-(dimethoxymethyl)piperidine (1.210 g, 7.60 mmol), Cs_2CO_3 (3.81 g, 11.69 mmol), Intermediate 237a (2 g, 5.84 mmol), and RuPhos (0.273 g, 0.58 mmol) in dioxane (30 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 5 h. After cooling to r.t., the mixture was diluted with EtOAc (150 mL), washed with water (150 mL) and brine (150 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to100% MeCN in water with 0.4% NH_4HCO_3) gave the title compound (1.400 g, 57%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.20 – 1.39 (2H, m), 1.42 (9H, s), 1.70 (3H, d), 2.54 – 2.65 (2H, m), 2.70 – 2.86 (1H, m), 2.90 - 2.98 (1H, m), 3.27 (6H, s), 3.48 – 2.55 (1H, m), 3.70 (2H, d), 3.77 (2H, d), 3.88 – 3.96 (1H, m), 4.08 (1H, d), 4.16-2.29 (1H, m), 6.84 – 6.95 (2H, m), 7.13 – 7.24 (2H, m); *m/z* (ES+) $[M+H]^+$ = 421.5.

Intermediate 237c:

(*R**)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

(Isomer 1)

and

Intermediate 237d:

(*R**)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

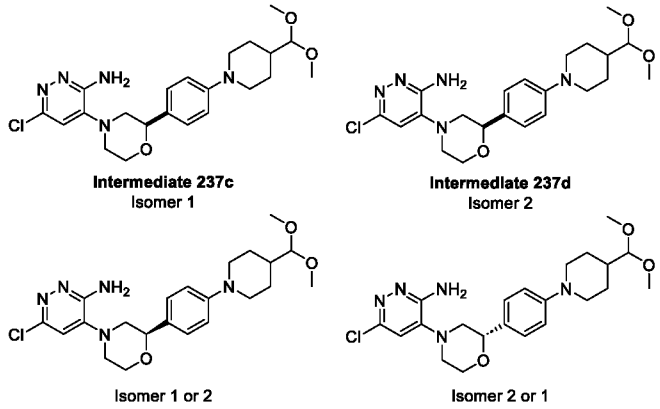
(Isomer 2)

((*absolute configurations not yet confirmed))

(*R*)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

and

(*S*)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol



[2567] HCl in MeOH (8 mL, 4 M) was added to Intermediate 237b (800 mg, 1.90 mmol). The mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure. The pH adjusted to 9 with the 7 M ammonia in MeOH solution. The solvent was removed under reduced pressure. DCM–MeOH (3:1, 15 mL) was added. The mixture was filtered. The filtrate was concentrated under reduced pressure. MeCN (10 mL), DIPEA (0.997 ml, 5.71 mmol) and 4-bromo-6-chloropyridazin-3-amine (397 mg, 1.90 mmol) were added. The resulting mixture was stirred at 80 °C for 2 days._The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 3 to 80% MeCN in water with 0.1% NH_4HCO_3) gave a racemic mixture of title compounds. Purification by chiral HPLC (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM= 3:1 with 0.5% 2 M NH_3 in MeOH; Mobile Phase B: EtOH; Flow rate: 10 mL/min; isocratic 50% B in 80 min) gave Intermediate 237c (220 mg, 26%, >99% ee) which eluted first from the column and Intermediate 237d (180 mg, 21%, >99% ee) which eluted second from the column as yellow solid. Intermediate 237c: ^{1}H NMR (DMSO-*d6*) δ 1.23 – 1.39 (2H, m), 1.63 – 1.79 (3H, m), 2.54 – 2.67 (3H, m), 2.73 – 2.84 (1H, m), 3.27 (6H, s), 3.20 - 3.40 (2H, m), 3.70 (2H, d), 3.94 (2H, dt), 4.08 (1H, d), 4.65 (1H, d), 6.31 (2H, s), 6.90 (2H, d), 6.94 (1H, s), 7.23 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 448.1. Intermediate 237d: ^{1}H NMR (DMSO-*d6*) δ 1.23 – 1.39 (2H, m), 1.63 – 1.79 (3H, m), 2.54 – 2.67 (3H, m), 2.73 – 2.84 (1H, m), 3.27 (6H, s), 3.20 - 3.40 (2H, m), 3.70 (2H, d), 3.94 (2H, dt), 4.08 (1H, d), 4.65 (1H, d), 6.31 (2H, s), 6.90 (2H, d), 6.94 (1H, s), 7.23 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 448.

Intermediate 237e:

(*R**)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

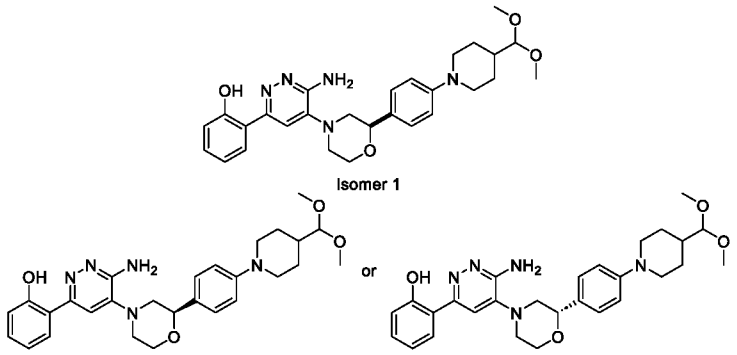
(Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

or

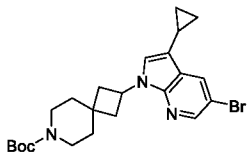
(*S*)-2-(6-Amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol



[2568] Prepared in an analogous manner to Intermediate 1e using Intermediate 237c (180 mg, 0.40 mmol). Purification by FSC (elution gradient: 0 to 50% DCM in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (140 mg, 69%) as a yellow solid. ^{1}H NMR (DMSO-d6) δ 1.22 (2H, s), 1.65 – 1.73 (3H, m), 2.52 – 2.65 (3H, m), 2.70 – 2.94 (2H, m), 3.28 (6H, s), 3.40 – 3.50 (2H, m), 3.65 - 3.73 (2H, m), 4.06 (1H, d), 4.21 (1H, t), 4.68 (1H, d), 6.43 (1H, s), 6.82 – 6.93 (4H, m), 7.21 – 7.27 (2H, m), 7.52 (1H, s), 7.61 – 7.75 (1H, m), 7.93 (1H, d), two exchangeable protons not observed; *m/z* (ES+) $[M+H]^+$ = 506.3.

Intermediate 237f:

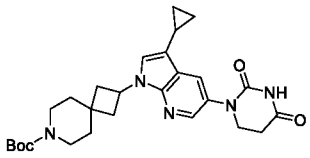
tert-Butyl 2-(5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[2569] A vial was charged with 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (600 mg, 2.53 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (611 mg, 2.53 mmol), 2-(tributyl-λ5-phosphaneylidene)acetonitrile (1222 mg, 5.06 mmol), and *m*-xylene (15 mL). The reaction was heated to 110 °C for 16 h. After cooling to r.t., the mixture was concentrate under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (1000 mg, 86%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 0.63 – 0.73 (2H, m), 0.82 – 0.90 (2H, m), 1.40 (9H, s), 1.57 – 1.67 (4H, m), 1.91 – 2.02 (1H, m), 2.16 – 2.27 (2H, m), 2.32 – 2.42 (2H, td), 3.21 – 3.34 (4H, m), 5.13 – 5.36 (1H, m), 7.59 (1H, s), 8.20 (1H, d), 8.26 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 460.2.

Intermediate 237g:

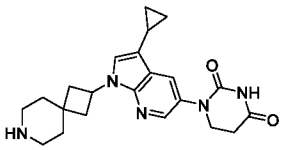
tert-Butyl 2-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[2570] A 40 mL vial was charged with dihydropyrimidine-2,4(1*H*,3*H*)-dione (873 mg, 7.65 mmol), *t*BuBrettPhos Pd G3 (327 mg, 0.38 mmol), Intermediate 237f (1762 mg, 3.83 mmol) and K_3PO_4 (1625 mg, 7.65 mmol), then the vial was capped and evacuated and backfilled with nitrogen. 1,4-Dioxane (20 mL) was added, then the mixture was sparged with nitrogen for 15 min. The mixture was stirred at 100 °C for 16 h. After cooling to r.t., the mixture was diluted with EtOAc (50 mL) and filtered through celite. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave title compound (1446 mg, 77%) as a brown dry film. ^{1}H NMR (DMSO-*d*6): δ 0.65 – 0.72 (2H, m), 0.84 – 0.92 (2H, m), 1.41 (9H, s), 1.59 – 1.69 (4H, m), 1.91 – 1.98 (1H, m), 2.22 – 2.29 (2H, m), 2.32 – 2.43 (2H, m), 2.72 – 2.80 (2H, m), 3.21 – 3.30 (2H, m), 3.36 (2H, d), 3.78 – 3.87 (2H, m), 5.20 – 5.36 (1H, m), 7.57 (1H, s), 7.96 (1H, d), 8.17 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ =494.3.

Intermediate 237h:

1-(3-Cyclopropyl-1-(7-azaspiro[3.5]nonan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2571] TFA (6.00 mL) was added to a stirred solution of Intermediate 237g (1.974 g, 4 mmol) in DCM (24 mL). The resulting solution was stirred for 2 h and concentrated under reduced pressure. Purification by ion exchange chromatography (Porpak Rxn CX 50g cartridge) eluting with 2 N NH_3 in MeOH gave the title compound (1.457 g, 93%) as a white solid. ^{1}H NMR(DMSO-*d*6): δ 0.67 - 0.74 (2H, m), 0.82 - 0.90 (2H, m), 1.60 (4H, dt), 1.88 - 2.00 (1H, m), 2.15 - 2.23 (2H, m), 2.30 - 2.38 (2H, m), 2.57 - 2.62 (2H, m), 2.67 - 2.72 (2H, m), 2.77 (2H, t), 3.82 (2H, t), 5.24 (1H, quin), 7.54 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.37 (1H, br s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ =394.4.

EXAMPLE 237:

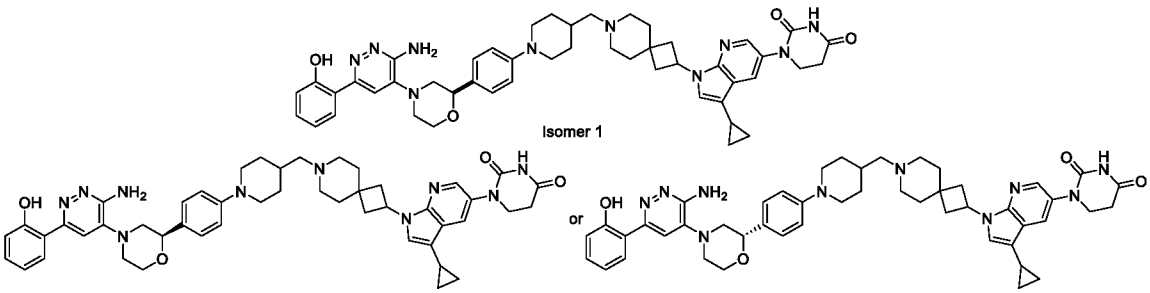
(*R**)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

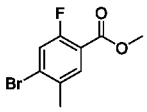


[2572] Intermediate 237e (60 mg, 0.12 mmol) was added in formic acid (2 mL). The resulting mixture was stirred at r.t. for 1h. The solvent was removed under reduced pressure. To the residue was added Intermediate 237h (46.7 mg, 0.12 mmol) in DCE (1.000 mL) and DMF (1.000 mL) warmed to 40°C over a period of 2 h, then added Sodium triacetoxyborohydride (75 mg, 0.36 mmol). The resulting mixture was stirred at r.t. for 1 h. Purification by preparative HPLC (Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12% B to 32% B in 8 min, 32% B) gave the title compound (12.70 mg, 12%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 0.64 – 0.73 (2H, m), 0.81 – 0.91 (2H, m), 1.07 – 1.34 (3H, m), 1.57 – 1.84 (7H, m), 1.89 – 1.98 (1H, m), 2.13 (2H, d), 2.16 – 2.47 (8H, m), 2.58 – 2.68 (2H, m), 2.76 (3H, t), 2.82 – 2.92 (1H, m), 3.67 (3H, d), 3.81 (2H, t), 3.93 – 4.10 (2H, m), 4.70 (1H, dd), 5.24 (1H, p), 6.43 (2H, s), 6.79 – 7.05 (4H, m), 7.17 – 7.40 (3H, m), 7.55 (2H, d), 7.87 – 7.99 (2H, m), 8.17 (1H, d), 10.40 (1H, s), one exchangeable proton not observed; *m/z* (ES+) $[M+H]^+$ = 837.5.

EXAMPLE 238

Intermediate 238a:

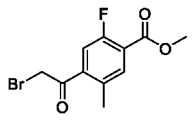
Methyl 4-bromo-2-fluoro-5-methylbenzoate



[2573] Concentrated sulfuric acid (4.57 mL, 85.82 mmol) was carefully added to a solution of 4-bromo-2-fluoro-5-methylbenzoic acid (10 g, 42.91 mmol) in methanol (120 mL), and the mixture was refluxed for 24 h. After cooling to r.t., the mixture was carefully added into water (300 mL). A precipitate formed which was collected by filtration, washed with sat. aq. $NaHCO_3$ (100 mL) and water (300 mL), and dried *in vacuo* to give title compound (9.50 g, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 3.94 (3H, s), 7.39 (1H, d), 7.82 (1H, d); *m/z* (ES^+) [M+Na] = 270.4.

Intermediate 238b:

Methyl 4-(2-bromoacetyl)-2-fluoro-5-methylbenzoate



[2574] Prepared in an analogous manner to Intermediate 228a using Intermediate 238a (5.00 g, 20.24 mmol). Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (5.50 g, 94%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.50 (3H, s), 3.98 (3H, s), 4.36 (2H, s), 7.40 (1H, d), 7.86 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 288.9.

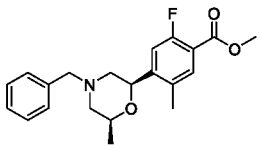
Intermediate 238c:

Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoate

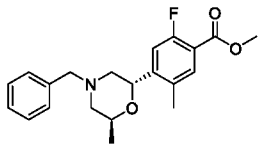
and

Intermediate 238d:

Methyl 4-((2*S*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoate



Intermediate 238c

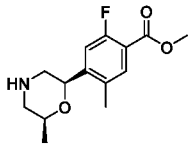


Intermediate 238d

[2575] Prepared in an analogous manner to Intermediate 65a using Intermediate 238b (2.00 g, 6.92 mmol) and (*S*)-1-(benzylamino)propan-2-ol (1.143 g, 6.92 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave Intermediate 238c (0.700 g, 28%) and Intermediate 238d (1.100 g, 44%) as yellow oils. Intermediate 238c: ^{1}H NMR (DMSO-*d6*) δ 1.15 (3H, d), 1.74 - 1.90 (2H, m), 2.24 (3H, s), 2.78 (1H, br d), 2.88 (1H, br d), 3.45 - 3.60 (2H, m), 3.84 (4H, s), 4.69 - 4.80 (1H, m), 7.23 (2H, br d), 7.30 - 7.37 (4H, m), 7.66 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 358.5. Intermediate 238d: ^{1}H NMR (DMSO-*d6*) δ 1.18 (3H, d), 2.20 - 2.25 (1H, m), 2.30 (3H, s), 2.45 - 2.49 (1H, m), 2.51 - 2.55 (1H, m), 2.66 - 2.73 (1H, m), 3.44 - 3.58 (2H, m), 3.75 -3.81 (1H, m), 3.84 (3H, s), 4.97 (1H, dd), 7.24 - 7.30 (1H, m), 7.36 (4H, d), 7.51 (1H, d), 7.65 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 358.5.

Intermediate 238e:

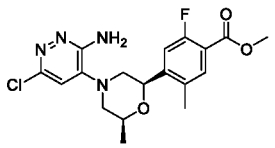
Methyl 2-fluoro-5-methyl-4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2576] Prepared in an analogous manner to Intermediate 65b starting from Intermediate 238c (1.2g, 3.36 mmol) to give the title compound (0.820 g, 91%) as a yellow oil. *m/z* (ES^+) $[M+H]^+$ = 268.3.

Intermediate 238f:

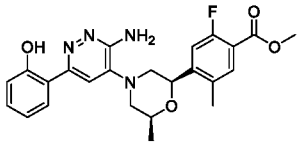
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoate



[2577] Prepared in an analogous manner to Intermediate 1d starting from Intermediate 238e (820mg, 3.07 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 30% MeOH in EtOAc) gave the title compound (550 mg, 50%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.22 (3H, d), 2.37 (3H, s), 2.43 - 2.48 (1H, m), 2.53 - 2.58 (1H, m), 3.43 (1H, br d), 3.49 - 3.53 (1H, m), 3.85 (3H, s), 4.07 - 4.11 (1H, m), 4.99 (1H, br d), 6.28 (2H, s), 6.98 (1H, s), 7.34 (1H, d), 7.71 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 395.2.

Intermediate 238g:

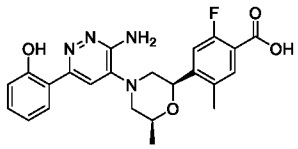
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoate



[2578] Prepared in an analogous manner to Intermediate 1e starting from Intermediate 238f (550 mg, 1.39 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (350 mg, 55%) as a light yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, d), 2.40 (3H, s), 2.63 (2H, d), 3.54 (2H, br t), 3.96 (3H, s), 4.10 (1H, ddd), 4.87 (2H, s), 4.96 (1H, br d), 6.88 - 6.95 (1H, m), 7.07 (1H, d), 7.30 - 7.34 (2H, m), 7.42 (1H, d), 7.59 (1H, dd), 7.77 (1H, d), 13.64 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 453.3.

Intermediate 238h:

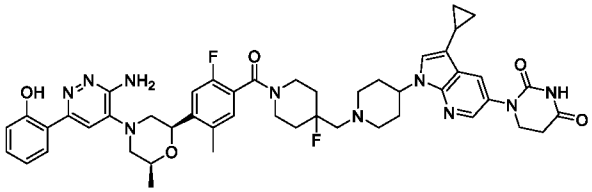
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoic acid



[2579] Prepared in an analogous manner to Intermediate 1f using Intermediate 238g. After cooling to r.t., EtOH was removed under reduced pressure. 6 M aq. HCl (1.05 mL) was added. A precipitate was formed which was collected by filtration, washed with water and dried *in vacuo* to give the title compound (310 mg, 92%) as an off-white solid. ^{1}H NMR (DMSO-*d6*) δ 1.26 (3H, d), 2.38 (3H, s), 2.63 - 2.70 (1H, m), 2.76 - 2.84 (1H, m), 3.38 - 3.43 (1H, m), 3.68 (2H, br d), 4.10 - 4.19 (1H, m), 5.04 (1H, br d), 6.95 (1H, br t), 7.00 (1H, br d), 7.06 - 7.18 (1H, m), 7.34 (2H, br d), 7.57 (1H, s), 7.70 (2H, br d), 12.92 - 13.70 (1H, m), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 439.3.

EXAMPLE 238:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

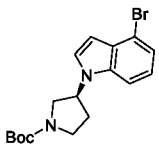


[2580] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 238h (40mg, 0.08 mmol) and Intermediate 20g (46.6 mg, 0.08 mmol). Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% formic acid) gave the title compound (42.0 mg, 55%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d6*) δ 0.63 - 0.69 (2H, m), 0.83 - 0.89 (2H, m), 1.26 (3H, d), 1.59 - 1.89 (5H, m), 1.89 - 1.96 (1H, m), 1.96 - 2.12 (3H, m), 2.32 - 2.40 (5H, m), 2.53 (1H, br s), 2.59 - 2.67 (2H, m), 2.71 - 2.79 (3H, m), 3.04 (2H, br s), 3.11 - 3.19 (1H, m), 3.29 (2H, br d), 3.55 (2H, br t), 3.82 (2H, t), 4.16 (1H, ddd), 4.30 (1H, br d), 4.56 - 4.64 (1H, m), 5.02 (1H, br d), 6.44 (2H, s), 6.85 - 6.92 (2H, m), 7.22 - 7.29 (2H, m), 7.35 (1H, d), 7.44 (1H, s), 7.58 (1H, s), 7.93 - 7.98 (2H, m), 8.17 (1H, d), 10.34 - 10.43 (1H, m), 14.01 - 14.42 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 889.7.

EXAMPLE 239

Intermediate 239a:

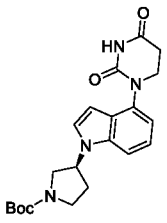
tert-Butyl (*S*)-3-(4-bromo-1*H*-indol-1-yl)pyrrolidine-1-carboxylate



[2581] Prepared in an analogous manner to Intermediate 234a starting from 4-bromo-1*H*-indole (1 g, 5.10 mmol) and *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (0.955 g, 5.10 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.600 g, 32%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, d), 2.33 – 2.42 (1H, m), 3.37 – 3.57 (4H, m), 3.76 – 3.83 (1H, m), 5.15 – 5.28 (1H, m), 6.46 (1H, d), 7.11 (1H, t), 7.28 (1H, d), 7.57 (1H, d), 7.63 (1H, d); *m/z* (ES$^+$) $[M+Na]^+$ = 387.1.

Intermediate 239b:

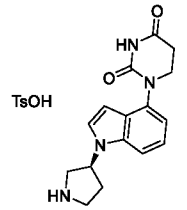
tert-Butyl (*S*)-3-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)pyrrolidine-1-carboxylate



[2582] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 239a (500 mg, 1.37 mmol). Purification by FSC (elution gradient: 0 to 60% EtOAc in petroleum ether) gave the title compound (270 mg, 49%) as a brown solid. 1H NMR (DMSO-d6) δ 1.42 (9H, d), 2.28 – 2.38 (2H, m), 2.77 (2H, t), 3.42 – 3.52 (3H, m), 3.76 – 3.82 (3H, m), 5.18 – 5.27 (1H, m), 6.47 (1H, d), 7.00 (1H, d), 7.18 (1H, t), 7.45 – 7.48 (1H, m), 7.54 (1H, d), 10.35 (1H, s); *m/z* (ES^+) $[M+Na]^+$ = 421.1.

Intermediate 239c:

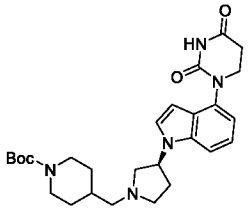
(*S*)-1-(1-(Pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2583] Prepared in an analogous manner to Intermediate 6e starting from Intermediate 239b (270 mg, 0.68 mmol) gave the title compound (200 mg, 63%) as a grey solid and TsOH salt. *m/z* (ES^+) $[M+H]^+$ = 299.1.

Intermediate 239d:

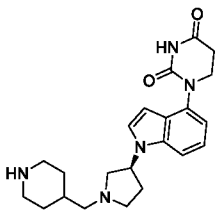
tert-Butyl (*S*)-4-((3-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1H-indol-1-yl)pyrrolidin-1-yl)methyl)piperidine-1-carboxylate



[2584] To a stirred solution of Intermediate 239c (180 mg, 0.60 mmol) in DCM (1 mL) and NMP (1 mL) was added *tert*-butyl 4-formylpiperidine-1-carboxylate (193 mg, 0.90 mmol). The reaction mixture was stirred at 60 °Cfor 1 h. Sodium triacetoxyborohydride (384 mg, 1.81 mmol) was added. The resulting mixture was stirred at r.t. for 1h. The reaction mixture diluted with EtOAc (20 mL), washed with sat. aq. NH_4Cl (7 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 15% MeOH in DCM) gave the title compound (140 mg, 47%) as a brown solid. ^1H NMR (DMSO-*d6*) δ 0.95 – 1.04 (2H, m), 1.39 (9H, s), 1.60 – 1.69 (2H, m), 1.70 – 1.78 (3H, m), 2.27 – 2.34 (2H, m), 2.34 – 2.47 (4H, m), 2.75–2.78 (2H, t), 2.85–2.91(1H,m), 2.99-3.07 (1H, m), 3.75 –3.80 (2H, t), 3.82 –4.01 (2H, m), 5.15 (1H, m), 6.42 (1H, d), 6.96 (1H, d), 7.13 (1H, m), 7.52 (1H, d), 7.62 (1H, d), 10.34 (1H, s); *m/z* (ES+) $[M+H]^+$= 496.4.

Intermediate 239e:

(*S*)-1-(1-(1-(Piperidin-4-ylmethyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2585] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 239d (120 mg, 0.24 mmol) to give the title compound (80 mg, 65%) as a grey solid and TFA salt. *m/z* (ES+) $[M+H]^+$ = 396.3.

EXAMPLE 239:

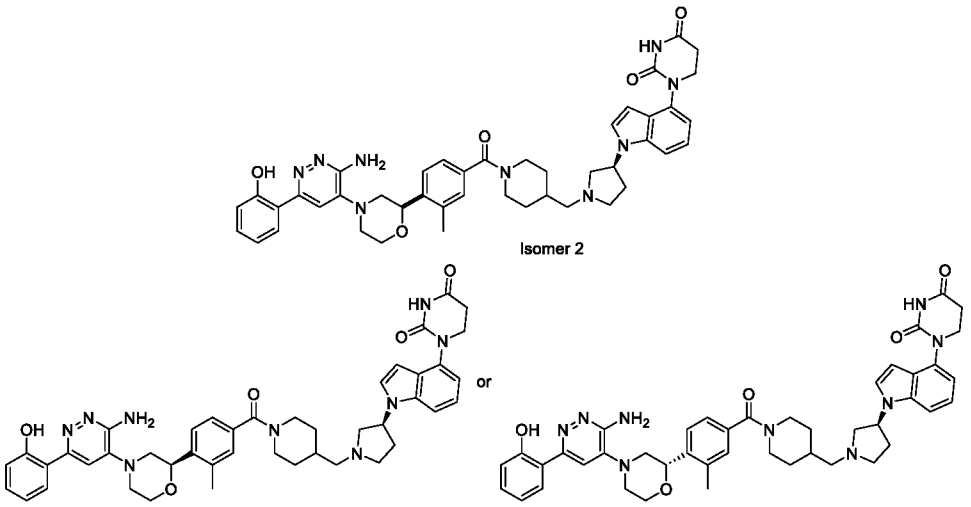
1-(1-((*S*)-1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*relative configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*S*)-1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

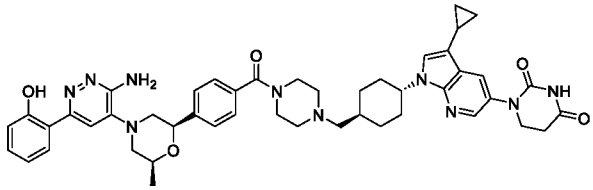


[2586] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 239e (24.33 mg, 0.06 mmol) and Intermediate 55j (25 mg, 0.06 mmol). Purification by RPC (elution gradient: 0 to 52% MeCN in water with 10mmol/L NH_4HCO_3 and 0.05% NH_3H_2O) gave the title compound (7.5 mg, 16%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.05 – 1.18 (2H, m), 1.70 – 1.88 (3H, m), 1.90 – 2.01 (1H, m), 2.32 – 2.44 (7H, m), 2.69 – 3.02 (9H, m), 3.45 – 3.57 (2H, m), 3.74 (2H, t), 3.83 – 4.15 (4H, m), 4.92 – 4.98 (1H, m), 5.03 – 5.14 (1H, m), 6.14 (2H, s), 6.36 (1H, d), 6.80 – 6.88 (2H, m), 6.92 (1H, d), 7.10 (1H, t),

7.14 – 7.22 (3H, m), 7.45 (1H, d), 7.48 – 7.56 (3H, m), 7.83 – 7.89 (1H, m), 9.99 (1H, s), 13.90 (1H, s); *m/z* (ES+) $[M+H]^+$ = 784.4.

EXAMPLE 240:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

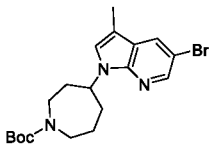


[2587] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 65e (40 mg, 0.10 mmol) and Intermediate 120d (44 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 65% MeCN in water with 10mmol/L NH_4HCO_3 and 0.05% NH_3H_2O) gave the title compound (30.0 mg, 36%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 0.62 – 0.67 (2H, m), 0.83 – 0.89 (2H, m), 1.12 (2H, q), 1.27 (3H, d), 1.62 – 1.65 (1H, m), 1.79 – 1.99 (8H, m), 2.20 (2H, d), 2.30 – 2.36 (1H, n), 2.40 – 2.45 (3H, m), 2.68 (1H, d), 2.77 (2H, t), 3.51 (2H, d), 3.58 (2H, d), 3.61 – 3.65 (2H, m), 3.82 (2H, t), 4.12 (1H, t), 4.60 (1H, d), 4.95 (1H, dd), 6.49 (2H, s), 6.88 (2H, dd), 7.21 – 7.27 (1H, m), 7.42 (3H, d), 7.51 – 7.59 (3H, m), 7.92 – 7.98 (2H, m), 8.16 (1H, d), 8.25 (1H, s), 10.39 (1H, s); *m/z* (ES+)$[M+H]^+$ = 839.4.

EXAMPLE 241

Intermediate 241a:

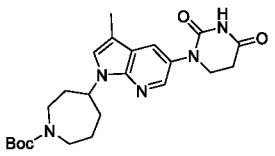
tert-Butyl 4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepane-1-carboxylate



[2588] Prepared in an analogous manner to Intermediate 234a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (800 mg, 3.79 mmol) and *tert*-butyl 4-hydroxyazepane-1-carboxylate (1224 mg, 5.69 mmol). The crude product was purified by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) to afford the title compound (1400 mg, 90%) as a yellow gum. ^{1}H NMR (DMSO-*d6*) δ 1.43 (9H, d), 1.65 – 1.76 (1H, m), 1.83 – 1.90 (2H, m), 1.96 – 2.06 (3H, m), 2.22 (3H, s), 3.23 – 3.30 (1H, m), 3.36 – 3.49 (2H, m), 3.54 – 3.68 (1H, m), 4.67 – 4.77 (1H, m), 7.44 (1H, d), 8.14 (1H, d), 8.23 – 8.26 (1H, m); *m/z* (ES+) $[M+H]^+$ = 408.1.

Intermediate 241b:

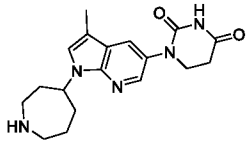
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepane-1-carboxylate



[2589] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 241a (800 mg, 1.96 mmol). Purification by RPC (elution gradient: 5 to 100% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (590 mg, 68%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.45 (9H, d), 1.68 – 1.79 (1H, m), 1.83 – 1.94 (2H, m), 1.97 – 2.11 (3H, m), 2.25 (3H, s), 2.76 (2H, t), 3.25 – 3.32 (1H, m), 3.37 – 3.50 (2H, m), 3.54 – 3.69 (1H, m), 3.81 (2H, t), 4.71 – 4.81 (1H, m), 7.43 (1H, d), 7.88 (1H, d), 8.17 (1H, t), 10.37 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 442.2.

Intermediate 241c:

1-(1-(Azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2590] TsOH (339 mg, 1.97 mmol) was added to Intermediate 241b (580 mg, 1.31 mmol) in MeCN (10 mL) at 25°C. The resulting mixture was stirred at 80 °C for 45 hours. The reaction mixture was diluted with MTBE (100 mL), filtered through filter paper, and dried under vacuum to afford the title compound (740 mg, 94%) as a white solid and TsOH salt, which was used without further purification. *m/z* (ES$^+$) $[M+H]^+$ = 342.1.

Intermediate 241d:

tert-Butyl (*R**)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepan-1-yl)methyl)-4-fluoropiperidine-1-carboxylate (Isomer 1)

and

Intermediate 241e:

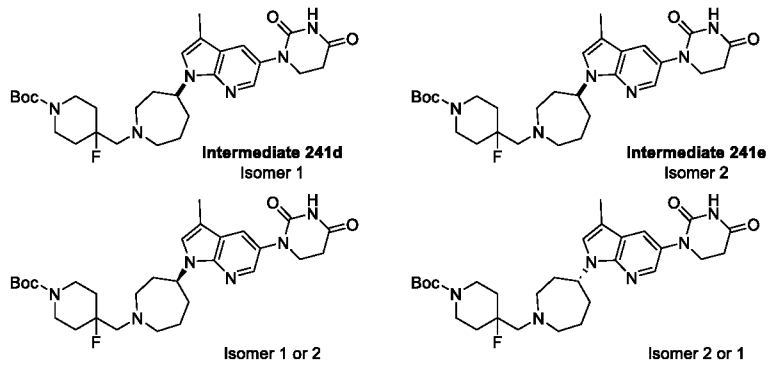
tert-Butyl (*R**)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepan-1-yl)methyl)-4-fluoropiperidine-1-carboxylate (Isomer 2)

((*absolute configurations not yet confirmed))

tert-Butyl (*S*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepan-1-yl)methyl)-4-fluoropiperidine-1-carboxylate

and

tert-Butyl (*R*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)azepan-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2591] Intermediate 6f (685 mg, 1.88 mmol) was added to DIPEA (0.655 mL, 3.75 mmol) and Intermediate 241c (750 mg, 1.25 mmol) in MeCN (20 mL). The resulting mixture was stirred at 80 °C for 16 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave a racemic mixture of the title compounds (300 mg, 43%) as a white solid. Purification by preparative HPLC (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MTBE with 0.5% 2 M NH_3 in MeOH, Mobile Phase B: EtOH; Flow rate: 20 mL/min; isocratic 20% B) gave Intermediate 241d (120 mg, 41%, >99% ee) which eluted first from the column as a white solid and Intermediate 241e (110 mg, 38%, >99% ee) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, d), 1.52 – 1.73 (3H, m), 1.75 – 1.99 (5H, m), 2.03 – 2.18 (2H, m), 2.26 (3H, s), 2.70 – 2.79 (4H, m), 2.81 – 2.92 (4H, m), 3.04 (2H, s), 3.71 – 3.84, (4H, m), 4.84 – 4.97 (1H, m), 7.46 (1H, s), 7.83 – 7.91 (1H, m), 8.14 – 8.21 (1H, m), 10.38 (1H, s); *m/z* (ES^+) [M+H]+ = 557.3.

EXAMPLE 241:

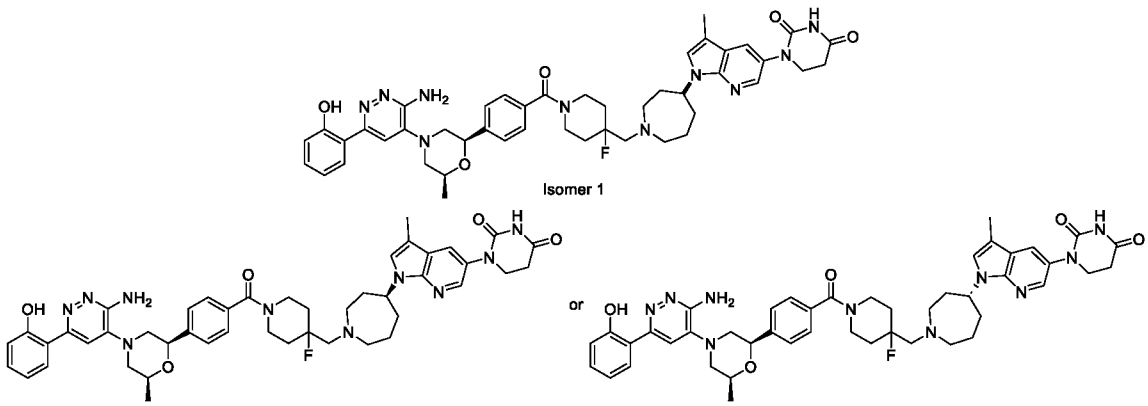
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

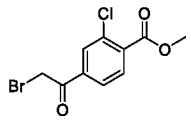


[2592] TFA (0.25 mL, 3.24 mmol) was added to a stirred solution of Intermediate 241d (70 mg, 0.13 mmol) in DCM (0.75 mL) at r.t. The resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure. To the residue was added DIPEA (0.066 mL, 0.38 mmol) and Intermediate 65e (53.7 mg, 0.13 mmol) in DMF (1 mL). To the resulting solution was added HATU in DMF (1 mL). The reaction mixture was stirred at r.t. for 30 min. and diluted with DCM–IPA (5:1, 50 mL), and washed sequentially with 2% aq. NH_4OH (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 50% MeCN in water with 0.1% FA) gave the title compound (20.0 mg, 18%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.24 –1.27 (3H, m), 1.68 – 1.74 (2H, m), 1.75 – 1.82 (2H, m), 1.88 (2H, d), 1.92 – 2.00 (2H, m), 2.07 – 2.16 (2H, m), 2.25 (3H, s), 2.55 (1H, d), 2.70 (1H, t), 2.73 – 2.79 (3H, m), 2.82 (1H, s), 2.83 – 2.92 (4H, m), 3.13 (1H, s), 3.48 – 3.55 (3H, m), 3.58 (1H, d), 3.80 (2H, t), 4.07 – 4.15 (1H, m), 4.29 (1H, s), 4.84 – 4.91 (1H, m), 4.95 (1H, d), 6.49 (2H, s), 6.84 – 6.91 (2H, m), 7.23 (1H, t), 7.41 – 7.49 (3H, m), 7.51 – 7.59 (3H, m), 7.87 (1H, d), 7.96 (1H, d), 8.17 (1H, d), 10.40 (1H, s), 14.23 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 242:

Intermediate 242a:

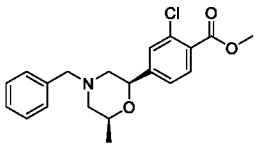
Methyl 4-(2-bromoacetyl)-2-chlorobenzoate



[2593] Prepared in an analogous manner to Intermediate 228a using methyl 2-chloro-4-iodobenzoate (10 g, 33.73 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (6.40 g, 65%) as a yellow solid.^{1}H NMR ($CDCl_3$) δ 3.99 (3H, s), 4.37 (2H, s), 7.90– 7.93 (2H, m), 8.05 – 8.08 (1H, m); mass not observed.

Intermediate 242b:

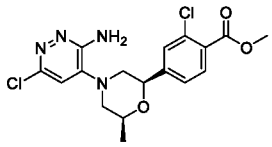
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2-chlorobenzoate



[2594] Prepared in an analogous manner to Intermediate 65a using Intermediate 242a (6 g, 20.58 mmol) and (*S*)-1-(benzylamino)propan-2-ol (3.74 g, 22.64 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (0.800 g, 10%) as an orange gum. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d), 1.91 (1H, t), 1.98 (1H, t), 2.82 (1H, d), 2.92 (1H, d), 3.51 – 3.61 (2H, m), 3.86 – 3.90 (1H, m), 3.94 (3H, s), 4.67 (1H, d), 7.30 – 7.32 (1H, m), 7.33 – 7.38 (5H, m), 7.50 (1H, d), 7.81 (1H, d); m/*z* (ES^+) $[M+H]^+$ = 360.0.

Intermediate 242c:

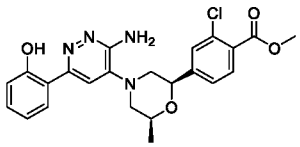
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoate



[2595] 1-Chloroethyl carbonochloridate (318 mg, 2.22 mmol) was added to Intermediate 242b (800 mg, 2.22 mmol) in DCE (5 mL). The resulting mixture was stirred at 80 °C for 1 h. The solvent was removed under reduced pressure. MeOH (5 mL) was added. The resulting mixture was stirred at 80 °C for 1h. The solvent was removed under reduced pressure. DMSO (5 mL), DIPEA (1.553 mL, 8.89 mmol) and 4-bromo-6-chloropyridazin-3-amine (695 mg, 3.33 mmol) were added. The resulting mixture was stirred at 80 °C for 16 h. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.5% NH_4HCO_3) gave the title compound (500 mg, 57%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.23 (3H, d), 2.43 – 2.50 (2H, m), 3.40 (1H, d), 3.55 (1H, d), 3.87 (3H, s), 4.01 – 4.08 (1H, m), 4.90 – 4.97 (1H, m), 6.36 (2H, s), 6.96 (1H, s), 7.49 – 7.54 (1H, m), 7.63 (1H, d), 7.84 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 397.2.

Intermediate 242d:

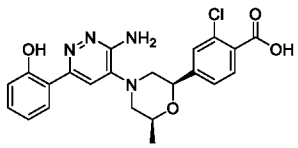
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoate



[2596] $Pd(dppf)Cl_2$ (92 mg, 0.13 mmol) was added to K_3PO_4 (801 mg, 3.78 mmol), (2-hydroxyphenyl)boronic acid (260 mg, 1.89 mmol) and Intermediate 242c (500 mg, 1.26 mmol) in dioxane (5 mL) and water (0.5 mL) under nitrogen. The resulting mixture was stirred at 60 °C for 16 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 3% MeOH in DCM) gave the title compound (270 mg, 47%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.26 (3H, d), 2.54 – 2.67 (1H, m), 3.44 – 3.63 (2H, m), 3.85 (3H, s), 3.97 – 4.06 (2H, m), 4.92 – 5.03 (1H, m), 6.49 (2H, s), 6.78 – 6.91 (2H, m), 7.17 – 7.25 (1H, m), 7.50 – 7.56 (2H, m), 7.64 (1H, d), 7.81 – 7.86 (1H, m), 7.93 (1H, d), 14.18 (1H, s); *m/z* (ES+) $[M+H]^+$ = 455.1.

Intermediate 242e:

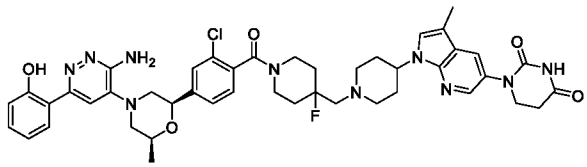
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoic acid



[2597] LiOH (142 mg, 5.94 mmol) was added to Intermediate 242d (270 mg, 0.59 mmol) in water (1.0 mL) and MeOH (1.0 mL). The resulting mixture was stirred at 60 °C for 1 h. Purification by RPC (elution gradient: 5 to 100% MeOH in water) gave the title compound (160 mg, 61%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.26 (3H, d), 2.54 – 2.66 (2H, m), 3.43 – 3.55 (2H, m), 4.03 – 4.11 (1H, m), 4.82 – 4.89 (1H, m), 6.46 (2H, s), 6.83 – 6.91 (2H, m), 7.19 – 7.26 (2H, m), 7.29 (2H, d), 7.54 (1H, s), 7.92 – 7.98 (1H, m), 14.21 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 441.2.

EXAMPLE 242:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

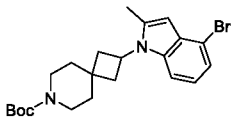


[2598] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 161a (30 mg, 0.07 mmol) and Intermediate 242e (29.9 mg, 0.07 mmol). Purification by preparative HPLC (elution gradient: 49 to 56% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (10.0 mg, 17%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.25 (3H, d), 1.64 – 1.78 (2H, m), 1.81 – 1.88 (3H, m), 1.98 – 2.10 (3H, m), 2.25 (3H, s), 2.31 – 2.40 (2H, t), 2.55 (1H, d), 2.59 – 2.72 (3H, m), 2.76 (2H, t), 3.02 – 3.08 (2H, m), 3.12 – 3.26 (3H, m), 3.48 – 3.55 (1H, m), 3.57 – 3.63 (1H, m), 3.81 (2H, t), 4.09 – 4.15 (1H, m), 4.28 – 4.35 (1H, m), 4.57 – 4.63 (1H, m), 4.96 (1H, d), 6.50 (2H, s), 6.86 – 6.90 (2H, m), 7.22 – 7.26 (1H, m), 7.40 – 7.54 (3H, m), 7.57 (1H, s), 7.62 (1H, d), 7.88 (1H, d), 7.95 – 7.98 (1H, m), 8.17 (1H, d), 10.39 (1H, s), 14.22 (1H, s); *m/z* (ES+) $[M+H]^+$ = 865.4.

EXAMPLE 243:

Intermediate 243a:

tert-Butyl 2-(4-bromo-2-methyl-1*H*-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

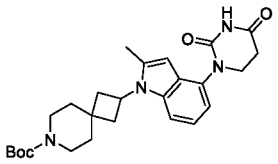


[2599] Prepared in an analogous manner to Intermediate 234a starting from *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (4.60 g, 19.04 mmol) and 4-bromo-2-methyl-1*H*-indole (2 g, 9.52 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (2.60 g, 63%) as a pale yellow solid. ^{1}H NMR (DMSO *d6*) δ 1.41 (9H, s), 1.54–1.75 (5H, m), 2.45 (4H, d),

2.56 (2H, t), 3.28 (2H, d), 3.38 (2H, d), 4.92–5.05 (1H, m), 6.19 (1H, t), 6.99 (1H, t), 7.20 (1H, d), 7.61 (1H, d); *m/z* (ES+) $[M+H]^+$ =433.1.

Intermediate 243b:

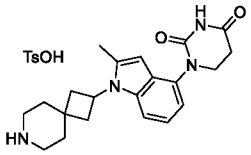
tert-Butyl 2-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1H-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[2600] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 243a (1 g, 2.31 mmol). Purification by FSC (elution gradient: 0 to 90% EtOAc in petroleum ether) gave the title compound (0.450 g, 42%) as a white solid. ^{1}H NMR (DMSO *d6*) δ 1.42 (9H, s), 1.64–1.74 (4H, m), 2.43 (3H, s), 2.50–2.51 (2H, d), 2.51–2.52 (2H, d), 2.75 (2H, t), 3.32 (4H, t), 3.74 (2H, t), 4.91–5.09 (1H, m), 6.16 (1H, s), 6.92 (1H, d), 7.07 (1H, t), 7.55 (1H, d), 10.32 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 467.1

Intermediate 243c:

1-(2-Methyl-1-(7-azaspiro[3.5]nonan-2-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2601] TsOH (317 mg, 1.84 mmol) was added to Intermediate 243b (430 mg, 0.92 mmol) in MeCN (9 mL). The resulting mixture was stirred at 80 °C for 2 h. After cooling to r.t., the mixture was concentrated under reduced pressure to give the title compound (480 mg, 70%) as a purple solid and TsOH salt. *m/z* (ES^+) $[M+H]^+$ =367.1.

EXAMPLE 243:

(*R**)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

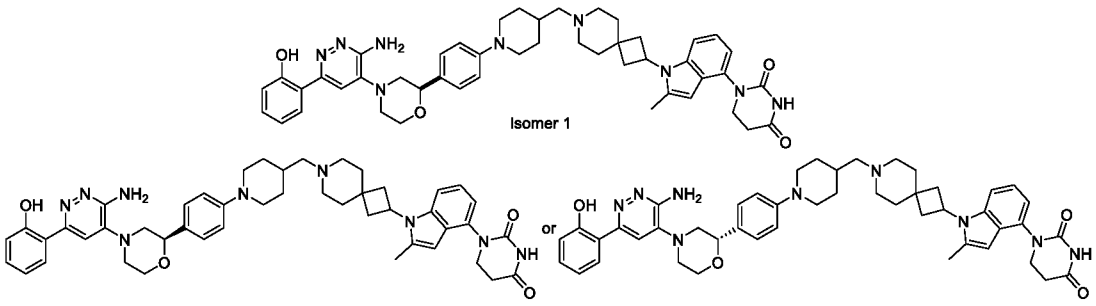
(Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

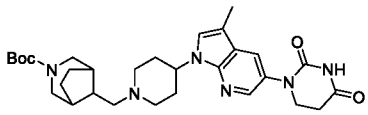


[2602] Formic acid (1.5 mL) was added to Intermediate 237e (85 mg, 0.17 mmol). The resulting mixture was stirred at 40 °C for 1 h. The mixture was concentrated under reduced pressure. Intermediate 243c (100 mg, 0.13 mmol) in DCE–NMP (1:1, 1.5 mL). The resulting solution was stirred for 10 min. Sodium triacetoxyborohydride (143 mg, 0.67 mmol) was added. The resulting mixture was stirred for 1 h. The reaction mixture was poured into sat. aq. Na_2CO_3 (15 mL). The mixture was extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (20 mg, 14%) as a white solid. ^{1}H NMR (DMSO *d6*) δ 1.22 (2H, d), 1.80 (7H, d), 2.28 (2H, s), 2.43 (7H, s), 2.57 (3H, t), 2.66 (2H, t), 2.71–2.81 (3H, m), 2.87 (1H, t), 3.45 (3H, d), 3.65–3.78 (4H, m), 4.03 (2H, t), 4.71 (1H, d), 4.97 (1H, t), 6.16 (1H, s), 6.45 (2H, s), 6.83–6.97 (5H, m), 7.07 (1H, t), 7.19–7.31 (3H, m), 7.55 (2H, t), 7.95 (1H, dd), 10.32 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES+) $[M+H]^+$ = 810.4.

EXAMPLE 244

Intermediate 244a:

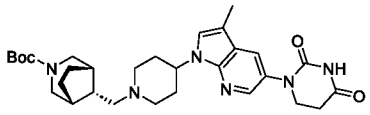
tert-Butyl 8-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-3-azabicyclo[3.2.1]octane-3-carboxylate



[2603] Sodium triacetoxyborohydride (111 mg, 0.52 mmol) was added to a stirred solution of Intermediate 93c (85 mg, 0.26 mmol) and *tert*-butyl 8-formyl-3-azabicyclo[3.2.1]octane-3-carboxylate (78 mg, 0.33 mmol) in DCM–*i*PrOH (4:1, 2.1 mL). The resulting solution was stirred at r.t. for 2 h. The reaction mixture was diluted with DCM (10 mL) and water (2 mL). The phases were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (127 mg, 88%) as a white solid and mixture of diastereomers. *m/z* (ES^+) $[M+H]^+$ = 552.

Intermediate 244b:

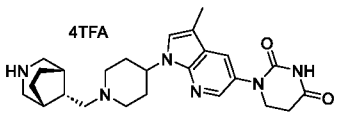
tert-Butyl (1*R*,5*S*,8*s*)-8-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-3-azabicyclo[3.2.1]octane-3-carboxylate



[2604] Purification of Intermediate 244a (127 mg, 0.23 mmol) by chiral SFC (Column: IH 21mm × 250 5μm, isocratic 15% MeOH with 0.2% NH_4OH in $scCO_2$) gave the title compound (30mg, 23%) which eluted second from the column. ^{1}H NMR (CD_2Cl_2) δ 1.47 (9H, s), 1.57 - 1.70 (2H, m, overlaps with residual water), 1.78 (2H, dt), 1.90 - 1.98 (1H, m), 1.99 - 2.18 (6H, m), 2.21 - 2.30 (2H, m), 2.33 - 2.35 (3H, m), 2.68 (2H, d), 2.89 (2H, t), 3.06 - 3.21 (4H, m), 3.55 (1H, br d), 3.62 (1H, br d), 3.91 (2H, t), 4.72 - 4.80 (1H, m), 7.23 (1H, s), 7.74 (1H, br s), 7.79 (1H, d), 8.21 (1H, d); *m/z* ES+ $[M+H]^+$ = 551.0.

Intermediate 244c:

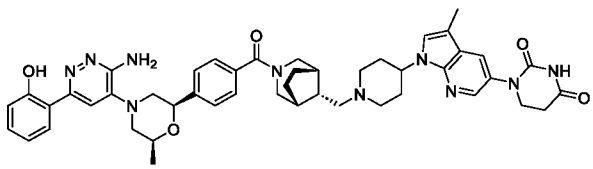
1-(1-(1-(((1*R*,5*S*,8*s*)-3-Azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2605] TFA (75 μl, 0.98 mmol) was added to a mixture of Intermediate 244b (27 mg, 0.05 mmol) in DCM (415 μl). The solution was allowed to stand at r.t. for 2.5 h. The reaction was diluted with DCM and concentrated under reduced pressure to afford the title compound (43.0 mg, 97%) as the *tetrakis* TFA salt based on a quantitative yield. *m/z*: ES^+ $[M+H]^+$ = 451.4

EXAMPLE 244:

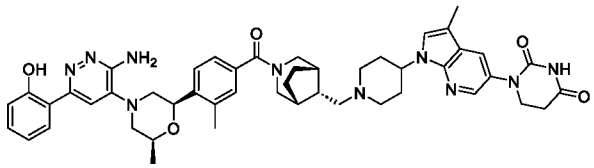
1-(1-(1-(((1*R*,5*S*,8*S*)-3-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2606] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 65e (9.73 mg, 0.02 mmol) and Intermediate 244c (21.6 mg, 0.02 mmol). Purification by RPC (elution gradient: 25 to 100% MeOH in water with 0.1% NH4OH) gave the title compound (11.0 mg, 55%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.21 - 1.30 (3H, m), 1.38 (1H, br s), 1.55 (1H, br s), 1.72 (2H, br s), 1.85 - 2.13 (6H, m), 2.15 - 2.29 (5H, m), 2.45 - 2.58 (2H, m, overlaps with residual solvent), 2.63 - 2.87 (5H, m), 3.04 - 3.20 (4H, m), 3.43 - 3.61 (3H, m), 3.81 (2H, t), 4.07 - 4.22 (2H, m), 4.65 (1H, br s), 4.94 (1H, br d), 6.50 (2H, s), 6.84 - 6.91 (2H, m), 7.23 (1H, t), 7.39 (2H, d), 7.47 - 7.55 (3H, m), 7.56 (1H, s), 7.89 (1H, d), 7.96 (1H, br d), 8.18 (1H, d), 10.41 (1H, s), 14.23 (1H, br s); *m/z* ES+ $[M+H]^+$ = 839.5.

EXAMPLE 245:

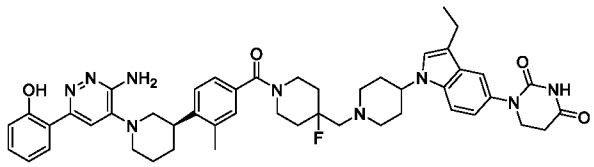
1-(1-(1-(((1*R*,5*S*,8*S*)-3-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2607] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 132e (9.1 mg, 0.02 mmol) and Intermediate 244c (17.8 mg, 0.02 mmol). Purification by RPC (elution gradient: 5 to 100% MeOH in 0.1% NH_4OH) and lyophilization from MeCN/MeOH/water gave the title compound (7.5 mg, 45%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.20 - 1.30 (3H, m), 1.37 (1H, br s), 1.54 (1H, br s), 1.71 (2H, br s), 1.83 - 1.95 (3H, m), 1.96 - 2.10 (3H, m), 2.11 - 2.20 (3H, m), 2.25 (3H, s), 2.41 (3H, s), 2.48 - 2.57 (1H, m, overlaps with residual solvent), 2.67 - 2.79 (5H, m), 3.04 - 3.16 (4H, m), 3.47 (1H, br d), 3.55 (2H, br d), 3.81 (2H, t), 4.07 - 4.23 (2H, m), 4.56 - 4.69 (1H, m), 5.03 (1H, br d), 6.44 (2H, s), 6.84 - 6.92 (2H, m), 7.20 (1H, s), 7.21 - 7.27 (2H, m), 7.51 (1H, s), 7.52 - 7.60 (2H, m), 7.88 (1H, d), 7.96 (1H, d), 8.18 (1H, d), 10.40 (1H, s), 14.23 (1H, br s); *m/z* ES$^+$ $[M+H]^+$ = 853.6.

EXAMPLE 246:

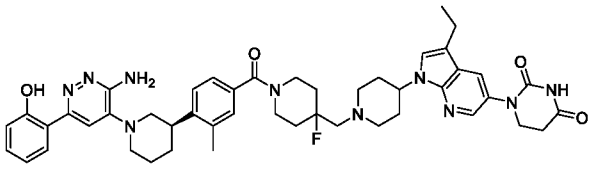
(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2608] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 12g (20.22 mg, 0.05 mmol) and Intermediate 8e (34.2 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (9.27 mg, 22%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.26 (3H, t), 1.59 - 1.80 (3H, m), 1.84 - 2.05 (9H, m), 2.36 - 2.45 (5H, m), 2.58 - 2.76 (7H, m), 2.81 - 2.93 (1H, m), 3.04 (2H, br d), 3.10 - 3.30 (3H, m), 3.35 - 3.66 (3H, m), 3.77 (2H, t), 4.11 - 4.38 (2H, m), 6.27 (2H, s), 6.85 - 6.92 (2H, m), 7.05 (1H, dd), 7.21 - 7.26 (3H, m), 7.31 (1H, s), 7.40 (1H, d), 7.43 (1H, d), 7.47 (1H, d), 7.57 (1H, s), 7.94 (1H, dd), 10.24 (1H, s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 842.5.

EXAMPLE 247:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

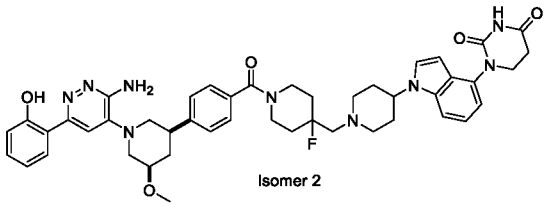


[2609] Prepared in an analogous manner to EXAMPLE 1 staring from Intermediate 12g (20.22 mg, 0.05 mmol) and Intermediate 149f (40.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (31.0 mg, 73%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.22 - 1.30 (3H, m), 1.60 - 2.19 (13H, m), 2.30 - 2.45 (5H, m), 2.58 - 2.81 (7H, m), 2.83 - 2.94 (1H, m), 2.96 - 3.28 (4H, m), 3.42 - 3.65 (3H, m), 3.81 (2H, t), 4.11 - 4.37 (1H, m), 4.52 - 4.69 (1H, m), 6.27 (2H, s), 6.86 - 6.91 (2H, m), 7.21 - 7.26 (3H, m), 7.41 (1H, d), 7.50 (1H, s), 7.57 (1H, s), 7.90 - 7.95 (2H, m), 8.17 (1H, d), 10.37 (1H, br s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 843.6

EXAMPLE 248:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

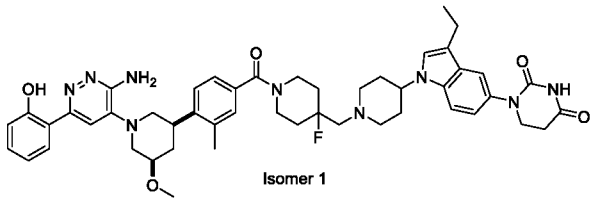


[2610] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 61k (12 mg, 0.03 mmol) and Intermediate 11b (23.1 mg, 0.03 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% formic acid) gave the title compound (8.0 mg, 37%) as an amorphous white solid. ^{1}H NMR (DMSO-*d6*) δ 1.62 - 1.81 (3H, m), 1.79 - 1.93 (4H, m), 1.93 - 2.03 (4H, m), 2.31 - 2.36 (1H, m), 2.39 - 2.45 (2H, m), 2.58 - 2.61 (1H, m), 2.63 - 2.67 (1H, m), 2.69 - 2.78 (4H, m), 3.02 - 3.06 (2H, m), 3.13 - 3.19 (2H, m), 3.49 - 3.55 (2H, m), 3.66 - 3.85 (6H, m), 4.31 - 4.38 (1H, m), 6.34 - 6.38 (2H, m), 6.39 - 6.42 (1H, m), 6.84 - 6.90 (2H, m), 6.91 - 6.99 (1H, m), 7.10 - 7.15 (1H, m), 7.17 - 7.25 (1H, m), 7.35 - 7.41 (2H, m), 7.41 - 7.47 (2H, m), 7.47 - 7.54 (3H, m), 7.58 (1H, s), 7.95 (1H, d), 10.33 (1H, s), 14.10 - 14.43 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 830.6.

EXAMPLE 249:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

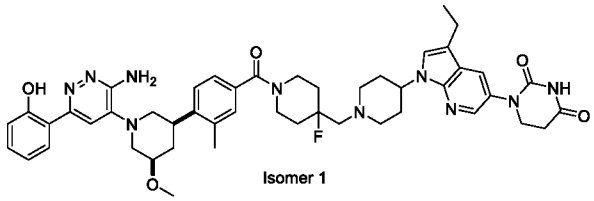


[2611] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 26j (24 mg, 0.04 mmol) and Intermediate 8e (27.3 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (23.0 mg, 66%) as an amorphous white solid. ^{1}H NMR (DMSO-*d*6) δ 1.24 (3H, t), 1.48 - 1.58 (1H, m), 1.63 - 1.79 (2H, m), 1.81 - 2.03 (6H, m), 2.23 - 2.30 (1H, m), 2.35 - 2.43 (5H, m), 2.42 - 2.47 (1H, m), 2.59 - 2.70 (4H, m), 2.70 - 2.73 (2H, m), 2.74 - 2.83 (1H, m), 2.99 - 3.06 (2H, m), 3.07 - 3.26 (2H, m), 3.30 - 3.34 (2H, m), 3.36 - 3.39 (3H, m), 3.41 - 3.46 (1H, m), 3.70 - 3.80 (3H, m), 3.80 - 3.86 (1H, m), 4.15 - 4.34 (2H, m), 6.31 (2H, s), 6.84 - 6.89 (2H, m), 7.03 (1H, dd), 7.20 - 7.25 (3H, m), 7.30 (1H, s), 7.37 - 7.43 (2H, m), 7.45 (1H, d), 7.59 (1H, s), 7.92 - 7.95 (1H, m), 10.21 (1H, s), 14.05 - 14.28 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 872.5.

EXAMPLE 250:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

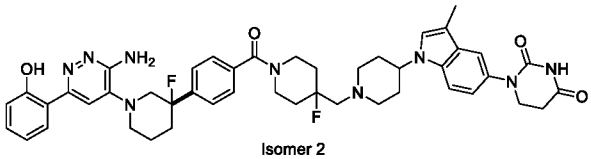


[2612] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 26j (24 mg, 0.04 mmol) and Intermediate 149f (32 mg, 0.04 mmol). Purification by RPC (elution gradient: 15 to 40% MeCN in water with 0.1% FA) gave the title compound (23.0 mg, 66%) as an amorphous white solid. ^{1}H NMR (DMSO-*d*6) δ 1.25 (3H, t), 1.46 - 1.61 (1H, m), 1.62 - 2.00 (6H, m), 2.00 - 2.13 (2H, m), 2.21 - 2.31 (1H, m), 2.32 - 2.44 (5H, m), 2.53 - 2.70 (5H, m), 2.71 - 2.82 (3H, m), 2.99 - 3.07 (2H, m), 3.07 - 3.22 (1H, m), 3.32 - 3.41 (5H, m), 3.40 - 3.48 (1H, m), 3.48 - 3.61 (1H, m), 3.73 - 3.86 (4H, m), 4.15 - 4.35 (1H, m), 4.56 - 4.63 (1H, m), 6.31 (2H, s), 6.84 - 6.89 (2H, m), 7.20 - 7.25 (3H, m), 7.39 - 7.43 (1H, m), 7.48 (1H, s), 7.59 (1H, s), 7.89 - 7.91 (1H, m), 7.91 - 7.98 (1H, m), 8.14 - 8.18 (1H, m), 10.35 (1H, s), 13.65 - 14.40 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 873.5.

EXAMPLE 251:

(*S**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



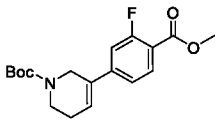
Isomer 2

[2613] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 138g (17 mg, 0.04 mmol) and Intermediate 1k (36 mg, 0.04 mmol). Purification by RPC (elution gradient: 5 to 40% MeCN in water with 0.1% FA) gave the title compound (18 mg, 56%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6) δ 1.61 - 2.03 (9H, m), 2.05 - 2.16 (1H, m), 2.17 - 2.30 (5H, m), 2.35 - 2.43 (2H, m), 2.57 - 2.65 (2H, m), 2.71 (2H, t), 2.90 - 2.98 (1H, m), 2.98 - 3.06 (2H, m), 3.07 - 3.22 (2H, m), 3.37 - 3.47 (2H, m), 3.61 - 3.69 (2H, m), 3.75 (2H, t), 4.18 - 4.35 (2H, m), 6.10 (2H, s), 6.84 - 6.90 (2H, m), 7.01 - 7.06 (1H, m), 7.19 - 7.25 (1H, m), 7.29 (1H, s), 7.38 (1H, d), 7.43 - 7.51 (3H, m), 7.56 - 7.62 (3H, m), 7.93 (1H, d), 10.23 (1H, s), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 832.5.

EXAMPLE 252

Intermediate 252a:

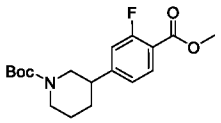
tert-Butyl 5-(3-fluoro-4-(methoxycarbonyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2614] Prepared in an analogous method to Intermediate 45a starting from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.00 g, 3.23 mmol) and methyl 4-bromo-2-fluorobenzoate (754 mg, 3.23 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexanes) gave the title compound (825 mg, 76%) as a colorless oil. ^{1}H NMR (DMSO-*d*6) δ 1.43 (9H, s), 2.23 - 2.33 (2H, m), 3.44 - 3.50 (2H, m), 3.82 - 3.88 (3H, m), 4.16 - 4.26 (2H, m), 6.52 - 6.60 (1H, m), 7.34 - 7.43 (2H, m), 7.82 - 7.90 (1H, m); *m/z* (ES$^+$) $[M-Boc+2H]^+$ = 236.1.

Intermediate 252b:

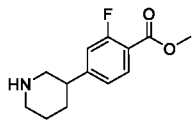
tert-Butyl 3-(3-fluoro-4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



[2615] Prepared in an analogous method to Intermediate 54b starting from Intermediate 252a (825 mg, 2.46 mmol). The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the title compound (733 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.49 (9H, s), 1.56 - 1.70 (2H, m), 1.75 - 1.86 (1H, m), 1.99 - 2.12 (1H, m), 2.62 - 2.96 (3H, m), 3.94 (3H, s), 4.07 - 4.31 (2H, m), 6.99 - 7.06 (1H, m), 7.08 - 7.17 (1H, m), 7.85 - 7.94 (1H, m); *m/z* (ES$^+$) $[M-Boc]^+$ = 238.2.

Intermediate 252c:

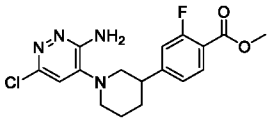
Methyl 2-fluoro-4-(piperidin-3-yl)benzoate



[2616] Prepared in an analogous method to Intermediate 1i starting from Intermediate 252b (100 mg, 0.30 mmol). The mixture was concentrated under reduced pressure to give the title compound (105 mg, 100%) in the form of a trifluoroacetic acid salt as a colorless oil. *m/z* (ES^+) $[M+H]^+$ = 238.8.

Intermediate 252d:

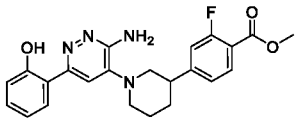
Methyl 4-(1-(3-amino-6-chloropyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoate



[2617] Prepared in an analogous method to Intermediate 1d starting from Intermediate 252c (445 mg, 2.54 mmol). Purification by FSC (elution gradient: 0 to 100% [3:1 EtOH/EtOAc] in hexanes) gave the title compound (354 mg, 52%) as an amorphous brown solid. ^{1}H NMR (DMSO-*d*6) δ 1.55 - 1.70 (1H, m), 1.80 - 1.89 (2H, m), 1.94 - 1.99 (1H, m), 2.59 - 2.65 (1H, m), 2.65 - 2.72 (1H, m), 3.10 - 3.19 (1H, m), 3.40 - 3.51 (2H, m), 3.85 (3H, s), 6.12 - 6.19 (2H, m), 6.96 (1H, s), 7.27 - 7.39 (2H, m), 7.75 - 7.89 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 365.0.

Intermediate 252e:

Methyl 4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoate

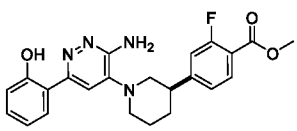


[2618] Prepared in an analogous method to Intermediate 1e starting from Intermediate 252d (354 mg, 0.97 mmol). Purification by FSC (elution gradient: 1 to 7% MeOH/ in DCM) gave the title compound (284 mg, 69%) as an amorphous brown solid. ^{1}H NMR (DMSO-*d*6) δ 1.60 - 1.73 (1H, m), 1.83 - 1.95 (2H, m), 1.96 - 2.03 (1H, m), 2.65 - 2.75 (1H, m), 2.77 - 2.85 (1H, m), 3.15 - 3.25 (1H, m), 3.48 - 3.56 (2H, m), 3.84 (3H, s), 6.21 - 6.36 (2H, m), 6.83 - 6.91 (2H, m), 7.18 - 7.26 (1H, m), 7.30 - 7.34 (1H, m), 7.35 - 7.41 (1H, m), 7.52 - 7.59 (1H, m), 7.83 - 7.89 (1H, m), 7.90 - 7.96 (1H, m), 14.13 - 14.38 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 423.4.

Intermediate 252f:

Methyl (*R**)-4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoate (Isomer 2)

((*absolute configuration not yet confirmed))



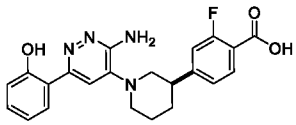
Isomer 2

[2619] Intermediate 252e (200 mg, 0.49 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak OJ 21 x 250 mm, mobile phase: 35% MeOH in $scCO_2$; Flow rate: 75.0 mL/min; BPR: 100 bar; Column temperature: 40°C to give the title compound that eluted second from the column (70 mg, 34% yield, 96% ee) as an off-white solid. *m/z* (ES^+) $[M+H]^+$ = 423.2.

Intermediate 252g:

(*R**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))



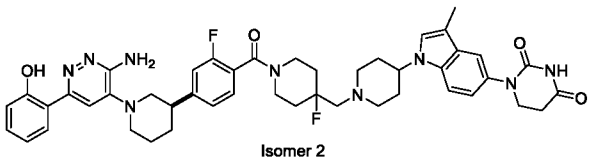
Isomer 2

[2620] Prepared in an analogous method to Intermediate 26j starting from Intermediate 252f (70 mg, 0.17 mmol). The reaction mixture was partially concentrated in vacuo, acidified with 1 M aq. HCl. A precipitate formed which was collected by filtration to give the title compound (48 mg, 71%) as an light yellow solid, which was carried forward without further purification. *m/z* (ES^-) $[M-H]^-$ = 407.2.

EXAMPLE 252:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

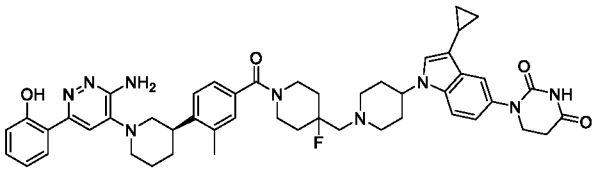


Isomer 2

[2621] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 252g (10.0 mg, 0.02 mmol) and Intermediate 1g (26.4 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (7.0 mg, 34%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6) δ 1.55 - 1.80 (3H, m), 1.83 - 2.03 (9H, m), 2.22 (3H, s), 2.40 (2H, br t), 2.55 - 2.68 (3H, m), 2.72 (3H, t), 2.82 (1H, br t), 3.02 (2H, br d), 3.15 (3H, br d), 3.54 (2H, br d), 3.76 (2H, t), 4.21 - 4.34 (2H, m), 6.29 (2H, s), 6.83 - 6.91 (2H, m), 7.04 (1H, dd), 7.19 - 7.25 (1H, m), 7.26 - 7.34 (3H, m), 7.35 - 7.42 (2H, m), 7.46 (1H, d), 7.56 (1H, s), 7.94 (1H, d), 10.23 (1H, s), 13.92 - 14.47 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 832.2.

EXAMPLE 253:

(*R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

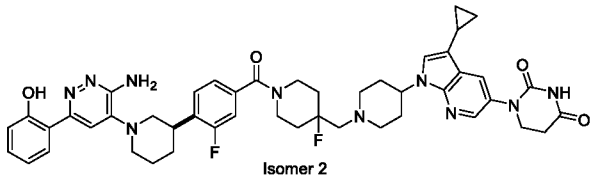


[2622] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 12g (15 mg, 0.04 mmol) and Intermediate 8e (31 mg, 0.04 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (19.7 mg, 62%) as an amorphous white solid. ^{1}H NMR (DMSO-*d*6) δ 0.56 - 0.65 (2H, m), 0.80 - 0.89 (2H, m), 1.22 - 1.29 (1H, m), 1.60 - 1.82 (4H, m), 1.85 - 2.14 (10H, m), 2.41 (3H, s), 2.74 (2H, s), 2.77 - 2.83 (1H, m), 2.87 - 2.93 (1H, m), 2.99 - 3.19 (3H, m), 3.21 - 3.31 (4H, m), 3.47 - 3.70 (3H, m), 3.78 (2H, s), 4.06 - 4.58 (2H, m), 6.20 - 6.72 (2H, m), 6.86 - 6.95 (2H, m), 7.04 - 7.11 (1H, m), 7.16 - 7.31 (4H, m), 7.25 - 7.30 (1H, m), 7.38 - 7.43 (1H, m), 7.46 - 7.51 (1H, m), 7.54 (2H, br d), 7.77 - 7.95 (1H, m), 10.25 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 854.4.

EXAMPLE 254:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



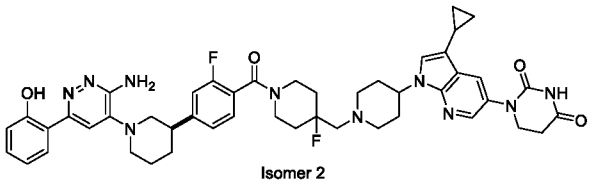
Isomer 2

[2623] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 57g (10 mg, 0.02 mmol) and Intermediate 20g (27 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (8.2 mg, 39%) as an amorphous white solid. ^{1}H NMR (DMSO-*d*6) δ 0.66 (2H, br d), 0.87 (2H, br d), 1.13 - 1.33 (1H, m), 1.62 - 2.24 (12H, m), 2.37 (1H, br s), 2.62 (2H, br s), 2.72 - 2.82 (3H, m), 3.01 (2H, br d), 3.06 - 3.23 (2H, m), 3.36 - 3.42 (2H, m), 3.43 - 3.54 (2H, m), 3.58 (3H, br s), 3.82 (2H, br t), 4.31 (1H, br s), 4.52 - 4.84 (1H, m), 6.16 - 6.80 (2H, m), 6.84 - 7.02 (2H, m), 7.24 - 7.32 (3H, m), 7.32 - 7.48 (1H, m), 7.56 (2H, br s), 7.78 - 7.88 (1H, m), 7.95 (1H, br s), 8.19 (1H, s), 10.38 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 859.5.

EXAMPLE 255:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

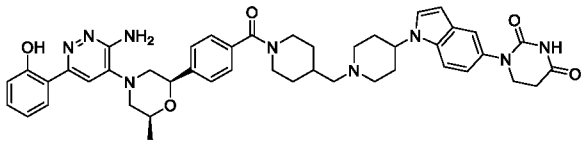


Isomer 2

[2624] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 252g (10 mg, 27 mmol) and Intermediate 20g (27.2 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 to 50% MeCN in water with 0.1% FA) gave the title compound (14 mg, 65%) as an amorphous white solid. ^{1}H NMR (DMSO-*d*6) δ 0.61 - 0.71 (m, 2H), 0.81 - 0.91 (m, 2H), 1.57 - 1.79 (m, 3H), 1.80 - 1.97 (m, 6H), 1.98 - 2.19 (m, 4H), 2.24 - 2.47 (m, 2H), 2.56 - 2.71 (m, 2H), 2.72 - 2.79 (m, 3H), 2.81 - 2.89 (m, 1H), 2.96 - 3.21 (m, 4H), 3.28 (br s, 2H), 3.34 - 3.40 (m, 1H), 3.52 - 3.63 (m, 2H), 3.82 (s, 2H), 4.25 - 4.39 (m, 1H), 4.52 - 4.76 (m, 1H), 6.24 - 6.48 (m, 2H), 6.90 (d, 2H), 7.22 - 7.28 (m, 1H), 7.28 - 7.36 (m, 2H), 7.39 (s, 1H), 7.42 - 7.46 (m, 1H), 7.56 (s, 1H), 7.88 - 7.93 (m, 1H), 7.94 - 7.98 (m, 1H), 8.16 - 8.21 (m, 1H), 10.38 (s, 1H); *m/z* (ES$^+$) $[M+H]^+$ = 859.5.

EXAMPLE 256:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

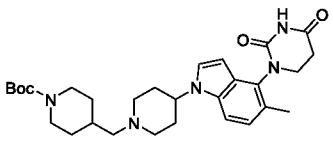


[2625] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 108b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (14.2 mg, 40%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.98 - 1.15 (2H, m), 1.25 (3H, d), 1.59 - 1.75 (1H, m), 1.76 - 2.03 (6H, m), 2.06 - 2.28 (4H, m), 2.50 - 2.57 (1H, m), 2.62 - 2.87 (4H, m), 2.98 (3H, br d), 3.38 - 3.66 (3H, m), 3.75 (2H, t), 4.04 - 4.17 (1H, m), 4.27 - 4.36 (1H, m), 4.47 (1H, br d), 4.93 (1H, dd), 6.35 - 6.53 (3H, m), 6.80 - 6.93 (2H, m), 7.05 (1H, dd), 7.17 - 7.25 (1H, m), 7.38 (2H, d), 7.44 (1H, d), 7.46 - 7.59 (5H, m), 7.94 (1H, dd), 10.23 (1H, br s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 798.7.

EXAMPLE 257

Intermediate 257a:

tert-Butyl 4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-5-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate

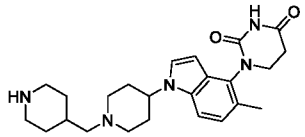


[2626] A 2 dram vial was charged with Intermediate 59e (50 mg, 0.15 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (49 mg, 0.23 mmol). DCM (2.5 mL) was added. The resulting mixture was

stirred at r.t. for 1 h. Sodium triacetoxyborohydride (81 mg, 0.38 mmol) was added. The resulting mixture was stirred at r.t. for 15 min. The mixture was diluted with EtOAc (30 mL), washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes, then 0 to 50% MeOH in EtOAc) gave the title compound (62 mg, 77%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.91 - 1.02 (2H, m), 1.38 (9H, s), 1.69 (3H, br d), 1.86 - 2.01 (4H, m), 2.09 - 2.20 (4H, m), 2.22 (3H, s), 2.61 - 2.88 (4H, m), 2.96 (2H, br d), 3.56 (1H, ddd), 3.70 - 3.78 (1H, m), 3.92 (2H, br d), 4.27 - 4.37 (1H, m), 6.38 (1H, d), 7.01 (1H, d), 7.42 (1H, d), 7.47 (1H, d), 10.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 524.3.

Intermediate 257b:

1-(5-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2627] A mixture of Intermediate 257a (62 mg, 0.12 mmol) and formic acid (6.8 mL, 178 mmol) was stirred at r.t. for 20 min and concentrated under reduced pressure. The residue was azeotroped with DCM (3x). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (32 mg, 64%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.92 - 1.05 (2H, m), 1.59 (1H, ddd), 1.66 (2H, br d), 1.88 - 2.04 (4H, m), 2.09 - 2.20 (4H, m), 2.23 (3H, s), 2.41 - 2.49 (2H, m), 2.69 - 2.78 (1H, m), 2.79 - 2.88 (1H, m), 2.89 - 3.02 (4H, m), 3.57 (1H, ddd), 3.70 - 3.82 (1H, m), 4.24 - 4.40 (1H, m), 6.39 (1H, d), 7.03 (1H, d), 7.43 (1H, d), 7.49 (1H, d), 10.30 (1H, br s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 424.4.

EXAMPLE 257:

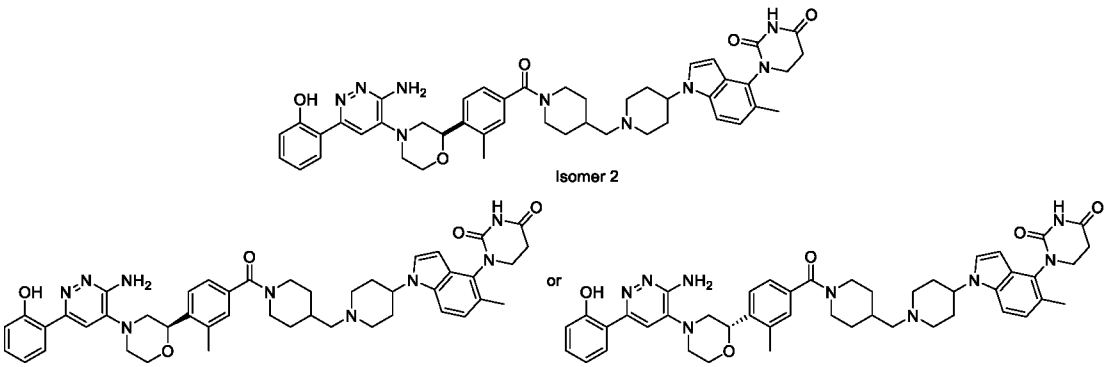
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

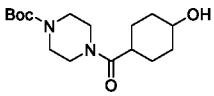


[2628] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (17 mg, 0.04 mmol) and Intermediate 257b (15 mg, 0.03 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (11.0 mg, 39%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.07 (2H, br d), 1.55 - 2.05 (7H, m), 2.14 (2H, br t), 2.22 (5H, s), 2.39 (3H, s), 2.69 - 2.92 (5H, m), 2.97 (3H, br d), 3.46 - 3.68 (4H, m), 3.73 (1H, ddd), 4.07 (2H, br d), 4.24 - 4.36 (1H, m), 4.46 (1H, br s), 4.90 - 5.05 (1H, m), 6.33 - 6.47 (3H, m), 6.81 - 6.92 (2H, m), 7.01 (1H, d), 7.15 - 7.26 (3H, m), 7.42 (1H, d), 7.46 (1H, d), 7.53 (1H, d), 7.56 (1H, s), 7.93 (1H, dd), 10.29 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.6.

EXAMPLE 258

Intermediate 258a:

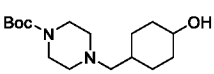
tert-Butyl 4-(4-hydroxycyclohexane-1-carbonyl)piperazine-1-carboxylate



[2629] HATU (72.5 g, 190.75 mmol) was added portion wise to 4-hydroxycyclohexane-1-carboxylic acid (25 g, 173.41 mmol), *tert*-butyl piperazine-1-carboxylate (35.5 g, 190.75 mmol) and Et_3N (48.3 mL, 346.81 mmol) in THF (500 mL) at 0°C. The resulting mixture was stirred at r.t. for 16 h and concentrated under reduced pressure. The residue was diluted with water (1.50 L). The mixture was extracted with DCM (3 x 1.5 L). The combined organic layers were washed with brine (1.40 L), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Trituration with EtOAc (500 mL) gave the title compound (44.0 g, 81%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.52 – 1.64 (4H, m), 1.86 –1.92 (2H, m), 1.93 – 2.02 (2H, m), 2.49 – 2.55 (1H, m), 3.38 – 3.60 (8H, m), 4.01 – 4.05 (1H, m), oxygen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 313.3.

Intermediate 258b:

tert-Butyl 4-((4-hydroxycyclohexyl)methyl)piperazine-1-carboxylate



[2630] BH_3·DMS in THF (400 mL, 800.00 mmol) was added dropwise to Intermediate 258a (42.5 g, 136.04 mmol) in THF (200 mL) at 0 °C under nitrogen. The resulting mixture was stirred at room r.t. for 16 h. The reaction mixture was quenched with MeOH (300 mL) at 0 °C. The mixture was concentrated

under reduced pressure. The crude residue was triturated with EtOAc (100 mL) to give the title compound (34.0 g, 84%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.31 – 1.43 (2H, m), 1.48 (9H, s), 1.50 – 1.79 (8H, m), 2.13 – 2.47 (6H, m), 3.40 – 3.48 (4H, m), 4.00 (1H, brs); *m/z* (ES^+) $[M+H]^+$ = 299.1.

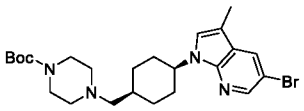
Intermediate 258c:

tert-Butyl 4-(((1*s*,4*s*)-4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate

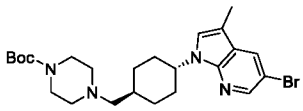
and

Intermediate 258d:

tert-Butyl 4-(((1*r*,4*r*)-4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



Intermediate 258c

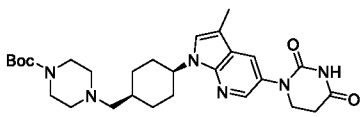


Intermediate 258d

[2631] Prepared in an analogous method to Intermediate 234a starting from Intermediate 258b (3 g, 10.05 mmol) and 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.122 g, 10.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.4% NH_4HCO_3) gave a mixture of cis and trans isomers (2.0 g, 41%) as a yellow solid. Purification by SFC (Column: CHIRALPAK IF 3*25 cm, 5 μm; elution gradient: isocratic 30% [1:1 MeCN:MeOH with 1% 2 M NH_3 in MeOH] in $scCO_2$; Flow rate: 100 mL/min) gave Intermediate 258c (900 mg, 18%) which eluted first from the column and Intermediate 258d (1.00 g, 20%) which eluted second from the column as a yellow solids. Intermediate 258c: ^{1}H NMR ($CDCl_3$) δ 1.23 – 1.30 (1H, m), 1.48 (9H, s), 1.74 – 1.89 (8H, m), 1.96 – 2.01 (1H, m), 2.26 – 2.29 (3H, m), 2.41 (5H, d), 3.44 (4H, t), 4.64 – 4.75 (1H, m), 7.12 (1H, s), 7.95 (1H, d), 8.30 (1H, d); *m/z* (ES+) $[M+H]^+$ = 491. Intermediate 258d: ^{1}H NMR ($CDCl_3$) δ 0.89 – 0.97 (2H, m), 1.13 – 1.26 (2H, m), 1.47 (9H, s), 1.64 – 1.77 (3H, m), 1.96 – 2.01 (2H, m), 2.05 – 2.10 (2H, m), 2.19 (2H, d), 2.26 (3H, d), 2.33 – 2.37 (3H, m), 3.41 – 3.45 (4H, m), 7.06 (1H, d), 7.93 (1H, d), 8.28 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 491.

Intermediate 258e:

tert-Butyl 4-(((1*s*,4*s*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate

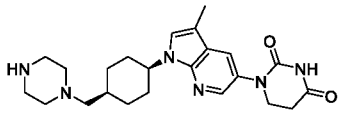


[2632] Dihydropyrimidine-2,4(1*H*,3*H*)-dione (627 mg, 5.49 mmol) was added to GPhos Pd G6 (87 mg, 0.09 mmol), GPhos (49.1 mg, 0.09 mmol), Cs_2CO_3 (1790 mg, 5.49 mmol) and Intermediate 258c (900 mg, 1.83 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 20% MeOH in DCM) gave the title compound (600 mg, 62%) as a yellow

solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, s), 1.60 – 1.72 (4H, m), 1.73– 1.81 (2H, m), 1.88 – 2.00 (3H, m), 2.26 (3H, s), 2.32– 2.39 (4H, m), 2.40– 2.45 (2H, m), 2.76 (2H, t), 3.29 – 3.32 (4H, m), 3.81 (2H, t), 4.54 – 4.72 (1H, m), 7.58 (1H, s), 7.87 (1H, d), 8.17 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 525.4.

Intermediate 258f:

1-(3-Methyl-1-((1*s*,4*s*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2633] TFA (1.06 mL, 13.7 mol) was added to a solution of Intermediate 258e (600 mg, 1.14 mmol) in DCM (3.2 mL). The resulting mixture was stirred at r.t. for 2 hours and concentrated under reduced pressure. The residue was dissolved in water (20 mL). DCM/IPA (2:1, 30 mL) and sat. aq. K_2CO_3 (20 mL) were added. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was azeotroped with hexanes (30 mL) to give the title compound (452 mg, 93%) as an off-white solid. ^{1}H NMR (DMSO-*d6*): δ 1.55 - 1.82 (7H, m), 1.85 - 2.02 (4H, m), 2.17 - 2.39 (8H, m), 2.63 - 2.78 (6H, m), 3.79 (2H, br t), 4.63 (1H, br t), 7.55 (1H, s), 7.85 (1H, d), 8.16 (1H, d), 10.14 - 10.55 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 425.4.

EXAMPLE 258:

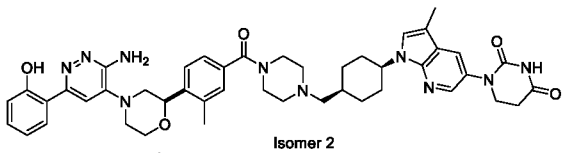
1-(1-((1*S*,4*s*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

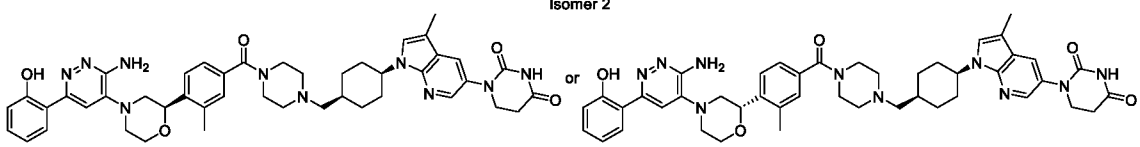
1-(1-((1*S*,4*s*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*S*,4*s*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 2



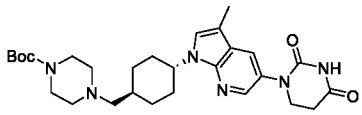
[2634] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 258f (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid

in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.6 mg, 70%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d6*): δ 1.59 - 1.73 (4H, m), 1.75 - 1.84 (2H, m), 1.89 - 2.03 (3H, m), 2.26 (3H, s), 2.32 - 2.50 (9H, m), 2.76 (2H, t), 2.80 - 2.94 (2H, m), 3.33 - 3.72 (6H, m), 3.81 (2H, t), 4.09 (2H, br d), 4.59 - 4.72 (1H, m), 4.85 - 5.08 (1H, m), 6.43 (2H, s), 6.79 - 6.93 (2H, m), 7.18 - 7.30 (3H, m), 7.50 - 7.61 (3H, m), 7.87 (1H, d), 7.95 (1H, dd), 8.17 (1H, d), 10.37 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 813.5.

EXAMPLE 259

Intermediate 259a:

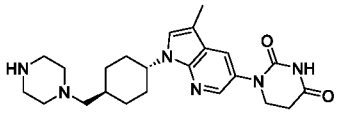
tert-Butyl 4-(((1*r*,4*r*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2635] Prepared in an analogous method to Intermediate 2b starting from Intermediate 258d (1 g, 2.03 mmol). Purification by FSC (elution gradient: 0 to 5% MeOH in DCM) gave the title compound (0.250 g, 23%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.07 – 1.18 (2H, m), 1.41 (9H, s), 1.61–1.65 (1H, s), 1.80 – 1.89 (2H, m), 1.89 – 1.97 (5H, m), 2.16 (2H, d), 2.26 (3H, d), 2.26–2.33 (4H, m), 2.76 (2H, t), 3.31 (3H, d), 3.81 (2H, t), 4.57 – 4.69 (1H, m), 7.45 (1H, d), 7.88 (1H, d), 8.17 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 525.1.

Intermediate 259b:

1-(3-Methyl-1-((1*r*,4*r*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2636] TFA (1.84 mL, 23.8 mmol) was added to a solution of Intermediate 259a (624 mg, 1.19 mmol) in DCM (5.5 mL). The resulting mixture was stirred at r.t. for 90 minutes and concentrated under reduced pressure. The residue was dissolved in water (20 mL). DCM/IPA (2:1, 30 mL) and sat. aq. K_2CO_3 (20 mL) were added. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (511 mg, 101%) as an off-white solid. Product contains ~7 wt% *i*PrOH. ^{1}H NMR (DMSO-*d6*): δ 1.04 - 1.14 (2H, m), 1.56 - 1.65 (1H, m), 1.73 - 1.94 (7H, m), 2.04 - 2.33 (9H, m), 2.58 - 2.80 (6H, m), 3.76 (2H, t), 4.55 - 4.64 (1H, m), 7.41 (1H, s), 7.83 (1H, d), 8.14 (1H, d), 9.95 - 10.78 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 425.4.

EXAMPLE 259:

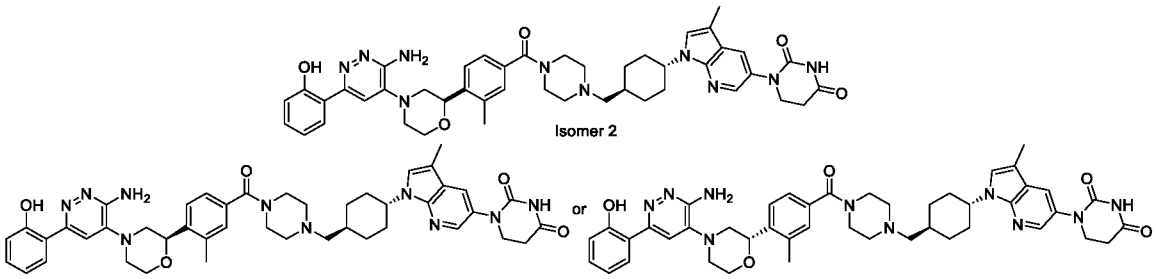
1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*R*,4*r*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2637] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 55j (20 mg, 0.05 mmol) and Intermediate 259b (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (30.1 mg, 83%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.05 - 1.19 (2H, m), 1.61 (1H, br d), 1.77 - 1.98 (6H, m), 2.18 (2H, br d), 2.24 (3H, s), 2.27 - 2.46 (7H, m), 2.74 (2H, t), 2.79 - 2.92 (2H, m), 3.31 - 3.42 (2H, m), 3.47 - 3.71 (4H, m), 3.79 (2H, t), 4.01 - 4.12 (2H, m), 4.53 - 4.66 (1H, m), 4.96 (1H, br d), 6.41 (2H, s), 6.79 - 6.92 (2H, m), 7.17 - 7.27 (3H, m), 7.42 (1H, s), 7.51 - 7.59 (2H, m), 7.86 (1H, d), 7.93 (1H, dd), 8.15 (1H, d), 10.36 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 813.5.

EXAMPLE 260:

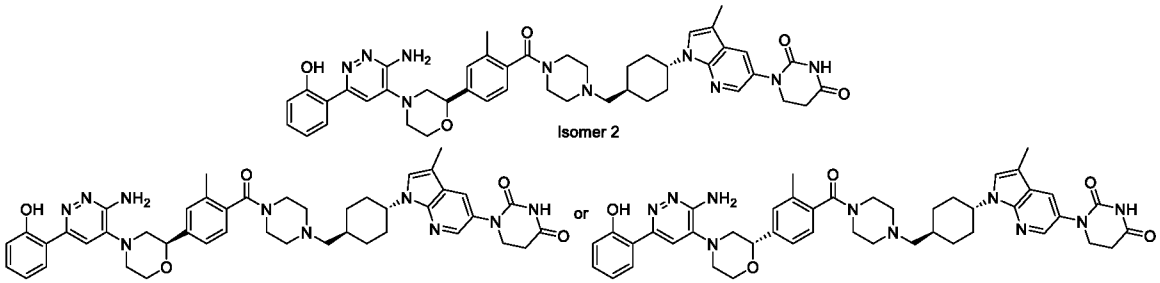
1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*R*,4*r*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

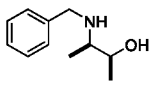


[2638] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 219d (20 mg, 0.05 mmol) and Intermediate 259b (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (22.0 mg, 60%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.04 - 1.17 (2H, m), 1.61 (1H, br s), 1.74 - 1.97 (6H, m), 2.13 - 2.45 (12H, m), 2.72 - 2.82 (3H, m), 2.87 (1H, td), 3.14 (2H, br s), 3.41 - 3.57 (2H, m), 3.66 (2H, br s), 3.79 (2H, t), 3.98 - 4.12 (2H, m), 4.50 - 4.65 (1H, m), 4.75 - 4.87 (1H, m), 6.45 (2H, s), 6.80 - 6.90 (2H, m), 7.15 (1H, d), 7.18 - 7.25 (1H, m), 7.31 (1H, br d), 7.35 (1H, s), 7.42 (1H, s), 7.55 (1H, s), 7.85 (1H, d), 7.90 - 7.95 (1H, m), 8.15 (1H, d), 10.36 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 813.5.

EXAMPLE 261

Intermediate 261a:

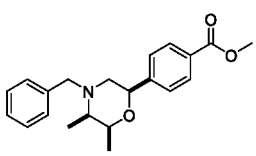
rac-(2*S*,3*R*)-3-(Benzylamino)butan-2-ol



[2639] Lithium perchlorate (11.1 g, 104 mmol) was added to a solution of *rac*-(2*R*,3*R*)-2,3-dimethyloxirane (6.22 mL, 69.3 mmol) and benzylamine (11.4 mL, 104 mmol) in MeCN (121 mL). The resulting mixture was stirred at 65 °C for 18 h. The mixture was concentrated under reduced pressure. Water (100 mL) and EtOAc (100 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [0.5% NH_4OH in MeOH] in DCM) and RPC (elution gradient: 0 to 50% MeCN in water with 0.1% NH_4OH) gave the title compound (5.81 g, 47%) as a white solid. ^{1}H NMR (DMSO-*d*6): δ 0.91 (3H, d), 1.00 (3H, d), 1.77 (1H, br s), 2.45 (1H, qd), 3.60 (1H, dt), 3.63 - 3.69 (1H, m), 3.71 - 3.78 (1H, m), 4.28 (1H, d), 7.16 - 7.23 (1H, m), 7.25 - 7.35 (4H, m); *m/z* (ES^+) $[M+H]^+$ = 180.2.

Intermediate 261b:

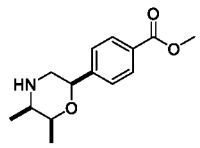
rac-Methyl 4-((2*R*,5*R*,6*S*)-4-benzyl-5,6-dimethylmorpholin-2-yl)benzoate



[2640] Methyl 4-(2-bromoacetyl)benzoate (8.32 g, 32.4 mmol) and K_2CO_3 (4.92 g, 35.6 mmol) were added to a solution of Intermediate 261a (5.80 g, 32.4 mmol) in MeCN (108 mL). The resulting mixture was stirred at r.t. for 15 hours. The mixture was filtered. The filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. DCM (50 mL), TFA (50 mL) and methyl(phenyl)silane (8.89 mL, 64.7 mmol) were added. The resulting mixture was stirred at 40 °C for 4 hours. The mixture was concentrated under reduced pressure. DCM (70 mL) and sat. aq. K_2CO_3/water (1:2, 90 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0 to 13% acetone in hexanes; 2nd purification: elution gradient: 0 to 40% EtOAc in hexanes; 3rd purification: 0 to 100% DCM in hexanes, then 0 to 40% EtOAc in DCM; 4th purification: 0 to 20% EtOAc in DCM) gave the title compound (5.65 g, 51%) as a yellow oil that solidified upon standing and a mixture of diastereomers of the title compound (2.94 g, 27%, d.r. ~ 3.7:1 of title compound with epimer at benzylic position) as a yellow oil that solidified upon standing. Only highly diastereomerically enriched title compound was used for subsequent steps. ^{1}H NMR (DMSO-*d*6): δ 0.95 (3H, d), 1.07 (3H, d), 2.37 (1H, t), 2.53 (1H, dd), 2.69 (1H, qd), 3.53 - 3.61 (1H, m), 3.65 - 3.71 (1H, m), 3.83 (3H, s), 3.94 (1H, qd), 4.64 (1H, dd), 7.20 - 7.27 (1H, m), 7.28 - 7.38 (4H, m), 7.46 (2H, d), 7.91 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 340.2.

Intermediate 261c:

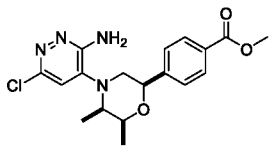
rac-Methyl 4-((2*R*,5*R*,6*S*)-5,6-dimethylmorpholin-2-yl)benzoate



[2641] MeOH (100 mL) was added to a mixture of Intermediate 261b (5.64 g, 16.6 mmol) and Pd/C (1.77 g, 1.66 mmol, 10 wt% palladium). The flask was evacuated and backfilled with hydrogen (3x). The resulting suspension was stirred at 60 °C under an atmosphere of hydrogen for 3 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES$^+$) $[M+H]^+$ = 250.4.

Intermediate 261d:

rac-Methyl 4-((2*R*,5*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoate

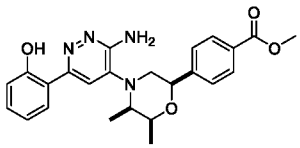


[2642] Intermediate 261c (4.14 g, 16.6 mmol) was dissolved in DMA (26 mL). The mixture was stirred at 50 °C and 15 mbar for 20 minutes. 4-Bromo-6-chloropyridazin-3-amine (6.92 g, 33.2 mmol), DIPEA (7.23 mL, 41.5 mmol) and sodium methanesulfinate (0.85 g, 8.30 mmol) were added. The resulting mixture

was stirred at 130 °C for 17 hours. More 4-bromo-6-chloropyridazin-3-amine (3.46 g, 16.6 mmol) and DIPEA (2.90 mL, 16.6 mmol) were added and stirring was continued at 130 °C for 5 hours. After cooling to r.t., the mixture was partially concentrated under reduced pressure. DCM (50 mL) and brine (50 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0 to 80% acetone in hexanes; 2nd purification: 0 to 50% acetone in hexanes) gave the title compound as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.89 (3H, d), 1.13 (3H, d), 3.04 (1H, dd), 3.10 - 3.19 (1H, m), 3.69 - 3.77 (1H, m), 3.85 (3H, s), 4.31 (1H, qd), 4.77 (1H, dd), 6.18 (2H, s), 6.91 (1H, s), 7.59 (2H, d), 7.96 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 377.2.

Intermediate 261e:

rac-Methyl 4-((2*R*,5*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoate



[2643] 1,4-Dioxane (55 mL) and water (6.2 mL) were added to a mixture of Intermediate 261d (2.32 g, 6.16 mmol), CPhos Pd G3 (124 mg, 0.15 mmol), CPhos (67 mg, 0.15 mmol), (2-hydroxyphenyl)boronic acid (1.10 g, 8.00 mmol) and K_2CO_3 (2.55 g, 18.5 mmol). The flask was evacuated and backfilled with nitrogen (5x). The mixture was stirred at 80 °C for 140 minutes. More CPhos Pd G3 (50 mg, 0.06 mmol) and CPhos (27 mg, 0.06 mmol) were added and stirring was continued at 80 °C for 30 minutes. More (2-hydroxyphenyl)boronic acid (423 mg g, 3.08 mmol) was added and stirring was continued at 80 °C for 100 minutes, After cooling to r.t., the mixture was concentrated under reduced pressure. DCM/IPA (3:1, 40 mL) and sat. aq. K_2CO_3 (30 mL) were added. The resulting biphasic mixture was stirred vigorously for 30 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (30 mL) and sat. aq. NH_4Cl (30 mL). The aq. NH_4Cl layer was extracted with DCM (30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% acetone in hexanes) gave the title compound (1.68 g, 63%) as a yellow solid and recovered Intermediate 261d (0.45 g, 19%) as a brown solid. Intermediate 261e: ^{1}H NMR (DMSO-*d*6): δ 0.94 (3H, d), 1.17 (3H, d), 3.12 (1H, dd), 3.39 (1H, t), 3.75 - 3.83 (1H, m), 3.88 (3H, s), 4.41 (1H, qd), 4.84 (1H, dd), 6.36 (2H, s), 6.79 - 6.85 (1H, m), 6.88 (1H, dd), 7.18 - 7.25 (1H, m), 7.50 (1H, s), 7.65 (2H, d), 7.93 (1H, dd), 8.00 (2H, d), 14.25 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 435.1.

Intermediate 261f:

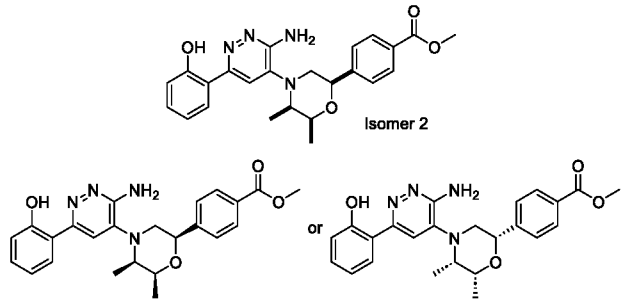
Methyl 4-((2*R**,5*R**,6*S**)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl 4-((2*R*,5*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoate

or

Methyl 4-((2*S*,5*S*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoate



[2644] Intermediate 261e (1.57 g, 3.61 mmol) was purified by preparative SFC (Column: OJ-H 250x21 mm, 5 μM; mobile phase: 25% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 90 mL/min; Column temperature: 40 °C) to give the title compound that eluted second from the column (684 mg, 44%, 95% ee) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 0.92 (3H, d), 1.16 (3H, d), 3.10 (1H, dd), 3.37 (1H, t), 3.74 - 3.81 (1H, m), 3.86 (3H, s), 4.40 (1H, qd), 4.82 (1H, dd), 6.34 (2H, s), 6.81 (1H, t), 6.86 (1H, d), 7.17 - 7.24 (1H, m), 7.49 (1H, s), 7.64 (2H, d), 7.91 (1H, d), 7.99 (2H, d), 14.23 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 435.3.

Intermediate 261g:

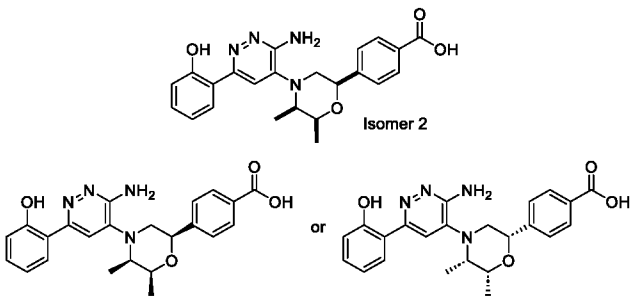
4-((2*R**,5*R**,6*S**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoic acid

or

4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoic acid



[2645] 3 M aq. NaOH (2.09 mL, 6.26 mmol) was added to a solution of Intermediate 261f (680 mg, 1.57 mmol) in EtOH (6.3 mL). The resulting mixture was stirred at 60 °C for 1 hour. After cooling to r.t., EtOH was removed under reduced pressure. 6 M aq. HCl (1.05 mL) was added. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (609 mg, 93%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 0.97 (3H, d), 1.16 (3H, d), 3.17 (1H, br d), 3.33 - 3.39 (1H, m), 3.83 (1H, br d), 4.32 - 4.46 (1H, m), 4.82 (1H, dd), 6.42 - 6.74 (2H, m), 6.85 (1H, t), 6.90 (1H, d), 7.25

(1H, t), 7.49 (1H, s), 7.60 (2H, d), 7.82 (1H, br d), 7.96 (2H, d), 11.86 - 14.79 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 421.3.

EXAMPLE 261:

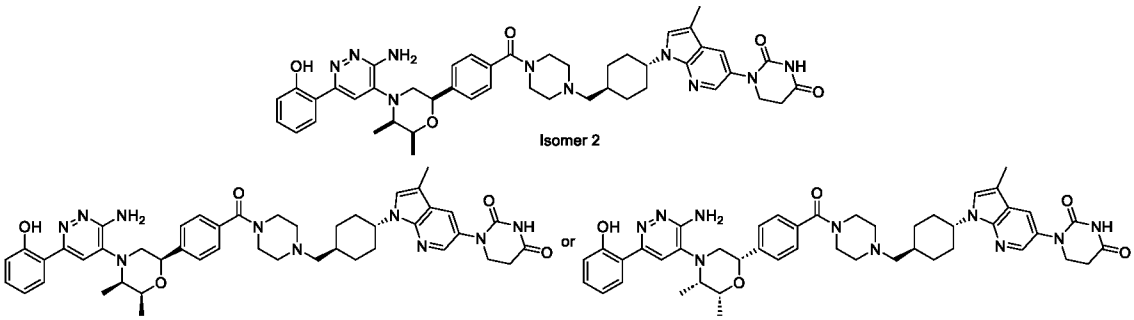
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R**,5*R**,6*S**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

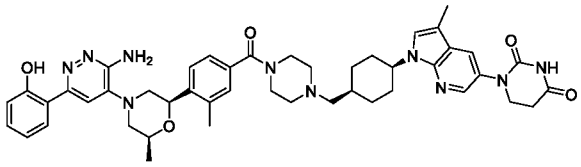
1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2646] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (19.7 mg, 55%) as an amorphous white solid, following lyophilization. ^1H NMR (DMSO-*d6*): δ 0.94 (3H, d), 1.07 - 1.21 (5H, m), 1.64 (1H, br s), 1.78 - 1.98 (6H, m), 2.21 (2H, br d), 2.26 (3H, s), 2.30 - 2.48 (4H, m), 2.76 (2H, t), 3.09 (1H, dd), 3.33 - 3.48 (3H, m), 3.65 (2H, br s), 3.75 - 3.85 (3H, m), 4.31 - 4.48 (1H, m), 4.55 - 4.69 (1H, m), 4.79 (1H, dd), 6.36 (2H, s), 6.84 (1H, t), 6.88 (1H, d), 7.17 - 7.25 (1H, m), 7.37 - 7.47 (3H, m), 7.52 (1H, s), 7.57 (2H, d), 7.88 (1H, d), 7.95 (1H, d), 8.17 (1H, d), 10.38 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.5.

EXAMPLE 262:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

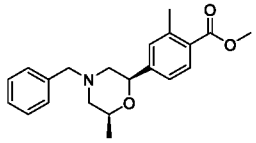


[2647] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 132e (20 mg, 0.05mmol) and Intermediate 258f (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (24.6 mg, 69%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 1.58 - 1.75 (4H, m), 1.78 (2H, br d), 1.87 - 2.07 (3H, m), 2.26 (3H, s), 2.33 - 2.58 (10H, m), 2.71 - 2.81 (3H, m), 3.33 - 3.48 (2H, m), 3.50 - 3.74 (4H, m), 3.81 (2H, t), 4.09 - 4.25 (1H, m), 4.54 - 4.75 (1H, m), 4.93 - 5.15 (1H, m), 6.43 (2H, s), 6.83 - 6.93 (2H, m), 7.19 - 7.30 (3H, m), 7.51 - 7.61 (3H, m), 7.87 (1H, d), 7.96 (1H, dd), 8.17 (1H, d), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 827.5.

EXAMPLE 263

Intermediate 263a:

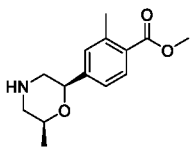
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2-methylbenzoate



[2648] (*S*)-1-(Benzylamino)propan-2-ol (3.74 g, 22.7 mmol) in MeCN (20 mL) was added to a suspension of Intermediate 49a (6.14 g, 22.7 mmol) and K_2CO_3 (3.44 g, 24.9 mmol) in MeCN (80 mL) at 0 °C. The resulting mixture was stirred for 15 hours gradually increasing the temperature to r.t. The mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. DCE (35 mL) and TFA (35 mL, 453 mmol) were added and the mixture was heated to 60 °C. Methyl(phenyl)silane (4.67 mL, 34.0 mmol) was added and the mixture was stirred at 60 °C for 60 minutes. The mixture was concentrated under reduced pressure. DCM (50 mL) and sat. aq. K_2CO_3/H_2O (60 mL, 1:2) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (5.19 g, 68%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.12 (3H, d), 1.77 (1H, t), 1.86 (1H, t), 2.48 (3H, s), 2.74 (1H, br d), 2.84 (1H, br d), 3.41 - 3.48 (1H, m), 3.48 - 3.55 (1H, m), 3.74 (1H, ddd), 3.79 (3H, s), 4.57 (1H, dd), 7.21 - 7.26 (3H, m), 7.27 - 7.34 (4H, m), 7.77 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 340.3.

Intermediate 263b:

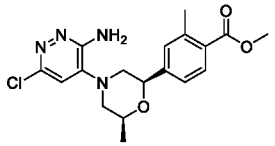
Methyl 2-methyl-4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2649] Prepared in an analogous method to Intermediate 65b using Intermediate 263a (5.19 g, 15.3 mmol). The crude product was used for the next step without further purification and quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 250.4.

Intermediate 263c:

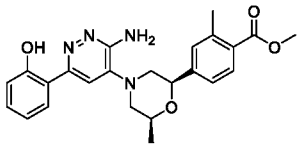
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoate



[2650] Prepared in an analogous method to Intermediate 1d starting from Intermediate 263b (3.81 g, 15.3 mmol). Purification by FSC (elution gradient: 0 to 70% acetone in hexanes) gave the title compound (4.70 g, 82%) as a yellow solid. ^1H NMR (DMSO-*d6*): δ 1.21 (3H, d), 2.41 - 2.50 (2H, m), 2.51 (3H, s), 3.38 (1H, br d), 3.46 - 3.55 (1H, m), 3.81 (3H, s), 3.98 - 4.08 (1H, m), 4.87 (1H, dd), 6.31 (2H, s), 6.93 (1H, s), 7.30 - 7.40 (2H, m), 7.81 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 377.0.

Intermediate 263d:

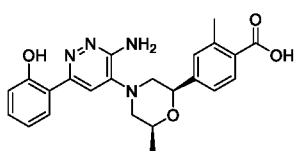
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoate



[2651] Prepared in an analogous method to Intermediate 1e starting from Intermediate 263c (4.70, 12.5 mmol). After cooling to r.t., the mixture was concentrated under reduced pressure. DCM–IPA (3:1, 50 mL) was added followed by sat. aq. K_2CO_3 (50 mL). The resulting mixture was stirred vigorously for 20 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3/H_2O (5:1, 2 x 50 mL) and sat. aq. NH_4Cl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 80% acetone in hexanes) gave the title compound (4.24 g, 78%) as a brown solid. ^1H NMR (DMSO-*d6*): δ 1.25 (3H, d), 2.53 (4H, s), 2.60 - 2.66 (1H, m), 3.45 - 3.51 (1H, m), 3.52 - 3.60 (1H, m), 3.82 (3H, s), 4.01 - 4.20 (1H, m), 4.93 (1H, dd), 6.46 (2H, s), 6.80 - 6.90 (2H, m), 7.17 - 7.24 (1H, m), 7.33 - 7.41 (2H, m), 7.53 (1H, s), 7.83 (1H, d), 7.92 (1H, dd), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 435.4.

Intermediate 263e:

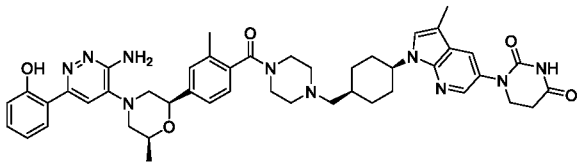
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoic acid



[2652] 3 M aq. NaOH (13.0 mL, 38.9 mmol) was added to a solution of Intermediate 263d (4.23 g, 9.74 mmol) in EtOH (38.9 mL). The resulting mixture was stirred at 60 °C for 60 minutes. After cooling to r.t., the mixture was partially concentrated under reduced pressure. 6 M aq. HCl (6.6 mL) was added. A precipitate formed which was collected by filtration, washed with water, hexanes, DCM–hexanes (1:1), and EtOAc, and dried *in vacuo* to give the title compound (3.42 g, 84%) as a yellowish solid. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, d), 2.53 (3H, s), 2.63 (1H, br t), 2.72 (1H, br t), 3.58 (1H, br d), 3.65 (1H, br d), 4.04 - 4.12 (1H, m), 4.91 (1H, dd), 6.91 (1H, t), 6.98 (1H, d), 7.07 (2H, br s), 7.27 - 7.32 (1H, m), 7.33 - 7.38 (2H, m), 7.55 (1H, s), 7.74 (1H, br d), 7.83 (1H, d), 13.08 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.4.

EXAMPLE 263:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2653] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 258f (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.5 mg, 77%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 1.55 - 1.86 (6H, m), 1.87 - 2.02 (3H, m), 2.25 (6H, d), 2.29 - 2.58 (7H, m), 2.70 (1H, br t), 2.76 (2H, t), 3.17 (2H, br s), 3.47 - 3.60 (2H, m), 3.69 (2H, br s), 3.81 (2H, t), 4.06 - 4.19 (1H, m), 4.57 - 4.72 (1H, m), 4.81 - 4.99 (1H, m), 6.40 - 6.51 (2H, m), 6.82 - 6.92 (2H, m), 7.17 (1H, d), 7.21 - 7.27 (1H, m), 7.29 - 7.39 (2H, m), 7.56 (2H, d), 7.87 (1H, d), 7.96 (1H, dd), 8.16 (1H, d), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 827.5.

EXAMPLE 264:

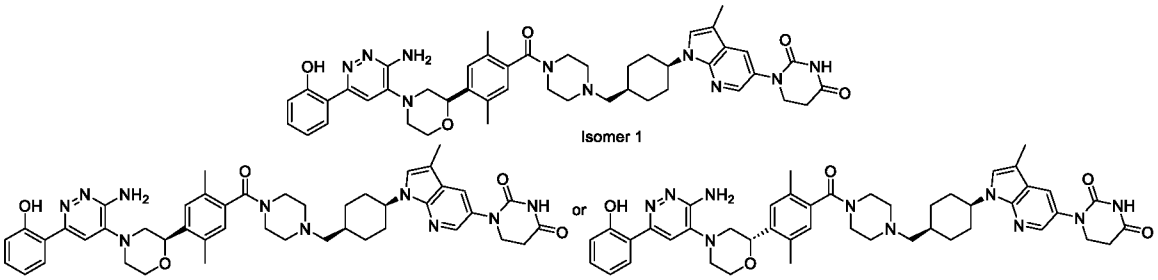
1-(1-((1*S*,4*s*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

1-(1-((1*S*,4*s*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

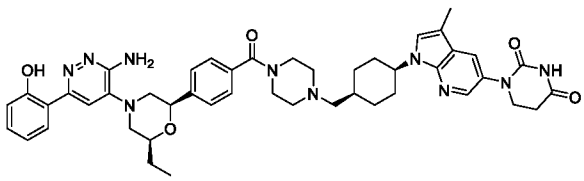
1-(1-((1*S*,4*s*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2654] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (20 mg, 0.05 mmol) and Intermediate 258f (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (20.1 mg, 56%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.61 - 1.73 (4H, m), 1.74 - 1.84 (2H, m), 1.89 - 2.02 (3H, m), 2.21 (3H, s), 2.26 (3H, s), 2.29 - 2.40 (5H, m), 2.43 - 2.52 (4H, m), 2.76 (2H, t), 2.80 - 2.97 (2H, m), 3.11 - 3.24 (2H, m), 3.52 (2H, br d), 3.68 (2H, br s), 3.81 (2H, t), 4.02 - 4.15 (2H, m), 4.57 - 4.74 (1H, m), 4.93 (1H, br d), 6.42 (2H, s), 6.82 - 6.93 (2H, m), 6.99 (1H, s), 7.24 (1H, br t), 7.38 (1H, s), 7.51 - 7.65 (2H, m), 7.87 (1H, d), 7.95 (1H, d), 8.16 (1H, d), 10.37 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.5.

EXAMPLE 265:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

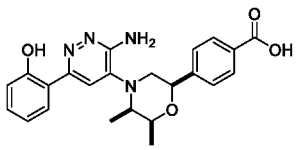


[2655] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 163f (20 mg, 0.05 mmol) and Intermediate 258f (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (21.9 mg, 61%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.54 - 1.80 (8H, m), 1.88 - 2.01 (3H, m), 2.24 (3H, s), 2.30 - 2.48 (6H, m), 2.52 - 2.59 (1H, m), 2.62 - 2.69 (1H, m), 2.74 (2H, t), 3.31 - 3.73 (6H, m), 3.79 (2H, t), 3.86 - 3.95 (1H, m), 4.56 - 4.71 (1H, m), 4.93 (1H, br d), 6.45 (2H, s), 6.80 - 6.90 (2H, m), 7.19 - 7.26 (1H, m), 7.41 (2H, d), 7.48 - 7.59 (4H, m), 7.85 (1H, d), 7.94 (1H, d), 8.15 (1H, d), 10.35 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.5.

EXAMPLE 266

Intermediate 266a:

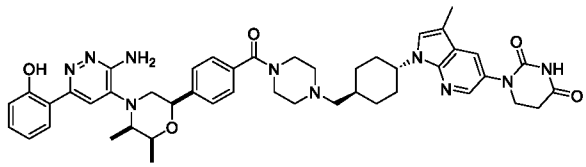
rac-4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoic acid



[2656] 3 M aq. NaOH (0.38 mL, 1.15 mmol) was added to a solution of Intermediate 261e (100 mg, 0.23 mmol) in EtOH (1.15 mL). The resulting mixture was stirred at 60 °C for 1 hour. After cooling to r.t., DCM/IPA (2:1, 10 mL), 1 M aq. HCl (1.45 mL) and water (10 mL) were added. The phases were separated. The aqueous layer was extracted with DCM/IPA (2:1, 2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 0.92 (3H, d), 1.15 (3H, d), 3.09 (1H, dd), 3.37 (1H, br t), 3.78 (1H, br dd), 4.39 (1H, br dd), 4.81 (1H, dd), 6.35 (2H, br s), 6.81 (1H, t), 6.86 (1H, d), 7.17 - 7.25 (1H, m), 7.48 (1H, s), 7.60 (2H, d), 7.91 (1H, d), 7.96 (2H, d), 13.59 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 421.3.

EXAMPLE 266:

rac-1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2657] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 266a (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.3 mg, 76%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.92 (3H, d), 1.07 - 1.20 (5H, m), 1.57 - 1.68 (1H, m), 1.78 - 1.98 (6H, m), 2.19 (2H, br d), 2.24 (3H, s), 2.29 - 2.47 (4H, m), 2.75 (2H, t), 3.07 (1H, dd), 3.31 - 3.46 (3H, m), 3.49 - 3.73 (2H, m), 3.75 - 3.83 (3H, m), 4.39 (1H, qd), 4.60 (1H, qd), 4.77 (1H, dd), 6.34 (2H, s), 6.79 - 6.84 (1H, m), 6.84 - 6.89 (1H, m), 7.17 - 7.24 (1H, m), 7.38 - 7.46 (3H, m), 7.50 (1H, s), 7.55 (2H, d), 7.86 (1H, d), 7.93 (1H, dd), 8.15 (1H, d), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 827.5.

EXAMPLE 267:

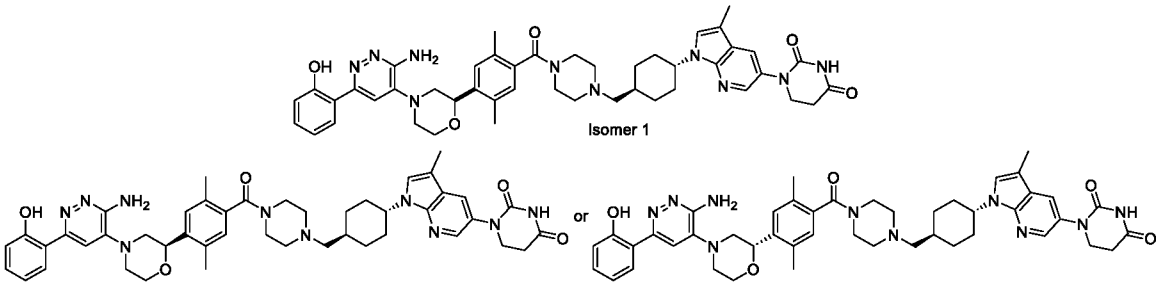
1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

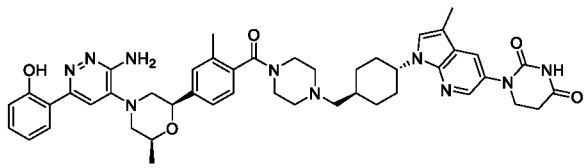
1-(1-((1*R*,4*r*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2658] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (23.8 mg, 67%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, q), 1.61 (1H, br s), 1.75 - 2.00 (6H, m), 2.13 - 2.48 (15H, m), 2.74 (2H, t), 2.78 - 2.92 (2H, m), 3.09 - 3.20 (2H, m), 3.50 (2H, br d), 3.65 (2H, br s), 3.79 (2H, t), 4.06 (2H, br d), 4.55 - 4.66 (1H, m), 4.91 (1H, br d), 6.41 (2H, s), 6.79 - 6.91 (2H, m), 6.97 (1H, s), 7.22 (1H, br t), 7.36 (1H, s), 7.42 (1H, s), 7.56 (1H, br s), 7.86 (1H, d), 7.93 (1H, d), 8.15 (1H, d), 10.36 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.6.

EXAMPLE 268:

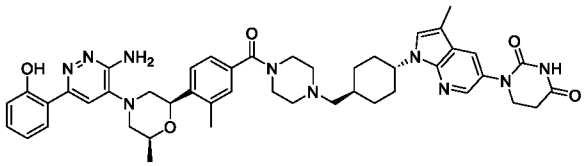
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2659] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.8 mg, 75%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.04 - 1.18 (2H, m), 1.24 (3H, d), 1.54 - 1.67 (1H, m), 1.71 - 2.00 (6H, m), 2.13 - 2.48 (12H, m), 2.50 - 2.56 (1H, m), 2.68 (1H, br t), 2.74 (2H, t), 3.07 - 3.20 (2H, m), 3.44 - 3.57 (2H, m), 3.59 - 3.73 (2H, m), 3.79 (2H, t), 4.03 - 4.17 (1H, m), 4.54 - 4.67 (1H, m), 4.87 (1H, br d), 6.44 (2H, br s), 6.83 - 6.91 (2H, m), 7.15 (1H, d), 7.19 - 7.25 (1H, m), 7.27 - 7.36 (2H, m), 7.42 (1H, s), 7.54 (1H, s), 7.85 (1H, d), 7.91 - 7.97 (1H, m), 8.15 (1H, d), 10.36 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.6.

EXAMPLE 269:

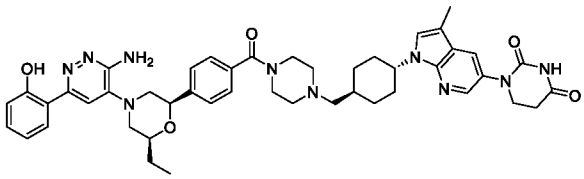
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2660] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 132e (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (26.6 mg, 74%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.12 (2H, q), 1.23 (3H, d), 1.55 - 1.66 (1H, m), 1.76 - 1.96 (6H, m), 2.18 (2H, br d), 2.24 (3H, s), 2.26 - 2.45 (7H, m), 2.50 - 2.56 (1H, m), 2.67 - 2.78 (3H, m), 3.31 - 3.42 (2H, m), 3.44 - 3.72 (4H, m), 3.79 (2H, t), 4.07 - 4.19 (1H, m), 4.54 - 4.66 (1H, m), 5.02 (1H, br d), 6.41 (2H, s), 6.80 - 6.92 (2H, m), 7.16 - 7.27 (3H, m), 7.42 (1H, s), 7.49 - 7.58 (2H, m), 7.86 (1H, d), 7.94 (1H, d), 8.15 (1H, d), 10.36 (1H, s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.6.

EXAMPLE 270:

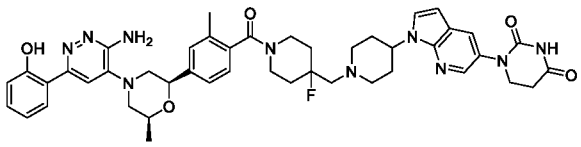
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2661] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 163f (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (28.0 mg, 78%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.00 (3H, t), 1.05 - 1.18 (2H, m), 1.56 - 1.68 (3H, m), 1.77 - 1.98 (6H, m), 2.18 (2H, br d), 2.24 (3H, s), 2.27 - 2.47 (4H, m), 2.55 (1H, br t), 2.66 (1H, t), 2.74 (2H, t), 3.31 - 3.71 (6H, m), 3.79 (2H, t), 3.87 - 3.95 (1H, m), 4.60 (1H, ddd), 4.86 - 5.01 (1H, m), 6.45 (2H, s), 6.82 - 6.91 (2H, m), 7.18 - 7.26 (1H, m), 7.35 - 7.44 (3H, m), 7.49 - 7.60 (3H, m), 7.86 (1H, d), 7.94 (1H, dd), 8.15 (1H, d), 10.36 (1H, s), 14.20 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 827.6.

EXAMPLE 271:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2662] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 166c (20 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (27.0 mg, 75%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.26 (3H, d), 1.50 - 1.91 (6H, m), 1.97 - 2.04 (1H, m), 2.05 - 2.16 (2H, m), 2.25 (3H, br s), 2.35 - 2.41 (2H, m), 2.52 - 2.73 (4H, m), 2.76 (2H, t), 3.01 - 3.27 (5H, m), 3.45 - 3.60 (2H, m), 3.81 (2H, t), 4.04 - 4.16 (1H, m), 4.20 - 4.45 (1H, m), 4.66 (1H, tt), 4.89 (1H, dd), 6.46 (2H, s), 6.50 (1H, d), 6.85 - 6.91 (2H, m), 7.17 - 7.28 (2H, m), 7.31 - 7.38 (2H, m), 7.56 (1H, s), 7.72 (1H, br d), 7.92 (1H, d), 7.96 (1H, dd), 10.39 (1H, s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 831.5.

EXAMPLE 272:

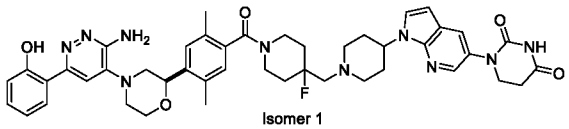
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

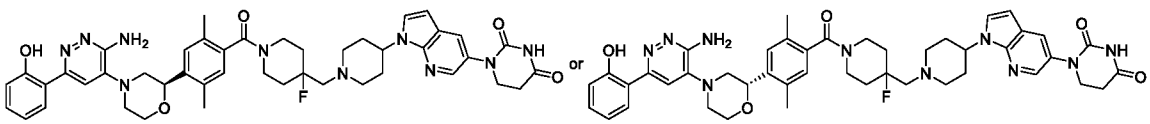
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 1



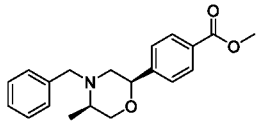
[2663] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (25 mg, 0.05 mmol) and Intermediate 166c (24 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (28.7 mg, 68%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.53 - 1.91 (5H, m), 1.97 - 2.15 (3H, m), 2.18 - 2.27 (3H, m), 2.32 - 2.44 (5H, m), 2.57 - 2.71 (2H, m), 2.76 (2H, t), 2.81 - 2.94 (2H, m), 2.98 - 3.27 (5H, m), 3.52 (2H, br d), 3.81 (2H, t), 4.03 - 4.13 (2H, m), 4.21 - 4.41 (1H, m), 4.66 (1H, br t), 4.93 (1H, br d), 6.43 (2H, s), 6.50 (1H, d), 6.82 - 6.91 (2H, m), 7.04 (1H, br s), 7.20 - 7.27 (1H, m), 7.39

(1H, s), 7.57 (1H, s), 7.72 (1H, br d), 7.92 (1H, d), 7.95 (1H, dd), 8.21 (1H, d), 10.39 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 831.6.

EXAMPLE 273

Intermediate 273a:

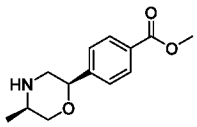
Methyl 4-((2*R*,5*R*)-4-benzyl-5-methylmorpholin-2-yl)benzoate



[2664] Methyl 4-(2-bromoacetyl)benzoate (15.56 g, 60.5 mmol) was slowly added to a suspension of (*R*)-2-(benzylamino)propan-1-ol (10.00 g, 60.5 mmol) and K_2CO_3 (8.36 g, 60.5 mmol) in MeCN (303 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes and at r.t. for 24 hours. The mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. DCE (70 mL), TFA (70 mL, 908 mmol) and triethylsilane (14.5 mL, 90.8 mmol) were added. The resulting mixture was stirred at 60 °C for 2 hours. More triethylsilane (4.83 mL, 30.3 mmol) was added and stirring was continued at 60 °C for 1.5 hours. The mixture was concentrated under reduced pressure. DCM (200 mL) and sat. aq. K_2CO_3/H_2O (1:3, 200 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (6.45 g, 33%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.10 (3H, d), 2.47 - 2.53 (1H, m), 2.54 - 2.59 (1H, m), 2.77 - 2.86 (1H, m), 3.57 (1H, d), 3.62 (1H, d), 3.71 (1H, dd), 3.80 - 3.87 (4H, m), 4.60 (1H, dd), 7.22 - 7.28 (1H, m), 7.31 - 7.39 (4H, m), 7.48 (2H, d), 7.92 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 326.2.

Intermediate 273b:

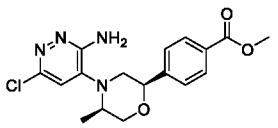
Methyl 4-((2*R*,5*R*)-5-methylmorpholin-2-yl)benzoate



[2665] MeOH (100 mL) was added to a mixture of Intermediate 273a (6.45 g, 19.8 mmol) and Pd/C (1.05 g, 0.99 mmol, 10 wt% palladium). Hydrogen was bubbled through the mixture for 10 minutes. The resulting suspension was stirred at 50 °C for 4 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure to give the title compound (4.28 g, 92%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.13 (3H, d), 2.28 - 2.47 (1H, m), 2.74 - 2.84 (1H, m), 2.85 - 2.97 (2H, m), 3.54 (1H, dd), 3.69 (1H, dd), 3.83 (3H, s), 4.48 (1H, dd), 7.50 (2H, d), 7.92 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 236.2.

Intermediate 273c:

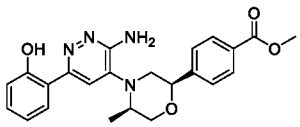
Methyl 4-((2*R*,5*R*)-4-(3-amino-6-chloropyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate



[2666] DMA (19.5 mL) and DIPEA (5.43 mL, 31.2 mmol) were added to a mixture of Intermediate 273b (2.93 g, 12.5 mmol), sodium methanesulfinate (1.27 g, 12.5 mmol) and 4-bromo-6-chloropyridazin-3-amine (6.50 g, 31.2 mmol). The resulting mixture was stirred at 130 °C for 17 hours. More sodium methanesulfinate (0.64 g, 6.23 mmol), 4-bromo-6-chloropyridazin-3-amine (2.60 g, 12.5 mmol) and DIPEA (2.18 mL, 12.5 mmol) were added. Stirring was continued at 130 °C for 21 hours. After cooling to r.t., the mixture was partially concentrated under reduced pressure. DCM/MeOH (10:1, 100 mL) and sat. aq. NH_4Cl/H_2O (1:1, 200 mL) were added and the phases were separated. The aqueous layer was extracted with DCM/MeOH (10:1, 2 x 100 mL). The combined organic layers were washed with sat. aq. K_2CO_3 (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 80% acetone in hexanes) gave the title compound (1.77 g, 39%) as a brown solid. ^{1}H NMR (DMSO-*d*6): δ 1.03 (3H, d), 3.05 (1H, dd), 3.22 - 3.29 (1H, m), 3.80 (1H, d), 3.85 (3H, s), 3.87 - 3.93 (1H, m), 4.20 (1H, dd), 4.70 (1H, dd), 6.20 (2H, s), 6.91 (1H, s), 7.60 (2H, d), 7.96 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 363.2.

Intermediate 273d:

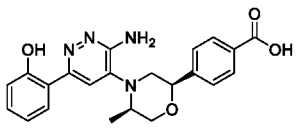
Methyl 4-((2*R*,5*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate



[2667] 1,4-Dioxane (44 mL) and water (4.9 mL) were added to a mixture of Intermediate 273c (1.76 g, 4.85 mmol), CPhos Pd G3 (156 mg, 0.19 mmol), CPhos (85 mg, 0.19 mmol), (2-hydroxyphenyl)boronic acid (1.00 g, 7.28 mmol) and K_2CO_3 (2.01 g, 14.6 mmol). The flask was evacuated and backfilled with nitrogen (5x). The mixture was stirred at 80 °C for 6 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM/IPA (3:1, 40 mL) and sat. aq. K_2CO_3/H_2O (3:1, 40 mL) were added. The resulting biphasic mixture was stirred vigorously for 30 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (30 mL) and sat. aq. NH_4Cl (30 mL). The aq. NH_4Cl layer was extracted with DCM (30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0 to 80% acetone in hexanes; 2nd purification: 0 to 80% EtOAc in hexanes) gave the title compound (1.00 g, 49%) as a yellow solid and recovered Intermediate 273c (0.55 g, 31%) as a brown solid. Intermediate 273d: ^{1}H NMR (DMSO-*d*6): δ 1.06 (3H, d), 3.11 (1H, dd), 3.48 (1H, t), 3.80 - 3.88 (4H, m), 3.94 (1H, br d), 4.29 (1H, dd), 4.75 (1H, dd), 6.36 (2H, s), 6.81 (1H, t), 6.86 (1H, dd), 7.16 - 7.23 (1H, m), 7.49 (1H, s), 7.64 (2H, d), 7.91 (1H, dd), 7.99 (2H, d), 14.24 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 421.1.

Intermediate 273e:

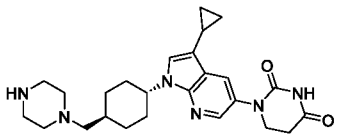
4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoic acid



[2668] 3 M aq. NaOH (3.62 mL, 10.9 mmol) was added to a solution of Intermediate 273d (1.52 g, 3.62 mmol) in EtOH (10.9 mL). The resulting mixture was stirred at 60 °C for 2 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. 6 M aq. HCl (1.81 mL) was added. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (1.41 g, 96%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 1.21 (3H, br d), 3.36 (1H, br d), 3.42 - 3.48 (1H, m), 3.87 (1H, d), 4.09 (1H, br s), 4.28 (1H, br d), 4.78 (1H, dd), 6.94 (1H, t), 7.04 (1H, br d), 7.14 - 7.45 (3H, m), 7.54 (1H, s), 7.57 - 7.68 (3H, m), 7.97 (2H, d), 11.28 - 14.94 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 407.3.

Intermediate 273f:

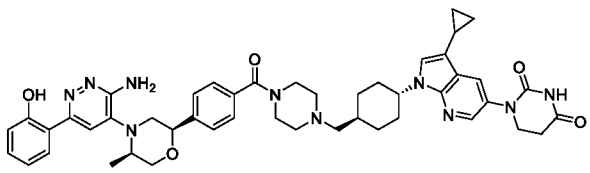
1-(3-Cyclopropyl-1-((1*r*,4*r*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2669] TFA (0.84 mL, 10.9 mmol) was added to a solution of Intermediate 120c (500 mg, 0.91 mmol) in DCM (2.5 mL). The resulting mixture was stirred at r.t. for 80 minutes and concentrated under reduced pressure. The residue was dissolved in water (20 mL). DCM/IPA (2:1, 30 mL) and sat. aq. K_2CO_3 (20 mL) were added. The phases were separated. The organic layers was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (430 mg, 105%) as a brown solid which contained ~8 wt% *i*PrOH. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.66 (2H, m), 0.83 - 0.88 (2H, m), 1.06 - 1.14 (2H, m), 1.61 (1H, ddd), 1.79 - 1.96 (8H, m), 2.11 (2H, d), 2.27 (4H, br s), 2.64 - 2.76 (6H, m), 3.79 (2H, t), 4.53 - 4.67 (1H, m), 7.38 (1H, s), 7.91 (1H, d), 8.15 (1H, d), 10.06 - 10.66 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 451.4.

EXAMPLE 273:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



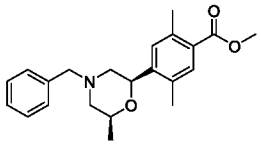
[2670] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (8 mg, 0.02 mmol) and Intermediate 273f (9 mg, 0.02 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (8.1 mg, 49%) as an

amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.56 - 0.68 (2H, m), 0.79 - 0.89 (2H, m), 1.01 - 1.17 (5H, m), 1.62 (1H, br s), 1.73 - 2.00 (7H, m), 2.19 (2H, br d), 2.25 - 2.48 (4H, m), 2.75 (2H, t), 3.10 (1H, br d), 3.34 - 3.72 (5H, m), 3.77 - 3.86 (3H, m), 3.94 (1H, br d), 4.28 (1H, br d), 4.55 - 4.65 (1H, m), 4.70 (1H, dd), 6.36 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.18 - 7.24 (1H, m), 7.38 (1H, s), 7.41 (2H, d), 7.50 (1H, s), 7.56 (2H, d), 7.90 - 7.97 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 839.5.

EXAMPLE 274

Intermediate 274a:

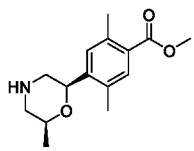
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2,5-dimethylbenzoate



[2671] (*S*)-1-(Benzylamino)propan-2-ol (3.40 g, 20.6 mmol) in MeCN (20 mL) was added dropwise to a suspension of Intermediate 228a (5.86 g, 20.6 mmol) and K_2CO_3 (3.12 g, 22.6 mmol) in MeCN at 0 °C. The resulting mixture was stirred for 15 hours gradually increasing the temperature to r.t. The mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. DCE (35 mL) and TFA (35 mL) were added and the mixture was heated to 60 °C. Methyl(phenyl)silane (4.23 mL, 30.8 mmol) was added. The resulting mixture weas stirred at 60 °C for 70 minutes. More methyl(phenyl)silane (1.40 mL, 10.2 mmol) was added and stirring was continued at 60 °C for 30 minutes. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM (50 mL) and sat. aq. K_2CO_3/H_2O (1:2, 60 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.11 g, 15%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 1.12 (3H, d), 1.76 - 1.86 (2H, m), 2.20 (3H, s), 2.45 (3H, s), 2.71 - 2.83 (2H, m), 3.44 - 3.54 (2H, m), 3.75 - 3.82 (4H, m), 4.69 (1H, dd), 7.21 - 7.25 (1H, m), 7.27 - 7.31 (5H, m), 7.58 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 354.1.

Intermediate 274b:

Methyl 2,5-dimethyl-4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate

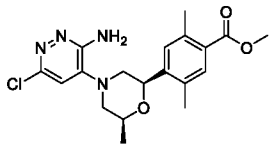


[2672] MeOH (8.7 mL) was added to a mixture of Intermediate 274a (1.08 g, 3.04 mmol) and Pd/C (0.324 g, 0.30 mmol, 10 wt% palladium). Hydrogen was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 60 °C under an atmosphere of hydrogen for 4 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced

pressure to give the title compound as a yellow oil. The product was used for the next step without further purification and quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 264.1.

Intermediate 274c:

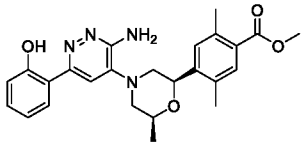
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoate



[2673] 4-Bromo-6-chloropyridazin-3-amine (825 mg, 3.96 mmol) and DIPEA (0.957 mL, 5.48 mmol) were added to a solution of Intermediate 273b (802 mg, 3.05 mmol) in butan-1-ol (5.1 mL). The resulting mixture was stirred at 115 °C for 14 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Sat. aq. NH_4Cl (30 mL) was added and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 43% acetone in hexanes) gave the title compound (913 mg, 77%) as a brown solid. ^1H NMR (DMSO-*d*6): δ 1.20 (3H, d), 2.33 (3H, s), 2.41 - 2.48 (4H, m), 2.55 (1H, dd), 3.38 - 3.49 (2H, m), 3.80 (3H, s), 4.01 - 4.10 (1H, m), 4.95 (1H, dd), 6.25 (2H, s), 6.95 (1H, s), 7.36 (1H, s), 7.62 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 391.1.

Intermediate 274d:

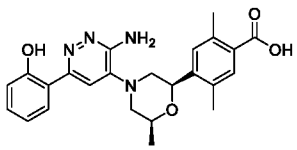
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoate



[2674] 1,4-Dioxane (8.4 mL) and water (0.84 mL) were added to a mixture of Intermediate 274c (906 mg, 2.32 mmol), (2-hydroxyphenyl)boronic acid (448 mg, 3.25 mmol), K_2CO_3 (801 mg, 5.79 mmol) and XPhos Pd G3 (294 mg, 0.35 mmol). The flask was evacuated and backfilled with nitrogen (3x). The mixture was stirred at 100 °C for 50 minutes. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM/IPA (3:1, 10 mL) and sat. aq. K_2CO_3 (10 mL) were added. The resulting biphasic mixture was stirred vigorously for 30 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 10 mL) and sat. aq. NH_4Cl (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% acetone in hexanes) gave the title compound (786 mg, 76%) as a yellow solid. ^1H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.36 (3H, s), 2.47 - 2.50 (3H, m), 2.51 - 2.57 (1H, m), 2.68 (1H, dd), 3.51 (2H, br d), 3.81 (3H, s), 4.08 - 4.20 (1H, m), 5.02 (1H, br d), 6.41 (2H, s), 6.79 - 6.91 (2H, m), 7.17 - 7.26 (1H, m), 7.41 (1H, s), 7.54 (1H, s), 7.64 (1H, s), 7.92 (1H, dd), 14.18 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 449.1.

Intermediate 274e:

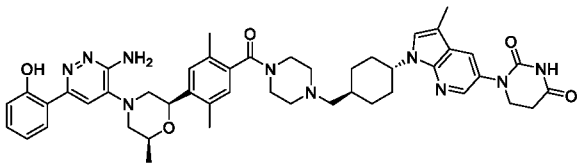
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoic acid



[2675] 3 M aq. NaOH (2.32 mL, 6.97 mmol) was added to a solution of Intermediate 274d (781 mg, 1.74 mmol) in EtOH (7.0 mL). The resulting mixture was stirred at 60 °C for 60 minutes. After cooling to r.t., the mixture was partially concentrated under reduced pressure. 1 M HCl (6.6 mL) was added. A precipitate formed which collected by filtration, washed with water, and dried *in vacuo* to give the title compound (604 mg, 80%) as a yellowish solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.35 (3H, s), 2.47 - 2.57 (4H, m), 2.69 (1H, dd), 3.47 - 3.56 (2H, m), 4.08 - 4.17 (1H, m), 5.00 (1H, dd), 6.42 (2H, s), 6.79 - 6.91 (2H, m), 7.16 - 7.27 (1H, m), 7.38 (1H, s), 7.54 (1H, s), 7.64 (1H, s), 7.92 (1H, dd), 12.45 - 14.27 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 435.2.

EXAMPLE 274:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2676] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20 mg, 0.05 mmol) and Intermediate 259b (18 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.7 mg, 73%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, q), 1.23 (3H, d), 1.54 - 1.67 (1H, m), 1.75 - 1.97 (6H, m), 2.14 - 2.46 (15H, m), 2.51 - 2.56 (1H, m), 2.74 (3H, t), 3.09 - 3.19 (2H, m), 3.51 (2H, br d), 3.65 (2H, br s), 3.79 (2H, t), 4.06 - 4.18 (1H, m), 4.55 - 4.66 (1H, m), 4.97 (1H, br d), 6.40 (2H, s), 6.80 - 6.91 (2H, m), 6.96 (1H, s), 7.22 (1H, br t), 7.34 (1H, s), 7.42 (1H, s), 7.55 (1H, br s), 7.85 (1H, d), 7.94 (1H, d), 8.15 (1H, d), 10.36 (1H, s), 14.19 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 841.6.

EXAMPLE 275:

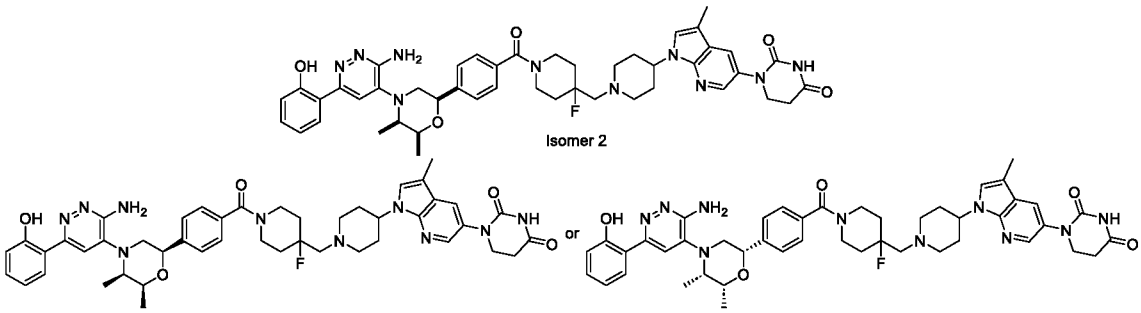
1-(1-(1-((1-(4-((2*R**,5*R**,6*S**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

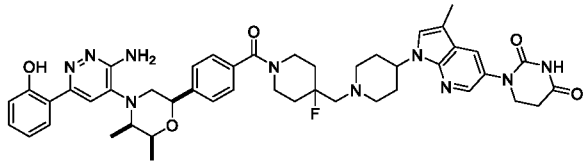
1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2677] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (28.6 mg, 78%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.94 (3H, d), 1.17 (3H, d), 1.65 - 2.14 (8H, m), 2.25 (3H, s), 2.38 (2H, br t), 2.57 - 2.71 (2H, m), 2.76 (2H, t), 2.96 - 3.31 (5H, m), 3.35 - 3.64 (2H, m), 3.81 (3H, br t), 4.15 - 4.36 (1H, m), 4.41 (1H, qd), 4.61 (1H, tt), 4.79 (1H, dd), 6.36 (2H, s), 6.80 - 6.86 (1H, m), 6.86 - 6.91 (1H, m), 7.19 - 7.26 (1H, m), 7.46 (2H, d), 7.51 (2H, d), 7.58 (2H, d), 7.88 (1H, d), 7.95 (1H, d), 8.18 (1H, d), 10.38 (1H, s), 14.16 - 14.38 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 276:

rac-1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

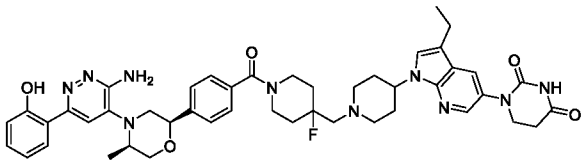


[2678] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 266a (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (33.5 mg, 92%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.93 (3H, d), 1.15 (3H, d), 1.63 - 2.12 (8H, m), 2.24 (3H, s), 2.36 (2H, br t), 2.56 - 2.68 (2H, m), 2.74 (2H, t), 3.00 - 3.29 (5H, m), 3.37 - 3.60 (2H, m), 3.79 (3H, br t), 4.26 (1H, br s), 4.36 - 4.44 (1H, m), 4.54 - 4.65 (1H, m), 4.77 (1H, dd), 6.34

(2H, s), 6.82 (1H, t), 6.86 (1H, d), 7.16 - 7.24 (1H, m), 7.44 (2H, d), 7.49 (2H, d), 7.56 (2H, d), 7.87 (1H, d), 7.91 - 7.97 (1H, m), 8.16 (1H, d), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 277:

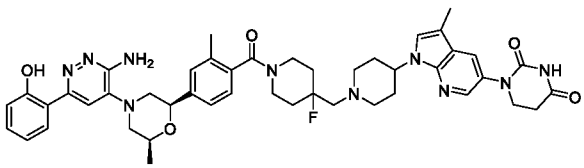
1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2679] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20 mg, 0.05 mmol) and Intermediate 149f (36 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (27.8 mg, 73%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.07 (3H, d), 1.25 (3H, t), 1.61 - 2.13 (8H, m), 2.36 (2H, br t), 2.57 - 2.71 (4H, m), 2.74 (2H, t), 2.96 - 3.29 (5H, m), 3.37 - 3.63 (2H, m), 3.76 - 3.87 (3H, m), 3.90 - 3.99 (1H, m), 4.28 (2H, br d), 4.60 (1H, tt), 4.70 (1H, dd), 6.36 (2H, s), 6.79 - 6.84 (1H, m), 6.86 (1H, dd), 7.17 - 7.24 (1H, m), 7.42 - 7.47 (2H, m), 7.49 (2H, d), 7.57 (2H, d), 7.90 (1H, d), 7.93 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 278:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2680] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (27.4 mg, 75%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 1.46 - 1.87 (6H, m), 1.94 - 2.10 (3H, m), 2.19 - 2.29 (6H, m), 2.35 (2H, br t), 2.50 - 2.64 (3H, m), 2.68 (1H, br t), 2.74 (2H, t), 3.02 (2H, br s), 3.19 (2H, br d), 3.43 - 3.60 (2H, m), 3.79 (2H, t), 4.01 - 4.15 (1H, m), 4.20 - 4.43 (1H, m), 4.52 - 4.66 (1H, m), 4.84 - 4.91 (1H, m), 6.45 (2H, s), 6.83 - 6.89 (2H, m), 7.22 (2H, td), 7.28 - 7.37 (2H, m), 7.46 (1H, s), 7.54 (1H, s), 7.86 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.36 (1H, br s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 845.6.

EXAMPLE 279:

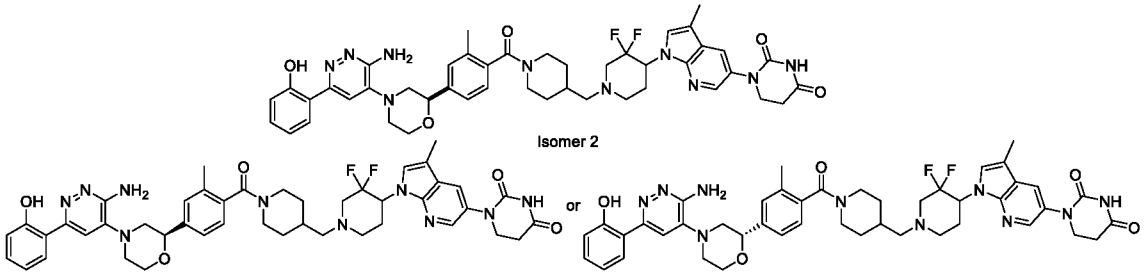
1-(1-(1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-(1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2681] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 219d (20 mg, 0.05 mmol) and Intermediate 220g (21 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (19.7 mg, 52%) as an amorphous white solid and mixture of diastereomers, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.90 - 1.19 (2H, m), 1.58 - 1.73 (1H, m), 1.81 - 1.98 (3H, m), 2.17 - 2.43 (10H, m), 2.54 - 2.65 (1H, m), 2.72 - 2.84 (4H, m), 2.89 (1H, td), 2.96 - 3.09 (2H, m), 3.21 - 3.38 (2H, m), 3.45 - 3.62 (2H, m), 3.82 (2H, t), 4.00 - 4.14 (2H, m), 4.55 (1H, br d), 4.83 (1H, br d), 5.13 - 5.32 (1H, m), 6.47 (2H, s), 6.83 - 6.93 (2H, m), 7.16 (1H, br d), 7.22 - 7.27 (1H, m), 7.28 - 7.40 (2H, m), 7.48 (1H, br s), 7.57 (1H, s), 7.89 - 7.99 (2H, m), 8.20 (1H, d), 10.40 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 849.6.

EXAMPLE 280

Intermediate 280a:

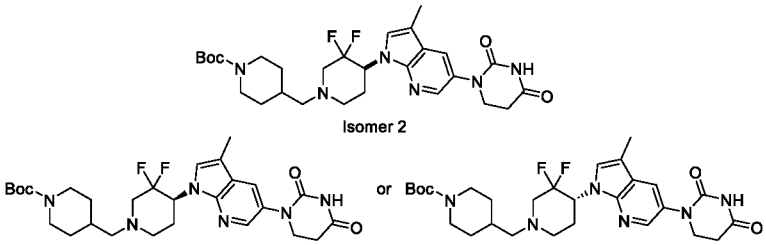
tert-Butyl (*S**)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate (Isomer 2)

((*absolute configuration not yet confirmed))

tert-Butyl (*S*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl (*R*)-4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2682] Prepared using the same method as for Intermediate 227a to give the title compound that eluted second from the column (198 mg, 37%, 93% ee) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 561.6.

Intermediate 280b:

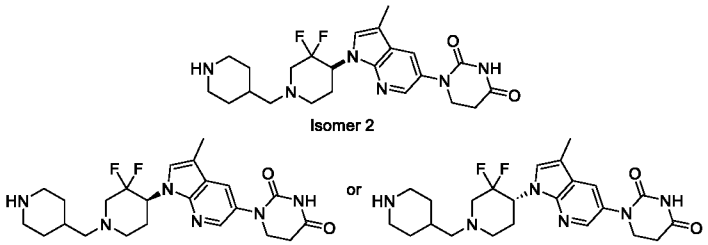
(*S**)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*S*)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*R*)-1-(1-(3,3-Difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2683] 2 M aq. H_2SO_4 (3.00 mL, 6.00 mmol) was added to a solution of Intermediate 280a (198 mg, 0.35 mmol) in THF (3.00 mL). The resulting mixture was stirred at 50 °C for 60 minutes. The mixture was diluted with DCM/IPA (3:1, 20 mL). Sat. aq. K_2CO_3 (20 mL) was added and the phases were separated. The aqueous layer was extracted with DCM/IPA (3:1, 2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (162 mg, 100%) as an off-white solid.

EXAMPLE 280:

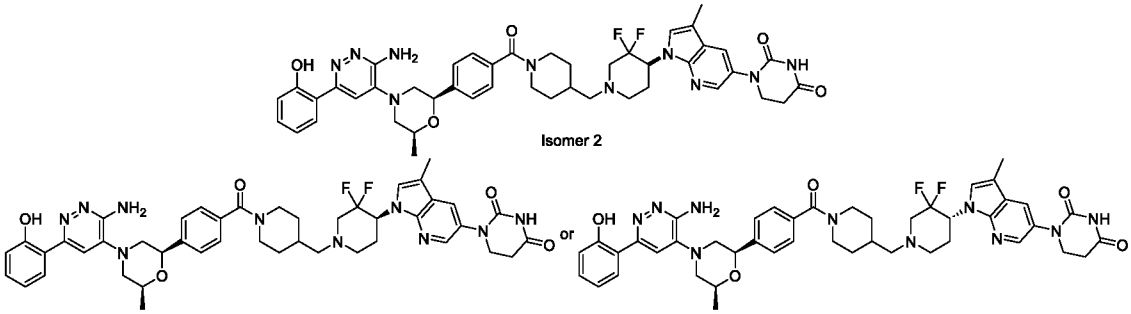
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*relative configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2684] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 280b (21 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (31.1 mg, 82%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.11 (2H, br d), 1.27 (3H, d), 1.62 - 1.94 (4H, m), 2.27 (3H, d), 2.32 - 2.45 (4H, m), 2.53 - 2.64 (2H, m), 2.66 - 2.72 (1H, m), 2.75 - 2.89 (3H, m), 3.02 (2H, br d), 3.25 (1H, br t), 3.49 - 3.70 (3H, m), 3.83 (2H, t), 4.07 - 4.18 (1H, m), 4.48 (1H, br d), 4.95 (1H, dd), 5.15 - 5.30 (1H, m), 6.48 (2H, s), 6.83 - 6.92 (2H, m), 7.21 - 7.27 (1H, m), 7.40 (2H, d), 7.49 (1H, br s), 7.53 (2H, d), 7.57 (1H, s), 7.91 - 7.98 (2H, m), 8.21 (1H, d), 10.40 (1H, br s), 14.22 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 849.5.

EXAMPLE 281:

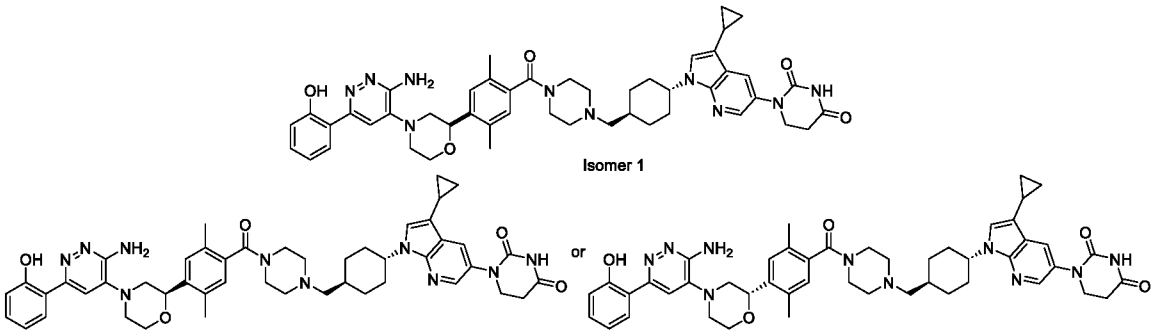
1-(1-((1*R*,4*r*)-4-((4-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

1-(1-((1*R*,4*r*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

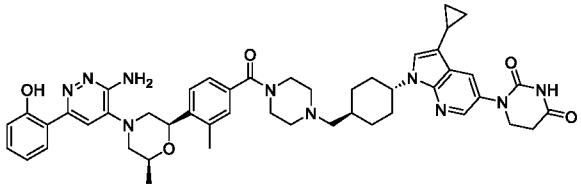
1-(1-((1*R*,4*r*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2685] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (20 mg, 0.05 mmol) and Intermediate 273f (21 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (12.8 mg, 31%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.68 (2H, m), 0.78 - 0.87 (2H, m), 1.01 - 1.16 (2H, m), 1.61 (1H, br d), 1.74 - 1.96 (7H, m), 2.13 - 2.45 (12H, m), 2.75 (2H, t), 2.79 - 2.93 (2H, m), 3.14 (2H, br s), 3.50 (2H, br d), 3.65 (2H, br s), 3.80 (2H, t), 4.06 (2H, br d), 4.54 - 4.64 (1H, m), 4.91 (1H, br d), 6.40 (2H, s), 6.80 - 6.90 (2H, m), 6.97 (1H, s), 7.22 (1H, br t), 7.37 (2H, d), 7.55 (1H, br s), 7.87 - 7.98 (2H, m), 8.15 (1H, d), 10.35 (1H, s), 13.81 - 14.57 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 853.6.

EXAMPLE 282:

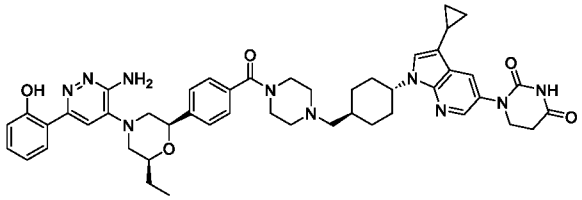
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2686] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 132e (20 mg, 0.05 mmol) and Intermediate 273f (21 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (22.3 mg, 55%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.68 (2H, m), 0.83 - 0.90 (2H, m), 1.06 - 1.18 (2H, m), 1.25 (3H, d), 1.63 (1H, br s), 1.81 - 1.98 (7H, m), 2.20 (2H, br d), 2.26 - 2.45 (7H, m), 2.55 (1H, br d), 2.70 - 2.82 (3H, m), 3.26 - 3.75 (6H, m), 3.82 (2H, t), 4.12 - 4.20 (1H, m), 4.57 - 4.66 (1H, m), 4.94 - 5.11 (1H, m), 6.42 (2H, s), 6.84 - 6.94 (2H, m), 7.19 - 7.29 (3H, m), 7.40 (1H, s), 7.53 - 7.59 (2H, m), 7.91 - 7.99 (2H, m), 8.17 (1H, d), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 853.6.

EXAMPLE 283:

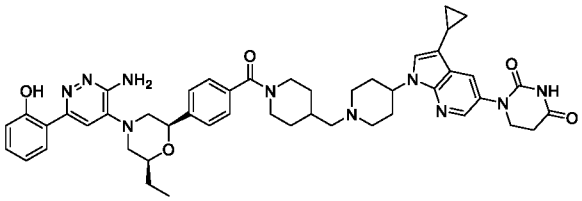
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2687] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 163f (20 mg, 0.05 mmol) and Intermediate 273f (21 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.7 mg, 63%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.59 - 0.68 (2H, m), 0.82 - 0.86 (2H, m), 1.00 (3H, t), 1.06 - 1.16 (2H, m), 1.60 (3H, quin), 1.78 - 1.95 (7H, m), 2.18 (2H, br d), 2.23 - 2.46 (4H, m), 2.56 (1H, br t), 2.62 - 2.70 (1H, m), 2.75 (2H, t), 3.31 - 3.70 (6H, m), 3.80 (2H, t), 3.87 - 3.94 (1H, m), 4.53 - 4.66 (1H, m), 4.93 (1H, br d), 6.45 (2H, s), 6.80 - 6.90 (2H, m), 7.17 - 7.25 (1H, m), 7.36 - 7.42 (3H, m), 7.52 (2H, d), 7.56 (1H, s), 7.90 - 7.96 (2H, m), 8.15 (1H, d), 10.35 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 853.6.

EXAMPLE 284:

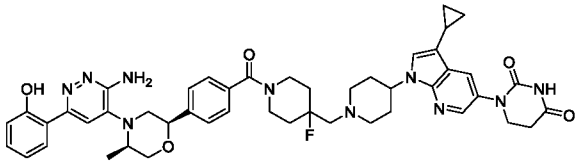
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2688] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 163f (20 mg, 0.05 mmol) and Intermediate 71c (21 mg, 0.04 mmol). Purification by RPC (elution gradient: 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (24.3 mg, 66%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.60 - 0.67 (2H, m), 0.79 - 0.87 (2H, m), 1.00 (3H, t), 1.03 - 1.17 (2H, m), 1.55 - 1.74 (3H, m), 1.75 - 1.87 (4H, m), 1.87 - 1.93 (1H, m), 1.97 - 2.14 (4H, m), 2.21 (2H, br s), 2.52 - 2.60 (1H, m), 2.61 - 2.69 (1H, m), 2.70 - 2.86 (3H, m), 2.89 - 3.11 (3H, m), 3.50 (1H, br d), 3.58 (2H, br d), 3.80 (2H, t), 3.85 - 3.93 (1H, m), 4.37 - 4.53 (1H, m), 4.54 - 4.63 (1H, m), 4.93 (1H, dd), 6.46 (2H, s), 6.81 - 6.91 (2H, m), 7.16 - 7.27 (1H, m), 7.38 (2H, d), 7.43 (1H, s), 7.51 (2H, d), 7.56 (1H, s), 7.90 - 7.97 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 853.7.

EXAMPLE 285:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2689] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20 mg, 0.05 mmol) and Intermediate 20g (25 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.3 mg, 69%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.62 - 0.68 (2H, m), 0.80 - 0.87 (2H, m), 1.07 (3H, d), 1.61 - 2.11 (9H, m), 2.35 (2H, br t), 2.56 - 2.67 (2H, m), 2.75 (2H, t), 2.97 - 3.29 (5H, m), 3.41 - 3.62 (2H, m), 3.76 - 3.87 (3H, m), 3.94 (1H, br d), 4.12 - 4.40 (2H, m), 4.58 (1H, tt), 4.70 (1H, dd), 6.36 (2H, s), 6.80 - 6.84 (1H, m), 6.86 (1H, dd), 7.16 - 7.25 (1H, m), 7.41 - 7.46 (3H, m), 7.50 (1H, s), 7.57 (2H, d), 7.89 - 7.97 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 14.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 857.6.

EXAMPLE 286:

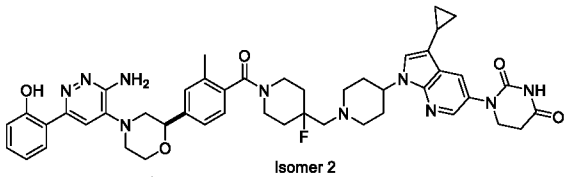
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

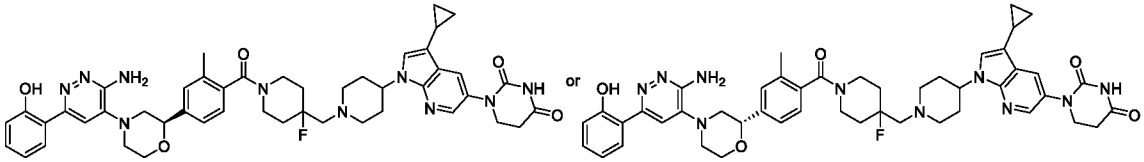
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Isomer 2



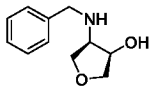
[2690] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 219d (20 mg, 0.05 mmol) and Intermediate 20g (25 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid

in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (21.4 mg, 56%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.59 - 0.70 (2H, m), 0.79 - 0.89 (2H, m), 1.51 - 1.86 (5H, m), 1.89 - 1.95 (1H, m), 1.96 - 2.12 (3H, m), 2.19 - 2.40 (5H, m), 2.57 - 2.69 (2H, m), 2.73 - 2.84 (3H, m), 2.85 - 2.94 (1H, m), 2.99 - 3.27 (5H, m), 3.43 - 3.60 (2H, m), 3.82 (2H, t), 4.00 - 4.14 (2H, m), 4.21 - 4.44 (1H, m), 4.54 - 4.65 (1H, m), 4.83 (1H, br d), 6.47 (2H, s), 6.84 - 6.92 (2H, m), 7.18 - 7.27 (2H, m), 7.33 (1H, br d), 7.37 (1H, s), 7.44 (1H, s), 7.57 (1H, s), 7.92 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 857.6.

EXAMPLE 287

Intermediate 287a:

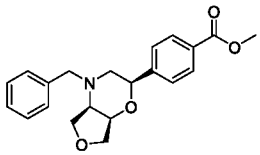
(3*R*,4*R*)-4-(Benzylamino)tetrahydrofuran-3-ol



[2691] Benzaldehyde (1.10 mL, 10.8 mmol) was added dropwise to a suspension of (3*R*,4*R*)-4-aminotetrahydrofuran-3-ol (926 mg, 8.98 mmol) and $MgSO_4$ (540 mg, 4.49 mmol) in THF (20.2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 5 hours and filtered. The filtrate was concentrated under reduced pressure. EtOH (13.5 mL) was added and the mixture was cooled to 0 °C. $NaBH_4$ (340 mg, 8.98 mmol) was added. The resulting mixture was stirred for 15 hours gradually increasing the temperature to r.t. The mixture was concentrated under reduced pressure. EtOAc (20 mL) was added. The mixture was extracted with 1 M aq. HCl (3 x 20 mL). The combined aqueous layers were basified with sat. aq. K_2CO_3 (40 mL). The mixture was extracted with 5% MeOH in DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.42 g, 82%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 2.13 (1H, br s), 3.11 (1H, td), 3.27 - 3.35 (1H, m), 3.59 (1H, dd), 3.63 - 3.69 (1H, m), 3.71 - 3.81 (3H, m), 4.10 (1H, br s), 4.95 (1H, br s), 7.20 - 7.25 (1H, m), 7.28 - 7.35 (4H, m); *m/z* (ES^+) $[M+H]^+$ = 194.1.

Intermediate 287b:

Methyl 4-((2*R*,4a*R*,7a*R*)-4-Benzylhexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate

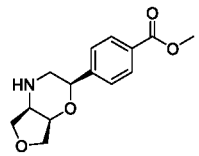


[2692] Intermediate 287a (1.41 g, 7.30 mmol) in MeCN (9.1 mL) was added dropwise to a suspension of methyl 4-(2-bromoacetyl)benzoate (1.88 g, 7.30 mmol) and K_2CO_3 (1.11 g, 8.03 mmol) in MeCN (27.4 mL) at 0 °C. The resulting mixture was stirred for 15 hours gradually increasing the temperature to r.t. The mixture was filtered. The solids were washed with DCM (2 x 20 mL). The combined filtrates were concentrated under reduced pressure. DCE (11.3 mL) and TFA (11.3 mL) were added and the mixture was heated to 60 °C. Methyl(phenyl)silane (1.51 mL, 11.0 mmol) was added. The resulting mixture was stirred at 60 °C for 1 hour. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM (50

mL) and sat. aq. K_2CO_3/H_2O (1:2, 90 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0 to 50% acetone in hexanes; 2nd purification: 0 to 40% EtOAc in hexanes) gave the title compound (493 mg, 19%) as a yellow oil. ^{1}H NMR (DMSO-*d*6): δ 2.51 - 2.58 (1H, m), 2.66 (1H, dd), 3.33 - 3.40 (1H, m), 3.61 - 3.75 (4H, m), 3.83 (3H, s), 3.87 (1H, dd), 3.95 - 3.99 (1H, m), 4.22 (1H, t), 4.69 (1H, dd), 7.24 - 7.28 (1H, m), 7.31 - 7.37 (4H, m), 7.49 (2H, d), 7.92 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 354.0.

Intermediate 287c:

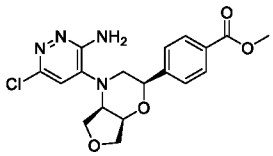
Methyl 4-((2*R*,4a*R*,7a*R*)-hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2693] MeOH (13.4 mL) was added to a mixture of Intermediate 287b (475 mg, 1.34 mmol) and Pd/C (143 mg, 0.13 mmol, 10 wt% palladium) under nitrogen. Hydrogen was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 60 °C under an atmosphere of hydrogen for 65 minutes. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 264.2.

Intermediate 287d:

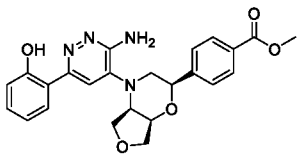
Methyl 4-((2*R*,4a*R*,7a*R*)-4-(3-amino-6-chloropyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoate



[2694] DMSO (2.7 mL) and DIPEA (0.70 mL, 4.03 mmol) were added to a mixture of Intermediate 287c (354 mg, 1.34 mmol), 4-bromo-6-chloropyridazin-3-amine (561 mg, 2.69 mmol) and sodium propane-2-sulfinate (87 mg, 0.67 mmol). The resulting mixture was stirred at 130 °C for 20 hours. After cooling to r.t., the mixture was diluted with EtOAc (50 mL), washed with brine (50 mL) and sat. aq. NH_4Cl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (177 mg, 34%) as a brown solid and 6:1 mixture with the corresponding *N*-methylmorpholine. ^{1}H NMR (DMSO-*d*6): δ 3.21 (1H, dd), 3.30 - 3.37 (1H, m), 3.54 (1H, t), 3.83 - 3.91 (5H, m), 3.98 (1H, dd), 4.30 - 4.38 (1H, m), 4.54 (1H, t), 4.80 (1H, br d), 6.36 (2H, s), 7.09 (1H, s), 7.61 (2H, d), 7.98 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 391.2.

Intermediate 287e:

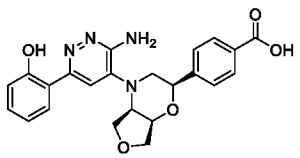
Methyl 4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2695] 1,4-Dioxane (3 mL) and water (0.3 mL) were added to a mixture of Intermediate 287d (170 mg, 0.43 mmol), (2-hydroxyphenyl)boronic acid (78 mg, 0.57 mmol), K_2CO_3 (150 mg, 1.09 mmol) and XPhos Pd G3 (55 mg, 0.07 mmol) under nitrogen. The flask was evacuated and backfilled with nitrogen (3x). The resulting mixture was stirred at 100 °C for 70 minutes. After cooling to r.t., the mixture was diluted with DCM/IPA (3:1, 10 mL) and sat. aq. K_2CO_3 (10 mL). The resulting biphasic mixture was stirred vigorously for 30 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (10 mL) and sat. aq. NH_4Cl (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (122 mg, 62%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 3.24 (1H, dd), 3.45 - 3.58 (2H, m), 3.83 - 3.89 (4H, m), 3.90 - 3.96 (1H, m), 4.00 (1H, dd), 4.38 - 4.46 (1H, m), 4.61 (1H, t), 4.84 (1H, br d), 6.53 (2H, br s), 6.80 - 6.92 (2H, m), 7.16 - 7.27 (1H, m), 7.55 - 7.68 (3H, m), 7.93 (1H, dd), 7.99 (2H, d), 14.18 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 449.3.

Intermediate 287f:

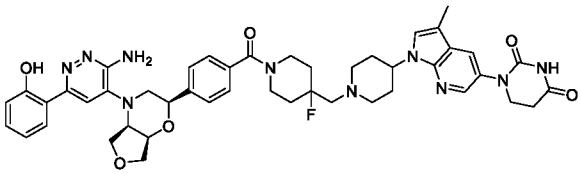
4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoic acid



[2696] 3 M aq. NaOH (0.34 mL, 1.01 mmol) was added to a solution of Intermediate 287e (113 mg, 0.25 mmol) in EtOH (4 mL). The resulting mixture was stirred at 60 °C for 1 hour. After cooling to r.t., the mixture was acidified to pH ~ 4 and extracted with DCM/IPA (3:1, 3 x 12 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (102 mg, 93%) as an off-white solid. ^{1}H NMR (DMSO-*d*6): δ 3.23 (1H, br d), 3.46 - 3.57 (2H, m), 3.86 (1H, d), 3.93 (1H, t), 4.00 (1H, dd), 4.42 (1H, td), 4.61 (1H, t), 4.83 (1H, br d), 6.53 (2H, s), 6.79 - 6.90 (2H, m), 7.22 (1H, t), 7.55 - 7.65 (3H, m), 7.93 (1H, d), 7.96 (2H, d), 12.24 - 14.92 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 435.2.

EXAMPLE 287:

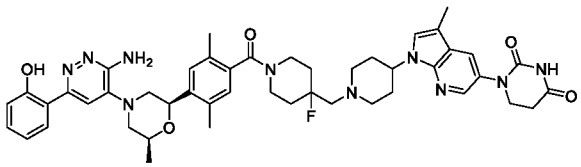
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2697] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (31.0 mg, 86%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.59 - 2.11 (8H, m), 2.23 (3H, s), 2.35 (2H, br t), 2.56 - 2.68 (2H, m), 2.74 (2H, t), 2.98 - 3.18 (3H, m), 3.20 - 3.31 (2H, m), 3.41 - 3.59 (3H, m), 3.79 (2H, t), 3.85 (1H, d), 3.94 (1H, br t), 4.01 (1H, dd), 4.27 (1H, br s), 4.42 (1H, td), 4.55 - 4.64 (2H, m), 4.79 (1H, dd), 6.52 (2H, s), 6.81 - 6.90 (2H, m), 7.19 - 7.24 (1H, m), 7.44 (2H, d), 7.48 (1H, s), 7.55 (2H, d), 7.63 (1H, s), 7.87 (1H, d), 7.91 - 7.96 (1H, m), 8.16 (1H, d), 10.37 (1H, s), 14.18 (1H, br s).; *m/z* (ES^+) $[M+H]^+$ = 859.5.

EXAMPLE 288:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

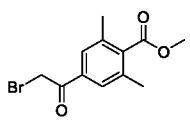


[2698] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (30.3 mg, 84%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 1.51 - 1.85 (5H, m), 1.95 - 2.08 (3H, m), 2.15 - 2.25 (6H, m), 2.29 - 2.39 (5H, m), 2.50 - 2.66 (3H, m), 2.74 (3H, t), 2.95 - 3.25 (5H, m), 3.52 (2H, br d), 3.79 (2H, t), 4.08 - 4.18 (1H, m), 4.20 - 4.44 (1H, m), 4.51 - 4.65 (1H, m), 4.98 (1H, br d), 6.40 (2H, s), 6.81 - 6.90 (2H, m), 6.95 - 7.06 (1H, m), 7.19 - 7.25 (1H, m), 7.35 (1H, s), 7.46 (1H, s), 7.55 (1H, s), 7.86 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.19 (1H, br s).; *m/z* (ES^+) $[M+H]^+$ = 859.6.

EXAMPLE 289

Intermediate 289a:

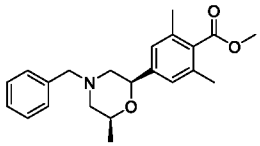
Methyl 4-(2-bromoacetyl)-2,6-dimethylbenzoate



[2699] Prepared in an analogous method to Intermediate 49a using methyl 4-bromo-2,6-dimethylbenzoate (6.00 g, 24.7 mmol) to give the title compound (5.90 g, 84%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.37 (6H, s), 3.95 (3H, s), 4.43 (2H, s), 7.64 (2H, s); mass not observed.

Intermediate 289b:

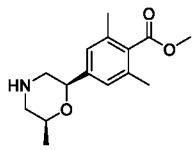
Methyl 4-((2*R*,6*S*)-4-benzyl-6-methylmorpholin-2-yl)-2,6-dimethylbenzoate



[2700] (*S*)-1-(Benzylamino)propan-2-ol (3.59 g, 21.7 mmol) in MeCN (20 mL) was added to a suspension of Intermediate 289a (5.90 g, 20.7 mmol) and K_2CO_3 (3.14 g, 22.7 mmol) in MeCN (80 mL) at 0 °C. The resulting mixture was stirred for 15 hours gradually increasing the temperature to r.t. The mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. DCM (32 mL) and TFA (32 mL, 413 mmol) were added and the mixture was heated to 40 °C. Methyl(phenyl)silane (4.26 mL, 31.0 mmol) was added and the mixture was stirred at 40 °C for 100 minutes. More methyl(phenyl)silane (1.42 mL, 10.3 mmol) was added and stirring was continued at 40 °C for 30 minutes. The mixture was concentrated under reduced pressure. DCM (50 mL) and sat. aq. K_2CO_3/H_2O (1:2, 60 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: elution gradient: 0 to 25% EtOAc in hexanes; 2nd purification: 0 to 25% acetone in hexanes) gave the title compound (5.64 g, 77%) as a yellowish oil. ^{1}H NMR (DMSO-*d*6): δ 1.11 (3H, d), 1.77 (1H, t), 1.86 (1H, t), 2.19 (6H, s), 2.74 (1H, br d), 2.79 (1H, br d), 3.47 (1H, d), 3.50 (1H, d), 3.68 - 3.76 (1H, m), 3.82 (3H, s), 4.49 (1H, dd), 7.03 (2H, s), 7.21 - 7.26 (1H, m), 7.27 - 7.34 (4H, m); *m/z* (ES$^+$) $[M+H]^+$ = 354.1.

Intermediate 289c:

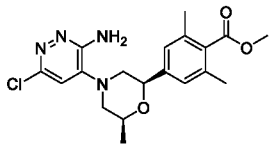
Methyl 2,6-dimethyl-4-((2*R*,6*S*)-6-methylmorpholin-2-yl)benzoate



[2701] MeOH (46 mL) was added to a mixture of Intermediate 289b (5.64 g, 16.0 mmol) and Pd/C (1.70 g, 1.60 mmol, 10 wt% palladium). Hydrogen was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 60 °C under an atmosphere of hydrogen for 3.5 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil which was used for the next step without further purification. Quantitative yield was assumed. ^{1}H NMR (DMSO-*d*6): δ 1.08 (3H, d), 2.21 (6H, s), 2.29 (1H, dd), 2.36 (1H, dd), 2.77 (1H, dd), 2.85 (1H, dd), 3.56 - 3.64 (1H, m), 3.82 (3H, s), 4.35 (1H, dd), 7.02 (2H, s), N*H* not observed; *m/z* (ES$^+$) $[M+H]^+$ = 264.1.

Intermediate 289d:

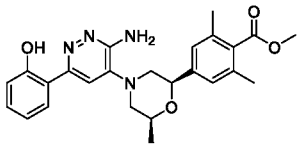
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoate



[2702] Prepared in an analogous method to Intermediate 1d starting from Intermediate 289c (4.20 g, 16.0 mmol) stirring at 115 °C for 17 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Sat. aq. NH_4Cl (80 mL) was added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% acetone in hexanes) gave the title compound (4.91 g, 79% over 2 steps) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.20 (3H, d), 2.22 (6H, s), 2.38 - 2.45 (1H, m), 2.47 - 2.53 (1H, m), 3.38 (1H, br d), 3.45 (1H, br d), 3.83 (3H, s), 3.94 - 4.04 (1H, m), 4.78 (1H, dd), 6.29 (2H, s), 6.93 (1H, s), 7.13 (2H, s); *m/z* (ES$^+$) $[M+H]^+$ = 391.0.

Intermediate 289e:

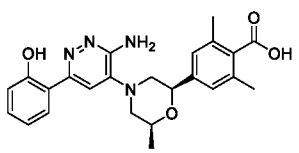
Methyl 4-((2*R*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoate



[2703] Prepared in an analogous method to Intermediate 1e starting from Intermediate 289d (4.91 g, 12.6 mmol) stirring at 100 °C for 50 minutes. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM–*i*PrOH (3:1, 60 mL) and sat. aq. K_2CO_3 (60 mL) were added. The biphasic mixture was stirred vigorously for 45 minutes. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (50 mL) and sat. aq. NH_4Cl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 43% acetone in hexanes) gave the title compound (4.08 g, 72%) as a yellow solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.24 (6H, s), 2.47 - 2.54 (1H, m), 2.63 (1H, dd), 3.49 (2H, br t), 3.84 (3H, s), 4.04 - 4.13 (1H, m), 4.74 - 4.95 (1H, m), 6.44 (2H, s), 6.81 - 6.90 (2H, m), 7.16 (2H, s), 7.19 - 7.24 (1H, m), 7.52 (1H, s), 7.93 (1H, dd), 14.18 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 449.1.

Intermediate 289f:

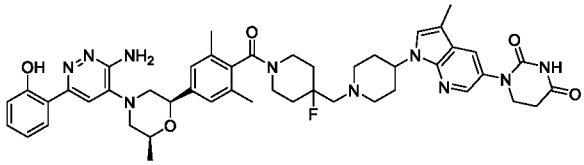
4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoic acid



[2704] 3 M aq. NaOH (12.1 mL, 36.3 mmol) was added to a solution of Intermediate 289e (4.08 g, 9.10 mmol). The resulting mixture was stirred at 60 °C for 60 minutes and concentrated under reduced pressure. EtOH (36 mL) was added and the mixture was stirred at 100 °C for 40 hours. After cooling to r.t., EtOH was removed under reduced pressure. The pH was adjusted to ~8 with 6 M aq. HCl. The mixture was washed with DCM (3 x 40 mL). The mixture was further acidified to pH 3. A precipitate formed which as collected by filtration, washed with water, and dried *in vacuo* to give the title compound (0.78 g, 20%) as a yellowish solid. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 2.28 (6H, s), 2.55 (1H, t), 2.67 (1H, t), 3.53 (2H, br t), 4.07 (1H, ddd), 4.75 - 4.91 (1H, m), 6.64 (2H, br s), 6.84 - 6.94 (2H, m), 7.14 (2H, s), 7.22 - 7.29 (1H, m), 7.52 (1H, s), 7.86 (1H, br d), 13.40 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 435.4.

EXAMPLE 289:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2705] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 289f (20 mg, 0.05 mmol) and Intermediate 161a (19 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (24.0 mg, 67%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.24 (3H, d), 1.47 - 1.87 (5H, m), 1.93 - 2.08 (3H, m), 2.15 (3H, d), 2.19 - 2.26 (6H, m), 2.30 - 2.39 (2H, m), 2.51 - 2.71 (4H, m), 2.74 (2H, t), 2.97 - 3.07 (2H, m), 3.08 - 3.21 (3H, m), 3.50 (2H, br dd), 3.79 (2H, t), 4.03 - 4.13 (1H, m), 4.29 - 4.40 (1H, m), 4.53 - 4.64 (1H, m), 4.77 - 4.88 (1H, m), 6.43 (2H, s), 6.83 - 6.91 (2H, m), 7.15 (2H, t), 7.19 - 7.25 (1H, m), 7.45 (1H, s), 7.54 (1H, s), 7.86 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.19 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 859.5.

EXAMPLE 290:

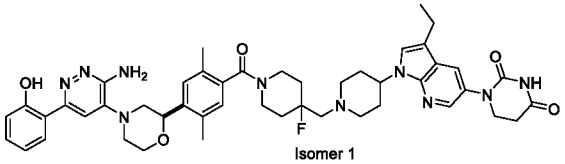
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

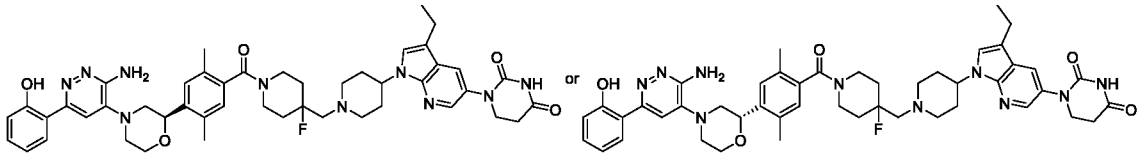
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



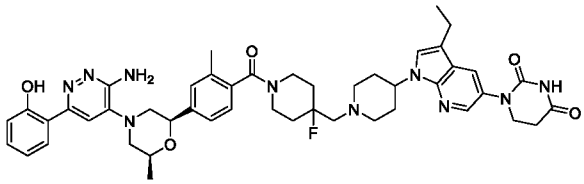
Isomer 1



[2706] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (25 mg, 0.05 mmol) and Intermediate 149f (41 mg, 0.05 mmol). Purification by RPC (1st purification: elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH; 2nd purification: elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (19.8 mg, 46%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.27 (3H, t), 1.52 - 1.90 (5H, m), 1.95 - 2.13 (3H, m), 2.15 - 2.27 (3H, m), 2.29 - 2.41 (5H, m), 2.55 - 2.72 (4H, m), 2.76 (2H, t), 2.80 - 2.92 (2H, m), 3.02 - 3.26 (5H, m), 3.52 (2H, br d), 3.81 (2H, t), 4.04 - 4.14 (2H, m), 4.23 - 4.41 (1H, m), 4.56 - 4.68 (1H, m), 4.94 (1H, br d), 6.43 (2H, s), 6.81 - 6.91 (2H, m), 7.05 (1H, br s), 7.20 - 7.26 (1H, m), 7.39 (1H, s), 7.49 (1H, s), 7.58 (1H, s), 7.92 (1H, d), 7.95 (1H, dd), 8.17 (1H, d), 10.38 (1H, s), 13.41 - 14.81 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 859.6.

EXAMPLE 291:

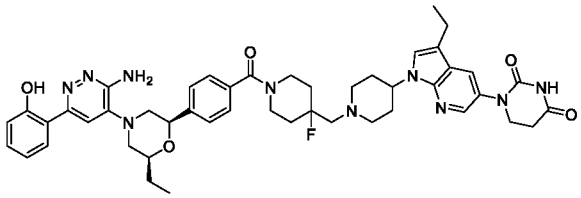
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2707] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 149f (35 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (27.8 mg, 75%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.24 - 1.31 (6H, m), 1.53 - 1.89 (5H, m), 1.96 - 2.13 (3H, m), 2.25 (3H, br s), 2.37 (2H, br t), 2.53 - 2.74 (6H, m), 2.76 (2H, t), 3.00 - 3.26 (5H, m), 3.47 - 3.61 (2H, m), 3.81 (2H, t), 4.11 (1H, ddd), 4.21 - 4.46 (1H, m), 4.56 - 4.68 (1H, m), 4.90 (1H, br d), 6.46 (2H, s), 6.84 - 6.93 (2H, m), 7.16 - 7.28 (2H, m), 7.33 (1H, br d), 7.37 (1H, s), 7.49 (1H, s), 7.56 (1H, s), 7.92 (1H, d), 7.96 (1H, dd), 8.17 (1H, d), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 859.6.

EXAMPLE 292:

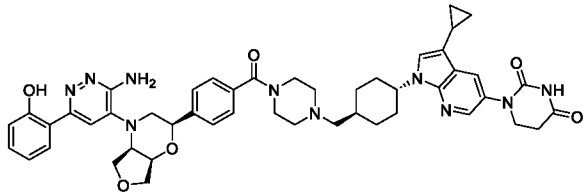
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2708] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 163f (20 mg, 0.05 mmol) and Intermediate 149f (38 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (28.2 mg, 69%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.02 (3H, t), 1.27 (3H, t), 1.59 - 2.15 (10H, m), 2.37 (2H, br t), 2.54 - 2.73 (6H, m), 2.76 (2H, t), 2.98 - 3.30 (4H, m), 3.34 - 3.66 (3H, m), 3.81 (2H, t), 3.88 - 3.97 (1H, m), 4.28 (1H, br d), 4.52 - 4.71 (1H, m), 4.88 - 5.05 (1H, m), 6.39 - 6.53 (2H, m), 6.80 - 6.94 (2H, m), 7.19 - 7.28 (1H, m), 7.45 (2H, d), 7.50 (1H, s), 7.52 - 7.61 (3H, m), 7.92 (1H, d), 7.96 (1H, dd), 8.17 (1H, d), 10.37 (1H, br s), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 859.7.

EXAMPLE 293:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2709] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (11 mg, 0.03 mmol) and Intermediate 273f (11 mg, 0.03 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (15.3 mg, 70%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.70 (2H, m), 0.81 - 0.90 (2H, m), 1.05 - 1.21 (2H, m), 1.63 (1H, br s), 1.72 - 2.02 (7H, m), 2.20 (2H, br d), 2.26 - 2.50 (4H, m), 2.77 (2H, t), 3.21 - 3.28 (1H, m), 3.34 - 3.50 (2H, m), 3.50 - 3.75 (4H, m), 3.82 (2H, t), 3.86 (1H, d), 3.96 (1H, br t), 4.02 (1H, dd), 4.43 (1H, td), 4.56 - 4.68 (2H, m), 4.75 - 4.88 (1H, m), 6.52 (2H, s), 6.82 - 6.93 (2H, m), 7.18 - 7.28 (1H, m), 7.40 (1H, s), 7.43 (2H, d), 7.56 (2H, d), 7.65 (1H, s), 7.92 - 7.99 (2H, m), 8.17 (1H, d), 10.37 (1H, s), 14.18 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 867.5.

EXAMPLE 294:

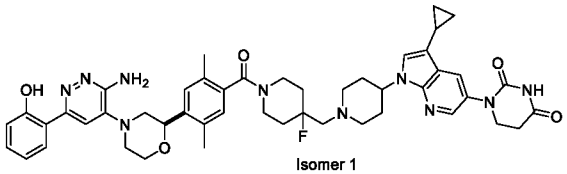
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

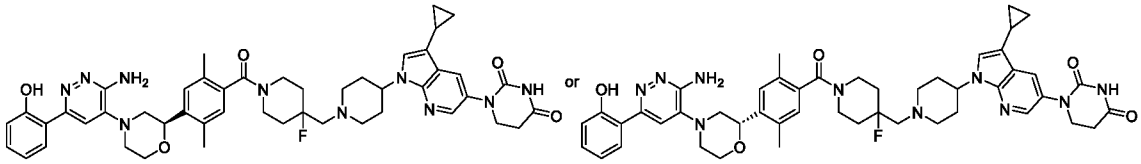
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



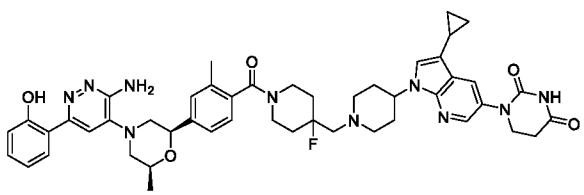
Isomer 1



[2710] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (25 mg, 0.05 mmol) and Intermediate 20g (28 mg, 0.05 mmol). Purification by RPC (1st purification: elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH; 2nd purification: elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (22.0 mg, 50%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.63 - 0.71 (2H, m), 0.82 - 0.90 (2H, m), 1.49 - 1.85 (5H, m), 1.89 - 1.95 (1H, m), 1.96 - 2.11 (3H, m), 2.15 - 2.26 (3H, m), 2.35 (5H, s), 2.56 - 2.68 (2H, m), 2.77 (2H, t), 2.80 - 2.93 (2H, m), 2.99 - 3.25 (5H, m), 3.52 (2H, br d), 3.82 (2H, t), 4.03 - 4.16 (2H, m), 4.21 - 4.41 (1H, m), 4.59 (1H, br t), 4.94 (1H, br d), 6.43 (2H, s), 6.84 - 6.92 (2H, m), 7.05 (1H, br s), 7.20 - 7.27 (1H, m), 7.39 (1H, s), 7.44 (1H, s), 7.58 (1H, s), 7.92 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 13.67 - 14.73 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 871.6.

EXAMPLE 295:

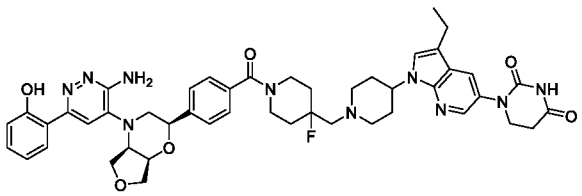
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2711] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20 mg, 0.05 mmol) and Intermediate 20g (24 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (31.6 mg, 84%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.63 - 0.69 (2H, m), 0.82 - 0.90 (2H, m), 1.26 (3H, d), 1.49 - 1.87 (5H, m), 1.89 - 1.95 (1H, m), 1.97 - 2.13 (3H, m), 2.25 (3H, br s), 2.31 - 2.41 (2H, m), 2.52 - 2.74 (4H, m), 2.77 (2H, t), 2.94 - 3.27 (5H, m), 3.46 - 3.62 (2H, m), 3.82 (2H, t), 4.07 - 4.17 (1H, m), 4.21 - 4.45 (1H, m), 4.54 - 4.65 (1H, m), 4.82 - 5.00 (1H, m), 6.46 (2H, s), 6.85 - 6.92 (2H, m), 7.14 - 7.27 (2H, m), 7.33 (1H, br d), 7.36 (1H, s), 7.44 (1H, s), 7.56 (1H, s), 7.93 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 871.6.

EXAMPLE 296:

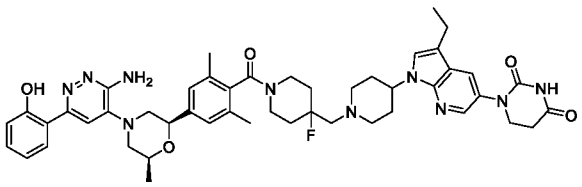
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2712] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20 mg, 0.05 mmol) and Intermediate 149f (34 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (31.7 mg, 87%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.25 (3H, t), 1.59 - 2.13 (8H, m), 2.36 (2H, br t), 2.55 - 2.71 (4H, m), 2.74 (2H, t), 2.99 - 3.31 (5H, m), 3.38 - 3.60 (3H, m), 3.79 (2H, t), 3.85 (1H, d), 3.94 (1H, br t), 4.01 (1H, dd), 4.26 (1H, s), 4.42 (1H, td), 4.55 - 4.66 (2H, m), 4.79 (1H, dd), 6.52 (2H, s), 6.81 - 6.90 (2H, m), 7.19 - 7.25 (1H, m), 7.44 (2H, d), 7.49 (1H, s), 7.55 (2H, d), 7.63 (1H, s), 7.90 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.37 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 873.5.

EXAMPLE 297:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

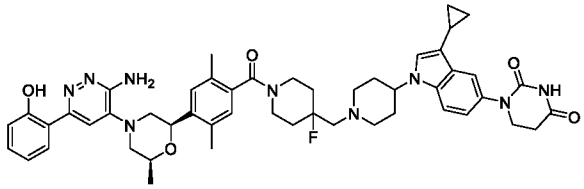


[2713] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 289f (20 mg, 0.05 mmol) and Intermediate 149f (34 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (23.7 mg, 65%) as

an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.22 - 1.28 (6H, m), 1.52 - 1.85 (5H, m), 1.96 - 2.11 (3H, m), 2.15 (3H, d), 2.22 (3H, d), 2.32 - 2.40 (2H, m), 2.51 - 2.71 (6H, m), 2.74 (2H, t), 3.03 (2H, br t), 3.09 - 3.23 (3H, m), 3.44 - 3.55 (2H, m), 3.79 (2H, t), 4.03 - 4.13 (1H, m), 4.28 - 4.39 (1H, m), 4.59 (1H, tt), 4.82 (1H, dd), 6.44 (2H, s), 6.81 - 6.91 (2H, m), 7.15 (2H, t), 7.18 - 7.25 (1H, m), 7.46 (1H, s), 7.54 (1H, s), 7.90 (1H, d), 7.94 (1H, dd), 8.15 (1H, d), 10.35 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 873.6.

EXAMPLE 298:

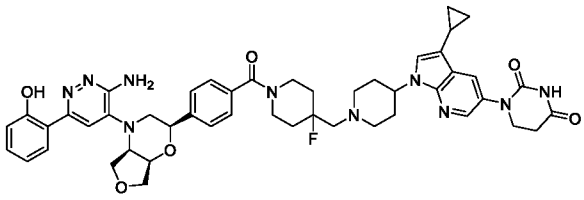
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2714] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20 mg, 0.05 mmol) and Intermediate 6h (29 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (24.9 mg, 67%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.59 (2H, br d), 0.76 - 0.89 (2H, m), 1.24 (3H, d), 1.48 - 2.02 (9H, m), 2.14 - 2.25 (3H, m), 2.29 - 2.41 (5H, m), 2.51 - 2.66 (3H, m), 2.69 - 2.79 (3H, m), 2.96 - 3.26 (5H, m), 3.51 (2H, br s), 3.76 (2H, t), 4.08 - 4.16 (1H, m), 4.19 - 4.37 (2H, m), 4.98 (1H, br d), 6.41 (2H, br s), 6.80 - 6.90 (2H, m), 6.96 - 7.06 (2H, m), 7.17 - 7.25 (2H, m), 7.35 (1H, br s), 7.45 (1H, d), 7.49 (1H, d), 7.55 (1H, br s), 7.94 (1H, br d), 10.24 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 884.6.

EXAMPLE 299:

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

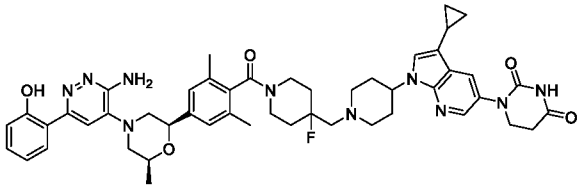


[2715] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20 mg, 0.05 mmol) and Intermediate 20g (23 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (31.8 mg, 86%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.61 - 0.70 (2H, m), 0.79 - 0.87 (2H, m), 1.59 - 2.11 (9H, m), 2.34 (2H, br t), 2.61 (2H, br d), 2.75 (2H, t), 2.96 - 3.30 (5H, m), 3.37 -

3.59 (3H, m), 3.80 (2H, t), 3.85 (1H, d), 3.94 (1H, br t), 4.01 (1H, dd), 4.26 (1H, br s), 4.42 (1H, td), 4.53 - 4.64 (2H, m), 4.79 (1H, dd), 6.52 (2H, br s), 6.81 - 6.89 (2H, m), 7.19 - 7.25 (1H, m), 7.41 - 7.47 (3H, m), 7.55 (2H, d), 7.63 (1H, s), 7.91 - 7.96 (2H, m), 8.16 (1H, d), 10.37 (1H, s), 14.18 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 885.5.

EXAMPLE 300:

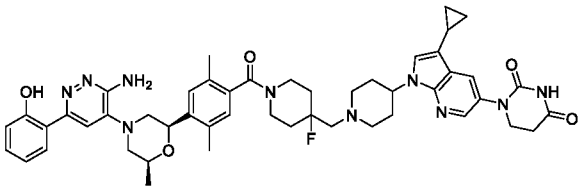
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2716] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 289f (20 mg, 0.05 mmol) and Intermediate 20g (23 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (22.3 mg, 60%) as an amorphous white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.62 - 0.67 (2H, m), 0.81 - 0.87 (2H, m), 1.24 (3H, d), 1.50 - 1.84 (5H, m), 1.87 - 1.94 (1H, m), 1.95 - 2.09 (3H, m), 2.15 (3H, d), 2.22 (3H, d), 2.29 - 2.39 (2H, m), 2.51 - 2.72 (4H, m), 2.75 (2H, t), 3.02 (2H, br t), 3.08 - 3.24 (3H, m), 3.45 - 3.58 (2H, m), 3.80 (2H, t), 4.07 (1H, ddd), 4.27 - 4.38 (1H, m), 4.53 - 4.61 (1H, m), 4.77 - 4.88 (1H, m), 6.44 (2H, s), 6.82 - 6.90 (2H, m), 7.15 (2H, t), 7.19 - 7.26 (1H, m), 7.41 (1H, s), 7.54 (1H, s), 7.90 - 7.98 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.20 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 885.6.

EXAMPLE 301:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2717] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20 mg, 0.05 mmol) and Intermediate 20g (23 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.3 mg, 74%) as an amorphous white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.66 (2H, q), 0.80 - 0.90 (2H, m), 1.26 (3H, d), 1.47 - 1.85 (5H, m), 1.89 - 1.95 (1H, m), 1.96 - 2.12 (3H, m), 2.16 - 2.28 (3H, m), 2.30 - 2.41 (5H, m), 2.52 - 2.69 (3H, m), 2.77 (3H, t), 2.98 - 3.27 (5H, m), 3.54 (2H, br d), 3.82 (2H, t), 4.09 - 4.18 (1H, m), 4.22 - 4.40 (1H, m), 4.54 - 4.66 (1H, m), 5.00 (1H, br d), 6.42 (2H, s), 6.82 - 6.94 (2H, m), 6.98 -

7.10 (1H, m), 7.20 - 7.27 (1H, m), 7.37 (1H, s), 7.39 - 7.48 (1H, m), 7.57 (1H, s), 7.92 - 7.99 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 14.21 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 885.6.

EXAMPLE 302:

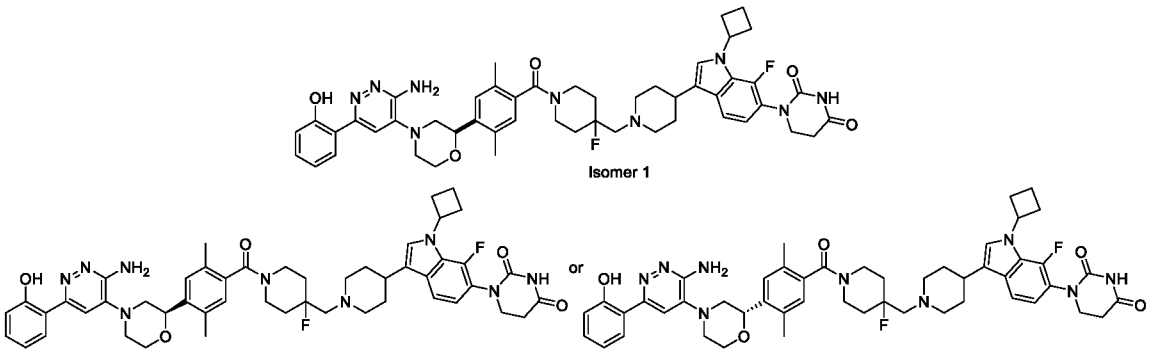
(*R**)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

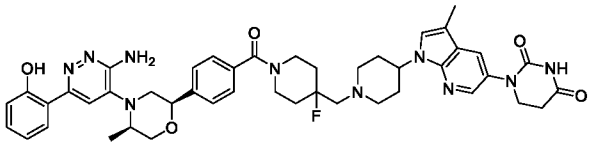
(*S*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1*H*-indol-6-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2718] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (20 mg, 0.05 mmol) and Intermediate 70g (36 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (17.8 mg, 46%) as an amorphous white solid, following lyophilization. ^1H NMR (DMSO-*d*6): δ 1.53 - 1.81 (7H, m), 1.86 (2H, br d), 1.96 (1H, br s), 2.15 - 2.23 (3H, m), 2.24 - 2.30 (2H, m), 2.33 (3H, s), 2.37 - 2.45 (4H, m), 2.53 - 2.63 (2H, m), 2.67 - 2.76 (3H, m), 2.78 - 2.90 (2H, m), 2.94 - 3.02 (2H, m), 3.05 - 3.25 (3H, m), 3.49 (2H, br s), 3.70 (2H, br t), 4.06 (2H, br d), 4.21 - 4.38 (1H, m), 4.91 (1H, br d), 5.04 (1H, quin), 6.42 (2H, br s), 6.81 - 6.89 (2H, m), 6.92 - 7.06 (2H, m), 7.21 (1H, t), 7.32 - 7.38 (2H, m), 7.47 (1H, s), 7.55 (1H, br s), 7.93 (1H, d), 10.41 (1H, s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 902.7.

EXAMPLE 303:

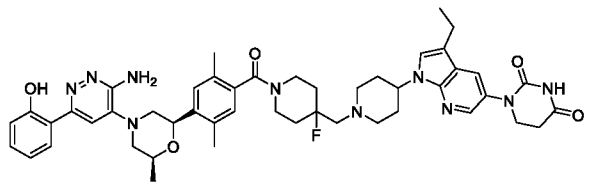
1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2719] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20 mg, 0.05 mmol) and Intermediate 161a (20 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 20 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (26.4 mg, 71%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.08 (3H, d), 1.64 - 2.17 (8H, m), 2.26 (3H, s), 2.38 (2H, br t), 2.59 - 2.70 (2H, m), 2.76 (2H, t), 2.99 - 3.31 (5H, m), 3.40 - 3.60 (2H, m), 3.75 - 3.87 (3H, m), 3.96 (1H, br d), 4.13 - 4.42 (2H, m), 4.55 - 4.66 (1H, m), 4.68 - 4.76 (1H, m), 6.38 (2H, br s), 6.84 (1H, t), 6.88 (1H, d), 7.17 - 7.26 (1H, m), 7.46 (2H, d), 7.49 (1H, s), 7.52 (1H, s), 7.59 (2H, d), 7.88 (1H, d), 7.95 (1H, br d), 8.18 (1H, d), 10.38 (1H, s), 14.27 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 831.8.

EXAMPLE 304:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

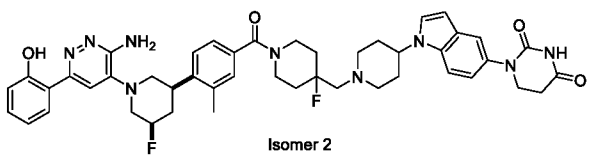


[2720] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20 mg, 0.05 mmol) and Intermediate 149f (34 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% formic acid in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (26.2 mg, 72%) as an amorphous white solid, following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.19 - 1.32 (6H, m), 1.47 - 1.87 (5H, m), 1.94 - 2.12 (3H, m), 2.14 - 2.26 (3H, m), 2.28 - 2.40 (5H, m), 2.51 - 2.79 (8H, m), 2.94 - 3.26 (5H, m), 3.45 - 3.58 (2H, m), 3.79 (2H, t), 4.05 - 4.17 (1H, m), 4.19 - 4.41 (1H, m), 4.59 (1H, br t), 4.98 (1H, br d), 6.41 (2H, br s), 6.79 - 6.90 (2H, m), 6.94 - 7.06 (1H, m), 7.22 (1H, t), 7.35 (1H, br s), 7.43 - 7.51 (1H, m), 7.55 (1H, br s), 7.90 (1H, d), 7.94 (1H, br d), 8.15 (1H, d), 10.37 (1H, s), 14.19 (1H, br d); *m/z* (ES^+) $[M+H]^+$ = 873.6.

EXAMPLE 305:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



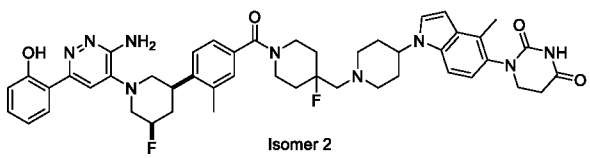
Isomer 2

[2721] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (8.0 mg, 0.02 mmol) and Intermediate 29a (9.5 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (5.40 mg, 34%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.94 - 0.98 (1H, m), 1.64 - 1.80 (2H, m), 1.84 - 2.06 (7H, m), 2.35 - 2.43 (5H, m), 2.61 - 2.68 (2H, m), 2.73 (2H, t), 2.76 - 2.93 (3H, m), 3.02 - 3.10 (2H, m), 3.12 - 3.23 (1H, m), 3.22 - 3.29 (1H, m), 3.38 - 3.47 (2H, m), 3.47 - 3.63 (2H, m), 3.77 (2H, t), 3.85 - 3.98 (1H, m), 4.09 - 4.44 (2H, m), 5.03 - 5.25 (1H, m), 6.36 - 6.44 (2H, m), 6.44 - 6.49 (1H, m), 6.84 - 6.92 (2H, m), 7.04 - 7.11 (1H, m), 7.21 - 7.29 (3H, m), 7.43 - 7.50 (1H, m), 7.50 - 7.57 (1H, m), 7.59 - 7.68 (1H, m), 7.91 - 8.01 (1H, m), 10.09 - 10.34 (1H, m), 13.97 - 14.28 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 832.5.

EXAMPLE 306:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



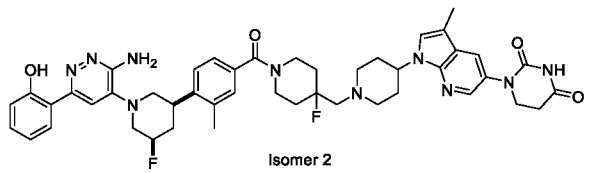
Isomer 2

[2722] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10.0 mg, 0.02 mmol) and Intermediate 32g (13.0 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (10.0 mg, 50%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.60 - 1.78 (2H, m), 1.80 - 2.04 (7H, m), 2.29 (3H, s), 2.34 - 2.44 (6H, m), 2.57 - 2.65 (2H, m), 2.67 - 2.81 (3H, m), 2.85 (1H, br t), 2.97 - 3.07 (2H, m), 3.10 - 3.25 (2H, m), 3.34 - 3.43 (2H, m), 3.44 - 3.57 (2H, m), 3.65 - 3.77 (1H, m), 3.82 - 3.96 (1H, m), 4.12 - 4.36 (2H, m), 5.03 - 5.22 (1H, m), 6.34 - 6.42 (2H, m), 6.49 - 6.54 (1H, m), 6.84 - 6.90 (2H, m), 6.99 (1H, d), 7.19 - 7.27 (3H, m), 7.34 - 7.39 (1H, m), 7.42 - 7.48 (1H, m), 7.51 (1H, d), 7.62 (1H, s), 7.86 - 8.02 (1H, m), 10.17 - 10.25 (1H, m), 14.04 - 14.17 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 846.6

EXAMPLE 307:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



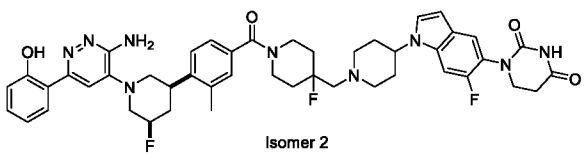
Isomer 2

[2723] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10.0 mg, 0.02 mmol) and Intermediate 161a (11.5 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (13.0 mg, 65%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.92 - 0.96 (1H, m), 1.62 - 1.78 (2H, m), 1.80 - 2.09 (7H, m), 2.21 - 2.26 (3H, m), 2.32 - 2.42 (6H, m), 2.56 - 2.66 (2H, m), 2.72 - 2.79 (3H, m), 2.82 - 2.89 (1H, m), 2.99 - 3.07 (2H, m), 3.10 - 3.21 (1H, m), 3.35 - 3.45 (2H, m), 3.46 - 3.61 (1H, m), 3.75 - 3.82 (2H, m), 3.85 - 3.94 (1H, m), 4.13 - 4.33 (1H, m), 4.50 - 4.63 (1H, m), 5.02 - 5.22 (1H, m), 6.29 - 6.48 (2H, m), 6.82 - 6.91 (2H, m), 7.17 - 7.29 (3H, m), 7.42 - 7.52 (2H, m), 7.58 - 7.64 (1H, m), 7.85 - 7.89 (1H, m), 7.91 - 8.00 (1H, m), 8.12 - 8.20 (1H, m), 10.31 - 10.40 (1H, m), 13.89 - 14.27 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 847.6.

EXAMPLE 308:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



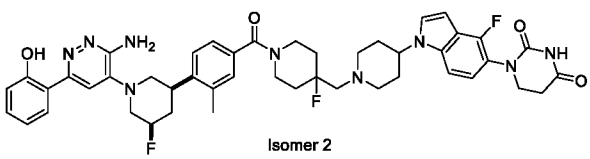
Isomer 2

[2724] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10.0 mg, 0.02 mmol) and Intermediate 5g (18.6 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (8.5 mg, 42%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 1.65 - 1.80 (2H, m), 1.85 - 2.04 (7H, m), 2.36 - 2.46 (6H, m), 2.59 - 2.68 (2H, m), 2.73 - 2.82 (3H, m), 2.85 - 2.92 (1H, m), 3.00 - 3.07 (2H, m), 3.11 - 3.20 (1H, m), 3.35 - 3.39 (1H, m), 3.38 - 3.60 (3H, m), 3.68 - 3.76 (2H, m), 3.89 - 3.94 (1H, m), 4.08 - 4.29 (1H, m), 4.30 - 4.37 (1H, m), 5.02 - 5.25 (1H, m), 6.38 - 6.45 (2H, m), 6.47 - 6.52 (1H, m), 6.85 - 6.93 (2H, m), 7.21 - 7.28 (3H, m), 7.45 - 7.50 (1H, m), 7.54 - 7.59 (3H, m), 7.62 - 7.66 (1H, m), 7.93 - 8.04 (1H, m), 10.26 - 10.46 (1H, m), 14.02 - 14.25 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 850.6.

EXAMPLE 309:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



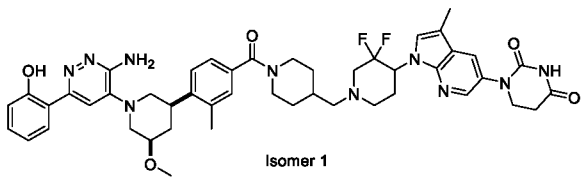
Isomer 2

[2725] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 222f (10.0 mg, 0.02 mmol) and Intermediate 3g (13.2 mg, 0.02 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (14.8 mg, 74%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.94 - 0.96 (1H, m), 1.59 - 1.79 (2H, m), 1.80 - 2.07 (7H, m), 2.33 - 2.45 (6H, m), 2.59 - 2.68 (2H, m), 2.70 - 2.81 (3H, m), 2.84 - 2.92 (1H, m), 3.00 - 3.21 (3H, m), 3.35 - 3.63 (3H, m), 3.68 - 3.74 (2H, m), 3.85 - 3.93 (1H, m), 4.15 - 4.31 (1H, m), 4.33 - 4.42 (1H, m), 5.05 - 5.26 (1H, m), 6.36 - 6.45 (2H, m), 6.53 - 6.59 (1H, m), 6.85 - 6.93 (2H, m), 7.08 - 7.18 (1H, m), 7.21 - 7.30 (3H, m), 7.40 - 7.50 (2H, m), 7.58 - 7.66 (2H, m), 7.90 - 8.05 (1H, m), 10.29 - 10.43 (1H, m), 14.02 - 14.21 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 850.4

EXAMPLE 310:

1-(1-(1-((1-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

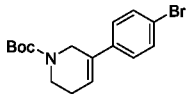


[2726] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (13 mg, 0.03 mmol) and Intermediate 220g (11.8 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (12.30 mg, 55%) as an amorphous white solid following lyophilization. ^{1}H NMR (DMSO-*d*6): δ 0.94 - 1.01 (2H, m), 1.02 - 1.14 (2H, m), 1.48 - 1.59 (1H, m), 1.60 - 1.73 (1H, m), 1.78 - 1.95 (3H, m), 2.23 - 2.31 (4H, m), 2.34 - 2.43 (6H, m), 2.53 - 2.65 (2H, m), 2.70 - 2.82 (4H, m), 3.00 (2H, br d), 3.20 - 3.28 (2H, m), 3.47 - 3.52 (1H, m), 3.57 - 3.70 (2H, m), 3.72 - 3.87 (5H, m), 4.39 - 4.55 (1H, m), 5.15 - 5.29 (1H, m), 6.24 - 6.37 (2H, m), 6.83 - 6.91 (2H, m), 7.16 - 7.26 (3H, m), 7.36 - 7.42 (1H, m), 7.44 - 7.49 (1H, m), 7.57 - 7.61 (1H, m), 7.89 - 7.97 (2H, m), 8.19 (1H, d), 10.29 - 10.44 (1H, m), 13.99 - 14.43 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 877.7.

EXAMPLE 311

Intermediate 311a:

tert-Butyl 5-(4-bromophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

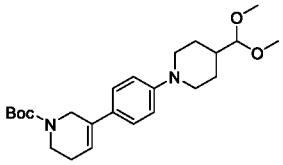


[2727] K_2CO_3 (4.69 g, 33.91 mmol) was added to 1,4-dibromobenzene (4 g, 16.96 mmol), *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (4.72 g, 15.26 mmol) and $PdCl_2$(dppf) (1.241 g, 1.70 mmol) in 1,4-dioxane (40 mL) and water (4 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with DCM (300 mL) and

filtered. The filtrate was washed with water (2 x 200 mL) and brine (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (2.0 g, 35%) as a colorless oil. ^{1}H NMR (DMSO-*d6*) δ 1.43 (9H, s), 2.20 – 2.28 (2H, m), 3.41 – 3.51 (2H, m), 4.14 – 4.23 (2H, m), 6.28 – 6.36 (1H, m), 7.33 – 7.41 (2H, m), 7.50 – 7.58 (2H, m); *m/z* (ES$^+$) $[M\text{-}tBu+2H]^+$ =282.0.

Intermediate 311b:

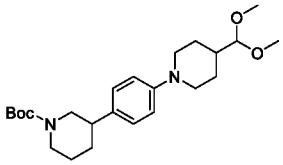
tert-Butyl 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



[2728] Cs_2CO_3 (4.82 g, 14.78 mmol) was added to Intermediate 311a (2 g, 5.91 mmol), 4-(dimethoxymethyl)piperidine (0.942 g, 5.91 mmol), Ruphos Pd G3 (0.495 g, 0.59 mmol) and Ruphos (0.276 g, 0.59 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. After cooling to r.t., the reaction mixture was filtered. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (1.80 g, 73%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.09 – 1.36 (2H, m), 1.43 (9H, s), 1.65 – 1.76 (3H, m), 2.22 (2H, d), 2.56 – 2.68 (2H, m), 3.27 (6H, s), 3.40 – 3.48 (2H, m), 3.72 (2H, d), 4.08 (1H, d), 4.15 (2H, d), 6.08 – 6.15 (1H, m), 6.90 (2H, d), 7.23 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 417.3.

Intermediate 311c:

rac-tert-Butyl (*R*)-3-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidine-1-carboxylate



[2729] Platinum(IV) oxide hydrate (0.275 g, 1.21 mmol) was added to Intermediate 311b (1.68 g, 4.03 mmol) in DCM (20 mL) under hydrogen. The resulting mixture was stirred at r.t. under an atmosphere of hydrogen for 16 h. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 20% EtOAc in DCM) gave the title compound (1.5 g, 89%) as a yellow oil. ^{1}H NMR (DMSO-*d6*) δ 1.16 – 1.22 (2H, m), 1.28 – 1.35 (2H, m), 1.40 (9H, s), 1.55 – 1.61 (1H, m), 1.65 – 1.74 (3H, m), 1.79 – 1.88 (1H, m), 2.41 – 2.48 (1H, m), 2.55 – 2.61 (2H, m), 2.73 (2H, d), 3.27 (6H, s), 3.64 (2H, d), 3.97 – 4.05 (2H, m), 4.06 – 4.10 (1H, m), 6.83 – 6.89 (2H, m), 7.07 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 419.1.

Intermediate 311d:

(*R**)-6-Chloro-4-(3-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)pyridazin-3-amine

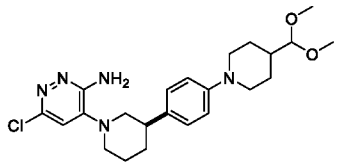
(Isomer 1)

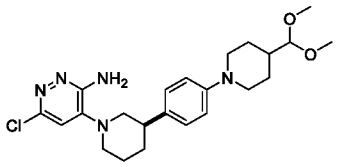
and

Intermediate 311e:

(*R**)-6-Chloro-4-(3-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)pyridazin-3-amine (Isomer 2)

((*absolute configurations not yet confirmed))



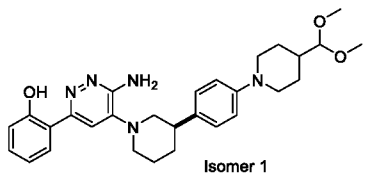


[2730] HCl in MeOH 4 M (20 mL) was added to Intermediate 311c (1.5 g, 3.58 mmol) under nitrogen. The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The pH was adjusted to to 9 with the 7 M ammonia in methanol solution. The solvent was removed under reduced pressure. The reaction mixture was diluted with DCM–MeOH (3:1, 15 mL). the mixture was filtered. The filtrate was removed under reduced pressure. To the residue was added DIPEA (2.504 mL, 14.33 mmol) and 4-bromo-6-chloropyridazin-3-amine (0.598 g, 2.87 mmol) and NMP (20 mL). The resulting mixture was stirred at 100 °C for 16 h. After cooling to r.t., the reaction mixture was diluted with EtOAc (50 mL), washed with sat. aq. NH_4Cl (3 x 25 mL) and brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 3 to 80% MeCN in water with 0.1% NH_4HCO_3) gave a racemic mixture of title compounds. Purification by SFC (Column: Lux 5um Cellulose-4, 5*25 cm, 5 μm; Flow rate: 100 mL/min; isocratic 55% MeOH:MeCN (1:1) in $scCO_2$; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.02; RT2(min): 8.48) gave Intermediate 311d (400 mg, 25%, >99% ee) which eluted first from the column as a white solid and Intermediate 311e (400 mg, 25%, >99% ee) which eluted second from the column as a white solid. Intermediate 331d: ^{1}H NMR (DMSO-*d6*) δ 1.22 – 1.41(2H, m), 1.47 – 1.63 (1H, m), 1.65 – 1.76 (3H, m), 1.76 – 1.94 (3H, m), 2.51 – 2.65 (4H, m), 2.85 – 2.98 (1H, m), 3.27 (6H, s), 3.41 (2H, d), 3.64 (2H, d), 4.08 (1H, d), 6.11 (2H, s), 6.82 – 6.93 (3H, m), 7.12 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 446.0. Intermediate 311e: ^{1}H NMR (DMSO-*d6*) δ 1.18 – 1.41 (2H, m), 1.47 – 1.61 (1H, m), 1.64 – 1.75 (3H, m), 1.77 – 1.94 (3H, m), 2.53 – 2.61 (4H, m), 2.87 – 2.97 (1H, m), 3.27 (6H, s), 3.41 (2H, d), 3.64 (2H, d), 4.08 (1H, d), 6.11 (2H, s), 6.83 – 6.92 (3H, m), 7.12 (2H, d); *m/z* (ES^+) [M+H]+ = 446.0.

Intermediate 311f:

(*R**)-2-(6-Amino-5-(3-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)pyridazin-3-yl)phenol (Isomer 1)

((*absolute configuration not yet confirmed))

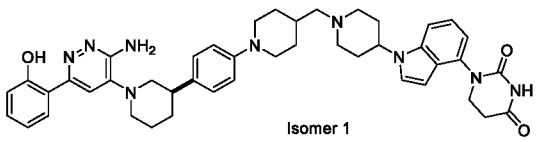


[2731] Cs_2CO_3 (219 mg, 0.67 mmol) was added to 2-Hydroxyphenylboronic acid (61.9 mg, 0.45 mmol), Pd(dppf)Cl_2 DCM adduct (18.31 mg, 0.02 mmol) and Intermediate 311d (100 mg, 0.22 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with saturated NH_4Cl (20 mL x 2), saturated brine (20 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure gave the title compound (85 mg, 75%) as an orange solid. ^{1}H NMR (DMSO-*d6*) δ 1.24 (1H, s), 1.36 (2H, d), 1.68 – 1.72 (2H, m), 1.86 – 2.05 (4H, m), 2.59 (2H, d), 2.63 – 2.76 (2H, m), 2.89 – 3.03 (1H, m), 3.26 – 3.28 (6H, s), 3.45 – 3.56 (2H, m), 3.63 – 3.67 (2H, d), 4.08 (1H, d), 6.27 (1H, s), 6.82 - 6.94 (5H, m), 7.16 (1H, d), 7.20 – 7.27 (1H, m), 7.52 (1H, s), 7.89 – 7.96 (1H, m); two exchangeable protons not observed; *m/z* (ES^+) $[M+H]^+$ = 504.1.

EXAMPLE 311:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

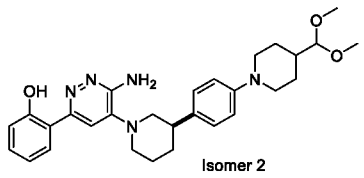
[2732] Formic acid (2 mL) was added to Intermediate 311f (60 mg, 0.12 mmol). The resulting mixture was stirred at 40 °C for 1 h. The solvent was removed under reduced pressure. Intermediate 10c (37.2 mg, 0.12 mmol) in DCE (2 mL) and NMP (2 mL) was added. The resulting mixture was stirred at 40 °C for 40 min. Sodium triacetoxyborohydride (126 mg, 0.60 mmol) was added. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (25 mL), washed with sat. aq. $NaHCO_3$ (3 x 5 mL) and brine (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: 50 to 70% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.1%NH_4OH in 8 min) gave the title compound (13.63 mg, 15%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.24 (2H, s), 1.64 (2H, s), 1.75 – 2.07 (9H, m), 2.11 – 2.39 (4H, m), 2.59 – 2.89 (6H, m), 3.11 (3H, s), 3.46 – 3.99 (6H, m), 4.38 (1H, s), 6.05 – 6.65(3H, m), 6.93 (5H, d), 7.20 (4H, d), 7.53 (3H, s), 7.93 (1H, s), 10.35 (1H, s), 14.30 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 754.4.

EXAMPLE 312

Intermediate 312a:

(*R**)-2-(6-Amino-5-(3-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)pyridazin-3-yl)phenol (Isomer 2)

((*absolute configuration not yet confirmed))

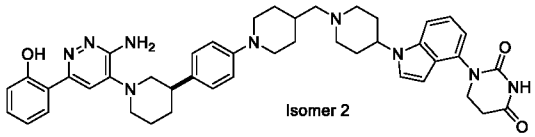


[2733] Prepared in an analogous method to Intermediate 311f starting from Intermediate 311e (100 mg, 0.22 mmol) to give the title compound (86 mg, 76%) as a brown solid. ^{1}H NMR (DMSO-*d6*) δ 0.85 (1H, d), 1.21 – 1.25 (1H, m), 1.30 – 1.35 (3H, m), 1.70 (2H, d), 1.85 – 1.95 (3H, m), 2.59 (1H, d), 2.65 – 2.73 (2H, m), 2.91 – 3.04 (1H, m), 3.26 (6H, s), 3.44 – 3.57 (2H, m), 3.65 (2H, d), 4.08 (1H, d), 6.27 (2H, s), 6.78 (1H, d), 6.83 – 6.92 (4H, m), 7.13 – 7.19 (2H, m), 7.20 – 7.27 (1H, m), 7.52 (1H, s), 7.92 (1H, d). 14.28 (1H,s); *m/z* (ES$^+$) $[M+H]^+$ = 504.1.

EXAMPLE 312:

(*R**)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

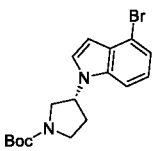


[2734] Prepared in an analogous method to EXAMPLE 311 starting from Intermediate 312a (63 mg, 0.13 mmol) and Intermediate 10c (39.1 mg, 0.13 mmol). Purification by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water with 10 mmol/L NH_4HCO_3 and 0.1% $NH_3.H_2O$, Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 50% B to 70% B in 8 min) to afford title compound (26.8 mg, 28%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.15 – 1.25 (2H, m), 1.53 – 1.70 (2H, m), 1.75 – 1.85 (3H, m), 1.88 – 2.02 (6H, m), 2.10 – 2.22 (2H, m), 2.25 (2H, d), 2.53 – 2.70 (4H, m), 2.71 – 2.79 (2H, m), 2.90 – 3.09 (3H, m), 3.45 – 3.55 (2H, m), 3.65 (2H, d), 3.73 – 3.82 (2H, m), 4.33 – 4.43 (1H, m), 6.27 (2H, s), 6.42 (1H, d), 6.83 – 6.93 (4H, m), 6.97 (1H, d), 7.11 – 7.19 (3H, m), 7.20 – 7.29 (1H, m), 7.48 – 7.58 (3H, m), 7.85 – 8.05 (1H, m), 10.35 (1H, s), 14.30 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 754.4.

EXAMPLE 313

Intermediate 313a:

tert-Butyl (*R*)-3-(4-bromo-1*H*-indol-1-yl)pyrrolidine-1-carboxylate

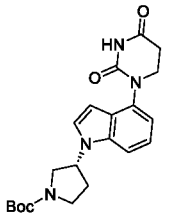


[2735] Prepared in an analogous method to Intermediate 234a starting from 4-bromo-1*H*-indole (1 g, 5.10 mmol) and *tert*-butyl (*S*)-3-hydroxypyrrolidine-1-carboxylate (0.955 g, 5.10 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.5% NH_4HCO_3) gave the title compound (0.600 g,

32%) as a yellow oil. ^{1}HNMR (DMSO-*d6*) δ 1.41 (9H, d), 2.25 – 2.43 (2H, m), 3.38 – 3.58 (3H, m), 3.80 (1H, t), 5.26 – 5.18 (1H, m), 6.46 (1H, d), 7.10 (1H, t), 7.28 (1H, d), 7.54 – 7.66 (2H, m); *m/z* (ES$^+$) [M-*t*Bu+2H]$^+$ =365.1.

Intermediate 313b:

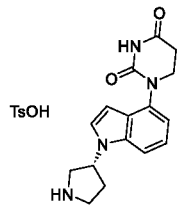
tert-Butyl (*R*)-3-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)pyrrolidine-1-carboxylate



[2736] Prepared in an analogous method to Intermediate 2b starting from Intermediate 313a (580 mg, 1.59 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (450 mg, 71%) as a yellow solid. ^{1}HNMR (DMSO-*d6*) δ 1.42 (9H, d), 2.34 – 2.40 (1H, m), 2.77 (2H, t), 3.38 – 3.56 (4H, m), 3.75 – 3.83 (3H, m), 5.14 – 5.28 (1H, m), 6.47 (1H, d), 7.00 (1H, d), 7.18 (1H, t), 7.44 – 7.50 (1H, m), 7.54 (1H, d), 10.35 (1H, s); *m/z* (ES$^+$) [M+Na]$^+$ =421.2.

Intermediate 313c:

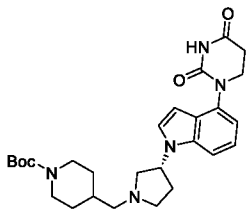
(*R*)-1-(1-(Pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2737] Prepared in an analogous method to Intermediate 6e starting from Intermediate 313b (440 mg, 1.10 mmol) to give the title compound (400 mg, 77%) as a gray solid and TsOH salt. *m/z* (ES$^+$) [M+H]$^+$ =299.2.

Intermediate 313d:

tert-Butyl (*R*)-4-((3-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-indol-1-yl)pyrrolidin-1-yl)methyl)piperidine-1-carboxylate

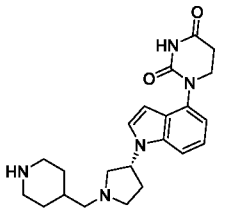


[2738] Prepared in an analogous method to Intermediate 108a starting from Intermediate 313c (380 mg, 0.81 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (258 mg, 1.21 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (350 mg, 87%) as a yellow oil. ^{1}HNMR (DMSO-*d6*) δ 0.95 – 1.08 (2H, m), 1.40 (9H, s), 1.62 – 1.68 (1H, m), 1.74 (2H, d), 2.27 – 2.34 (2H, m), 2.35 – 2.47 (3H, m), 2.76 (2H, t), 2.84 – 2.92 (1H, m), 2.98 – 3.09 (1H, m),3.33 – 3.35 (2H, m), 3.78 (2H,

t), 3.87 – 3.99 (3H, m), 5.15 (1H, s), 6.42 (1H, d), 6.96 (1H, d), 7.14 (1H, t), 7.52 (1H, d), 7.62 (1H, d), 10.34 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 496.0.

Intermediate 313e:

(*R*)-1-(1-(1-(Piperidin-4-ylmethyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2739] Prepared in an analogous method to Intermediate 1i starting from Intermediate 313d (340 mg, 0.69 mmol) to give the title compound (300 mg, 86%) as a yellow solid and TFA salt. *m/z* (ES^+) $[M+H]^+$ =396.2.

EXAMPLE 313:

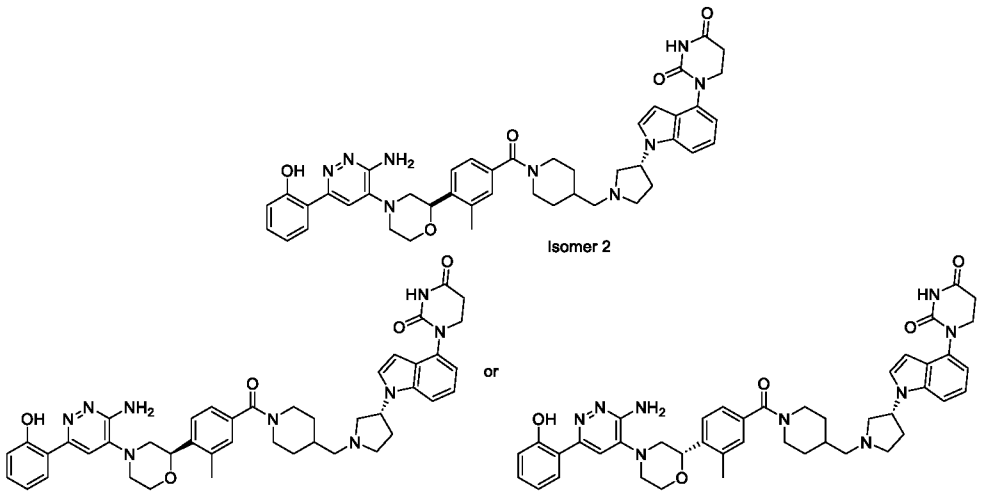
1-(1-((*R*)-1-((1-(4-((*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((*R*)-1-((1-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

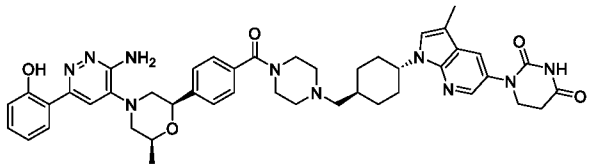


[2740] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 313e (30 mg, 0.08 mmol) and Intermediate 55j (30.8 mg, 0.08 mmol). Purification by preparative HPLC (elution gradient: 45

to 50% MeCN in water with NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (9.60 mg, 16%) as a white solid. ^{1}HNMR (DMSO-*d6*) δ 1.04 – 1.19 (2H, m), 1.24 (1H, s), 1.61 – 1.91 (3H, m), 1.91 – 2.02 (1H, m), 2.28 – 2.48 (7H, m), 2.67 – 2.96 (8H, m), 2.98 – 3.08 (2H, m), 3.48 – 3.65 (3H, m), 3.77 (2H, t), 4.09 (2H, d), 4.47 (1H, s), 4.95 – 5.00 (1H, m), 5.11 – 5.19 (1H, m), 6.33 – 6.51 (3H, m), 6.83 – 6.91 (2H, m), 6.96 (1H, d), 7.14 (1H, t), 7.19 – 7.27 (3H, m), 7.50 – 7.60 (1H, m), 7.62 (1H, d), 7.92 – 7.98 (1H, m), 10.33 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 784.4.

EXAMPLE 314:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2741] Intermediate 259a (100 mg, 0.19 mmol) was added to TFA (1 mL) and DCM (1 mL). The resulting mixture was stirred at r.t. for 40 min. The solvent was removed under reduced pressure. DIPEA (0.100 mL, 0.57 mmol), Intermediate 65e (54.2 mg, 0.13 mmol) and DMF (2.00 mL) were added. The resulting mixture was stirred at r.t. for 10 minutes. HATU (50.7 mg, 0.13 mmol) was added. The reaction mixture was stirred at r.t. for 30 min. The mixture was diluted with DCM:IPA (5:1), washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Mobile Phase A: Water with 10mmol/L NH_4HCO_3 and 0.05% NH_4OH, Mobile Phase B: MeCN Gradient: 14% B to 35% B) gave the title compound (40.0 mg, 26%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ1.09 – 1.18 (2H, m), 1.27 (3H, d), 1.62 –1.65 (1H, m), 1.79 – 1.88 (2H, m), 1.90 – 1.98 (4H, m), 2.20 (2H, d), 2.25 (3H, d), 2.33 (2H, d), 2.42 –2.45 (2H, m), 2.52 – 2.58 (2H, m), 2.66 – 2.72 (1H, m), 2.76 (2H, t), 3.37 – 3.42 (2H, m), 3.51 (1H, d), 3.58 (1H, d), 3.63 –3.65 (1H, m), 3.81 (2H, t), 4.08 – 4.15 (1H, m), 4.58 – 4.66 (1H, m), 4.92 – 4.98 (1H, m), 6.49 (2H, s), 6.84 – 6.92 (2H, m), 7.22 – 7.26 (1H, m), 7.40 – 7.46 (3H, m), 7.52 – 7.58 (3H, m), 7.88 (1H, d), 7.94 – 7.98 (1H, m), 8.17 (1H, d), 10.39 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 813.5.

EXAMPLE 315:

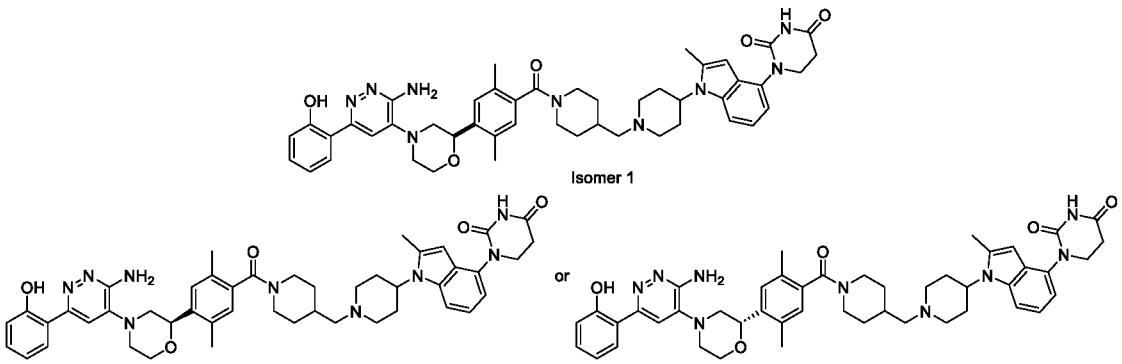
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2742] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 228f (40 mg, 0.10 mmol) and Intermediate 22d (40.3 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 20% water in MeCN) and preparative HPLC (elution gradient: 42 to 61% MeCN in water with 10 mmol/L NH_4HCO_3+0.1% NH_4OH) gave the title compound (6.3 mg, 8%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.08 (2H, s),1.32 (1H, s), 1.70 (1H, s), 1.77 (2H, d), 1.88 (2H, s), 2.13 (2H, s), 2.18 (2H, s), 2.24 (3H, s), 2.35 (4H, s), 2.44 (4H, s), 2.74 (2H, t), 2.87 (3H, s), 3.00 (3H, s), 3.51 (2H, s), 3.74 (2H, t), 4.09 (2H, d), 4.23 (1H, s), 4.56 (1H, d), 4.93 (1H, d), 6.16 (1H, s), 6.44 (2H, s), 6.89 (3H, d), 6.96–7.1 (2H, m), 7.23 (1H, d), 7.38 (1H, s), 7.46 (1H, d), 7.58 (1H, s), 7.96 (1H, d), 10.30 (1H, s), 14.21 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 826.4.

EXAMPLE 316

Intermediate 316a:

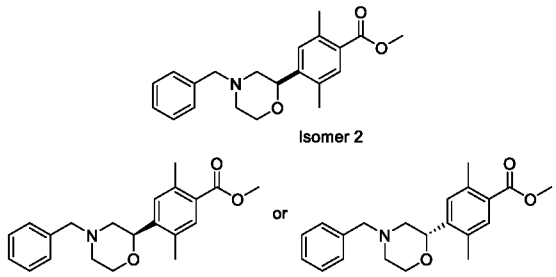
Methyl (*R**)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-benzylmorpholin-2-yl)-2,5-dimethylbenzoate



[2743] Prepared using the same method as for Intermediate 228b, isolating the compound that eluted second from the column (1.60 g, 35%, 96%ee) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.85–2.27 (5H,

m), 2.46 (3H, s), 2.77 (2H, dd), 3.53 (2H, d), 3.69–3.75 (1H, m), 3.80 (3H, s), 3.91–3.99 (1H, m), 4.66 (1H, dd), 7.21–7.31 (1H, m), 7.32 (5H, t), 7.59 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 340.1.

Intermediate 316b:

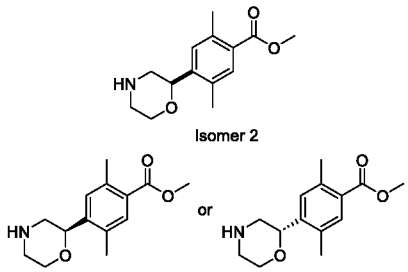
Methyl (*R**)-2,5-dimethyl-4-(morpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-2,5-dimethyl-4-(morpholin-2-yl)benzoate

or

Methyl (*S*)-2,5-dimethyl-4-(morpholin-2-yl)benzoate



[2744] Prepared in an analogous method to Intermediate 65b starting from Intermediate 316a (800 mg, 2.36 mmol) to give the title compound (570 mg, 97%) as a yellow solid. ^1H NMR (DMSO *d6*) δ 2.28 (3H, s), 2.47 (3H, s), 2.50-2.52 (2H, m), 2.7–2.8 (2H, m), 2.90 (1H, dd), 2.59-3.67 (1H, m), 3.81 (3H, s), 4.47–4.67 (1H, m), 7.31 (1H, s), 7.61 (1H, s), nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 250.1.

Intermediate 316c:

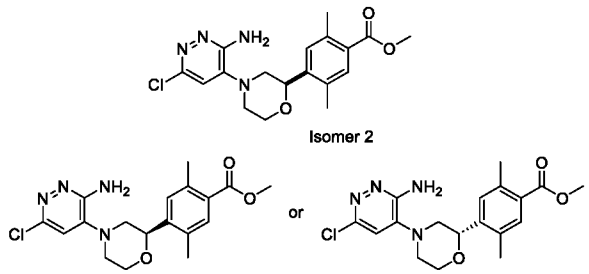
Methyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Methyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate



[2745] Prepared in an analogous method to Intermediate 1d starting from Intermediate 316b (550 mg, 2.21 mmol). Purification by FSC (elution gradient: 0 to 90% EtOAc in petroleum ether) gave the title compound (760 mg, 91%) as a yellow solid. ^1H NMR (DMSO-*d6*) δ 2.35 (3H, s), 2.49 (3H, s), 2.63 (1H, dd), 2.76–2.89 (1H, m), 3.43 (2H, dd), 3.82 (3H, s), 3.98–4.06 (2H, m), 4.92 (1H, dd), 6.29 (2H, s), 6.97 (1H, s), 7.39 (1H, s), 7.64 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 377.1.

Intermediate 316d:

Methyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate

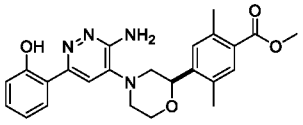
(Isomer 2)

((*absolute configuration not yet confirmed))

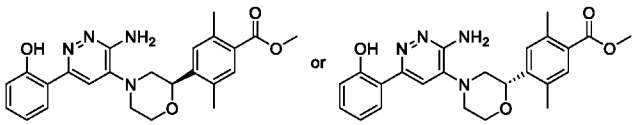
Methyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate

or

Methyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoate



Isomer 2



[2746] Prepared in an analogous method to Intermediate 1e starting from Intermediate 316c (740 mg, 1.96 mmol). After cooling to r.t., the reaction mixture was poured into water (75 mL). A precipitate formed which was collected by filtration and dried *in vacuo* to give the title compound (778 mg, 91%) as yellow solid which was used for the next step without further purification. ^{1}H NMR (DMSO-*d6*) δ 2.37 (3H, s), 2.50 (3H, d), 2.74–2.95 (1H, m), 3.51 (2H, d), 3.58 (3H, s), 3.83 (3H, s), 4.93–5 (1H, m), 6.45 (2H, s), 6.84-6.90 (2H, m), 7.23 (1H, t), 7.44 (1H, s), 7.57 (1H, s), 7.66 (1H, s), 7.94 (1H, dd), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 435.1.

Intermediate 316e:

(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid

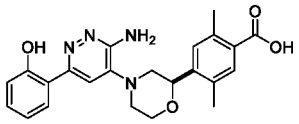
(Isomer 2)

((*absolute configuration not yet confirmed))

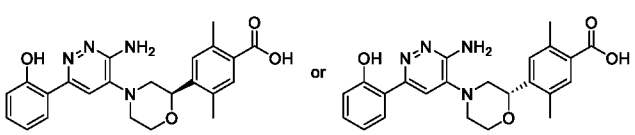
(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoic acid



Isomer 2



[2747] LiOH (418 mg, 17.45 mmol) was added to Intermediate 316d (758 mg, 1.74 mmol) in MeOH (8 mL) and water (8 mL) under nitrogen. The resulting mixture was stirred at 60 °C for 1 h. After cooling to r.t., the reaction mixture was acidified with 1 M aq. HCl. A precipitate formed which was collected by filtration, washed with water (2 mL) and dried *in vacuo* to give the title compound (600 mg, 82%) as a

yellow solid, which was used without further purification. ^{1}H NMR (DMSO-*d6*) δ 2.35 (3H, s), 2.46 – 2.49 (3H, m), 2.69 – 2.96 (2H, m), 3.50 (2H, d), 4.08 (2H, d), 4.95 (1H, d), 6.40 – 6.45 (2H, m), 6.80 – 6.91 (2H, m), 7.18 – 7.28 (1H, m), 7.40 (1H, s), 7.55 (1H, s), 7.65 (1H, s), 7.93 (1H, d), 2 heteroatom-bound protons not observed; *m/z* (ES$^+$) $[M+H]^+$ = 421.1.

EXAMPLE 316:

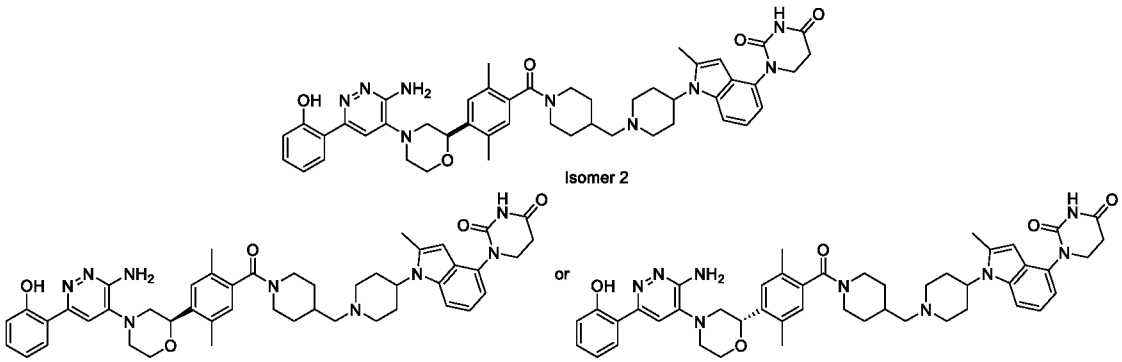
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

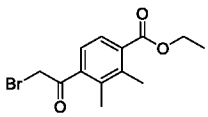


[2748] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 316e (40 mg, 0.10 mmol) and Intermediate 22d (40.3 mg, 0.10 mmol). Purification by RPC (elution gradient: 0 to 20% water in MeCN) and preparative HPLC (Column: Xbridge Prep C18 OBD, 30*150 mm, 5 µm, elution gradient: 41 to 59% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH in 8 min) gave the title compound (6.3 mg, 8%) as a white solid. ^{1}H NMR (DMSO *d6*) δ 0.97–1.03 (2H, m), 1.25 (1H, d), 1.65–1.93 (5H, m), 2.10–2.30 (7H, m), 2.31–2.40 (4H, m), 2.42–2.49 (4H, m), 2.74 (2H, t), 2.79–2.92 (3H, m), 3.00 (3H, s), 3.47 – 3.51 (2H, m), 3.74 (2H, t), 4.09 (2H, d), 4.20–4.23 (1H, m), 4.56 (1H, d), 4.93 (1H, d), 6.14 (1H, s), 6.43 (2H, s), 6.89 (3H, d), 7.04 (2H, t), 7.24 (1H, t), 7.38 (1H, s), 7.46 (1H, d), 7.58 (1H, s), 7.96 (1H, d), 10.30 (1H, s), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 826.5.

EXAMPLE 317

Intermediate 317a:

Ethyl 4-(2-bromoacetyl)-2,3-dimethylbenzoate



[2749] Prepared in an analogous method to Intermediate 228a starting from ethyl 4-bromo-2,3-dimethylbenzoate (5 g, 19.45 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (4.20 g, 72%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.31–1.34 (3H, m), 2.23 (3H, s), 2.36 (3H, d), 4.32 (2H, d), 4.84 (2H, d), 7.51–7.57 (1H, m), 7.60 (1H, d); mass not observed.

Intermediate 317b:

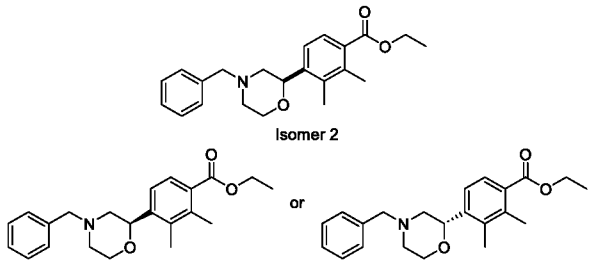
Ethyl (*R**)-4-(4-benzylmorpholin-2-yl)-2,3-dimethylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Ethyl (*R*)-4-(4-benzylmorpholin-2-yl)-2,3-dimethylbenzoate

or

Ethyl (*S*)-4-(4-benzylmorpholin-2-yl)-2,3-dimethylbenzoate



[2750] Prepared in an analogous method to Intermediate 65a starting from Intermediate 317a (4.1 g, 13.70 mmol) and *N*-benzylethanolamine (2.072 g, 13.70 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) and preparative SFC (Column: CHIRAL ART Cellulose-SC, 3*25 cm, 5 μm; Mobile Phase B: IPA; Flow rate: 100 mL/min; isocratic 30% *i*PrOH in $scCO_2$) gave the title compound (1.600 g, 33%, 98% ee) which eluted second from the column as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.29 (3H, t), 1.85 (1H, dd), 2.14 (3H, s), 2.19 (1H, t), 2.33 (3H, s), 2.72 (1H, d), 2.84 (1H, d), 3.52 (2H, d), 3.74 (1H, t), 3.92–4 (1H, m), 4.24-4.30 (2H, m), 4.73 (1H, dd), 7.24-7.29 (1H, m), 7.33 (5H, d), 7.48 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 354.1.

Intermediate 317c:

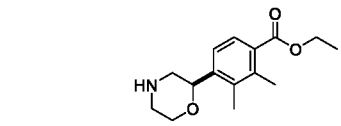
Ethyl (*R**)-2,3-dimethyl-4-(morpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

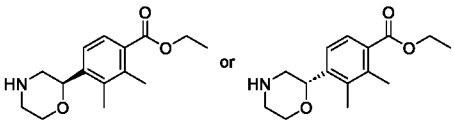
Ethyl (*R*)-2,3-dimethyl-4-(morpholin-2-yl)benzoate

or

Ethyl (*S*)-2,3-dimethyl-4-(morpholin-2-yl)benzoate



Isomer 2



[2751] Prepared in an analogous method to Intermediate 65b starting from Intermediate 317b (800 mg, 2.26 mmol) gave the title compound (590 mg, 99%) as a yellow solid. The product was used in the next step directly without further purification. ^{1}H NMR (DMSO-*d6*) δ 1.30 (3H, t), 2.22 (3H, s), 2.36 (3H, s), 2.3–2.44 (1H, m), 2.66–2.86 (2H, m), 2.90 (1H, dd), 3.55–3.74 (1H, m), 3.60-3.71 (1H, m), 4.28 (2H, d), 4.62 (1H, d), 7.33 (1H, d), 7.49 (1H, d), nitrogen-bound proton not observed; *m/z* (ES$^+$) [M+H]$^+$ =264.1.

Intermediate 317d:

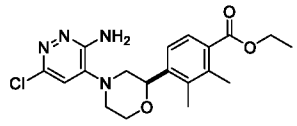
Ethyl (*R**)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

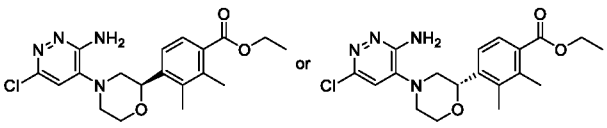
Ethyl (*R*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate

or

Ethyl (*S*)-4-(4-(3-amino-6-chloropyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate



Isomer 2



[2752] Prepared in an analogous method to Intermediate 1d starting from Intermediate 317c (590 mg, 2.24 mmol). Purification by FSC (elution gradient: 0 to 90% EtOAc in petroleum ether) gave the title compound (760 mg, 87%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.31 (3H, t), 2.28 (3H, s), 2.37 (3H, s), 2.51–2.61 (1H, m), 2.79-2.88 (1H, m), 3.37 (1H, d), 3.49 (1H, d), 4.02–4.12 (2H, m), 4.25-4.32 (2H, m), 5.01 (1H, dd), 6.30 (2H, s), 6.97 (1H, s), 7.40 (1H, d), 7.51 (1H, d); *m/z* (ES$^+$) [M+H]$^+$ =391.1.

Intermediate 317e:

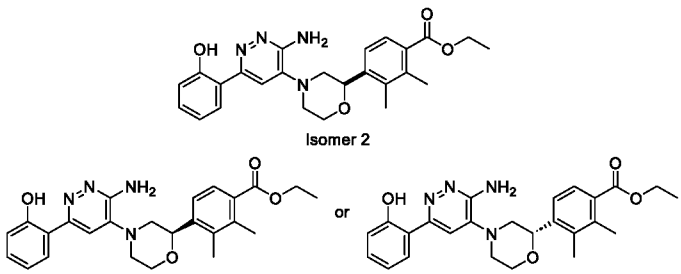
Ethyl (*R**)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate (Isomer 2)

((*absolute configuration not yet confirmed))

Ethyl (*R*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate

or

Ethyl (*S*)-4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoate



[2753] Prepared in an analogous method to Intermediate 1e starting from Intermediate 317d (760 mg, 1.94 mmol). After cooling to r.t., the mixture was poured into water (75 mL). A precipitate formed which was collected by filtration and dried *in vacuo* to give the title compound (860 mg, 99%) as a yellow solid, which was used for the next step without further purification. ^{1}H NMR (DMSO-*d6*) δ 1.3–1.32 (3H, m), 2.30 (3H, s), 2.39 (3H, s), 2.66–2.76 (1H, m), 2.91 (1H, s), 3.46–3.56 (2H, m), 4.06–4.14 (2H, m), 4.27–4.3 (2H, m), 4.98–5.09 (1H, m), 6.46 (2H, s), 6.82–6.92 (2H, m), 7.19–7.28 (1H, m), 7.39–7.46 (1H, m), 7.48–7.58 (3H, m), 7.9–7.97 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 449.1.

Intermediate 317f:

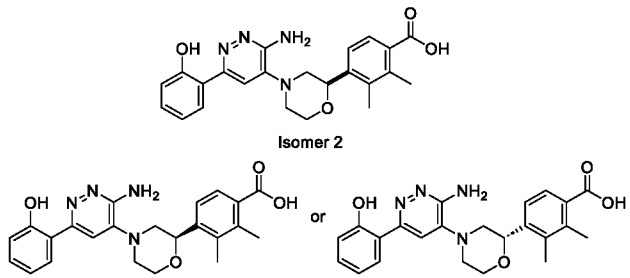
(*R**)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoic acid

or

(*S*)-4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoic acid



[2754] Prepared in an analogous method to Intermediate 316e starting from Intermediate 317e (820 mg, 1.83 mmol) gave the title compound (620 mg, 81%) as a yellow solid. The product was used in the next step directly without further purification. ^{1}HNMR (DMSO-*d6*) δ 2.29 (3H, s), 2.40 (3H, s), 2.65 – 2.76 (1H, m), 2.77 – 2.94 (1H, m), 3.49 – 3.57 (2H, m), 4.06 – 4.14 (2H, m), 4.97 – 5.06 (1H, m), 6.44 (2H, s), 6.80 – 6.91 (2H, m), 7.19 – 7.26 (1H, m), 7.42 (1H, d), 7.51 – 7.57 (2H, m), 7.93 (1H, d), 13.47 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ =421.1.

EXAMPLE 317:

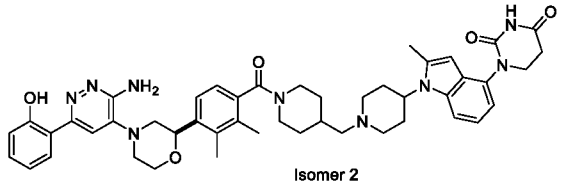
(*R**)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

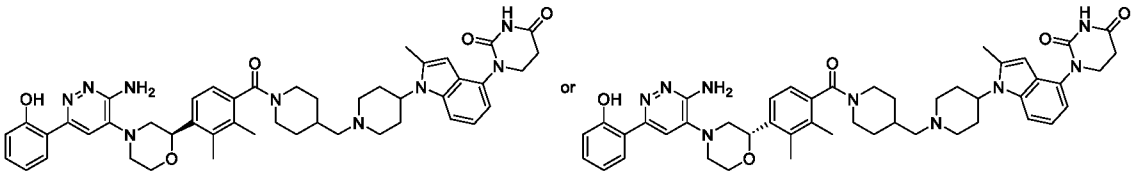
(*R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



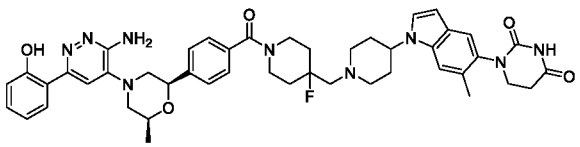
Isomer 2



[2755] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 317f (40 mg, 0.10 mmol) and Intermediate 22d (40.3 mg, 0.10 mmol). Purified by RPC (elution gradient: 0 to 20% MeCN in water) and preparative HPLC (Column: Xbridge Prep C18 OBD, 30*150 mm, 5μm; Flow rate: 60 mL/min; elution gradient: 40 to 58% MeCN in water with 10mmol/L NH_4HCO_3 and 0.1% NH_4OH) to give the title compound (11.2 mg, 14%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 0.75 – 1.34 (5H, m), 1.55 – 1.98 (6H, m), 2.03 – 2.46 (12H, m), 2.62 – 3.13 (8H, m), 3.44 – 3.60 (2H, m), 3.73 (2H, t), 4.09 (2H, d), 4.17 – 4.29 (1H, m), 4.50 – 4.65 (1H, m), 5.02 (1H, d), 6.15 (1H, s), 6.44 (2H, s), 6.82 – 6.94 (3H, m), 6.95 – 7.09 (2H, m), 7.18 – 7.28 (1H, m), 7.36 – 7.49 (2H, m), 7.58 (1H, d), 7.95 (1H, t), 10.29 (1H, s), 14.20 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 826.4.

EXAMPLE 318:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2756] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20 mg, 0.05 mmol) and Intermediate 24b (21.73 mg, 0.05 mmol). Purified by preparative HPLC (Column: Sunfire Prep C18 OBD column, 30*150mm, 5um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 31% B in 8 min) to give the title compound (14.30 mg, 34%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.27 (3H, d), 1.62 – 1.80 (2H, m), 1.81 – 1.90 (3H, m), 1.92 – 2.02 (3H, m),

2.28 (3H, s), 2.38 – 2.45 (2H, m), 2.56 (1H, d), 2.60 – 2.80 (5H, m), 3.05 (2H, d), 3.14 (1H, s), 3.48 – 3.62 (5H, m), 3.72 – 3.80 (1H, m), 4.05 – 4.18 (1H, m), 4.19 – 4.40 (2H, m), 4.85 – 5.01 (1H, m), 6.40 (1H, d), 6.49 (2H, s), 6.80 – 6.92 (2H, m), 7.18 – 7.25 (1H, m), 7.38 – 7.49 (5H, m), 7.50 – 7.60 (3H, m), 7.92 – 7.99 (1H, m), 10.26 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 830.4.

EXAMPLE 319

Intermediate 319a:

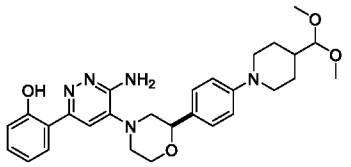
(*R**)-2-(6-amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol (Isomer 2)

((*absolute configuration not yet confirmed))

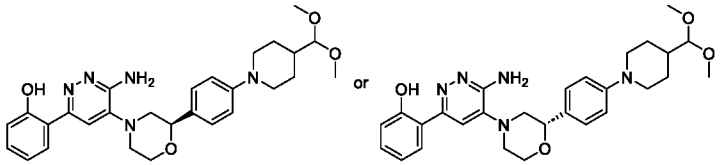
(*R*)-2-(6-amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol

or

(*S*)-2-(6-amino-5-(2-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)morpholino)pyridazin-3-yl)phenol



Isomer 2



[2757] Prepared in an analogous method to Intermediate 1e starting from Intermediate 237d (170 mg, 0.38 mmol). Purification by FSC (elution gradient: 0 to 5% MeOH in DCM) gave the title compound (157 mg, 82%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.30 – 1.42 (2H, m), 1.67 – 1.77 (3H, m), 2.53 – 2.67 (2H, m), 2.70 – 2.94 (2H, m), 3.28 (6H, s), 3.41 – 3.53 (2H, m), 3.70 (2H, d), 4.00 – 4.10 (3H, m), 4.23 (1H, t), 6.43 (1H, s), 6.89 (3H, q), 7.19 – 7.32 (3H, m), 7.55 (1H, s), 7.64 – 7.77 (1H, m), 7.91 – 7.99 (1H, m), two heteroatom-bound protons not observed; *m/z* (ES+) $[M+H]^+$ = 506.2.

EXAMPLE 319:

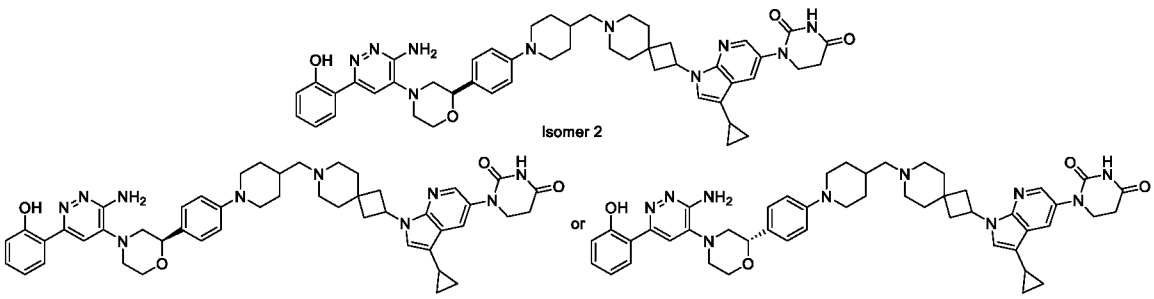
(*R**)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2758] Prepared in an analogous method to EXAMPLE 237 starting from Intermediate 319a (50 mg, 0.10 mmol) and Intermediate 237h (38.9 mg, 0.10 mmol). Purification by preparative HPLC (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm, elution gradient: 12 to 32% MeCN in water with 0.1% FA) gave the title compound (16.80 mg, 19%) as a yellow solid. ^{1}H NMR (DMSO-*d6*) δ 0.65 – 0.74 (2H, m), 0.82 – 0.94 (2H, m), 1.10 – 1.27 (2H, m), 1.63 – 1.83 (7H, m), 1.90 – 1.98 (1H, m), 2.13 – 2.25 (4H, m), 2.27 – 2.43 (5H, m), 2.64 (2H, t), 2.71 – 2.82 (3H, m), 2.86 (1H, t), 3.45 (3H, d), 3.68 (2H, d), 3.81 (2H, t), 3.94 – 4.08 (2H, m), 4.70 (1H, d), 5.18 – 5.31 (1H, m), 6.46 (2H, s), 6.83 – 6.97 (4H, m), 7.21 – 7.30 (3H, m), 7.56 (2H, d), 7.92 – 7.98 (2H, m), 8.17 (1H, d), 8.20 (1H, s), 10.41 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) [M+H]+ = 837.5.

EXAMPLE 320:

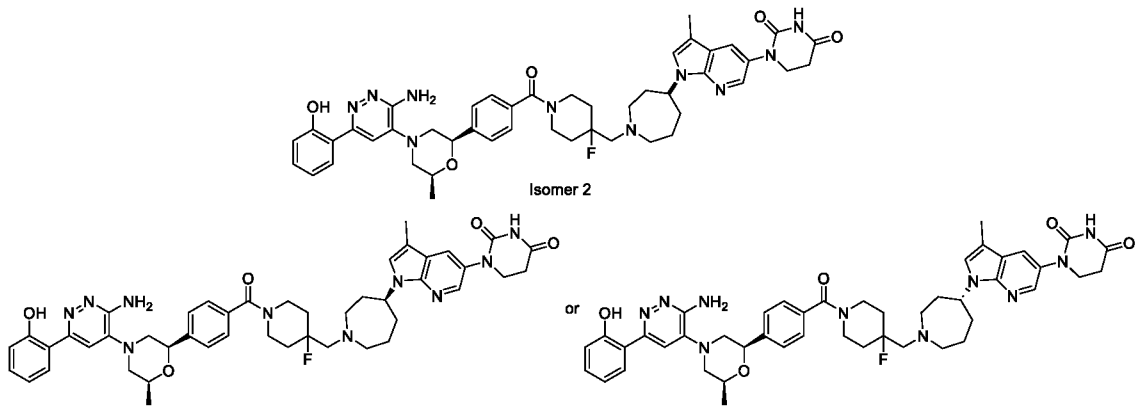
1-(1-((*S**)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-((*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

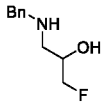


[2759] Intermediate 241e (60 mg, 0.11 mmol) was added in DCM (1 mL) and TFA (0.300 mL). The resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (2 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the residue were added Intermediate 65e (52.6 mg, 0.13 mmol), DIPEA (0.028 mL, 0.16 mmol) and DMF (1.0 mL) followed by HATU (49.2 mg, 0.13 mmol). The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM–IPA (5:1, 10 mL), washed with aq. NH_4OH (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (elution gradient: 10 to 30% MeCN in water with 0.1% FA, Flow rate: 60 mL/min) gave the title compound (7.42 mg, 8%) as a white solid. ^{1}HNMR (DMSO-*d6*) δ 1.26 (3H, d), 1.61 – 1.73 (2H, m), 1.75 – 1.83 (2H, m), 1.84 – 1.92 (2H, m), 1.92 – 2.04 (2H, m), 2.07 – 2.17 (2H, m), 2.25 (3H, s), 2.55 (1H, d), 2.65 – 2.73 (1H, m), 2.73 – 2.79 (3H, m), 2.82 (1H, s), 2.83 – 2.95 (4H, m), 3.01 – 3.22 (2H, m), 3.49 – 3.54 (2H, m), 3.58 (1H, d), 3.80 (2H, t), 4.04 – 4.16 (1H, m), 4.29 (1H, s), 4.81 – 4.92 (1H, m), 4.92 – 4.99 (1H, m), 6.49 (2H, s), 6.84 – 6.92 (2H, m), 7.20 – 7.27 (1H, m), 7.41 – 7.50 (3H, m), 7.51 – 7.59 (3H, m), 7.87 (1H, d), 7.93 – 7.98 (1H, m), 8.17 (1H, d), 10.40 (1H, s), 14.23 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.7.

EXAMPLE 321

Intermediate 321a:

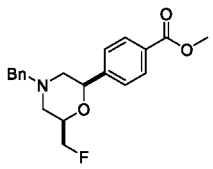
1-(Benzylamino)-3-fluoropropan-2-ol



[2760] Benzylamine (5.63 g, 52.58 mmol) was added to 2-(fluoromethyl)oxirane (4 g, 52.58 mmol) in *i*-PrOH (40 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 6 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeCN in water with 0.01% NH_4HCO_3) gave the title compound (6.0 g, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.67 – 2.81 (2H, m), 2.86 (2H, d), 3.84 (2H, dd), 3.88 – 3.98 (1H, m), 4.41 (2H, dddd), 7.18 – 7.45 (5H, m); *m/z* (ES^+) $[M+H]^+$ =184.1.

Intermediate 321b:

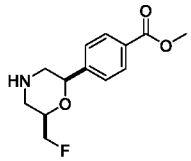
rac-Methyl 4-((2*R*,6*R*)-4-benzyl-6-(fluoromethyl)morpholin-2-yl)benzoate



[2761] Intermediate 321a (1.5 g, 8.19 mmol) was added to methyl 4-(2-bromoacetyl)benzoate (2.105 g, 8.19 mmol) and DIPEA (4.29 mL, 24.56 mmol) in DCM (40 mL) under nitrogen. The resulting mixture was stirred at r.t. for 4 h. The reaction mixture was washed with sat. aq. NH_4Cl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. DCM (40 mL) and triethylsilane (2.86 g, 24.56 mmol) were added and the mixture was cooled to 0 °C. Boron trifluoride etherate (3.49 g, 24.56 mmol) was added slowly and the mixture was stirred at 0 °C for 2 h. TFA (4.00 mL) was added slowly. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with MeOH (10 mL). The mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 60% MeOH in water with 0.01% NH_4HCO_3) gave the title compound (1.30 g, 46%) as a colorless oil. ^{1}H NMR (DMSO-*d6*) δ 1.95 (2H, dt), 2.80 (1H, dt), 2.92 (1H, dt), 3.46 – 3.63 (2H, m), 3.85 (3H, s), 3.89 – 4.01 (1H, m), 4.40 – 4.61 (2H, m), 4.72 (1H, dd), 7.24 – 7.30 (1H, m), 7.30 – 7.36 (4H, m), 7.50 (2H, d), 7.91 – 7.97 (2H, m); *m/z* (ES^+) $[M+H]^+$ =344.2.

Intermediate 321c:

rac-Methyl 4-((2*R*,6*R*)-6-(fluoromethyl)morpholin-2-yl)benzoate



[2762] $Pd(OH)_2$/C (0.523 g, 3.73 mmol, 10 wt% palladium) was added to Intermediate 321b (1.28 g, 3.73 mmol) in MeOH (100 mL). The resulting mixture was stirred at r.t under hydrogen atmosphere for 16 h. The mixture was filtered through celite. The filtrate was concentrated under reduced pressure to give the title compound (0.900 g, 95%). The product was used in the next step directly without further purification. ^{1}H NMR (DMSO-*d6*) δ 2.40 (1H, dd), 2.49 – 2.53 (2H, m), 2.85 (1H, dd), 2.96 (1H, dd), 3.18 (1H, s), 3.85 (3H, s), 4.38 – 4.46 (1H, m), 4.48 – 4.55 (1H, m), 4.58 (1H, dd), 7.49 (2H, d), 7.92 – 7.98 (2H, m); *m/z* (ES^+) $[M+H]^+$ = 254.2.

Intermediate 321d:

Methyl 4-((2*R**,6*R**)-4-(3-amino-6-chloropyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate (isomer 1)

and

Intermediate 321e:

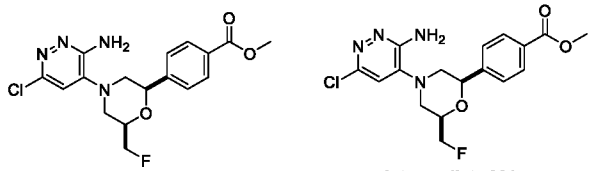
Methyl 4-((2*R**,6*R**)-4-(3-amino-6-chloropyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate (isomer 2)

((*absolute configurations not yet confirmed))

Methyl 4-((2*R*,6*R*)-4-(3-amino-6-chloropyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate

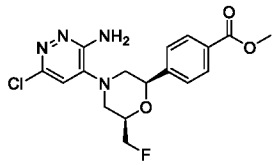
and

Methyl 4-((2*S*,6*S*)-4-(3-amino-6-chloropyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate

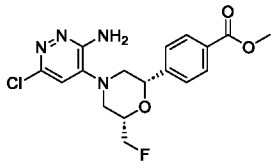


Intermediate 321d
Isomer 1

Intermediate 321e
Isomer 2



Isomer 1 or 2



Isomer 2 or 1

[2763] Prepared in an analogous method to Intermediate 1d starting from Intermediate 321c (900 mg, 3.55 mmol). Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4HCO_3) and preparative SFC (column: CHIRALPAK IF 3*25 cm, 5 μm; Flow rate: 100 mL/min; isocratic 50% [MeOH–MeCN (1:1) in $scCO_2$) gave Intermediate 321d (470 mg, 35%, >99% ee) which eluted first from the column and Intermediate 321e (570 mg, 42%, >95% ee) which eluted second from the column as a pale yellow solids. ^{1}H NMR (DMSO-*d6*) δ 2.52 – 2.70 (2H, m), 3.40 – 3.59 (2H, m), 3.84 (3H, s), 4.15 – 4.31 (1H, m), 4.50 (1H, qd), 4.59 – 4.72 (1H, m), 4.99 (1H, dd), 6.40 (2H, s), 6.98 (1H, s), 7.54 – 7.65 (2H, m), 7.92 – 8.03 (2H, m); *m/z* (ES^+) $[M+H]^+$ =381.2.

Intermediate 321f:

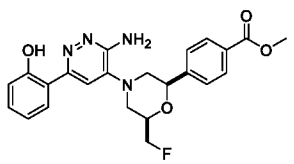
Methyl 4-((2*R**,6*R**)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate (Isomer 2)

((*absolute configuration not yet confirmed))

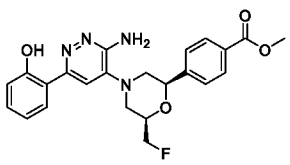
Methyl 4-((2*R*,6*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate

or

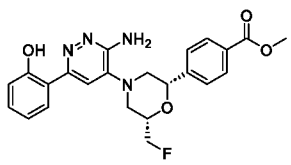
Methyl 4-((2*S*,6*S*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoate



Isomer 2



or



[2764] Prepared in an analogous method to Intermediate 1e starting from Intermediate 321e (0.57 g, 1.50 mmol. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (0.350 g, 53%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 2.73 (2H, td), 3.58 (2H, dd), 3.87 (3H, s), 4.26 – 4.40 (1H, m), 4.50 – 4.76 (2H, m), 5.06 (1H, dd), 6.56 (2H, s), 6.83 – 6.92 (2H, m), 7.23 (1H, ddd), 7.57 – 7.66 (3H, m), 7.94 (1H, dd), 7.98 – 8.04 (2H, m), 14.16 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 439.3.

Intermediate 321g:

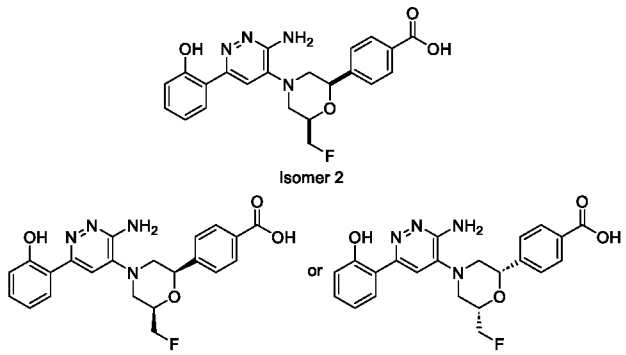
4-((2*R**,6*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoic acid (Isomer 2)

((*absolute configuration not yet confirmed))

4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoic acid

or

4-((2*S*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoic acid



[2765] Prepared in an analogous method to Intermediate 316e starting from Intermediate 321f (0.35 g, 0.80 mmol) to give the title compound (0.270 g, 80%) as a white solid, which was used without further purification. ^{1}H NMR (DMSO-*d6*) δ 2.74 (2H, t), 3.57 (2H, dd), 4.33 (1H, dddd), 4.63 (2H, dddd), 5.04 (1H, dd), 6.56 (2H, s), 6.83 – 6.93 (2H, m), 7.20 – 7.28 (1H, m), 7.55 – 7.64 (3H, m), 7.92 – 8.02 (3H, m), 13.87 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 425.2.

EXAMPLE 321:

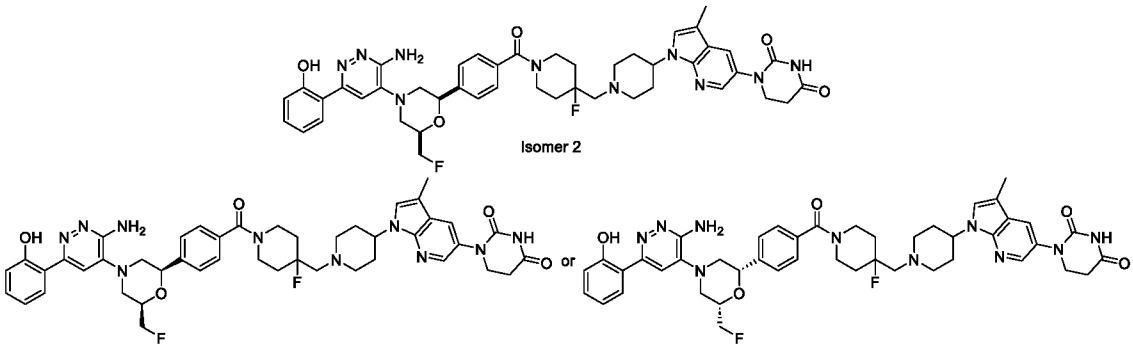
1-(1-(1-((1-(4-((2*R**,6*R**)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

1-(1-(1-((1-(4-((2*R*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

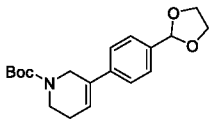


[2766] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 321g (0.04 g, 0.09 mmol) and Intermediate 161a (0.042 g, 0.09 mmol). Purification by preparative HPLC (Column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; elution gradient: 17 to 27% MeCN in water with 0.1% FA) gave the title compound (23.0 mg, 29%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.58 – 2.18 (7H, m), 2.27 (3H, s), 2.37 (1H, s), 2.63 (1H, s) 2.72 (1H, s), 2.73 – 2.85 (4H, m), 3.09 (2H, d), 3.24 – 3.30 (2H, m), 3.34 – 3.43 (3H, m), 3.52 (1H, s), 3.60 (2H, t), 3.81 (2H, t), 4.20 – 4.42 (2H, m), 4.63 (2H, dddd), 5.01 (1H, dd), 6.59 (2H, d), 6.85 – 6.95 (2H, m), 7.22 – 7.30 (1H, m), 7.46 (2H, d), 7.57 (2H, d), 7.61 (1H, s), 7.92 (2H, d), 8.17 (1H, d), 10.40 (1H, s), 14.12 (1H, s), one proton not resolved; *m/z* (ES$^+$) $[M+H]^+$ = 849.6.

EXAMPLE 322

Intermediate 322a:

tert-Butyl 5-(4-(1,3-dioxolan-2-yl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

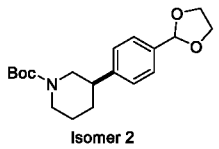


[2767] 2-(4-Bromophenyl)-1,3-dioxolane (0.8 g, 3.49 mmol) was added to *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.134 g, 3.67 mmol), K_2CO_3 (1.448 g, 10.48 mmol) and $PdCl_2$(dppf) (0.256 g, 0.35 mmol) in 1,4-dioxane (10 mL) and water (2.000 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1%NH_4HCO_3) gave the title compound (0.800 g, 69%) as a pale yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.43 (9H, s), 2.22 – 2.29 (2H, m), 3.47 (2H, t), 3.92 – 3.98 (2H, m), 4.03 – 4.08 (2H, m), 4.16 – 4.24 (2H, m), 5.73 (1H, s), 6.25 – 6.35 (1H, m), 7.42 (4H, s); *m/z* (ES$^+$) $[M-t\text{Bu}+2H]^+$ =276.1.

Intermediate 322b:

tert-Butyl (*S**)-3-(4-(1,3-dioxolan-2-yl)phenyl)piperidine-1-carboxylate (Isomer 2)

((*absolute configuration not yet confirmed))

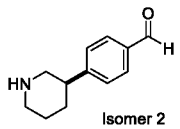


[2768] Intermediate 233a (2.8 g, 8.45 mmol) was added to Pd/C (0.899 g, 8.45 mmol) in MeOH (50 mL). The resulting mixture was stirred at r.t under an atmosphere of hydrogen for 1 h. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) and preparative SFC (Column: CHIRALPAK AD-3, 4.6*50mm, 3µm; Flow rate: 200 mL/min; 40isocratic % MeOH in $scCO_2$) gave the title compound (1.800 g, 64%, 99% ee) that eluted second from the column as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.41 (9H, s), 1.43 – 1.50 (1H, m), 1.59 – 1.74 (2H, m), 1.88 (1H, dd), 2.60 – 2.65 (1H, m), 2.69 – 2.96 (2H, m), 3.90 – 4.00 (4H, m), 4.02 – 4.06 (2H, m), 5.70 (1H, s), 7.29 (2H, d), 7.36 – 7.40 (2H, m); *m/z* (ES^+) $[M-t\text{Bu}+2H]^+$ = 278.2.

Intermediate 322c:

(*S**)-4-(Piperidin-3-yl)benzaldehyde (Isomer 2)

((*absolute configuration not yet confirmed))

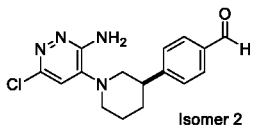


[2769] 10 M aq. HCl (2 mL, 20.00 mmol) was added to Intermediate 322b (0.9 g, 2.70 mmol) in MeOH (5 mL). The resulting mixture was stirred at r.t. for 4 h and concentrated under reduced pressure to give the title compound (0.600 g, 98%) as a colorless oil. The product was used in the next step directly without further purification. *m/z* (ES^+) $[M+H]^+$ = 190.0.

Intermediate 322d:

(*S**)-4-(1-(3-Amino-6-chloropyridazin-4-yl)piperidin-3-yl)benzaldehyde (Isomer 2)

((*absolute configuration not yet confirmed))

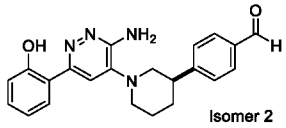


[2770] DIPEA (1.70 mL, 9.75 mmol) and 6-chloropyridazin-3-amine (0.678 g, 3.25 mmol) were added to Intermediate 322c (0.80 g, 4.23 mmol) in MeCN (5 mL). The resulting mixture was stirred at 80 °C for 16 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.300 g, 29%) as a pale yellow solid. ^{1}H NMR (DMSO-*d6*) δ 1.60 –1.70 (1H, m), 1.79 – 1.93 (2H, m), 1.94 – 2.05 (1H, m), 2.60 – 2.74 (2H, m), 3.15 – 3.21 (1H, m), 3.39 – 3.56 (2H, m), 6.17 (2H, s), 6.96 (1H, s), 7.57 (2H, d), 7.88 (2H, d), 9.99 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 317.1

Intermediate 322e:

(*S**)-4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzaldehyde (Isomer 2)

((*absolute configuration not yet confirmed))

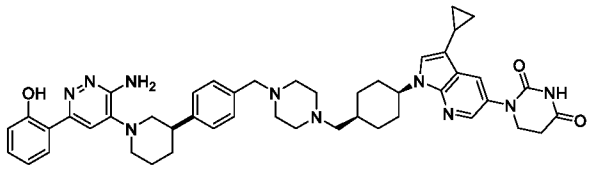


[2771] Prepared in an analogous method to Intermediate 1e starting from Intermediate 322d (290 mg, 0.92 mmol). Purification by preparative TLC (EtOAc:petroleum ether = 1:1) gave the title compound (160 mg, 47%) as a tan solid. ^{1}H NMR (DMSO-*d6*) δ 1.23 (1H, s), 1.61 – 1.77 (1H, m), 1.86 – 2.03 (3H, m), 2.67 – 2.90 (2H, m), 3.16 – 3.27 (1H, m), 3.55 (1H, d), 6.29 (2H, s), 6.79 – 6.99 (2H, m), 7.15 – 7.33 (1H, m), 7.53 – 7.73 (3H, m), 7.80 – 8.04 (3H, m), 9.99 (1H, s), 14.23 (1H, s); *m/z* (ES$^+$) [M+H]$^+$ = 375.3.

EXAMPLE 322:

1-(1-((1*S*,4*s*)-4-((4-(4-((*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))



[2772] TFA (6 mL) was added to a stirred solution of Intermediate 118d (150 mg, 0.27 mmol) in DCM (6 mL). The resulting mixture was stirred at r.t. for 30 min. The solvent was removed under reduced pressure. To the residue was added Intermediate 322e in DCE (6 mL) and NMP (6 mL). The resulting mixture was stirred at 60 °C for 2 days. After cooling to r.t., sodium triacetoxyborohydride (693 mg, 3.27 mmol) was added. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (250 mL), washed with sat. aq. $NaHCO_3$ (3 x 200 mL) and brine (3 x 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; elution gradient: 48 to 65% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (3.8 mg, 2%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 0.61 – 0.69 (2H, m), 0.78 – 0.91 (2H, m), 1.25 (1H, d), 1.55-1.72 (5H, m), 1.76 (2H, d), 1.78 – 2.02 (8H, m), 2.22 – 2.46 (8H, m), 2.65 – 2.81 (4H, m), 3.05 (1H, d), 3.44 (2H, s), 3.54 (2H, d), 3.81 (2H, t), 4.59 (1H, d), 6.29 (2H, s), 6.87 (2H, t), 7.19 – 7.34 (5H, m), 7.53 (2H, d), 7.91 – 7.94 (2H, m), 8.16 (1H, d), 10.40 (1H, s), 14.30 (1H, s); *m/z* (ES$^+$) [M+H]$^+$ = 809.5.

EXAMPLE 323:

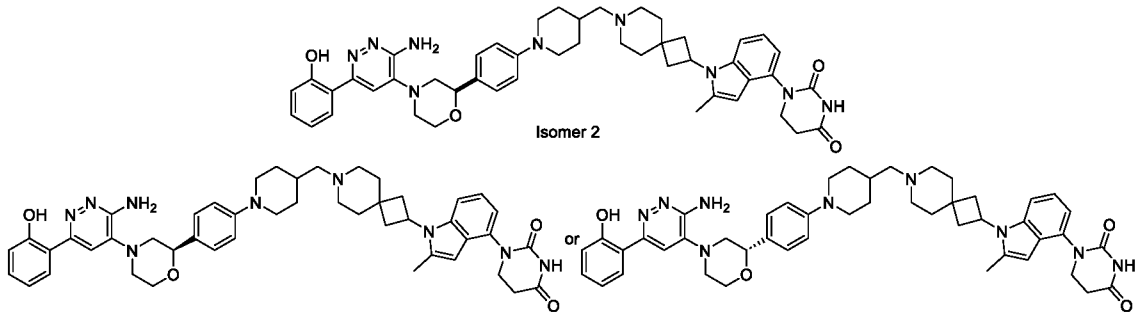
(*R**)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

((*absolute configuration not yet confirmed))

(*R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

(*S*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

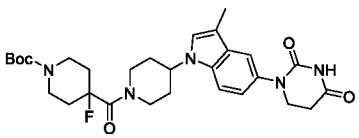


[2773] Prepared in an analogous method to EXAMPLE 237 starting from Intermediate 319a (95 mg, 0.19 mmol) and Intermediate 243c (103 mg, 0.28 mmol). Purification by preparative HPLC (elution gradient: 11 to 32% MeCN in water with 0.1%FA; Flow rate: 60 mL/min) gave the title compound (24.2 mg, 16%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.18 – 1.23 (3H, m), 1.74 –1.81 (7H, m), 2.14 (2H, d), 2.30 – 2.34 (2H, m), 2.38 – 3.43 (5H, m), 2.54 – 2.7 (4H, m), 2.72 – 2.79 (3H, m), 2.87 (1H, d), 3.42 – 3.46 (3H, m), 3.64 – 3.77 (4H, m), 3.95 – 4.08 (2H, m), 4.70 (1H, d), 4.96 (1H, t), 6.15 (1H, s), 6.46 (2H, s), 6.84 – 6.95 (5H, m), 7.07 (1H, t), 7.21 – 7.29 (3H, m), 7.55 (2H, t), 7.95 (1H, d), 10.33 (1H, s), 14.24 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 810.4.

EXAMPLE 324

Intermediate 324a:

tert-Butyl 4-(4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-indol-1-yl)piperidine-1-carbonyl)-4-fluoropiperidine-1-carboxylate



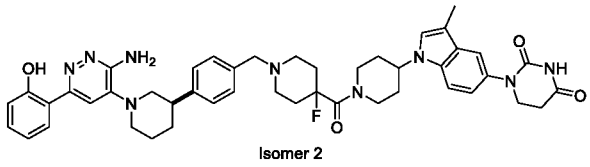
[2774] Intermediate 1i (200 mg, 0.61 mmol) was added to 1-(*tert*-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (167 mg, 0.67 mmol), HATU (233 mg, 0.61 mmol) and DIPEA (0.321 mL, 1.84 mmol) in DMF (2 mL). The resulting mixture was stirred at r.t. for 2 h. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1%NH_4HCO_3) gave the title compound (200 mg, 58.7 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 1.42 (9H, s), 1.85 (2H, s), 1.99 (6H, d), 2.23 (3H, s), 2.73 (2H, t), 2.89 (1H, s), 3.09 (2H, s), 3.27 (1H, s), 3.78 (2H, t), 3.84 (2H, d), 4.51 (2H, s), 4.61 – 4.72 (1H, m), 7.04 – 7.11 (1H, m), 7.34 (1H, s), 7.41 (1H, d), 7.53 (1H, d), 10.26 (1H, s). *m/z* (ES$^+$), $[M+H]^+$ = 556.4.

EXAMPLE 324:

(*R*)-1-(1-(1-(1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)-4-fluoropiperidine-4-carbonyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(Isomer 2)

((*absolute configuration not yet confirmed))



Isomer 2

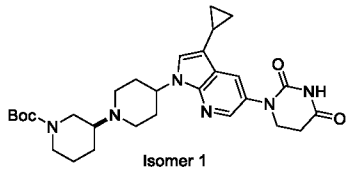
[2775] TFA (1 mL, 12.98 mmol) was added to Intermediate 324a (148 mg, 0.27 mmol) in DCM (3 mL). The resulting mixture was stirred at r.t for 1 h. The solvent was removed under reduced pressure to afford the crude amine. To the crude amine was added Intermediate 322e (100 mg, 0.27 mmol) in DCM (3 mL). The mixture was stirred at 50 °C for 30 min. After cooling to r.t., sodium triacetoxyborohydride (226 mg, 1.07 mmol) was added. The resulting mixture was stirred at r.t for 4 h. The reaction mixture was diluted with DCM (15 mL), washed with sat. aq. $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; elution gradient: 19 to 35% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH; Flow rate: 25 mL/min) gave the title compound (32.5 mg, 15%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.59 – 1.71 (1H, m), 1.74 – 2.07 (11H, m), 2.15 – 2.34 (6H, m), 2.63 – 2.81 (6H, m), 3.07 (1H, t), 3.45 – 3.61 (5H, m), 3.77 (2H, t), 4.50 (2H, s), 4.58 – 4.73 (1H, m), 6.28 (2H, s), 6.83 – 6.93 (2H, m), 7.04 – 7.12 (1H, m), 7.19 – 7.36 (6H, m), 7.38 – 7.44 (1H, m), 7.48 – 7.58 (2H, m), 7.88 – 7.97 (1H, m), 10.26 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 814.4.

EXAMPLE 325

Intermediate 325a:

tert-Butyl (*R*)-4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-[1,3'-bipiperidine]-1'-carboxylate (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

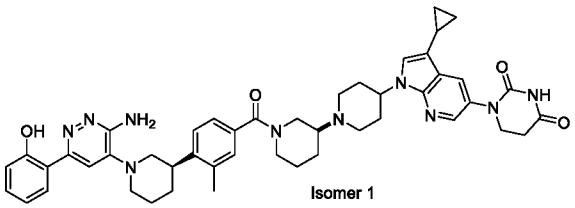
[2776] Sodium triacetoxyborohydride (2.70 g, 12.73 mmol) was added to *tert*-butyl 3-oxopiperidine-1-carboxylate (1.691 g, 8.49 mmol) and Intermediate 7e (1.5 g, 4.24 mmol) in DCM (20 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was poured into sat. aq. Na_2CO_3 (300 mL). The mixture was extracted with DCM (3 x 300 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (CHIRALPAK IA 2*25 cm, 5 μm; Flow rate: 20 mL/min; isocratic 30% EtOH in [MTBE with 0.5% 2 M NH_3 in MeOH]) gave the title compound (0.380 g, 17%, 95% ee) which eluted first from the column as a white solid. ^{1}H

NMR (DMSO-*d6*) δ 0.62–0.72 (2H, m), 0.8–0.92 (2H, m), 1.27–1.39 (1H, m), 1.41 (9H, s), 1.67 (2H, t), 1.78–2.12 (6H, m), 2.25–2.46 (3H, m), 2.62–2.82 (4H, m), 3.04 (2H, t), 3.72–4.09 (4H, m), 4.50–4.66 (1H, m), 7.46 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.40 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 537.3.

EXAMPLE 325:

1-(1-((*S**)-1'-(4-((*R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-[1,3'-bipiperidin]-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



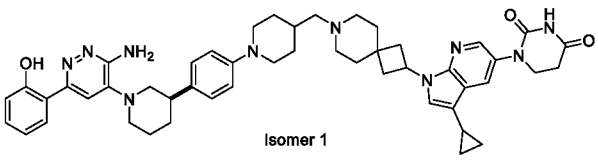
Isomer 1

[2777] TsOH (37 mg, 0.21 mmol) was added to Intermediate 325 a (100 mg, 0.18 ml) in MeCN (3 mL). The resulting mixture was stirred at 70 °C for 16 h. After cooling to r.t., the mixture was concentrated under reduced pressure. To the residue was added a solution of Intermediate 12g (111 mg, 0.27 mmol) and DIPEA (0.200 mL, 1.15 mmol) in DMF (2 mL). HATU (105 mg, 0.27 mmol) was added. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was poured into DCM (25mL), washed with sat. aq. $NaHCO_3$ (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; elution gradient: 21 to 29% MeCN in water with 0.1% FA) gave the title compound (30.0 mg, 16%) as a white solid. ^1H NMR (DMSO-*d6*) δ 0.65 (2H, d), 0.85 (2H, d), 1.39–1.42 (1H, s), 1.48–1.71 (3H, m), 1.75–2.10 (10H, m), 2.36–2.42 (4H, m), 2.63–2.8 (4H, m), 2.82–2.97 (2H, m), 3.07 (3H, s), 3.24–3.28 (1H, m), 3.45–3.75 (3H, m), 3.78–3.83 (2H, m), 4.45 (2H, d), 6.29 (2H, s), 6.83–6.92 (2H, m), 7.22 (3H, d), 7.37–7.49 (2H, m), 7.57 (1H, s), 7.91–7.98 (2H, m), 8.17 (1H, s), 10.40 (1H, s), 14.27 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 823.5.

EXAMPLE 326:

(*R**)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1)

((*absolute configuration not yet confirmed))



Isomer 1

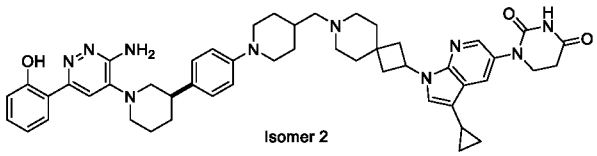
[2778] Prepared in an analogous method to EXAMPLE 311 starting from Intermediate 311f (80 mg, 0.16 mmol) and Intermediate 237h (89 mg, 0.13 mmol). Purification by preparative HPLC (Xselect CSH

C18 OBD Column 30*150mm 5μm; Flow rate: 60 mL/min; elution gradient: 13 to 35% MeCN in water with 0.1% FA) gave the title compound (21.00 mg, 16%) as a white solid. ^{1}H NMR (DMSO *d6)* δ 0.65–0.73 (2H, m), 0.83–0.92 (2H, m), 1.13–1.26 (3H, m), 1.54–1.81 (8H, m), 1.87 (1H, s), 1.90–1.99 (3H, m), 2.22 (4H, t), 2.31–2.38 (4H, m), 2.42 (1H, s), 2.60 (2H, d), 2.63–2.73 (2H, m), 2.77 (2H, t), 2.96 (1H, s), 3.44–3.57 (2H, m), 3.64 (2H, d), 3.82 (2H, t), 5.21–5.3 (1H, m), 6.27 (2H, s), 6.83–6.93 (4H, m), 7.17 (2H, d), 7.2–7.28 (1H, m), 7.55 (2H, d), 7.89–7.98 (2H, m), 8.13–8.2 (1H, m), 10.40 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 835.6.

EXAMPLE 327:

(*R**)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 2)

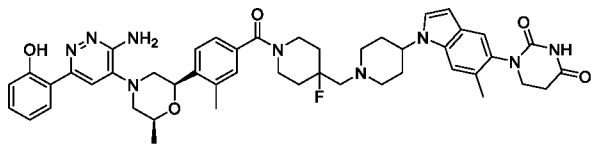
((*absolute configuration not yet confirmed))



[2779] Prepared in an analogous method to EXAMPLE 311 starting from Intermediate 312a (100 mg, 0.20 mmol) and Intermediate 237h (98 mg, 0.14 mmol). Purification by preparative HPLC (Xselect CSH C18 OBD Column 30*150mm 5μm; Flow rate: 60 mL/min; elution gradient: 19 to 32% MeCN in water with 0.1% FA) gave the title compound (21.6 mg, 13%) as a white solid. ^{1}H NMR (DMSO *d6*) δ 0.67 – 0.72 (2H, m), 0.84 – 0.9 (2H, m), 1.19 (2H, d), 1.24 (1H, s), 1.59 – 1.79 (8H, m), 1.85 – 1.97 (4H, m), 2.15 (2H, d), 2.21 (2H, t), 2.32 (5H, t), 2.60 (2H, t), 2.70 (2H, t), 2.76 (2H, t), 2.96 (1H, t), 3.51(2H, s), 3.60 – 3.65 (2H, d), 3.81 (2H, t), 5.2 – 5.3 (1H, m), 6.27 (2H, s), 6.84 – 6.92 (4H, m), 7.16 (2H, d), 7.2 – 7.26 (1H, m), 7.54 (2H, d), 7.9 – 7.97 (2H, m), 8.17 (1H,d), 10.40 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 835.6.

EXAMPLE 328:

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

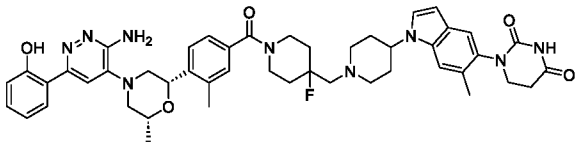


[2780] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 24b (118 mg, 0.27 mmol) and Intermediate 132e (80 mg, 0.19 mmol). Purification by preparative HPLC (Sunfire Prep C18 OBD column, 30*150mm, 5um; Flow rate: 60 mL/min; elution gradient: 17 to 31% MeCN in water with 0.1% FA) gave the title compound (44.8 mg, 28%) as a white solid. ^{1}H NMR (DMSO-*d6*) δ 1.25 (3H, d),

1.59 – 1.80 (2H, m), 1.81 – 2.09 (6H, m), 2.28 (3H, s), 2.35 – 2.49 (5H, m), 2.60 – 2.70 (2H, m), 2.71 – 2.85 (3H, m), 3.00 – 3.25 (4H, m), 3.45 – 3.60 (5H, m), 3.70 – 3.85 (1H, m), 4.05 – 4.20 (1H, m), 4.21 – 4.40 (2H, m), 5.04 (1H, d), 6.40 (3H, d), 6.69 – 7.01 (2H, m), 7.19 – 7.31 (3H, m), 7.42 (3H, d), 7.56 (2H, d), 7.86 – 8.05 (1H, m), 10.27 (1H, s), 14.23 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 844.5.

EXAMPLE 329:

1-(1-(1-((1-(4-((2*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

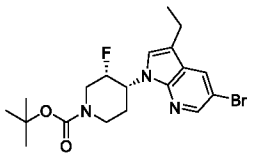


[2781] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 24b (118 mg, 0.27 mmol) and Intermediate 188e (80 mg, 0.19 mmol). Purification by preparative HPLC (elution gradient: 30*150mm, 5um; Flow rate: 60 mL/min; elution gradient: 17 to 31% MeCN in water with 0.1% FA) gave the title compound (50.1 mg, 31%) as a white solid. ^{1}H NMR (DMSO-d6) δ 1.25 (3H, d), 1.63 – 1.82 (2H, m), 1.83 – 2.09 (6H, m), 2.28 (3H, s), 2.36 – 2.49 (5H, m), 2.54 (1H, d), 2.61 (1H, s), 2.67 (1H, s), 2.68 – 2.82 (3H, m), 2.95 – 3.28 (4H, s), 3.49 – 3.60 (4H, m), 3.70 – 3.81 (1H, m), 4.06 – 4.21 (1H, m), 4.22 – 4.42 (2H, m), 4.96 – 5.15 (1H, m), 6.35 – 6.55 (3H, m), 6.79 – 6.96 (2H, m), 7.15 – 7.34 (3H, m), 7.42 (2H, d), 7.48 (1H, d), 7.56 (2H, d), 7.85 – 8.06 (1H, m), 10.27 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 844.4.

EXAMPLE 330

Intermediate 330a:

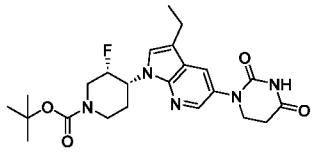
tert-Butyl (3*S*,4*R*)-4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2782] 5-Bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 8.89 mmol) was added to a solution of *tert*-butyl (3*S*,4*S*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (3.90 g, 17.8 mmol) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (4.29 g, 17.8 mmol) in toluene (15 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (1.80 g, 47%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 1.19 – 1.28 (3H, m), 1.42 (9H, s), 1.73 – 1.85 (1H, m), 2.25 – 2.42 (1H, m), 2.64 – 2.74 (2H, m), 3.01 – 3.36 (2H, m), 4.15 – 4.35 (2H, m), 4.75 – 5.17 (2 H, m), 7.43 – 7.48 (1H, m), 8.24 (1H, d), 8.29 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 425.9.

Intermediate 330b:

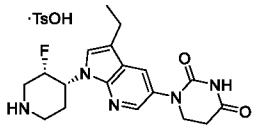
tert-Butyl (3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2783] Intermediate 330a (1.75 g, 4.10 mmol) was added to a suspension of dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.41 g, 12.3 mmol), EPhos (0.22 g, 0.41 mmol), EPhos Pd G4 (0.38 g, 0.41 mmol) and Cs_2CO_3 (2.67 g, 8.21 mmol) in 1,4-dioxane (15 mL) under nitrogen. The resulting mixture was stirred at 90 °C for 16 hours. After cooling to r.t., the mixture was filtered. The filtrate was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (0.41 gm 21%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.16 – 1.20 (1H, m), 1.24 – 1.29 (3H, m), 1.43 (9H, s), 1.75 – 1.84 (1H, m), 2.28 – 2.40 (1H, m), 2.66 – 2.74 (2H, m), 2.74 – 2.81 (2H, m), 3.80 – 3.85 (2H, m), 4.01 – 4.06 (1H, m), 4.10 – 4.43 (2H, m), 4.89 (1H, d), 5.05 – 5.19 (1H, m), 7.44 (1H, d), 7.98 (1H, d), 8.21 (1H, d), 10.42 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 460.1.

Intermediate 330c:

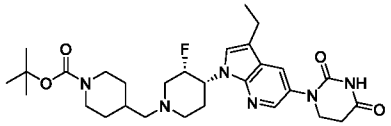
1-(3-Ethyl-1-((3*S*,4*R*)-3-Fluoropiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2784] Intermediate 330b (0.40 g, 0.87 mmol) was added to *p*-toluenesulfonic acid (225 mg, 1.31 mmol) in MeCN (5 mL). The resulting mixture was stirred at 80 °C for 8 hours. After cooling to r.t., the mixture was diluted with MTBE (15 mL). The mixture was filtered. The filtercake was dried *in vacuo* to give the title compound (0.36 g, 67%) as a white solid and TsOH salt. ^{1}H NMR (DMSO-d_6) δ 1.23–1.31 (3H, m), 2.02–2.13 (1H, m), 2.29 (3H, s), 2.53–2.64 (1H, m), 2.67–2.81 (4H, m), 3.29 – 3.50 (2H, m), 3.54 – 3.73 (2H, m), 3.79 – 3.86 (2H, m), 5.11–5.37 (2H, m), 7.08–7.14 (2H, m), 7.35–7.38 (1H, m), 7.45–7.5 (2H, m), 8.01 (1H, d), 8.23 (1H, d), 8.78 (1H, s), 9.11 (1H, s), 10.41 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 360.1.

Intermediate 330d:

tert-Butyl 4-(((3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

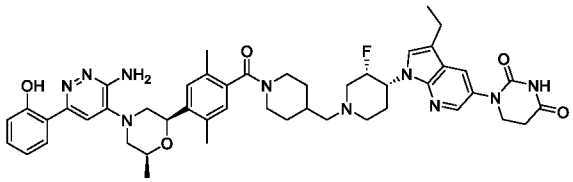


[2785] Intermediate 330c (300 mg, 0.56 mmol) was added to a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (241 mg, 1.13 mmol) in DMF (5 mL). The resulting mixture was stirred at 40 °C for 45 minutes. After cooling to r.t., sodium triacetoxyborohydride (478 mg, 2-26 mmol) was added. The resulting mixture was stirred at r.t. for 1 hour. The mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. Purification by RPC (elution gradient: 0 to 40% MeCN in water with 0.1% NH_4HCO_4) gave the title compound (201 mg, 63%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.93 – 1.02 (2H, m), 1.25 – 1.28 (3H, m), 1.37 – 1.39 (1H, m), 1.40 (9H, s), 1.67 – 1.74 (3H, m), 1.75 – 1.82 (1H, m), 2.19 – 2.35 (4H, m), 2.39 – 2.50 (1H, m), 2.68 – 2.74 (3H, m), 2.75 – 2.78 (2H, m), 3.02 (1H, d), 3.12 – 3.28 (1H, m), 3.80 – 3.84 (2H, m), 3.90 – 3.98 (2H, m), 4.77 – 4.97 (2H, m), 7.44 (1H, d), 7.97 (1H, d), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 557.5.

EXAMPLE 330:

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2786] Intermediate 330d (40 mg, 0.07 mmol) was added to DCM–TFA (1:1, 4 mL). The resulting mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure. DIPEA (0.038 mL, 0.22 mmol) in DMF (2 mL) was added. The resulting mixture was stirred at r.t. for 30 minutes. In a separate vial, Intermediate 274e (22 mg, 0.05 mmol) was added to a solution of DIPEA (0.038 mL, 0.22 mmol) and HATU (19 mg, 0.05 mmol) in DMF (2 mL). The resulting mixture was stirred at r.t. for 30 minutes. The solution from the first vial was added to the second solution. The resulting mixture was stirred at r.t. for 30 minutes. The mixture was diluted with DCM (50 mL), washed with 0.3% aq. NH_4OH (3 x 20 mL), sat. aq. Na_2CO_3 (3 x 20 mL), and brine (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; Flow rate: 60 mL/min; elution gradient: 43% to 58% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH]) gave the title compound (17.5 mg, 27%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.06 – 1.10 (2H, s), 1.23 – 1.29 (6H, m), 1.62 – 1.67 (1H, m), 1.74 – 1.91 (3H, m), 2.18 – 2.23 (4H, m), 2.28 – 2.34 (6H, m), 2.41 – 2.48 (2H, m), 2.53 – 2.56 (1H, m), 2.67 – 2.81 (6H, m), 2.94 – 3.09 (2H, m), 3.19 – 3.22 (1H, m), 3.49 – 3.53 (2H, m), 3.78 – 3.85 (2H, m), 4.10 – 4.18 (1H, m), 4.51 – 4.56 (1H, m), 4.79 – 5.02 (3H, m), 6.43 (2H, s), 6.84 – 6.91 (2H, m), 6.97 (1H, d), 7.21 – 7.27 (1H, m), 7.36 (1H, s), 7.44 (1H, s), 7.53 – 7.60 (1H, m), 7.94 – 7.98 (2H, m), 8.20 (1H, d), 10.40 (1H, s), 14.16 – 14.29 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 873.8.

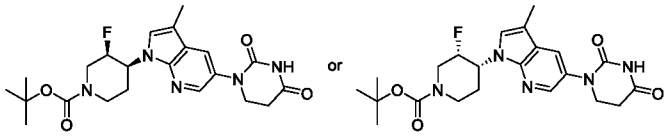
EXAMPLE 331

Intermediate 331a:

tert-Butyl (3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

or

tert-Butyl (3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



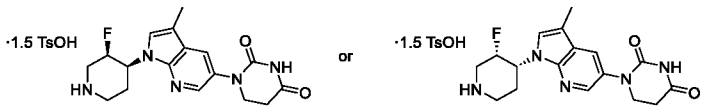
[2787] Prepared using the same method as described for Intermediate 235b, isolating the compound that eluted first from the column (420 mg, 26%, >99% ee) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.46 (9H, s), 1.87 – 1.90 (1H, m), 2.06 – 2.18 (1H, m), 2.24 – 2.31 (3H, m), 2.67 – 2.81 (2H, m), 3.03 (2H, s), 3.78 – 3.86 (2H, m), 4.03 (1H, s), 4.37 (1H, s), 4.89 – 5.12 (2H, m), 7.63 (1H, d), 7.92 (1H, d), 8.18 (1H, d), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 446.1.

Intermediate 331b:

1-(1-((3*R*,4*S*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



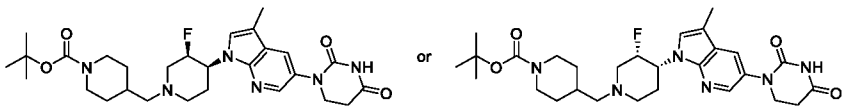
[2788] *p*-Toluenesulfonic acid (139 mg, 0.81 mmol) was added to Intermediate 331a (180 mg, 0.40 mmol) in MeCN (5 mL). The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the reaction mixture was poured into MTBE (20 mL). The mixture was filtered. The filtercake was dried *in vacuo* to give title compound (210 mg, 75%) as a white solid and 1.5 TsOH salt. *m/z* (ES$^+$) $[M+H]^+$ = 346.1.

Intermediate 331c:

tert-Butyl 4-(((3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl 4-(((3*S*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2789] Intermediate 331b (200 mg, 0.58 mmol) was added to a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (124 mg, 0.58 mmol) in DCE (1 mL) and NMP (1 mL). The resulting mixture was stirred at 40 °C for 30 minutes. After cooling to r.t., sodium triacetoxyborohydride (491 mg, 2.32 mmol) was added. The resulting mixture was stirred at r.t. for 1 hour. The reaction mixture was poured into sat. aq. $NaHCO_3$ (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were dried

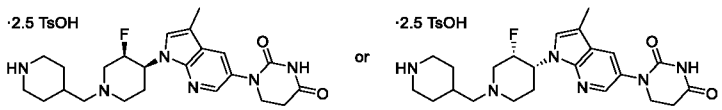
over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (180 mg, 57%) as a yellow solid.^{1}H NMR (DMSO-d_6) δ 1.40 (9H, d), 1.63–1.74 (3H, m), 1.75 – 1.81 (1H, m), 2.21 – 2.26 (6H, m), 2.29–2.37 (1H, m), 2.39–2.48 (2H, m), 2.66 – 2.69(2H, m), 2.74–2.82 (3H, m), 3.00 – 3.04 (1H, m), 3.16–3.24 (1H, m), 3.79–3.84 (2H, m), 3.88–3.99 (2H, m), 4.77–4.96 (2H, m), 7.45 (1H, s), 7.91–7.95 (1H, m), 8.17–8.23 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 543.3.

Intermediate 331d:

1-(1-((3*R*,4*S*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



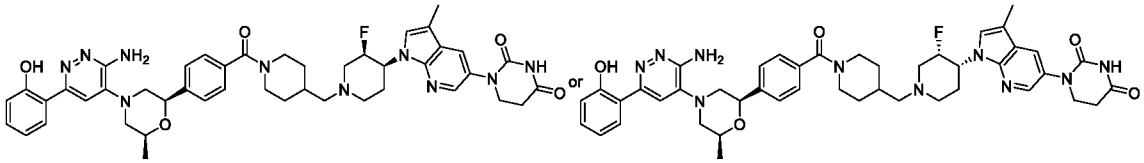
[2790] Prepared in an analogous manner to Intermediate 331b using Intermediate 331c (170 mg, 0.31 mmol) and *p*-toluenesulfonic acid (108 mg, 0.63 mmol) to give the title compound (130 mg, 47%) as a pale yellow solid and 2.5 TsOH salt. ^{1}H NMR (DMSO-d_6) δ 1.36 – 1.48 (2H, m), 1.85 – 2 (2H, m), 2.15 (2H, d), 2.29 (3H, s), 2.69 – 2.74 (1H, m), 2.75 – 2.8 (2H, m), 2.86 – 2.98 (3H, m), 3.13 (2H, s), 3.32 (2H, d), 3.64 – 3.73 (2H, m), 3.81 – 3.86 (2H, m), 3.98 (1H, d), 5.13 – 5.4 (2H, m), 7.34 (1H, s), 7.98 (1H, d), 8.25 (1H, d), 10.42 (1H, s), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 443.1.

EXAMPLE 331:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2791] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20.3 mg, 0.05 mmol) and Intermediate 331d (38.3 mg, 0.05 mmol). Upon completion of the reaction, the mixture was diluted with DCM (10 mL), washed with 2% aq. NH_4OH (3 x 5 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), and brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification

by preparative HPLC (Column: Xbridge Prep C18 OBD, 30*150 mm, 5μm; Flow rate: 60ml/min; elution gradient: 38% to 54% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH]) gave the title compound (33.3 mg, 35%) as a white solid.^{1}H NMR (DMSO-d_6) δ 1.08 – 1.12 (2H, m), 1.27 (3H, d), 1.67 – 1.70 (1H, m), 1.75 – 1.91 (3H, m), 2.21 – 2.30 (5H, m), 2.33 – 2.39 (2H, m), 2.53 – 2.58 (2H, m), 2.63–2.65 (1H, m), 2.77 (2H, t), 3.01 – 3.06 (2H, m), 3.20 – 3.25 (2H, m), 3.35 – 3.38 (1H, m), 3.48 – 3.52 (1H, m), 3.56 – 3.60 (1H, m), 3.82 (2H, t), 4.11 – 4.14 (1H, m), 4.47 –4.49 (1H, m), 4.78–5.01 (3H, m), 6.49 (2H, s), 6.82–6.92 (2H, m), 7.21–7.27 (1H, m), 7.40 (2H, d), 7.44 (1H, s), 7.48–7.62 (3H, m), 7.93 (1H, d), 7.94–7.98 (1H, m), 8.20 (1H, d), 10.40 (1H, s), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 831.4.

EXAMPLE 332

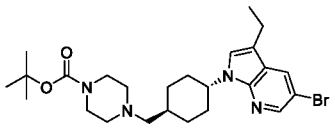
Intermediate 332a:

tert-Butyl 4-(((1*r*,4*r*)-4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate

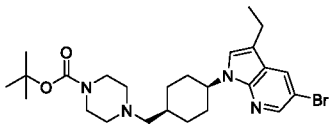
and

Intermediate 332b:

tert-Butyl 4-(((1*s*,4*s*)-4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



Intermediate 332a

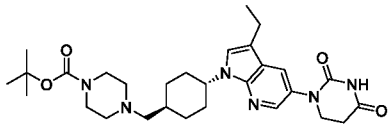


Intermediate 332b

[2792] Prepared in an analogous manner to Intermediate 234a starting from Intermediate 258b (12.7 g, 42.7 mmol) and 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (6.00 g, 26.7 mmol), stirring at 100 °C for 30 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4HCO_3) and preparative SFC (column: CHIRAL ART Amylose-SA, 3*25 cm, 5 μm; isocratic 15% [IPA with 0.1% 7 M NH_3 in MeOH] in $scCO_2$; flow rate: 100 mL/min; back pressure: 100 bar) gave Intermediate 332a (0.88 g, 7%) and Intermediate 332b (2.60 g, 19%) as pale yellow solids. Intermediate 332a: ^{1}H NMR ($CDCl_3$) δ 1.25 – 1.35 (4H, m), 1.49 (9H, s), 1.58 – 1.86 (4H, m), 1.97 – 2.17 (4H, m), 2.21 – 2.25 (2H, m), 2.38 – 2.45 (4H, m), 2.66 – 2.79 (2H, m), 3.41 – 3.49 (4H, m), 4.61 – 4.75(1H, m), 7.08 (1H, s), 7.99 (1H, d), 8.30 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 505.1. Intermediate 332b: ^{1}H NMR ($CDCl_3$) δ 1.20 – 1.27 (2H, m), 1.29 – 1.35 (3H, m), 1.48 (9H, s), 1.59 – 1.66 (2H, m), 1.71 – 1.81 (2H, m), 1.82 – 1.88 (1H, m), 1.98 – 2.05 (2H, m), 2.08 – 2.16 (2H, m), 2.19 – .25 (2H, m), 2.39 – 2.46 (2H, m), 2.70 – 2.76 (2H, m), 3.41 – 3.47 (4H, m), 4.65 – 4.71 (1H, m), 7.08 (1H, s), 7.99 (1H, d), 8.30 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 505.2.

Intermediate 332c:

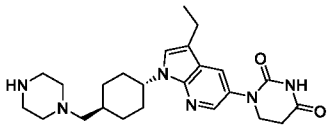
tert-Butyl 4-(((1*r*,4*r*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2793] GPhos Pd G6 TES (0.23 g, 0.25 mmol) was added to a mixture of GPhos (0.13 g, 0.25 mmol), Intermediate 332a (1.25 g, 2.47 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.13 g, 9.89 mmol) and Cs_2CO_3 (2.42 g, 7.42 mmol) in 1,4-dioxane (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. After cooling to r.t., the mixture was diluted with DCM (30 mL) and filtered. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (0.81 g, 60%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.08 – 1.12 (2H, m), 1.26 (3H, t), 1.32 – 1.39 (2H, m), 1.40 (9H, s) 1.52 – 1.72 (3H, m), 1.81 – 1.97 (2H, m), 2.15 – 2.18 (2H, m), 2.23 – 2.33 (4H, m), 2.65 – 2.74 (2H, m), 2.76 (2H, t), 3.28– 1.3.33 (4H, m) 3.81 (2H, t), 4.57 – 4.61 (1H, m), 7.46 (1H, s), 7.91 (1H, d), 8.16 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 539.2.

Intermediate 332d:

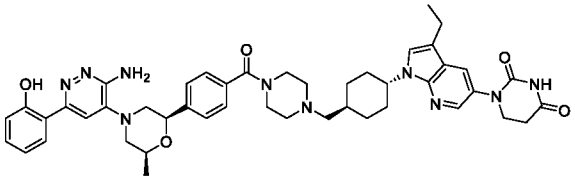
1-(3-Ethyl-1-((1*r*,4*r*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2794] *p*-Toluenesulfonic acid (388 mg, 2.26 mmol) was added to Intermediate 332c (810 mg, 1.50 mmol) in MeCN (6 mL). The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in MeOH and basified with DIPEA (1 mL). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (430 mg, 65%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.02 – 1.17 (2H, m), 1.21 – 1.30 (3H, m), 1.60– 1.64 (1H, m), 1.78 – 1.97 (6H, m), 2.09 – 2.14 (2H, m), 2.22 – 2.27 (4H, m), 2.61 – 2.72 (6H, m), 2.72 – 2.79 (2H, m), 3.72 – 3.85 (2H, m), 4.54 – 4.66 (1H, m), 7.45 (1H, s), 7.90 (1H, d), 8.15 (1H, d), 10.40 (1H, s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 439.3.

EXAMPLE 332:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



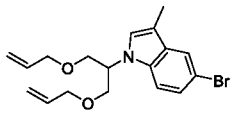
[2795] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20.3 mg, 0.05 mmol) and Intermediate 332d (38.3 mg, 0.05 mmol). Upon completion of the reaction, the mixture was diluted with DCM–IPA (3:1, 25 mL). The mixture was washed with sat. aq. $NaHCO_3$ (2 x 25 mL),

dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; elution gradient: 49 to 61% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH]; flow rate: 25 mL/min) gave the title compound (16.6 mg, 29%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.07 – 1.20 (2H, m), 1.20 – 1.32 (6H, m), 1.59 – 1.71 (1H, m), 1.80 – 2.01 (6H, m), 2.17 – 2.20 (2H, m), 2.34 – 2.41 (4H, m), 2.54 – 2.57 (1H, m), 2.63 – 2.73 (3H, m), 2.76 (2H, t), 3.40 – 3.45 (2H, m), 3.49 – 3.53 (1H, m), 3.55 – 3.72 (3H, m), 3.81 (2H, t), 4.06 – 4.19 (1H, m), 4.56 – 4.68 (1H, m), 4.89 – 5.00 (1H, m), 6.49 (2H, s), 6.83 – 6.94 (2H, m), 7.24 (1H, t), 7.36 – 7.48 (3H, m), 7.50 – 7.61 (3H, m), 7.91 (1H, d), 7.96 (1H, d), 8.17 (1H, d), 10.39 (1H, s), 14.23 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 827.4.

EXAMPLE 333

Intermediate 333a:

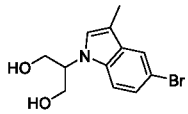
1-(1,3-*bis*(Allyloxy)propan-2-yl)-5-bromo-3-methyl-1*H*-indole



[2796] Prepared in an analogous manner to Intermediate 234a using 5-bromo-3-methyl-1*H*-indole (15.0 g, 71.4 mmol) and 1,3-bis(allyloxy)propan-2-ol (18.5 g, 107.1 mmol), stirring at 100 °C or 16 hours. Purification by FSC (elution gradient: 0 to 100% DCM in petroleum ether) gave the title compound (18.0 g, 69%) as a yellow liquid. ^{1}H NMR (DMSO-d_6) δ 2.22 (3H, d), 3.73 – 3.79 (4H, m), 3.88 – 3.93 (4H, m), 4.79 (1H, p), 5.08 – 5.12 (2H, m), 5.13 – 5.18 (2H, m), 5.73 – 5.84 (2H, m), 7.19 – 7.22 (1H, m), 7.30 (1H, d), 7.46 (1H, d), 7.65 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 363.9.

Intermediate 333b:

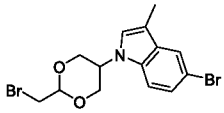
2-(5-Bromo-3-methyl-1*H*-indol-1-yl)propane-1,3-diol



[2797] Tetrakis(triphenylphosphine)palladium(0) (2.86 g, 2.47 mmol) was added to Intermediate 333a (18.0 g, 49.4 mmol) and 1,3-dimethylbarbituric acid (15.4 g, 98.8 mmol) in MeOH (50 mL) under nitrogen. The resulting mixture was stirred at r.t. for 16 hours and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (9.40 g, 66%) as a yellow gum.^{1}H NMR (DMSO-d_6) δ 2.24 (3H, d), 3.69 – 3.83 (4H, m), 4.37 – 4.45 (1H, m), 4.88 (2H, t), 7.19 – 7.23 (1H, m), 7.30 (1H, d), 7.41 (1H, d), 7.65 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 283.9.

Intermediate 333c:

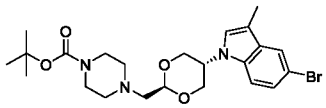
5-Bromo-1-((2*r*,5*r*)-2-(bromomethyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indole



[2798] PPTS (1.95 g, 7.74 mmol) was added to a mixture of Intermediate 333b (11.0 g, 38.7 mmol) and 2-bromo-1,1-dimethoxyethane (7.85 g, 46.5 mmol) in toluene (60 mL). The resulting mixture was stirred at 115°C for 16 hours. After cooling to r.t., the mixture was diluted with DCM (500 mL), washed with sat. aq. $NaHCO_3$ (2 x 250 mL) and brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1%NH_4HCO_3) gave the title compound (6.50 g, 43%) as a yellow solid and mixture of diastereomers. ^{1}H NMR (DMSO-d_6) δ 2.22 – 2.29 (3H, m), 3.55 – 3.63 (2H, m), 4.09 – 4.25 (3H, m), 4.33 – 4.53 (2H, m), 4.98 – 5.07 (1H, m), 7.22 – 7.26 (1H, m), 7.34 – 7.42 (1H, m), 7.59 – 7.68 (1H, m), 7.69 – 7.80 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 387.8.

Intermediate 333d:

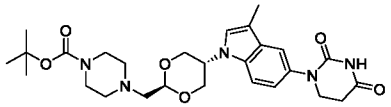
tert-Butyl 4-(((2*r*,5*r*)-5-(5-bromo-3-methyl-1*H*-indol-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



[2799] KI (11.1 g, 67.1 mmol) was added to a solution of Intermediate 333c (8.70 g, 22.4 mmol), *tert*-butyl piperazine-1-carboxylate (8.33 g, 44.7 mmol) and DIPEA (9.76 mL, 55.9 mmol) in DMF (40 mL). The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was diluted with EtOAc (300 mL), washed with water (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) and preparative SFC (column: CHIRALPAK IG, 3*25 cm, 5 µm; isocratic 50% MeOH in $scCO_2$; flow rate: 100 mL/min) gave the title compound (2.60 g, 23%) as a grey solid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 2.21 (3H, s), 2.41 – 4.49 (4H, m), 2.49 – 2.54 (2H, m), 3.26 – 3.33 (4H, m), 4.01 – 4.10 (2H, m), 4.11 – 4.18 (2H, m), 4.65 – 4.75 (1H, m), 4.92 (1H, t), 7.20 – 7.26 (1H, m), 7.33 (1H, s), 7.61 (1H, d), 7.65 – 7.69 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 494.1.

Intermediate 333e:

tert-Butyl 4-(((2*r*,5*r*)-5-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-indol-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate

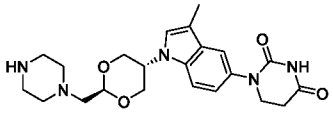


[2800] GPhos (0.27 g, 0.51 mmol) was added to Intermediate 333d (2.50 g, 5.06 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (3.46 g, 30.3 mmol), GPhos Pd G6 (0.48 g, 0.51 mmol) and Cs_2CO_3 (4.12 g, 12.6 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Trituration with EtOAc:petroleum ether (1:1, 2 x 150 mL) gave the title compound (2.10 g, 79%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.41 (9H, s), 2.23 (3H, s), 2.42 – 2.48 (4H, m), 2.52 – 5.58 (2H, m), 2.73 (2H, t), 3.28 – 3.34

(4H, m), 3.77 (2H, t), 4.04 – 4.12 (2H, m), 4.12 – 4.19 (2H, m), 4.65 – 4.75 (1H, m), 4.93 (1H, t), 7.06 – 7.11 (1H, m), 7.31 (1H, s), 7.41 (1H, d), 7.61 (1H, d), 10.27 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 528.3.

Intermediate 333f:

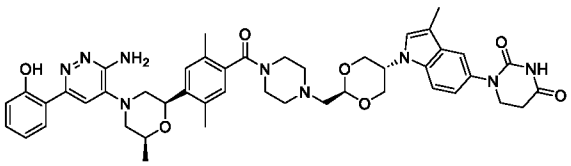
1-(3-Methyl-1-((2*r*,5*r*)-2-(piperazin-1-ylmethyl)-1,3-dioxan-5-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2801] *p*-Toluenesulfonic acid (0.49 g, 2.84 mmol) was added to Intermediate 333e (1.00 g, 1.90 mmol) in MeCN (40 mL). The resulting mixture was stirred at 80 °C for 6 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. MeOH (5 mL) and DIPEA (1 mL) were added. The resulting mixture was stirred at r.t. for 2 hours and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.46 g, 56%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 2.36 – 2.45 (4H, m), 2.47 – 2.53 (2H, m), 2.69 (3H, s), 2.74 (2H, t), 3.19 – 3.30 (2H, m), 3.77 (2H, t), 4.07 (2H, t), 4.11 – 4.18 (2H, m), 4.66 – 4.74 (1H, m), 4.88 – 4.93 (1H, m), 7.06 – 7.11 (1H, m), 7.30 – 7.33 (1H, m), 7.41 (1H, d), 7.61 (1H, d), 10.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 428.5.

EXAMPLE 333:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2802] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (50 mg, 0.12 mmol) and Intermediate 333f (45 mg, 0.12 mmol). Upon completion of the reaction, the mixture was diluted with DCM–IPA (5:1, 50 mL), washed with sat. aq. $NaHCO_3$ (2 x 25 mL), 2% aq. NH_4OH (2 x 25 mL), and water (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: Xbridge Prep Shield RP18 OBD, 30*150 mm, 5μm; elution gradient: 41 to 61% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (17.5 mg, 17%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, d), 2.22 (6H, d), 2.34 (3H, s), 2.42 – 2.46 (2H, m), 2.55 – 2.63 (4H, m), 2.73 (3H, t), 2.91 – 2.96 (1H, m), 3.16 (2H, t), 3.52 (2H, d), 3.62 – 3.68 (2H, m), 3.77 (2H, t), 4.06 – 4.19 (5H, m), 4.67 – 4.74 (1H, m), 4.91 – 4.95 (1H, m), 4.97 – 5.01 (1H, m), 6.43 (2H, s), 6.84 – 6.90 (2H, m), 6.98 (1H, s), 7.07 – 7.11 (1H, m), 7.21 – 7.26 (1H, m), 7.31 (1H, s), 7.36 (1H, s), 7.41 (1H, d), 7.56 (1H, s), 7.61 (1H, d), 7.95 – 8.00 (1H, m), 10.29 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 844.4.

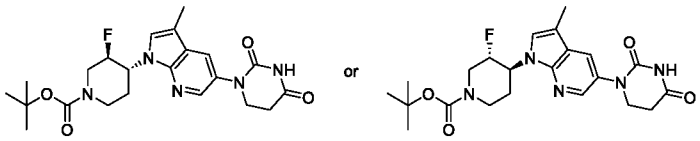
EXAMPLE 334

Intermediate 334a:

tert-Butyl (3*R*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

or

tert-Butyl (3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



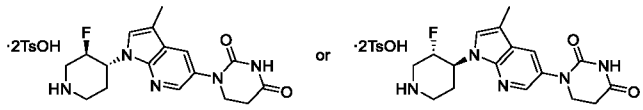
[2803] Prepared using the same method as described for Intermediate 235b, isolating the compound that eluted third from the column (200 mg, 12%, >99% ee) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.44 (9H, s), 1.76 – 1.79 (1H, m), 2.26 (3H, d), 2.28 – 2.42 (1H, m), 2.73 – 2.81 (2H, m), 3.10 – 3.13 (2H, m), 3.78 – 3.86 (2H, m), 4.22 – 4.26 (2H, m), 4.88 – 4.90 (1H, m), 5.04 – 5.16 (1H, m), 7.44 (1H, s), 7.94 (1H, d), 8.21 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 446.2.

Intermediate 334b:

1-(1-((3*R*,4*R*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



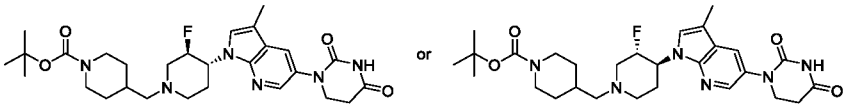
[2804] Prepared in an analogous manner to Intermediate 331b using Intermediate 334a (200 mg, 0.45 mmol) and *p*-toluenesulfonic acid (155 mg, 0.90 mmol) to give the title compound (250 mg, 81%) as a yellow solid and 2 TsOH salt. ^{1}H NMR (DMSO-d_6) δ 2.12–2.21 (1H, m), 2.28 (3H, s), 2.30 (6 H, s), 2.41–2.48 (1H, m), 2.74–2.82 (2H, m), 3.19–3.33 (2H, m), 3.44 (1H, d), 3.71–3.87 (3H, m), 5.1–5.19 (1H, m), 5.29–5.48 (1H, m), 7.14 (4H, d), 7.39 (1H, s), 7.52 (4H, d), 7.96 (1H, d), 8.22 (1H, d), 8.91 (1H, brs), 9.92 (1H, brs),10.42 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 346.1.

Intermediate 334c:

tert-Butyl 4-(((3*R*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl 4-(((3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



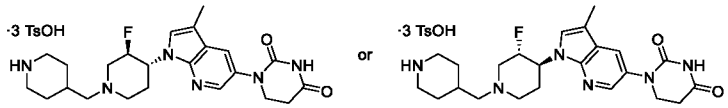
[2805] Prepared in an analogous manner to Intermediate 331c using Intermediate 334b (240 mg, 0.69 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (190 mg, 50%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.38 (9H, s), 1.62–1.77 (3H, m), 1.87 – 1.89 (1H, m), 2.00 – 2.17 (4H, m), 2.21 – 2.31 (6H, m), 2.59 – 2.81 (5H, m), 2.88 – 2.91 (1H, m), 3.75 – 3.84 (2H, m), 3.90 – 3.94 (2H, m), 4.68 – 4.70 (1H, m), 4.94–5.22 (1H, m), 7.59 (1H, d), 7.89 (1H, d), 8.16 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 543.3.

Intermediate 334d:

1-(1-((3*R*,4*R*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



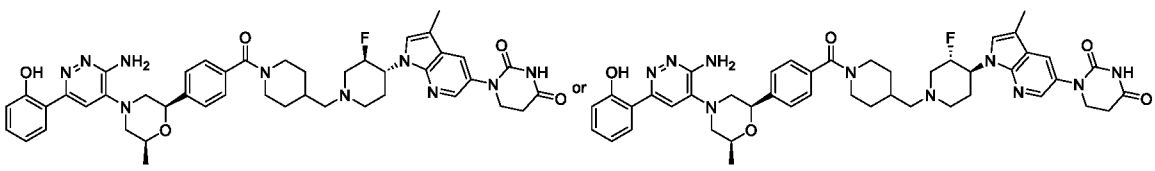
[2806] Prepared in an analogous manner to Intermediate 331b using Intermediate 334c (180 mg, 0.33 mmol) and *p*-toluenesulfonic acid (171 mg, 1.00 mmol) to give the title compound (230 mg, 72%) as a white solid and 3 TsOH salt. ^{1}H NMR (DMSO-d_6) δ 1.32–1.46 (2H, m), 1.89–2.03 (2H, m), 2.19 – 2.21 (2H, m), 2.27 (3H, s), 2.30 (9 H, s), 2.57 – 2.69 (1H, m), 2.74–2.80 (2H, m), 2.89 – 2.91 (2H, m), 3.16 – 3.19 (2H, m), 3.29 – 3.33 (3H, m), 3.36 – 3.40 (1H, m), 3.71 – 3.73 (1H, m), 3.79–3.86 (2H, m), 4.04 – 4.07 (1H, m), 5.10 – 5.14 (1H, m), 5.41–5.62 (1H, m), 7.14 (6H, d), 7.36 (1H, s), 7.52 (6H, d), 7.97 (1H, d), 8.22 (1H, d), 8.26 (1H, brs), 8.53 (1H, brs), 10.42 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 443.2.

EXAMPLE 334:

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2807] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (28 mg, 0.07 mmol) and Intermediate 334d (50 mg, 0.11 mmol). Upon completion of the reaction, the mixture was diluted with DCM (50 mL), washed with 2% aq. NH_4OH (3 x 5 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), and brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xbridge Prep C18 OBD, 30*150 mm, 5μm; elution gradient: 49 to 65% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (28.0 mg, 29%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.11 – 1.14 (2H, d), 1.26 (3H, d), 1.66 – 1.69 (1H, m), 1.86 – 1.90 (3H, m), 2.14 – 2.18 (3H, m), 2.25 (3H, d), 2.30 – 2.34 (2H, m), 2.53 – 2.55 (1H, m), 2.66 – 2.68 (1H, m), 2.76 (2H, t), 2.97 – 3.01 (3H, m), 3.44–3.66 (4H, m), 3.81 (2H, t), 4.09 – 4.12 (1H, m), 4.46 – 4.49 (1H, m), 4.70 – 4.73 (1H, m), 4.89 – 5.21 (2H, m), 6.48 (2H, d), 6.82–6.93 (2H, m), 7.18–7.27 (1H, m), 7.34–7.45 (2H, m), 7.46 – 7.65 (4H, m), 7.79 – 8.02 (2H, m), 8.17 (1H, d), 10.39 (1H, s), 14.21 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 831.4.

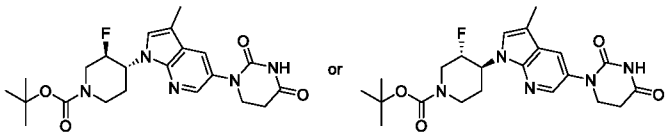
EXAMPLE 335

Intermediate 335a:

tert-Butyl (3*R*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

or

tert-Butyl (3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



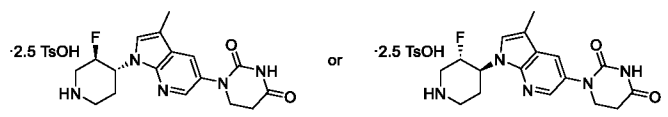
[2808] Prepared using the same method as described for Intermediate 235b, isolating the compound that eluted fourth from the column (220 mg, 13%, 98.7% ee) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.44 (9H, s), 1.79 (1H, d), 2.22 – 2.30 (3H, m), 2.31 – 2.41 (1H, m), 2.71 – 2.84 (2H, m), 2.99 – 3.31 (2H, m), 3.77 – 3.87 (2H, m), 4.10 – 4.44 (2H, m), 4.89 (1H, d), 5.04 – 5.20 (1H, m), 7.44 (1H, s), 7.94 (1H, d), 8.21 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 446.2.

Intermediate 335b:

1-(1-((3*R*,4*R*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



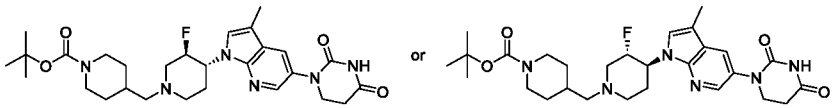
[2809] Prepared in an analogous manner to Intermediate 331b using Intermediate 335a (200 mg, 0.45 mmol) and *p*-toluenesulfonic acid (155 mg, 0.90 mmol) to give the title compound (260 mg, 84%) as a yellow solid and 2.5 TsOH salt. *m/z* (ES^+) $[M+H]^+$ = 346.1.

Intermediate 335c:

tert-Butyl 4-(((3*R*,4*R*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

or

tert-Butyl 4-(((3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



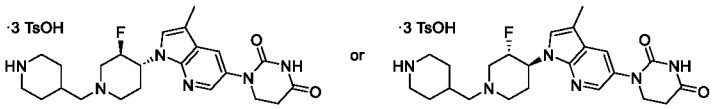
[2810] Prepared in an analogous manner to Intermediate 331c using Intermediate 335b (154 mg, 0.72 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (160 mg, 41%) as a yellow solid. ^1H NMR (DMSO-d_6) δ 0.93 –0 .97 (2H, m), 1.38 (9H, s), 1.67 – 1.70 (3H, m), 1.86 – 1.89 (1H, m), 2.05 – 2.08 (1H, m), 2.11 – 2.18 (3H, m), 2.24 (3H, d), 2.25 – 2.27 (1H, m), 2.26 – 2.29 (1H, m), 2.59–2.81 (4H, m), 2.88 – 2.91 (1H, m), 3.72–3.83 (2H, m), 3.91 – 3.93 (2H, m), 4.68 – 4.71 (1H, m), 4.94–5.23 (1H, m), 7.59 (1H, d), 7.89 (1H, d), 8.16 (1H, d), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 543.3.

Intermediate 335d:

1-(1-((3*R*,4*R*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



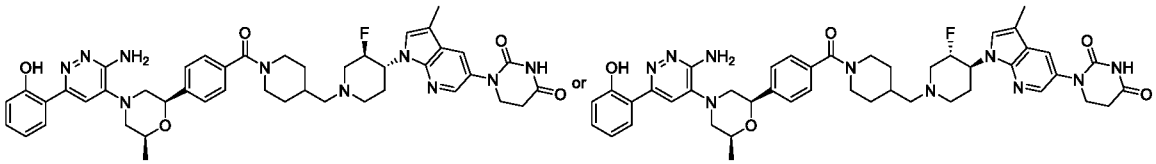
[2811] Prepared in an analogous manner to Intermediate 331b using Intermediate 335c (150 mg, 0.28 mmol) and *p*-toluenesulfonic acid (143 mg, 0.83 mmol) to give the title compound (200 mg, 75%) as a white solid and 3 TsOH salt. *m/z* (ES^+) $[M+H]^+$ = 443.2.

EXAMPLE 335:

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

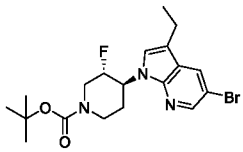


[2812] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (28 mg, 0.07 mmol) and Intermediate 335d (50 mg, 0.11 mmol). Upon completion of the reaction, the mixture was diluted with DCM (10 mL), washed with 2% aq. NH_4OH (3 x 5 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), and brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xbridge Prep C18 OBD, 30*150 mm, 5μm; elution gradient: 35 to 51% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.1% NH_4OH) gave the title compound (26.0 mg, 27%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.10 – 1.13 (2H, m), 1.26 (3H, d), 1.68 – 1.71 (1H, m), 1.85 – 1.88 (3H, m), 2.17 (3H, s), 2.22 – 2.28 (3H, m), 2.31 – 2.35 (2H, m), 2.54 – 2.57 (1H, m), 2.64 – 2.70 (1H, m), 2.76 (2H, t), 2.97 – 3.01 (3H, m), 3.48 – 3.53 (2H, m), 3.56 – 3.59 (2H, m), 3.81 (2H, t), 4.09 – 4.12 (1H, m), 4.47 – 4.50 (1H, m), 4.70 – 4.73 (1H, m), 4.92 – 4.96 (1H, m), 4.99–5.21 (1H, m), 6.48 (2H, s), 6.81–6.97 (2H, m), 7.15–7.28 (1H, m), 7.39 (2H, d), 7.48–7.64 (4H, m), 7.85–8.03 (2H, m), 8.17 (1H, d), 10.39 (1H, s), 14.21 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 831.4.

EXAMPLE 336

Intermediate 336a:

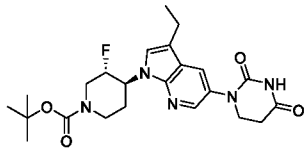
tert-Butyl (3*S*,4*S*)-4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2813] Prepared in an analogous method to Intermediate 330a using 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.00 g, 4.44 mmol) and *tert*-butyl (3*S*,4*R*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (1.07 g, 4.89 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.69 g, 36%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t), 1.45 (9H, s), 1.86 – 1.96 (1H, m), 2.04 – 2.17 (1H, m), 2.63 – 2.74 (2H, m), 2.98 – 3.02 (2H, m), 4.01 – 4.05 (1H, m), 4.36 – 4.39 (1H, m), 4.85 – 5.13 (2H, m), 7.70 (1H, s), 8.16 – 8.32 (2H, m); *m/z* (ES$^+$) $[M+H]^+$ = 426.0.

Intermediate 336b:

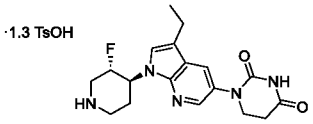
tert-Butyl (3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2814] Prepared in an analogous method to Intermediate 330b using Intermediate 336a (450 mg, 1.06 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (240 mg, 50%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t), 1.46 (9H, s), 1.89 – 1.95 (1H, m), 2.11 – 2.18 (1H, m), 2.66 – 2.74 (2H, m), 2.77 (2H, t), 2.96 – 3.01 (2H, m), 3.82 (2H, t), 3.97 – 4.07 (1H, m), 4.36 – 4.38 (1H, m), 4.92 – 5.14 (2H, m), 7.67 (1H, s), 7.95 (1H, d), 8.18 (1H, d), 10.42 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 460.2.

Intermediate 336c:

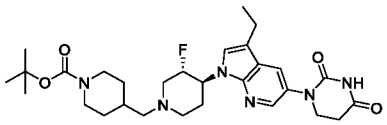
1-(3-Ethyl-1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2815] *p*-Toluenesulfonic acid (108 mg, 0.63 mmol) was added to Intermediate 336b (240 mg, 0.52 mmol) in MeCN (4 mL). The resulting mixture was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was concentrated under reduced pressure to give the title compound (270 mg, 89%) as a yellow solid and 1.3 TsOH salt which was used for the next step without further purification. *m/z* (ES$^+$) $[M+H]^+$ = 360.2.

Intermediate 336d:

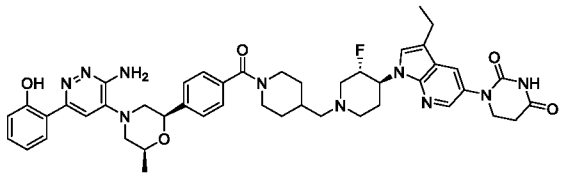
tert-Butyl 4-(((3*S*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate



[2816] Prepared in an analogous method to Intermediate 331c using Intermediate 336c (390 mg, 0.67 mmol). Purification by RPC (elution gradient: 5 to 100% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (240 mg, 64%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.91 – 1.02 (2H, m) ,1.28 (3H, t), 1.40 (9H, s), 1.67 – 1.76 (3H, m), 1.87 – 1.93 (1H, m), 2.11 – 2.21 (3H, m), 2.25 – 2.32 (2H, m), 2.67 – 2.72 (3H, m), 2.76 (2H, t), 2.88 – 2.91 (1H, m), 3.30 – 3.33 (2H, m), 3.82 (2H, t), 3.89 – 3.94 (2H, m), 4.68 – 4.77 (1H, m), 5.04 – 5.20 (1H, m), 7.63 (1H, s), 7.94 (1H, d), 8.18 (1H, d), 10.41 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 557.3.

EXAMPLE 336:

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

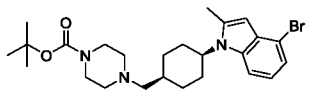


[2817] Intermediate 336d (120 mg, 0.2 mmol) was added to a mixture of DCM (2 mL) and TFA (0.6 mL). The resulting mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure. DMF (1 mL) and DIPEA (0.11 mL, 0.65 mmol) were added. The resulting mixture was stirred at r.t. for 30 minutes. In a separate flask, DIPEA (0.11 mL, 0.65 mmol) was added to a solution of Intermediate 65e (70 mg, 0.17 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 30 minutes. The two mixtures were combined and stirred at r.t. for 1 hour. The mixture was diluted with DCM–IPA (3:1, 50 mL), washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (Column: Xselect CSH Prep Fluoro-Phenyl OBD column, 30*150mm, 5um, elution gradient: 17 to 26% MeCN in water with 0.1% FA) gave the title compound (30.0 mg, 16%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.09 – 1.13 (2H, m), 1.22 – 1.31 (6H, m), 1.35 – 1.42 (1H, m), 1.71 – 1.75 (1H, m), 1.87 – 1.90 (3H, m), 2.18 (3H, d), 2.33 – 2.37 (2H, m), 2.54 – 2.59 (1H, m), 2.66 – 2.73 (3H, m), 2.73 – 2.79 (3H, m), 2.91 – 2.94 (1H, m), 3.04 – 3.08 (1H, m), 3.34 – 3.39 (1H, m), 3.48 – 3.52 (1H, m), 3.57 – 3.59 (1H, m), 3.81 (2H, t), 4.11 – 4.14 (1H, m), 4.47 – 4.50 (1H, m), 4.72 – 4.75 (1H, m), 4.93 – 4.98 (1H, m), 5.04 – 5.21 (1H, m), 6.49 (2H, s), 6.85 – 6.91 (2H, m), 7.21 – 7.27 (1H, m), 7.40 (2H, d), 7.53 (2H, d), 7.57 (1H, s), 7.62 (1H, s), 7.92 – 7.99 (2H, m), 8.17 (1H, d), 10.39 (1H, s), 14.22 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 845.4.

EXAMPLE 337

Intermediate 337a:

tert-Butyl 4-(((1*s*,4*s*)-4-(4-bromo-2-methyl-1*H*-indol-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate

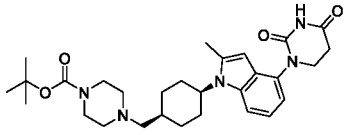


[2818] Prepared in an analogous manner to Intermediate 234a starting from Intermediate 258b (2.00 g, 6.70 mmol) and 4-bromo-2-methyl-1*H*-indole (1.08 g, 5.16 mmol) in *m*-xylenes (20 mL), stirring at 120 °C for 16 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4HCO_3) and preparative SFC (column: CHIRAL ART Amylose-SA, 3*25 cm, 5 μm; isocratic 25% MeOH in $scCO_2$; flow rate: 100 mL/min; back pressure: 100 bar) gave the title compound (0.20 g, 7%) as a colorless liquid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 1.56 – 1.63 (2H, m), 1.64 – 1.72 (2H, m), 1.80 – 1.86 (2H, m), 1.97 – 2.06 (1H, m), 2.14 – 2.26

(2H, m), 2.37 – 2.40 (4H, m), 2.44 – 2.47 (5H, m), 3.29 – 3.35 (4H, m), 4.23 – 4.27 (1H, m), 6.17 (1H, s), 6.97 (1H, t), 7.16 (1H, d), 7.50 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 490.3.

Intermediate 337b:

tert-Butyl 4-(((1*s*,4*s*)-4-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methyl-1*H*-indol-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



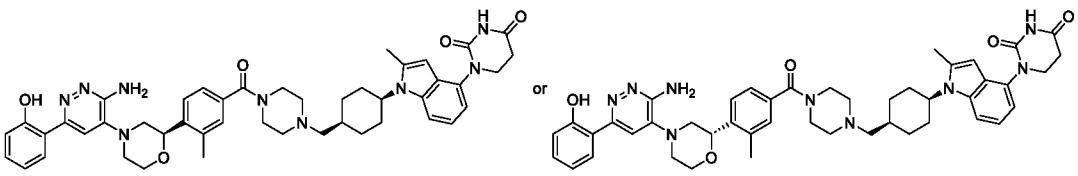
[2819] Cs_2CO_3 (399 mg, 1.22 mmol) was added to a mixture of GPhos Pd G6 (39 mg, 0.04 mmol), GPhos (22 mg, 0.04 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (116 mg, 1.02 mmol) and Intermediate 337a (200 mg, 0.41 mmol) in 1,4-dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. After cooling to r.t., the mixture filtered. The filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (100 mg, 46%) as a white solid. ^1H NMR (DMSO-d_6) δ 1.10 – 1.14 (2H, m), 1.39 (9H, s), 1.73 – 1.83 (3H, m), 1.88 – 1.96 (2H, m), 2.11 – 2.17 (2H, m), 2.19 – 2.36 (6H, m), 2.41 (3H, s), 2.72 (2H, t),3.27 – 3.35 (4H, m) 3.72 (2H, t), 4.19 – 4.27 (1H, m), 6.12 (1H, s), 6.86 (1H, d), 7.00 (1H, t), 7.55 (1H, d), 10.29 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 524.3.

EXAMPLE 337:

1-(1-((1*R*,4*s*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*R*,4*s*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



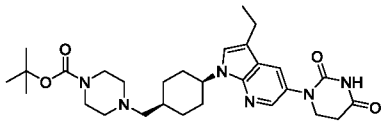
[2820] Prepared in an analogous method to EXAMPLE 330 using Intermediate 80e (22 mg, 0.05 mmol) and Intermediate 337b (40 mg, 0.08 mmol). Purification by preparative HPLC (column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; elution gradient: 13 to 28% MeCN in [water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH]) gave the title compound (15.0 mg, 23%) as a white solid. ^1H NMR (DMSO-d_6) δ 1.10 – 1.13 (2H, m), 1.28 – 1.31 (1H, m), 1.77 – 1.85 (3H, m), 1.95 (2H, dd), 2.18 – 2.22 (2H, m), 2.27 – 2.31 (2H, d), 2.40 – 2.44 (9H, m), 2.74 (2H, t), 2.81 – 2.91 (2H, m), 3.40 – 3.43 (1H, m), 3.50 – 3.57 (3H, m), 3.59 – 3.68 (2H, m), 3.74 (2H, t), 4.07 – 4.10 (2H, d), 4.21 – 4.25 (1H, m), 4.97 (1H, dd), 6.14

(1H, s), 6.46 (2H, s), 6.81 – 6.93 (3H, m), 7.02 (1H, t), 7.20 – 7.30 (3H, m), 7.51 – 7.63 (3H, m), 7.96 (1H, dd), 10.31 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 812.4.

EXAMPLE 338

Intermediate 338a:

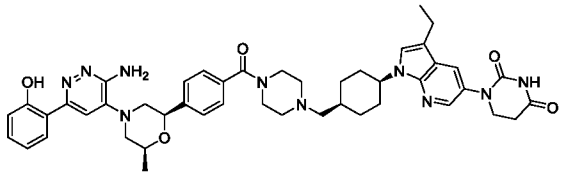
tert-Butyl 4-(((1*s*,4*s*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate



[2821] GPhos Pd G6 (0.49 g, 0.51 mmol) was added to a mixture of Cs_2CO_3 (3.35 g, 10.3 mmol), GPhos (0.28 g, 0.51 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.47 g, 12.9 mmol) and Intermediate 332b (2.60 g, 5.14 mmol) in 1,4-dioxane (16 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. After cooling to r.t., the mixture was diluted with DCM (30 mL) and filtered. The filtrate was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (1.40 g, 50%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t), 1.41 (9H, s), 1.60 – 1.70 (4H, m), 1.74 – 1.80 (2H, m), 2.29 – 2.41 (4H, m), 2.41 – 2.47 (2H, m), 2.70 (2H, q), 2.76 (2H, t), 3.27 – 3.38 (7H, m), 3.81 (2H, t), 4.62 – 4.67 (1H, m), 7.57 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.38 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 539.3.

EXAMPLE 338:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

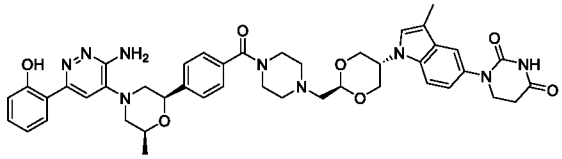


[2822] Intermediate 338a (30 mg, 0.06 mmol) was dissolved in DCM (0.5 mL) and TFA (0.5 mL). The resulting mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure. DIPEA (9.7 µL, 0.06 mmol) in DMF (0.5 mL) was added and the mixture was stirred at 40 °C for 30 minutes. In a separate vial, a mixture of Intermediate 65e (23 mg, 0.06 mmol), DIPEA (9.7 µL, 0.06 mmol) and HATU (21 mg, 0.06 mmol) in DMF (0.5 mL) was stirred at 40 °C for 30 minutes. The two solutions were combined and stirred at r.t. for 1 hour. The mixture was diluted with DCM (10 mL), washed with 2% aq. NH_4OH (3 x 5 mL), sat. aq. $NaHCO_3$ (3 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xselect CSH Prep C18 OBD, 30*150mm, 5um; elution gradient: 12 to 34% MeCN in [water with 0.1% FA]; flow rate: 60 mL/min) gave the title compound (25.0 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.21 – 1.25 (2H, m), 1.26 – 1.28 (3H, m), 1.29 – 1.32 (1H, m), 1.66 – 1.73 (4H, m), 1.75 – 1.79 (2H, m), 1.91 – 2.02 (3H, m), 2.37 – 2.43 (2H,

m), 2.45 – 2.52 (3H, n), 2.53 – 2.59 (1H, m), 2.68 – 2.73 (3H, m), 2.76 (2H, t), 3.23 – 3.45 (4H, m), 3.48 – 3.54 (1H, m), 3.58 (1H, dd), 3.63 – 3.67 (1H, m), 3.81 (2H, t), 4.06 – 4.19 (1H, m), 4.62 – 4.68 (1H, m), 4.93 – 4.97 (1H, m), 6.49 (2H, s), 6.84 – 6.92 (2H, m), 7.24 (1H, ddd), 7.40 – 7.45 (2H, m), 7.52 – 7.55 (2H, m), 7.56 – 7.59 (2H, m), 7.90 (1H, d), 7.96 (1H, dd), 8.16 (1H, d), 10.38 (1H, s), 14.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 827.4.

EXAMPLE 339:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

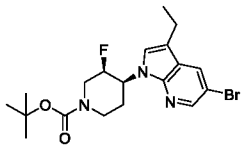


[2823] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (48 mg, 0.12 mmol) and Intermediate 333f (50 mg, 0.12 mmol). Upon completion of the reaction, the mixture was diluted with DCM–IPA (5:1, 50 mL), washed with sat. aq. $NaHCO_3$ (2 x 25 mL) and water (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xbridge Prep C18 OBD, 30*150 mm, 5μm; elution gradient: 10 to 30% MeCN in water with 0.1% FA) gave the title compound (57.4 mg, 58%) as a pink solid. ^{1}H NMR (DMSO-d_6) δ 1.20 – 1.30 (4H, m), 2.22 (3H, s), 2.44 – 2.49 (1H, m), 2.52 – 2.63 (5H, m), 2.65 – 2.74 (3H, m), 3.33 – 3.38 (2H, m), 3.51 – 3.63 (4H, m), 3.77 (2H, t), 4.09 – 4.20 (5H, m), 4.65 – 4.71 (1H, m), 4.91 – 4.98 (2H, m), 6.49 (2H, s), 6.84 – 6.92 (2H, m), 7.03 – 7.12 (1H, m), 7.20 – 7.26 (1H, m), 7.31 (1H, s), 7.37 – 7.46 (3H, m), 7.48 – 7.58 (3H, m), 7.61 (1H, d), 7.90 – 7.99 (1H, m), 10.28 (1H, s), one heteroatom-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 816.4.

EXAMPLE 340

Intermediate 340a:

tert-Butyl (3*R*,4*S*)-4-(5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate

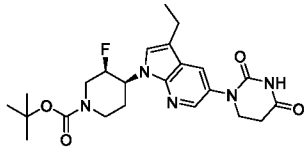


[2824] Prepared in an analogous method to Intermediate 330a using 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 8.89 mmol) and *tert*-butyl (3*R*,4*R*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (3.31 g, 15.1 mmol), stirring at 100 °C for 24 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 80% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (2.50 g, 66%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t), 1.43 (9H, s), 1.76 – 1.82

(1H, m), 2.27 – 2.38 (1H, m), 2.67 – 2.72 (2H, m), 2.99 – 3.31 (2H, m), 4.15 – 4.37 (2H, m), 4.82 – 4.97 (1H, m), 5.03 – 5.12 (1H, m), 7.46 (1H, d), 8.24 (1H, d), 8.30 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 426.0.

Intermediate 340b:

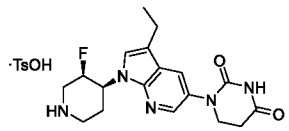
tert-Butyl (3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2825] Prepared in an analogous method to Intermediate 126b using Intermediate 340a (2.50 g, 5.86 mmol), stirring at 100 °C for 24 hours. After cooling to r.t., the mixture was diluted with DCM (100 mL), washed with sat. aq. K_2CO_3 (2 x 75 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether, then 0 to 3% MeOH in DCM) gave the title compound (1.40 g, 52%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.26 (3H, t), 1.43 (9H, s), 1.77 – 1.82 (1H, m), 2.31 – 2.38 (1H, m), 2.68 – 2.73 (2H, m), 2.77 (2H, t), 3.00 – 3.09 (1H, m), 3.13 – 3.23 (1H, m), 3.82 (2H, t), 4.13 – 4.38 (2H, m), 4.83 – 4.99 (1H, m), 5.07 – 5.18 (1H, m), 7.44 (1H, d), 7.98 (1H, d), 8.21 (1H, d), 10.42 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 460.1.

Intermediate 340c:

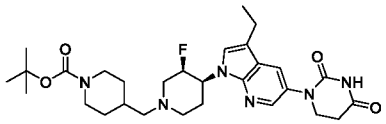
1-(3-Ehyl-1-((3*R*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2826] Prepared in an analogous method to Intermediate 330c using Intermediate 340b (1.40 g, 3.05 mmol) and *p*-toluenesulfonic acid (0.89 g, 5.18 mmol), stirring at 80 °C for 24 hours, to give the title compound (1.30 g, 80%) as a white solid and tosic acid salt. ^{1}H NMR (DMSO-d_6) δ 1.26 (3H, t), 2.05 – 2.10 (2H, m), 2.29 (3H, s), 2.57 – 2.65 (1H, m), 2.71 – 2.79 (4H, m), 3.41 – 3.59 (2H, m), 3.62 – 3.74 (2H, m), 3.83 (2H, t), 5.24 – 5.37 (1H, d), 7.11 (2H, d), 7.34 – 7.37 (1H, m), 7.48 (2H, d), 8.01 (1H, d), 8.23 (1H, d), 8.78 (1H, s), 9.13 (1H, d), 10.42 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 360.1.

Intermediate 340d:

tert-Butyl 4-(((3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

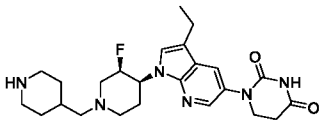


[2827] Intermediate 340c (1.40 g, 3.90 mmol) was added to *tert*-butyl 4-formylpiperidine-1-carboxylate (1.66 g, 7.79 mmol) in DMF (14 mL). The resulting mixture was stirred at 40 °C for 2 hours.

Sodium triacetoxyborohydride (3.30 g, 15.6 mmol) was added. The mixture was stirred at 40 °C for 30 minutes. After cooling to r.t., the mixture was diluted with DCM (75 mL), washed with sat. aq. $NaHCO_3$ (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.799 g, 36%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.93 – 1.00 (2H, m), 1.27 (3H, t), 1.38 – 1.39 (1H, m), 1.40 (9H, s), 1.67 – 1.74 (3H, m), 1.76 – 1.81 (1H, m), 2.22 – 2.31 (3H, m), 2.39 – 2.48 (2H, m), 2.68 – 2.73 (3H, m), 2.77 (2H, t), 3.00 – 3.04 (1H, d), 3.17 – 3.23 (1H, m), 3.82 (2H, t), 3.91 – 3.97 (2H, m), 4.81 – 4.95 (2H, m), 7.44 (1H, d), 7.97 (1H, d), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 557.3.

Intermediate 340e:

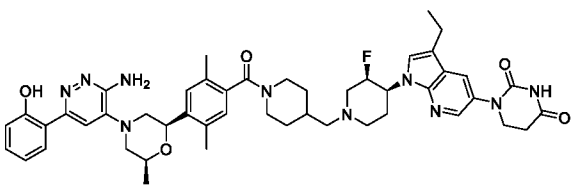
1-(3-Ethyl-1-((3*R*,4*S*)-3-fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2828] TFA (1.65 mL, 21.3 mmol) was added to a solution of Intermediate 340d (792 mg, 1.42 mmol) in DCM (4.9 mL). The resulting mixture was stirred at r.t. for 90 minutes and concentrated under reduced pressure. The residue was dissolved in water (1 mL). DCM–MeOH (2:1, 45 mL) and 5 M aq. K_2CO_3 (50 mL) were added. The phases were separated. The organic layer was washed with 5 M aq. K_2CO_3 (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (629 mg, 97%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.89 - 1.00 (2H, m), 1.25 (3H, t), 1.50 - 1.67 (3H, m), 1.72 - 1.79 (1H, m), 2.11 - 2.46 (7H, m), 2.69 (2H, q), 2.75 (2H, t), 2.89 (2H, br d), 2.96 - 3.04 (1H, m), 3.12 - 3.20 (1H, m), 3.80 (2H, t), 4.73 - 4.99 (2H, m), 7.42 (1H, s), 7.94 (1H, d), 8.18 (1H, d), 10.33 (1H, br s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 457.3.

EXAMPLE 340:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

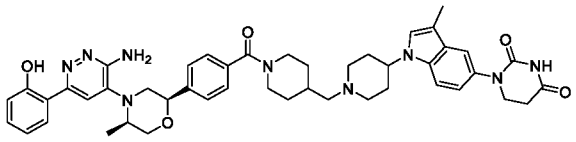


[2829] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20.0 mg, 0.05 mmol) and Intermediate 340e (21.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.7 mg, 64%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.86 - 1.15 (2H, m), 1.21 - 1.27 (6H, m), 1.51 - 1.69 (1H, m), 1.71 - 1.92 (3H, m), 2.10 - 2.57 (12H, m), 2.63 - 2.82 (6H, m), 2.90 - 3.07 (2H, m), 3.14 -

3.24 (1H, m), 3.27 - 3.37 (1H, m), 3.52 (2H, br d), 3.80 (2H, t), 4.04 - 4.19 (1H, m), 4.44 - 4.60 (1H, m), 4.75 - 4.95 (2H, m), 4.97 (1H, br d), 6.40 (2H, br s), 6.81 - 6.90 (2H, m), 6.91 - 7.01 (1H, m), 7.17 - 7.26 (1H, m), 7.30 - 7.37 (1H, m), 7.41 (1H, br s), 7.55 (1H, br s), 7.88 - 8.01 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.19 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 873.5.

EXAMPLE 341:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

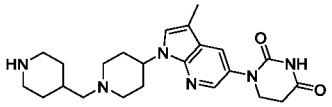


[2830] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.3 mg, 0.05 mmol) and Intermediate 113b (38.3 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (26.1 mg, 64%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 0.94 - 1.17 (5H, m), 1.60 - 1.98 (7H, m), 2.06 - 2.29 (7H, m), 2.66 - 2.89 (3H, m), 2.90 - 3.15 (4H, m), 3.51 (1H, br t), 3.62 (1H, br s), 3.75 (2H, t), 3.83 (1H, br d), 3.90 - 4.00 (1H, m), 4.18 - 4.35 (2H, m), 4.48 (1H, br s), 4.70 (1H, br d), 6.36 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.01 - 7.08 (1H, m), 7.21 (1H, t), 7.29 (1H, s), 7.35 - 7.42 (3H, m), 7.45 (1H, d), 7.50 (1H, s), 7.55 (2H, br d), 7.93 (1H, br d), 10.23 (1H, s), 14.25 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 812.3.

EXAMPLE 342

Intermediate 342a:

1-(3-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



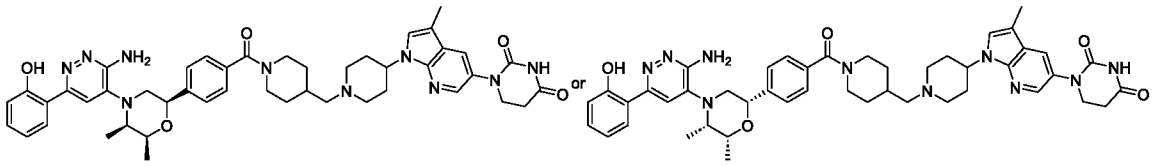
[2831] TFA (1.29 mL, 16.8 mmol) was added to a solution of Intermediate 201a (440 mg, 0.84 mmol) in DCM (3.9 mL). The resulting mixture was stirred at r.t. for 35 minutes and concentrated under reduced pressure. Water (10 mL), DCM–IPA (2:1, 30 mL) and sat. aq. K_2CO_3 (20 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (322 mg, 90%) as a white solid. ^1H NMR (DMSO-d_6) δ 0.95 (2H, qd), 1.50 - 1.66 (3H, m), 1.81 - 1.88 (2H, m), 1.96 - 2.11 (4H, m), 2.14 (2H, d), 2.23 (3H, s), 2.37 - 2.45 (2H, m), 2.69 (2H, t), 2.85 - 2.92 (2H, m), 2.94 (2H, br d), 3.76 (2H, t), 4.58 (1H, td), 7.46 (1H, s), 7.84 (1H, d), 8.14 (1H, d), 9.53 - 11.21 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 425.4.

EXAMPLE 342:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

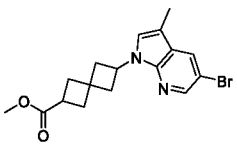


[2832] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 342a (18.4 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (34.3 mg, 96%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, d), 1.15 (5H, d), 1.67 (1H, br d), 1.85 (4H, br d), 1.97 - 2.15 (4H, m), 2.23 (5H, s), 2.69 - 2.87 (3H, m), 2.93 - 3.13 (4H, m), 3.41 (1H, br t), 3.61 (1H, br s), 3.74 - 3.85 (3H, m), 4.36 - 4.42 (1H, m), 4.48 (1H, br d), 4.56 - 4.65 (1H, m), 4.77 (1H, dd), 6.35 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.15 - 7.27 (1H, m), 7.39 (2H, d), 7.48 (1H, s), 7.50 (1H, s), 7.55 (2H, d), 7.87 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.37 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 827.4.

EXAMPLE 343

Intermediate 343a:

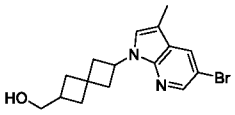
rac-Methyl 6-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptane-2-carboxylate



[2833] To a stirred solution of 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.50 g, 7.11 mmol) and *rac*-methyl 6-hydroxyspiro[3.3]heptane-2-carboxylate (1.45 g, 8.53 mmol) in toluene (20 mL) under nitrogen was added 2-(tributyl-λ^5-phosphanylidene)acetonitrile (2.79 mL, 10.7 mmol). The resulting mixture was stirred at 100 °C overnight. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (2.01 g, 78%) as an orange solid. ^{1}H NMR (DMSO-d_6) δ 2.22 - 2.29 (5H, m), 2.31 - 2.38 (1H, m), 2.44 (3H, br dd), 2.52 (1H, br s), 2.58 - 2.67 (1H, m), 3.07 - 3.15 (1H, m), 3.61 (3H, s), 5.04-5.16 (1H, m), 7.58 (1H, s), 8.11 - 8.19 (1H, m), 8.25 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 363.2.

Intermediate 343b:

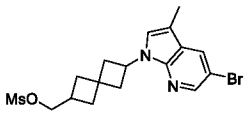
rac-(6-(5-Bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methanol



[2834] Lithium tetrahydroborate, 2 M in THF (6.19 mL, 12.39 mmol) was added drop wise to a stirred solution of Intermediate 343a (1.80 g, 4.96 mmol) in THF (20 mL). The resulting mixture was stirred at 50 °C for 3 h. After cooling to r.t., the mixture was diluted with EtOAc (50 mL) and quenched carefully by addition of sat. aq. NH_4Cl (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.40 g, 84%) as an oil. ^1H NMR ($CDCl_3$) δ 1.27 - 1.33 (1H, m), 1.90 (1H, dd), 1.98 (1H, dd), 2.16 (1H, br s), 2.29 (3H, s), 2.32 - 2.45 (3H, m), 2.49 (2H, br d), 2.67 - 2.77(1H, m), 3.64 (2H, br s), 5.16 - 5.28 (1H, m), 7.28 (1H, s), 7.95 (1H, d), 8.30 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 335.1.

Intermediate 343c:

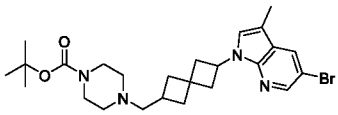
rac-(6-(5-Bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl methanesulfonate



[2835] Methanesulfonic anhydride (0.68 mL, 3.58 mmol) was added dropwise to a solution of Intermediate 343b (1.00 g, 2.98 mmol) and triethylamine (0.50 mL, 3.58 mmol) in DCM (15 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at r.t. for 1 h. The mixture was diluted with DCM (40 mL), washed with sat. aq. $NaHCO_3$ (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.10 g, 89%) as a yellow gum, which was used for the next step without further purification. *m/z* (ES^+) $[M+H]^+$ = 413.2.

Intermediate 343d:

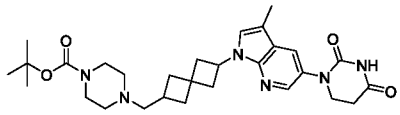
rac-tert-Butyl 4-((6-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



[2836] A mixture of *tert*-butyl piperazine-1-carboxylate (0.68 g, 3.63 mmol), Intermediate 343c (1.00 g, 2.42 mmol) and DIPEA (0.85 mL, 4.84 mmol) in DMF (15 mL) was stirred at 90 °C for 17 h. After cooling to r.t., the mixture was diluted with EtOAc (50 mL), washed with sat. aq. NH_4Cl (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (0.900 g, 74%) as a yellow gum. ^1H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.79 - 1.93 (2H, m), 2.14 - 2.21 (2H, m), 2.29 (3H, s), 2.33 - 2.44 (9H, m), 2.46 - 2.56 (2H, m), 2.68 - 2.77 (1H,m), 3.41 - 3.47 (4H, m), 5.13 - 5.26 (1H, m), 7.95 (1H, d), 8.30 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 503.2.

Intermediate 343e:

rac-tert-Butyl 4-((6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



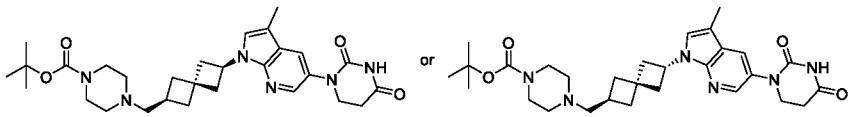
[2837] Prepared in an analogous manner to Intermediate 237g using Intermediate 343d (900 mg, 1.79 mmol). Trituration with diethyl ether (50 mL) gave the title compound (760 mg, 79%) as a light brown solid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 1.75 (1H, dd), 1.83 (1H, dd), 2.13 (1H, br t), 2.25 - 2.29 (7H, m), 2.34 - 2.36 (2H, m), 2.40 - 2.43 (2H,m), 2.44 - 2.46 (2H, m), 2.56 - 2.62 (1H, m), 2.76 (2H, t), 3.18 - 3.22 (2H, m), 3.29 (3H, br s), 3.80 (2H, t), 5.10 (1H, quin), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 537.5.

Intermediate 343f:

tert-Butyl 4-(((2*S*,4*s*,6*S*)-6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate

or

tert-Butyl 4-(((2*R*,4*r*,6*R*)-6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



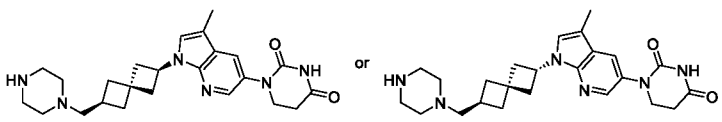
[2838] Intermediate 343e (1.05 g, 4.79 mmol) was dissolved in MeOH. The resulting solution was purified using the following SFC conditions: Column: Chiralpak IH 4.6x150mm; mobile phase: 25% MeOH with 0.2% NH_4OH in $scCO_2$; Flow rate: 100 mL/min to afford the title compound which eluted second from the column (145 mg, 20%, 98% ee) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 1.71 - 1.77 (1H, m), 1.79 - 1.86 (1H, m), 2.09 - 2.18 (1H, m), 2.26 (7H, s), 2.31 - 2.37 (3H, m), 2.38 -2.44 (3H, m), 2.45 - 2.49 (1H, m), 2.56 - 2.61 (1H, m), 2.76 (2H, t), 3.29 (4H, br s), 3.80 (2H, t), 5.04 - 5.15 (1H, m), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 537.6.

Intermediate 343g:

1-(3-Methyl-1-((2*S*,4*s*,6*S*)-6-(piperazin-1-ylmethyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(3-Methyl-1-((2*R*,4*r*,6*R*)-6-(piperazin-1-ylmethyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2839] TFA (0.35 mL, 4.47 mmol) was added to a stirred solution of Intermediate 343f (140 mg, 0.26 mmol) in DCM (4 mL). The resulting solution stirred at r.t. for 1 h and concentrated under reduced pressure.

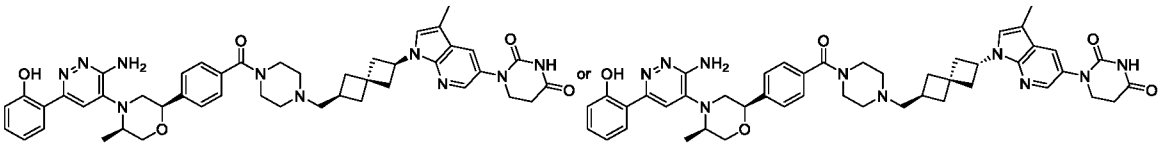
The residue was dissolved in DCM/IPA (8:1, 45 mL) and washed with sat. aq. K_2CO_3 (10 mL). The aqueous layer extracted with DCM/IPA. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (90 mg, 92%) as a white solid. *m/z* (ES^+) $[M+H]^+$ = 437.4.

EXAMPLE 343:

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



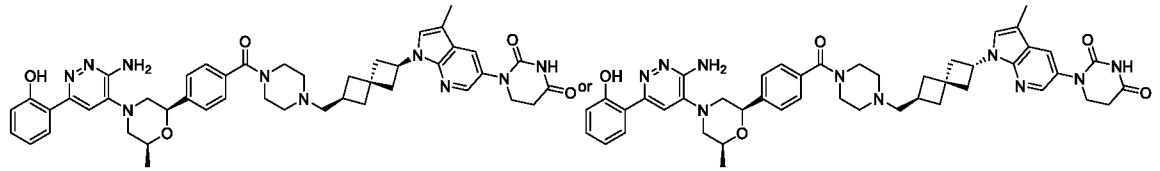
[2840] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (15 mg, 0.04 mmol) and Intermediate 343g (16 mg, 0.04 mmol). Purification by RPC (elution gradient: 40 to 80% MeCN in water with 0.2% NH_4OH) gave the title compound (12.0 mg, 39%) as a white solid, following lyophilization. ^1H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.77 (1H, br dd), 1.85 (1H, br dd), 2.11 - 2.20 (1H, m), 2.26 (3H, s), 2.28 - 2.49 (11H, m), 2.52 - 2.53 (1H, m), 2.52 - 2.64 (1H, m), 2.76 (2H, t), 3.10 (1H, br d), 3.35 - 3.40 (1H, m), 3.52 (1H, br t), 3.62 (2H, br s), 3.80 (2H, t), 3.84 (1H, br d), 3.95 (1H, br d), 4.29 (1H, br d), 4.71 (1H, br d), 5.10 (1H, quin), 6.37 (2H, br s), 6.83 (1H, t), 6.88 (1H, d), 7.22 (1H, t), 7.42 (2H, d), 7.53 (2H, d), 7.57 (2H, d), 7.87 (1H, d), 7.94 (1H, d), 8.17 (1H, d),10.42 (1H, br s), 14.1 (1H, br. s); *m/z* (ES^+) $[M+H]^+$ = 825.5.

EXAMPLE 344:

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



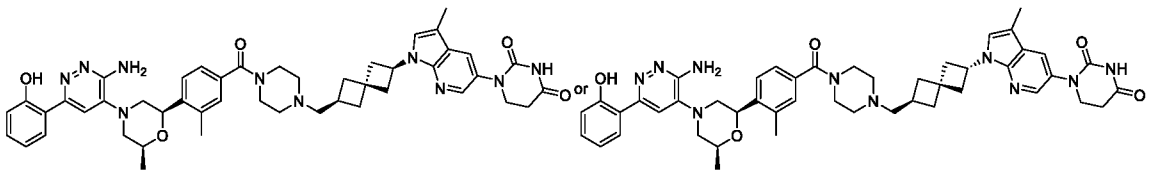
[2841] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (15 mg, 0.04 mmol) and Intermediate 343g (16 mg, 0.04 mmol). Purification by RPC (elution gradient: 40 to 80% MeCN in water with 0.2% NH_4OH) gave the title compound as a white solid (12.0 mg, 39%) following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.26 (3H, d), 1.76 (1H, br dd), 1.80 - 1.90 (1H, m), 2.10 - 2.17 (1H, m), 2.25 (3H, s), 2.28 - 2.47 (11H, m), 2.48 - 2.51 (2H, m), 2.53 - 2.62 (2H, m), 2.68 (1H, br t), 2.75 (2H, t), 3.51 (1H, br d), 3.58 (3H, br d), 3.80 (2H, t), 4.07 - 4.18 (1H, m), 4.94 (1H, br d), 5.10 (1H, br t), 6.47 (2H, s), 6.82 - 6.91 (2H, m), 7.20 - 7.26 (1H, m), 7.40 (2H, d), 7.51 - 7.55 (3H, m), 7.57 (1H, s), 7.87 (1H, d), 7.93 - 7.99 (1H, m), 8.17 (1H, d), 10.13 -10.70 (1H, br s), 13.78 - 14.59 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 825.8.

EXAMPLE 345:

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

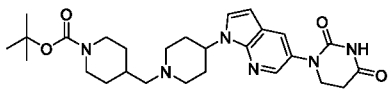


[2842] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 132e (15 mg, 0.04 mmol) and Intermediate 343g (16 mg, 0.04 mmol). Purification by RPC (elution gradient: 40 to 80% MeCN in water with 0.2% NH_4OH) gave the title compound as a white solid (10.0 mg, 33%) following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, d), 1.72 - 1.89 (2H, m), 2.12 - 2.18 (1H, m), 2.25 (3H, s), 2.31 (2H, br d), 2.37 - 2.47 (10H, m), 2.51 - 2.63 (5H, m), 2.70 - 2.80 (3H, m), 3.50 - 3.65 (5H, m), 3.80 (2H, t), 4.10 - 4.20 (1H, m), 4.99 - 5.16 (2H, m), 6.42 (2H, s), 6.82 - 6.92 (2H, m), 7.18 - 7.26 (3H, m), 7.48 - 7.57 (3H, m), 7.87 (1H, d), 7.95 (1H, d), 8.17 (1H, d), 10.38 (1H, s), 14.00 - 14.45 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 839.4.

EXAMPLE 346

Intermediate 346a:

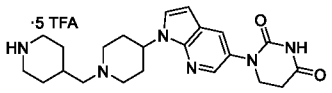
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2843] Sodium triacetoxyhydroborate (234 mg, 1.10 mmol) was added to a stirred mixture of Intermediate 166a (173 mg, 0.55 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (147 mg, 0.69 mmol) in DCM–IPA (10:1, 4.3 mL). The resulting mixture was stirred at r.t. for 1 h. The mixture was diluted with DCM (10 mL) and water (2 mL). The phases were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 50 to 100% EtOAc in hexanes, then 0 to 20% MeOH in EtOAc) gave the title compound (230 mg, 82%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.92 - 1.03 (2H, m), 1.40 (9H, s), 1.71 (3H, br d), 1.84 - 1.96 (2H, m), 2.04 - 2.16 (4H, m), 2.20 (2H, br d), 2.60 - 2.82 (4H, m), 2.99 (2H, br d), 3.81 (2H, t), 3.94 (2H, br d), 4.62 - 4.71 (1H, m), 6.50 (1H, d), 7.74 (1H, d), 7.92 (1H, d), 8.21 (1H, d), 10.38 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 511.3.

Intermediate 346b:

1-(1-(1-(Piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



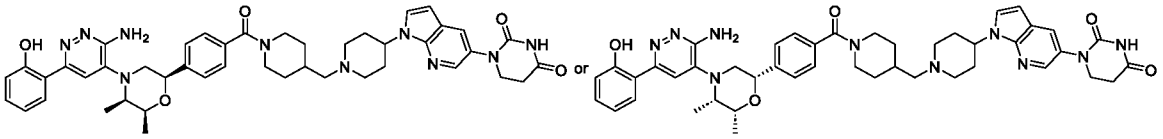
[2844] TFA (0.35 ml, 4.50 mmol) was added to a chalky suspension of Intermediate 346a (0.23 g, 0.45 mmol) in DCM (1.1 ml). The resulting solution was stirred at r.t. for 3 h and concentrated under reduced pressure. The resulting oil was azeotroped with DCM to afford the title compound (0.443 g, 100%) as a 5 TFA salt. *m/z* (ES$^+$) $[M+H]^+$ = 411.4.

EXAMPLE 346:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2845] Prepared in an analogous manner to Example 1 starting from Intermediate 261g (21 mg, 0.05 mmol) and Intermediate 346b (49 mg, 0.05 mmol) using γ-valerolactone as the solvent. Purification by RPC (elution gradient: 10 to 100% MeOH in water with 0.1% FA) and lyophilization from MeCN–MeOH–water gave the title compound (35.0 mg, 86%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, br d), 1.16 (5H, br d), 1.71 (1H, br s), 1.80 - 1.99 (4H, m), 2.16 (2H, br d), 2.24 - 2.47 (4H, m), 2.73 - 2.87 (3H, m), 3.10 (4H, br d), 3.42 (2H, br t), 3.63 (1H, br s), 3.75 - 3.87 (3H, m), 4.41 (1H, br d), 4.50 (1H, br s), 4.68 - 4.82 (2H, m), 6.36 (2H, br s), 6.52 (1H, d), 6.84 (1H, t), 6.88 (1H, d), 7.22 (1H, br t), 7.38 - 7.45 (2H, m), 7.52

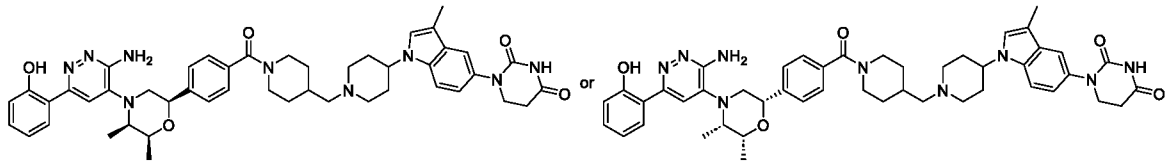
(1H, s), 7.54 - 7.59 (2H, m), 7.72 (1H, d), 7.91 - 8.00 (2H, m), 8.20 - 8.24 (1H, m), 10.39 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 813.3.

EXAMPLE 347:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

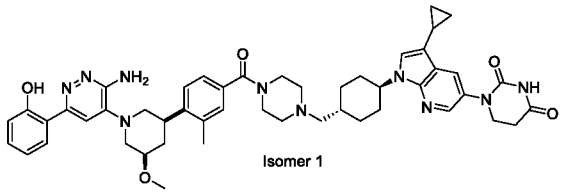
1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2846] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (21 mg, 0.05 mmol) and Intermediate 113b (38 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4OH) gave the title compound (30.4 mg, 74%) as a white solid, following lyophilization. ^1H NMR (DMSO-d_6) δ 0.95 (3H, d), 1.05 - 1.14 (2H, m), 1.17 (3H, d), 1.63 - 1.77 (1H, m), 1.79 - 2.02 (6H, m), 2.16 (2H, br t), 2.20 - 2.29 (5H, m), 2.73 (2H, t), 2.76 - 2.87 (1H, m), 2.93 - 3.15 (4H, m), 3.43 (1H, br t), 3.63 (1H, br s), 3.73 - 3.85 (3H, m), 4.23 - 4.34 (1H, m), 4.37 - 4.44 (1H, m), 4.50 (1H, br s), 4.75 - 4.83 (1H, m), 6.36 (2H, br s), 6.81 - 6.86 (1H, m), 6.89 (1H, d), 7.06 (1H, dd), 7.23 (1H, t), 7.31 (1H, s), 7.38 - 7.44 (3H, m), 7.45 - 7.50 (1H, m), 7.52 (1H, s), 7.57 (2H, d), 7.95 (1H, d), 10.25 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 826.7.

EXAMPLE 348:

1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed))

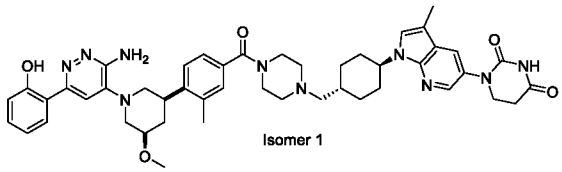


[2847] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (48 mg, 0.08 mmol) and intermediate 273f (54 mg, 0.12 mmol). After completion of the reaction, the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 10 to 40% [10% MeOH in DCM with 1% NH_4OH] in DCM) and RPC (elution gradient: 15 to 50% MeCN in water with 0.1% FA) gave the title compound (17.0 mg, 25%) as a white solid, following lyophilization. ^1H NMR (DMSO-d_6) δ 0.61 - 0.65 (2H, m), 0.82 - 0.89 (2H, m), 1.20 - 1.35 (2H, m), 1.55 - 1.67 (1H, m), 1.84 - 1.99 (8H, m), 2.21

- 2.31 (1H, m), 2.37 - 2.43 (3H, m), 2.67 - 2.72 (1H, m), 2.74 - 2.78 (2H, m), 2.93 - 3.02 (1H, m), 3.03 - 3.08 (2H, m), 3.09 - 3.22 (2H, m), 3.27 - 3.36 (2H, m), 3.35 - 3.38 (3H, m), 3.41 - 3.54 (2H, m), 3.54 - 3.64 (2H, m), 3.71 - 3.78 (1H, m), 3.79 - 3.83 (2H, m), 3.89 - 4.06 (2H, m), 4.49 - 4.67 (2H, m), 6.94 - 6.98 (1H, m), 7.00 - 7.05 (1H, m), 7.28 - 7.32 (2H, m), 7.33 - 7.38 (2H, m), 7.43 - 7.46 (1H, m), 7.58 (1H, s), 7.62 (1H, br d), 7.94 (1H, d), 8.16 (1H, d), 10.36 (1H, s), three heteroatom-bound protons not observed; *m/z* (ES^+) $[M+H]^+$ = 867.8.

EXAMPLE 349:

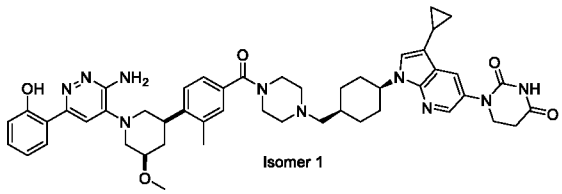
1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed))



[2848] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (48 mg, 0.08 mmol) and intermediate 259b (51 mg, 0.12 mmol). After completion of the reaction, the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 10 to 40% [10% MeOH in DCM with 1% NH_4OH] in DCM) and RPC (elution gradient: 15 to 50% MeCN in water with 0.1% FA) gave the title compound (17.0 mg, 25%) as a white solid, following lyophilization. ^1H NMR (DMSO-d_6) δ 1.29 (2H, br d), 1.60 (1H, q), 1.85 - 2.00 (7H, m), 2.22 - 2.30 (4H, m), 2.37 - 2.44 (3H, m), 2.66 - 2.73 (1H, m), 2.73 - 2.78 (2H, m), 2.93 - 3.01 (1H, m), 3.03 - 3.19 (4H, m), 3.26 - 3.36 (2H, m), 3.36 - 3.40 (3H, m), 3.42 - 3.57 (2H, m), 3.57 - 3.69 (2H, m), 3.73 - 3.78 (1H, m), 3.78 - 3.83 (2H, m), 3.83 - 3.96 (1H, m), 3.96 - 4.05 (1H, m), 4.51 - 4.71 (2H, m), 6.96 (1H, t), 7.03 (1H, d), 7.30 - 7.33 (1H, m), 7.36 - 7.40 (1H, m), 7.40 - 7.50 (3H, m), 7.56 - 7.59 (1H, m), 7.61 (1H, br d), 7.88 (1H, d), 8.16 (1H, d), 10.37 (1H, s), three heteroatom-bound protons not observed; *m/z* (ES^+) $[M+H]^+$ = 841.6

EXAMPLE 350:

1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed))

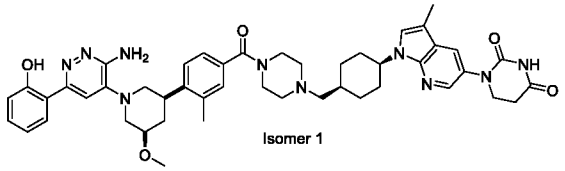


[2849] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (24 mg, 0.04 mmol) and intermediate 217a (49 mg, 0.05 mmol). After completion of the reaction, the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 10 to 40% [10% MeOH in

DCM with 1% NH_4OH] in DCM) gave the title compound (9.5 mg, 27%) as a white solid. ^1H NMR (DMSO-d_6) δ 0.61 - 0.68 (2H, m), 0.79 - 0.90 (2H, m), 1.49 - 1.58 (1H, m), 1.59 - 1.70 (4H, m), 1.72 - 1.82 (2H, m), 1.87 - 2.01 (4H, m), 2.25 - 2.30 (1H, m), 2.37 - 2.40 (3H, m), 2.42 - 2.46 (2H, m), 2.74 - 2.81 (3H, m), 3.27 - 3.32 (7H, m), 3.36 - 3.38 (3H, m), 3.39 - 3.47 (2H, m), 3.54 - 3.70 (2H, m), 3.74 - 3.87 (4H, m), 4.62 (1H, br t), 6.32 (2H, s), 6.84 - 6.90 (2H, m), 7.19 - 7.25 (3H, m), 7.37 - 7.43 (1H, m), 7.47 - 7.50 (1H, m), 7.56 - 7.62 (1H, m), 7.90 - 7.97 (2H, m), 8.15 (1H, d), 10.35 (1H, s), 13.91 - 14.45 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 867.8.

EXAMPLE 351:

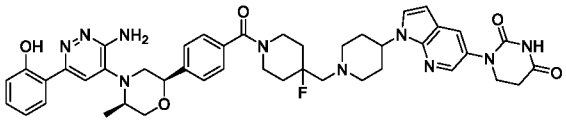
1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed))



[2850] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 26j (24 mg, 0.04 mmol) and intermediate 258f (20 mg, 0.05 mmol). After completion of the reaction, the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 10 to 50% [10% MeOH in DCM with 1% NH_4OH] in DCM) gave the title compound (24.6 mg, 73%) as a white solid. ^1H NMR (DMSO-d_6) δ 1.18 - 1.30 (2H, m), 1.48 - 1.60 (1H, m), 1.60 - 1.72 (4H, m), 1.72 - 1.80 (2H, m), 1.87 - 2.00 (3H, m), 2.22 - 2.29 (4H, m), 2.35 - 2.43 (5H, m), 2.72 - 2.82 (3H, m), 3.27 - 3.36 (7H, m), 3.36 - 3.38 (3H, m), 3.38 - 3.48 (2H, m), 3.73 - 3.89 (4H, m), 4.63 (1H, br t), 6.32 (2H, s), 6.84 - 6.90 (2H, m), 7.18 - 7.26 (3H, m), 7.40 (1H, d), 7.53 - 7.57 (1H, m), 7.59 (1H, s), 7.85 (1H, d), 7.94 (1H, d), 8.15 (1H, d), 10.36 (1H, s), 14.00 - 14.53 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 841.7.

EXAMPLE 352:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2851] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 166c (19.2 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.4 mg, 75%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.62 - 2.16 (8H, m), 2.32 - 2.43 (2H, m), 2.60 - 2.71 (2H, m), 2.76 (2H, t), 3.00 - 3.30 (5H, m), 3.53 (2H, br t), 3.76 - 3.87 (3H, m), 3.96 (1H, br d), 4.11 - 4.42 (2H, m), 4.58 - 4.77 (2H, m), 6.38 (2H, s), 6.51 (1H, d), 6.84 (1H, t), 6.86 - 6.92 (1H,

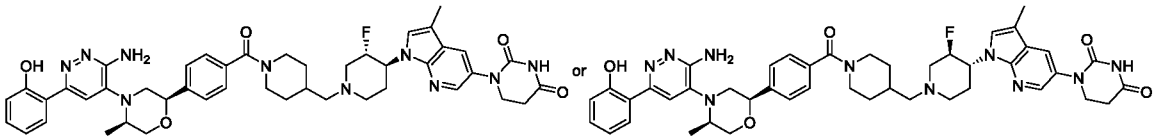
m), 7.16 - 7.27 (1H, m), 7.46 (2H, d), 7.52 (1H, s), 7.59 (2H, d), 7.74 (1H, d), 7.89 - 7.98 (2H, m), 8.21 (1H, d), 10.39 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 817.6.

EXAMPLE 353:

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

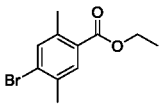


[2852] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 334d (42.9 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (33.6 mg, 90%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 1.00 - 1.17 (5H, m), 1.58 - 1.75 (1H, m), 1.87 (3H, br d), 2.16 (3H, br d), 2.24 (3H, s), 2.28 - 2.39 (2H, m), 2.69 - 3.15 (6H, m), 3.32 - 3.36 (1H, m), 3.51 (1H, br t), 3.56 - 3.70 (1H, m), 3.76 - 3.86 (3H, m), 3.94 (1H, br d), 4.28 (1H, br d), 4.48 (1H, br s), 4.64 - 4.77 (2H, m), 4.99 - 5.19 (1H, m), 6.37 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.15 - 7.25 (1H, m), 7.40 (2H, d), 7.51 (1H, s), 7.53 - 7.61 (3H, m), 7.89 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.38 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 831.4.

EXAMPLE 354

Intermediate 354a:

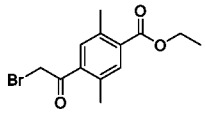
Ethyl 4-bromo-2,5-dimethylbenzoate



[2853] H_2SO_4 (0.23 mL, 4.37 mmol) was added to a solution of 4-bromo-2,5-dimethylbenzoic acid (10.0 g, 43.7 mmol) in EtOH (156 mL). The resulting mixture was stirred at reflux for 46 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. EtOAc (50 mL) and 1 M aq. NaOH (50 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (9.47 g, 84%) as a colorless oil that solidified upon standing for 3 days at r.t. to give a white solid. ^1H NMR (DMSO-d_6) δ 1.30 (3H, t), 2.33 (3H, s), 2.44 (3H, s), 4.27 (2H, q), 7.56 (1H, s), 7.73 (1H, s); mass not observed.

Intermediate 354b:

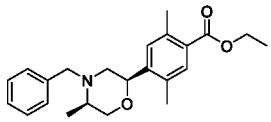
Ethyl 4-(2-bromoacetyl)-2,5-dimethylbenzoate



[2854] $PdCl_2(PPh_3)_2$ (0.78 g, 1.10 mmol) was added to a solution of Intermediate 354a (9.46 g, 36.8 mmol) and tributyl(1-ethoxyvinyl)stannane (13.1 mL, 38.6 mmol) in 1,4-dioxane (153 mL). The flask was evacuated and backfilled with argon (3x). The resulting mixture was stirred at 90 °C for 19.5 hours. After cooling to r.t., water (51 mL) was added and the mixture was cooled to 0 °C. NBS (7.20 g, 40.5 mmol) was added. The resulting mixture was stirred at 0 °C for 20 minutes and concentrated under reduced pressure. EtOAc (100 mL) and 1 M aq. KF (150 mL) were added and the mixture was stirred at r.t. for 15 minutes. The mixture was filtered. The filtercake was washed with EtOAc (2 x 20 mL). The layers of the combined filtrates were separated. The organic layer was washed with 1 M aq. KF (3 x 120 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound as a brown solid which was used for the next step without further purification. Quantitative yield was assumed. ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t), 2.49 (3H, s), 2.60 (3H, s), 4.36 - 4.44 (4H, m), 7.47 (1H, s), 7.79 (1H, s); mass not observed.

Intermediate 354c:

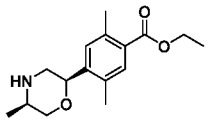
Ethyl 4-((2*R*,5*R*)-4-benzyl-5-methylmorpholin-2-yl)-2,5-dimethylbenzoate



[2855] (*R*)-2-(Benzylamino)propan-1-ol (6.08 g, 36.8 mmol) was slowly added to a suspension of Intermediate 354b (11.0 g, 36.8 mmol) and K_2CO_3 (5.09 g, 36.8 mmol) in MeCN (150 mL) at 0 °C. The resulting mixture was stirred at r.t. for 17 hours. The mixture was filtered. The filtercake was washed with DCM. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in DCM (60 mL). TFA (14.2 mL, 184 mmol) was added. The resulting mixture was stirred at 40 °C for 1 hour. Methyl(phenyl)silane (7.58 mL, 55.2 mmol) was added. The resulting mixture was stirred at 40 °C for 22 hours. More methyl (phenyl)silane (2.73 mL, 18.4 mmol) was added and stirring was continued at 40 °C for 5 hours. The mixture was concentrated under reduced pressure. EtOAc (100 mL) and 5 M aq. K_2CO_3–water (1:1, 100 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0 to 20% acetone in hexanes; 2nd purification: 0 to 25% EtOAc in hexanes) gave the title compound (4.73 g, 35%, 1st eluting diastereomer) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.14 (3H, d), 1.30 (3H, t), 2.20 (3H, s), 2.39 - 2.50 (5H, m), 2.84 (1H, br d), 3.60 (1H, s), 3.61 - 3.66 (1H, m), 3.71 (1H, br d), 3.85 (1H, dd), 4.23 - 4.30 (2H, m), 4.65 (1H, dd), 7.22 - 7.28 (1H, m), 7.30 - 7.40 (5H, m), 7.56 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 368.3.

Intermediate 354d:

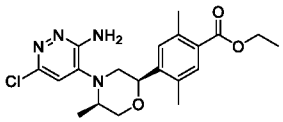
Ethyl 2,5-dimethyl-4-((2*R*,5*R*)-5-methylmorpholin-2-yl)benzoate



[2856] A 250 mL flask was charged with Intermediate 354c (4.73 g, 12.9 mmol) and Pd/C (0.68 g, 0.64 mmol, 10 wt% Pd). The flask was evacuated and backfilled with nitrogen (2x). EtOH (52 mL) was added. The flask was evacuated and backfilled with hydrogen (3x). The resulting mixture was stirred at 60 °C under an atmosphere of hydrogen for 6 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with EtOH. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 278.2.

Intermediate 354e:

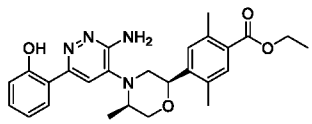
Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-chloropyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoate



[2857] DMSO (26 mL) was added to a mixture of Intermediate 354d (3.57 g, 12.9 mmol), 4-bromo-6-chloropyridazine-3-amine (5.37 g, 25.7 mmol) and potassium fluoride (2.24 g, 38.6 mmol). The flask was evacuated and backfilled with nitrogen (2x). The resulting mixture was stirred at 120 °C for 40 hours. After cooling to r.t., the mixture was added into a stirred mixture of water and brine (4:1, 256 mL). A precipitate formed which was collected by filtration, washed with water (5 x 25 mL), and dried *in vacuo*. The solids were suspended in DCM and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 20 to 50% acetone in hexanes) gave the title compound (2.78 g, 53%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 1.06 (3H, d), 1.31 (3H, t), 2.29 (3H, s), 2.47 - 2.53 (3H, m), 2.92 (1H, dd), 3.22 - 3.29 (1H, m), 3.78 (1H, d), 3.85 - 3.95 (1H, m), 4.21 (1H, dd), 4.28 (2H, q), 4.68 - 4.83 (1H, m), 6.18 (2H, s), 6.90 (1H, s), 7.44 (1H, s), 7.61 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 405.3.

Intermediate 354f:

Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazine-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoate

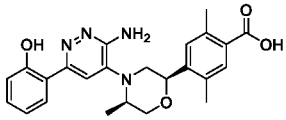


[2858] A 250 mL flask was charged with Intermediate 354e (2.77 g, 6.83 mmol), CPhos Pd G3 (0.28 g, 0.34 mmol), CPhos (0.15 g, 0.34 mmol), (2-hydroxyphenyl)boronic acid (1.41 g, 10.3 mmol) and K_2CO_3 (2.83 g, 20.5 mmol). 1,4-Dioxane (54 mL) and water (6 mL) were added. The flask was evacuated and backfilled with argon (3x). The resulting mixture was stirred at 90 °C for 2 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM–IPA (3:1, 50 mL) and 5 M aq. K_2CO_3 (50 mL)

were added. The resulting biphasic mixture was stirred vigorously for 30 minutes. The phases were separated. The organic layer was washed with 5 M aq. K_2CO_3 (2 x 50 mL) and sat. aq. NH_4Cl (50 mL). The aq. NH_4Cl layer was backextracted with DCM (20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 20 to 37% [3:1 EtOAc:EtOH] in hexanes; 2nd purification: elution gradient: 20 to 45% acetone in hexanes) gave the title compound (2.43 g, 77%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d), 1.31 (3H, t), 2.32 (3H, s), 2.52 (3H, s), 3.01 (1H, br d), 3.45 (1H, t), 3.83 (1H, d), 3.94 (1H, br d), 4.22 - 4.35 (3H, m), 4.81 (1H, dd), 6.35 (2H, s), 6.76 - 6.82 (1H, m), 6.86 (1H, dd), 7.15 - 7.25 (1H, m), 7.49 (2H, d), 7.63 (1H, s), 7.84 - 7.98 (1H, m), 14.24 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 463.3.

Intermediate 354g:

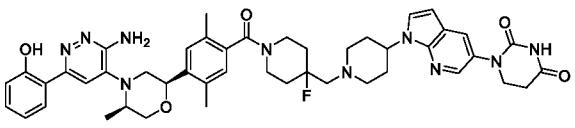
4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoic acid



[2859] 3 M aq. NaOH (5.25 mL, 15.7 mmol) was added to a solution of Intermediate 354f (2.43 g, 5.25 mmol) in EtOH (16 mL). The resulting mixture was stirred at 60 °C for 3 hours and concentrated under reduced pressure. Water (50 mL) and 6 M aq. HCl (5.5 mL) were added. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (2.30 g, 100%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.11 (3H, br d), 2.31 (3H, s), 2.53 (3H, s), 3.05 (1H, br d), 3.45 (1H, br t), 3.83 (1H, d), 3.92 - 4.02 (1H, m), 4.23 - 4.33 (1H, m), 4.81 (1H, dd), 6.53 (2H, br s), 6.83 (1H, t), 6.88 (1H, d), 7.18 - 7.27 (1H, m), 7.46 (1H, s), 7.48 (1H, s), 7.64 (1H, s), 7.85 (1H, br d), 13.21 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 435.3.

EXAMPLE 354:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione



[2860] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 166c (17.9 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.3 mg, 72%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, br d), 1.46 - 1.93 (5H, m), 1.93 - 2.15 (3H, m), 2.17 - 2.45 (8H, m), 2.56 - 2.69 (2H, m), 2.74 (2H, t), 2.96 - 3.28 (6H, m), 3.49 (1H, br d), 3.74 - 3.85 (3H, m), 3.91 - 4.03 (1H, m), 4.21 - 4.43 (2H, m), 4.64 (1H, br t), 4.75 - 4.84 (1H, m), 6.34 (2H, br s), 6.49 (1H, d), 6.82 (1H, br t), 6.86 (1H, d), 6.93 - 7.09 (1H, m), 7.17 - 7.25 (1H, m), 7.45 (1H, s), 7.49 (1H,

br s), 7.67 - 7.75 (1H, m), 7.87 - 7.91 (1H, m), 7.93 (1H, br d), 8.19 (1H, s), 10.37 (1H, s), 14.25 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 355:

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

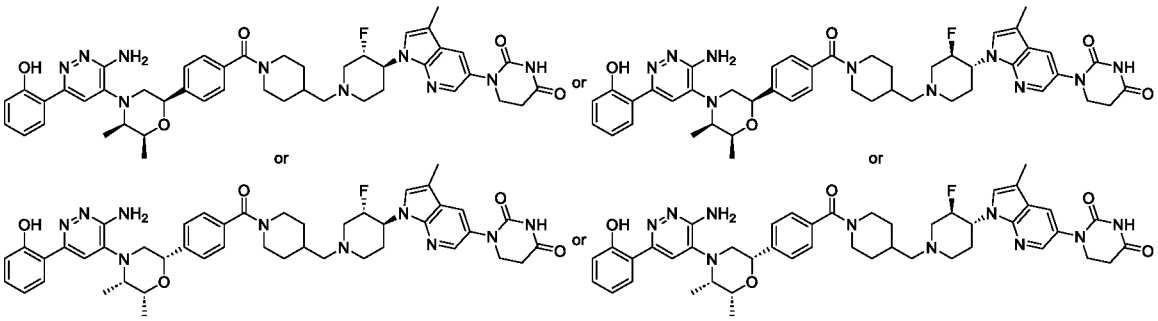
1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2861] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 334d (41.5 mg, 0.04 mmol, Isomer 1). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (35.2 mg, 96%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 0.92 (3H, d), 1.02 - 1.20 (5H, m), 1.59 - 1.97 (4H, m), 2.16 (3H, br d), 2.24 (3H, s), 2.28 - 2.38 (2H, m), 2.70 - 3.13 (6H, m), 3.32 - 3.35 (1H, m), 3.41 (1H, br t), 3.53 - 3.70 (1H, m), 3.74 - 3.84 (3H, m), 4.34 - 4.42 (1H, m), 4.42 - 4.54 (1H, m), 4.66 - 4.81 (2H, m), 5.00 - 5.17 (1H, m), 6.35 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.15 - 7.25 (1H, m), 7.40 (2H, d), 7.50 (1H, s), 7.55 (2H, d), 7.58 (1H, s), 7.89 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.38 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 356:

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

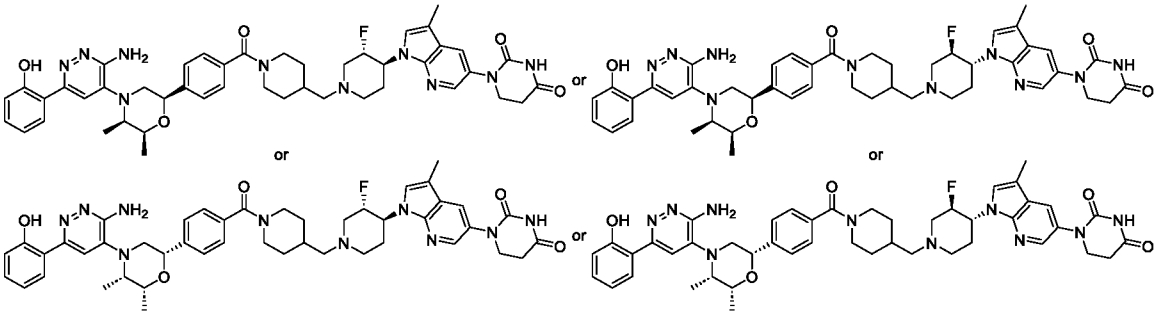
1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

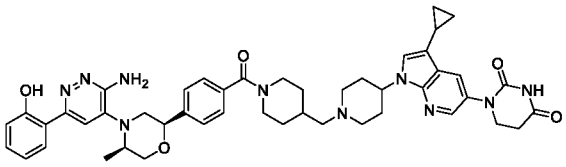
1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2862] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 335d (41.5 mg, 0.04 mmol, Isomer 2). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (30.0 mg, 82%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, d), 1.01 - 1.21 (5H, m), 1.58 - 1.99 (4H, m), 2.09 - 2.21 (3H, m), 2.24 (3H, s), 2.27 - 2.38 (2H, m), 2.71 - 3.15 (6H, m), 3.32 - 3.36 (1H, m), 3.41 (1H, br t), 3.61 (1H, br s), 3.74 - 3.83 (3H, m), 4.35 - 4.42 (1H, m), 4.43 - 4.56 (1H, m), 4.66 - 4.75 (1H, m), 4.77 (1H, dd), 5.00 - 5.18 (1H, m), 6.35 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.21 (1H, t), 7.40 (2H, d), 7.50 (1H, s), 7.55 (2H, d), 7.58 (1H, s), 7.89 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.38 (1H, s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 845.5.

EXAMPLE 357:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

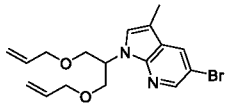


[2863] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 71c (20.2 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA, then 30 to 90% MeCN in water with 0.1% NH_4OH) and FSC (elution gradient: 1 to 15% [0.1% NH_4OH in MeOH] in DCM) gave the title compound (18.2 mg, 49%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.62 - 0.67 (2H, m), 0.78 - 0.87 (2H, m), 1.02 - 1.17 (5H, m), 1.54 - 1.95 (6H, m), 1.98 - 2.15 (4H, m), 2.17 - 2.29 (2H, m), 2.68 - 3.20 (7H, m), 3.51 (1H, br t), 3.55 - 3.70 (1H, m), 3.75 - 3.87 (3H, m), 3.90 - 3.99 (1H, m), 4.23 - 4.33 (1H, m), 4.38 - 4.54 (1H, m), 4.55 - 4.64 (1H, m), 4.70 (1H, dd), 6.36 (2H, s), 6.82 (1H, t), 6.86 (1H, d), 7.17 - 7.24 (1H, m), 7.40 (2H, d), 7.43 (1H, s), 7.50 (1H, s), 7.55 (2H, d), 7.89 - 7.96 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 14.24 (1H, br s).; *m/z* (ES^+) $[M+H]^+$ = 839.8.

EXAMPLE 358

Intermediate 358a:

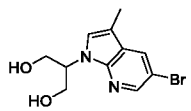
1-(1,3-*bis*(Allyloxy)propan-2-yl)-5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine



[2864] 2-(Tributyl-λ^5-phosphanylidene)acetonitrile (3.23 mL, 12.3 mmol) was added to a suspension of 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 9.48 mmol) and 1,3-*bis*(allyloxy)propan-2-ol (2.17 mL, 12.3 mmol) in toluene (42 mL). The resulting mixture was stirred at 100 °C for 16 hours. More 1,3-*bis*(allyloxy)propan-2-ol (0.83 mL, 4.74 mmol) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (1.24 mL, 4.74 mmol) were added and stirring was continued at 100 °C for 4 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 40% EtOAc in hexanes) gave the title compound (2.78 g, 7.61 mmol) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 3.71 - 3.78 (2H, m), 3.79 - 3.85 (2H, m), 3.86 - 3.95 (4H, m), 5.03 - 5.19 (5H, m), 5.68 - 5.83 (2H, m), 7.46 (1H, s), 8.15 (1H, d), 8.25 (1H, d); *m/z* (ES^+) $[M+H]^+$ = 365.2.

Intermediate 358b:

2-(5-Bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol

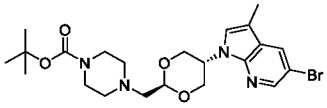


[2865] $Pd(PPh_3)_4$ (0.88 g, 0.76 mmol) and 1,3-dimethylpyrimidine2,4,6(1*H*,3*H*,5*H*)-trione (2.37 g, 15.2 mmol) were added to a solution of Intermediate 358a (2.78 g, 7.60 mmol) in MeOH (50 mL). The resulting mixture was stirred at r.t. under an atmosphere of nitrogen for 24 hours and concentrated under reduced pressure. Trituration with DCM–hexanes (2:1) and Et_2O gave the title compound (1.73 g, 80%) as

an off-white solid.^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 3.76 (4H, t), 4.76 (1H, quin), 4.85 (2H, t), 7.43 (1H, s), 8.13 (1H, d), 8.23 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 285.0.

Intermediate 358c:

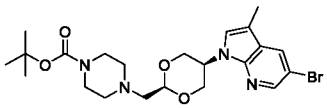
tert-Butyl 4-(((2*r*,5*r*)-5-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



and

Intermediate 358d:

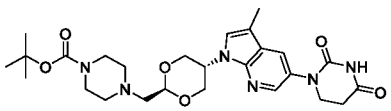
tert-Butyl 4-(((2*s*,5*s*)-5-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



[2866] Toluene (41 mL) and 2-bromo-1,2-dimethoxyethane (0.58 mL, 4.92 mmol) were added to a mixture of Intermediate 358b (1.17 g, 4.10 mmol) and 4-methylbenzenesulfonic acid hydrate (0.16 g, 0.82 mmol). The resulting mixture was stirred at 115 °C for 65 hours. After cooling to r.t., the mixture was diluted with EtOAc (50 mL), washed with sat. aq. $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. *tert*-Butyl piperazine1-1carboxylate (1.53 g, 8.20 mmol), potassium iodide (0.68 g, 4.10 mmol) and DMF (12 mL) were added. The resulting mixture was stirred at 85 °C for 22 hours. After cooling to r.t., the mixture was diluted with EtOAc (80 mL), washed with brine (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 48% acetone in hexanes) gave Intermediate 358c (0.435 g, 21%) and Intermediate 358d (1.28 g, 63%) as off-white solids. Intermediate 358c: ^{1}H NMR (DMSO-d_6) δ 1.38 (9H, s), 2.21 (3H, s), 2.43 (4H, br t), 2.53 (2H, d), 3.30 (4H, s), 4.07 - 4.20 (4H, m), 4.80 - 4.95 (2H, m), 7.47 (1H, s), 8.19 (1H, d), 8.29 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 495.2. Intermediate 358d: ^{1}H NMR (DMSO-d_6) 1.38 (9H, s), 2.26 (3H, s), 2.40 - 2.47 (4H, m), 2.56 (2H, d), 3.30 (4H, s), 4.07 (2H, br d), 4.30 (2H, br d), 4.75 (1H, br s), 4.91 - 5.00 (1H, m), 7.79 (1H, s), 8.19 (1H, d), 8.25 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 495.2.

Intermediate 358e:

tert-Butyl 4-(((2*r*,5*r*)-5-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate

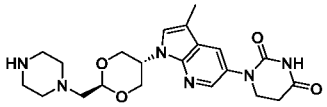


[2867] A 40 mL vial was charged with Intermediate 358c (430 mg, 0.87 mmol), K_3PO_4 (553 mg, 2.60 mmol), dihydropyrimidine-2,4(1*H*,3*H*)-dione (198 mg, 1.74 mmol) and *t*BuBrettPhos Pd G3 (74 mg, 0.09 mmol). 1,4-Dioxane (7 mL) was added. Argon was bubbled through the mixture for 5 minutes. The resulting

mixture was stirred at 90 °C for 18 hours. After cooling to r.t., more *t*BuBrettPhos Pd G3 (37 mg, 0.04 mmol) was added. Argon was bubbled through the mixture for 3 minutes. The resulting mixture was stirred at 90 °C for 24 hours. After cooling to r.t., the mixture was diluted with EtOAc (30 mL), washed with water (30 mL) and water/brine (1:5, 2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc:EtOH] in hexanes) and trituration with Et_2O gave the title compound (264 mg, 58%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 1.39 (9H, s), 2.23 (3H, s), 2.43 (4H, br t), 2.54 (2H, d), 2.75 (2H, t), 3.30 (4H, s), 3.79 (2H, t), 4.11 - 4.25 (4H, m), 4.85 - 4.98 (2H, m), 7.44 (1H, s), 7.86 - 7.95 (1H, m), 8.21 (1H, d), 10.38 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 529.3.

Intermediate 358f:

1-(3-Methyl-1-((2*r*,5*r*)-2-(piperazin-1-ylmethyl)-1,3-dioxan-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



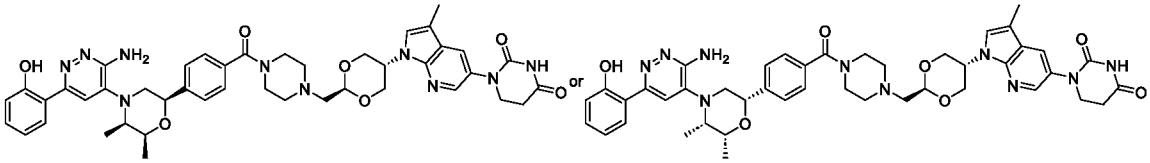
[2868] TFA (1.19 mL, 15.4 mmol) was added to a solution of Intermediate 358e (325 mg, 0.61 mmol) in DCM (3.5 mL). The resulting mixture was stirred at r.t. for 55 minutes and concentrated under reduced pressure. Water (5 mL), DCM–IPA (2:1, 15 mL) and sat. aq. K_2CO_3 (10 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (229 mg, 87%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.69 - 2.11 (1H, m), 2.21 - 2.27 (3H, m), 2.32 - 2.45 (4H, m), 2.48 (2H, br d), 2.60 - 2.71 (4H, m), 2.74 (2H, t), 3.80 (2H, t), 4.10 - 4.22 (4H, m), 4.81 - 5.03 (2H, m), 7.46 (1H, s), 7.91 (1H, d), 8.22 (1H, s), 10.40 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 429.3.

EXAMPLE 358:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

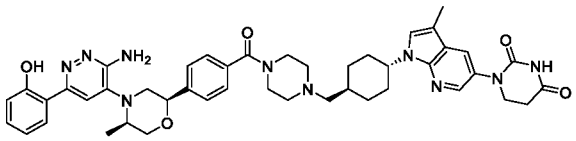


[2869] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 358f (18.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (29.7 mg, 83%) as a

white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, d), 1.16 (3H, d), 2.25 (3H, s), 2.41 - 2.68 (6H, m), 2.76 (2H, t), 3.09 (1H, br d), 3.29 - 3.45 (3H, m), 3.62 (2H, br s), 3.76 - 3.85 (3H, m), 4.14 - 4.26 (4H, m), 4.40 (1H, q), 4.78 (1H, br d), 4.90 - 5.02 (2H, m), 6.37 (2H, br s), 6.83 (1H, t), 6.88 (1H, d), 7.22 (1H, t), 7.43 (2H, d), 7.47 (1H, s), 7.51 (1H, s), 7.57 (2H, d), 7.89 - 7.98 (2H, m), 8.20 - 8.26 (1H, m), 10.41 (1H, s), 14.27 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 831.5.

EXAMPLE 359:

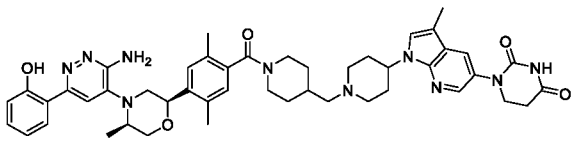
1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2870] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 259b (19.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (7.1 mg, 35%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.02 - 1.20 (5H, m), 1.63 (1H, br s), 1.76 - 2.00 (6H, m), 2.19 (2H, br d), 2.24 (3H, s), 2.28 - 2.48 (4H, m), 2.75 (2H, t), 3.09 (1H, dd), 3.32 - 3.73 (5H, m), 3.77 - 3.86 (3H, m), 3.90 - 3.98 (1H, m), 4.28 (1H, br d), 4.56 - 4.65 (1H, m), 4.70 (1H, dd), 6.36 (2H, s), 6.79 - 6.84 (1H, m), 6.86 (1H, dd), 7.16 - 7.25 (1H, m), 7.37 - 7.45 (3H, m), 7.50 (1H, s), 7.56 (2H, d), 7.86 (1H, d), 7.93 (1H, dd), 8.15 (1H, d), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 813.4.

EXAMPLE 360:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



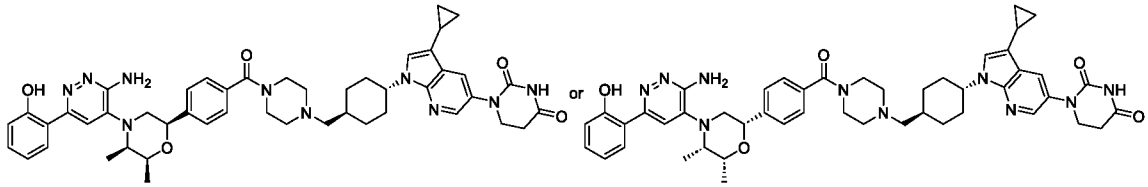
[2871] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 342a (17.8 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.5 mg, 73%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.81 - 1.16 (5H, m), 1.58 - 1.70 (1H, m), 1.85 (4H, br d), 1.94 - 2.37 (15H, m), 2.68 - 2.83 (3H, m), 2.89 - 3.09 (4H, m), 3.22 - 3.39 (1H, m), 3.42 - 3.59 (1H, m), 3.71 - 3.87 (3H, m), 3.90 - 4.02 (1H, m), 4.28 (1H, br d), 4.47 - 4.67 (2H, m), 4.78 (1H, br d), 6.34 (2H, br s), 6.75 - 6.88 (2H, m), 6.89 - 7.04 (1H, m), 7.20 (1H, br t), 7.36 - 7.58 (3H, m), 7.84 - 7.89 (1H, m), 7.94 (1H, br d), 8.16 (1H, s), 10.36 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 841.6.

EXAMPLE 361:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



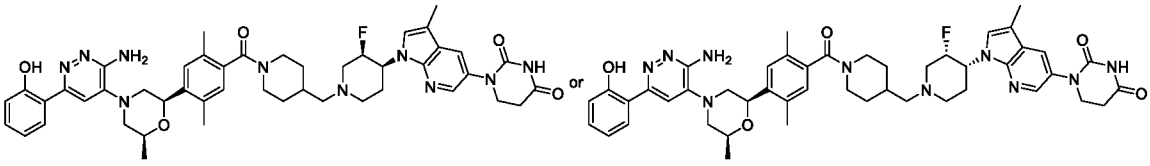
[2872] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 273f (19.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) and FSC (elution gradient: 1 to 12% [0.1% NH_4OH in MeOH] in DCM) gave the title compound (14.2 mg, 39%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.63 (2H, q), 0.80 - 0.87 (2H, m), 0.92 (3H, d), 1.04 - 1.19 (5H, m), 1.56 - 1.68 (1H, m), 1.75 - 2.01 (7H, m), 2.13 - 2.23 (2H, m), 2.23 - 2.47 (4H, m), 2.75 (2H, t), 3.07 (1H, br d), 3.32 - 3.73 (5H, m), 3.75 - 3.83 (3H, m), 4.34 - 4.42 (1H, m), 4.60 (1H, br t), 4.72 - 4.82 (1H, m), 6.34 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.21 (1H, t), 7.34 - 7.45 (3H, m), 7.50 (1H, s), 7.55 (2H, d), 7.88 - 7.97 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.24 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 853.5.

EXAMPLE 362:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2873] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20.0 mg, 0.05 mmol) and Intermediate 235e (36.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (29.2 mg, 81%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.88 - 1.18 (2H, m), 1.25 (3H, d), 1.56 - 1.71 (1H, m), 1.73 - 1.91 (3H, m), 2.12 - 2.54 (15H, m), 2.70 - 2.86 (4H, m), 2.94 - 3.08 (2H, m), 3.14 - 3.26

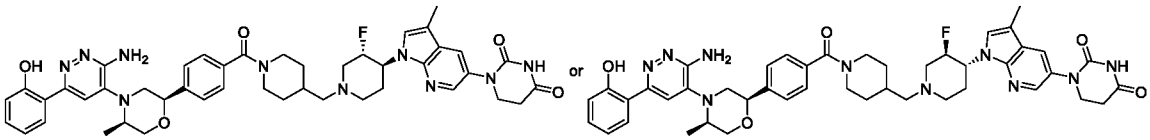
(1H, m), 3.33 (1H, d), 3.53 (2H, br s), 3.82 (2H, t), 4.07 - 4.23 (1H, m), 4.54 (1H, br d), 4.77 - 4.96 (2H, m), 4.99 (1H, br d), 6.43 (2H, br s), 6.83 - 6.91 (2H, m), 6.93 - 7.05 (1H, m), 7.24 (1H, br t), 7.30 - 7.39 (1H, m), 7.44 (1H, br s), 7.56 (1H, br s), 7.93 (1H, d), 7.96 (1H, br d), 8.20 (1H, d), 10.40 (1H, s), 14.22 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 859.4.

EXAMPLE 363:

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



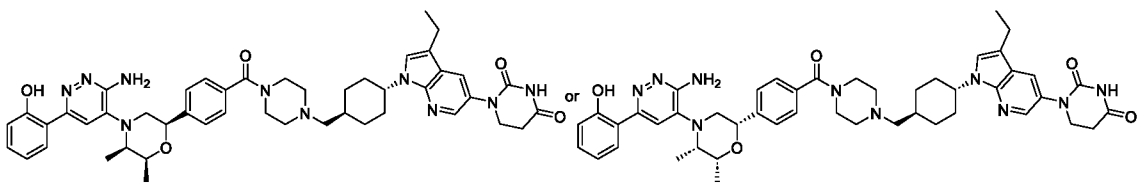
[2874] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 335d (42.9 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (33.3 mg, 90%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 0.99 - 1.18 (5H, m), 1.59 - 1.94 (4H, m), 2.10 - 2.21 (3H, m), 2.24 (3H, s), 2.28 - 2.38 (2H, m), 2.70 - 2.85 (3H, m), 2.92 (1H, br s), 2.98 - 3.16 (2H, m), 3.32 - 3.38 (1H, m), 3.51 (1H, br t), 3.56 - 3.70 (1H, m), 3.75 - 3.87 (3H, m), 3.94 (1H, br d), 4.28 (1H, br d), 4.37 - 4.60 (1H, m), 4.65 - 4.79 (2H, m), 5.00 - 5.19 (1H, m), 6.37 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.21 (1H, t), 7.40 (2H, d), 7.51 (1H, s), 7.53 - 7.62 (3H, m), 7.89 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.38 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 831.4.

EXAMPLE 364:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

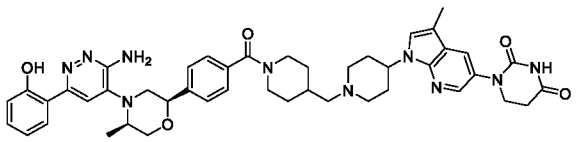
1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2875] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 332d (19.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (19.8 mg, 54%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, d), 1.06 - 1.21 (5H, m), 1.27 (3H, t), 1.65 (1H, br d), 1.78 - 2.06 (6H, m), 2.21 (2H, br d), 2.28 - 2.49 (4H, m), 2.70 (2H, q), 2.76 (2H, t), 3.09 (1H, br dd), 3.33 - 3.74 (5H, m), 3.76 - 3.87 (3H, m), 4.40 (1H, br dd), 4.63 (1H, br t), 4.73 - 4.85 (1H, m), 6.36 (2H, br s), 6.80 - 6.86 (1H, m), 6.88 (1H, d), 7.19 - 7.26 (1H, m), 7.43 (2H, d), 7.46 (1H, s), 7.52 (1H, s), 7.57 (2H, d), 7.91 (1H, d), 7.93 - 7.99 (1H, m), 8.17 (1H, d), 10.37 (1H, s), 14.27 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 841.5.

EXAMPLE 365:

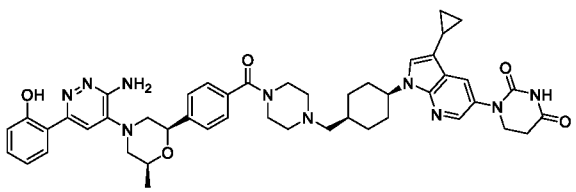
1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2876] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 342a (19.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (34.4 mg, 95%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.96 - 1.18 (5H, m), 1.61 - 1.74 (1H, m), 1.76 - 1.90 (4H, m), 1.95 - 2.14 (4H, m), 2.16 - 2.32 (5H, m), 2.70 - 2.87 (3H, m), 2.91 - 3.16 (4H, m), 3.51 (1H, br t), 3.55 - 3.69 (1H, m), 3.79 (2H, t), 3.82 (1H, d), 3.94 (1H, br d), 4.24 - 4.31 (1H, m), 4.35 - 4.55 (1H, m), 4.56 - 4.64 (1H, m), 4.69 (1H, dd), 6.37 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.40 (2H, d), 7.48 (1H, s), 7.51 (1H, s), 7.55 (2H, d), 7.87 (1H, d), 7.94 (1H, d), 8.16 (1H, d), 10.37 (1H, s), 13.78 - 14.71 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 813.4.

EXAMPLE 366:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2877] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (20.0 mg, 0.05 mmol) and Intermediate 217a (35.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (24.0 mg, 64%) as a

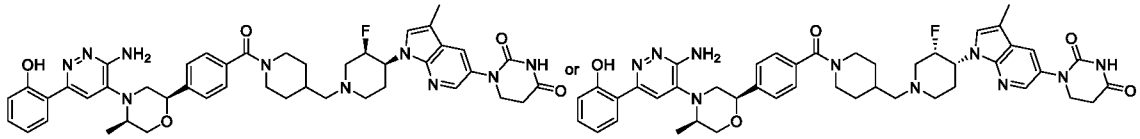
white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.63 - 0.69 (2H, m), 0.82 - 0.90 (2H, m), 1.27 (3H, d), 1.60 - 1.72 (4H, m), 1.79 (2H, br d), 1.88 - 2.05 (4H, m), 2.32 - 2.49 (5H, m), 2.52 - 2.59 (2H, m), 2.69 (1H, t), 2.77 (2H, t), 3.33 - 3.74 (6H, m), 3.82 (2H, t), 4.06 - 4.19 (1H, m), 4.54 - 4.71 (1H, m), 4.95 (1H, dd), 6.47 (2H, s), 6.83 - 6.91 (2H, m), 7.19 - 7.27 (1H, m), 7.42 (2H, d), 7.51 (1H, s), 7.54 (2H, d), 7.56 (1H, s), 7.91 - 7.99 (2H, m), 8.16 (1H, d), 10.37 (1H, s), 14.21 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 839.4.

EXAMPLE 367:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



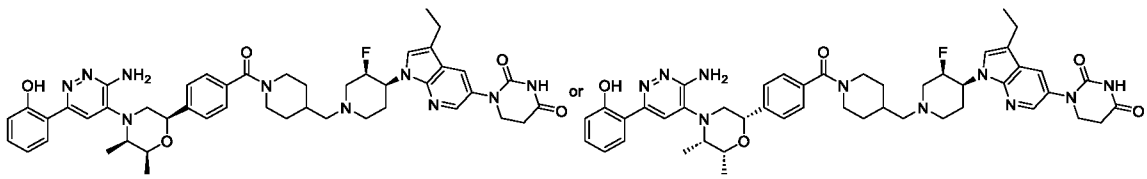
[2878] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (13.8 mg, 0.03 mmol) and Intermediate 235e (27.0 mg, 0.03 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (18.7 mg, 73%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.03 - 1.21 (5H, m), 1.60 - 1.96 (4H, m), 2.22 - 2.57 (8H, m), 2.70 - 2.91 (3H, m), 2.94 - 3.15 (3H, m), 3.17 - 3.27 (1H, m), 3.53 (1H, br t), 3.66 (1H, br s), 3.78 - 3.88 (3H, m), 3.96 (1H, br d), 4.30 (1H, br d), 4.49 (1H, br s), 4.67 - 4.75 (1H, m), 4.78 - 4.97 (2H, m), 6.38 (2H, br s), 6.84 (1H, t), 6.88 (1H, d), 7.22 (1H, t), 7.39 - 7.47 (3H, m), 7.52 (1H, s), 7.57 (2H, d), 7.91 - 7.99 (2H, m), 8.20 (1H, d), 10.39 (1H, s), 14.27 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 831.5.

EXAMPLE 368:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

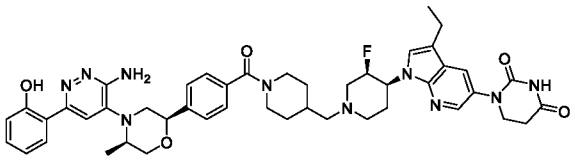
1-(1-((3*R*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2879] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 340e (21.7 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.6 mg, 68%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, d), 1.01 - 1.18 (5H, m), 1.25 (3H, t), 1.57 - 1.90 (4H, m), 2.19 - 2.48 (5H, m), 2.69 (2H, q), 2.75 (3H, br t), 2.96 - 3.12 (3H, m), 3.20 (1H, br t), 3.38 - 3.45 (1H, m), 3.50 - 3.69 (1H, m), 3.75 - 3.86 (3H, m), 4.33 - 4.42 (1H, m), 4.47 (1H, br s), 4.72 - 4.95 (3H, m), 6.37 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.39 (2H, d), 7.43 (1H, s), 7.50 (1H, s), 7.55 (2H, d), 7.91 - 8.00 (2H, m), 8.18 (1H, d), 10.40 (1H, s), 14.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 859.5.

EXAMPLE 369:

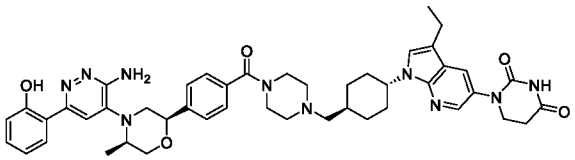
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2880] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 340e (22.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.3 mg, 61%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.96 - 1.17 (5H, m), 1.24 (3H, t), 1.54 - 1.93 (4H, m), 2.12 - 2.48 (5H, m), 2.69 (2H, q), 2.72 - 2.90 (3H, m), 2.94 - 3.14 (3H, m), 3.16 - 3.27 (1H, m), 3.51 (1H, br t), 3.55 - 3.72 (1H, m), 3.74 - 3.86 (3H, m), 3.89 - 3.99 (1H, m), 4.28 (1H, br d), 4.36 - 4.60 (1H, m), 4.69 (1H, br d), 4.77 - 4.96 (2H, m), 6.39 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.35 - 7.46 (3H, m), 7.50 (1H, s), 7.55 (2H, br d), 7.89 - 8.00 (2H, m), 8.18 (1H, s), 10.40 (1H, s), 14.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 845.4.

EXAMPLE 370:

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



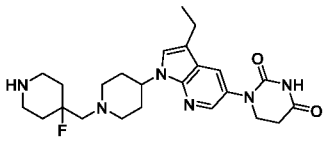
[2881] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 332d (19.6 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (22.0 mg, 60%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.97 - 1.19 (5H, m), 1.25 (3H, t), 1.56 - 1.69

(1H, m), 1.76 - 2.01 (6H, m), 2.19 (2H, br d), 2.25 - 2.47 (4H, m), 2.68 (2H, q), 2.75 (2H, t), 3.03 - 3.14 (1H, m), 3.31 - 3.45 (2H, m), 3.46 - 3.72 (3H, m), 3.76 - 3.86 (3H, m), 3.94 (1H, br d), 4.21 - 4.37 (1H, m), 4.55 - 4.66 (1H, m), 4.70 (1H, dd), 6.36 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.21 (1H, t), 7.37 - 7.46 (3H, m), 7.50 (1H, s), 7.56 (2H, d), 7.89 (1H, d), 7.93 (1H, d), 8.15 (1H, d), 10.35 (1H, s), 14.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 827.5.

EXAMPLE 371

Intermediate 371a:

1-(3-Ethyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



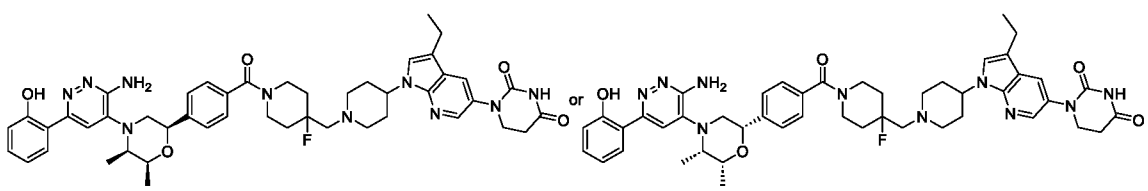
[2882] TFA (11.3 mL, 147 mmol) was added to a solution of Intermediate 149e (8.16 g, 14.7 mmol) in DCM (34 mL). The resulting mixture was stirred at r.t. for 6 hours and concentrated under reduced pressure. Water (20 mL), sat. aq. K_2CO_3 (80 mL) and DCM–IPA (2:1, 100 mL) were added. The phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (7.11 g, 106%, containing 6 wt% IPA) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t), 1.51 - 1.65 (2H, m), 1.66 - 1.75 (2H, m), 1.78 - 2.00 (3H, m), 2.06 (2H, qd), 2.32 (2H, br t), 2.55 (2H, s), 2.63 - 2.78 (8H, m), 3.03 (2H, br d), 3.76 - 3.84 (2H, m), 4.54 - 4.67 (1H, m), 7.50 (1H, s), 7.89 (1H, d), 8.15 (1H, d), 10.34 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 457.3.

EXAMPLE 371:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

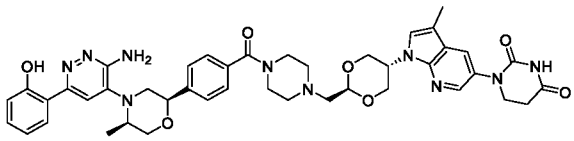


[2883] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 371a (19.7 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.3 mg, 74%) as a

white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, d), 1.15 (3H, d), 1.25 (3H, t), 1.61 - 2.12 (8H, m), 2.36 (2H, br t), 2.56 - 2.71 (4H, m), 2.74 (2H, t), 2.97 - 3.29 (5H, m), 3.37 - 3.62 (2H, m), 3.72 - 3.83 (3H, m), 4.25 (1H, br s), 4.35 - 4.42 (1H, m), 4.54 - 4.64 (1H, m), 4.77 (1H, dd), 6.34 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.44 (2H, d), 7.49 (2H, d), 7.56 (2H, d), 7.90 (1H, d), 7.93 (1H, d), 8.16 (1H, d), 10.36 (1H, s), 14.24 (1H, br s).; *m/z* (ES$^+$) $[M+H]^+$ = 859.6.

EXAMPLE 372:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

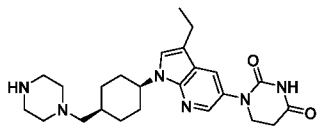


[2884] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 358f (19.2 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (32.9 mg, 90%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.06 (3H, d), 2.23 (3H, s), 2.44 - 2.64 (6H, m), 2.75 (2H, t), 3.09 (1H, br d), 3.31 (2H, s), 3.50 (1H, br t), 3.63 (2H, br s), 3.77 - 3.86 (3H, m), 3.94 (1H, br d), 4.11 - 4.22 (4H, m), 4.28 (1H, br d), 4.70 (1H, br d), 4.86 - 4.98 (2H, m), 6.37 (2H, br s), 6.81 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.41 (2H, d), 7.45 (1H, s), 7.50 (1H, s), 7.56 (2H, d), 7.89 - 7.97 (2H, m), 8.19 - 8.24 (1H, m), 10.39 (1H, s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 817.5.

EXAMPLE 373

Intermediate 373a:

1-(3-Ethyl-1-((1*s*,4*s*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



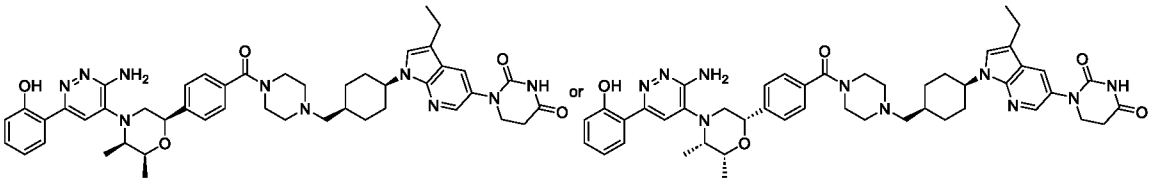
[2885] *p*-Toluenesulfonic acid (0.81 g, 4.68 mmol) was added to Intermediate 338a (1.40 g, 2.60 mmol) in MeCN (20 mL). The resulting mixture was stirred at 80 °C for 24 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. MeOH (5 mL) and DIPEA (3 mL) were added. The resulting mixture was stirred at r.t. for 1 hour and concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 30% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (0.71 g, 61%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t), 1.60 – 1.69 (4H, m), 1.75 – 1.79 (2H, m), 1.90 – 2.01 (3H, m), 2.30 – 2.36 (4H, m), 2.36 – 2.39 (2H, m), 2.65 – 2.73 (6H, m), 2.76 (2H, t), 3.16 – 3.29 (1H, brs), 3.81 (2H, t), 4.62 – 4.64(1H, m), 7.56 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.39 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 439.3.

EXAMPLE 373:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((1*S*,4*s*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

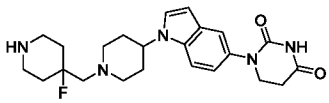


[2886] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 373a (20.9 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (29.4 mg, 74%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, d), 1.15 (3H, d), 1.26 (3H, t), 1.61 - 1.73 (4H, m), 1.73 - 1.83 (2H, m), 1.89 - 2.02 (3H, m), 2.31 - 2.54 (6H, m), 2.68 (2H, q), 2.75 (2H, t), 3.08 (1H, br d), 3.33 - 3.71 (5H, m), 3.75 - 3.83 (3H, m), 4.34 - 4.45 (1H, m), 4.64 (1H, br t), 4.74 - 4.80 (1H, m), 6.34 (2H, br s), 6.78 - 6.84 (1H, m), 6.86 (1H, d), 7.21 (1H, t), 7.42 (2H, d), 7.50 (1H, s), 7.52 - 7.59 (3H, m), 7.89 (1H, d), 7.93 (1H, br d), 8.15 (1H, d), 10.35 (1H, br s), 14.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 841.5.

EXAMPLE 374

Intermediate 374a:

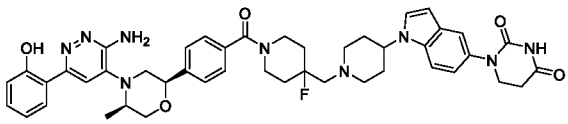
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2887] TFA (1.46 mL, 19.0 mmol) was added to a solution of Intermediate 2d (1.00 g, 1.90 mmol) in DCM (4.4 mL). The resulting mixture was stirred at r.t. for 50 minutes and concentrated under reduced pressure. DCM–IPA (2:1, 30 mL), water (10 mL) and sat. aq. K_2CO_3 (20 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (0.95 g, 117%, containing 12 wt% IPA and minor impurities) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.54 - 1.67 (2H, m), 1.69 - 1.79 (2H, m), 1.80 - 1.94 (3H, m), 1.96 - 2.07 (2H, m), 2.39 (2H, br t), 2.52 - 2.61 (2H, m), 2.64 - 2.75 (6H, m), 3.04 (2H, br d), 3.74 (2H, t), 4.29 - 4.38 (1H, m), 6.45 (1H, d), 7.07 (1H, dd), 7.44 (1H, d), 7.52 (1H, d), 7.54 (1H, d), 9.63 - 11.08 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 428.3.

EXAMPLE 374:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



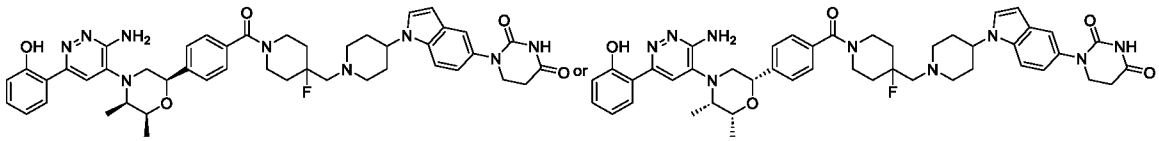
[2888] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 374a (21.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) and FSC (elution gradient: 1 to 8% [0.1% NH_4OH in MeOH] in DCM) gave the title compound (7.1 mg, 35%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 2.09 (8H, br s), 2.37 - 2.50 (2H, m), 2.59 - 2.69 (2H, m), 2.73 (2H, t), 2.99 - 3.31 (5H, m), 3.53 (2H, br t), 3.77 (2H, t), 3.84 (1H, br d), 3.96 (1H, br d), 4.12 - 4.42 (3H, m), 4.68 - 4.79 (1H, m), 6.38 (2H, br s), 6.46 (1H, d), 6.81 - 6.86 (1H, m), 6.86 - 6.92 (1H, m), 7.08 (1H, dd), 7.17 - 7.28 (1H, m), 7.42 - 7.49 (3H, m), 7.49 - 7.57 (3H, m), 7.58 (2H, d), 7.87 - 8.02 (1H, m), 10.25 (1H, s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 816.5.

EXAMPLE 375:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

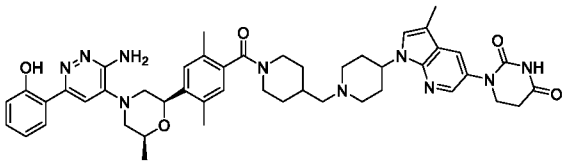
1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2889] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (15.0 mg, 0.04 mmol) and Intermediate 374a (15.3 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (17.0 mg, 57%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, d), 1.17 (3H, d), 1.63 - 2.07 (8H, m), 2.43 (2H, br t), 2.59 - 2.69 (2H, m), 2.73 (2H, t), 2.98 - 3.31 (5H, m), 3.42 (1H, br t), 3.50 (1H, br s), 3.72 - 3.84 (3H, m), 4.15 - 4.48 (3H, m), 4.79 (1H, br dd), 6.36 (2H, br s), 6.46 (1H, d), 6.84 (1H, t), 6.88 (1H, d), 7.08 (1H, dd), 7.22 (1H, t), 7.42 - 7.48 (3H, m), 7.50 - 7.61 (5H, m), 7.95 (1H, br d), 10.25 (1H, s), 14.26 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 830.5.

EXAMPLE 376:

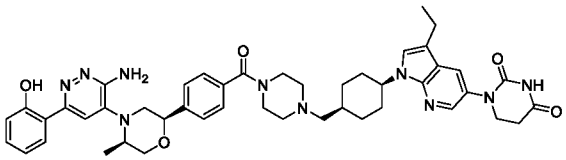
1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2890] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20.0 mg, 0.05 mmol) and Intermediate 342a (17.8 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (31.1 mg, 88%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.88 - 1.15 (2H, m), 1.25 (3H, d), 1.57 - 1.71 (1H, m), 1.75 - 1.91 (4H, m), 1.96 - 2.28 (12H, m), 2.32 - 2.42 (3H, m), 2.52 - 2.58 (1H, m), 2.69 - 2.85 (4H, m), 2.92 - 3.07 (3H, m), 3.33 - 3.37 (1H, m), 3.53 (2H, br s), 3.81 (2H, t), 4.07 - 4.20 (1H, m), 4.49 - 4.69 (2H, m), 4.99 (1H, br d), 6.42 (2H, s), 6.83 - 6.91 (2H, m), 6.92 - 7.04 (1H, m), 7.24 (1H, t), 7.32 - 7.40 (1H, m), 7.49 (1H, s), 7.57 (1H, br s), 7.88 (1H, d), 7.96 (1H, br d), 8.17 (1H, d), 10.38 (1H, s), 14.04 - 14.40 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 841.4.

EXAMPLE 377:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

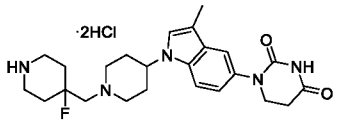


[2891] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 373a (21.6 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (29.0 mg, 71%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.28 (3H, t), 1.61 - 1.75 (4H, m), 1.80 (2H, br d), 1.92 - 2.03 (3H, m), 2.32 - 2.60 (6H, m), 2.70 (2H, q), 2.76 (2H, t), 3.11 (1H, br d), 3.34 - 3.75 (5H, m), 3.79 - 3.88 (3H, m), 3.93 - 4.00 (1H, m), 4.30 (1H, br d), 4.62 - 4.77 (2H, m), 6.38 (2H, br s), 6.81 - 6.86 (1H, m), 6.86 - 6.91 (1H, m), 7.18 - 7.26 (1H, m), 7.44 (2H, d), 7.52 (1H, s), 7.55 - 7.61 (3H, m), 7.91 (1H, d), 7.95 (1H, br d), 8.17 (1H, d), 10.37 (1H, s), 14.27 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 827.4.

EXAMPLE 378

Intermediate 378a:

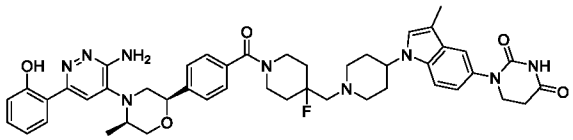
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2892] TFA (10.8 mL, 140 mmol) was added to a solution of Intermediate 1j (7.60 g, 14.0 mmol) in DCM (129 mL). The resulting mixture was stirred at r.t. for 2 hours and concentrated under reduced pressure. MeOH (50 mL) was added. The resulting solution was cooled to 0 °C. HCl, 4 M in 1,4-dioxane (30 mL, 120 mmol) was added which led to the formation of a precipitate. The mixture was warmed to r.t., stirred at r.t. for 20 minutes and concentrated under reduced pressure to give the title compound (6.96 g, 96%) as a 2 HCl salt. *m/z* (ES^+) $[M+H]^+$ = 442.4.

EXAMPLE 378:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

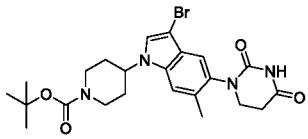


[2893] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 378a (23.0 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.2 mg, 73%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 1.06 (3H, d), 1.61 - 2.05 (8H, m), 2.22 (3H, s), 2.39 (2H, br t), 2.56 - 2.67 (2H, m), 2.71 (2H, t), 2.95 - 3.30 (5H, m), 3.38 - 3.58 (2H, m), 3.75 (2H, t), 3.83 (1H, d), 3.90 - 3.97 (1H, m), 4.15 - 4.43 (3H, m), 4.63 - 4.77 (1H, m), 6.37 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.04 (1H, br d), 7.20 (1H, t), 7.30 (1H, s), 7.38 (1H, s), 7.41 - 7.48 (3H, m), 7.50 (1H, s), 7.57 (2H, d), 7.93 (1H, d), 10.24 (1H, s), 14.26 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 830.5.

EXAMPLE 379

Intermediate 379a:

tert-Butyl 4-(3-bromo-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate

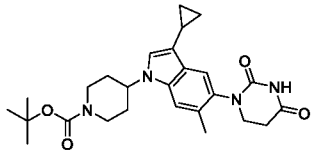


[2894] NBS (0.85 g, 4.78 mmol) was added to a solution of Intermediate 21d (2.00 g, 4.69 mmol) in DCM (50 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes. The mixture was washed with sat. aq. $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (2.64 g, 111%, containing 12 wt% DCM) as a white solid, which was used for the next step without further purification. ^1H NMR (DMSO-d_6) δ 1.43 (9H, s), 1.75 -

1.95 (4H, m), 2.29 (3H, s), 2.74 (2H, t), 2.84 - 3.10 (2H, m), 3.55 (1H, dt), 3.79 (1H, dt), 4.04 - 4.20 (2H, m), 4.53 - 4.63 (1H, m), 7.30 (1H, s), 7.55 (1H, s), 7.73 (1H, s), 10.27 (1H, s); *m/z* (ES^+) $[M+NH_4]^+$ = 522.2.

Intermediate 379b:

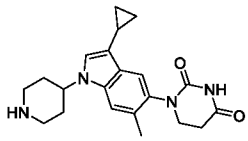
tert-Butyl 4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidine-1-carboxylate



[2895] A 40 mL vial was charged with Intermediate 379a (1.00 g, 1.98 mmol), $PdCl_2$(dtbpf) (0.13 g, 0.20 mmol), K_3PO_4 (1.26 g, 5.94 mmol) and cyclopropylboronic acid (0.43 g, 4.95 mmol). Toluene (17.5 mL) and water (1.75 mL) were added. Argon was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 70 °C for 60 minutes. After cooling to r.t., sat. aq. $NaHCO_3$ (30 mL) was added. The mixture was extracted with DCM (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (0.80 g, 86%) as an off-white solid. ^1H NMR (DMSO-d_6) δ 0.53 - 0.63 (2H, m), 0.76 - 0.82 (2H, m), 1.42 (9H, s), 1.72 - 1.90 (5H, m), 2.26 (3H, s), 2.74 (2H, t), 2.93 (2H, br s), 3.55 (1H, dt), 3.71 - 3.82 (1H, m), 4.10 (2H, br d), 4.38 - 4.50 (1H, m), 7.17 (1H, s), 7.36 (1H, s), 7.45 (1H, s), 10.23 (1H, s); *m/z* (ES^+) $[M+NH_4]^+$ = 484.3.

Intermediate 379c:

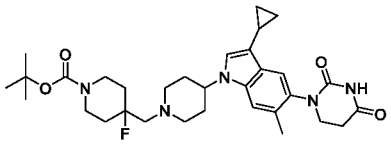
1-(3-Cyclopropyl-6-methyl-1-(piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2896] TFA (2.62 mL, 34.0 mmol) was added to a solution of Intermediate 379b (0.79 g, 1.70 mmol) in DCM (7.9 mL). The resulting mixture was stirred at r.t. for 15 minutes and concentrated under reduced pressure. DCM–IPA (2:1, 30 mL) and sat. aq. K_2CO_3–water (2:1, 30 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (0.628 g, 101%, containing 12 wt% IPA) as a pink solid, which was used for the next step without further purification. ^1H NMR (DMSO-d_6) δ 0.50 - 0.67 (2H, m), 0.79 - 0.88 (2H, m), 1.71 - 1.90 (5H, m), 1.95 - 2.10 (1H, m), 2.27 (3H, s), 2.61 - 2.71 (2H, m), 2.75 (2H, t), 3.05 (2H, br d), 3.57 (1H, dt), 3.73 - 3.83 (1H, m), 4.18 - 4.42 (1H, m), 7.11 (1H, s), 7.36 (1H, s), 7.46 (1H, s), 9.82 - 10.55 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 367.3.

Intermediate 379d:

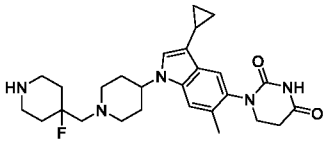
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2897] A 40 mL vial was charged with Intermediate 379c (0.40 g, 1.09 mmol) and Intermediate 6f (0.80 g, 2.18 mmol). 1,4-Dioxane (6.7 mL) and DIPEA (0.57 mL, 3.27 mmol) were added. The resulting mixture was stirred at 85 °C for 5.3 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM (20 mL) and sat. aq. NH_4Cl (20 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc:EtOH] in hexanes) gave the title compound (0.41 g, 65%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.53 - 0.66 (2H, m), 0.82 (2H, dd), 1.42 (9H, s), 1.52 - 1.68 (2H, m), 1.80 - 2.01 (7H, m), 2.27 (3H, s), 2.38 (2H, br t), 2.55 - 2.63 (2H, m), 2.75 (2H, t), 3.02 (4H, br d), 3.52 - 3.60 (1H, m), 3.67 - 3.81 (3H, m), 4.17 - 4.30 (1H, m), 7.17 (1H, s), 7.35 (1H, s), 7.46 (1H, s), 10.24 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 582.4.

Intermediate 379e:

1-(3-Cyclopropyl-1-(1-((4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



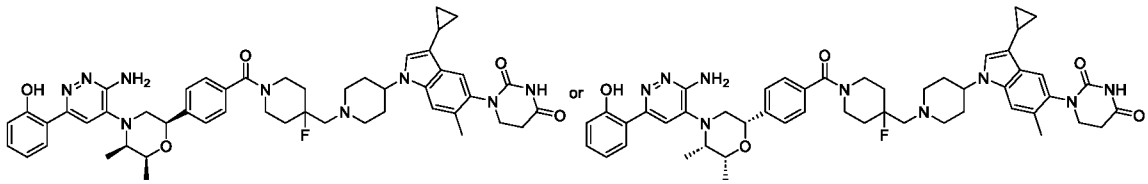
[2898] 2 M aq. H_2SO_4 (1.74 mL, 3.48 mmol) was added to a suspension of Intermediate 379d (0.41 g, 0.70 mmol) in THF (3.5 mL). The resulting mixture was stirred at 50 °C for 3.5 hours. After cooling to r.t., sat. aq. K_2CO_3 (50 mL), water (20 mL) and DCM–IPA (3:1, 20 mL) were added and the phases were separated. The aqueous layer was extracted with DCM–IPA (2:1, 2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (0.34 g, 102%, containing 3 wt% DCM) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.56 - 0.66 (2H, m), 0.82 (2H, dd), 1.52 - 1.66 (2H, m), 1.67 - 1.76 (2H, m), 1.78 - 1.89 (3H, m), 1.90 - 2.02 (2H, m), 2.27 (3H, s), 2.33 - 2.40 (2H, m), 2.52 - 2.58 (2H, m), 2.66 - 2.79 (6H, m), 3.02 (2H, br d), 3.54 - 3.61 (1H, m), 3.74 - 3.84 (1H, m), 4.17 - 4.29 (1H, m), 7.18 (1H, s), 7.35 (1H, s), 7.46 (1H, s), 10.24 (1H, br s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 482.3.

EXAMPLE 379:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

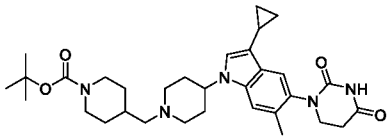


[2899] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 379e (20.8 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (29.8 mg, 78%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.54 - 0.64 (2H, m), 0.77 - 0.85 (2H, m), 0.92 (3H, d), 1.15 (3H, d), 1.63 - 2.02 (9H, m), 2.25 (3H, s), 2.38 (2H, br t), 2.57 - 2.68 (2H, m), 2.73 (2H, t), 2.96 - 3.30 (5H, m), 3.36 - 3.59 (3H, m), 3.72 - 3.82 (2H, m), 4.15 - 4.33 (2H, m), 4.36 - 4.43 (1H, m), 4.77 (1H, br d), 6.35 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.15 (1H, s), 7.21 (1H, t), 7.34 (1H, s), 7.41 - 7.47 (3H, m), 7.50 (1H, s), 7.56 (2H, d), 7.89 - 7.97 (1H, m), 10.24 (1H, s), 14.26 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 884.6.

EXAMPLE 380

Intermediate 380a:

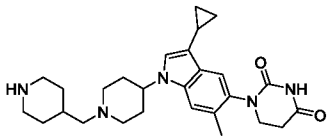
tert-Butyl 4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-indol-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2900] *tert*-Butyl 4-formylpiperidine-1-carboxylate (175 mg, 0.82 mmol) was added to a solution of Intermediate 379c (200 mg, 0.55 mmol) in DCM (5.5 mL). The resulting mixture was stirred at r.t. for 30 minutes. Sodium triacetoxyborohydride (231 mg, 1.09 mmol) was added. The resulting mixture was stirred at r.t. for 20 minutes. Sat. aq. $NaHCO_3$ (25 mL), 30% aq. NH_4OH (1 mL) and DCM (15 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc:EtOH] in hexanes) gave the title compound (251 mg, 82%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 0.54 - 0.68 (2H, m), 0.75 - 0.84 (2H, m), 0.88 - 1.01 (2H, m), 1.38 (9H, s), 1.69 (3H, br d), 1.77 - 1.98 (5H, m), 2.04 - 2.21 (4H, m), 2.25 (3H, s), 2.53 - 2.81 (4H, m), 2.89 - 3.04 (2H, m), 3.55 (1H, dt), 3.76 (1H, dt), 3.92 (2H, br d), 4.21 (1H, br t), 7.15 (1H, s), 7.33 (1H, s), 7.44 (1H, s), 10.22 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 564.4.

Intermediate 380b:

1-(3-Cyclopropyl-6-methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



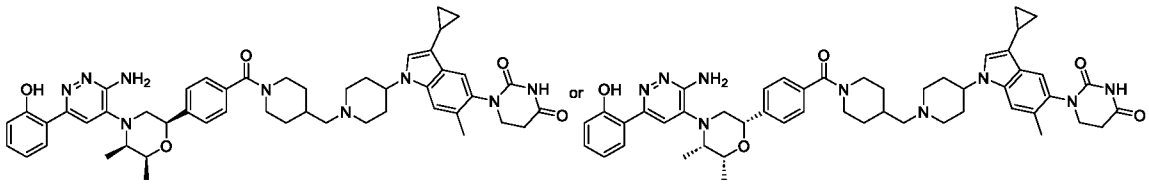
[2901] TFA (1.00 mL, 13.0 mmol) was added to a solution of Intermediate 380a (245 mg, 0.43 mmol) in DCM (3.0 mL). The resulting mixture was stirred at r.t. for 25 minutes and concentrated under reduced pressure. Water (5 mL), DCM–IPA (2:1, 24 mL) and sat. aq. K_2CO_3 (20 mL) were added and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (210 mg, 104%, containing 9 wt% IPA) as a red solid. ^{1}H NMR (DMSO-d_6) δ 0.54 - 0.63 (2H, m), 0.77 - 0.82 (2H, m), 0.90 - 1.00 (2H, m), 1.50 - 1.58 (1H, m), 1.59 - 1.65 (2H, m), 1.78 - 1.96 (6H, m), 2.08 (2H, br t), 2.14 (2H, br d), 2.25 (3H, s), 2.42 (2H, br t), 2.72 (2H, t), 2.90 (4H, br dd), 3.54 (1H, dt), 3.71 - 3.79 (1H, m), 4.15 - 4.25 (1H, m), 7.15 (1H, s), 7.33 (1H, s), 7.43 (1H, s), 9.88 - 10.55 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 464.4.

EXAMPLE 380:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



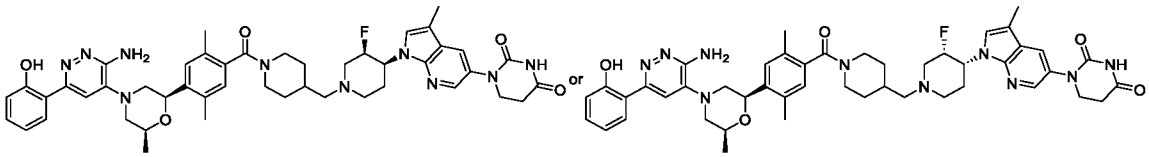
[2902] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (15.0 mg, 0.04 mmol) and Intermediate 380b (15.0 mg, 0.03 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (15.9 mg, 57%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.53 - 0.65 (2H, m), 0.77 - 0.86 (2H, m), 0.94 (3H, d), 1.00 - 1.21 (5H, m), 1.63 - 2.02 (8H, m), 2.08 - 2.31 (7H, m), 2.69 - 3.21 (7H, m), 3.42 (1H, br t), 3.50 - 3.71 (2H, m), 3.73 - 3.86 (2H, m), 4.15 - 4.30 (1H, m), 4.32 - 4.65 (2H, m), 4.79 (1H, dd), 6.36 (2H, br s), 6.80 - 6.86 (1H, m), 6.88 (1H, d), 7.16 (1H, s), 7.19 - 7.27 (1H, m), 7.35 (1H, s), 7.41 (2H, d), 7.46 (1H, s), 7.52 (1H, s), 7.56 (2H, d), 7.95 (1H, d), 10.24 (1H, s), 14.27 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 866.6.

EXAMPLE 381:

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

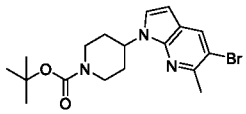


[2903] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20.0 mg, 0.05 mmol) and Intermediate 331d (36.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (31.8 mg, 88%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.88 - 1.17 (2H, m), 1.25 (3H, d), 1.58 - 1.73 (1H, m), 1.74 - 1.95 (3H, m), 2.14 - 2.54 (15H, m), 2.69 - 2.83 (4H, m), 2.93 - 3.08 (2H, m), 3.15 - 3.26 (1H, m), 3.33 (1H, s), 3.53 (2H, br s), 3.82 (2H, t), 4.09 - 4.18 (1H, m), 4.47 - 4.60 (1H, m), 4.78 - 4.95 (2H, m), 4.99 (1H, br d), 6.43 (2H, s), 6.83 - 6.91 (2H, m), 6.92 - 7.03 (1H, m), 7.20 - 7.27 (1H, m), 7.32 - 7.38 (1H, m), 7.40 - 7.47 (1H, m), 7.53 - 7.59 (1H, m), 7.93 (1H, d), 7.94 - 7.99 (1H, m), 8.20 (1H, d), 10.40 (1H, s), 14.22 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 859.4.

EXAMPLE 382

Intermediate 382a:

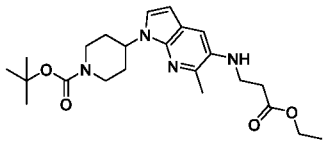
tert-Butyl 4-(5-bromo-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2904] A 250 mL flask was charged with 5-bromo-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 23.7 mmol) and *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.62 g, 23.7 mmol) and Cs_2CO_3 (11.6 g, 35.5). DMF (59 mL) was added. The resulting mixture was stirred at 75 °C for 4 hours. More *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.62 g, 23.7 mmol) and Cs_2CO_3 (7.72 g, 23.7) were added after 4 and 8 hours. After the final addition, stirring was continued at 75 °C for 15 hours. After cooling to r.t., the mixture was filtered. The filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with brine (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 15% acetone in hexanes) gave the title compound (7.44 g, 80%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.42 (9H, s), 1.83 - 1.98 (4H, m), 2.63 (3H, s), 2.76 - 3.20 (2H, m), 4.10 (2H, br d), 4.74 - 4.88 (1H, m), 6.40 (1H, d), 7.65 (1H, d), 8.15 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 394.2.

Intermediate 382b:

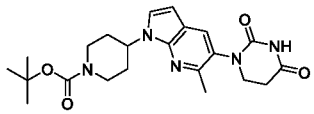
tert-Butyl 4-(5-((3-ethoxy-3-oxopropyl)amino)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[2905] A 250 mL flask was charged with Intermediate 382a (7.27 g, 18.4 mmol), Cs_2CO_3 (21.6 g, 66.4 mmol), ethyl 3-aminopropanoate hydrochloride (4.25 g, 27.7 mmol), $Pd_2(dba)_3$ (0.84 g, 0.92 mmol) and CPhos (0.81 g, 1.84 mmol). 1,4-Dioxane (100 mL) was added. The flask was evacuated and backfilled with argon (5x). The resulting mixture was stirred at 90 °C for 6 hours. After cooling to r.t., the mixture was filtered. The filtercake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by FSC (1st purification: elution gradient: 0 to 30% acetone in hexanes; 2nd purification: elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (5.44 g, 69%) as an orange oil. *m/z* (ES^+) $[M+H]^+$ = 431.4.

Intermediate 382c:

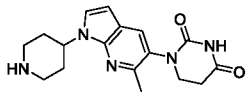
tert-Butyl 4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



Potassium cyanate (5.12 g, 63.2 mmol) was added to a solution of Intermediate 382b (5.44 g, 12.6 mmol) in DCM (25 mL) and acetic acid (25 mL). The resulting mixture was stirred at r.t. for 20 minutes. The mixture was diluted with DCM (100 mL), washed with water (150 mL), sat. aq. $NaHCO_3$ (150 mL) and brine–sat. aq. $NaHCO_3$ (1:1, 150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in EtOH (100 mL). Sodium ethanolate, 21 wt% in EtOH (9.43 mL, 25.3 mmol) was added. The resulting mixture was stirred at r.t. for 60 minutes. Water (100 mL), sat. aq. NH_4Cl (100 mL) and DCM (100 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Trituration with Et_2O gave the title compound (4.09 g, 76%) as a white solid. ^1H NMR (DMSO-d_6) δ 1.43 (9H, s), 1.82 - 1.98 (4H, m), 2.43 (3H, s), 2.68 - 2.84 (2H, m), 2.86 - 3.10 (2H, m), 3.58 (1H, dt), 3.78 (1H, ddd), 3.96 - 4.29 (2H, m), 4.77 - 4.92 (1H, m), 6.43 (1H, d), 7.64 (1H, d), 7.85 (1H, s), 10.35 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 428.3.

Intermediate 382d:

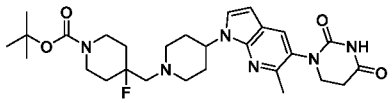
1-(6-Methyl-1-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2906] 2 M aq. H_2SO_4 (8.77 mL, 17.5 mmol) was added to a suspension of Intermediate 382c (1.50 g, 3.51 mmol) in THF (8.77 mL). The resulting mixture was stirred at 50 °C for 130 minutes. After cooling to r.t., sat. aq. K_2CO_3 (20 mL), water (60 mL) and DCM–IPA (2:1, 50 mL) were added and the phases were separated. The aqueous layer was extracted with DCM–IPA (2:1, 2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.15 g, 100%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.78 - 1.94 (4H, m), 1.96 - 2.31 (1H, m), 2.43 (3H, s), 2.62 - 2.84 (4H, m), 3.06 (2H, br d), 3.58 (1H, dt), 3.73 - 3.82 (1H, m), 4.65 - 4.79 (1H, m), 6.43 (1H, d), 7.58 (1H, d), 7.84 (1H, s), 10.35 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 328.2.

Intermediate 382e:

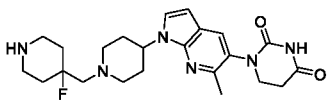
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carboxylate



[2907] A 40 mL vial was charged with Intermediate 382d (0.70 g, 2.14 mmol) and Intermediate 6f (1.56 g, 4.28 mmol). 1,4-Dioxane (13 mL) and DIPEA (1.12 mL, 6.41 mmol) were added. The resulting mixture was stirred at 85 °C for 15 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. DCM (20 mL) and sat. aq. NH_4Cl (20 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc:EtOH] in hexanes) gave the title compound (0.65 g, 56%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 1.52 - 1.69 (2H, m), 1.84 (4H, br d), 1.98 - 2.12 (2H, m), 2.36 (2H, br t), 2.43 (3H, s), 2.54 - 2.64 (2H, m), 2.67 - 2.75 (1H, m), 2.76 - 2.85 (1H, m), 3.03 (4H, br d), 3.53 - 3.62 (1H, m), 3.68 - 3.83 (3H, m), 4.64 (1H, tt), 6.43 (1H, d), 7.63 (1H, d), 7.84 (1H, s), 10.34 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 543.3.

Intermediate 382f:

1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2908] 2 M aq. H_2SO_4 (2.75 mL, 5.50 mmol) was added to a suspension of Intermediate 382e (596 mg, 1.10 mmol) in THF (5.5 mL). The resulting mixture was stirred at 50 °C for 2 hours. After cooling to r.t., sat. aq. K_2CO_3 (40 mL), water (100 mL) and DCM–IPA (2:1, 60 mL) were added and the phases were separated. The aqueous layer was extracted with DCM–IPA (2:1, 2 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (486 mg, 100%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.50 - 1.66 (2H, m), 1.67 - 1.77 (2H, m), 1.84 (2H, br d), 1.91 - 2.18 (3H, m), 2.28 - 2.38 (2H, m), 2.43 (3H, s), 2.50 - 2.58 (2H, m), 2.60 - 2.88 (6H, m), 3.03

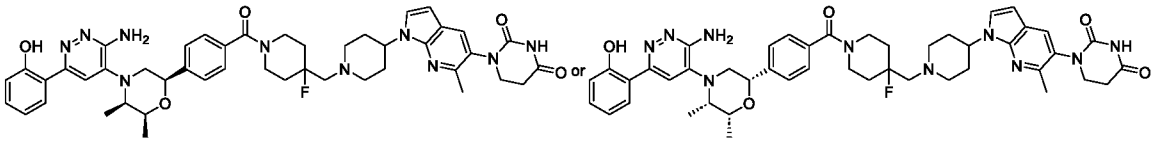
(2H, br d), 3.58 (1H, dt), 3.77 (1H, ddd), 4.59 - 4.70 (1H, m), 6.42 (1H, d), 7.64 (1H, d), 7.84 (1H, s), 10.35 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 443.1.

EXAMPLE 382:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

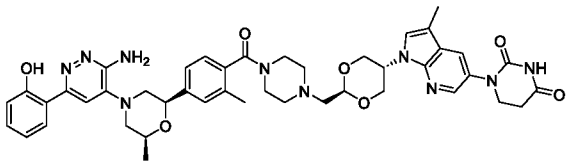
1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2909] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (15.0 mg, 0.04 mmol) and Intermediate 382f (14.4 mg, 0.03 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (20.5 mg, 75%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 0.93 (3H, d), 1.15 (3H, d), 1.58 - 2.14 (8H, m), 2.33 - 2.46 (5H, m), 2.57 - 2.68 (2H, m), 2.68 - 2.84 (2H, m), 2.96 - 3.29 (5H, m), 3.35 - 3.64 (3H, m), 3.72 - 3.84 (2H, m), 4.25 (1H, br s), 4.36 - 4.44 (1H, m), 4.59 - 4.70 (1H, m), 4.77 (1H, dd), 6.34 (2H, br s), 6.43 (1H, d), 6.78 - 6.84 (1H, m), 6.85 - 6.90 (1H, m), 7.16 - 7.26 (1H, m), 7.44 (2H, d), 7.50 (1H, s), 7.56 (2H, d), 7.63 (1H, d), 7.84 (1H, s), 7.89 - 7.99 (1H, m), 10.35 (1H, s), 14.25 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 383:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

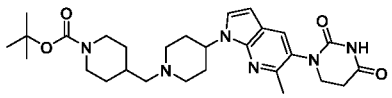


[2910] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20.0 mg, 0.05 mmol) and Intermediate 358f (20.4 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (28.6 mg, 72%) as a white solid following lyophilization. ^1H NMR (DMSO-d_6) δ 1.24 (3H, d), 2.23 (6H, s), 2.35 - 2.46 (2H, m), 2.50 - 2.62 (5H, m), 2.65 - 2.72 (1H, m), 2.74 (2H, t), 3.13 (2H, br s), 3.46 - 3.57 (2H, m), 3.60 - 3.72 (2H, m), 3.79 (2H, t), 4.04 - 4.22 (5H, m), 4.84 - 4.97 (3H, m), 6.44 (2H, s), 6.81 - 6.90 (2H, m), 7.15 (1H, d), 7.18 - 7.25 (1H, m), 7.26 - 7.36 (2H, m), 7.44 (1H, s), 7.54 (1H, s), 7.90 (1H, d), 7.92 - 7.97 (1H, m), 8.21 (1H, d), 10.38 (1H, s), 14.19 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 831.4.

EXAMPLE 384

Intermediate 384a:

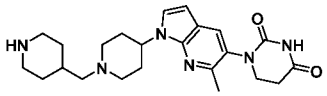
tert-Butyl 4-((4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate



[2911] *tert*-Butyl 4-formylpiperidine-1-carboxylate (394 mg, 1.85 mmol) was added to a solution of Intermediate 382d (403 mg, 1.23 mmol) in DCM (12 mL). The resulting mixture was stirred at r.t. for 30 minutes. Sodium triacetoxyborohydride (522 mg, 2.46 mmol) was added. The resulting mixture was stirred at r.t. for 20 minutes. Sat. aq. $NaHCO_3$ (20 mL), 30% aq. NH_4OH (1 mL) and DCM (15 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% [3:1 EtOAc:EtOH] in hexanes) gave the title compound (520 mg, 81%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.90 - 1.03 (2H, m), 1.38 (9H, s), 1.62 - 1.77 (3H, m), 1.81 - 1.92 (2H, m), 1.97 - 2.15 (4H, m), 2.19 (2H, br d), 2.43 (3H, s), 2.59 - 2.85 (4H, m), 2.92 - 3.03 (2H, m), 3.58 (1H, dt), 3.77 (1H, ddd), 3.85 - 4.06 (2H, m), 4.59 - 4.72 (1H, m), 6.42 (1H, d), 7.63 (1H, d), 7.84 (1H, s), 10.34 (1H, s).; *m/z* (ES^+) $[M+H]^+$ = 525.3.

Intermediate 384b:

1-(6-Methyl-1-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



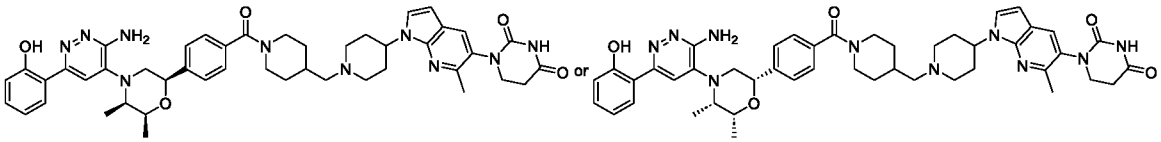
[2912] 2 M aq. H_2SO_4 (2.44 mL, 4.88 mmol) was added to a suspension of Intermediate 384a (512 mg, 0.98 mmol) in THF (4.9 mL). The resulting mixture was stirred at 50 °C for 2 hours. After cooling to r.t., sat. aq. $NaHCO_3$ (30 mL), water (10 mL) and DCM–IPA (2:1, 25 mL) were added and the phases were separated. The aqueous layer was extracted with DCM–IPA (2:1, 2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (246 mg, 59%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.88 - 1.04 (2H, m), 1.47 - 1.70 (3H, m), 1.86 (2H, br s), 1.95 - 2.12 (4H, m), 2.16 (2H, br d), 2.37 - 2.48 (5H, m), 2.67 - 2.75 (1H, m), 2.76 - 2.84 (1H, m), 2.90 (2H, br d), 2.96 (2H, br d), 3.53 - 3.62 (1H, m), 3.72 - 3.83 (1H, m), 4.58 - 4.73 (1H, m), 6.42 (1H, d), 7.63 (1H, d), 7.84 (1H, s), 9.43 - 11.52 (1H, m), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 425.2.

EXAMPLE 384:

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

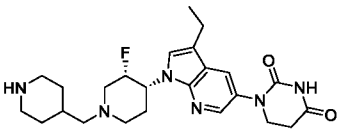


[2913] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (15.0 mg, 0.04 mmol) and Intermediate 384b (13.8 mg, 0.03 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (21.6 mg, 81%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, br d), 1.02 - 1.20 (5H, m), 1.56 - 1.93 (5H, m), 1.95 - 2.17 (4H, m), 2.23 (2H, br s), 2.43 (3H, s), 2.66 - 2.87 (3H, m), 2.91 - 3.13 (4H, m), 3.41 (1H, br t), 3.51 - 3.70 (2H, m), 3.72 - 3.82 (2H, m), 4.32 - 4.59 (2H, m), 4.60 - 4.71 (1H, m), 4.72 - 4.82 (1H, m), 6.34 (2H, br s), 6.42 (1H, d), 6.78 - 6.84 (1H, m), 6.84 - 6.89 (1H, m), 7.16 - 7.25 (1H, m), 7.39 (2H, d), 7.50 (1H, s), 7.55 (2H, br d), 7.63 (1H, d), 7.84 (1H, s), 7.90 - 7.97 (1H, m), 10.35 (1H, s), 14.24 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 827.5.

EXAMPLE 385

Intermediate 385a:

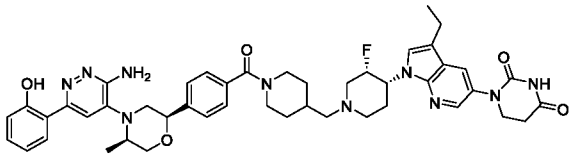
1-(3-Ethyl-1-((3*S*,4*R*)-3-fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2914] TFA (0.40 mL, 5.15 mmol) was added to a solution of Intermediate 330d (191 mg, 0.34 mmol) in DCM (1.2 mL). The resulting mixture was stirred at r.t. for 90 minutes and concentrated under reduced pressure. The residue was dissolved in water (5 mL). DCM–MeOH (3:1, 20 mL) and 5 M aq. K_2CO_3 (30 mL) were added. The phases were separated. The organic layer was washed with 5 M aq. K_2CO_3 (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (146 mg, 93%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.91 - 1.01 (2H, m), 1.25 - 1.29 (3H, m), 1.55 - 1.73 (3H, m), 1.76 - 1.82 (1H, m), 2.15 - 2.49 (7H, m), 2.65 - 2.73 (2H, m), 2.77 (2H, t), 2.91 (2H, br d), 2.97 - 3.05 (1H, m), 3.15 - 3.23 (1H, m), 3.82 (2H, t), 4.75 - 5.00 (2H, m), 7.44 (1H, s), 7.96 (1H, d), 8.20 (1H, d), 10.38 (1H, br s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 457.4.

EXAMPLE 385:

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



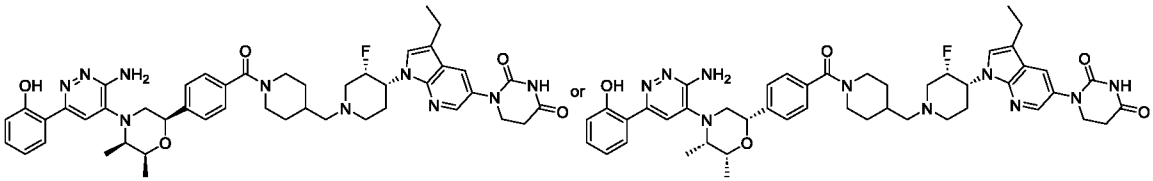
[2915] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 385a (22.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (23.4 mg, 56%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.99 - 1.18 (5H, m), 1.24 (3H, t), 1.56 - 1.95 (4H, m), 2.18 - 2.48 (5H, m), 2.69 (2H, q), 2.75 (3H, br t), 2.94 - 3.13 (3H, m), 3.15 - 3.27 (1H, m), 3.51 (1H, br t), 3.55 - 3.72 (1H, m), 3.75 - 3.87 (3H, m), 3.90 - 3.99 (1H, m), 4.28 (1H, br d), 4.47 (1H, br s), 4.69 (1H, br d), 4.77 - 5.00 (2H, m), 6.39 (2H, br s), 6.82 (1H, t), 6.86 (1H, d), 7.20 (1H, t), 7.35 - 7.46 (3H, m), 7.51 (1H, s), 7.55 (2H, d), 7.91 - 8.00 (2H, m), 8.18 (1H, d), 10.40 (1H, s), 14.28 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 386:

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

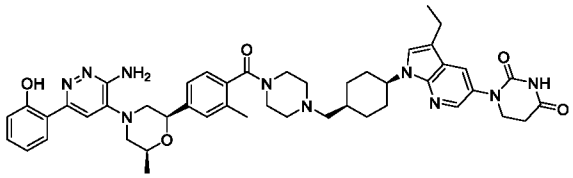
1-(1-((3*S*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2916] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (20.0 mg, 0.05 mmol) and Intermediate 385a (21.7 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (23.4 mg, 57%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, d), 1.02 - 1.20 (5H, m), 1.26 (3H, t), 1.60 - 1.97 (4H, m), 2.18 - 2.50 (5H, m), 2.70 (2H, q), 2.74 - 2.88 (3H, m), 3.06 (3H, br dd), 3.18 - 3.30 (1H, m), 3.42 (1H, br t), 3.54 - 3.74 (1H, m), 3.75 - 3.89 (3H, m), 4.37 - 4.44 (1H, m), 4.45 - 4.56 (1H, m), 4.74 - 4.98 (3H, m), 6.39 (2H, br s), 6.83 (1H, t), 6.88 (1H, d), 7.22 (1H, t), 7.38 - 7.47 (3H, m), 7.52 (1H, s), 7.56 (2H, d), 7.92 - 8.01 (2H, m), 8.20 (1H, d), 10.42 (1H, s), 14.30 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 859.4.

EXAMPLE 387:

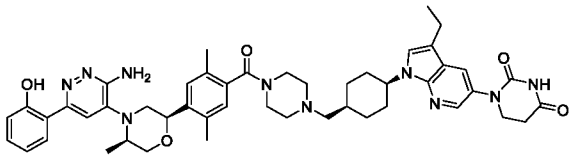
1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2917] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (20.0 mg, 0.05 mmol) and Intermediate 373a (20.9 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (31.4 mg, 78%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.23 - 1.30 (6H, m), 1.56 - 1.83 (6H, m), 1.88 - 2.03 (3H, m), 2.24 (3H, s), 2.27 - 2.58 (7H, m), 2.63 - 2.72 (3H, m), 2.72 - 2.78 (2H, m), 3.11 - 3.22 (2H, m), 3.45 - 3.58 (2H, m), 3.60 - 3.76 (2H, m), 3.80 (2H, t), 4.18 (1H, dd), 4.56 - 4.74 (1H, m), 4.79 - 4.99 (1H, m), 6.38 - 6.50 (2H, m), 6.81 - 6.91 (2H, m), 7.16 (1H, d), 7.23 (1H, ddd), 7.29 - 7.38 (2H, m), 7.55 (2H, d), 7.89 (1H, d), 7.95 (1H, dd), 8.15 (1H, d), 10.36 (1H, s), 14.20 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 841.5.

EXAMPLE 388:

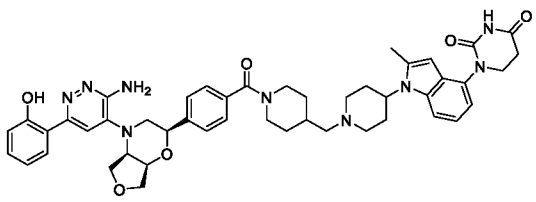
1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2918] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 373a (20.2 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (32.4 mg, 82%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.10 (3H, d), 1.26 (3H, t), 1.55 - 1.83 (6H, m), 1.87 - 2.03 (3H, m), 2.20 - 2.56 (12H, m), 2.69 (2H, q), 2.75 (2H, t), 2.94 - 3.06 (1H, m), 3.11 - 3.23 (2H, m), 3.43 - 3.56 (1H, m), 3.61 - 3.75 (2H, m), 3.77 - 3.86 (3H, m), 3.90 - 4.05 (1H, m), 4.28 (1H, br d), 4.58 - 4.72 (1H, m), 4.75 - 4.84 (1H, m), 6.35 (2H, br s), 6.76 - 6.90 (2H, m), 6.99 (1H, s), 7.15 - 7.29 (1H, m), 7.39 - 7.59 (3H, m), 7.89 (1H, d), 7.94 (1H, dd), 8.15 (1H, d), 10.28 (1H, br s), 14.17 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 855.6.

EXAMPLE 389:

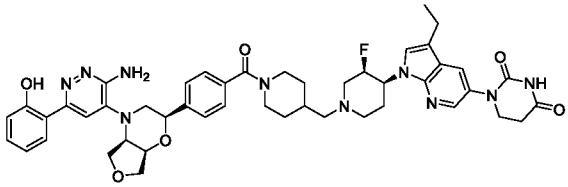
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2919] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 165a (19.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (19.4 mg, 50%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.99 - 1.20 (2H, m), 1.61 - 1.96 (5H, m), 2.06 - 2.17 (2H, m), 2.18 - 2.29 (2H, m), 2.33 - 2.48 (5H, m), 2.68 - 2.88 (3H, m), 3.00 (3H, br d), 3.23 (1H, dd), 3.46 - 3.68 (3H, m), 3.72 (2H, t), 3.85 (1H, d), 3.95 (1H, br t), 3.98 - 4.05 (1H, m), 4.17 - 4.27 (1H, m), 4.35 - 4.56 (2H, m), 4.61 (1H, t), 4.80 (1H, dd), 6.14 (1H, s), 6.51 (2H, s), 6.80 - 6.91 (3H, m), 7.03 (1H, t), 7.22 (1H, ddd), 7.37 - 7.42 (2H, m), 7.45 (1H, d), 7.50 - 7.58 (2H, m), 7.63 (1H, s), 7.95 (1H, dd), 10.28 (1H, s), 13.97 - 14.41 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 840.4.

EXAMPLE 390:

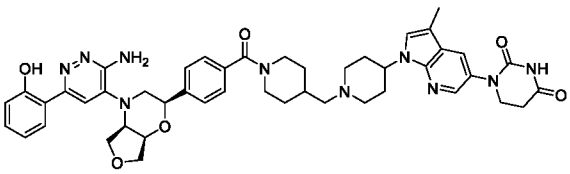
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2920] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 340e (21.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (27.1 mg, 67%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.00 - 1.17 (2H, m), 1.25 (3H, t), 1.54 - 1.94 (4H, m), 2.09 - 2.48 (5H, m), 2.61 - 2.90 (5H, m), 2.92 - 3.12 (2H, m), 3.14 - 3.28 (2H, m), 3.44 - 3.72 (3H, m), 3.76 - 3.87 (3H, m), 3.90 - 3.97 (1H, m), 3.98 - 4.06 (1H, m), 4.34 - 4.56 (2H, m), 4.60 (1H, t), 4.75 - 4.98 (3H, m), 6.50 (2H, s), 6.81 - 6.96 (2H, m), 7.16 - 7.29 (1H, m), 7.36 - 7.45 (3H, m), 7.54 (2H, d), 7.63 (1H, s), 7.90 - 8.00 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.17 (1H, br s); *m/z* (ES^+) $[M+H]^+$ = 873.5.

EXAMPLE 391:

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



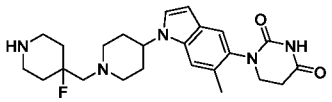
[2921] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 342a (19.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (29.2 mg, 75%) as a

white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.98 - 1.19 (2H, m), 1.57 - 1.91 (5H, m), 1.97 - 2.15 (4H, m), 2.17 - 2.30 (5H, m), 2.70 - 2.90 (3H, m), 2.91 - 3.16 (3H, m), 3.20 - 3.26 (1H, m), 3.46 - 3.70 (3H, m), 3.79 (2H, t), 3.85 (1H, d), 3.91 - 3.98 (1H, m), 3.98 - 4.05 (1H, m), 4.35 - 4.54 (2H, m), 4.55 - 4.67 (2H, m), 4.76 - 4.83 (1H, m), 6.50 (2H, s), 6.80 - 6.93 (2H, m), 7.16 - 7.27 (1H, m), 7.40 (2H, d), 7.47 (1H, d), 7.53 (2H, d), 7.63 (1H, s), 7.87 (1H, d), 7.94 (1H, dd), 8.16 (1H, d), 10.36 (1H, s), 14.17 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 841.4.

EXAMPLE 392

Intermediate 392a:

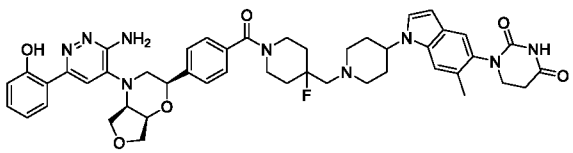
1-(1-(1-((4-Fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2922] HCl, 4 M in 1,4-dioxane (4.96 mL, 19.9 mL) was added to a solution of Intermediate 24a (1.08 g, 1.98 mmol) in 1,4-dioxane (5.0 mL). The resulting mixture was stirred at r.t. for 90 minutes and concentrated under reduced pressure. DCM–IPA (2:1, 15 mL) and sat. aq. K_2CO_3–water (4:1, 15 mL) were added and the phases were separated. The aqueous layer was extracted with DCM–IPA (2:1, 2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (897 mg, 102%, containing 5 wt% IPA) as a white solid. *m/z* (ES$^+$) $[M+H]^+$ = 442.3.

EXAMPLE 392:

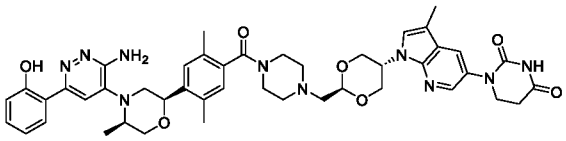
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2923] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 392a (20.3 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (23.3 mg, 59%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.60 - 2.06 (8H, m), 2.27 (3H, s), 2.41 (2H, br t), 2.56 - 2.77 (4H, m), 2.97 - 3.30 (5H, m), 3.38 - 3.63 (4H, m), 3.70 - 3.78 (1H, m), 3.85 (1H, d), 3.91 - 3.97 (1H, m), 3.98 - 4.04 (1H, m), 4.10 - 4.37 (2H, m), 4.42 (1H, td), 4.60 (1H, t), 4.73 - 4.87 (1H, m), 6.39 (1H, d), 6.50 (2H, s), 6.79 - 6.92 (2H, m), 7.22 (1H, ddd), 7.37 - 7.49 (5H, m), 7.51 - 7.59 (2H, m), 7.63 (1H, s), 7.94 (1H, dd), 10.23 (1H, s), 14.17 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 858.4.

EXAMPLE 393:

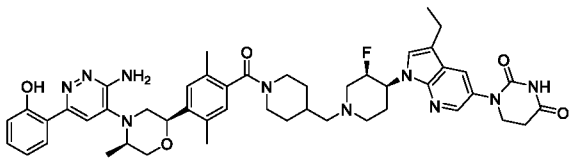
1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2924] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 358f (19.7 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 70% MeCN in water with 0.1% NH_4OH) gave the title compound (28.1 mg, 72%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, br d), 2.17 - 2.47 (11H, m), 2.51 - 2.69 (4H, m), 2.75 (2H, t), 3.00 (1H, br d), 3.16 (2H, br s), 3.41 - 3.57 (1H, m), 3.65 (2H, br s), 3.75 - 3.85 (3H, m), 3.89 - 4.00 (1H, m), 4.08 - 4.23 (4H, m), 4.27 (1H, br d), 4.73 - 4.81 (1H, m), 4.84 - 4.98 (2H, m), 6.34 (2H, br s), 6.81 (1H, t), 6.86 (1H, d), 6.97 (1H, s), 7.20 (1H, t), 7.45 (2H, s), 7.49 (1H, br s), 7.86 - 7.97 (2H, m), 8.21 (1H, d), 10.38 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 845.4.

EXAMPLE 394:

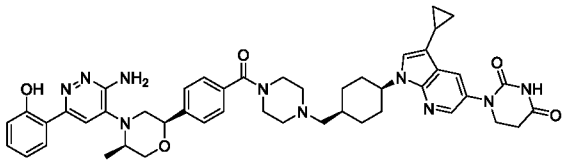
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2925] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 340e (21.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (25.1 mg, 63%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 0.88 - 1.17 (5H, m), 1.25 (3H, t), 1.55 - 1.71 (1H, m), 1.74 - 1.94 (3H, m), 2.13 - 2.48 (11H, m), 2.69 (2H, q), 2.73 - 2.84 (3H, m), 2.93 - 3.11 (3H, m), 3.14 - 3.25 (1H, m), 3.31 - 3.40 (1H, m), 3.42 - 3.59 (1H, m), 3.76 - 3.86 (3H, m), 3.89 - 4.01 (1H, m), 4.28 (1H, br d), 4.54 (1H, br d), 4.72 - 4.98 (3H, m), 6.34 (2H, br s), 6.77 - 6.84 (1H, m), 6.86 (1H, br d), 6.90 - 7.05 (1H, m), 7.20 (1H, br t), 7.38 - 7.46 (2H, m), 7.47 - 7.55 (1H, m), 7.89 - 7.98 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.25 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 873.5.

EXAMPLE 395:

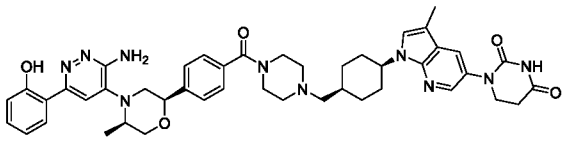
1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2926] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 217a (22.3 mg, 0.03 mmol). Purification by RPC (elution gradient: 0 to 95% MeCN in water with 0.1% formic acid) gave the title compound (8.0 mg, 29%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-d6) δ 0.67 (2H, br d), 0.82 - 0.91 (2H, m), 1.08 (3H, br d), 1.67 (4H, br d), 1.80 (2H, br d), 1.89 - 2.03 (4H, m), 2.35 - 2.49 (4H, m), 2.77 (2H, br t), 3.11 (1H, br d), 3.43 - 3.49 (3H, m), 3.50 - 3.57 (2H, m), 3.66 (2H, br d), 3.79 - 3.87 (3H, m), 3.96 (1H, br d), 4.30 (1H, br d), 4.64 (1H, br t), 4.72 (1H, br d), 6.38 (2H, br s), 6.84 (1H, br t), 6.88 (1H, br d), 7.23 (1H, br t), 7.44 (2H, br d), 7.52 (2H, br d), 7.58 (2H, br d), 7.91 - 7.98 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 13.98 - 14.66 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 839.6.

EXAMPLE 396:

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

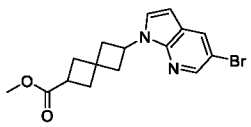


[2927] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 273e (20.0 mg, 0.05 mmol) and Intermediate 258f (20.9 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 95% MeCN in water with 0.1% formic acid) gave the title compound (25.0 mg, 63%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-d6) δ 1.08 (3H, br d), 1.62 - 1.74 (4H, m), 1.79 (2H, br d), 1.97 (3H, br d), 2.26 (3H, s), 2.32 - 2.50 (6H, m), 2.76 (2H, t), 3.11 (1H, br d), 3.42 - 3.48 (1H, m), 3.53 (2H, br t), 3.66 (2H, br s), 3.77 - 3.88 (3H, m), 3.96 (1H, br d), 4.30 (1H, br d), 4.65 (1H, br t), 4.72 (1H, br d), 6.38(2H, br s), 6.84 (1H, br t), 6.88 (1H, d), 7.22 (1H, br t), 7.44 (2H, br d), 7.52 (1H, s), 7.55 - 7.61 (3H, m), 7.87 (1H, d), 7.95 (1H, br d), 8.17 (1H, d), 10.38 (1H, s), 14.27 (1H, br d); *m/z* (ES$^+$) $[M+H]^+$ = 813.7.

EXAMPLE 397

Intermediate 397a:

rac-Methyl 6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptane-2-carboxylate

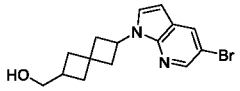


[2928] Prepared in an analogous method to Intermediate 343a starting from 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (1.50 g, 7.61 mmol) and *rac*-methyl 6-hydroxyspiro[3.3]heptane-2-carboxylate (1.56 g, 9.14 mmol). Purification by FSC (elution gradient: 0 to 60% EtOAc in hexanes) gave the title compound (1.20

g, 45%) as a light orange gum. ^{1}H NMR (DMSO-d6) δ 2.27 (2H, d), 2.33 - 2.39 (1H, m), 2.43 - 2.48 (2H, m), 2.51 - 2.53 (1H, m), 2.55 (1H, d), 2.63 (1H, br dd), 3.06 - 3.20 (1H, m), 3.61 (3H, s), 5.12 (1H, t), 6.49 (1H, d), 7.81 (1H, d), 8.20 (1H, d), 8.25 - 8.35 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 349.1.

Intermediate 397b:

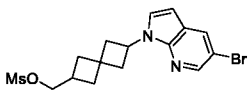
rac-(6-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methanol



[2929] Prepared in an analogous method to Intermediate 343b starting from Intermediate 397a (2.20 g, 6.30 mmol). Purification by FSC (elution gradient: 0 to 100% EOAc in hexanes) gave the title compound (1.90 g, 94 %) as a thick oil. ^{1}H NMR (DMSO-d6) δ 1.82 (1H, dd), 1.91 (1H, dd), 2.01 - 2.07 (1H, m), 2.18 - 2.24 (1H, m), 2.28 - 2.34 (1H, m), 2.39 - 2.49 (3H, m), 2.54 -2.60 (1H, m), 3.31 - 3.39 (2H, m), 4.48 (1H, t), 5.03 - 5.19 (1H, m), 6.48 (1H, d), 7.81 (1H, d), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 321.1

Intermediate 397c:

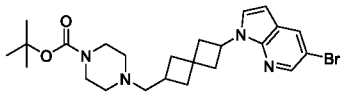
rac-(6-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl methanesulfonate



[2930] Prepared in an analogous method to Intermediate 343c starting from Intermediate 397b (1.90 g, 5.91 mmol). After completion of the reaction, the mixture was diluted with DCM (50 mL), washed with sat. aq. $NaHCO_3$ (30 mL) and water (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give title compound (2.30 g, 97%) as a light yellow gum, which was used for the next step without further purification. ^{1}H NMR (DMSO-d6) δ 1.92 (1H, dd), 2.01 (1H, dd), 2.12 - 2.19 (1H, m), 2.29 - 2.36 (1H, m), 2.48 (2H, s), 2.52 - 2.56 (1H, m), 2.59 - 2.66 (2H, m), 3.19 (3H, s), 4.19 (2H, d), 5.13 (1H, s), 6.49 (1H, d), 7.82 (1H, d), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 399.2.

Intermediate 397d:

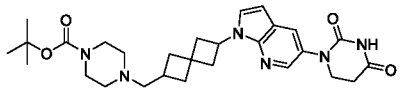
rac-tert-Butyl 4-((6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



[2931] Prepared in an analogous method to Intermediate 343d starting from Intermediate 397c (2.00 g, 5.01 mmol) and *tert*-butyl piperazine-1-carboxylate (1.40 g, 7.51 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.60 g, 65%) as a light yellow solid. ^{1}H NMR (DMSO-d6) δ 1.39 (9H, s), 1.41 (1H, s), 1.70 - 1.87 (2H, m), 2.13 (1H, br s), 2.24 - 2.36 (7H, m), 2.39 - 2.47 (3H, m), 2.57 - 2.65 (1H, m), 3.26 - 3.32 (4H, m), 5.05 - 5.18 (1H, m), 6.49 (1H, d), 7.81 (1H, d), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 489.2.

Intermediate 397e:

rac-tert-Butyl 4-((6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1H-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



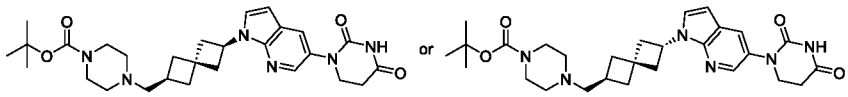
[2932] Prepared in an analogous method to Intermediate 343e starting from Intermediate 397d (1.50 g, 3.06 mmol) and dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.87 g, 7.66 mmol). After cooling to r.t., the mixture was diluted with EtOAc (100 mL). The mixture was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Trituration with diethyl ether (50 mL) gave the title compound (0.91 g, 56%) as a light brown solid. *m/z* (ES^+) $[M+H]^+ = 523.3$.

Intermediate 397f:

tert-Butyl 4-(((2*S*,4*s*,6*S*)-6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate

or

tert-Butyl 4-(((2*R*,4*r*,6*R*)-6-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)spiro[3.3]heptan-2-yl)methyl)piperazine-1-carboxylate



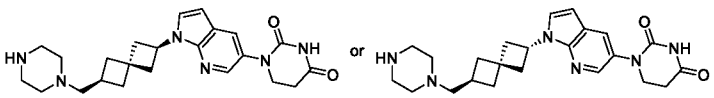
[2933] Intermediate 397e (950 mg, 1.82 mmol) was purified by preparative chiral HPLC (ChiralPak IM 3 x 100 mm, 3 µm, isocratic 35% [1:1 DCM:MeOH] in water with 0.2% NH_4OH) to give the title compound (166 mg, 17%, >99% ee) which eluted second from the column. ^1H NMR (DMSO-d6) δ 1.40 (9H, s), 1.71 - 1.79 (1H, m), 1.81 - 1.91 (1H, m), 2.10 - 2.19 (1H, m), 2.25 - 2.37 (7H, m), 2.38 - 2.47 (3H, m), 2.51 (2H, br s), 2.51- 2.56 (1H, m), 2.58 - 2.67 (1H, m), 2.75 (2H, t), 3.34 (2H, s), 3.80 (2H, t), 5.14 (1H, quin), 6.51 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.20 (1H, d), 10.41 (1H, s); *m/z* (ES^+) $[M+H]^+ = 523.6$.

Intermediate 397g:

1-(1-((2*S*,4*s*,6*S*)-6-(Piperazin-1-ylmethyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*R*,4*r*,6*R*)-6-(Piperazin-1-ylmethyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



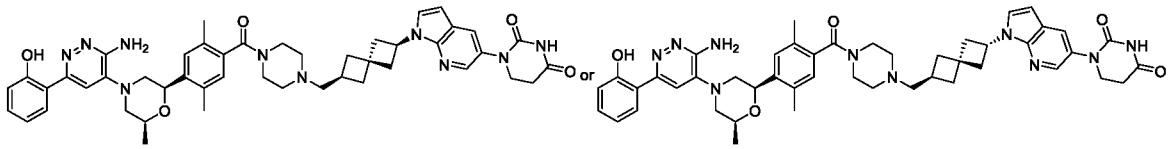
[2934] TFA (0.442 mL, 5.74 mmol) was added to a stirred solution of Intermediate 397f (200 mg, 0.38 mmol) in DCM (3 mL). The resulting solution was stirred at r.t. for 1 hour. The solvent was removed under reduced pressure. Purification by ion exchange chromatography (Porpak Rxn CX 5g cartridge) eluting with 2N NH_3 in MeOH gave the title compound (125 mg, 77%) as a white solid. *m/z* (ES^+) $[M+H]^+ = 423.2$.

EXAMPLE 397:

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

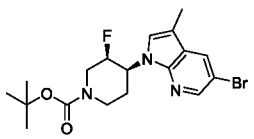


[2935] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (20.0 mg, 0.05 mmol), and Intermediate 397g (19.5 mg, 0.05 mmol). Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4OH) gave the title compound (25.0 mg, 65%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-d6) δ 1.11 (3H, br d), 1.77 (1H, br d), 1.86 (1H, br dd), 2.12 - 2.19 (1H, m), 2.22 - 2.36 (9H, m), 2.37 - 2.48 (7H, m), 2.54 (1H, br s), 2.62 (1H, br s), 2.76 (2H, t), 3.02 (1H, br d), 3.11 - 3.20 (2H, m), 3.44 - 3.58 (1H, m), 3.65 (2H, br s), 3.77 - 3.85 (3H, m), 3.96 (1H, br s), 4.29 (1H, br d), 4.79 (1H, br d), 5.14 (1H, quin), 6.36 (2H, br s), 6.51 (1H, d), 6.83 (1H, t), 6.88 (1H, d), 6.98 (1H, s), 7.22 (1H, t), 7.46 (1H, s), 7.51 (1H, br s), 7.77 (1H, d), 7.91 (1H, d), 7.95 (1H, d), 8.20 (1H, d), 10.38 (1H, s), 14.27 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 839.7.

EXAMPLE 398

Intermediate 398a:

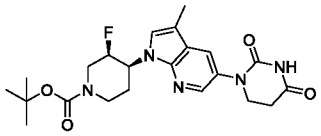
tert-Butyl (3*R*,4*S*)-4-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2936] Prepared in an analogous method to Intermediate 126a using 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.69 g, 8.00 mmol) and *tert*-butyl (3*R*,4*R*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (2.11 g, 9.60 mmol), stirring at 100 °C overnight. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 5 to 25% EtOAc in hexanes) gave the title compound (1.82 g, 55%) as a colorless dry film. ^{1}H NMR (DMSO-d6) δ 1.40 - 1.45 (9H, m), 1.74 - 1.81 (1H, m), 2.22 - 2.25 (3H, m), 2.25 - 2.37 (1H, m), 2.92 - 3.27 (2H, m), 4.05 - 4.43 (2H, m), 4.77 - 4.97 (1H, m), 4.99 - 5.13 (1H, m), 7.44 (1H, s), 8.20 (1H, d), 8.28 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 412.1.

Intermediate 398b:

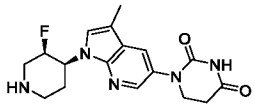
tert-Butyl (3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate



[2937] Prepared in an analogous method to Intermediate 93b using Intermediate 398a (1.72 g, 4.17 mmol), stirring at 90 °C for 27 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was partitioned between DCM and water. The phases were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 5 to 25% [10% MeOH in DCM with 1% NH_4OH] in DCM) gave the title compound (1.51 g, 81%) as a grey solid. ^{1}H NMR (DMSO-d6) δ 1.40 - 1.46 (9H, m), 1.78 (1H, br d), 2.24 (3H, s), 2.27 - 2.38 (1H, m), 2.75 (2H, t), 3.16 (2H, d), 3.81 (2H, t), 4.10 - 4.44 (2H, m), 4.78 - 4.99 (1H, m), 5.02 - 5.18 (1H, m), 7.42 (1H, s), 7.92 (1H, d), 8.19 (1H, d), 10.37 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 446.1.

Intermediate 398c:

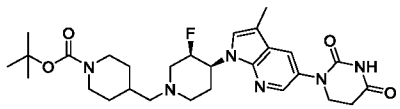
1-(1-((3*R*,4*S*)-3-Fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2938] TFA (5.22 mL, 67.8 mmol) was added to a solution of Intermediate 398b (1.51 g, 3.39 mmol) in DCM (12 mL). The resulting mixture was stirred at r.t. for 90 minutes. The mixture was concentrated under reduced pressure. Et_2O was added and the mixture was sonicated. The mixture was allowed to settle for 30 minutes. The liquids were decanted off. The residue was dried *in vacuo*. MeOH (20 mL) and tetraalkylammonium carbonate resin (3 g) were added. The resulting mixture was stirred at r.t. for 30 minutes. DCM (10 mL) was added. The mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound (1.10 g, 94%) as a light grey solid. ^{1}H NMR (DMSO-d6) δ 1.69 (1H, br d), 2.15 - 2.26 (4H, m), 2.71 - 2.80 (3H, m), 2.83 - 3.01 (1H, m), 3.04 - 3.14 (1H, m), 3.14 - 3.19 (1H, m), 3.76 - 3.83 (2H, m), 4.63 - 4.83 (1H, m), 4.91 - 5.04 (1H, m), 7.38 (1H, s), 7.91 (1H, d), 8.18 (1H, d), 10.37 (1H, s), one nitrogen-bound proton not observed; *m/z* (ES^+) $[M+H]^+$ = 346.0.

Intermediate 398d:

tert-Butyl 4-(((3*R*,4*S*)-4-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-3-fluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

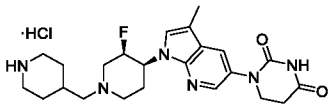


[2939] A solution of Intermediate 398c (1.10 g, 3.18 mmol) and *tert*-butyl 4-formylpiperidine-1-carboxylate (0.68 g, 3.18 mmol) in DCM (30 mL) and MeOH (3 mL) was stirred at r.t. for 1 hour. Sodium triacetoxyborohydride (1.01 g, 4.78 mmol) was added. The resulting mixture was stirred at r.t. for 4 hours. The mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 10%

MeOH in DCM with 1% NH_4OH) gave the title compound (1.39 g, 80%) as a white solid. ^1H NMR (DMSO-d6) δ 0.95 (2H, br d), 1.38 (9H, s), 1.64 - 1.72 (3H, m), 1.76 (1H, br d), 2.16 - 2.26 (6H, m), 2.28 - 2.36 (1H, m), 2.36 - 2.43 (1H, m), 2.63 - 2.79 (4H, m), 2.96 - 3.04 (1H, m), 3.15 - 3.23 (1H, m), 3.80 (2H, t), 3.92 (2H, br d), 4.75 - 4.95 (2H, m), 7.43 (1H, s), 7.91 (1H, d), 8.18 (1H, d), 10.37 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 543.2.

Intermediate 398e:

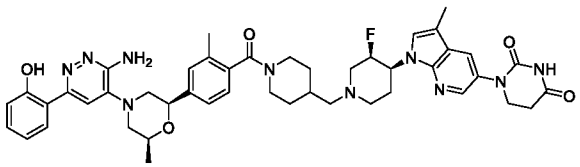
1-(1-((3*R*,4*S*)-3-Fluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2940] TFA (3.98 mL, 51.6 mmol) was added to a solution of Intermediate 398d (1.40 g, 2.58 mmol) in DCM (8.9 mL). The resulting mixture was stirred at r.t. for 90 minutes. The mixture was concentrated under reduced pressure. Et_2O was added. The resulting mixture was sonicated and then allowed to settle for 30 minutes. The liquids were decanted off. The residue was dried *in vacuo*. MeOH (20 mL) and 4 M HCl in 1,4-dioxane (20 mL) were added. The resulting mixture was stirred at r.t. for 30 minutes. The mixture was concentrated under reduced pressure to give the title compound (1.35 g, 95%) as a solid and HCl salt (3 eq. of HCl were assumed based on the obtained mass). *m/z* (ES^+) $[M+H]^+$ = 443.3.

EXAMPLE 398:

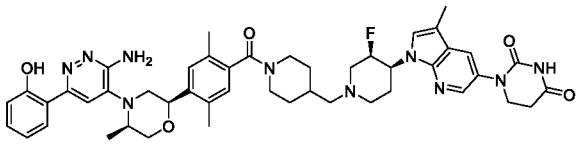
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2941] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 263e (25.2 mg, 0.06 mmol), and Intermediate 398e (39.7 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 50% MeCN in water with 0.1% formic acid) gave the title compound (27.2 mg, 54%) as a white solid, following lyophilization. ^1H NMR (DMSO-d6) δ 1.16 - 1.42 (2H, m), 1.46 - 1.54 (3H, m), 1.79 - 1.95 (1H, m), 1.97 - 2.17 (3H, m), 2.40 - 2.47 (2H, m), 2.51 - 2.71 (4H, m), 2.73 - 2.81 (3H, m), 2.90 - 2.97 (1H, m), 2.99 - 3.03 (2H, m), 3.18 - 3.24 (1H, m), 3.38 - 3.47 (1H, m), 3.50 - 3.62 (6H, m), 3.70 - 3.84 (2H, m), 4.05 (2H, t), 4.27 - 4.39 (1H, m), 4.78 (1H, br d), 5.00 - 5.21 (3H, m), 6.69 (2H, br s), 7.08 - 7.16 (2H, m), 7.33 - 7.51 (2H, m), 7.52 - 7.63 (2H, m), 7.66 (1H, br s), 7.79 (1H, s), 8.12 - 8.24 (2H, m), 8.40 - 8.46 (1H, m), 10.62 (1H, s), 14.01 - 14.57 (1H, m); *m/z* (ES^+) $[M+H]^+$ = 845.5.

EXAMPLE 399:

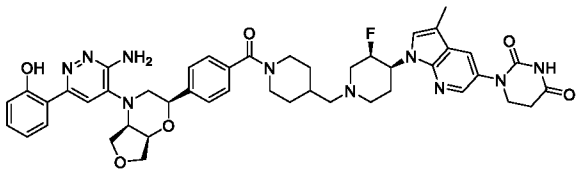
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2942] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (26.1 mg, 0.06 mmol), and Intermediate 398e (39.7 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 50% MeCN in water with 0.1% formic acid) gave the title compound (33.0 mg, 64%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-d6) δ 0.89 - 1.18 (5H, m), 1.59 - 1.71 (1H, m), 1.73 - 1.91 (3H, m), 2.19 - 2.46 (14H, m), 2.71 - 2.82 (3H, m), 2.94 - 3.08 (3H, m), 3.17 - 3.24 (1H, m), 3.32 - 3.38 (1H, m), 3.48 - 3.55 (1H, m), 3.78 - 3.86 (3H, m), 3.90 - 4.01 (1H, m), 4.25 - 4.31 (1H, m), 4.49 - 4.59 (1H, m), 4.76 - 4.95 (3H, m), 6.34 (2H, br s), 6.70 - 6.89 (2H, m), 6.89 - 7.07 (1H, m), 7.15 - 7.24 (1H, m), 7.40 - 7.55 (3H, m), 7.89 - 7.98 (2H, m), 8.15 - 8.23 (1H, m), 10.38 (1H, s), 13.44 - 15.20 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 859.7.

EXAMPLE 400:

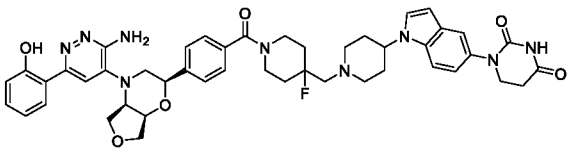
1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2943] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (26.1 mg, 0.06 mmol), and Intermediate 398e (39.7 mg, 0.07 mmol). Purification by RPC (elution gradient: 20 to 50% MeCN in water with 0.1% formic acid) gave the title compound (25.1 mg, 49%) as a white solid, following lyophilization. ^{1}H NMR (DMSO-d6) δ 1.02 - 1.17 (2H, m), 1.58 - 1.93 (4H, m), 2.24 - 2.31 (5H, m), 2.31 - 2.47 (2H, m), 2.72 - 2.86 (3H, m), 2.97 - 3.11 (2H, m), 3.19 - 3.26 (2H, m), 3.33 - 3.41 (2H, m), 3.52 - 3.63 (2H, m), 3.75 - 3.82 (2H, m), 3.82 - 3.89 (1H, m), 3.90 - 3.98 (1H, m), 3.98 - 4.04 (1H, m), 4.35 - 4.54 (2H, m), 4.58 - 4.66 (1H, m), 4.74 - 4.95 (3H, m), 6.50 (2H, br s), 6.79 - 6.93 (2H, m), 7.18 - 7.25 (1H, m), 7.37 - 7.44 (3H, m), 7.54 (2H, d), 7.63 (1H, s), 7.89 - 7.95 (2H, m), 8.14 - 8.20 (1H, m), 10.37 (1H, s), 13.63 - 14.71 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 859.4.

EXAMPLE 401:

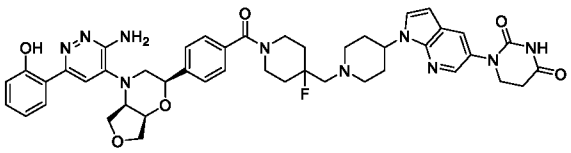
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2944] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 374a (19.7 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) and FSC (elution gradient: 80 to 100% EtOAc in hexanes, then 0 to 20% MeOH in EtOAc) gave the title compound (11.3 mg, 29%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.63 - 2.03 (8H, m), 2.41 (2H, br t), 2.58 - 2.68 (2H, m), 2.71 (2H, br t), 2.96 - 3.27 (5H, m), 3.42 - 3.60 (3H, m), 3.75 (2H, br t), 3.85 (1H, br d), 3.94 (1H, br t), 3.98 - 4.05 (1H, m), 4.17 - 4.38 (2H, m), 4.39 - 4.46 (1H, m), 4.58 - 4.64 (1H, m), 4.76 - 4.83 (1H, m), 6.44 (1H, br d), 6.50 (2H, br s), 6.82 - 6.90 (2H, m), 7.06 (1H, br d), 7.22 (1H, br t), 7.41 - 7.48 (3H, m), 7.50 - 7.58 (4H, m), 7.63 (1H, s), 7.94 (1H, br d), 10.23 (1H, s), 14.16 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 844.4.

EXAMPLE 402:

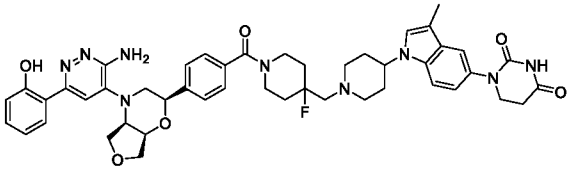
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2945] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 166c (19.7 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (30.1 mg, 77%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.65 - 2.16 (8H, m), 2.31 - 2.43 (2H, m), 2.55 - 2.69 (2H, m), 2.72 - 2.79 (2H, m), 2.98 - 3.29 (5H, m), 3.38 - 3.64 (3H, m), 3.79 (2H, t), 3.85 (1H, d), 3.90 - 4.03 (2H, m), 4.14 - 4.37 (1H, m), 4.38 - 4.46 (1H, m), 4.57 - 4.70 (2H, m), 4.80 (1H, dd), 6.43 - 6.61 (3H, m), 6.81 - 6.93 (2H, m), 7.17 - 7.27 (1H, m), 7.44 (2H, d), 7.55 (2H, d), 7.63 (1H, s), 7.72 (1H, d), 7.90 (1H, d), 7.94 (1H, dd), 8.19 (1H, d), 10.37 (1H, s), 14.03 - 14.31 (1H, m); *m/z* (ES$^+$) $[M+H]^+$ = 845.5.

EXAMPLE 403:

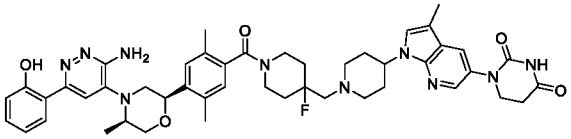
1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2946] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 287f (20.0 mg, 0.05 mmol) and Intermediate 378a (22.0 mg, 0.05 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (26.9 mg, 68%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.61 - 2.06 (8H, m), 2.22 (3H, d), 2.32 - 2.45 (2H, m), 2.55 - 2.68 (2H, m), 2.71 (2H, t), 2.95 - 3.29 (5H, m), 3.36 - 3.63 (3H, m), 3.75 (2H, t), 3.85 (1H, d), 3.90 - 3.97 (1H, m), 3.98 - 4.05 (1H, m), 4.14 - 4.35 (2H, m), 4.37 - 4.45 (1H, m), 4.60 (1H, t), 4.72 - 4.88 (1H, m), 6.51 (2H, s), 6.81 - 6.90 (2H, m), 7.04 (1H, dd), 7.22 (1H, ddd), 7.30 (1H, d), 7.38 (1H, d), 7.41 - 7.49 (3H, m), 7.55 (2H, d), 7.63 (1H, s), 7.94 (1H, dd), 10.23 (1H, s), 14.16 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 858.4.

EXAMPLE 404:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

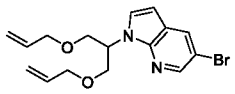


[2947] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 354g (20.0 mg, 0.05 mmol) and Intermediate 161a (18.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (26.5 mg, 74%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.11 (3H, br d), 1.46 - 1.89 (5H, m), 1.94 - 2.13 (3H, m), 2.18 - 2.43 (11H, m), 2.57 - 2.71 (2H, m), 2.76 (2H, t), 2.98 - 3.30 (6H, m), 3.42 - 3.61 (1H, m), 3.76 - 3.87 (3H, m), 3.91 - 4.03 (1H, m), 4.22 - 4.45 (2H, m), 4.60 (1H, br t), 4.74 - 4.89 (1H, m), 6.36 (2H, br s), 6.84 (1H, br t), 6.88 (1H, d), 6.97 - 7.10 (1H, m), 7.22 (1H, t), 7.43 - 7.59 (3H, m), 7.89 (1H, s), 7.95 (1H, br d), 8.18 (1H, s), 10.38 (1H, s), 14.27 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 859.4.

EXAMPLE 405

Intermediate 405a:

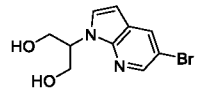
1-(1,3-*bis*(Allyloxy)propan-2-yl)-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine



[2948] Prepared in an analogous manner to Intermediate 234a using 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (25.0 g, 127 mmol) and 1,3-*bis*(allyloxy)propan-2-ol (49.0 g, 203 mmol), stirring at 100 °C for 24 hours. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (30.0 g, 67%) as a red liquid. ^{1}H NMR (DMSO-d_6) δ 3.78 – 3.82 (2H, m), 3.86 – 3.89 (2H, m), 3.90 – 3.92 (4H, m), 5.05 – 5.07 (1H, m), 5.07 – 5.09 (1H, m), 5.11 – 5.12 (1H, m), 5.14 – 5.16 (1H, m), 5.17 – 5.23 (1H, m), 5.73 – 5.81 (2H, m), 6.49 (1H, d), 7.71 (1H, d), 8.19 (1H, d), 8.31 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 351.0.

Intermediate 405b:

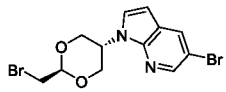
2-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol



[2949] Prepared in an analogous method to Intermediate 333b using Intermediate 405a (13.0 g, 37.0 mmol), stirring at r.t. for 16 hours. The mixture was concentrated under reduced pressure. Trituration with DCM–hexanes (1:1) gave the title compound (8.00 g, 80%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.76 – 3.82 (4H, t), 4.79 – 4.86 (1H, m), 4.88 – 4.93 (2H, t), 6.44 (1H, d), 7.66 (1H, d), 8.18 (1H, d), 8.27 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 270.8.

Intermediate 405c:

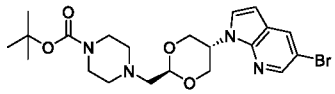
5-Bromo-1-((2*r*,5*r*)-2-(bromomethyl)-1,3-dioxan-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine



[2950] Intermediate 405b (8.00 g, 29.5 mmol) was added to 2-bromo-1,1-dimethoxyethane (5.98 g, 35.4 mmol) and *p*-toluenesulfonic acid (10.2 g, 5.90 mmol) in toluene (80 mL). The resulting mixture was stirred at 100 °C for 35 hours. After cooling to r.t., the mixture was diluted with EtOAc (200 mL), washed with sat. aq. $NaHCO_3$ (2 x 150 mL) and brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.50 g, 4%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.58 (2H, d), 4.22 – 4.30 (4H, m), 4.97 – 5.02 (2H, m), 6.55 (1H, d), 7.75 (1H, d), 8.26 (1H, d), 8.35 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 374.9.

Intermediate 405d:

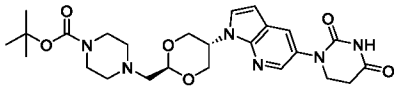
tert-Butyl 4-(((2*r*,5*r*)-5-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



[2951] A mixture of Intermediate 405c (500 mg, 1.33 mmol), *tert*-butyl piperazine-1-carboxylate (495 mg, 2.66 mmol), DIPEA (0.581 mL, 3.32 mmol) and potassium iodide (662 mg, 3.99 mmol) in DMF (5 mL) was stirred at 80 °C for 16 hours. After cooling to r.t., the mixture was diluted with DCM (25 mL), washed with sat. aq. NH_4Cl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (450 mg, 70%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.49 (9H, s), 2.52 – 2.65 (4H, m), 2.68 – 2.74 (2H, m), 3.50 – 3.56 (4H, m), 4.22 – 4.29 (2H, m), 4.31 – 4.35 (2H, m), 4.90 – 4.97 (1H, m), 5.02 – 5.08 (1H, m), 6.45 (1H, d), 7.18 (1H, d), 8.03 (1H, d), 8.34 (1H, d); *m/z* (ES$^+$) $[M+H]^+$ = 480.9.

Intermediate 405e:

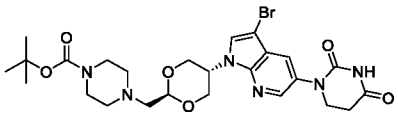
tert-Butyl 4-(((2*r*,5*r*)-5-(5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



[2952] Prepared in an analogous method to Intermediate 333e using Intermediate 405d (900 mg, 1.87 mmol), stirring at 90 °C for 24 hours. After cooling to r.t., the mixture was diluted with DCM (25 mL), washed with sat. aq. K_2CO_3 (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 3% MeOH in DCM) gave the title compound (400 mg, 41%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 2.48 – 2.53 (3H, m), 2.55 – 2.58 (2H, m), 2.75 (2H, t), 3.28 – 3.33 (4H, m), 3.80 (2H, t), 4.16 – 4.26 (5H, m), 4.89 – 4.94 (1H, m), 4.97 – 5.04 (1H, m), 6.56 (1H, d), 7.68 – 7.71 (1H, d), 7.95 (1H, d), 8.26 (1H, d), 10.42 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 515.3.

Intermediate 405f:

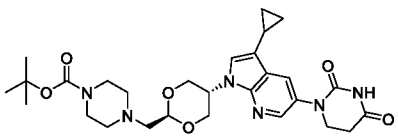
tert-Butyl 4-(((2*r*,5*r*)-5-(3-bromo-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate



[2953] Intermediate 405e (400 mg, 0.78 mmol) was added to NBS (152 mg, 0.86 mmol) in DCM (4 mL). The resulting mixture was stirred a r.t. for 1 hour. The mixture was diluted with DCM (20 mL), washed with sat. aq. $NaHCO_3$ (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (380 mg, 82%) as a brown solid. The product was used for the next step without further purification. *m/z* (ES$^+$) $[M+H]^+$ = 593.4.

Intermediate 405g:

tert-Butyl 4-(((2*r*,5*r*)-5-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1,3-dioxan-2-yl)methyl)piperazine-1-carboxylate

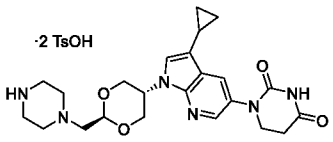


[2954] Cyclopropylboronic acid (82 mg, 0.96 mmol) was added to a mixture of Intermediate 405f (380 mg, 0.64 mmol), Pd(dtbpf)Cl_2 (42 mg, 0.06 mmol) and K_3PO_4 (408 mg, 1.92 mmol) in 1,4-dioxane (4.0 mL) and water (0.4 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 4 hours. After cooling to r.t., the mixture was diluted with DCM (25 mL), washed with sat. aq. $NaHCO_3$ (2 x 20 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 70% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (150 mg, 42%) as a red solid. ^{1}H NMR (DMSO-d_6) δ 0.62 – 0.64 (2H, m), 0.85 – 0.89 (2H, m), 1.14 – 1.20 (1H, m), 1.40 (9H, s),

1.44 – 1.47 (1H, m), 1.89 – 1.95 (1H, m), 2.43 – 2.47 (4H, m), 2.54 – 2.57 (2H, m), 2.77 (2H, t), 3.29 – 3.31 (2H, m), 3.82 (2H, t), 4.12 – 4.20 (4H, m), 4.87 – 4.95 (2H, m), 7.43 (1H, s), 7.97 – 8.00 (1H, d), 8.22 (1H, d), 10.41 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 555.3.

Intermediate 405h:

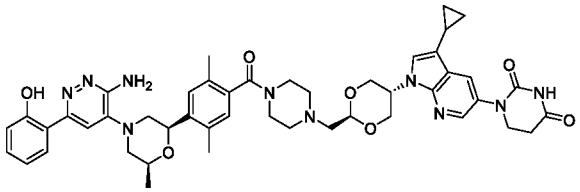
1-(3-Cyclopropyl-1-((2*r*,5*r*)-2-(piperazin-1-ylmethyl)-1,3-dioxan-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2955] Intermediate 405g (100 mg, 0.18 mmol) was added to *p*-toluenesulfonic acid (47 mg, 0.27 mmol) in MeCN (3 mL). The resulting mixture was stirred at 80 °C for 24 hours. After cooling to r.t., MTBE (3 mL) was added. The resulting suspension was filtered. The solids were washed with MTBE (1 mL) and dried *in vacuo* to give the title compound (70 mg, 48%) as a white solid and 2 TsOH salt. ^{1}H NMR (DMSO-d_6) δ 0.61 – 0.65 (2H, m), 0.86 – 0.91 (2H, m), 1.90 – 1.96 (1H, m), 2.29 (6H, s), 2.77 (2H, t), 3.45 – 3.55 (6H, m), 3.74 – 3.88 (6H, m), 4.21 – 4.26 (2H, m), 4.28 – 4.34 (2H, m), 5.01 – 5.09 (1H, m), 5.19 – 5.23 (1H, m), 7.14 (4 H, d),7.45 (1H, s), 7.51(4H, d). 8.23 (1H, d), 8.95 (2H, brs),10.42 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 455.2.

EXAMPLE 405:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



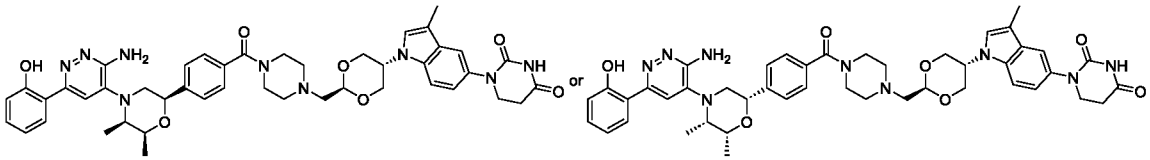
[2956] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 274e (16.3 mg, 0.04 mmol) and Intermediate 405h (30.0 mg, 0.04 mmol). After completion of the reaction, the mixture was diluted with DCM (15 mL), washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xselect CSH Prep Phenyl-Hexyl OBD column, 19*250 mm, 5 µm; elution gradient: isocratic 24% MeCN in water with 0.1% formic acid) gave the title compound (13.6 mg, 40%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.61 – 0.65 (2H, m), 0.85 – 0.90 (2H, m), 1.22 – 1.27 (3H, d), 1.89 – 1.95 (1H, m), 2.21 (3H, s), 2.34 (3H, s), 2.39 – 2.47 (3H, m), 2.55 – 2.60 (4H, m), 2.72 – 2.79 (3H, m), 3.11 – 3.18 (2H, m), 3.51 – 3.54 (2H, m), 3.62 – 3.68 (2H, m), 3.82 (2H, t), 4.11 – 4.20 (5H, m), 4.88 – 5.00 (3H, m), 6.43 (2H, s), 6.81 – 6.91 (2H, m), 6.98 (1H, s), 7.21 – 7.26 (1H, m), 7.36 (1H, s), 7.43 (1H, s), 7.56 (1H, s), 7.95 (1H, d), 7.99 (1H, d), 8.22 (1H, d), 10.41 (1H, s), 14.09 – 14.30 (1H, s); *m/z* (ES^+) $[M+H]^+$ = 871.4.

EXAMPLE 406:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

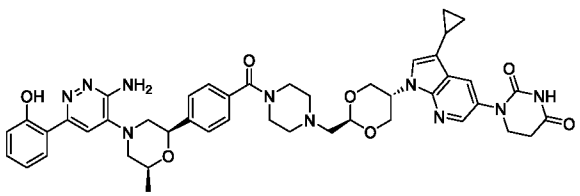
1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2957] Intermediate 261g (40.0 mg, 0.10 mmol) was added to a solution of HATU (36.2 mg, 0.10 mmol) and DIPEA (0.05 mL, 0.29 mmol) in DMF (1.5 mL). The resulting mixture was stirred at r.t. for 30 minutes. In a separate flask, Intermediate 333f (40.7 mg, 0.10 mmol) was added to a solution of DIPEA (0.05 mL, 0.29 mmol) in DMF (1.5 mL). The resulting mixture was stirred at r.t. for 30 minutes. The two solutions were combined and stirred at r.t. for 30 minutes. The mixture was diluted with DCM (100 mL), washed with sat. aq. Na_2CO_3 (3 x 50 mL) and brine (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xbridge Prep Shield RP18 OBD, 30*150 mm, 5μm; elution gradient: 39 to 59% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (15.2 mg, 19%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.94 (3H, d), 1.16 (3H, d), 2.22 (3H, s), 2.58 – 2.64 (4H, m), 2.71 – 2.76 (2H, m), 3.06 – 3.12 (1H, m), 3.33 – 3.36 (3H, m), 3.38 – 3.46 (2H, m), 3.63 – 3.67 (2H, m), 3.75 – 3.82 (3H, m), 4.06 – 4.12 (2H, m), 4.13 – 4.19 (2H, m), 4.37 – 4.44 (1H, m), 4.67 – 4.75 (1H, m), 4.76 – 4.81 (1H, m), 4.91 – 4.98 (1H, m), 6.37 (2H, s), 6.81 – 6.86 (1H, m), 6.86 – 6.93 (1H, m), 7.05 – 7.12 (1H, m), 7.17 – 7.25 (1H, m), 7.28 – 7.32 (1H, m), 7.4 – 7.46 (3H, m), 7.52 (1H, s), 7.57 (2H, d), 7.62 (1H, d), 7.93–7.97 (1H, m), 10.28 (1H, s), 14.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 830.3.

EXAMPLE 407:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



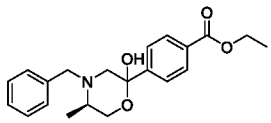
[2958] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 65e (15.3 mg, 0.04 mmol) and Intermediate 405h (30.0 mg, 0.04 mmol). After completion of the reaction, the mixture was

diluted with DCM (15 mL), washed with sat. aq. Na_2CO_3 (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xselect CSH Prep Fluoro-Phenyl OBD column, 30*150 mm, 5 μm; elution gradient: 15 to 30% MeCN in water with 0.1% formic acid) gave the title compound (29.9 mg, 90%) as a white solid and formic acid salt. ^{1}H NMR (DMSO-d_6) δ 0.61 – 0.65 (2H, m), 0.85 – 0.90 (2H, m), 1.24 – 1.28 (3H, m), 1.90 – 1.94 (1H, m), 2.52 – 2.54 (3H, m), 2.55 – 2.57 (1H, m), 2.58 – 2.61 (2H, m), 2.65 – 2.71 (1H, m), 2.78 (2H, t), 3.47 – 3.54 (2H, m), 3.55 – 3.60 (2H, m), 3.60 – 3.69 (3H, m), 3.80 – 3.84 (2H, m), 4.09 – 4.21 (5H, m), 4.88 – 4.97 (3H, m), 6.49 (2H, s), 6.85 – 6.90 (2H, m), 7.21 – 7.26 (1H, m), 7.40 – 7.44 (3H, m), 7.51 – 7.57 (3H, m), 7.94 – 7.97 (1H, m), 7.99 (1H, d), 8.22 (1H, d), 8.33 (1H, s), 10.41 (1H, s), 14.08 – 14.41 (1H, m), one heteroatom-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 843.3.

EXAMPLE 408

Intermediate 408a:

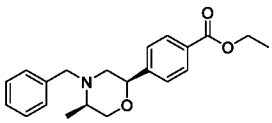
Ethyl 4-((5*R*)-4-benzyl-2-hydroxy-5-methylmorpholin-2-yl)benzoate



[2959] (*R*)-2-(Benzylamino)propan-1-ol (3.05 g, 18.4 mmol) was added to a suspension of ethyl 4-(2-bromoacetyl)benzoate (5.00 g, 18.4 mmol) and K_2CO_3 (2.80 g, 20.3 mmol) in an ice bath while keeping the internal temperature below 5 °C. The cooling bath was removed. The mixture was stirred at r.t. for 24 hours. The mixture was filtered. The filtercake was washed with DCM (50 mL). The combined filtrates were concentrated under reduced pressure to give the title compound as an orange oil, which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES$^+$) $[M+H]^+$ = 356.5.

Intermediate 408b:

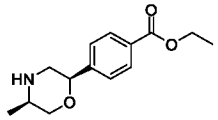
Ethyl 4-((2*R*,5*R*)-4-benzyl-5-methylmorpholin-2-yl)benzoate



[2960] TFA (23.7 mL, 307 mmol) was added to a solution of Intermediate 408a (5.46 g, 15.4 mmol) in DCM (23.7 mL). The resulting mixture was stirred at 40 °C for 1 hour. Triethylsilane (3.68 mL, 23.1 mmol) was added. The resulting orange solution was stirred at 40 °C for 4 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (3 x 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by FSC (elution gradient: 5 to 25% EtOAc in hexanes) gave the title compound (1.24 g, 24%) as an orange oil. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d), 1.30 (3H, t), 2.44 - 2.47 (1H, m), 2.52 - 2.56 (1H, m), 2.77 - 2.82 (1H, m), 3.53 - 3.62 (2H, m), 3.70 (1H, dd), 3.80 (1H, dd), 4.26 - 4.34 (2H, m), 4.58 (1H, dd), 7.21 - 7.28 (1H, m), 7.28 -7.36 (4H, m), 7.46 (2H, d), 7.90 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 340.6.

Intermediate 408c:

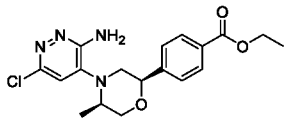
Ethyl 4-((2*R*,5*R*)-5-methylmorpholin-2-yl)benzoate



[2961] Pd/C (0.39 g, 0.18 mmol, 10 wt% Pd) was added to a solution of Intermediate 408b (1.24 g, 3.65 mmol) in methanol (12.5 mL). The resulting suspension was stirred under an atmosphere of hydrogen at 50 °C for 4 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure to give the title compound (0.816 g, 90%) as a pale orange oil, which was used for the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 1.15 (3H, d), 1.31 (3H, t), 2.76 - 2.87 (1H, m), 2.87 - 2.96 (2H, m), 3.18 - 3.40 (1H, m), 3.55 (1H, dd), 3.70 (1H, dd), 4.30 (2H, q), 4.49 (1H, dd), 7.50 (2H, d), 7.92 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 250.2.

Intermediate 408d:

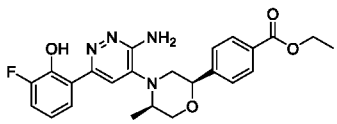
Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-chloropyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate



A solution of Intermediate 408c (125 mg, 0.50 mmol) in DMSO (1.2 mL) was added to a stirred mixture of potassium fluoride (87 mg, 1.50 mmol) and 4-bromo-6-chloropyridazine-3-amine (156 mg, 0.75 mmol) under nitrogen. The resulting suspension was stirred at 120 °C for 40 hours. After cooling to r.t., EtOAc (6 mL) and brine (6 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 6 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 50 to 100% EtOAc in hexanes) gave the title compound (150 mg, 79%) as an orange dry film. ^{1}H NMR (DMSO-d_6) δ 1.05 (3H, d), 1.33 (3H, t), 3.07 (1H, dd), 3.27 (1H, t), 3.82 (1H, d), 3.87 - 3.95 (1H, m), 4.22 (1H, dd), 4.33 (2H, q), 4.71 (1H, dd), 6.22 (2H, s), 6.92 (1H, s), 7.62 (2H, d), 7.97 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 377.2.

Intermediate 408e:

Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-(3-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate

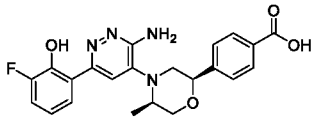


[2962] XPhos Pd G3 (112 mg, 0.13 mmol) was added to a mixture of Intermediate 408d (500 mg, 1.33 mmol), (3-fluoro-2-hydroxyphenyl)boronic acid (310 mg, 1.99 mmol), XPhos (63 mg, 0.13 mmol) and Cs_2CO_3 (1.30 g, 3.98 mmol) in 1,4-dioxane (5.0 mL) and water (0.5 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 4 hours. After cooling to r.t., the reaction mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1%NH_4HCO_3) gave the

title compound (410 mg, 68%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.33 (3H, t), 3.07 – 3.19 (1H, m), 3.48 – 3.50 (1H, m), 3.85 – 3.87(1H, m), 3.96 – 3.98 (1H, m), 4.27 – 4.40 (3H, m), 4.71 – 4.81 (1H, m), 6.53 (2H, s), 6.71 – 6.84 (1H, m), 7.11 – 7.24 (1H, m), 7.53 (1H, s), 7.61 – 7.69 (2H, m), 7.74 – 7.83 (1H, m), 7.95 – 8.04 (2H, m), 15.02 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 453.1.

Intermediate 408f:

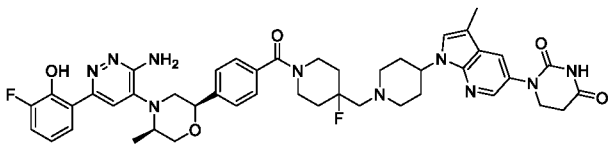
4-((2*R*,5*R*)-4-(3-Amino-6-(3-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoic acid



[2963] LiOH (106 mg, 4.42 mmol) was added to a mixture of Intermediate 408e (400 mg, 0.88 mmol) in THF (4.0 mL) and water (4.0 mL). The resulting mixture was stirred at 60 °C for 2 hours. The mixture was concentrated under reduced pressure. Water was added and the mixture was acidified with 2 M aq. HCl to pH 5. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (310 mg, 83%) as a yellow solid, which was used for the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 1.13 (3H, d), 3.17 – 3.26 (1H, m), 3.43 – 3.53 (1H, m), 3.85 – 3.88 (1H, d), 3.95 – 4.04 (1H, m), 4.27 – 4.35 (1H, m), 4.72 – 4.82 (1H, m), 6.81 – 7.00 (3H, m), 7.20 – 7.28 (1H, m), 7.54 (1H, s), 7.62 (2H, d), 7.67 (1H, d), 7.98 (2H, d), 13.55 (2H, s); *m/z* (ES$^+$) $[M+H]^+$ = 425.1.

EXAMPLE 408:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

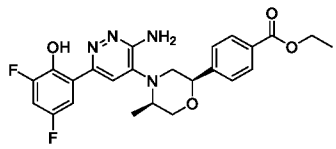


[2964] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 408f (35.0 mg, 0.08 mmol) and Intermediate 161a (36.5 mg, 0.08 mmol). After completion of the reaction, the mixture was diluted with DCM (15 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: YMC-Actus Triant C18 ExRs Column, 30*250 mm, 5μm; elution gradient: 42 to 62% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (25.7 mg, 36%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.57 – 2.02 (6H, m), 2.03 – 2.14 (2H, m), 2.25 (3H, s), 2.38 (2H, t), 2.56 – 2.70 (2H, m), 2.76 (2H, t), 2.99 – 3.17 (3H, m), 3.18 – 3.31 (2H, m) 3.44 – 3.61(2H, m), 3.72 – 3.91 (3H, m), 3.92 – 4.02 (1H, m), 4.19 – 4.44 (2H, m), 4.52 – 4.66 (1H, m), 4.67 – 4.76 (1H, m), 6.51 (2H, s), 6.71 – 6.87 (1H, m), 7.13 – 7.26 (1H, m), 7.39 – 7.63 (6H, m), 7.81 (1H, d), 7.89 (1H, d), 8.18 (1H, d), 10.39 (1H, s), 15.02 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 849.4.

EXAMPLE 409

Intermediate 409a:

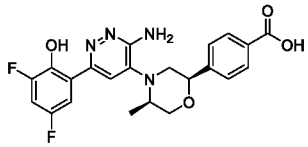
Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-(3,5-difluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate



[2965] Prepared in an analogous method to Intermediate 408e using Intermediate 408d (500 mg, 1.33 mmol) and (3,5-difluoro-2-hydroxyphenyl)boronic acid (323 mg, 1.86 mmol), stirring at 80 °C for 22 hours. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (500 mg, 80%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.33 (3H, t), 3.08 – 3.15 (1H, m), 3.48 – 3.56 (1H, m), 3.85 – 3.87 (1H, d), 3.95 – 4.01 (1H, m), 4.29 – 4.36 (3H, m), 4.73 – 4.79 (1H, m), 6.60 (2H, s), 7.16 – 7.24 (1H, m), 7.55 (1H, s), 7.64 (2H, d), 7.74 – 7.81 (1H, m), 7.99 (2H, d), 14.87 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 471.1.

Intermediate 409b:

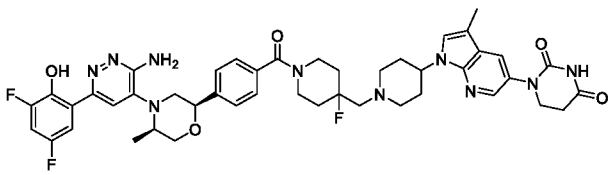
4-((2*R*,5*R*)-4-(3-Amino-6-(3,5-difluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoic acid



[2966] LiOH (127 mg, 5.31 mmol) was added to a mixture of Intermediate 409a (500 mg, 1.06 mmol) in MeOH (5 mL) and water (5 mL). The resulting mixture was stirred at 60 °C for 2 hours. The mixture was acidified to pH 5 with 1 M aq. HCl. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (360 mg, 77%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, d), 3.11 – 3.16 (1H, m), 3.47 – 3.54 (1H, m), 3.84 – 3.87 (1H, m), 3.93 – 3.99 (1H, m), 4.29 – 4.33 (1H, m), 4.72 – 4.77 (1H, m), 6.77 (2H, s), 7.22–7.33 (1H, m), 7.55 (1H, s), 7.6–7.65 (2H, m), 7.72–7.76 (1H, m), 7.97–8.00 (2H, m), 13.67 (2H, brs); *m/z* (ES$^+$) $[M+H]^+$ = 443.1.

EXAMPLE 409:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3,5-difluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

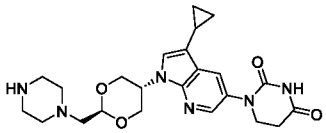


[2967] Prepared in an analogous method to EXAMPLE 406 using Intermediate 409b (40.0 mg, 0.09 mmol) and Intermediate 161a (40.0 mg, 0.09 mmol). After completion of the reaction, the mixture was diluted with DCM (10 mL), washed with sat. aq. Na_2CO_3 (3 x 5 mL) and brine (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: YMC-Actus Triant C18 ExRs Column, 30*250 mm, 5μm; elution gradient: 44 to 64% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.5% NH_4OH) gave the title compound (39.6 mg, 50%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.67 – 1.79 (2H, m), 1.82 –1.87 (3H, m), 2.05 – 2.10 (3H, m), 2.25 (3H, s), 2.33 – 2.39 (2H, m), 2.63 (2H, d), 2.73 – 2.79 (2H, m), 3.01 – 3.14 (4H, m), 3.28– 3.31 (1H, m), 3.48 – 3.59 (2H, m), 3.78 – 3.87 (3H, m), 3.91 – 3.98 (1H, m), 4.22–4.36 (2H, m), 4.56–4.66 (1H, m), 4.68–4.73 (1H, m), 6.60 (2H, s), 7.22–7.28 (1H, m), 7.45–7.50 (3H, m), 7.55–7.6 (3H, m), 7.8–7.85 (1H, m), 7.89 (1H, d), 8.18 (1H, d), 10.39 (1H, s), 14.87 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 867.3.

EXAMPLE 410

Intermediate 410a:

1-(3-Cyclopropyl-1-((2*r*,5*r*)-2-(piperazin-1-ylmethyl)-1,3-dioxan-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



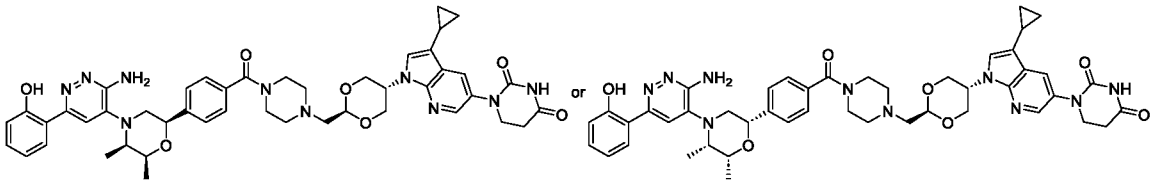
[2968] Intermediate 405g (100 mg, 0.18 mmol) was added to a mixture of DCM (3 mL) and TFA (1 mL). The resulting mixture was stirred at r.t. for 1 hour. The mixture was diluted with DCM (15 mL), washed with sat. aq. Na_2CO_3 (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 50% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (80 mg, 98%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.61 – 0.65 (2H, m), 0.85 – 0.90 (2H, m), 1.90 – 1.94 (1H, m), 2.38 – 2.43 (4H, m), 2.48 (2H, d), 2.66 – 2.70 (4H, m), 2.77 (2H, t), 3.82 (2H, t), 4.11 – 4.19 (4H, m), 4.86 (1H, t), 4.90 – 4.94 (1H, m), 7.44 (1H, s), 7.99 (1H, d), 8.22 (1H, d), 10.41 (1H, s), one nitrogen-bound proton not observed; *m/z* (ES$^+$) $[M+H]^+$ = 455.1.

EXAMPLE 410:

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

or

1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

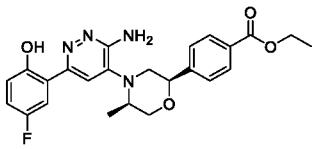


[2969] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 261g (27.8 mg, 0.07 mmol) and Intermediate 410a (30.0 mg, 0.07 mmol). After completion of the reaction, the mixture was diluted with DCM (15 mL), washed with 3% aq. NH_4OH (2 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparative HPLC (column: Xbridge Prep Phenyl OBD, 19*250 mm, 5 μm; elution gradient: 43 to 60% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (27.2 mg, 48%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.61 – 0.65 (2H, m), 0.85 – 0.89 (2H, m), 0.91 – 0.94 (3H, d), 1.13 – 1.17 (3H, d), 1.89 – 1.95 (1H, m), 2.55 – 2.62 (4H, m), 2.73 – 2.79 (2H, t), 3.04 – 3.10 (1H, m), 3.30 – 3.34 (3H, m), 3.37 – 3.44 (2H, m), 3.57 – 3.68 (2H, m), 3.78 – 3.84 (3H, m), 4.11 – 4.21 (4H, m), 4.37 – 4.43 (1H, m), 4.75 – 4.80 (1H, m), 4.88 – 4.96 (2H, m), 6.38 (2H, s), 6.79 – 6.88 (2H, m), 7.19 – 7.23 (1H, m), 7.39 – 7.44 (3H, m), 7.51 (1H, s), 7.54 – 7.59 (2H, m), 7.92 – 7.96 (1H, m), 7.98 (1H, d), 8.22 (1H, d), 10.41 (1H, s), 14.28 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 857.3.

EXAMPLE 411

Intermediate 411a:

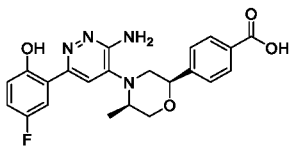
Ethyl 4-((2*R*,5*R*)-4-(3-amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoate



[2970] Prepared in an analogous method to Intermediate 408e using Intermediate 408d (500 mg, 1.33 mmol) and (5-fluoro-2-hydroxyphenyl)boronic acid (310 mg, 1.99 mmol), stirring at 80 °C for 16 hours. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (520 mg, 87%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d), 1.31 – 1.39 (3H, m), 3.06 – 3.18 (1H, m), 3.50 – 3.53 (1H, m), 3.84 – 3.88 (1H, m), 3.90 – 4.03 (1H, m), 4.27 – 4.39 (3H, m), 4.70 – 4.82 (1H, m), 6.50 (2H, s), 6.84 – 6.93 (1H, m), 7.00 – 7.10 (1H, m), 7.53 (1H, s), 7.65 (2H, d), 7.84 – 7.92 (1H, m), 8.00 (2H, d), 14.15 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 453.1.

Intermediate 411b:

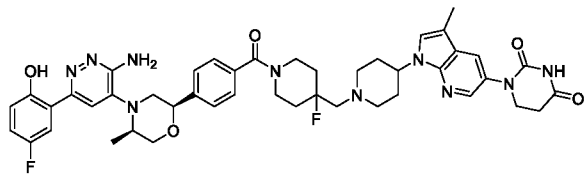
4-((2*R*,5*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoic acid



[2971] LiOH (265 mg, 11.1 mmol) was added to a mixture of Intermediate 411a (500 mg, 1.11 mmol) in water (10 mL) and MeOH (10 mL). The resulting mixture was stirred at 60 °C for 5 hours. The mixture was acidified to pH 5 with 2 M aq. HCl. A precipitate formed which was collected by filtration, washed with water, and dried *in vacuo* to give the title compound (410 mg, 87%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.18 – 1.25 (3H, m), 3.34 – 3.49 (2H, m), 3.86 – 3.89 (1H, m), 3.98 – 4.13 (1H, m), 4.28 (1H, d), 4.72 – 4.84 (1H, m), 7.02 – 7.13 (1H, m), 7.20 – 7.29 (1H, m), 7.46 – 7.53 (1H, m), 7.54 – 7.65 (3H, m), 7.97 (2H, d), four heteroatom-bound protons not observed; *m/z* (ES$^+$) $[M+H]^+$ = 425.2.

EXAMPLE 411:

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

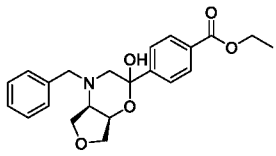


[2972] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 411b (25.0 mg, 0.06 mmol) and Intermediate 161a (26.1 mg, 0.06 mmol). After completion of the reaction, the mixture was diluted with DCM (20 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (column: YMC-Actus Triant C18 ExRs Column, 30*250 mm, 5 μm; elution gradient: 42 to 62% MeCN in water with 10 mmol/L NH_4HCO_3 and 0.05% NH_4OH) gave the title compound (11.0 mg, 22%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.07 (3H, d), 1.62 – 1.79 (2H, m), 1.81 – 1.90 (3H, m), 1.99 – 2.08 (2H, m), 2.10 – 2.14 (1H, m), 2.25 (3H, d), 2.31 – 2.42 (2H, m), 2..59 – 2.70 (2H, m), 2.76 (2H, t), 3.01 – 3.18 (4H, m), 3.22 – 3.32 (1H, m), 3.45 – 3.62 (2H, m), 3.78 – 3.88 (3H, m), 3.94 (1H, d), 4.25 – 4.37 (2H, m), 4.55 – 4.67 (1H, m), 4.68 – 4.75 (1H, m), 6.49 (2H, s), 6.84 – 6.92 (1H, m), 7.02 – 7.11 (1H, m), 7.44 – 7.53 (3H, m), 7.53 – 7.63 (3H, m), 7.88 – 7.95 (2H, m), 8.18 (1H, d), 10.41 (1H, s), 14.16 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 849.3.

EXAMPLE 412

Intermediate 412a:

Ethyl 4-((4a*R*,7a*R*)-4-benzyl-2-hydroxyhexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate

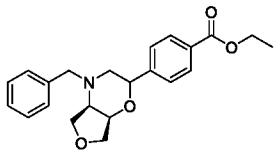


[2973] A solution of Intermediate 287a (6.54 g, 33.8 mmol) in DMF (20 mL) was added to a suspension of $NaHCO_3$ (2.98 g, 25.5 mmol), ethyl 4-(2-bromoacetyl)benzoate (8.74 g, 32.2 mmol) and potassium iodide (5.35 g, 32.2 mmol) in DMF (61 mL) over 10 minutes while keeping the internal temperature below 5 °C. The resulting mixture was stirred for 16 hours gradually increasing the temperature to 16 °C and at

r.t. for 4 hours. The mixture was diluted with EtOAc (170 mL), washed with 5% aq. LiCl (3 x 170 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as an orange gum and mixture of diastereomers (~7:1) which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES^+) $[M+H]^+$ = 384.4.

Intermediate 412b:

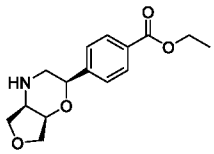
Ethyl 4-((4a*R*,7a*R*)-4-benzylhexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2974] TFA (12.4 mL, 161 mmol) was added dropwise to a solution of Intermediate 412a (12.4 g, 32.2 mmol) in DCM (110 mL) keeping the temperature below 40 °C. The resulting mixture was stirred at 40 °C for 1 hour. Methyl(phenyl)silane (6.64 mL, 48.4 mmol) was added. The resulting mixture was stirred at 40 °C for 20 hours. The mixture was cooled to 0 °C. 15% aq. K_2CO_3 (120 mL) was added slowly keeping the temperature below 20 °C. The mixture was stirred at r.t. for 1 hour. The phases were separated. The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as an orange oil and mixture of diastereomers (~7:1) which was used for the next step without further purification. *m/z* (ES^+) $[M+H]^+$ = 368.3.

Intermediate 412c:

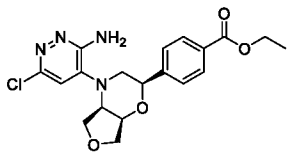
Ethyl 4-((2*R*,4a*R*,7a*R*)-hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2975] Pd/C (3.43 g, 1.61 mmol, 10 wt% Pd) was added to a solution of Intermediate 412b (11.8 g, 32.2 mmol) in MeOH (120 mL). The resulting suspension was stirred at 50 °C under an atmosphere of hydrogen for 4 hours. After cooling to r.t., the mixture was filtered through a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure. The residue was dissolved in CPME (60 mL) at 95 °C, cooled to r.t. over 1 hour, and stirred at r.t. for 3 hours and at 0 °C for 1 hour. A precipitate formed which was collected by filtration, washed with cold CPME (10 mL), and dried under a flow of nitrogen to give the title compound (5.66 g, 63% over 3 steps) as a white solid and single diastereomer. ^1H NMR (DMSO-d_6) δ 1.31 (3H, t), 2.59 - 2.68 (1H, m), 2.71 - 2.77 (1H, m), 2.82 (1H, br s), 3.41 - 3.48 (1H, m), 3.62 (1H, t), 3.72 - 3.82 (2H, m), 3.92 (1H, dd), 4.05 (1H, t), 4.30 (2H, q), 4.48 (1H, dd), 7.47 (2H, d), 7.93 (2H, d); *m/z* (ES^+) $[M+H]^+$ = 278.2.

Intermediate 412d:

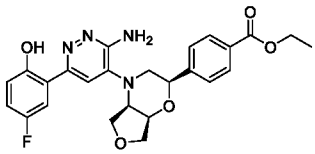
Ethyl 4-((2*R*,4a*R*,7a*R*)-4-(3-amino-6-chloropyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2976] A 2 dram vial was charged with Intermediate 412c (300 mg, 1.08 mmol), potassium fluoride (126 mg, 2.16 mmol) and 4-bromo-6-chloropyridazin-3-amine (676 mg, 3.25 mmol). DMSO (2.2 mL) was added. The resulting mixture was stirred at 120 °C for 30 hours. After cooling to r.t., the mixture was poured into water–brine (4:1, 50 mL). A precipitate formed which was collected by filtration, washed with water (3 x 20 mL), and dried in vacuo. The solids were suspended in DCM and filtered through a pad of Celite with DCM. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% acetone in hexanes) gave the title compound (346 mg, 79%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t), 3.21 (1H, br d), 3.28 - 3.39 (1H, m), 3.55 (1H, t), 3.81 - 3.93 (2H, m), 3.98 (1H, dd), 4.28 - 4.39 (3H, m), 4.52 - 4.59 (1H, m), 4.80 (1H, br d), 6.34 (2H, s), 7.08 (1H, s), 7.60 (2H, d), 7.98 (2H, d); *m/z* (ES$^+$) $[M+H]^+$ = 405.3.

Intermediate 412e:

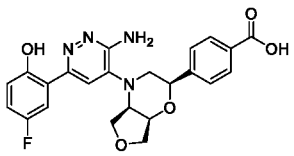
Ethyl 4-((2*R*,4a*R*,7a*R*)-4-(3-amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoate



[2977] A 40 mL vial was charged with Intermediate 412d (330 mg, 0.82 mmol), CPhos Pd G3 (33 mg, 0.04 mmol), CPhos (18 mg, 0.04 mmol), K_2CO_3 (338 mg, 2.45 mmol) and (5-fluoro-2-hydroxyphenyl)boronic acid (191 mg, 1.22 mmol). 1,4-Dioxane (7.3 mL) and water (0.8 mL) were added. The vial was evacuated and back-filled with argon (3x). The resulting mixture was stirred at 90 °C for 2 hours. After cooling to r.t., sat. aq. $NaHCO_3$ (20 mL) was added. The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RPC (elution gradient: 30 to 90% MeCN in water with 0.1% NH_4OH) and FSC (elution gradient: 0 to 80% acetone in hexanes) gave the title compound (300 mg, 77%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t), 3.23 (1H, br d), 3.47 - 3.57 (2H, m), 3.83 - 3.96 (2H, m), 3.99 - 4.05 (1H, m), 4.32 (2H, q), 4.37 - 4.47 (1H, m), 4.63 (1H, t), 4.83 (1H, br d), 6.59 (2H, s), 6.87 (1H, dd), 7.06 (1H, td), 7.54 - 7.67 (3H, m), 7.86 (1H, dd), 7.99 (2H, d), 14.00 (1H, s); *m/z* (ES$^+$) $[M+H]^+$ = 481.3.

Intermediate 412f:

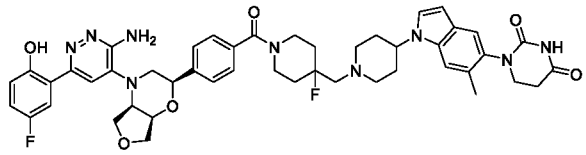
4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoic acid



[2978] 1.5 M aq. NaOH (1.23 mL, 1.83 mmol) was added to a solution of Intermediate 412e (295 mg, 0.61 mmol) in EtOH (3.7 mL). The resulting mixture was stirred at 60 °C for 90 minutes. The mixture was concentrated under reduced pressure. Water (5 mL) was added. 6 M aq. HCl (0.65 mL) was added dropwise while stirring. A precipitate formed which was collected by filtration, washed with water (2 x 10 mL), and dried in vacuo to give the title compound (224 mg, 81%) as a yellowish solid. ^{1}H NMR (DMSO-d_6) δ 3.26 (1H, br d), 3.48 - 3.59 (2H, m), 3.87 (1H, d), 3.89 - 3.96 (1H, m), 4.01 (1H, dd), 4.37 - 4.47 (1H, m), 4.57 - 4.68 (1H, m), 4.82 (1H, br d), 6.73 (2H, br s), 6.86 - 6.92 (1H, m), 7.08 (1H, td), 7.59 (2H, d), 7.63 (1H, s), 7.81 (1H, br dd), 7.97 (2H, d), 13.34 (2H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 453.3.

EXAMPLE 412:

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



[2979] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 412f (20.0 mg, 0.04 mmol) and Intermediate 392a (19.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0.1% FA in water, then 30 to 90% MeCN in water with 0.1% NH_4OH) gave the title compound (26.9 mg, 68%) as a white solid following lyophilization. ^{1}H NMR (DMSO-d_6) δ 1.60 - 2.04 (8H, m), 2.27 (3H, s), 2.41 (2H, br t), 2.57 - 2.80 (4H, m), 3.04 (2H, br d), 3.08 - 3.28 (3H, m), 3.35 - 3.62 (4H, m), 3.69 - 3.78 (1H, m), 3.85 (1H, br d), 3.93 (1H, br t), 3.98 - 4.05 (1H, m), 4.12 - 4.35 (2H, m), 4.38 - 4.45 (1H, m), 4.58 - 4.66 (1H, m), 4.78 (1H, br d), 6.39 (1H, d), 6.59 (2H, br s), 6.87 (1H, dd), 7.06 (1H, td), 7.38 - 7.42 (2H, m), 7.43 - 7.48 (3H, m), 7.55 (2H, br d), 7.63 (1H, s), 7.88 (1H, dd), 10.23 (1H, s), 14.01 (1H, br s); *m/z* (ES$^+$) $[M+H]^+$ = 876.4.

SMARCA2, SMARCA4 and PBRM1 Degradation Assays

[2980] A high throughput immunofluorescence assay was used to measure changes in SMARCA2, SMARCA4 and PBRM1 protein levels upon compound treatment. 5,000 Hela cells were seeded into each well in a 384-well plate in 30 µL RPMI+10% FBS. Cells were incubated with increasing concentrations of compounds (10-point dose response from 1 nM to 31.7 µM, 0.3% final DMSO) for 24h before being fixed for analysis. Cells were incubated with paraformaldehyde (2% final concentration) for 20 minutes at r.t. The plate was then aspirated using a Biotek plate washer before 30 µL ice-cold MeOH was added to

permeabilize the cells. After 5 minutes incubation in MeOH at r.t. the plate was washed once with PBS, and incubated with block solution (PBS+1%BSA+0.3% Triton-X100) for 1h at r.t. After blocking, the plate was again aspirated and 20 µL primary antibody dilution (SMARCA2, cell signaling #11966, 1:1000; SMARCA4, cell signaling #52251, 1:1000; PBRM1, Bethyl A700-019, 1:200 diluted in blocking solution) was added into each well and the plate was left at r.t. for incubation for 2h. The plate was then washed and aspirated, and 20 µL secondary antibody dilution (goat-anti-rabbit, Invitrogen #A-11034; goat-anti-mouse, Invitrogen #A-11032; Hoechst 33342; 1: 1000 in block solution) was added and the plate was incubated at r.t. in the dark for 1h. After a final wash, the plate was read on the Operetta CLS imager using the appropriate channels. The percentage of degradation was calculated as $F_{Compound}/F_{DMSO} \times 100\%$ (F:fluorescence intensity).

Endogenous SALL4 Degradation Assay:

[2981] The neuroblastoma cell line, Kelly, was used to monitor the degradation of the endogenous SALL4 protein using a SDS-PAGE assay. Kelly cells were grown in RPMI 1640 medium supplemented with 10% fetal calf serum. Cells were splitted every 4 days at 1/10 ratio. Cells with less than 10 passages were used for the experiments.

[2982] For the experiment, the cells were seeded in 12 well plates at 500,000 cells per well in a final volume of 1mL of medium. The next day, the cells were dosed at 1µM and/or 10µM with the different compounds. After 24h of treatment, the cells were lysed in RIPA buffer plus protease cocktail inhibitors (100µL/well) for 20min on ice. Lysates were collected and spinned at 10000*g* for 5min. The supernatant was collected and mix with sample buffer 4X containing a sample reducing agent (25µL), then boil 5min at 85c. Lysates was stored at -20°C.

[2983] For the SDS-PAGE analysis, samples were loaded on precast gel (4-12%), runned at 150V constant on ice and transferred into membranes using P0 program from the fast transfer iBlot2 device (Thermofischer). Membranes were then incubated in LI-COR blocking solution (Intercept) for 30min, then with primary antibodies overnight at 4°C. The membranes were then washed for a minimum of 30min with TBS-tween 0.1% and incubated with secondary antibodies for LI-COR detection (1h diluted at 1/10000). After several washes in PBS-Tween 0.1%, the membranes were analyzed by the Li-COR Odyssey CLx imaging system for protein level detection. GAPDH was used as loading control.

List of reagents

Reagent	Source	Catalogue number
Kelly cells	Sigma-Aldrich	92110411
RPMI 1640 with Glutamine	Thermofischer	11875093
RIPA Lysis and Extraction Buffer	Thermofischer	89900
Halt™ Protease Inhibitor Cocktail (100X)	Thermofischer	78430
NuPAGE™ LDS Sample Buffer (4X)	Thermofischer	NP0007
NuPAGE™ Sample Reducing Agent (10X)	Thermofischer	NP0004
NuPAGE™ 4-12% Bis-Tris Protein Gels, 1.5 mm, 15-well	Thermofischer	NP0336BOX
iBlot™ 2 Transfer Stacks, nitrocellulose, regular size	Thermofischer	IB23001

Reagent	Source	Catalogue number
Intercept™ Blocking Buffer	LI-COR	927-60001
SALL4 antibody	Proteintech	24500-1-AP
GAPDH antibody	Proteintech	60004-1-Ig
IRDye™ 800CW Donkey anti-Rabbit IgG Secondary Antibody	LI-COR	926-32213
IRDye™ 800CW Donkey anti-Mouse IgG Secondary Antibody	LI-COR	926-32212

Endogenous Ikaros 1 (IKZF1) Degradation Assay:

[2984] The leukemia cell line, NB4, was used to monitor the degradation of the endogenous IKZF1 protein using a SDS-PAGE assay. NB4 cells were grown in RPMI 1640 medium supplemented with 10% fetal calf serum. Cells were then split every 3 days at 1/10 ratio. Cells with less than 10 passages were used for the experiments.

[2985] For the experiment, the cells were seeded in 12 well plates at 1,000,000 cells per well in a final volume of 1mL of medium. The next day, the cells were dosed at 1µM and/or 10µM with the different compounds. After 24h of treatment, the cells were lysed in RIPA buffer plus protease cocktail inhibitors (100µL/well) for 20 minutes on ice. Lysates were then collected and spun at 10000*g* for 5 minutes. The supernatant was then collected and mixed with sample buffer 4X containing a sample reducing agent (25µL), then boiled for 5 minutes at 85°C. Lysates were stored at -20°C. For the SDS-PAGE analysis, samples were loaded on precast gel (4-12%), run at 150V constant on ice and transferred into membranes using P0 program from the fast transfer iBlot2 device (Thermofischer). Membranes were then incubated in LI-COR blocking solution (Intercept) for 30 minutes, then with primary antibodies overnight at 4°C. The membranes were then washed for a minimum of 30 minutes with TBS-tween 0.1% and incubated with secondary antibodies for LI-COR detection (1h diluted at 1/10000). After several washes in PBS-Tween 0.1%, the membranes are analyzed by the Li-COR Odyssey CLx imaging system for protein level detection. GAPDH is used as loading control.

List of reagents

Reagent	Source	Catalogue number
NB4 cells	DSMZ	ACC-207
RPMI 1640 with Glutamine	Thermofischer	11875093
RIPA Lysis and Extraction Buffer	Thermofischer	89900
Halt™ Protease Inhibitor Cocktail (100X)	Thermofischer	78430
NuPAGE™ LDS Sample Buffer (4X)	Thermofischer	NP0007
NuPAGE™ Sample Reducing Agent (10X)	Thermofischer	NP0004
NuPAGE™ 4-12% Bis-Tris Protein Gels, 1.5 mm, 15-well	Thermofischer	NP0336BOX
iBlot™ 2 Transfer Stacks, nitrocellulose, regular size	Thermofischer	IB23001
Intercept™ Blocking Buffer	LI-COR	927-60001
IKZF1 antibody	Cell Signaling	14859
GAPDH antibody	Proteintech	60004-1-Ig
IRDye™ 800CW Donkey anti-Rabbit IgG Secondary Antibody	LI-COR	926-32213
IRDye™ 800CW Donkey anti-Mouse IgG Secondary Antibody	LI-COR	926-32212

Clearance Assay: Metabolic Stability Assessment using human liver microsomes (HLM)

[2986] The stability of control (phenacetin, verapamil, diclofenac, imiprimine, benzydamine and metoprolol) and test compounds was evaluated using 1 mg/mL HLM (150 mixed gender donor pool) containing 1 mM NADPH, and 1 μM test compound/control. 222.5 μL of HLM mixture containing 1.12 mg/mL HLM in phosphate buffer pH 7.4 was mixed with 25 μL 10 mM NADPH and pre-warmed at 37°C for 8 minutes prior to addition of 2.5 μL of 100 μM test compound/control prepared in DMSO. Aliquots (20 μL) were removed at 0.5, 5, 10, 15, 20 and 30 minutes and quenched with 100 μL of cold stop solution (100% ACN with 100 nM of alprazolam, caffeine and tolbutamide as internal standards). Samples were centrifuged for 20 minutes at 4,000 rpm and 4°C and a 40 μL aliquot of supernatant was mixed with 160 μL pure water for LC-MS/MS analysis. Each incubation was conducted in singlicate. Peak areas were determined from extracted ion chromatograms and percent (%) parent remaining was calculated from peak area of test compound/control. The slope value, k, was determined by linear regression of the natural logarithm of percent parent remaining vs. incubation time curve, using Microsoft Excel. The in vitro half-life was calculated from –(natural logarithm (ln) of 2 / k), and converted to *in vitro* intrinsic clearance using Equation 1.

$$\boldsymbol{in\ vitro\ CLint} = \frac{ln2}{t_{1/2}} \times \frac{\boldsymbol{incubation\ volume\ (\mu L)}}{\boldsymbol{protein\ concentration\ (mg)}} \quad \text{Equation 1}$$

Human Hepatocyte Clint assay

[2987] Human Hepatocyte CLint. Metabolism is initiated by addition of compound to the hepatocyte incubation giving a compound concentration of 1 μM with 1 X 10^6 hepatocytes/ml. Samples of the incubation at 37°C are taken regularly over 120 min into cold acetonitrile (5:1) containing internal standards. Samples are then centrifuged and 40 μl of supernatant is diluted with 160 μl of water (30 μl of supernatant is diluted with 180 μl water for human hepatocytes) before analysis by LCMSMS. The natural log of % parent remaining at each time point is plotted against time to half-life and subsequently Cl_{int}.

SALL-4 and AIOLOS Luciferase degrader assays

[2988] *Cell lines:* HiBiT-IKZF3 MM.1S cells (obtained from Promega) were grown in RPMI-1640 (Gibco), supplemented with 10% FBS and GlutaMAX (Gibco). HiBiT-SALL4 SK-N-DZ cells (obtained from Promega) were grown in DMEM (high glucose) (Gibco), supplemented with 10% FBS, GlutaMAX (Gibco), Sodium Pyruvate (1mM) (Gibco) and 1% Non-essential Amino Acids (NEAA) (Sigma).

[2989] *HiBiT assay:* Compound assay-ready-plates were prepared using acoustic dispensing (Echo), generating 12-point, half-log dose-responses with a top concentration of 30μM. Wells were backfilled with DMSO to 0.3% DMSO. DMSO and Pomalidomide (30 μM) were used as spot controls across the plates to define the scale range. HiBiT-IKZF3 MM.1S cells and HiBiT-SALL4 SK-N-DZ cells were started from cryovials into their respective media and dispensed onto compound assay-ready-plates at either 3000 (SALL4) or 20.000 (AIOLOS) cells/well using a multidrop combi. Plates were subsequently spun for 1 min

at 300xg and incubated for 6h at 37°C, 5% CO2 in a humidified incubator. HiBiT Lytic Detection Reagents (Promega) was prepared according to manufacturer's instructions, and 5 µl/well of the lytic detection mix was added to each plate using a multidrop combi. Plates were spun for 1 min at 300g, placed on an orbital shaker at 300rpm for 30 min before reading luminescence on a Envision-1 plate reader according to manufacturer's instructions.

[2990] *Data analysis:* Raw signals were analysed in Genedata Screener using 'Neutral Controls minus Inhibitors' method and dose-response curves were drawn using 'Smart Fit' condensing method to calculate DC50 values. Compounds were accepted as active when ≥ 30% response was observed.

[2991] Potential cytotoxicity of PROTACs reviewed in alternative cell screen in parallel with degradation assays, enabling consolidation of whether IC50s generated in degradation assays represent true activity or whether it is inconclusive due to potential cytotoxicity associated with PROTACs.

[2992] The SMARCA2 degradation of representative Compounds of the Disclosure of provided in Table 1.

Table 1

Example No.	SMARCA2 DC_{50} (µM)	SMARCA2 D_{max} (%)
1	0.112	76.8
2	0.0171	82.6
3	0.0433	73.7
4	0.0876	71.1
5	0.0402	78.6
6	0.126	73.0
7	0.0523	76.6
8	0.455	65.0
9	0.0402	78.7
10	0.00405	83.2
11	0.0267	57.1
12	0.0255	75.5
13	0.242	72.2
14	0.147	68.3
15	0.0624	78.3
16	0.0936	71.4
17	0.0312	77.2
18	0.574	59.2
19	1.01	27.7
20	0.022	90.9
21	0.022	93.8
22	0.003	84.0

23	0.005	88.2
24	0.053	87.1
25	0.003	82.9
26	0.051	86.3
27	0.0188	86.9
28	0.015	85.3
29	0.012	87.1
30	0.0183	83.9
31	0.023	83.7
32	0.041	84.4
33	0.025	78.0
34	0.031	81.7
35	0.090	81.3
36	0.039	81.0
37	0.073	83.5
38	0.013	83.7
39	0.089	81.9
40	0.053	78.8
41	0.023	77.1
42	0.157	73.5
43	0.091	75.4
44	0.158	75.3
45	0.033	77.4
46	0.015	80.2
47	0.0241	77.0
48	0.084	74.6
49	0.007	73.5
50	0.083	70.8
51	0.182	72.5
52	0.107	72.2
53	0.094	66.5
54	0.199	75.6
55	0.083	65.8
56	0.149	67.9
57	0.038	69.4
58	0.127	70.3
59	0.073	69.4
60	0.222	63.4
61	0.002	90.4

62	0.017	83.8
63	0.041	80.6
64	0.086	77.7
65	0.004	79.3
66	0.004	88.8
67	0.0222	87.9
68	0.015	88.7
69	0.007	80.1
70	0.091	86.1
71	0.015	84.4
72	0.044	80.3
73	0.003	84.4
74	0.136	79.1
75	0.003	81.3
76	0.006	80.4
77	0.006	78.3
78	0.044	80.4
79	0.196	80.1
80	0.007	76.0
81	0.015	75.8
82	0.0140	78.0
83	0.003	79.2
84	0.091	74.9
85	0.004	77.6
86	0.022	78.2
87	0.017	73.6
88	0.023	72.1
89	0.033	74.2
90	0.277	69.6
91	0.043	72.7
92	0.165	70.3
93	0.016	84.6
94	0.007	80.9
95	0.100	74.7
96	0.239	77.8
97	0.286	74.7
98	0.070	79.3
99	0.022	87.1
100	0.029	85.9

101	0.050	74.6
102	0.052	83.6
103	0.012	85.0
104	0.109	80.5
105	0.025	74.5
106	0.192	62.1
107	0.003	87.9
108	0.007	85.0
109	0.012	75.7
110	0.121	76.3
111	0.171	74.8
112	0.022	78.1
113	0.031	75.6
114	0.121	79.0
115	0.065	71.5
116	0.051	77.2
117	0.204	72.9
118	0.023	87.9
119	0.008	84.6
120	0.022	88.3
121	0.043	72.6
122	0.169	71.1
123	0.576	66.2
124	0.034	70.5
125	0.045	88.3
126	0.059	88.4
127	0.017	82.2
128	0.043	79.4
129	0.351	80.6
130	0.021	76.0
131	0.074	72.6
132	0.003	85.9
133	0.022	77.9
134	0.001	75.6
135	0.019	78.0
136	0.040	76.2
137	0.026	73.7
138	0.025	86.3
139	0.094	84.5

140	0.073	72.5
141	0.045	74.0
142	0.073	70.1
143	0.006	66.9
144	0.023	85.0
145	0.040	88.2
146	0.034	85.1
147	0.180	72.5
148	0.173	70.5
149	0.034	77.4
150	0.085	72.5
151	0.063	82.2
152	0.015	84.5
153	0.018	86.4
154	0.082	83.1
155	0.008	83.1
156	0.188	81.7
157	0.134	81.5
158	0.044	87.3
159	0.049	83.6
160	0.023	82.7
161	0.038	86.2
162	0.024	80.9
163	0.021	83.9
164	0.016	84.7
165	0.004	83.3
166	0.024	84.4
167	0.075	83.6
168	0.018	83.0
169	0.020	80.1
170	0.022	81.0
171	0.066	78.6
172	0.051	69.6
173	0.002	85.6
174	0.069	77.2
175	0.222	55.9
176	0.078	80.3
177	0.033	89.9
178	0.003	87.9

179	0.008	88.5
180	0.028	89.6
181	0.020	87.9
182	0.069	86.0
183	0.012	84.8
184	0.010	82.8
185	0.077	63.9
186	0.037	81.1
187	0.041	77.8
188	0.020	69.8
189	0.004	87.1
190	0.006	82.7
191	0.002	82.3
192	0.016	74.8
193	0.063	72.9
194	0.024	70.0
195	0.028	72.5
196	0.014	72.4
197	0.010	88.3
198	0.032	80.8
199	0.044	77.7
200	0.028	80.6
201	0.018	74.0
202	0.097	76.6
203	0.030	87.5
204	0.056	85.6
205	0.021	86.9
206	0.002	88.6
207	0.045	85.8
208	0.035	79.9
209	0.012	73.6
210	0.010	73.2
211	0.077	73.1
212	0.012	76.2
213	0.014	73.9
214	0.037	66.9
215	0.166	75.5
216	0.029	77.5
217	0.025	83.5

218	0.021	82.5
219	0.002	82.9
220	0.014	84.4
221	0.032	82.3
222	0.023	83.2
223	0.236	72.0
224	0.015	63.5
225	0.050	77.6
226	0.014	84.0
227	0.012	88.5
228	0.017	88.8
229	0.015	87.6
230	0.016	85.0
231	0.023	87.0
232	0.030	83.7
233	0.026	79.8
234	0.020	89.6
235	0.015	84.5
236	0.019	90.5
237	0.073	73.6
238	0.298	73.2
239	0.0099	85.6
240	0.023	89.2
241	0.043	87.3
242	0.067	79.7
243	0.0062	88.2
244	0.036	81.0
245	0.065	73.8
246	0.242	81.2
247	0.053	83.9
248	0.038	65.3
249	0.071	81.5
250	0.015	86.3
251	0.459	69.6
252	0.424	66.6
253	0.289	68.0
254	0.236	68.1
255	0.133	71.6
256	0.0030	82.5

257	0.0079	80.5
258	0.019	87.6
259	0.022	79.2
260	0.035	77.3
261	0.014	92.7
262	0.017	88.1
263	0.019	89.8
264	0.021	90.9
265	0.019	91.0
266	0.033	86.1
267	0.0085	92.2
268	0.0199	85.8
269	0.018	85.7
270	0.035	83.5
271	0.016	80.8
272	0.017	83.0
273	0.022	90.6
274	0.0079	90.4
275	0.025	89.9
276	0.054	82.3
277	0.033	88.9
278	0.025	83.4
279	0.017	81.0
280	0.023	80.3
281	0.015	92.2
282	0.025	90.2
283	0.043	85.7
284	0.022	82.3
285	0.033	90.9
286	0.038	82.9
287	0.035	85.0
288	0.012	89.3
289	0.041	78.6
290	0.033	86.1
291	0.035	81.2
292	0.133	79.8
293	0.021	89.6
294	0.030	89.8
295	0.029	85.0

296	0.080	84.3
297	0.036	75.5
298	0.068	84.0
299	0.055	86.9
300	0.119	79.1
301	0.022	89.9
302	0.064	85.2
303	0.016	91.1
304	0.039	87.9
305	0.020	87.6
306	0.179	75.0
307	0.042	84.6
308	0.038	84.4
309	0.100	68.5
310	0.0073	89.5
311	0.010	89.2
312	0.029	68.8
313	0.025	66.4
314	0.018	91.1
315	0.0011	90.7
316	0.0032	84.0
317	0.0055	76.7
318	0.019	82.1
319	0.017	87.7
320	0.029	88.0
321	0.035	81.4
322	0.034	80.9
323	0.0018	92.8
324	0.053	76.2
325	0.108	64.4
326	0.041	83.5
327	0.062	80.8
328	0.015	82.8
329	0.038	70.3
330	0.088	74.4
331	0.039	63.6
332	0.032	83.3
333	0.015	81.4
334	0.003	95.6

335	0.011	91.3
336	0.028	83.6
337	0.005	60.4
338	0.023	85.8
339	0.033	69.9
340	0.026	86.4
341	0.027	84.2
342	0.012	85.1
343	0.024	84.0
344	0.033	74.3
345	0.073	68.2
346	0.013	77.8
347	0.018	85.2
348	0.014	94.0
349	0.009	90.4
350	0.021	89.3
351	0.011	89.0
352	0.019	86.7
353	0.002	96.1
354	0.011	89.6
355	0.003	93.5
356	0.010	87.4
357	0.011	92.4
358	0.010	89.0
359	0.014	90.2
360	0.006	89.8
361	0.017	91.5
362	0.013	89.6
363	0.009	90.7
364	0.017	88.4
365	0.008	91.2
366	0.014	89.9
367	0.011	87.1
368	0.028	86.5
369	0.021	84.8
370	0.023	87.3
371	0.035	89.0
372	0.010	86.6
373	0.039	84.1

374	0.021	86.1
375	0.026	85.6
376	0.008	85.1
377	0.032	86.3
378	0.062	85.1
379	0.142	81.4
380	0.037	81.0
381	0.028	79.7
382	0.045	74.8
383	0.025	73.1
384	0.028	71.6
385	0.054	66.4
386	0.208	58.6
387	0.024	82.9
388	0.030	86.2
389	0.008	74.6
390	0.026	81.8
391	0.021	78.2
392	0.021	81.2
393	0.004	90.4
394	0.026	91.2
395	0.031	88.2
396	0.028	86.8
397	0.029	85.9
398	0.072	82.6
399	0.015	90.3
400	0.036	85.1
401	0.054	78.5
402	0.031	76.1
403	0.106	78.7
404	0.014	88.1
405	0.011	85.4
406	0.044	82.2
407	0.016	79.9
408	0.028	76.2
409	0.083	76.8
410	0.018	90.6
411	0.021	83.8
412	0.030	77.6

[2993] The SMARCA4 and PBRMI degradation of representative Compounds of the Disclosure of provided in Table 2.

Table 2

Example No.	SMARCA4 DC_{50} (μM)	SMARCA4 D_{max} (%)	PBRM1 DC_{50} (μM)	PBRM1 D_{max} (%)
3	>3.33	20.4	>3.33	48.4
4	>1.01	11.5	3.33	39.0
8	>1.01	7.5	3.33	31.0
12	>31.7	22.9	0.335	57.8
16	>1.01	19.8	>0.319	48.1
26	>1.01	11.1	0.140	62.4
31	>1.009	33.2	0.147	56.6
32	>31.67	26.2	0.318	72.3
33	>31.67	19.3	>0.319	38.9
34	>1.009	22.5	0.153	61.2
38	>0.319	29.7	0.0530	72.6
40	>1.009	26.3	>1.009	48.7
44	>1.009	22.5	>3.333	45.2
49	>0.106	10.0	>0.106	17.3
51	>1.009	17.6	>1.009	35.1
52	>3.333	9.2	0.310	55.9
53	>31.67	8.7	0.522	53.5
54	>3.333	20.1	>10.0	40.6
55	>1.009	4.8	>1.009	20.3
60	>31.67	9.9	0.642	66.9
62	>0.319	31.4	0.231	53.2
77	>0.319	20.6	>0.319	24.9
78	>1.009	23.5	>1.009	46.4
84	>3.333	19.3	>31.67	39.6
86	>0.319	26.1	0.361	57.0
91	>1.009	3.6	0.223	58.0
92	>1.009	4.3	>3.333	38.5
95	>0.319	7.7	>1.009	33.1

96	>10.0	22.6	>1.009	40.9
102	>1.009	30.9	0.613	57.6
113	>0.319	19.0	0.115	58.3
114	>3.333	23.3	0.261	72.3
122	>3.333	9.1	0.927	48.3
123	>3.333	11.4	1.209	53.4
130	>1.009	9.5	>1.009	46.6
131	>3.333	20.6	>3.333	48.5
136	>0.319	18.2	0.179	59.4
137	>1.009	9.6	>1.009	36.6
140	>31.67	11.0	>3.333	37.5
141	>3.333	9.3	>0.319	49.9
142	1.009	11.1	0.139	62.4
147	>31.67	14.1	>31.67	28.8
149	1.009	22.1	0.319	40.2
150	31.67	4.1	1.009	33.4
153	0.319	22.8	0.319	48.6
154	3.333	26.5	3.333	46.2
155	0.106	16.4	0.036	72.3
159	1.009	20.7	0.146	72.3
161	1.009	34.8	0.999	50.8
162	1.009	34.8	1.009	32.4
163	1.009	30.5	1.009	23.2
164	0.106	32.5	0.319	46.0
171	1.009	21.1	0.319	39.7
172	3.333	7.7	0.319	36.3
182	3.333	35.1	0.779	57.1
185	1.009	10.9	0.139	67.4
186	0.319	13.9	0.090	70.6
187	0.319	25.6	0.124	67.7
195	0.319	9.3	0.072	64.1
197	0.319	33.9	0.189	53.3
198	1.009	27.0	1.009	50.0

200	0.319	30.3	0.046	59.5
201	0.319	14.4	0.106	38.1
208	0.319	18.4	0.050	53.4
211	0.319	14.1	0.319	49.6
215	31.67	2.0	1.009	29.4
216	3.333	14.4	0.274	61.1
218	1.009	17.4	0.319	36.2
220	0.319	21.2	0.030	74.4
221	1.009	19.0	0.087	66.6
222	3.333	22.9	3.333	47.2
223	31.670	2.2	3.333	29.7
226	0.319	29.1	0.072	80.2
227	0.319	33.7	0.018	84.3
228	0.319	25.4	0.283	51.6
229	0.319	32.2	0.008	85.1
230	0.319	24.0	0.031	79.2
232	1.009	32.3	0.319	45.9
233	1.009	15.0	0.106	46.0
235	>31.67	13.2	0.144	57.0
242	>1.009	18.3	>1.009	34.9
245	>1.009	15.4	>1.009	31.4
246	>3.333	52.5	0.590	69.4
247	>3.333	29.6	0.559	59.7
249	>3.333	12.4	0.236	74.9
250	>0.319	13.2	0.159	65.4
252	>31.67	15.1	>1.009	42.0
253	>1.009	9.8	0.918	51.3
259	>31.67	6.1	>0.319	50.2
260	>0.319	12.3	0.433	52.5
261	>1.009	25.9	0.030	81.3
266	>1.009	14.6	0.087	80.8
269	>1.009	30.8	0.170	60.2
270	>1.009	21.5	0.129	61.3

271	>0.106	28.7	>0.319	38.1
272	>0.319	24.2	>0.319	37.2
273	>1.009	31.1	0.040	91.7
275	>31.67	15.7	>1.009	49.2
276	>31.67	3.5	>10.0	49.4
277	>31.67	3.8	1.16	56.2
278	>0.319	26.2	>0.319	45.3
281	>0.319	40.3	0.134	70.5
282	>1.009	27.9	0.063	74.8
283	>10	30.9	0.211	70.0
285	>31.67	14.9	0.360	61.7
287	>31.67	2.9	>1.009	27.4
289	>1.009	17.5	>0.319	51.8
290	>31.67	7.5	0.801	54.9
291	>1.009	13.5	>1.009	38.8
292	>31.67	23.7	>31.67	32.7
293	>1.009	8.8	0.074	84.5
294	>1.009	35.4	0.649	53.5
296	>31.67	0.5	>1.009	36.7
297	>31.67	8.8	0.617	49.1
298	>31.67	32.3	0.550	60.7
299	>31.67	0.4	>1.009	48.5
300	>1.009	17.5	0.504	53.8
301	>1.009	39.7	0.446	61.2
302	>31.67	33.7	0.226	70.6
303	>1.009	12.9	>1.009	46.8
304	>1.009	23.9	0.584	55.5
306	>3.333	12.4	0.342	67.0
307	>1.009	17.1	>1.009	43.5
309	>31.67	7.9	>3.333	20.2
314	>0.319	34.6	0.061	72.7
321	>1.009	18.3	>0.319	35.0
324	>1.009	16.6	>31.67	25.4

329	>0.319	19.8	>1.009	20.1
330	>31.67	2.5	>0.319	41.6
331	>31.67	12.5	>0.319	26.5
332	>3.333	11.4	0.118	68.0
333	>0.319	13.7	0.255	49.1
339	>31.67	6.5	>0.319	37.8
340	>31.67	22.4	>0.319	47.4
341	>31.67	15.1	0.104	75.3
342	>31.67	2.4	0.044	65.1
343	>1.009	12.2	>3.333	49.7
344	>1.009	14.4	>1.009	38.9
346	>31.67	1.2	>0.319	37.0
347	>31.67	10.9	0.075	63.6
352	>0.319	15.9	>1.009	29.2
354	>0.319	27.2	>1.009	33.2
357	>1.009	22.0	0.024	93.3
358	>31.67	-0.7	>0.319	44.5
359	>3.333	31.3	0.044	72.5
360	>1.009	15.2	>0.319	42.2
361	>3.333	26.6	0.030	77.8
362	>1.009	28.1	0.071	59.6
364	>1.009	15.2	0.053	75.6
365	>0.319	16.7	0.044	81.4
367	>1.009	9.6	0.065	65.1
368	>31.67	12.6	0.146	65.3
369	>31.67	-0.17	0.064	72.3
370	>31.67	26.7	0.065	77.0
371	>31.67	9.5	>3.333	41.0
372	>0.319	11.4	0.188	54.8
373	>31.67	9.6	>1.009	43.6
374	>1.009	30.9	>3.333	44.6
375	>1.009	17.6	>1.009	36.8
376	>0.319	17.4	0.034	66.7

377	>3.333	13.9	0.148	58.0
378	>31.67	9.1	2.00	55.3
379	>3.333	12.4	>10.0	14.2
380	>1.009	20.2	>0.319	17.4
381	>31.67	6.6	>0.319	54.1
382	>31.67	0.8	>3.333	9.6
383	>31.67	7.1	>0.319	48.9
384	>31.67	3.6	>3.333	9.7
385	>31.67	6.5	>1.009	29.3
386	>31.67	6.5	>0.319	16.4
388	>31.67	27.7	>31.67	42.6
389	>31.67	8.8	>0.106	26.4
390	>31.67	0.2	0.197	53.4
391	>31.67	-3.5	>0.319	42.3
392	>31.67	9.9	>3.333	41.0
393	>0.106	25.6	>0.106	37.0
394	>3.333	24.5	0.469	53.2
395	>3.333	22.5	0.376	78.3
396	>1.009	25.1	0.254	69.3
397	>1.009	18.9	>1.009	33.9
398	>31.67	15.4	0.213	50.0
399	>1.009	18.2	>0.319	47.9
400	>31.67	2.1	>0.319	46.4
401	>31.67	0.9	>0.319	30.0
402	>31.67	2.3	>31.67	6.7
403	>31.67	1.9	>1.009	29.6
404	>1.009	35.5	>1.009	39.8
405	>0.319	17.9	0.185	56.3
406	>31.67	7.1	0.174	53.4
407	>31.67	2.7	>0.319	46.7
408	>31.67	5.4	>1.009	33.9
409	>31.67	-2.7	>0.319	33.0
410	>31.67	5.8	0.079	69.4

411	>31.67	4.7	>1.009	35.5
412	>31.67	9.0	>3.333	24.9

[2994] The in vitro intrinsic clearance of representative Compounds of the Disclosure in human liver microsomes and hepatocytes are provided in Table 3.

Table 3

Example No.	*In-vitro* human liver microsomes intrinsic clearance (uL/min/mg)	*In-vitro* human hepatocytes intrinsic clearance (uL/min/mg) (uL/min/1x10^6 cells)
1	<13.25	3.4
2	28.80	2.9
3	23.03	-
4	17.00	-
5	32.45	4.6
6	9.145	4.1
7	12.40	3.3
8	8.380	-
9	18.90	3.8
10	17.00	5.9
11	21.85	5.3
12	20.75	8.0
13	42.00	-
14	12.80	-
15	25.25	6.4
16	15.00	2.4
17	11.015	2.1
18	21.9	-
19	16.2	-
20	29.6	5.7
21	19.5	2.5

22	6.3	-
23	21.15	4.0
24	33.8	-
25	14.6	-
26	21.0	2.9
27	31.1	4.6
28	33.45	4.2
29	23.767	2.5
30	37.0	-
31	23.8	2.9
32	31.65	4.0
33	57.8	4.5
34	20.533	1.2
35	25.65	2.5
36	36.0	5.0
37	21.4	5.0
38	27.5	3.5
39	17.9	3.1
40	24.8	1.9
41	21.1	-
42	34.0	-
43	27.5	4.2
44	21.3	5.9
45	41.7	-
46	16.4	2.2
47	28.7	-
48	29.1	-
49	24.1	-
50	41.3	5.5

51	36.0	1.9
52	25.3	-
53	11.3	-
54	17.5	-
55	58.9	-
56	32.5	-
57	21.9	-
58	25.4	-
59	16.4	-
60	27.0	-
61	8.4	-
62	65.9	2.2
63	13.6	1.2
64	21.8	< 1
65	< 3	3.1
66	11.4	< 1
67	10.8	< 1
68	22.3	-
69	13.9	< 1
70	10.5	5.0
71	13.6	< 1
72	10.2	2.9
73	24.9	< 1
74	19.1	< 1
75	<3.6	1.9
76	33.3	-
77	17.6	2.2
78	15.6	2.1
79	< 3	< 1

80	20.1	2.7
81	12.4	4.0
82	6.0	< 1
83	11.5	2.6
84	< 3	5.5
85	18.3	< 1
86	19.9	< 1
87	47.1	-
88	6.7	< 1
89	18.0	3.4
90	13.6	2.7
91	21.8	-
92	28.9	-
93	15.3	1.4
94	5.9	-
95	32.1	5.6
96	16.9	1.4
97	9.4	-
98	12.1	1.5
99	20.6	3.9
100	21.3	3.2
101	8.8	2.4
102	12.7	2.8
103	22.0	< 1
104	10.7	2.7
105	20.5	2.2
106	32.0	-
107	10.6	-
108	12.2	-

109	57.2	8.9
110	9.7	1.4
111	6.1	< 1
112	8.8	2.6
113	123	< 1
114	6.1	< 1
115	13.9	3.7
116	13.1	3.2
117	11.9	2.1
118	< 3	5.4
119	156.9	-
120	10.8	6.2
121	184.9	-
122	< 3	7.3
123	10.6	-
124	< 8.5	-
125	< 3	2.1
126	35.2	5.1
127	31.0	-
128	49.2	-
129	72.0	-
130	47.7	6.8
131	12.7	-
132	19.6	-
133	17.3	< 1
134	16.8	2.3
135	< 3	-
136	13.9	1.3
137	10.5	< 1

138	<16.2	3.9
139	14.2	3.4
140	59.1	-
141	21.4	3.8
142	35.3	3.7
143	< 3	2.9
144	27.5	5.0
145	11.4	3.5
146	35.5	4.9
147	19.7	3.0
148	13.2	2.7
149	< 3	-
150	19.5	-
151	<8.5	3.7
152	21.0	4.6
153	38.3	5.7
154	27.6	6.9
155	21.6	3.8
156	18.0	-
157	10.8	-
158	14.1	-
159	8.8	4.0
160	24.2	4.0
161	45.7	6.2
162	21.1	4.2
163	11.5	4.9
164	32.6	5.1
165	< 3	-
166	92.9	10.7

167	4.2	-
168	34.8	7.5
169	60.4	-
170	33.7	-
171	23.4	-
172	70.0	-
173	23.6	-
174	40.5	-
175	56.7	-
176	17.7	7.6
177	19.1	-
178	32.9	-
179	30.1	-
180	20.3	-
181	11.3	-
182	22.5	5.3
183	16.3	6.3
184	26.9	3.3
185	21.9	-
186	11.4	4.5
187	11.8	< 1
188	12.6	-
189	14.1	-
190	10.8	-
191	18.0	-
192	14.6	< 1
193	18.4	-
194	25.1	-
195	19.2	-

196	22.8	-
197	24.9	4.4
198	15.2	2.3
199	6.8	-
200	9.8	6.5
201	14.0	-
202	11.9	-
203	33.9	8.6
204	22.9	4.4
205	21.6	4.9
206	12.9	-
207	15.1	3.1
208	35.8	8.8
209	16.1	-
210	25.1	8.5
211	53.3	-
212	18.8	6.2
213	12.5	6.3
214	6.3	-
215	5.9	-
216	28.4	-
217	<4.0	2.7
218	93.3	12.2
219	5.0	-
220	16.7	4.5
221	9.6	3.8
222	16.4	6.2
223	18.5	-
224	35.0	-

225	11.3	-
226	28.3	3.9
227	17.9	5.9
228	25.1	4.7
229	27.5	11.4
230	8.6	10.9
231	< 3	6.3
232	17.1	4.0
233	27.8	5.2
234	128	-
235	15.5	6.4
236	108.2	-
237	10.2	-
238	11.5	-
239	60.6	-
240	< 3	-
241	109.4	-
242	5.4	-
243	9.6	-
244	15.1	1.7
245	29.4	-
246	22.2	-
247	31.9	5.7
248	15.4	-
249	15.3	5.8
250	25.9	4.0
251	34.0	-
252	20.9	-
253	11.8	-

254	16.0	-
255	12.5	2.1
256	11.5	-
257	16.2	-
258	9.3	-
259	20.6	3.8
260	18.5	3.3
261	10.7	2.6
262	< 3	-
263	< 3	-
264	< 3	-
265	17.8	-
266	16.7	7.1
267	19.4	5.1
268	7.6	1.1
269	11.8	3.3
270	8.5	2.6
271	26.1	7.0
272	46.4	7.6
273	13.5	2.2
274	9.8	-
275	26.3	7.3
276	29.6	-
277	15.3	4.4
278	15.2	3.1
279	17.1	4.9
280	9.9	6.4
281	32.2	-
282	14.0	< 1

283	5.7	2.8
284	4.0	4.4
285	12.5	3.3
286	10.9	3.0
287	32.8	-
288	15.2	4.9
289	17.3	-
290	16.5	5.0
291	5.9	3.6
292	5.1	-
293	12.1	2.6
294	18.2	5.0
295	9.8	< 1
296	20.1	4.1
297	10.8	2.0
298	16.6	-
299	13.2	2.8
300	10.2	-
301	9.9	3.8
302	28.7	-
303	28.9	4.0
304	13.9	3.9
305	24.3	7.4
306	12.5	-
307	31.4	6.9
308	21.5	-
309	21.5	-
310	27.2	-
311	9.6	1.8

312	15.0	-
313	103.7	-
314	8.8	2.4
315	< 3	-
316	27.2	5.2
317	23.6	-
318	<7.9	3.7
319	13.6	-
320	131.5	-
321	20.2	4.5
322	<6.3	5.5
323	< 3	-
324	20.4	5.1
325	97.9	-
326	< 3	2.8
327	26.3	-
328	9.5	6.3
329	8.2	-
330	10.9	-
331	17.2	-
332	< 3.5	< 1
333	19.1	-
334	14.9	-
335	11.6	-
336	5.8	-
337	5.0	-
338	< 3	-
339	11.2	-
340	12.1	< 1

341	16.9	< 1
342	16.7	1.7
343	14.7	4.1
344	11.7	< 1
345	8.8	-
346	30.8	-
347	16.0	< 1
348	9.6	-
349	11.8	-
350	4.1	-
351	8.9	-
352	41.9	4.0
353	31.9	-
354	31.0	7.4
355	19.2	-
356	19.1	-
357	27.8	3.1
358	32.8	4.5
359	25.8	6.7
360	28.1	3.1
361	15.6	4.2
362	16.7	< 1
363	33.7	-
364	< 5.1	< 1
365	26.2	1.5
366	< 3	-
367	49.8	3.0
368	33.0	7.7
369	37.9	-

370	<13.2	3.0
371	18.7	1.4
372	63.7	-
373	< 3	-
374	20.5	3.3
375	37.9	-
376	10.5	< 1
377	9.4	2.6
378	10.8	-
379	5.9	-
380	< 3	< 1
381	12.5	-
382	31.5	4.0
383	27.2	-
384	10.7	-
385	38.2	-
386	30.5	-
387	< 2.4	-
388	< 4.0	1.4
389	< 4.9	-
390	48.0	-
391	18.9	-
392	16.4	< 1
393	46.4	-
394	21.1	4.3
395	5.8	-
396	17.7	-
397	25.1	-
398	18.1	5.3

399	36.6	-
400	56.5	-
401	27.3	-
402	58.0	-
403	18.3	-
404	23.5	-
405	36.7	6.5
406	21.0	-
407	17.5	1.5
408	22.0	-
409	17.8	-
410	17.2	< 1
411	19.5	2.9
412	15.6	< 1

[2995] The SALL4 and IKZF1 degradation activities of representative Compounds of the Disclosure are provided in Table 4.

Table 4

Example No.	SALL4 degrader IC50 (μM)	IKZF1 degrader at 10μM
1	>30	
4	>30	
10	>30	
12	>30	
16	>30	
17	>30	
20	>30	No
21	>30	No
22	>30	No
24	>30	
26	>30	No
31	>30	No

32	>30	
33	>30	No
34	>30	No
35	>30	No
36	>30	No
40	>30	
42	>30	No
45	>30	No
47	>30	No
55	>30	No
59	>30	No
60	>30	No
61	>30	No
64	>30	No
65	>30	
66	>30	No
67	>30	No
68	>30	No
70	>30	
73	>30	
75	>30	No
77	>30	No
79	>30	No
80	>30	No
81	>30	
83	>30	
88	>30	No
90	>30	
92	>30	
93	>30	No
95	>30	
98	>30	No
100	>30	

102	>30	
106	>30	No
110	>30	
116	>30	
117	>30	
119	>30	
122	>30	
123	>30	
123	>30	
125	>30	
126	>30	
127	>30	
128	>30	
129	>30	
130	>30	No
132	>30	
133	>30	
134	>30	
135	>30	
136	>30	No
137	>30	
138	>30	
144	>30	
153	>30	
160	>30	No
162	>30	
163	>30	
176	>30	
187	>30	
199	>30	
203	>30	No
225	>30	

[2996] The SALL4 and AIOLOS degradation activities of representative Compounds of the Disclosure are provided in Table 5.

Table 5

Example No.	SALL4 degrader IC50 (μM)	AIOLOS degrader IC50 (μM)
1	>30	-
4	>30	-
10	>30	-
12	>30	-
16	>30	-
17	>30	-
20	>30	-
21	>30	-
22	>30	-
24	>30	-
26	>30	-
31	>30	-
32	>30	-
33	>30	-
34	>30	-
35	>30	-
36	>30	-
40	>30	-
42	>30	-
45	>30	-
47	>30	-
55	>30	-
59	>30	-
60	>30	-
61	>30	-
64	>30	-
65	>30	-
66	>30	-
67	>30	-

68	>30	-
70	>30	-
73	>30	-
75	>30	-
77	>30	-
79	>30	-
80	>30	-
81	>30	-
83	>30	-
88	>30	-
90	>30	-
92	>30	-
93	>30	-
95	>30	-
98	>30	-
100	>30	-
102	>30	-
106	>30	-
110	>30	>30
116	>30	-
117	>30	-
119	>30	-
122	>30	-
123	>30	-
124	>30	-
125	>30	-
126	>30	-
127	>30	-
128	>30	-
129	>30	-
130	>30	-
132	>30	-
133	>30	-

134	>30	-
135	>30	-
136	>30	-
137	>30	-
138	>30	-
144	>30	-
153	>30	-
160	>30	-
162	>30	-
163	>30	-
176	>30	-
187	>30	-
199	>30	-
203	>30	-
225	>20.9	-
237	>30	-
250	>30	>30
261	>30	>30
269	-	>30
275	>30	>30
293	>1.1	>30
303	>30	>30
304	-	>30
314	>30	>30
332	>30	>30
340	>30	>30
341	>30	>30
342	>30	>30
343	>30	>30
346	-	>30
347	>30	>30
352	>30	>30
354	>30	>30

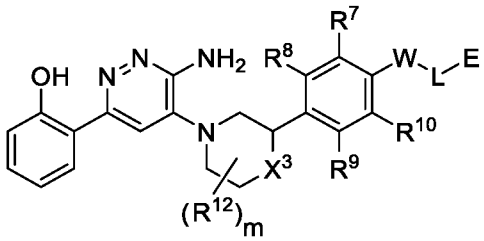
358	>30	>30
360	>30	>30
361	>30	>30
362	>30	>30
364	>30	>30
367	>30	>30
369	>30	>30
370	>30	>30
374	>30	>30
377	>30	>30
378	>30	>30
389	>30	>30
390	>30	>30
391	>30	>30
392	>30	>30
394	>30	>30
395	-	>30
397	-	>30
399	-	>30
406	-	>30
408	>30	>30
410	-	>30
411	>30	>30

[2997] Having now fully described the compounds, compositions, the methods herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof. All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

V. Statements

[2998] The present disclosure also provides the following Statements.

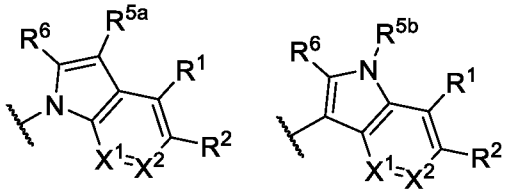
[2999] Statement 1. A compound having Formula (I), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(I),

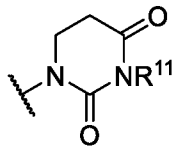
wherein:

[3000] E is:



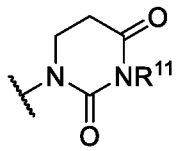
E-1 or E-2 ;

[3001] R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or



;

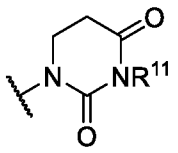
[3002] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or



;

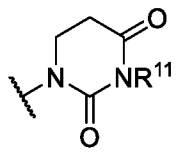
[3003] with the provisos:

[3004] (i) when R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^2 is:



; and

[3005] (ii) when R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^1 is:



;

[3006] R^{11} is hydrogen or -$(C_1\text{-}C_6)$alkyl-O-P(=O)-$(OH)_2$;

[3007] X^1 is CR^3 or N;

[3008] R^3 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

[3009] X^2 is CR^4 or N;

[3010] R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[3011] R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

[3012] R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

[3013] R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

[3014] X^3 is $-(CR^{13a}R^{13b})_n-$ or -O-;

[3015] n is 0 or 1

[3016] each R^{13a} and R^{13b} is independently H, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[3017] L is $-G^1$-G^2-G^3-G^4-, wherein G^1 is attached to W;

[3018] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[3019] G^2 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[3020] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[3021] G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[3022] W is -C(=O)-;

[3023] R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[3024] R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

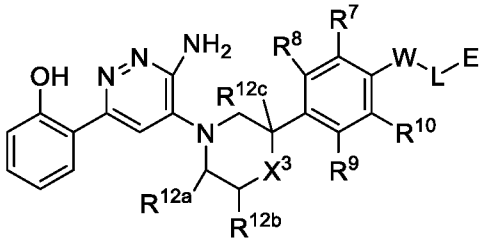
[3025] R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[3026] R^{10} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[3027] each R^{12} is independently halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy; and

[3028] m is 0, 1, 2, 3, or 4.

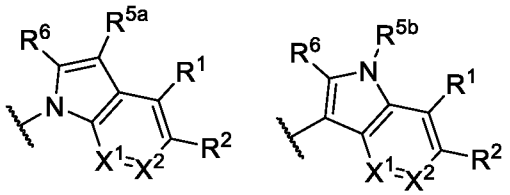
[3029] Statement 2. A compound having Formula (IA), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(IA),

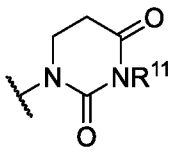
wherein:

[3030] E is:



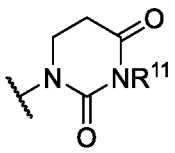
E-1 or E-2 ;

[3031] R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

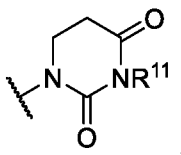
[3032] R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

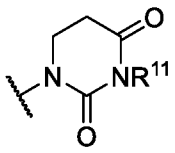
[3033] with the provisos:

[3034] (i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

[3035] (ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

[3036] R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

[3037] X^1 is CR^3 or N;

[3038] R^3 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[3039] X^2 is CR^4 or N;

[3040] R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

[3041] R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

[3042] R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

[3043] R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

[3044] X^3 is $-(CR^{13a}R^{13b})_n$- or -O-;

[3045] n is 0 or 1

[3046] each R^{13a} and R^{13b} is independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

[3047] L is $-G^1$-G^2-G^3-G^4-, wherein G^1 is attached to W;

[3048] G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[3049] G^2 is $(C_1$-$C_6)$alkylenyl, -C(=O)-, or a direct bond;

[3050] G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

[3051] G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

[3052] W is -C(=O)-, $-CH_2$-, or a direct bond;

[3053] R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[3054] R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

[3055] R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

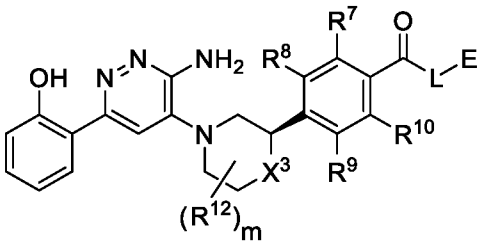
[3056] R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

[3057] R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

[3058] R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl ; and

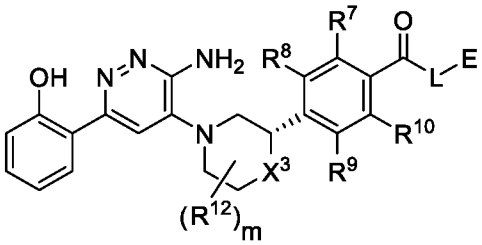
[3059] R^{12c} is hydrogen or halogen.

[3060] Statement 3. The compound, or pharmaceutically acceptable salt thereof, according to Statement 1 having Formula (II):



(II).

[3061] Statement 4. The compound, or pharmaceutically acceptable salt thereof, according to Statement 1 having Formula (III):



(III).

[3062] Statement 5. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-4, wherein X^3 is -($CR^{13a}R^{13b}$)-.

[3063] Statement 6. The compound, or pharmaceutically acceptable salt thereof, according to Statement 5, wherein R^{13a} and R^{13b} are hydrogen.

[3064] Statement 7. The compound, or pharmaceutically acceptable salt thereof, according to Statement 5, wherein R^{13a} and R^{13b} are fluoro.

[3065] Statement 8. The compound, or pharmaceutically acceptable salt thereof, according to Statement 5, wherein R^{13a} is methyl or methoxy; and R^{13b} is hydrogen.

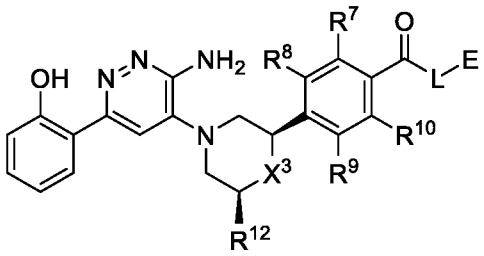
[3066] Statement 9. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-4, wherein X^3 is -O-.

[3067] Statement 10. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1 or 3-9, wherein m is 0.

[3068] Statement 11. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1 or 3-9, wherein m is 2.

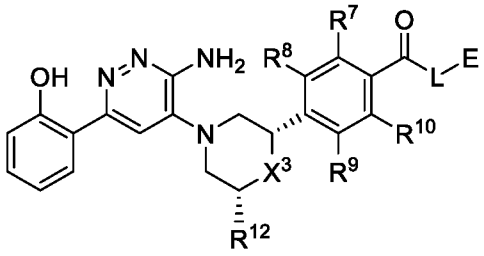
[3069] Statement 12. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1 or 3-9, wherein m is 1.

[3070] Statement 13. The compound, or pharmaceutically acceptable salt thereof, according to Statement 12 having Formula (IV):



(IV).

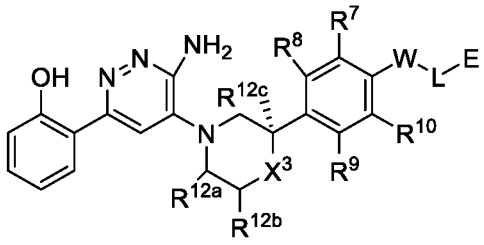
[3071] Statement 14. The compound, or pharmaceutically acceptable salt thereof, according to Statement 12 having Formula (V):



(V).

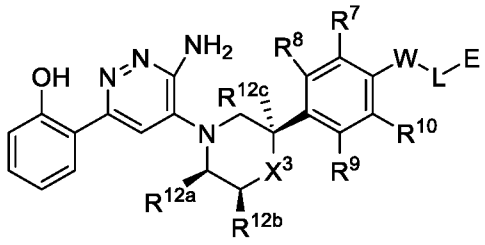
[3072] Statement 15. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 12-14, wherein each R^{12} is fluoro, methyl, ethyl, or methoxy.

[3073] Statement 16. The compound, or pharmaceutically acceptable salt thereof, according to Statement 2, having Formula (VIII):



(VIII).

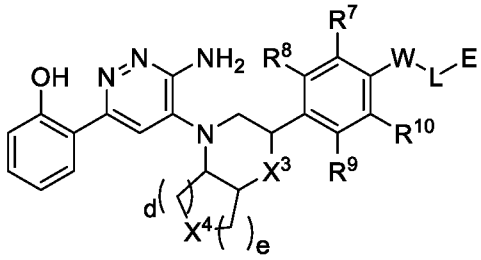
[3074] Statement 17. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 2 or 16, having Formula (IX):



(IX).

[3075] Statement 18. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 2 or 16-17, wherein R^{12a} is hydrogen and R^{12b} is hydrogen, fluoro, methyl, ethyl, or methoxy.

[3076] Statement 19. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to Statement 2 having Formula (X):



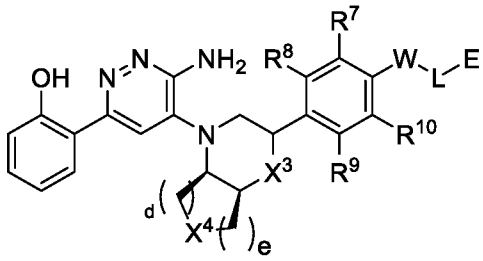
(X)

wherein:

[3077] X^4 is O; and

[3078] d and e are independently 1 or 2.

[3079] Statement 20. The compound, or pharmaceutically acceptable salt thereof, according to Statement 2 having Formula (XI):



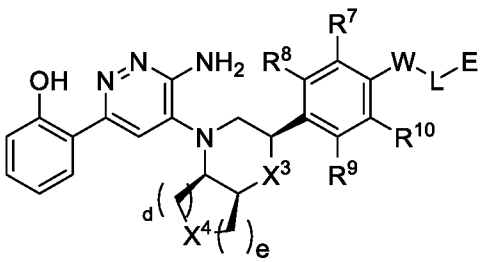
(XI)

wherein:

[3080] X^4 is O; and

[3081] d and e are independently 1 or 2.

[3082] Statement 21. The compound, or pharmaceutically acceptable salt thereof, according to Statement 2 having Formula (XII):



(XII)

wherein:

[3083] X^4 is O; and

[3084] d and e are independently 1 or 2.

[3085] Statement 22. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-21, wherein E is E-1.

[3086] Statement 23. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is hydrogen.

[3087] Statement 24. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is (C_1-C_6)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[3088] Statement 25. The compound, or pharmaceutically acceptable salt thereof, according to Statement 24, wherein R^{5a} is methyl, ethyl, isopropyl, or -CF_3.

[3089] Statement 26. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is (C_3-C_6)cycloalkyl.

[3090] Statement 27. The compound, or pharmaceutically acceptable salt thereof, according to Statement 26, wherein R^{5a} is cyclopropyl.

[3091] Statement 28. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[3092] Statement 29. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is cyano.

[3093] Statement 30. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[3094] Statement 31. The compound, or pharmaceutically acceptable salt thereof, according to Statement 22, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6)alkyl.

[3095] Statement 32. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-21, wherein E is E-2.

[3096] Statement 33. The compound, or pharmaceutically acceptable salt thereof, according to Statement 32, wherein R^{5b} is hydrogen.

[3097] Statement 34. The compound, or pharmaceutically acceptable salt thereof, according to Statement 32, wherein R^{5b} is (C_1-C_6)alkyl.

[3098] Statement 35. The compound, or pharmaceutically acceptable salt thereof, according to Statement 34, wherein R^{5b} is methyl.

[3099] Statement 36. The compound, or pharmaceutically acceptable salt thereof, according to Statement 32, wherein R^{5b} is (C_3-C_6)cycloalkyl.

[3100] Statement 37. The compound, or pharmaceutically acceptable salt thereof, according to Statement 36, wherein R^{5b} is cyclopropyl or cyclobutyl.

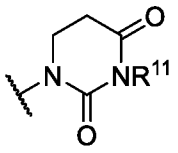
[3101] Statement 38. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-37, wherein R^6 is hydrogen.

[3102] Statement 39. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-37, wherein R^6 is $(C_1\text{-}C_6)$alkyl.

[3103] Statement 40. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-37, wherein R^6 is cyano.

[3104] Statement 41. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-40, wherein:

[01003] R^1 is:



; and

[3105] R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

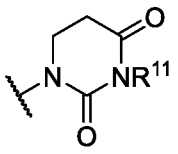
[3106] Statement 42. The compound, or pharmaceutically acceptable salt thereof, according to Statement 41, wherein R^2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[3107] Statement 43. The compound, or pharmaceutically acceptable salt thereof, according to Statement 42, wherein R^2 is hydrogen, fluoro, or methyl.

[3108] Statement 44. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 41-43, wherein R^{11} is hydrogen.

[3109] Statement 45. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-40, wherein:

[3110] R^2 is:



; and

[3111] R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

[3112] Statement 46. The compound, or pharmaceutically acceptable salt thereof, according to Statement 45, wherein R^1 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

[3113] Statement 47. The compound, or pharmaceutically acceptable salt thereof, according to Statement 45, wherein R^1 is hydrogen, fluoro, or methyl.

[3114] Statement 48. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 45-47, wherein R^{11} is hydrogen.

[3115] Statement 49. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-48, wherein X^1 is CR^3.

[3116] Statement 50. The compound, or pharmaceutically acceptable salt thereof, according to Statement 49, wherein R^3 is hydrogen.

[3117] Statement 51. The compound, or pharmaceutically acceptable salt thereof, according to Statement 49, wherein R^3 is halogen.

[3118] Statement 52. The compound, or pharmaceutically acceptable salt thereof, according to Statement 51, wherein R^3 is fluoro.

[3119] Statement 53. The compound, or pharmaceutically acceptable salt thereof, according to Statement 49, wherein R^3 is $(C_1\text{-}C_6)$alkyl.

[3120] Statement 54. The compound, or pharmaceutically acceptable salt thereof, according to Statement 53, wherein R^3 is methyl.

[3121] Statement 55. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-48, wherein X^1 is N.

[3122] Statement 56. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-55, wherein X^2 is CR^4.

[3123] Statement 57. The compound, or pharmaceutically acceptable salt thereof, according to Statement 56, wherein R^4 is hydrogen.

[3124] Statement 58. The compound, or pharmaceutically acceptable salt thereof, according to Statement 56, wherein R^4 is halogen.

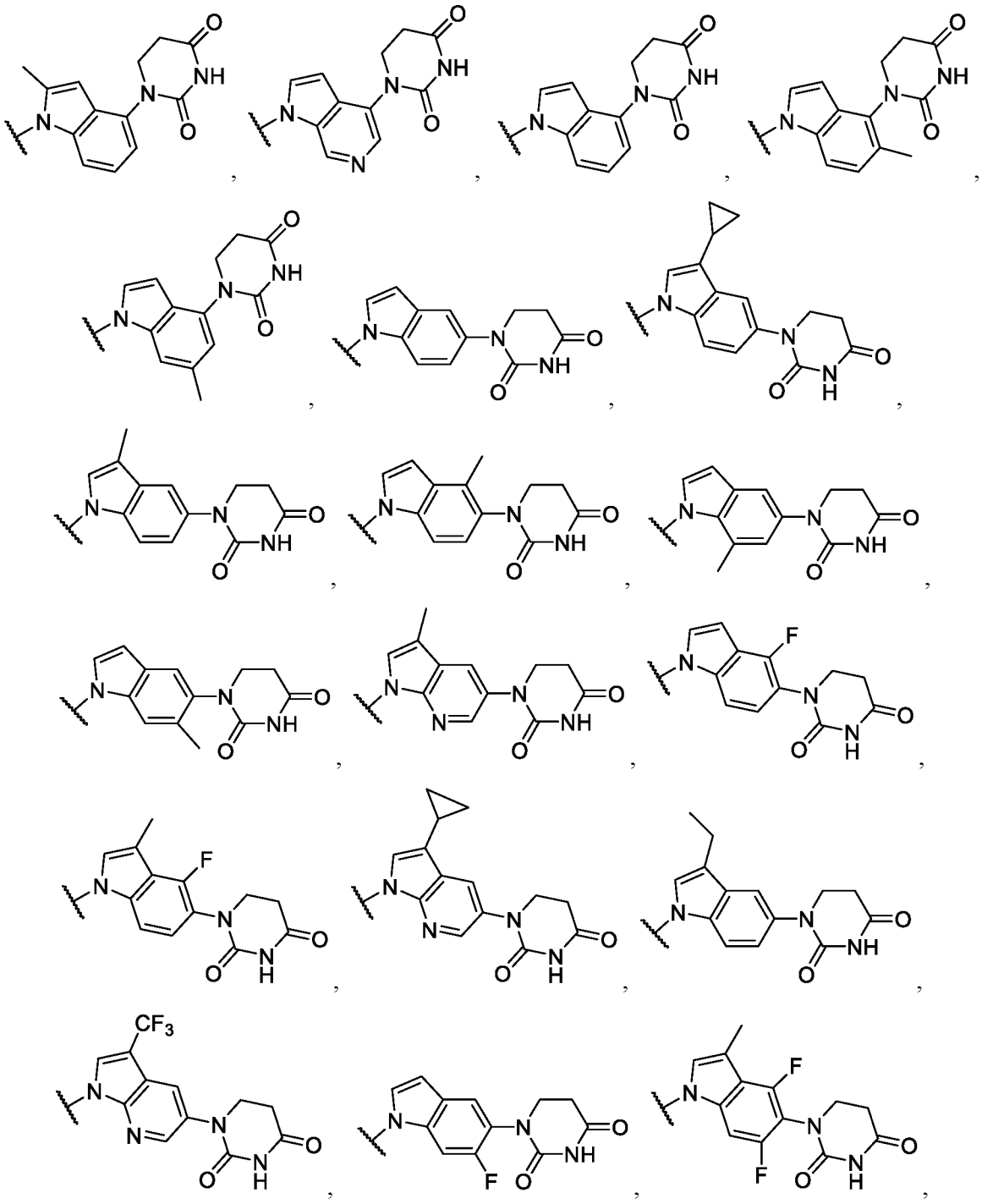
[3125] Statement 59. The compound, or pharmaceutically acceptable salt thereof, according to Statement 58, wherein R^4 is fluoro.

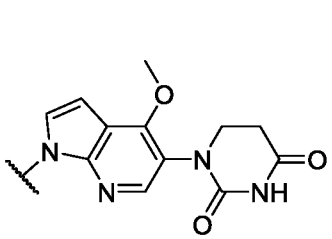
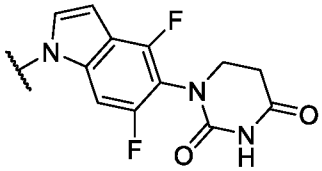
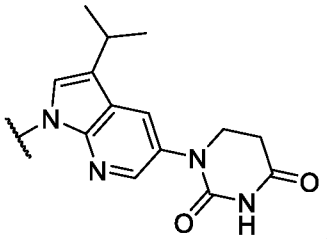
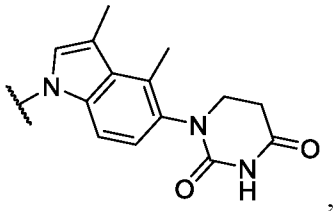
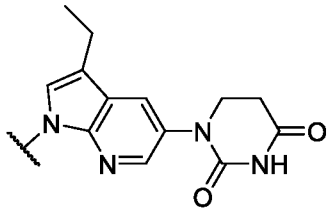
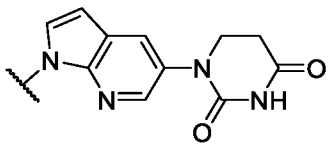
[3126] Statement 60. The compound, or pharmaceutically acceptable salt thereof, according to Statement 56, wherein R^4 is $(C_1\text{-}C_6)$alkyl.

[3127] Statement 61. The compound, or pharmaceutically acceptable salt thereof, according to Statement 60, wherein R^4 is methyl.

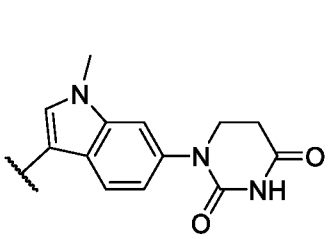
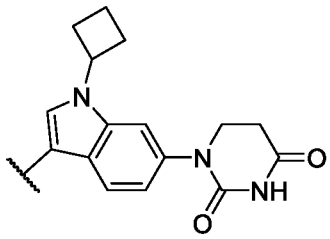
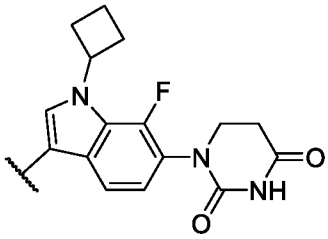
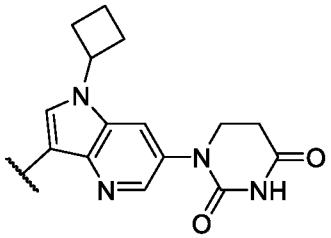
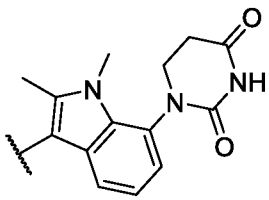
[3128] Statement 62. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-55, wherein X^2 is N.

[3129] Statement 63. The compound of Statement 22, wherein E-1 is:




,

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,

,

, or

.

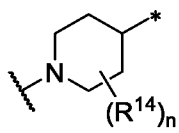
[3130] Statement 64. The compound of Statement 32, wherein E-2 is:


,

,

,

, or

.

[3131] Statement 65. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-64, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[3132] Statement 66. The compound, or pharmaceutically acceptable salt thereof, according to Statement 65, wherein:

[3133] G^1 is:


;

[3134] each R^{14} is independently halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

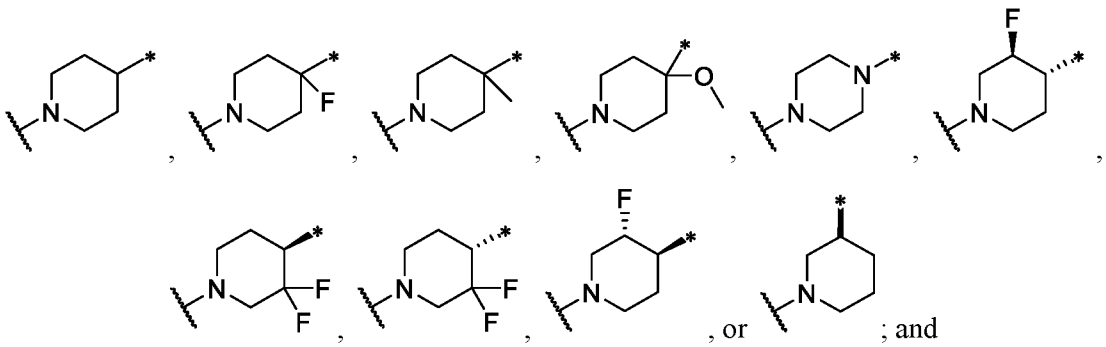
[3135] n is 0, 1, 2, or 3; and

[3136] the bond marked with an "*" is attached to G^2.

[3137] Statement 67. The compound, or pharmaceutically acceptable salt thereof, according to Statement 66, wherein n is 0.

[3138] Statement 68. The compound, or pharmaceutically acceptable salt thereof, according to Statement 66, wherein R^{14} is fluoro, methyl, or methoxy; and n is 1, or 2.

[3139] Statement 69. The compound, or pharmaceutically acceptable salt thereof, according Statement 65, wherein G^1 is:



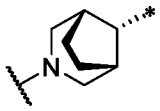
; and

[3140] the bond marked with an "*" is attached to G^2.

[3141] Statement 70. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-64, wherein G^1 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[3142] Statement 71. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-64, wherein G^1 is a 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

[3143] Statement 72. The compound, or pharmaceutically acceptable salt thereof, according to Statement 71, wherein G^1 is:



; and

[3144] the bond marked with an "*" is attached to G^2.

[3145] Statement 73. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-72, wherein G^2 is a direct bond.

[3146] Statement 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-72, wherein G^2 is $(C_1\text{-}C_6)$alkylenyl.

[3147] Statement 75. The compound, or pharmaceutically acceptable salt thereof, according to Statement 74, wherein G^2 is $-CH_2-$ or $-CH(CH_3)-$.

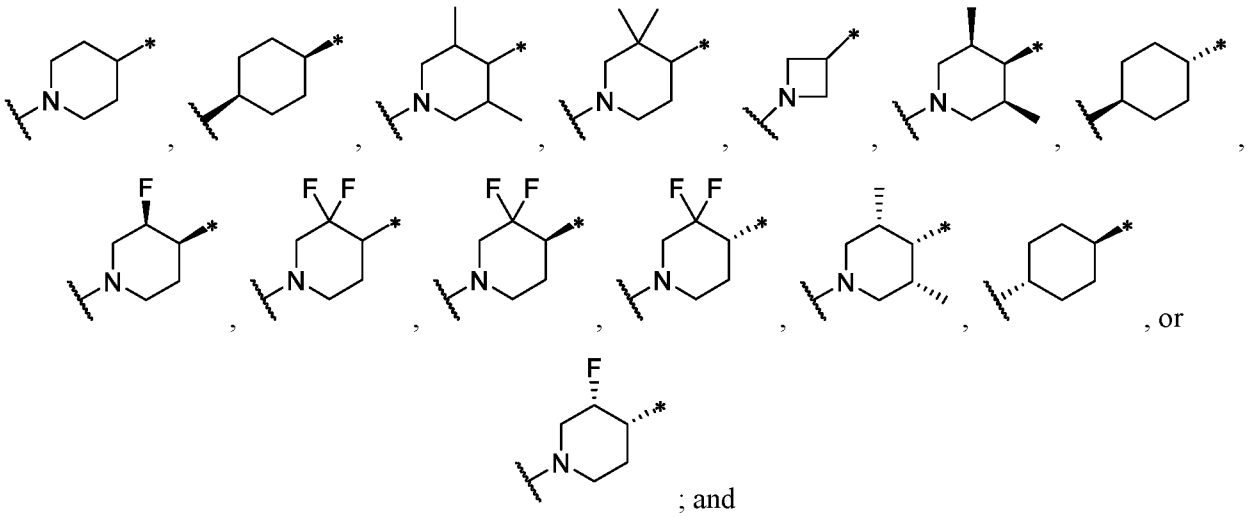
[3148] Statement 76. The compound, or pharmaceutically acceptable salt thereof, according to Statement 1-68, wherein G^2 is $-C(=O)-$.

[3149]

[3150] Statement 77. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1 or 3-76, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally

substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[3151] Statement 78. The compound, or pharmaceutically acceptable salt thereof, according Statement 77, wherein G^3 is:

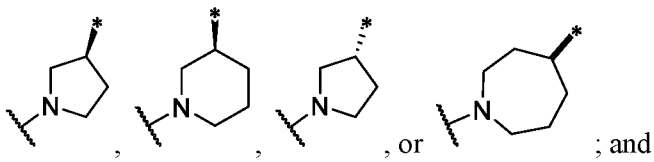


; and

[3152] the bond marked with an "*" is attached to G^4.

[3153] Statement 79. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 2-9 or 18-76, wherein G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[3154] Statement 80. The compound, or pharmaceutically acceptable salt thereof, according to Statement 79, wherein G^3 is:

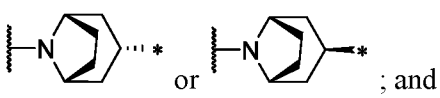


; and

[3155] the bond marked with an "*" is attached to G^4.

[3156] Statement 81. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-76, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[3157] Statement 82. The compound, or pharmaceutically acceptable salt thereof, according to Statement 81, wherein G^3 is:

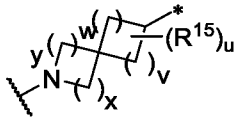


; and

[3158] the bond marked with an "*" is attached to G^4.

[3159] Statement 83. The compound, or pharmaceutically acceptable salt thereof, according to Statement 81, wherein:

[3160] G^3 is:



;

[3161] each R^{15} is independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

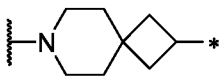
[3162] u is 0, 1, 2, or 3;

[3163] v, w, x, and t are independently 1, 2, or 3; and

[3164] the bond marked with an "*" is attached to G^4.

[3165] Statement 84. The compound, or pharmaceutically acceptable salt thereof, according to Statement 83, wherein v, w, x, and y are independently 1 or 2.

[3166] Statement 85. The compound, or pharmaceutically acceptable salt thereof, according to Statement 84, wherein G^3 is:



; and

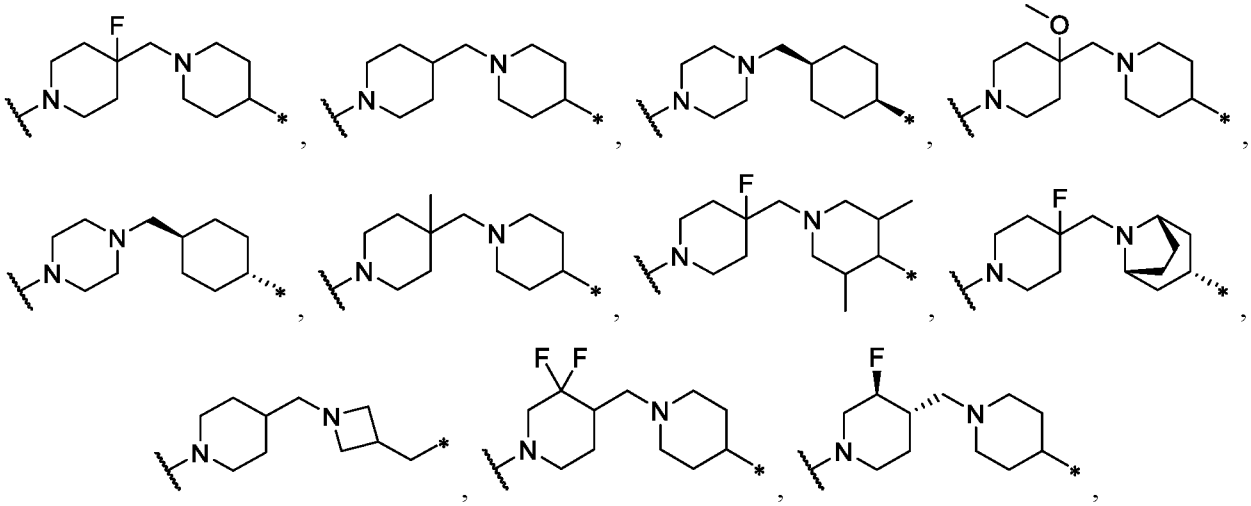
[3167] the bond marked with an "*" is attached to G^4.

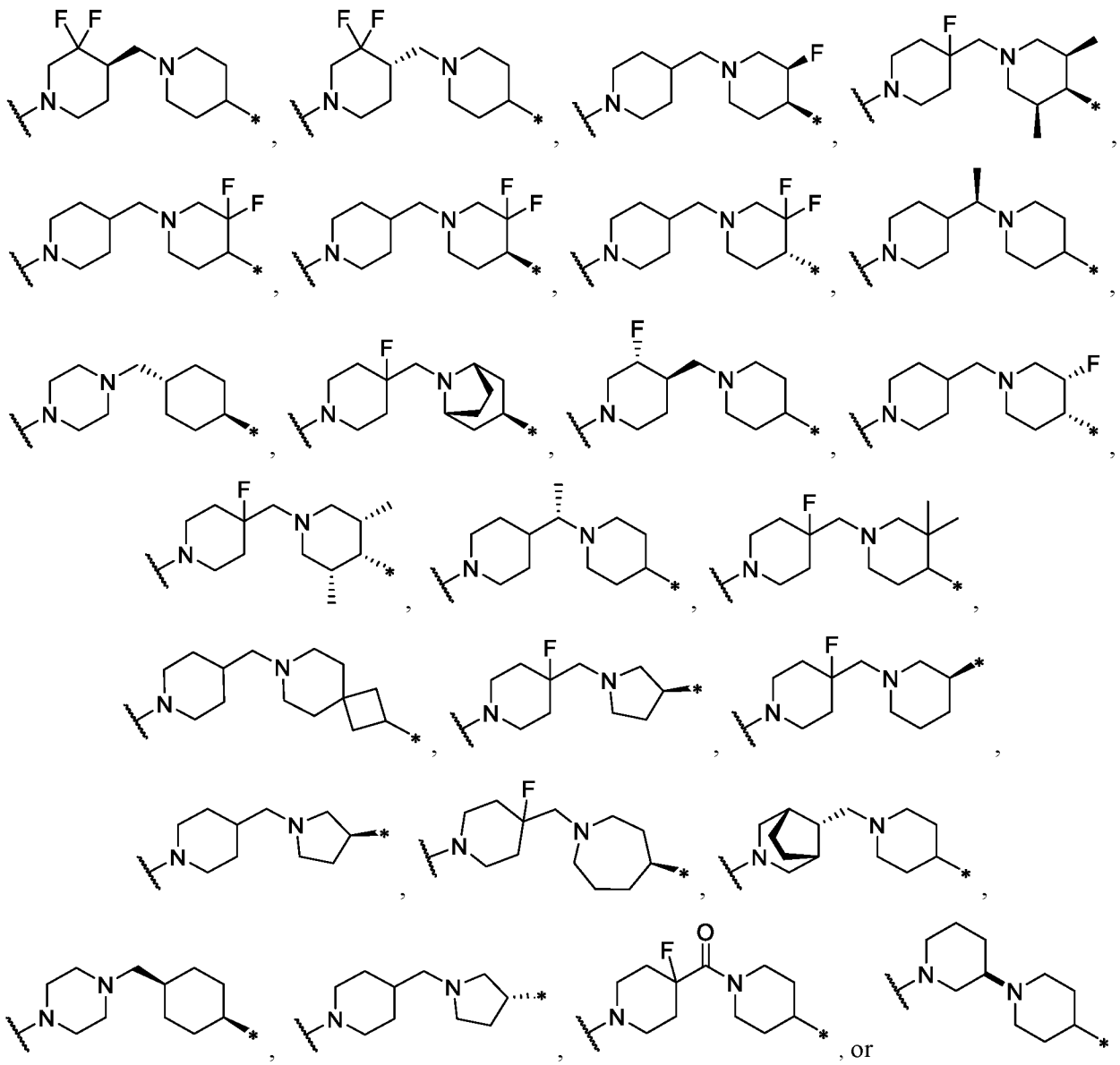
[3168] Statement 86. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-76, wherein G^3 is (C_3-C_6)cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano.

[3169] Statement 87. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-86, wherein G^4 is (C_1-C_6)alkylenyl.

[3170] Statement 88. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-86, wherein G^4 is a direct bond.

[3171] Statement 89. The compound, or pharmaceutically acceptable salt thereof, of any one of Statements 1-64, wherein L is:





; and

[3172] the bond marked with an "*" is attached to E.

[3173] Statement 90. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-89, wherein R^7 is halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen.

[3174] Statement 91. The compound, or pharmaceutically acceptable salt thereof, according to Statement 90, wherein R^7 is halogen or $(C_1$-$C_6)$alkyl.

[3175] Statement 92. The compound, or pharmaceutically acceptable salt thereof, according to Statement 91, wherein R^7 is fluoro or methyl.

[3176] Statement 93. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 90-92, wherein R^8, R^9, and R^{10} are hydrogen.

[3177] Statement 94. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-89, wherein R^8 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[3178] Statement 95. The compound, or pharmaceutically acceptable salt thereof, according to Statement 94, wherein R^8 is halogen or $(C_1\text{-}C_6)$alkyl.

[3179] Statement 96. The compound, or pharmaceutically acceptable salt thereof, according to Statement 95, wherein R^8 is fluoro or methyl.

[3180] Statement 97. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 94-96, wherein R^7, R^9, and R^{10} are hydrogen.

[3181] Statement 98. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-89, wherein R^9 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

[3182] Statement 99. The compound, or pharmaceutically acceptable salt thereof, according to Statement 98, wherein R^9 is halogen.

[3183] Statement 100. The compound, or pharmaceutically acceptable salt thereof, according to Statement 99, wherein R^9 is fluoro.

[3184] Statement 101. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 98-100, wherein R^7, R^8, and R^{10} are hydrogen.

[3185] Statement 102. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-89, wherein R^{10} is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

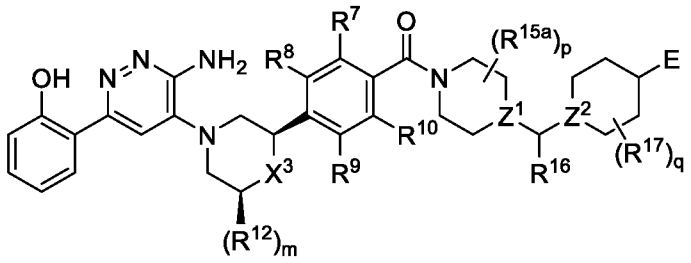
[3186] Statement 103. The compound, or pharmaceutically acceptable salt thereof, according to Statement 102, wherein R^{10} is halogen.

[3187] Statement 104. The compound, or pharmaceutically acceptable salt thereof, according to Statement 103, wherein R^{10} is fluoro.

[3188] Statement 105. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 102-104, wherein R^7, R^8, and R^9 are hydrogen.

[3189] Statement 106. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-89, wherein R^7, R^8, R^9, and R^{10} are hydrogen.

[3190] Statement 107. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1, 5-9, 63, or 64, having Formula (VI):



(VI),

wherein:

[3191] R^{15a} is fluoro;

[3192] p is 0, 1, or 2;

[3193] Z^1 is CR^{15b} or N;

[3194] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[3195] R^{16} is hydrogen or methyl;

[3196] Z^2 is CH or N;

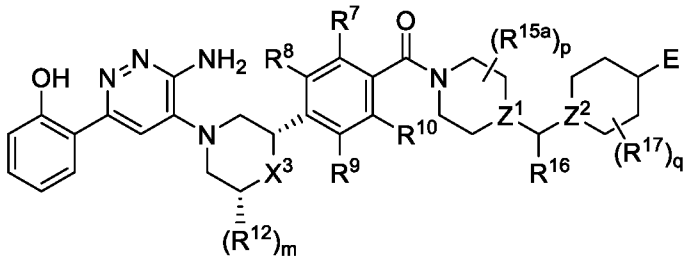
[3197] R^{17} is fluoro or methyl;

[3198] q is 0, 1, or 2;

[3199] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[3200] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

[3201] Statement 108. The compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1, 5-9, 63, or 64, having Formula (VII):



(VII),

wherein:

[3202] R^{15a} is fluoro;

[3203] p is 0, 1, or 2;

[3204] Z^1 is CR^{15b} or N;

[3205] R^{15b} is hydrogen, fluoro, methyl, or methoxy;

[3206] R^{16} is hydrogen or methyl;

[3207] Z^2 is CH or N;

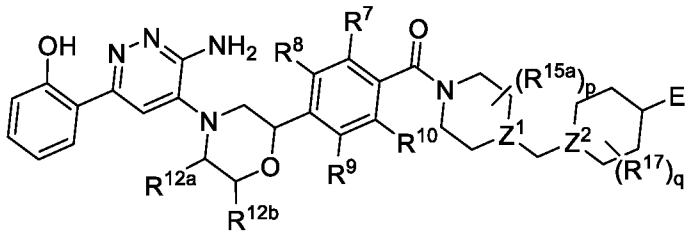
[3208] R^{17} is fluoro or methyl;

[3209] q is 0, 1, or 2;

[3210] R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

[3211] R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, -CF_3, cyclopropyl, methoxy, or cyano.

[3212] Statement 109. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to Statement 2, having Formula (XIII):



(XIII),

wherein:

[3213] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[3214] R^{12a} and R^{12b} are independently hydrogen or methyl;

[3215] R^{15a} is fluoro;

[3216] p is 0, 1, or 2;

[3217] Z^1 is CR^{15b} or N;

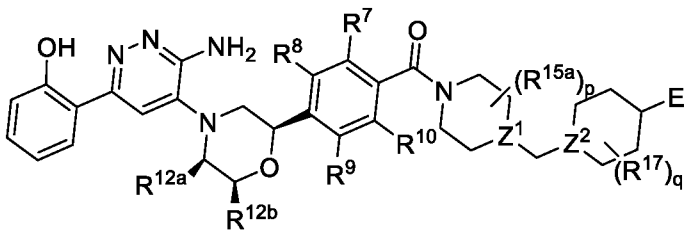
[3218] R^{15b} is hydrogen or fluoro;

[3219] Z^2 is CH or N;

[3220] R^{17} is fluoro; and

[3221] q is 0, 1, or 2.

[3222] Statement 110. The compound, or pharmaceutically acceptable salt thereof, according to Statement 2, having Formula (XIV):



(XIV),

wherein:

[3223] R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

[3224] R^{12a} and R^{12b} are independently hydrogen or methyl;

[3225] R^{15a} is fluoro;

[3226] p is 0, 1, or 2;

[3227] Z^1 is CR^{15b} or N;

[3228] R^{15b} is hydrogen or fluoro;

[3229] Z^2 is CH or N;

[3230] R^{17} is fluoro; and

[3231] q is 0, 1, or 2.

[3232] Statement 111. The compound according to Statement 1 selected from any one or more of the compounds:

[3233] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3234] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3235] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3236] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3237] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3238] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3239] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3240] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3241] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3242] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3243] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3244] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3245] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3246] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3247] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3248] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3249] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3250] (S*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3251] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3252] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3253] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3254] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3255] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3256] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3257] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3258] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3259] (R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3260] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3261] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3262] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3263] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3264] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3265] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3266] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3267] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3268] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3269] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3270] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3271] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3272] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3273] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3274] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3275] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3276] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3277] rac-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3278] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3279] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3280] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3281] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3282] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3283] (R)-2-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

[3284] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3285] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3286] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3287] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3288] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3289] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3290] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3291] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3292] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3293] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3294] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3295] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3296] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3297] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3298] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3299] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3300] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3301] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3302] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3303] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

[3304] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3305] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3306] (R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3307] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3308] (S)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3309] (S)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3310] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3311] (R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3312] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3313] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3314] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3315] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3316] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3317] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3318] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3319] (S)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3320] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3321] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3322] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3323] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3324] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3325] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3326] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3327] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3328] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3329] (R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3330] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3331] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3332] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3333] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3334] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3335] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3336] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3337] rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3338] rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3339] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3340] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3341] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3342] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3343] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3344] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3345] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3346] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3347] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3348] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3349] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3350] 1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3351] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3352] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3353] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3354] 1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3355] rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3356] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3357] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3358] 1-(1-((1R,3s,5S)-8-((1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3359] 1-(1-((1R,3s,5S)-8-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3360] 1-(1-(1-((1-(4-((3R*,5S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3361] (R)-1-(1-((1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3362] 1-(1-(1-(-1-(1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3363] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3364] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3365] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3366] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3367] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3368] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3369] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3370] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3371] (R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3372] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3373] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3374] 1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3375] (R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1H-indol-7-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3376] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3377] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3378] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3379] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3380] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3381] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3382] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3383] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3384] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3385] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3386] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3387] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3388] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3389] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3390] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3391] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3392] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3393] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3394] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3395] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3396] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3397] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3398] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3399] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3400] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3401] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3402] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3403] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3404] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3405] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3406] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3407] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3408] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3409] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3410] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3411] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3412] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3413] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3414] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3415] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3416] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3417] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3418] 1-(1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3419] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3420] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3421] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3422] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3423] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3424] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3425] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3426] 1-(1-(1-((1-(4-((2S,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3427] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3428] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3429] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3430] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3431] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3432] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3433] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3434] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3435] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3436] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3437] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3438] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3439] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3440] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3441] 1-(1-(1-(((S*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3442] 1-(1-(-1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3443] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3444] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3445] 1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3446] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3447] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3448] 1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3449] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3450] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3451] rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3452] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3453] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3454] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3455] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3456] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3457] rel-1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3458] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3459] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3460] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3461] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3462] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3463] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3464] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

[3465] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3466] or pharmaceutically acceptable salts thereof.

[3467] Statement 112. The compound according to Statement 1 selected from any one or more of the compounds:

[3468] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3469] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3470] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3471] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3472] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3473] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3474] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3475] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3476] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3477] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3478] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3479] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3480] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3481] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3482] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3483] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3484] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3485] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3486] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3487] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3488] rac-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3489] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3490] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3491] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3492] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3493] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-;

[3494] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3495] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3496] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3497] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3498] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3499] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

[3500] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3501] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3502] (S)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3503] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3504] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3505] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3506] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3507] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3508] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3509] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3510] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3511] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3512] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3513] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3514] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3515] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3516] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3517] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3518] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3519] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3520] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3521] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3522] rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3523] rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3524] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3525] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3526] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3527] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3528] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3529] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3530] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3531] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3532] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3533] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3534] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3535] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3536] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3537] 1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3538] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3539] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3540] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3541] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3542] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3543] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3544] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3545] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3546] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3547] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3548] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3549] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3550] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3551] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3552] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3553] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3554] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3555] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3556] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3557] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3558] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3559] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3560] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3561] (R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3562] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3563] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3564] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3565] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3566] 1-(1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3567] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3568] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3569] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3570] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3571] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3572] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3573] 1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3574] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3575] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3576] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3577] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3578] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3579] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3580] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3581] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3582] 1-(1-(1-(((S*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3583] 1-(1-(-1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3584] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3585] 1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3586] 1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3587] 1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3588] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3589] 1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3590] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3591] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3592] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3593] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3594] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3595] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3596] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3597] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3598] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3599] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3600] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3601] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3602] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3603] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3604] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3605] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3606] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3607] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3608] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3609] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3610] (R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3611] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3612] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3613] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3614] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3615] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3616] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3617] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3618] (R)-2-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

[3619] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3620] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3621] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3622] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3623] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3624] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3625] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3626] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3627] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3628] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3629] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3630] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3631] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3632] 1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3633] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3634] 1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3635] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3636] 1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3637] rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3638] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3639] 1-(1-(1-((1-(4-((3R*,5S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3640] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3641] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3642] 1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3643] (R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3644] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3645] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3646] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3647] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3648] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3649] (R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3650] 1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3651] 1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3652] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3653] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3654] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3655] 1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3656] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3657] 1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3658] 1-(1-(1-((1-(4-((2S,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3659] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3660] rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3661] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3662] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3663] (R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

[3664] 1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3665] or pharmaceutically acceptable salts thereof.

[3666] Statement 113. The compound according to Statement 2 selected from any one or more of the compounds:

[3667] 1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)pyrrolidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3668] 1-(1-((3S*,4R*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3669] 1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3670] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3671] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3672] 1-(1-((S)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3673] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3674] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3675] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3676] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3677] 1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3678] 1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3679] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3680] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3681] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3682] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3683] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3684] (S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3685] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3686] (R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3687] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3688] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3689] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3690] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3691] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione

[3692] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3693] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3694] 1-(1-((1R,4r)-4-((4-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3695] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3696] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3697] 1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3698] 1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3699] rac-1-(1-((1R,4r)-4-((4-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3700] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3701] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3702] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3703] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3704] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3705] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3706] 1-(1-((1R,4r)-4-((4-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3707] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3708] 1-(1-(1-((1-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3709] rac-1-(1-(1-((1-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3710] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3711] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3712] 1-(1-(1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3713] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3714] 1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3715] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3716] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3717] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3718] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3719] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3720] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3721] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3722] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3723] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3724] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3725] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3726] 1-(1-((1R,4r)-4-((4-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3727] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3728] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3729] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3730] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3731] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3732] 1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3733] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3734] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3735] (R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3736] 1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3737] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3738] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3739] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3740] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3741] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3742] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3743] 1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3744] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3745] (R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3746] 1-(1-((R)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3747] 1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3748] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3749] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3750] (R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3751] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3752] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3753] 1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3754] 1-(1-(1-((1-(4-((2R*,6R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3755] 1-(1-((1S,4s)-4-((4-(4-((R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3756] (R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3757] (R)-1-(1-(1-(1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)-4-fluoropiperidine-4-carbonyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3758] 1-(1-((S*)-1'-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-[1,3'-bipiperidin]-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3759] (R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

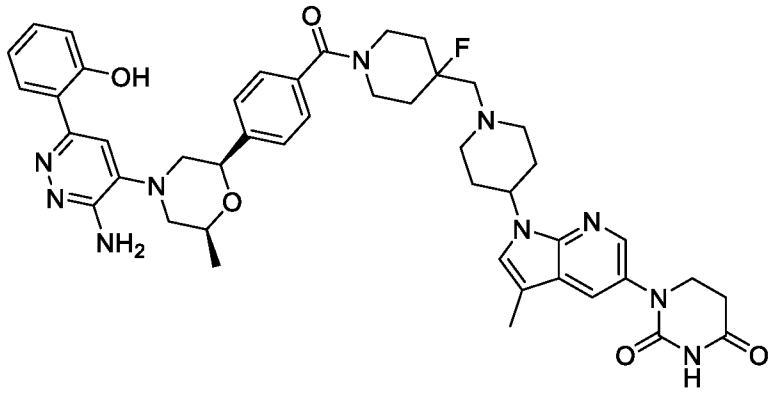
[3760] (R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3761] 1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

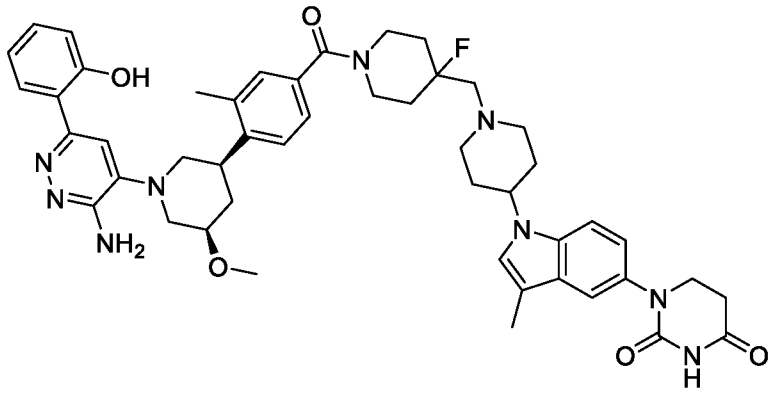
[3762] 1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

[3763] or pharmaceutically acceptable salts thereof.

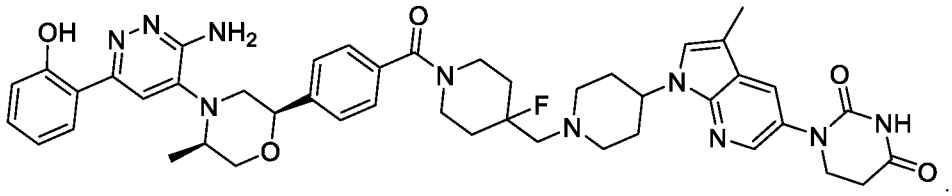
[3764] Statement 114. The compound, or pharmaceutically acceptable salt thereof, according to Statement 111, wherein the compound is:



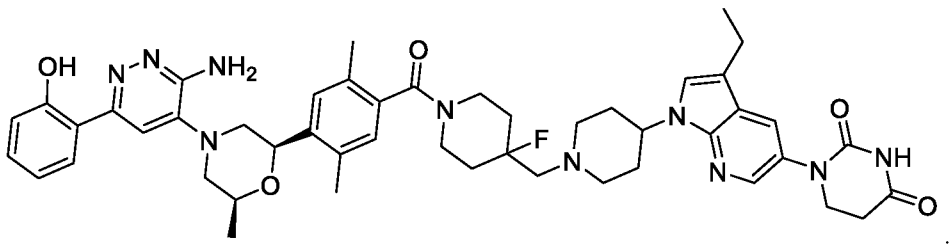
[3765] Statement 115. The compound, or pharmaceutically acceptable salt thereof, according to Statement 111, wherein the compound is:



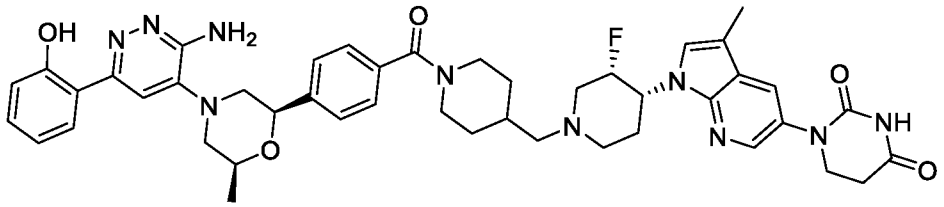
[3766] Statement 116. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



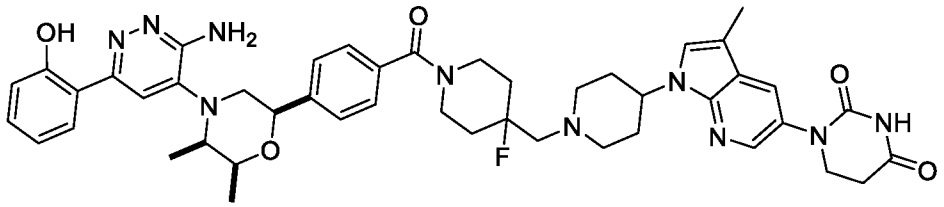
[3767] Statement 117. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



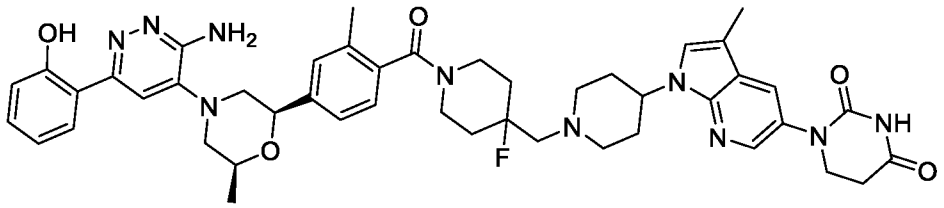
[3768] Statement 118. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



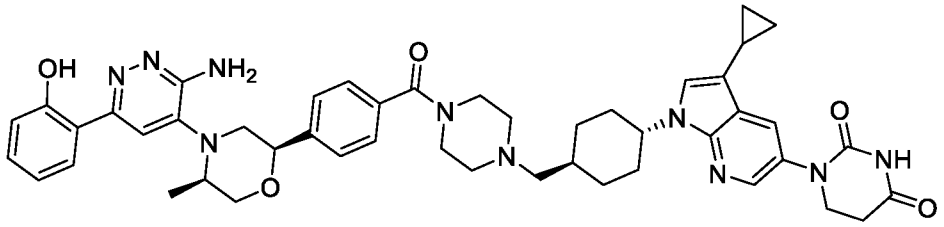
[3769] Statement 119. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



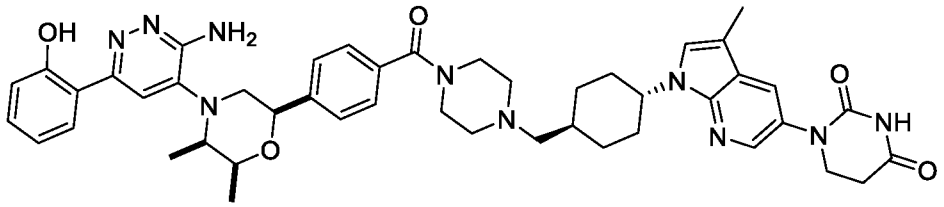
[3770] Statement 120. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



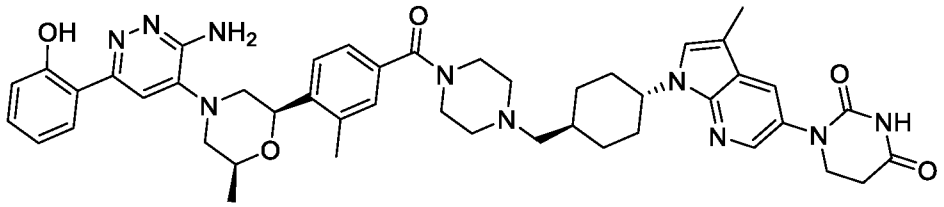
[3771] Statement 121. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



[3772] Statement 122. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



[3773] Statement 123. The compound, or pharmaceutically acceptable salt thereof, according to Statement 113, wherein the compound is:



[3774] Statement 124. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, and a pharmaceutically acceptable excipient.

[3775] Statement 125. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124.

[3776] Statement 126. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124.

[3777] Statement 127. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124.

[3778] Statement 128. The method of Statement 127, wherein the cancer is a SMARCA2-sensitive cancer.

[3779] Statement 129. The method of Statement 127, wherein the cancer is a SMARCA2-mutated cancer.

[3780] Statement 130. The method of any one of Statements 127-129, wherein the cancer is a solid tumor.

[3781] Statement 131. The method of any one of Statements 127-129, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[3782] Statement 132. A compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 for use in degrading SMARCA2 protein in a human.

[3783] Statement 133. A compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 for use in reducing the level of SMARCA2 activity in a human.

[3784] Statement 134. A compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 for use in treating cancer in a human.

[3785] Statement 135. The compound for use of Statement 134, wherein the cancer is a SMARCA2-sensitive cancer.

[3786] Statement 136. The compound for use of Statement 134, wherein the cancer is a SMARCA2-mutated cancer.

[3787] Statement 137. The compound for use of any one of Statements 134-136, wherein the cancer is a solid tumor.

[3788] Statement 138. The compound for use of any one of Statements 134-136, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[3789] Statement 139. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[3790] Statement 140. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

[3791] Statement 141. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Statements 1-123, or the composition of Statement 124 in the manufacture of a medicament for treating cancer in a human.

[3792] Statement 142. The compound, or pharmaceutical acceptable salt thereof, for use of Statement 141, wherein the cancer is a SMARCA2-sensitive cancer.

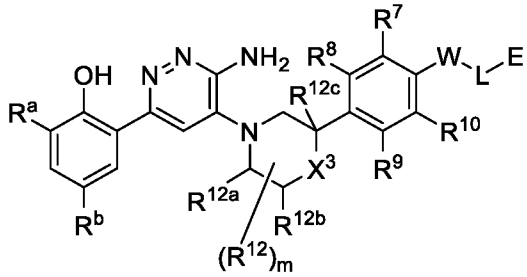
[3793] Statement 143. The compound, or pharmaceutically acceptable salt thereof, for use of Statement 141, wherein the cancer is a SMARCA2-mutated cancer.

[3794] Statement 144. The compound for use of any one of Statements 141-143, wherein the cancer is a solid tumor.

[3795] Statement 145. The compound for use of any one of Statements 141-143, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

WHAT IS CLAIMED IS:

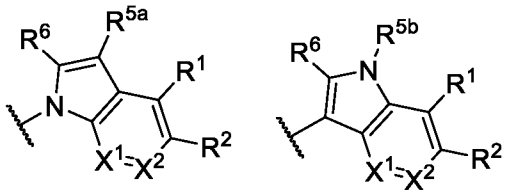
1. A compound having Formula (A), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(A),

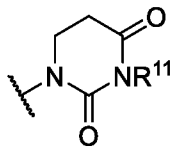
wherein:

E is:



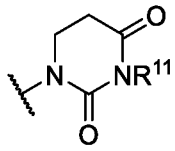
E-1 or E-2 ;

R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

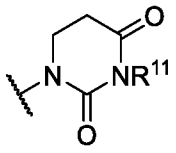
R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

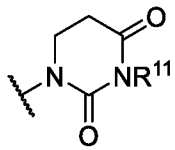
with the provisos:

(i) when R^1 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^2 is:



; and

(ii) when R^2 is hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy, then R^1 is:



;

R^{11} is hydrogen or -(C_1-C_6)alkyl-O-P(=O)-$(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

X^3 is $-(CR^{13a}R^{13b})_n-$ or -O-;

n is 0 or 1

each R^{13a} and R^{13b} is independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

L is $-G^1$-G^2-G^3-G^4-, wherein G^1 is attached to W;

G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

G^2 is $(C_1$-$C_6)$alkylenyl, -C(=O)-, or a direct bond;

G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

W is -C(=O)-, $-CH_2-$, or a direct bond;

R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

m is 0, 1, 2, 3, or 4;

R^{12a} and R^{12b} are each independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen; or

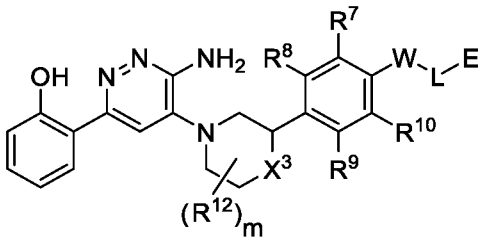
R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted (C_5-C_7)cycloalkyl;

R^{12c} is hydrogen or halogen;

R^a is hydrogen or halogen; and

R^b is hydrogen or halogen.

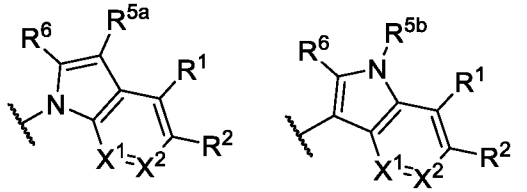
2. A compound having Formula (I), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(I),

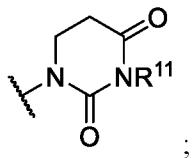
wherein:

E is:



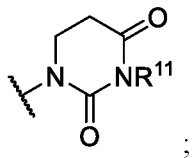
E-1 or E-2 ;

R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

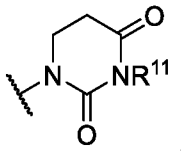
R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

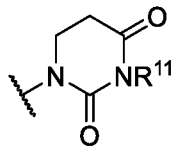
with the provisos:

(i) when R^1 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy, then R^2 is:



; and

(ii) when R^2 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy, then R^1 is:



;

R^{11} is hydrogen or -$(C_1$-$C_6)$alkyl-O-P(=O)-$(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

R^{5a} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1$-$C_6)$alkyl;

R^{5b} is hydrogen, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl;

R^6 is hydrogen, $(C_1$-$C_6)$alkyl, or cyano;

X^3 is -$(CR^{13a}R^{13b})_n$- or -O-;

n is 0 or 1

each R^{13a} and R^{13b} is independently H, halogen, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy;

L is -G^1-G^2-G^3-G^4-, wherein G^1 is attached to W;

G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

G^2 is $(C_1$-$C_6)$alkylenyl or a direct bond;

G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally

substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

G^4 is (C_1-C_6)alkylenyl or a direct bond;

W is -C(=O)-;

R^7 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

R^8 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

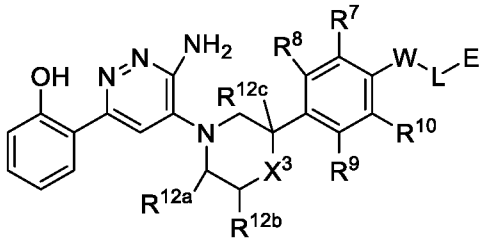
R^9 is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

R^{10} is hydrogen, halogen, (C_1-C_6)alkyl, cyano, or (C_3-C_6)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one, two, or three halogen;

each R^{12} is independently halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

m is 0, 1, 2, 3, or 4.

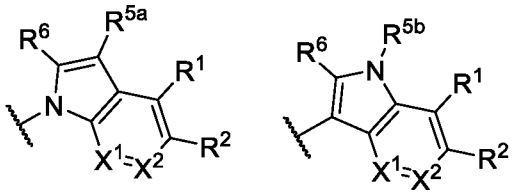
3. A compound having Formula (IA), or pharmaceutically acceptable salt and/or stereoisomer thereof:



(IA),

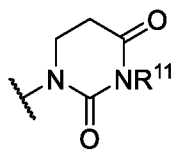
wherein:

E is:



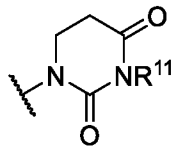
E-1 or E-2 ;

R^1 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

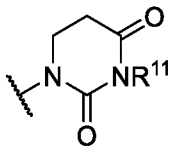
R^2 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or



;

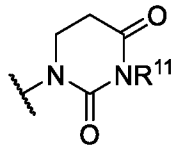
with the provisos:

(i) when R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^2 is:



; and

(ii) when R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy, then R^1 is:



;

R^{11} is hydrogen or $-(C_1\text{-}C_6)$alkyl-O-P(=O)-$(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

R^{5a} is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl;

R^{5b} is hydrogen, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl;

R^6 is hydrogen, $(C_1\text{-}C_6)$alkyl, or cyano;

X^3 is $-(CR^{13a}R^{13b})_n$- or -O-;

n is 0 or 1

each R^{13a} and R^{13b} is independently hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

L is $-G^1\text{-}G^2\text{-}G^3\text{-}G^4$-, wherein G^1 is attached to W;

G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano; or $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

G^2 is $(C_1\text{-}C_6)$alkylenyl, -C(=O)-, or a direct bond;

G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano; or $(C_3$-$C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, or cyano;

G^4 is $(C_1$-$C_6)$alkylenyl or a direct bond;

W is -C(=O)-, $-CH_2-$, or a direct bond;

R^7 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^8 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^9 is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

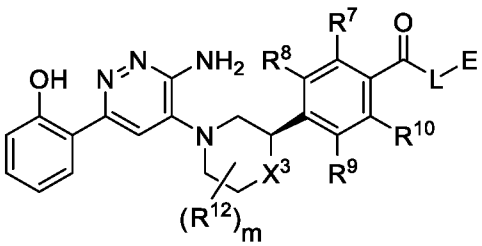
R^{10} is hydrogen, halogen, $(C_1$-$C_6)$alkyl, cyano, or $(C_3$-$C_6)$cycloalkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen;

R^{12a} and R^{12b} are each independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, wherein $(C_1$-$C_6)$alkyl is optionally substituted with one, two, or three halogen; or

R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted $(C_5$-$C_7)$cycloalkyl ; and

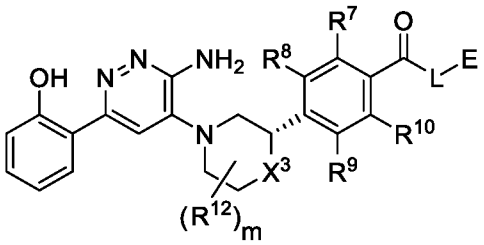
R^{12c} is hydrogen or halogen.

4. The compound, or pharmaceutically acceptable salt thereof, according to claims 1 or 2 having Formula (II):



(II).

5. The compound, or pharmaceutically acceptable salt thereof, according to claims 1 or 2 having Formula (III):



(III).

6. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X^3 is -($CR^{13a}R^{13b}$)-.

7. The compound, or pharmaceutically acceptable salt thereof, according to claim 6, wherein R^{13a} and R^{13b} are hydrogen.

8. The compound, or pharmaceutically acceptable salt thereof, according to claim 6, wherein R^{13a} and R^{13b} are fluoro.

9. The compound, or pharmaceutically acceptable salt thereof, according to claim 6, wherein R^{13a} is methyl or methoxy; and R^{13b} is hydrogen.

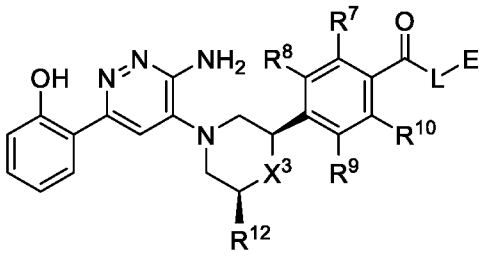
10. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X^3 is -O-.

11. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 2, or 4-10, wherein m is 0.

12. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 2, or 4-10, wherein m is 2.

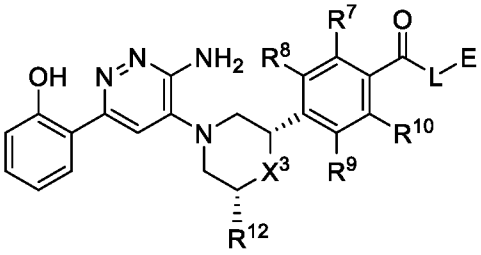
13. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 2, or 4-10, wherein m is 1.

14. The compound, or pharmaceutically acceptable salt thereof, according to claim 2 having Formula (IV):



(IV).

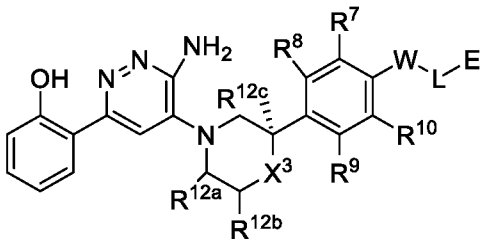
15. The compound, or pharmaceutically acceptable salt thereof, according to claim 2 having Formula (V):



(V).

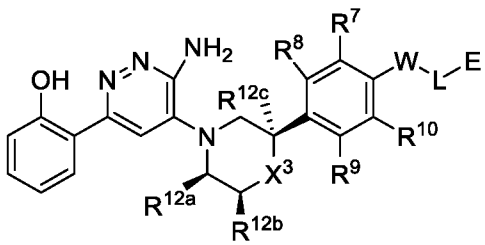
16. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 13-15, wherein each R^{12} is fluoro, methyl, ethyl, or methoxy.

17. The compound, or pharmaceutically acceptable salt thereof, according to claim 3, having Formula (VIII):



(VIII).

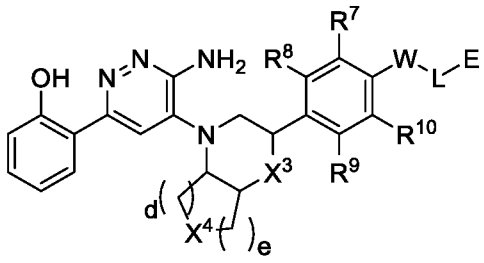
18. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 3 or 17, having Formula (IX):



(IX).

19. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 3, 17, or 18, wherein R^{12a} is hydrogen and R^{12b} is hydrogen, fluoro, methyl, ethyl, or methoxy.

20. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to claim 3 having Formula (X):



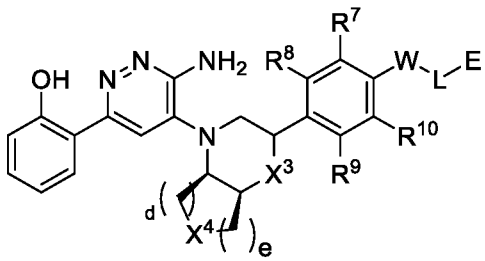
(X)

wherein:

X^4 is O; and

d and e are independently 1 or 2.

21. The compound, or pharmaceutically acceptable salt thereof, according to claim 3 having Formula (XI):



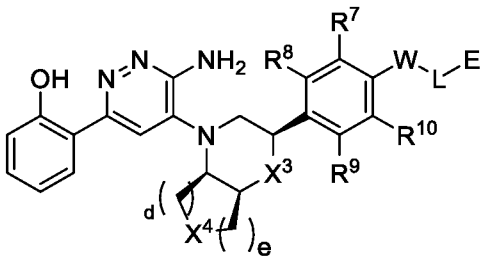
(XI)

wherein:

X^4 is O; and

d and e are independently 1 or 2.

22. The compound, or pharmaceutically acceptable salt thereof, according to claim 3 having Formula (XII):



(XII)

wherein:

X^4 is O; and

d and e are independently 1 or 2.

23. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-22, wherein E is E-1.

24. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is hydrogen.

25. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is $(C_1\text{-}C_6)$alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

26. The compound, or pharmaceutically acceptable salt thereof, according to claim 25, wherein R^{5a} is methyl, ethyl, isopropyl, or $-CF_3$.

27. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is $(C_3\text{-}C_6)$cycloalkyl.

28. The compound, or pharmaceutically acceptable salt thereof, according to claim 27, wherein R^{5a} is cyclopropyl.

29. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

30. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is cyano.

31. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

32. The compound, or pharmaceutically acceptable salt thereof, according to claim 23, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1\text{-}C_6)$alkyl.

33. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-22, wherein E is E-2.

34. The compound, or pharmaceutically acceptable salt thereof, according to claim 33, wherein R^{5b} is hydrogen.

35. The compound, or pharmaceutically acceptable salt thereof, according to claim 33, wherein R^{5b} is $(C_1\text{-}C_6)$alkyl.

36. The compound, or pharmaceutically acceptable salt thereof, according to claim 35, wherein R^{5b} is methyl.

37. The compound, or pharmaceutically acceptable salt thereof, according to claim 33, wherein R^{5b} is $(C_3\text{-}C_6)$cycloalkyl.

38. The compound, or pharmaceutically acceptable salt thereof, according to claim 37, wherein R^{5b} is cyclopropyl or cyclobutyl.

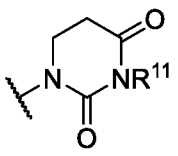
39. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-38, wherein R^6 is hydrogen.

40. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-38, wherein R^6 is $(C_1\text{-}C_6)$alkyl.

41. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-38, wherein R^6 is cyano.

42. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-41, wherein:

R^1 is:



; and

R^2 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

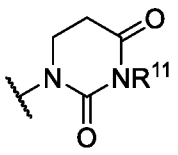
43. The compound, or pharmaceutically acceptable salt thereof, according to claim 42, wherein R^2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

44. The compound, or pharmaceutically acceptable salt thereof, according to claim 43, wherein R^2 is hydrogen, fluoro, or methyl.

45. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 42-44, wherein R^{11} is hydrogen.

46. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-41, wherein:

R^2 is:



; and

R^1 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

47. The compound, or pharmaceutically acceptable salt thereof, according to claim 46, wherein R^1 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl.

48. The compound, or pharmaceutically acceptable salt thereof, according to claim 46, wherein R^1 is hydrogen, fluoro, or methyl.

49. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 46-48, wherein R^{11} is hydrogen.

50. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-49, wherein X^1 is CR^3.

51. The compound, or pharmaceutically acceptable salt thereof, according to claim 50, wherein R^3 is hydrogen.

52. The compound, or pharmaceutically acceptable salt thereof, according to claim 50, wherein R^3 is halogen.

53. The compound, or pharmaceutically acceptable salt thereof, according to claim 52, wherein R^3 is fluoro.

54. The compound, or pharmaceutically acceptable salt thereof, according to claim 50, wherein R^3 is $(C_1\text{-}C_6)$alkyl.

55. The compound, or pharmaceutically acceptable salt thereof, according to claim 54, wherein R^3 is methyl.

56. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-49, wherein X^1 is N.

57. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-56, wherein X^2 is CR^4.

58. The compound, or pharmaceutically acceptable salt thereof, according to claim 57, wherein R^4 is hydrogen.

59. The compound, or pharmaceutically acceptable salt thereof, according to claim 57, wherein R^4 is halogen.

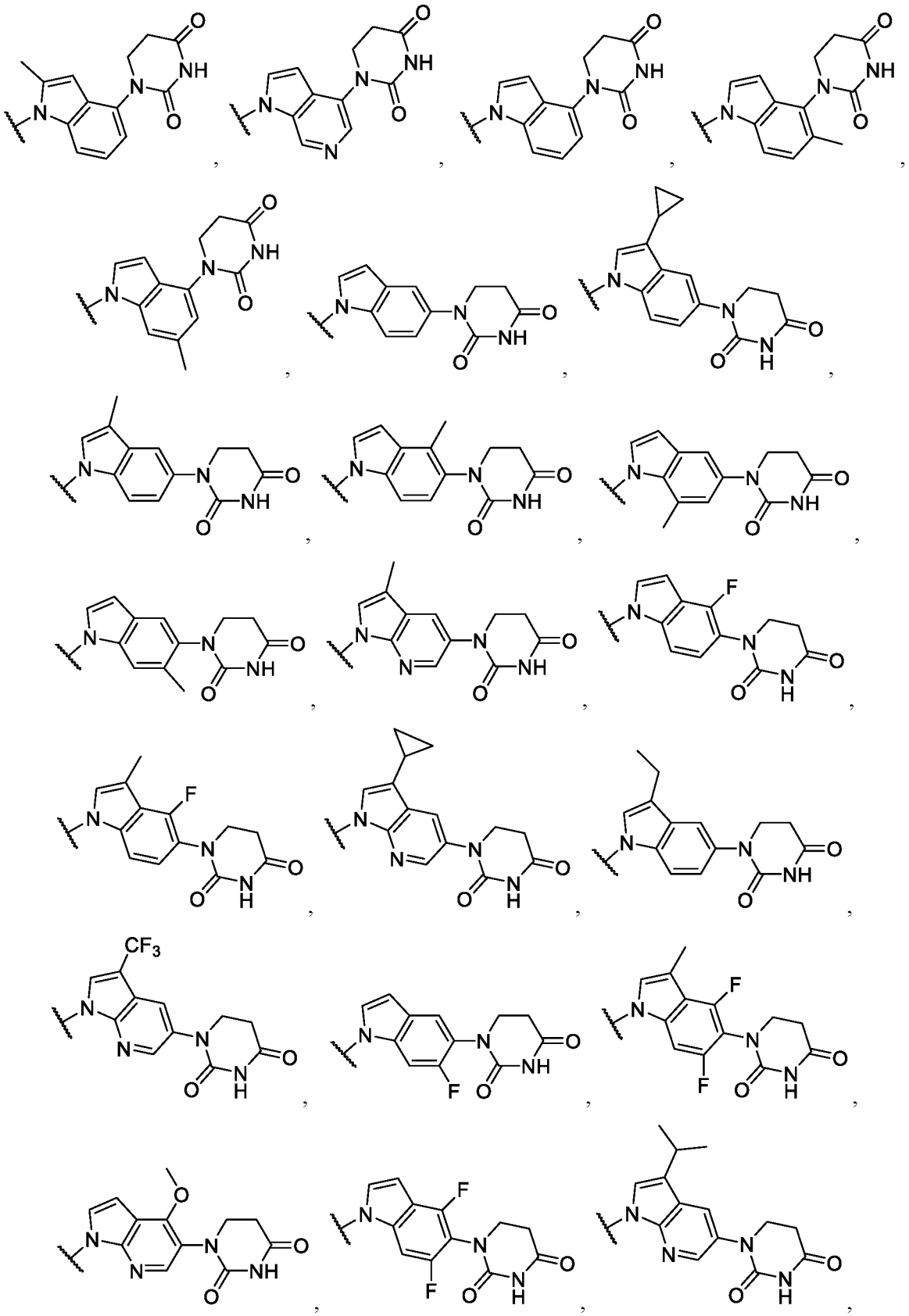
60. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein R^4 is fluoro.

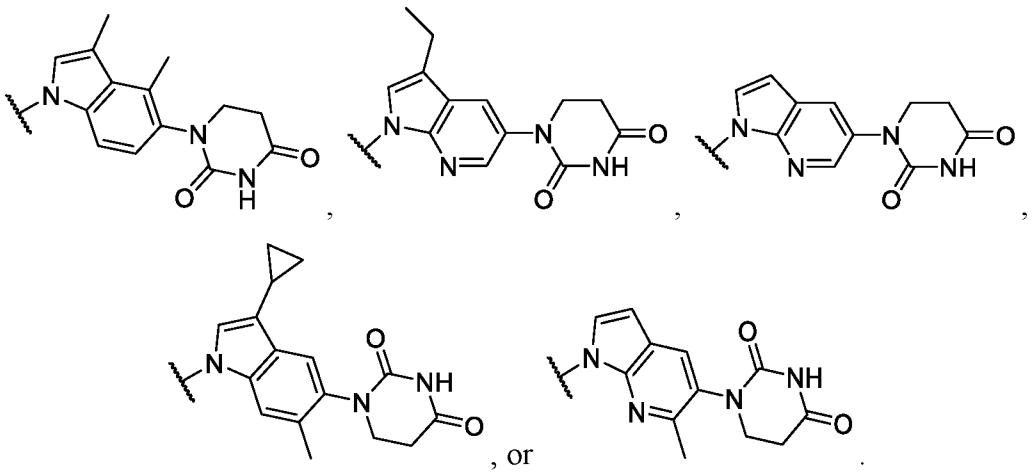
61. The compound, or pharmaceutically acceptable salt thereof, according to claim 57, wherein R^4 is $(C_1\text{-}C_6)$alkyl.

62. The compound, or pharmaceutically acceptable salt thereof, according to claim 61, wherein R^4 is methyl.

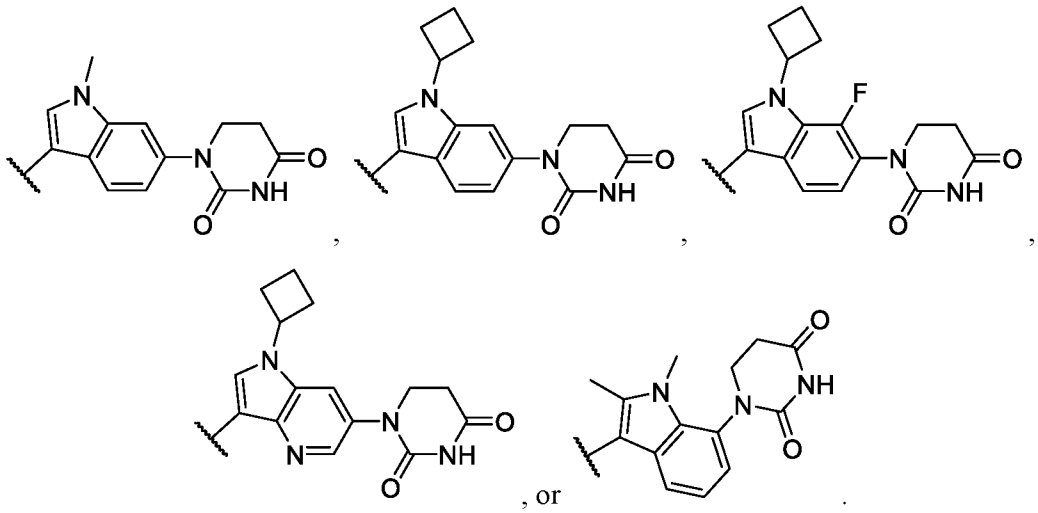
63. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-56, wherein X^2 is N.

64. The compound of claim 23, wherein E-1 is:





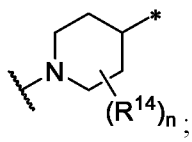
65. The compound of claim 33, wherein E-2 is:



66. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-65, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

67. The compound, or pharmaceutically acceptable salt thereof, according to claim 66, wherein:

G^1 is:



each R^{14} is independently halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

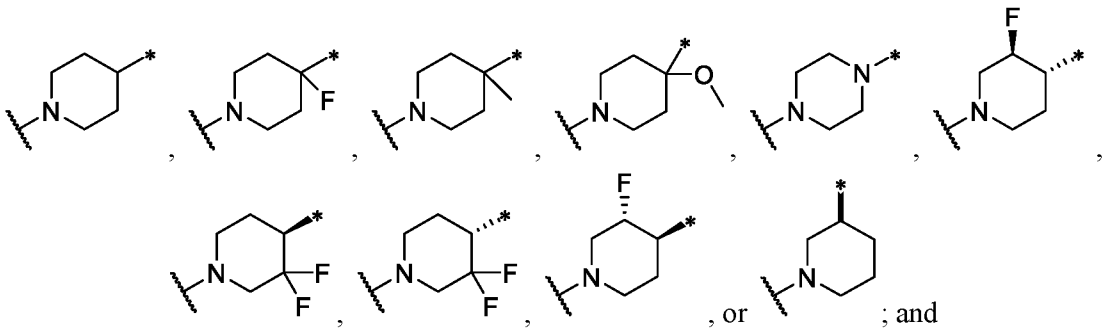
n is 0, 1, 2, or 3; and

the bond marked with an "*" is attached to G^2.

68. The compound, or pharmaceutically acceptable salt thereof, according to claim 67, wherein n is 0.

69. The compound, or pharmaceutically acceptable salt thereof, according to claim 67, wherein R^{14} is fluoro, methyl, or methoxy; and n is 1, or 2.

70. The compound, or pharmaceutically acceptable salt thereof, according claim 66, wherein G^1 is:



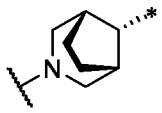
; and

the bond marked with an "*" is attached to G^2.

71. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-65, wherein G^1 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

72. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-65, wherein G^1 is a 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

73. The compound, or pharmaceutically acceptable salt thereof, according to claim 72, wherein G^1 is:



; and

the bond marked with an "*" is attached to G^2.

74. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-73, wherein G^2 is a direct bond.

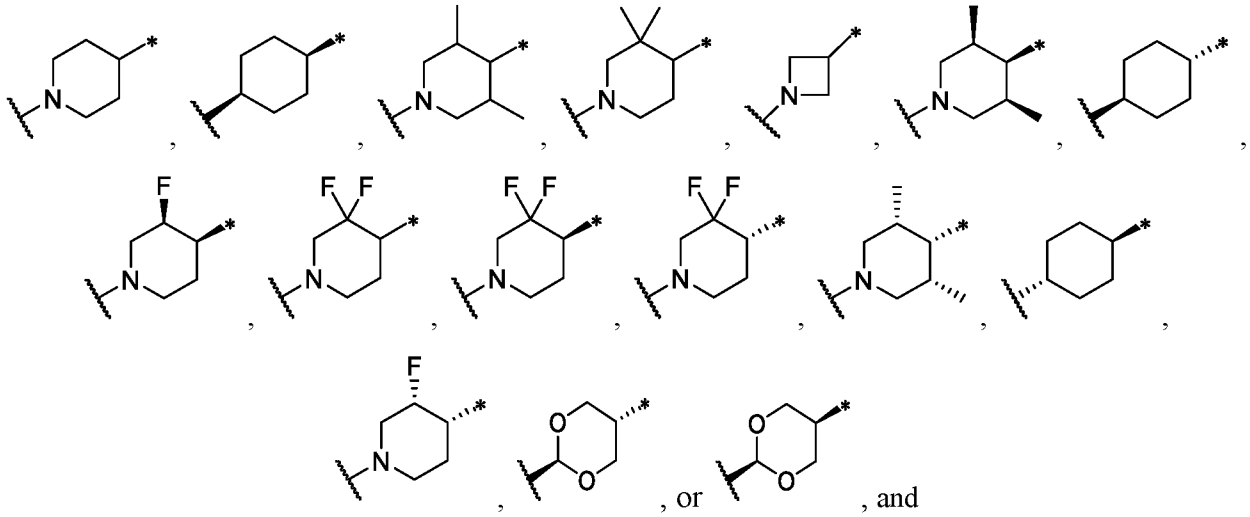
75. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-73, wherein G^2 is $(C_1\text{-}C_6)$alkylenyl.

76. The compound, or pharmaceutically acceptable salt thereof, according to claim 75, wherein G^2 is $-CH_2-$ or $-CH(CH_3)-$.

77. The compound, or pharmaceutically acceptable salt thereof, according to claim 1-73, wherein G^2 is –C(=O)-.

78. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-73, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

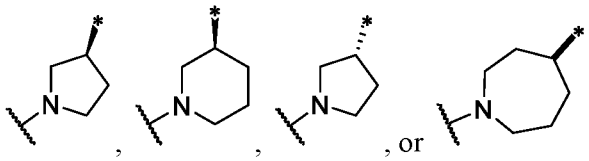
79. The compound, or pharmaceutically acceptable salt thereof, according claim 78, wherein G^3 is:



the bond marked with an "*" is attached to G^4.

80. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-77, wherein G^3 is 4- to 7-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

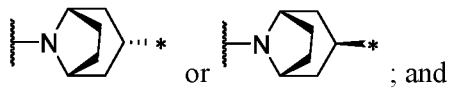
81. The compound, or pharmaceutically acceptable salt thereof, according to claim 80, wherein G^3 is:



the bond marked with an "*" is attached to G^4.

82. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-77, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

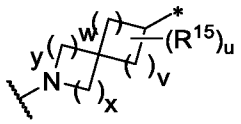
83. The compound, or pharmaceutically acceptable salt thereof, according to claim 82, wherein G^3 is:

 ; and

the bond marked with an "*" is attached to G^4.

84. The compound, or pharmaceutically acceptable salt thereof, according to claim 82, wherein:

G^3 is:

 ;

each R^{15} is independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano;

u is 0, 1, 2, or 3;

v, w, x, and t are independently 1, 2, or 3; and

the bond marked with an "*" is attached to G^4.

85. The compound, or pharmaceutically acceptable salt thereof, according to claim 84, wherein v, w, x, and y are independently 1 or 2.

86. The compound, or pharmaceutically acceptable salt thereof, according to claim 85, wherein G^3 is:

 ; and

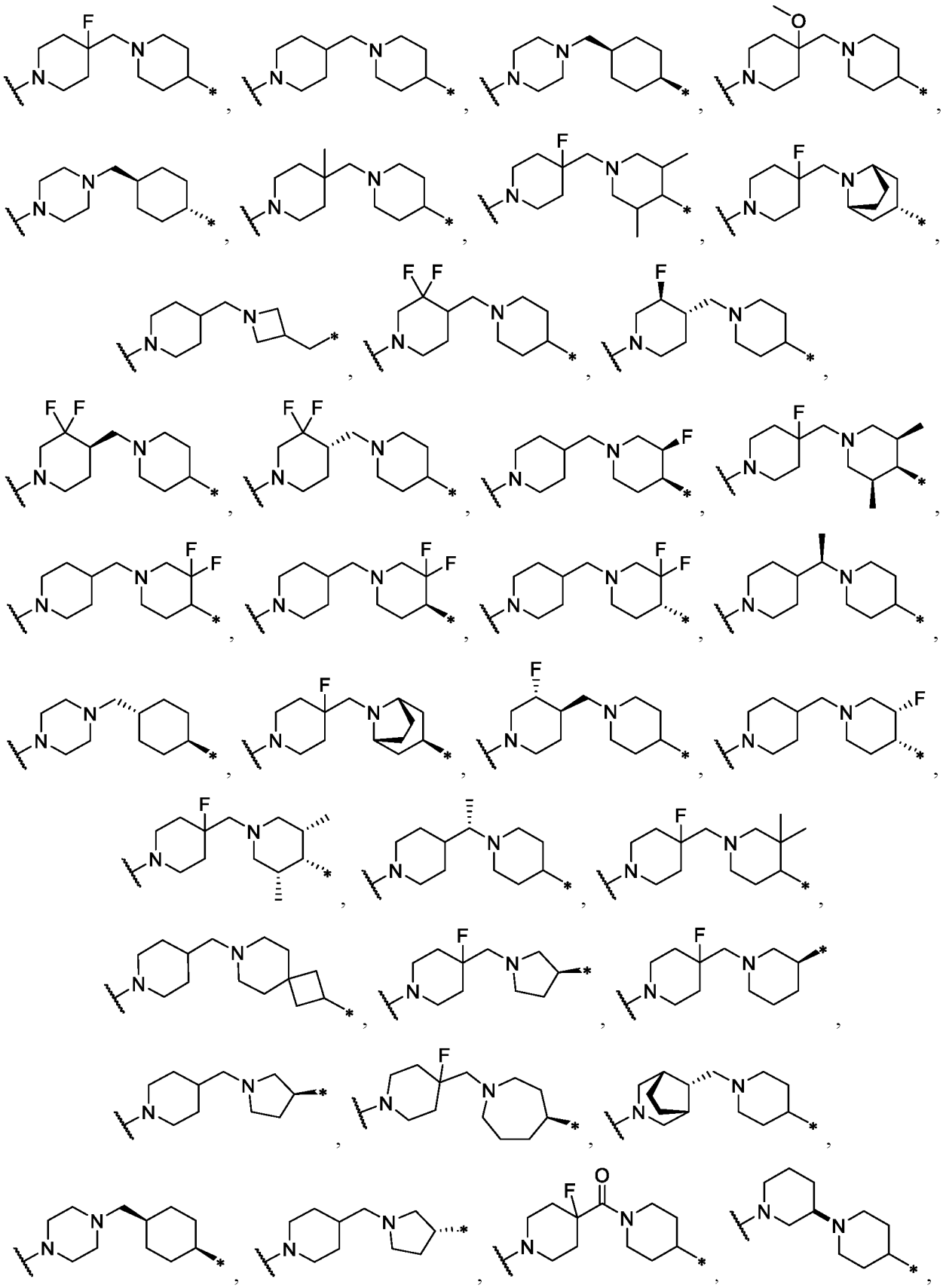
the bond marked with an "*" is attached to G^4.

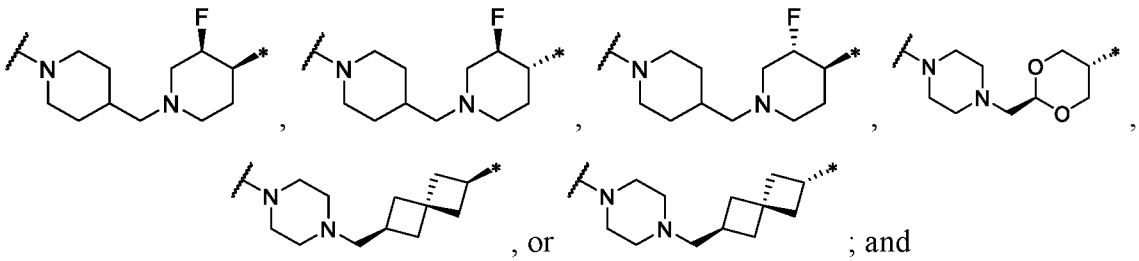
87. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-77, wherein G^3 is $(C_3\text{-}C_6)$cycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or cyano.

88. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-87, wherein G^4 is $(C_1\text{-}C_6)$alkylenyl.

89. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-87, wherein G^4 is a direct bond.

90. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-65, wherein L is:





, or ; and

the bond marked with an "*" is attached to E.

91. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-90, wherein R^7 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

92. The compound, or pharmaceutically acceptable salt thereof, according to claim 91, wherein R^7 is halogen or $(C_1\text{-}C_6)$alkyl.

93. The compound, or pharmaceutically acceptable salt thereof, according to claim 92, wherein R^7 is fluoro or methyl.

94. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 91-93, wherein R^8, R^9, and R^{10} are hydrogen.

95. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-90, wherein R^8 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

96. The compound, or pharmaceutically acceptable salt thereof, according to claim 95, wherein R^8 is halogen or $(C_1\text{-}C_6)$alkyl.

97. The compound, or pharmaceutically acceptable salt thereof, according to claim 96, wherein R^8 is fluoro or methyl.

98. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 95-97, wherein R^7, R^9, and R^{10} are hydrogen.

99. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-90, wherein R^9 is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

100. The compound, or pharmaceutically acceptable salt thereof, according to claim 99, wherein R^9 is halogen.

101. The compound, or pharmaceutically acceptable salt thereof, according to claim 100, wherein R^9 is fluoro.

102. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 99-101, wherein R^7, R^8, and R^{10} are hydrogen.

103. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-90, wherein R^{10} is halogen, $(C_1\text{-}C_6)$alkyl, cyano, or $(C_3\text{-}C_6)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen.

104. The compound, or pharmaceutically acceptable salt thereof, according to claim 103, wherein R^{10} is halogen.

105. The compound, or pharmaceutically acceptable salt thereof, according to claim 104, wherein R^{10} is fluoro.

106. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 103-105, wherein R^7, R^8, and R^9 are hydrogen.

107. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-90, wherein R^7, R^8, R^9, and R^{10} are hydrogen.

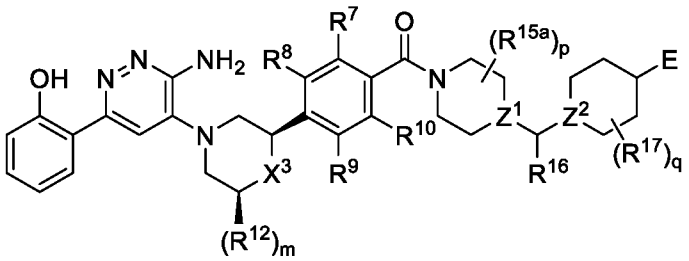
108. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 6-13, or 23-107, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one, two, or three halogen; and m is 0.

109. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 6-13, or 23-107, wherein R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocycloalkyl or an optionally substituted $(C_5\text{-}C_7)$cycloalkyl; and m is 0.

110. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 6-13, or 23-109, wherein R^a is fluoro and R^b is hydrogen.

111. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 6-13, or 23-110, wherein R^a is hydrogen and R^b is fluoro.

112. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 2, 6-10, 64, or 65, having Formula (VI):



(VI),

wherein:

R^{15a} is fluoro;

p is 0, 1, or 2;

Z^1 is CR^{15b} or N;

R^{15b} is hydrogen, fluoro, methyl, or methoxy;

R^{16} is hydrogen or methyl;

Z^2 is CH or N;

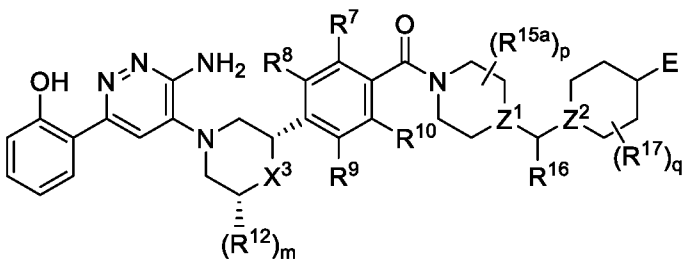
R^{17} is fluoro or methyl;

q is 0, 1, or 2;

R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

113. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 2, 6-10, 64, or 65, having Formula (VII):



(VII),

wherein:

R^{15a} is fluoro;

p is 0, 1, or 2;

Z^1 is CR^{15b} or N;

R^{15b} is hydrogen, fluoro, methyl, or methoxy;

R^{16} is hydrogen or methyl;

Z^2 is CH or N;

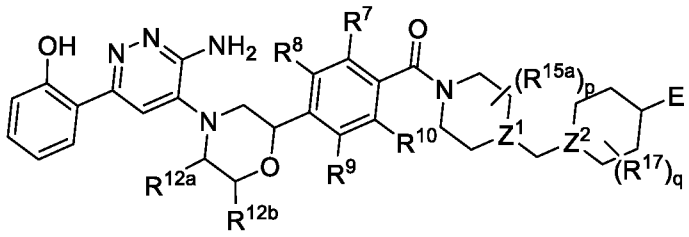
R^{17} is fluoro or methyl;

q is 0, 1, or 2;

R^{12} is fluoro, methyl, ethyl, or methoxy; and m is 1; or R^{12} is hydrogen; and m is 0;

R^7, R^8, R^9, and R^{10} are independently hydrogen, fluoro, chloro, methyl, $-CF_3$, cyclopropyl, methoxy, or cyano.

114. The compound, pharmaceutically acceptable salt and/or stereoisomer thereof, according to any one of claims 3, 64, or 65 having Formula (XIII):



(XIII),

wherein:

R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

R^{12a} and R^{12b} are independently hydrogen or methyl;

R^{15a} is fluoro;

p is 0, 1, or 2;

Z^1 is CR^{15b} or N;

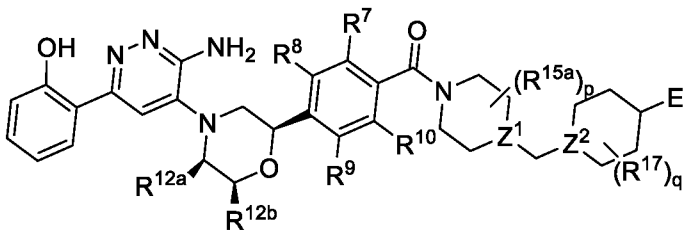
R^{15b} is hydrogen or fluoro;

Z^2 is CH or N;

R^{17} is fluoro; and

q is 0, 1, or 2.

115. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 3, 64, or 65, having Formula (XIV):



(XIV),

wherein:

R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

R^{12a} and R^{12b} are independently hydrogen or methyl;

R^{15a} is fluoro;

p is 0, 1, or 2;

Z^1 is CR^{15b} or N;

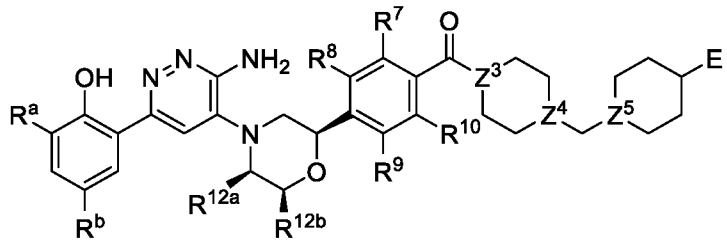
R^{15b} is hydrogen or fluoro;

Z^2 is CH or N;

R^{17} is fluoro; and

q is 0, 1, or 2.

116. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 64, or 65, having Formula (XV):



(XV)

wherein:

R^a and R^b are independently hydrogen or fluoro;

R^7, R^8, R^9, and R^{10} are independently hydrogen or methyl;

R^{12a} and R^{12b} are independently hydrogen or methyl; or

R^{12a} and R^{12b} taken together with the carbon atoms to which they are attached form a 5-membered heterocycloalkyl;

Z^3 is CH or N.

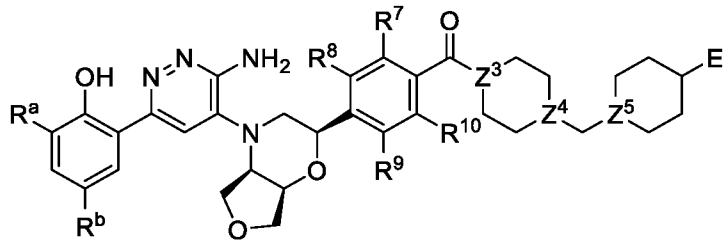
Z^4 is CR^{15b} or N;

R^{15b} is hydrogen or fluoro; and

Z^5 is CH or N.

117. The compound, or pharmaceutically acceptable salt thereof, according to claim 16, wherein R^{12a} and R^{12b} are independently hydrogen or methyl.

118. The compound, or pharmaceutically acceptable salt thereof, according to claim 16 having Formula (XVI):



(XVI).

119. The compound according to claim 1 selected from any one or more of the compounds:

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-

methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)pyrrolidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-

yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-

2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-

2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-2-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-

yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-pyrrolo[3,2-b]pyridin-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-

yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-

yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-

4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3,5-difluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,3s,5S)-8-((1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,3s,5S)-8-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-((1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(-1-(1-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-

yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(3-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(3-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1,2-dimethyl-1H-indol-7-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-

yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione ;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((S*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(-1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rel-1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

or pharmaceutically acceptable salts thereof.

120. The compound according to claim 1 selected from any one or more of the compounds:

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-

dione;

(S)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-

yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((3R,5S)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-

3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3,4-dimethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((3R,4R)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-

yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,5-difluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-

yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-

3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-((1R,4r)-4-((4-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)yridazine-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione ;

1-(1-(1-(((R*)-1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-

3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((S*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(-1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-

yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((R*)-1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((3S,4S*,5R)-1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-

dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-ethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4,6-difluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-

yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-3-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-cyclopropylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-2-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-5-(4-((4-(3-cyclopropyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)piperidin-1-yl)methyl)-4-fluoropiperidine-1-carbonyl)benzonitrile;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)meth*yl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-(trifluoromethyl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-

b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methoxybenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methoxypiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)-3,5-dimethylpiperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methylpiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4,4-difluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,4S*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-4-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6R)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2S,6S)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rel-(R)-1-(1-(1-((1-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

1-(1-(1-((1-(4-((R*)-4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

or pharmaceutically acceptable salts thereof.

121. The compound according to claim 1 selected from any one or more of the compounds:

1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)pyrrolidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((3S*,4R*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-3-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-fluoro-5-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-chlorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-(((1R,5S,8S)-3-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3-fluoropiperidin-3-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-2-fluorobenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-5-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione

1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-((1R,4r)-4-((4-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R*,5R*,6S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

rac-1-(1-(1-((1-(4-((2R,5R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-ethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,4aR,7aR)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2H-furo[3,4-b][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,6-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(3-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-cyclobutyl-7-fluoro-1H-indol-6-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,5R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-fluoropiperidin-3-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-4-fluoro-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((3R*,5R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((R)-1-((1-(4-((R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperidin-4-yl)methyl)pyrrolidin-3-yl)-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1R,4r)-4-((4-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(1-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-2,3-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)azepan-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R*,6R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-(fluoromethyl)morpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((1S,4s)-4-((4-(4-((R*)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-2-methyl-1H-indol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(1-(1-(1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)benzyl)-4-fluoropiperidine-4-carbonyl)piperidin-4-yl)-3-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((S*)-1'-(4-((R)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)-3-methylbenzoyl)-[1,3'-bipiperidin]-4-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R*)-1-(1-(7-((1-(4-(1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperidin-3-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(1-((1-(4-((2R,6S)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

1-(1-(1-((1-(4-((2S,6R)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1H-indol-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

or pharmaceutically acceptable salts thereof.

122. The compound according to claim 1 selected from any one or more of the compounds:

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-

methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*s*)-4-((4-(4-((*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*s*)-4-((4-(4-((*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)morpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

1-(1-((1*R*,4*r*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

1-(1-((1*S*,4*s*)-4-((4-(4-((3*R**,5*R**)-1-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methoxypiperidin-3-yl)-3-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Isomer 1) ((*absolute configuration not yet confirmed));

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-

pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*R*,4*r*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-cyclopropyl-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*S*,4*R*)-1-((1-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-2-methyl-1*H*-indol-4-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((1*S*,4*s*)-4-((4-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*S*,4*s*,6*S*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*R*,4*r*,6*R*)-6-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)spiro[3.3]heptan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((3*R*,4*S*)-1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)-2-methylbenzoyl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-3-methyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)-2,5-dimethylbenzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-6-methylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(3,5-difluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*R*,5*R*,6*S*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-((2*r*,5*R*)-2-((4-(4-((2*S*,5*S*,6*R*)-4-(3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-5,6-dimethylmorpholin-2-yl)benzoyl)piperazin-1-yl)methyl)-1,3-dioxan-5-yl)-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione;

1-(1-(1-((1-(4-((2*R*,5*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)-5-methylmorpholin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione; and

1-(1-(1-((1-(4-((2*R*,4a*R*,7a*R*)-4-(3-Amino-6-(5-fluoro-2-hydroxyphenyl)pyridazin-4-yl)hexahydro-2*H*-furo[3,4-*b*][1,4]oxazin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-6-methyl-1*H*-indol-5-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione,

or pharmaceutically acceptable salts thereof.

123. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, and a pharmaceutically acceptable excipient.

124. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123.

125. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123.

126. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123.

127. The method of claim 126, wherein the cancer is a SMARCA2-sensitive cancer.

128. The method of claim 126, wherein the cancer is a SMARCA2-mutated cancer.

129. The method of any one of claims 126-128, wherein the cancer is a solid tumor.

130. The method of any one of claims 126-128, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

131. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 for use in degrading SMARCA2 protein in a human.

132. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 for use in reducing the level of SMARCA2 activity in a human.

133. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 for use in treating cancer in a human.

134. The compound for use of claim 133, wherein the cancer is a SMARCA2-sensitive cancer.

135. The compound for use of claim 133, wherein the cancer is a SMARCA2-mutated cancer.

136. The compound for use of any one of claims 133-135, wherein the cancer is a solid tumor.

137. The compound for use of any one of claims 133-135, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

138. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

139. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

140. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-122, or the composition of claim 123 in the manufacture of a medicament for treating cancer in a human.

141. The compound, or pharmaceutical acceptable salt thereof, for use of claim 140, wherein the cancer is a SMARCA2-sensitive cancer.

142. The compound, or pharmaceutically acceptable salt thereof, for use of claim 140, wherein the cancer is a SMARCA2-mutated cancer.

143. The compound for use of any one of claims 141-143, wherein the cancer is a solid tumor.

144. The compound for use of any one of claims 141-143, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055751

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/55
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/195201 A1 (ARVINAS OPERATIONS INC [US]; GENENTECH INC [US]) 10 October 2019 (2019-10-10)	1-89, 91-111, 117, 123-144
A	claims 1-48 paragraphs [001390], [001391]	90, 112-116, 118-122

Y	WO 2019/207538 A1 (AURIGENE DISCOVERY TECH LTD [IN]) 31 October 2019 (2019-10-31)	1-89, 91-111, 117, 123-144
A	claims 1-43	90, 112-116, 118-122

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2024	30/09/2024

Name and mailing address of the ISA/	Authorized officer
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	claims 1-23	90, 112-116, 118-122

Y	WO 2016/138114 A1 (GENENTECH INC [US]; CONSTELLATION PHARMACEUTICALS INC [US]) 1 September 2016 (2016-09-01)	1-89, 91-111, 117, 123-144
A	example 10 of table on page 179; example 59 of table on page 188	90, 112-116, 118-122

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A	page 2, lines 34-39 claims 1-71 at least examples 11, 13-18, 40, 45, 48-51, 53, 72-75, 111-119	90, 112-116, 118-122

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