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(54) Benævnelse: **Substituerede pyrazolo[1,5-A]pyridin-forbindelser som RET-kinase-inhibitorer**

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DESCRIPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

BACKGROUND

[0001] The present disclosure relates to novel compounds which exhibit Rearranged during Transfection (RET) kinase inhibition, pharmaceutical compositions comprising the compounds, processes for making the compounds, and the use of the compounds in therapy. More particularly, it relates to substituted pyrazolo[1,5-a]pyridine compounds useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders. US 2012/0277247 describes certain pyrazolopyridine compounds as JAK inhibitors.

[0002] RET is a single-pass transmembrane receptor belonging to the tyrosine kinase superfamily that is required for normal development, maturation and maintenance of several tissues and cell types (Mulligan, L. M., Nature Reviews Cancer, 2014, 14, 173-186). The extracellular portion of the RET kinase contains four calcium-dependent cadherin-like repeats involved in ligand binding and a juxtamembrane cysteine-rich region necessary for the correct folding of the RET extracellular domain, while the cytoplasmic portion of the receptor includes two tyrosine kinase subdomains.

[0003] RET signaling is mediated by the binding of a group of soluble proteins of the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which also includes neurturin (NTRN), artemin (ARTN) and persephin (PSPN) (Arighi et al., Cytokine Growth Factor Rev., 2005, 16, 441-67). Unlike other receptor tyrosine kinases, RET does not directly bind to GFLs and requires an additional co-receptor: that is, one of four GDNF family receptor-α (GFRα) family members, which are tethered to the cell surface by a glycosylphosphatidylinositol linkage. GFLs and GFRα family members form binary complexes that in turn bind to RET and recruit it into cholesterol-rich membrane subdomains, which are known as lipid rafts, where RET signaling occurs.

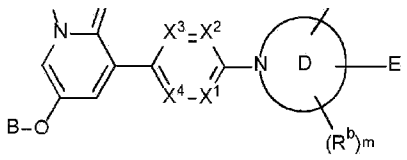
[0004] Upon binding of the ligand-co-receptor complex, RET dimerization and autophosphorylation on intracellular tyrosine residues recruits adaptor and signaling proteins to stimulate multiple downstream pathways. Adaptor protein binding to these docking sites leads to activation of Ras-MAPK and PI3K-Akt/mTOR signaling pathways or to recruitment of the CBL family of ubiquitin ligases that functions in RET downregulation of the RET-mediated functions.

[0005] Aberrant RET expression and/or activity have been demonstrated in different cancers, gastrointestinal disorders and irritable bowel syndrome (IBS).

SUMMARY OF THE INVENTION

[0006] It has now been found that substituted pyrazolo[1,5-a]pyridine compounds are inhibitors of RET kinase, and are useful for treating proliferative diseases and cancers.

[0007] Accordingly, provided herein is a compound of the Formula **I:**



I

or pharmaceutically acceptable salt or solvate thereof, wherein A, B, X^1, X^2, X^3, X^4, Ring D, E, R^a, R^b, n and m are as defined herein.

[0008] Also provided herein is a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

[0009] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0010] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer and/or inhibiting metastasis associated with a particular cancer.

[0011] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of irritable bowel syndrome (IBS) or pain associated with IBS.

[0012] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, and diarrhea, associated with treatment, including chemotherapeutic treatment.

[0013] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for use in the inhibition of RET kinase activity.

[0014] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a RET-associated disease or disorder.

[0015] Also provided herein is a pharmaceutical combination for treating cancer (e.g., a RET-associated cancer, and RET-associated cancer having one or more RET inhibitor resistance mutations) in a patient in need thereof, which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier, wherein the compound of Formula I or the pharmaceutically acceptable salt or solvate thereof and the additional therapeutic are formulated as separate compositions or dosages for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the cancer. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of cancer. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use.

[0016] Also provided herein is a pharmaceutical combination for treating irritable bowel syndrome (IBS) in a patient in need thereof, which comprises administering (a) a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use for the treatment of IBS, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the IBS. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of the IBS. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use.

[0017] Also provided herein is a process for preparing a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

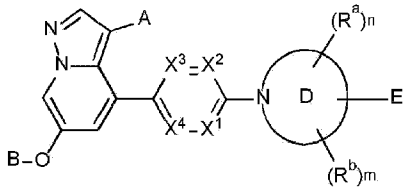
[0018] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof obtained by a process of preparing the compound as defined herein.

[0019] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used.

[0020] Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0021] 1. A compound of the Formula I:



I

and pharmaceutically acceptable salts thereof, wherein:

X^1, X^2, X^3 and X^4 are independently CH, CCH_3, CF or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

A is H, CN, Cl, methyl, ethyl or cyclopropyl;

B is:

1. (a) hydrogen,
2. (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
3. (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
4. (d) dihydroxyC3-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

5. (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
6. (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- and (C1-C6 alkoxy)C(=O)-;
7. (g) $hetAr^1$C1-C3 alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;
8. (h) (C3-C6 cycloalkyl)C1-C3 alkyl-,
9. (i) ($hetCyc^a$)C1-C3 alkyl-,
10. (j) $hetCyc^a$,
11. (k) (R^1R^2N)C(=O)C1-C6 alkyl- where R^1 and R^2 are independently selected from H and C1-C6 alkyl,
12. (l) (R^1R^2N)C(=O)-, where R^1 and R^2 are independently selected from H and C1-C6 alkyl, or
13. (m) $hetCyc^a$C(=O)C1-C6 alkyl-;

$hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo, and (C1-C6 alkoxy)C(=O)-;

Ring D is

1. (i) a saturated monocyclic 4-7 membered heterocyclic ring having one ring heteroatom which is nitrogen,

each R^a is independently C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl-;

R^b is (a) hydroxy,

(c) $hetCyc^bCH_2$- wherein $hetCyc^b$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and wherein $hetCyc^b$ is optionally substituted with C1-C6 alkyl (optionally substituted with 1-3 fluoros),

(e) R^cR^dN- or

(f) $R^cR^dNCH_2$-;

R^c is hydrogen or C1-C6 alkyl; and

R^d is hydrogen or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

n is 0, or 1;

m is 0 or 1;

E is:

(d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros,

(e) $hetAr^2$C1-C6 alkyl-,

(g) Ar^1O-,

(h) $hetAr^2O$-,

(l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl, or

(m) $hetAr^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), C3-C6 cycloalkyl, hydroxyC1-C6 alkyl, (C1-C6 alkyl)SO_2-, R^eR^fN- and (R^eR^fN)C1-C6 alkyl- where each R^e and R^f is independently H or C1-C6 alkyl;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S, or a 9-10 membered bicyclic heteroaryl having 1-2 ring nitrogen atoms, wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros) and hydroxyC1-C6 alkoxy.

[0022] For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, methoxyethyl comprises an ethyl backbone with a methoxy substituent.

[0023] The term "halogen" means -F (sometimes referred to herein as "fluoro" or "fluoros"), -Cl, -Br and -I.

[0024] The terms "C1-C3 alkyl", "C3-C6 alkyl", "C1-C6 alkyl", and "C2-C6 alkyl" as used herein refer to saturated linear or branched-chain monovalent hydrocarbon radicals of one to three, three to six, one to six, or two to six carbon atoms, respectively. Examples include, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, isobutyl, sec-butyl, tert-butyl, 2-methyl-2-propyl, pentyl, neopentyl, and hexyl.

[0025] The term "C1-C6 alkyl optionally substituted with 1-3 fluoros" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one to three hydrogen atoms is replaced with one to three fluoro atoms, respectively. Examples include, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-and trifluoroethyl.

[0026] The term "C1-C6 alkoxy" as used herein refer to saturated linear or branched-chain monovalent alkoxy radicals of one to six carbon atoms, wherein the radical is on the oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[0027] The term "(C1-C6 alkoxy)C1-C6 alkyl" as used herein refers to saturated linear or branched-chain monovalent radicals of one to six carbon atoms, wherein one of the carbon atoms is substituted with a C1-C6 alkoxy group as defined herein. Examples include methoxymethyl (CH_3OCH_2-) and methoxyethyl ($CH_3OCH_2CH_2$-).

[0028] The term "(C1-C6 alkoxy)C1-C6 alkoxy" as used herein refers to a C1-C6 alkoxy radical as defined herein, wherein one of the carbon atoms is substituted with a C1-C6 alkoxy group as defined herein. Examples include methoxymethoxy (CH_3OCH_2O-) and ethoxymethoxy (CH_3CH_2O-CH_2O-).

[0029] The terms "hydroxyC1-C6 alkyl" and "hydroxyC2-C6 alkyl", as used herein refers to saturated linear or branched-chain monovalent alkyl radicals of one to six or two to six carbon atoms, respectively, wherein one of the carbon atoms is substituted with a hydroxy group.

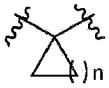
[0030] The term "dihydroxyC3-C6 alkyl" as used herein refers to a C3-C6 alkyl radical as defined herein, wherein two hydrogen atoms are replaced with a hydroxy group, provided the hydroxy groups are not on the same carbon.

[0031] The term "(R^1R^2N)C1-C6 alkyl" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a R^1R^2N- group, wherein R^1 and R^2 are as defined herein.

[0032] The term "hetAr^1C1-C6 alkyl" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetAr^1 group, wherein hetAr^1 is as defined herein.

[0033] The term "C3-C6 cycloalkyl" as used herein refers to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0034] The term "C3-C6 cycloalkylidene ring" as used herein refers to a divalent C3-C6 cycloalkane ring derived from a saturated 3-6 membered hydrocarbon ring by removal of two hydrogen atoms from the same carbon atom, for example, cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene. It can be represented in illustrative fashion by the following structure in which n is 1, 2 or 3:



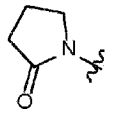
[0035] The term "(C3-C6 cycloalkyl)C1-C3 alkyl" as used herein refers to a C1-C3 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a C3-C6 cycloalkyl ring. An example is cyclobutylmethyl.

[0036] The term "(hetCyc^a)C1-C3 alkyl" as used herein refers to a C1-C3 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetCyc^a group, wherein hetCyc^a is as defined herein.

[0037] The term "Ar^1C1-C6 alkyl" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with an Ar^1 group, wherein Ar^1 is as defined herein.

[0038] The terms "hetAr^2C1-C6 alkyl" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetAr^2 group, wherein hetAr^2 is as defined herein.

[0039] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom, i.e., =O. For example, in one embodiment when referring to $hetCyc^a$, a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and substituted with an oxo may be, for example, a pyrrolidinyl ring substituted with oxo (e.g., a pyrrolidinonyl ring), which may be represented by the structure:



[0040] The term "spirocyclic ring" as used herein refers to a group having two rings joined by a spirocyclic linkage through a common single carbon atom, wherein each ring is a 4-7-membered ring (including the common carbon atom).

[0041] The term "heterospirocyclic" as used herein refers to a group having two rings joined by a spirocyclic linkage through a carbon atom, wherein each ring has 4 to 6 ring atoms (with one ring carbon atom being common to both rings), and wherein one of the ring atoms is a nitrogen atom.

[0042] The term "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[0043] The term "tautomer" as used herein refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium, and it is to be understood that compounds provided herein may be depicted as different tautomers, and when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the invention, and the naming of the compounds does not exclude any tautomer.

[0044] It will be appreciated that certain compounds provided herein may contain one or more centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers, a racemic mixture, or in an enantiomerically pure form.

[0045] In certain embodiments of Formula **I,** X^1, X^2, X^3 and X^4 are independently CH or CF. In certain embodiments, each of X^1, X^2, X^3 and X^4 is CH.

[0046] In certain embodiments of Formula **I,** X^1, X^2, X^3 and X^4 are independently CH, CF or N, wherein one of X^1, X^2, X^3 and X^4 is N and the remainder are independently CH or CF. In certain embodiments of Formula **I,** X^1 is N, and X^2, X^3 and X^4 are independently CH or CF. In certain embodiments, X^1 is N, and X^2, X^3 and X^4 are CH.

[0047] In certain embodiments of Formula I, X^1, X^2, X^3 and X^4 are independently CH, CF or N, wherein two of X^1, X^2, X^3 and X^4 are N. In certain embodiments of Formula I, X^1 and X^3 are N and X^2 and X^4 are independently CH or CF. In one embodiment, X^1 and X^3 are N and X^2 and X^4 are CH.

[0048] In certain embodiments of Formula I, A is H.

[0049] In certain embodiments of Formula I, A is Cl.

[0050] In certain embodiments of Formula I, A is CN.

[0051] In certain embodiments of Formula I, A is methyl.

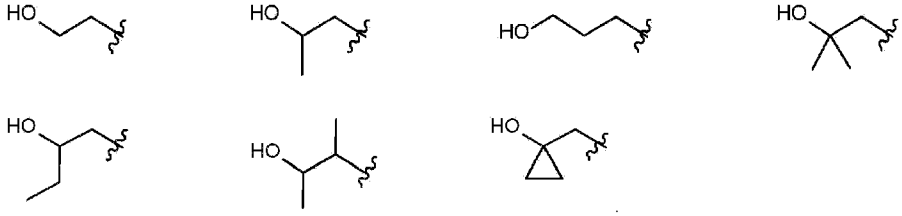
[0052] In certain embodiments of Formula I, A is ethyl.

[0053] In certain embodiments of Formula I, A is cyclopropyl.

[0054] In certain embodiments of Formula I, B is hydrogen.

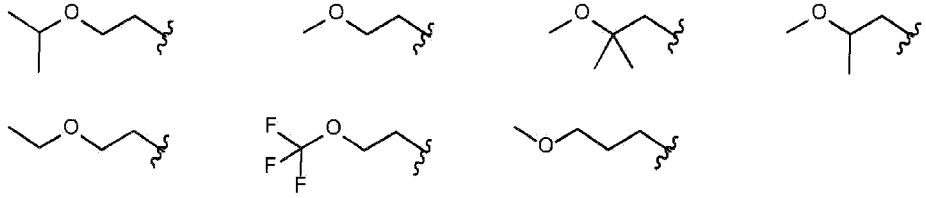
[0055] In certain embodiments of Formula I, B is C1-C6 alkyl optionally substituted with 1-3 fluoros. Examples include methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 2-ethylbutyl, neopentyl, difluoromethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl. In certain embodiments, B is methyl or ethyl.

[0056] In certain embodiments of Formula I, B is hydroxyC2-C6 alkyl wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In certain embodiments, the alkyl portion is unsubstituted. Examples include the structures:

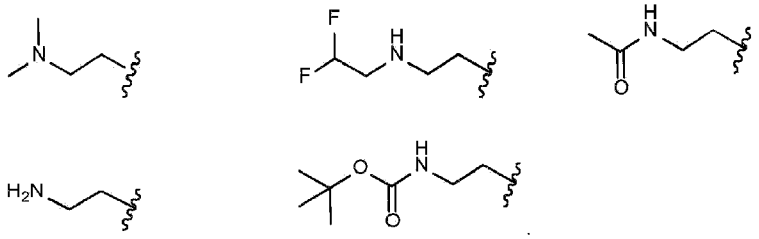


[0057] In certain embodiments of Formula I, B is dihydroxyC3-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. An example includes 2,3-dihydroxypropyl.

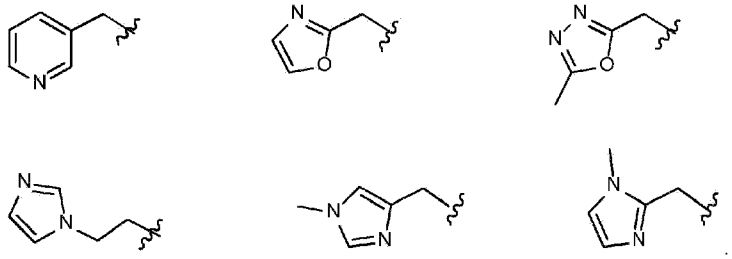
[0058] In certain embodiments of Formula I, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In certain embodiments of Formula I, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros. Examples include the structures:



[0059] In certain embodiments of Formula I, B is (R^1R^2N)C1-C6 alkyl-, where R^1 and R^2 are independently H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-. Examples of (R^1R^2N)C1-C6 alkyl- include the structures:

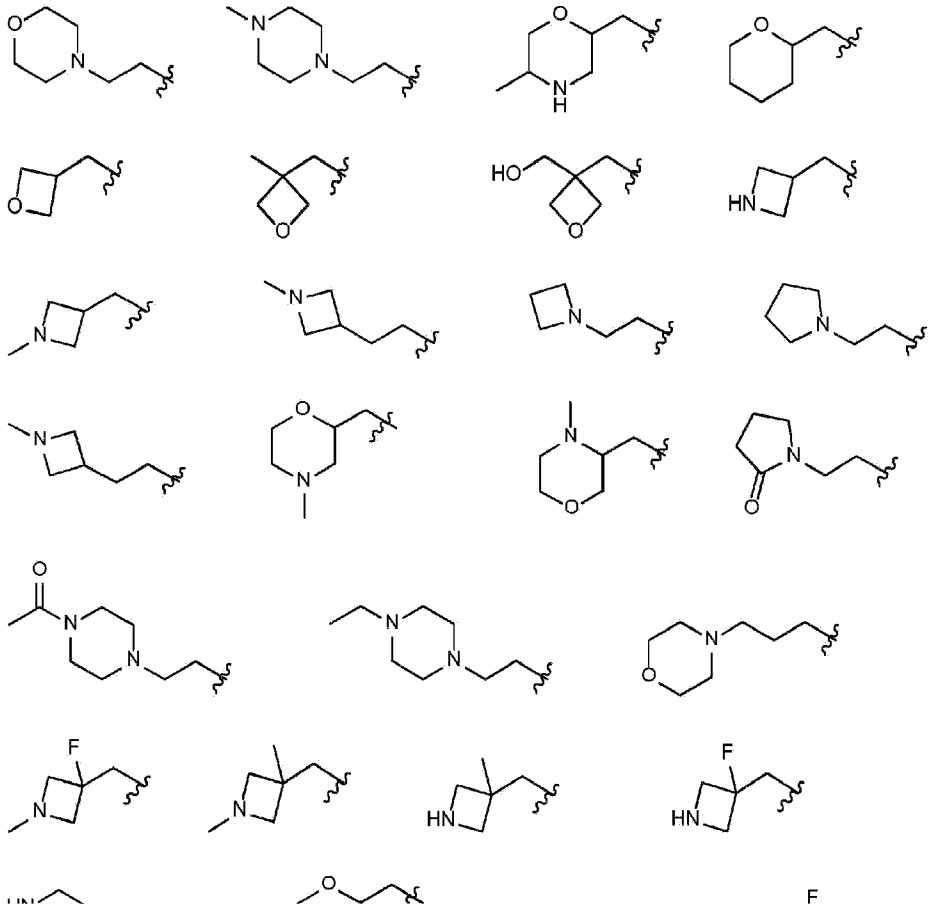


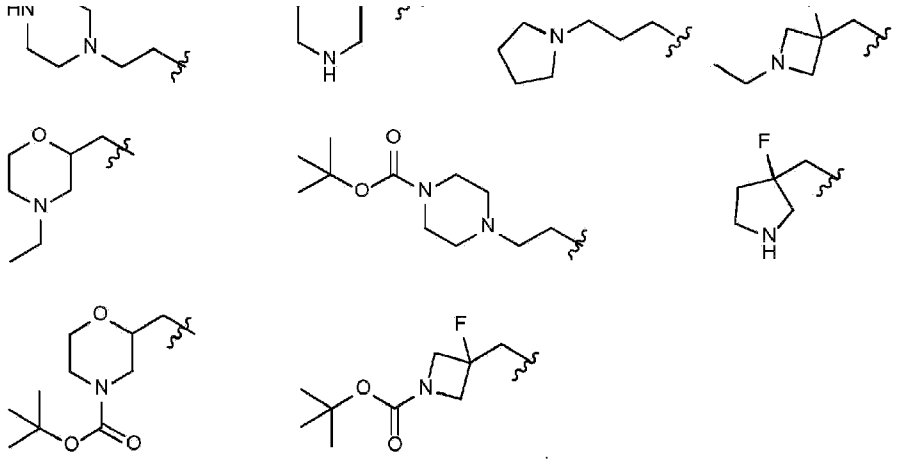
[0060] In certain embodiments of Formula **I**, B is hetAr^{1}C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents. In certain embodiments, hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O and is optionally substituted with C1-C6 alkyl. Examples of hetAr^{1}C1-C3 alkyl- include the structures:



[0061] In certain embodiments of Formula **I**, B is (C3-C6 cycloalkyl)C1-C3 alkyl- wherein said cycloalkyl is optionally substituted with OH. An example is cyclobutylmethyl.

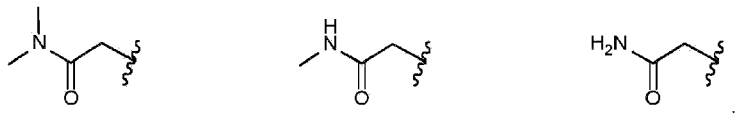
[0062] In certain embodiments of Formula **I**, B is (hetCyc^a)C1-C3 alkyl-, where hetCyc^a is as defined for Formula I. In certain embodiments of Formula **I**, B is (hetCyc^a)C1-C3 alkyl-, where hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-. Examples include the structures:



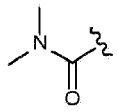


[0063] In certain embodiments of Formula I, B is $hetCyc^a$, where $hetCyc^2$ is as defined for Formula I. In certain embodiments, $hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros) or hydroxyC1-C6 alkyl-. Examples include the structures:

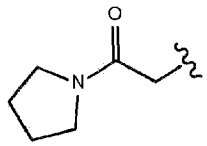
[0064] In certain embodiments of Formula I, B is $(R^1R^2N)C(=O)C1$-C6 alkyl- where R^1 and R^2 are independently selected from H and C1-C6 alkyl. Examples include the structures:



[0065] In certain embodiments of Formula I, B is $(R^1R^2N)C(=O)$-, where R^1 and R^2 are independently selected from H and C1-C6 alkyl. Examples include the structure:



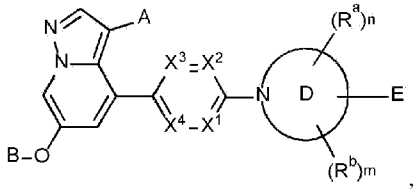
[0066] In certain embodiments of Formula I, B is $hetCyc^aC(=O)C1$-C6 alkyl- where $hetCyc^a$ is as defined for Formula I. An example includes the structure:



[0067] In certain embodiments of Formula I, B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros or (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In certain embodiments of Formula I, B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros or (c)

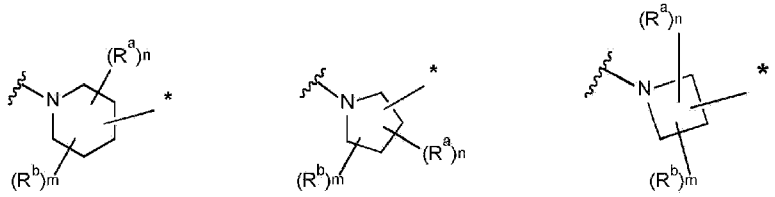
hydroxyC2-C6 alkyl-.

[0068] Referring now to Ring D of Formula I,



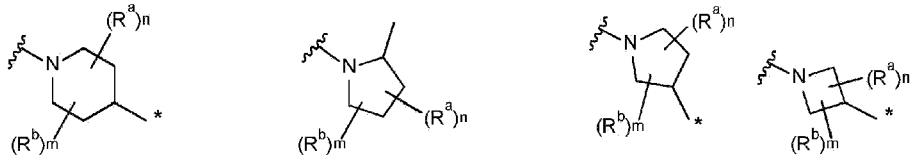
I

Ring D is (a saturated monocyclic 4-7 membered heterocyclic ring having one ring heteroatom which is nitrogen. The phrase "having one ring heteroatom which is nitrogen" when Ring D is a saturated monocyclic 4-7 membered heterocyclic ring means that said ring nitrogen atom is the nitrogen atom shown in Ring D of Formula I. Examples include the structures:



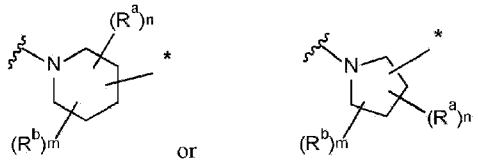
[0069] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group, and R^a, n, R^b and m are as defined for Formula I. In one embodiment, n is 0. In one embodiment, n is 1. In one embodiment, m is 0 or 1. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, n is 0 and m is 0 or 1. In one embodiment, n is 0 or 1 and m is 0.

[0070] In one embodiment of Formula I, Ring D is a saturated monocyclic 4-6 membered heterocyclic ring having one ring heteroatom which is nitrogen selected from the structures



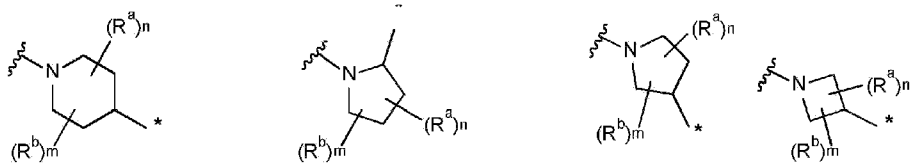
[0071] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group, and R^a, n, R^b and m are as defined for Formula I. In one embodiment, n is zero. In one embodiment, n is one. In one embodiment, m is 0 or 1. In one embodiment, m is 0. In one embodiment, m is 1.

[0072] In certain embodiments of Formula I, Ring D is a saturated monocyclic 5-6 membered heterocyclic ring having one ring heteroatom which is nitrogen having the structure:

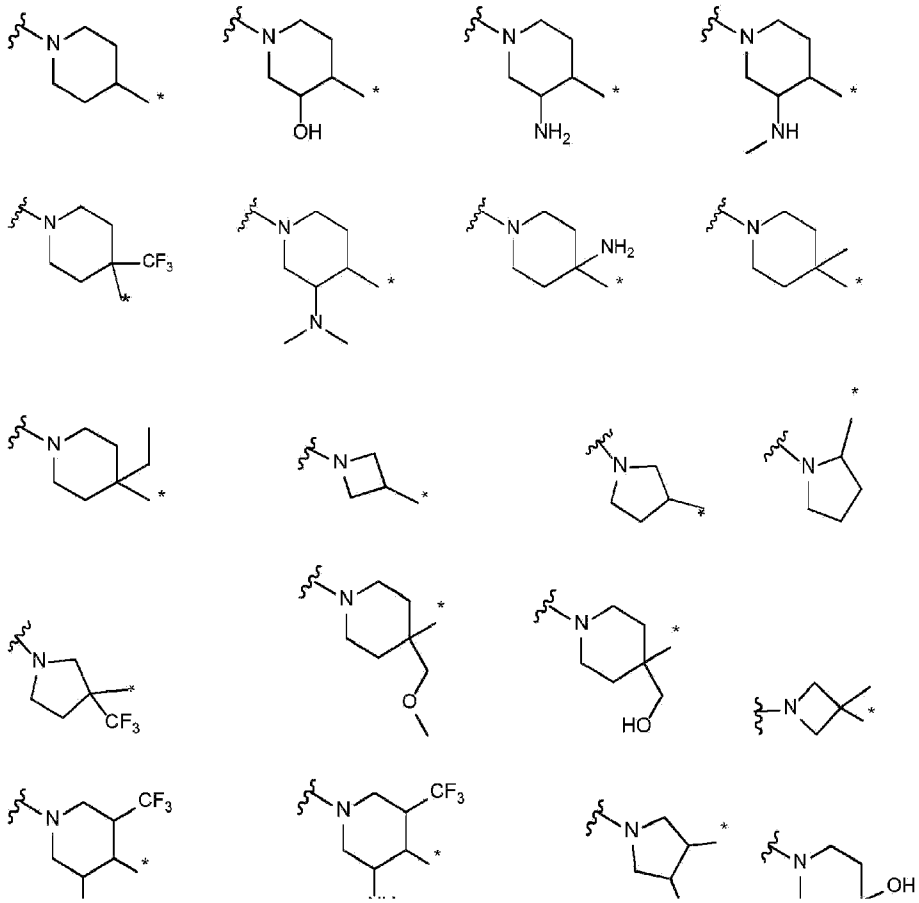


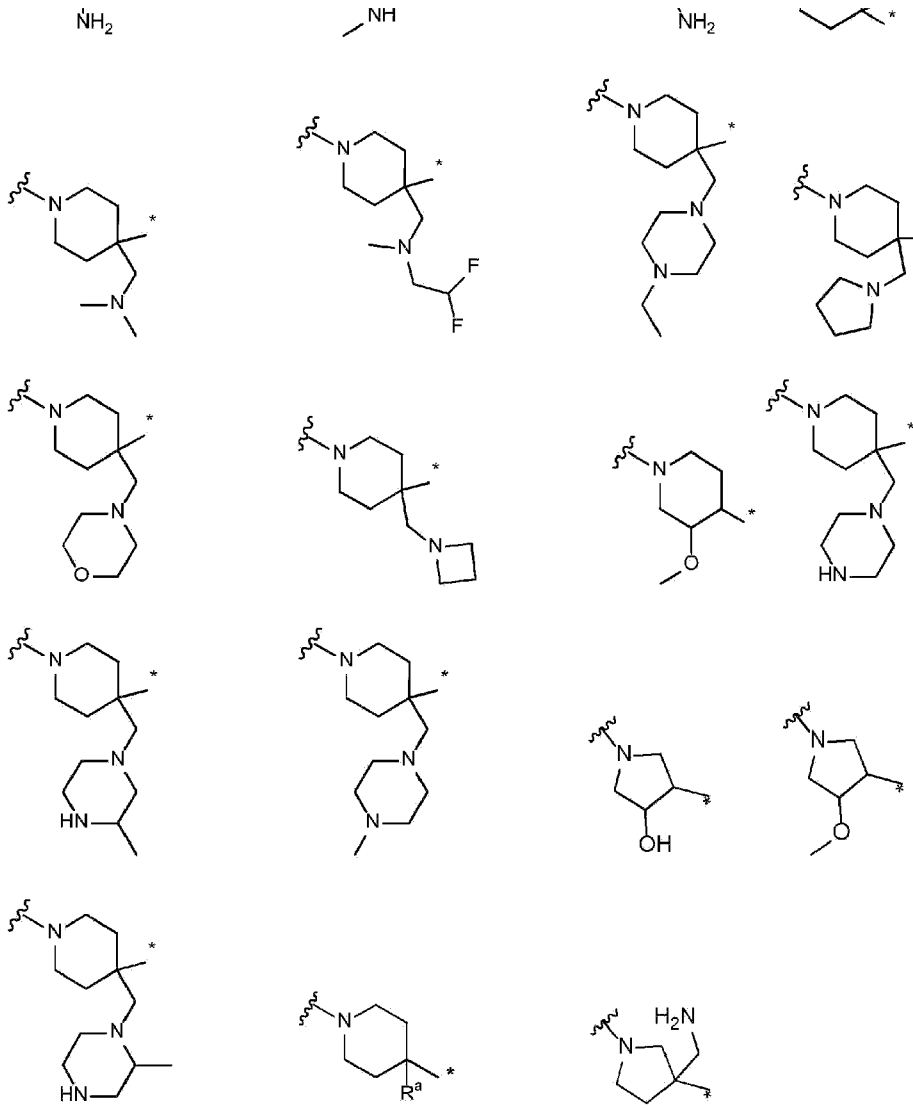
[0073] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group, and R^a, n, R^b and m are as defined for Formula I. In one embodiment, each R^a is independently selected from C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl-. In one embodiment, n is 0. In one embodiment, n is 1. In one embodiment, m is 0 or 1. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, Ring D is a saturated monocyclic 6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, Ring D is a saturated monocyclic 5 membered heterocyclic ring having one ring heteroatom which is nitrogen

[0074] In certain embodiments of Formula I, Ring D is a saturated monocyclic 4-6 membered heterocyclic ring having one ring heteroatom which is nitrogen selected from the structures:



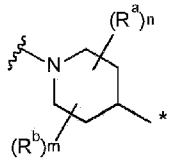
[0075] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group, and R^a, n, R^b and m are as defined for Formula I. In one embodiment, each R^a is independently selected from C1-C6 alkyl (optionally substituted with 1-3 fluoros) or (C1-C6 alkoxy)C1-C6 alkyl-. In one embodiment, n is 0. In one embodiment, n is one. In one embodiment, m is 0 or 1. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, n is 0 or 1 and m is 0 or 1. Examples when Ring D is an optionally substituted saturated 4-7 membered heterocyclic ring include the structures:



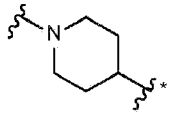


wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and asterisk indicates the point of attachment to the E group.

[0076] In one embodiment, Ring D is a saturated monocyclic 6 membered heterocyclic ring having one ring heteroatom which is nitrogen which may be represented by the structure:



where n and m are zero, that is, Ring D may be represented by the structure:

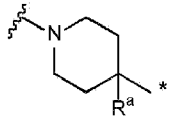


wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to the E group.

[0077] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, R^b is (a) OH, (c) $hetCyc^bCH_2$-wherein $hetCyc^b$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein

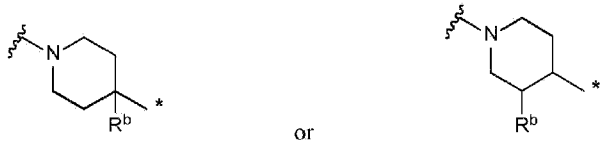
hetCyc^b is optionally substituted with C1-C6 alkyl (optionally substituted with 1-3 fluoros), (e) R^cR^dN- or (f) $R^cR^dNCH_2$-; R^c is hydrogen or C1-C6 alkyl; and R^d is hydrogen or C1-C6 alkyl (optionally substituted with 1-3 fluoros).

[0078] In one embodiment, Ring D is a saturated monocyclic 6-membered heterocyclic ring having one ring heteroatom which is nitrogen which may be represented by the structure:



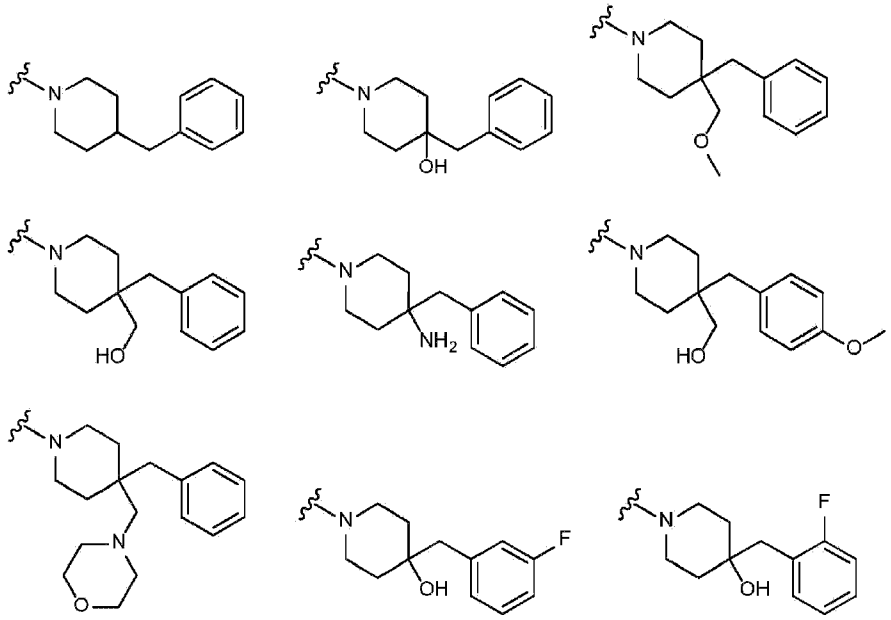
wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to the E group, and R^a is C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl-. In one embodiment, R^a is C1-C6 alkyl.

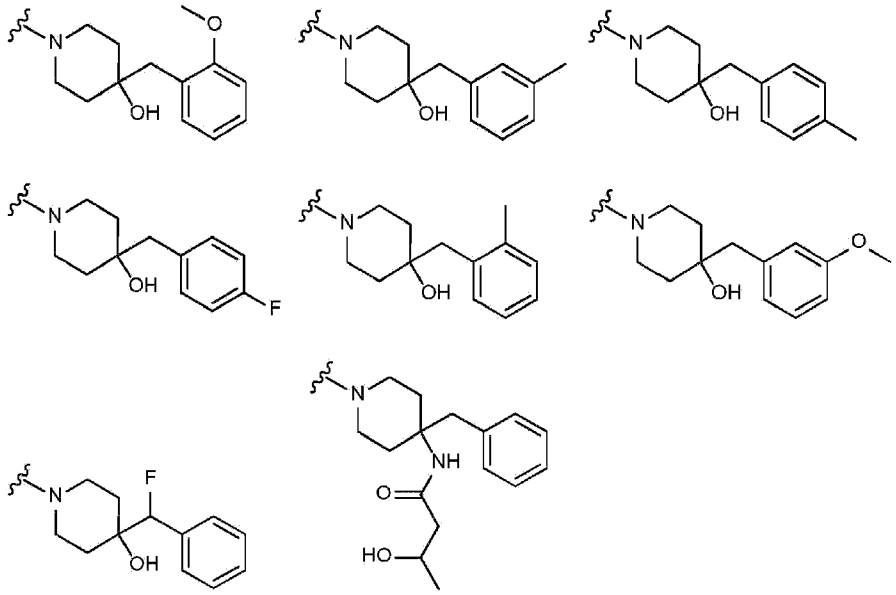
[0079] In one embodiment, Ring D is a saturated monocyclic 6-membered heterocyclic ring having one ring heteroatom which is nitrogen which may be represented by the structures:



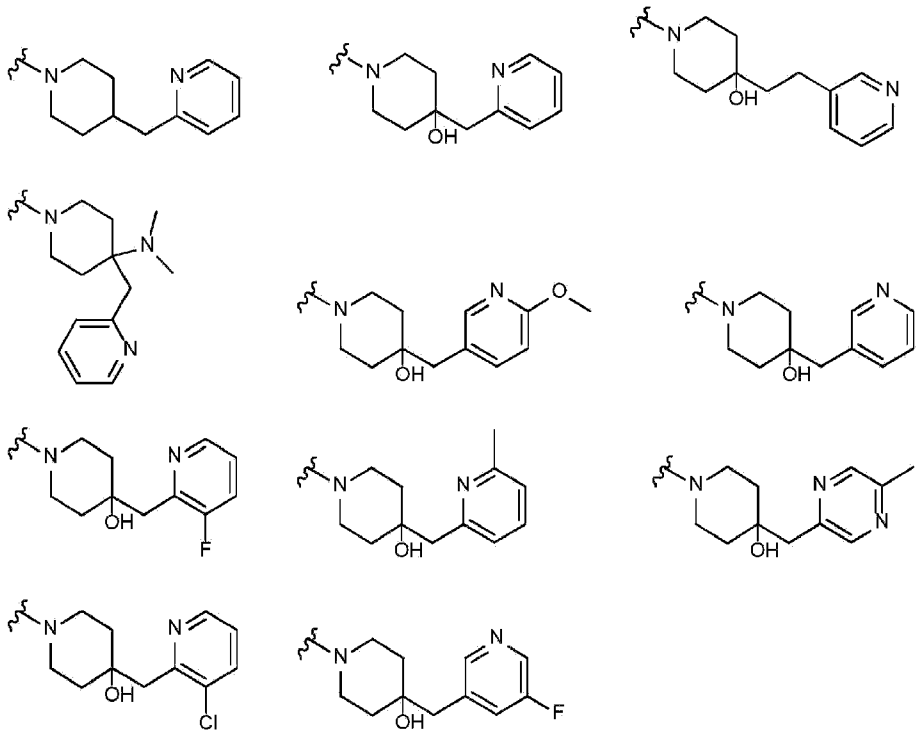
wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to the E group, and R^b is (a) OH, (c) hetCyc$^bCH_2$- , (e) R^cR^dN- or (f) $R^cR^dNCH_2$-; R^c is hydrogen or C1-C6 alkyl; R^d is hydrogen or C1-C6 alkyl (optionally substituted with 1-3 fluoros); and hetCyc^b is as defined for Formula I. In one embodiment, R^b is (c) hetCyc$^bCH_2$- , (e) R^cR^dN- or (f) $R^cR^dNCH_2$-; R^c is hydrogen or C1-C6 alkyl; R^d is hydrogen or C1-C6 alkyl (optionally substituted with 1-3 fluoros); and hetCyc^b is as defined for Formula I.

[0080] In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, R^b is OH. In one embodiment, n is 0, 1 or 2 and m is 0 or 1. In one embodiment, n is 0 and m is 0 or 1. Examples include the structures:

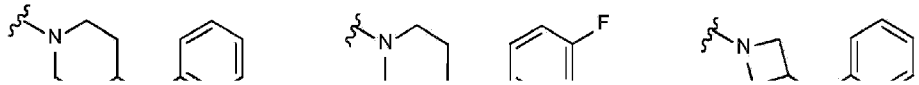


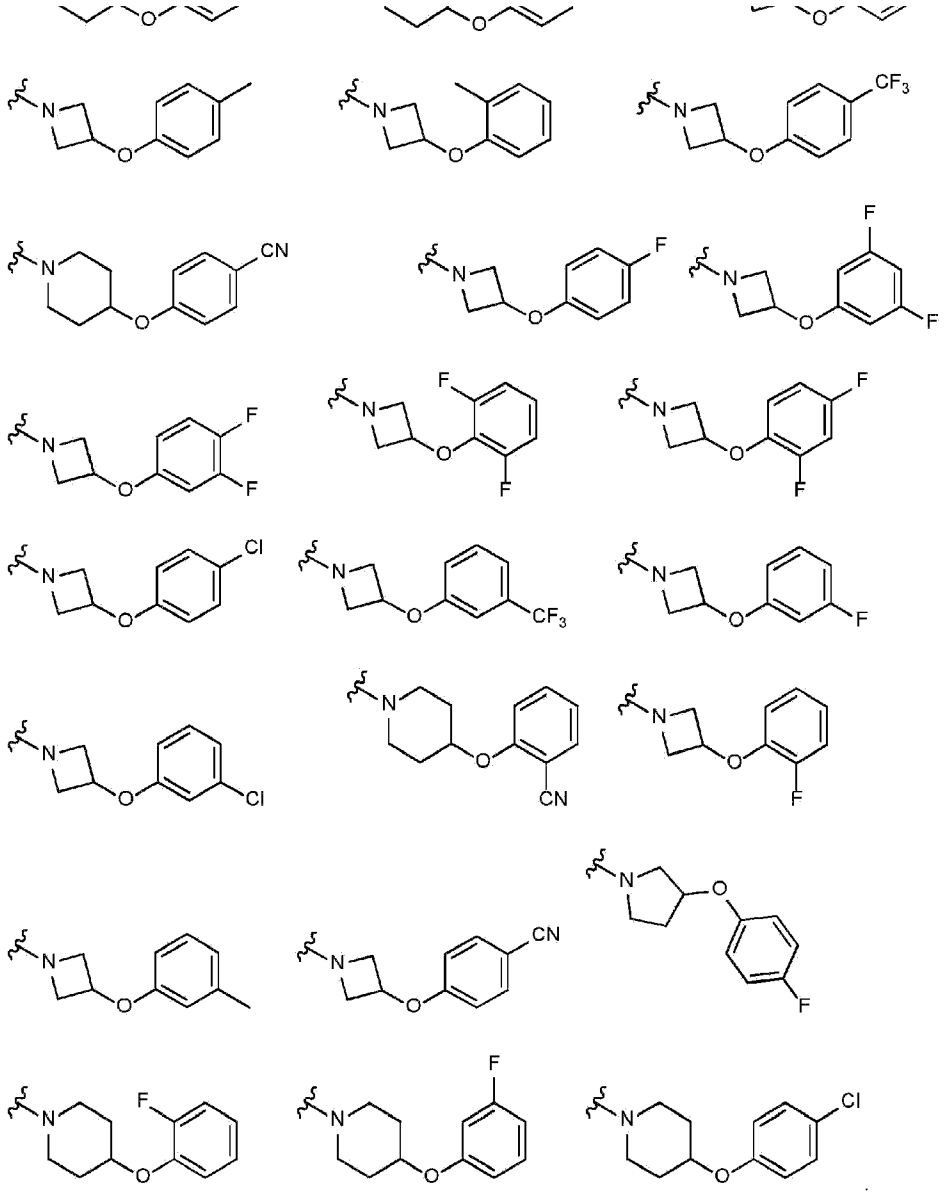


[0081] In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, n is 0 or 1 and m is 0 or 1. In one embodiment, n is 0 and m is 0. In one embodiment, n is 0 and m is 1. In one embodiment, R^b is (a) hydroxy, (e) R^cR^dN- Examples include the structures:

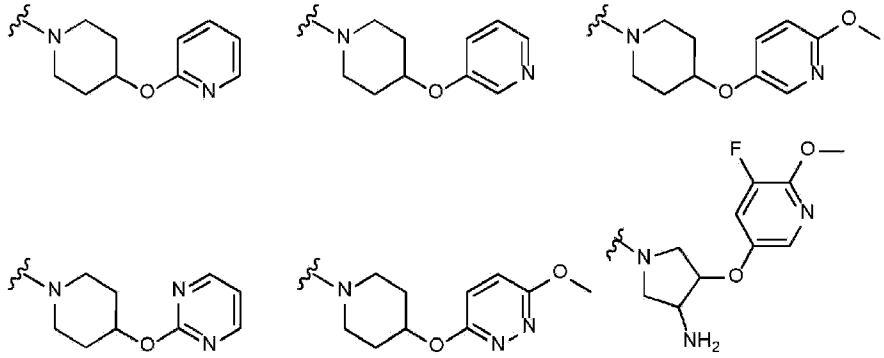


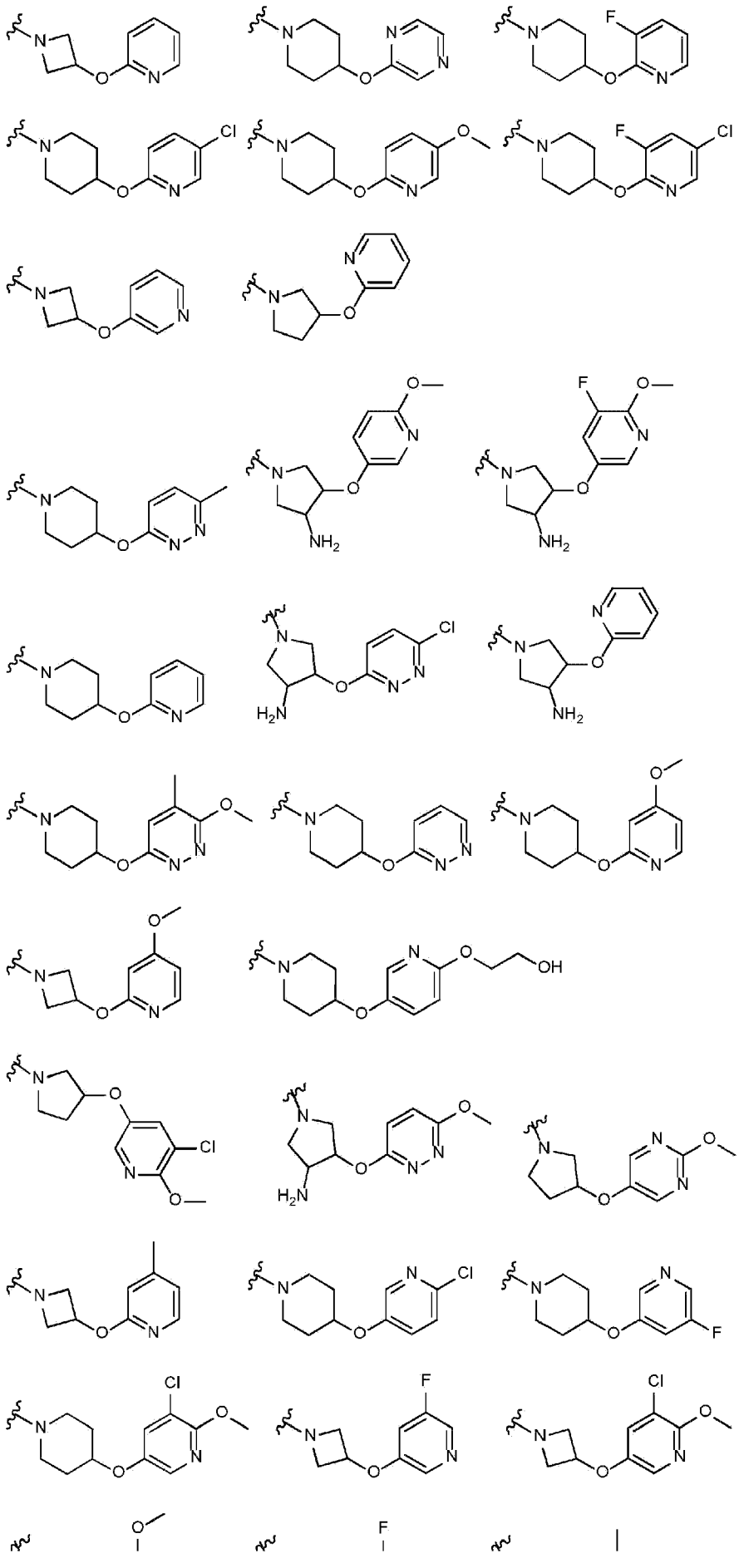
[0082] In one embodiment, Ring D is a saturated 4 or 6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, n is 0, 1 or 2 and m is 0 or 1. In one embodiment, n is 0 and m is 0. Examples include the structures:

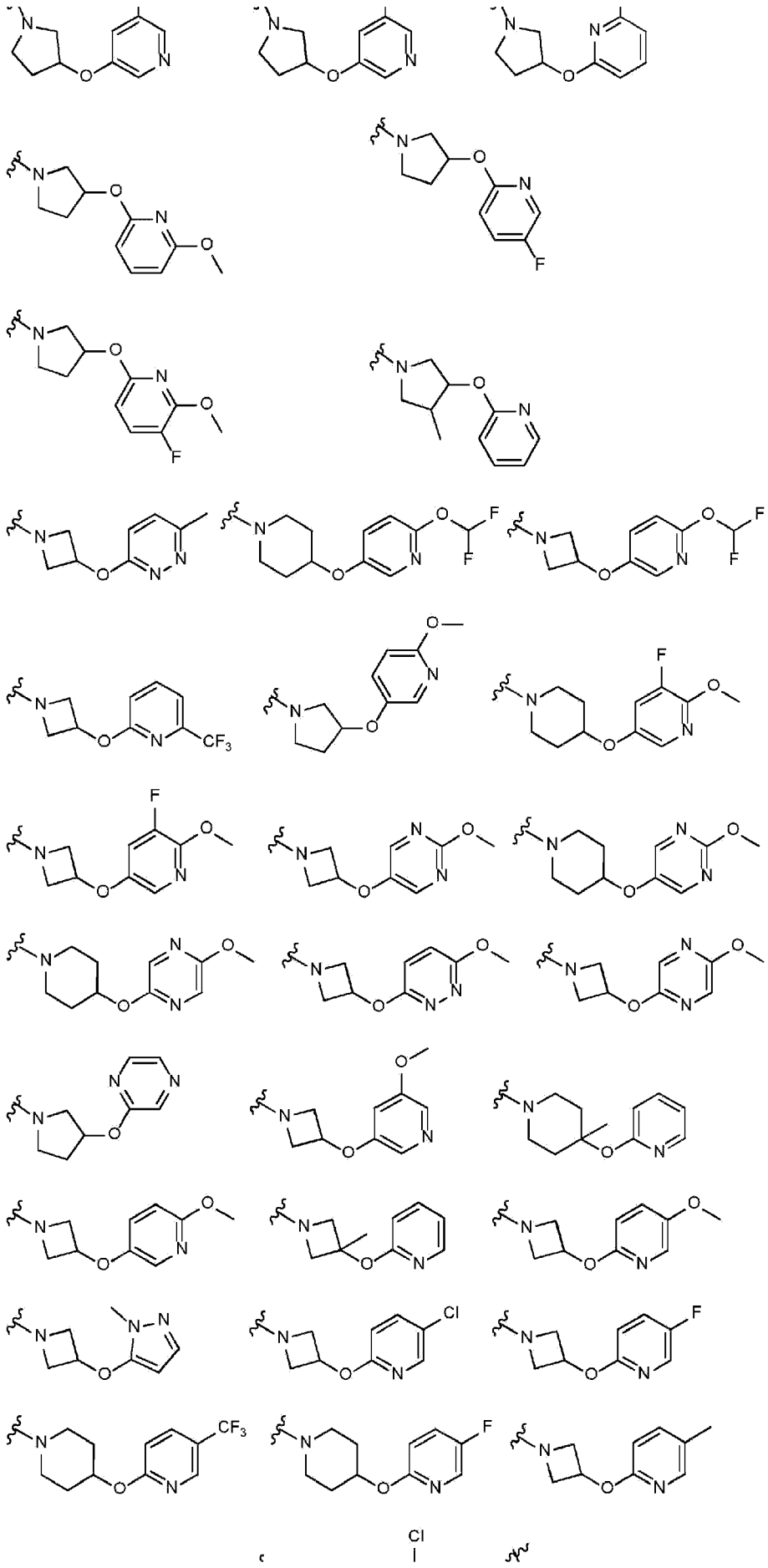


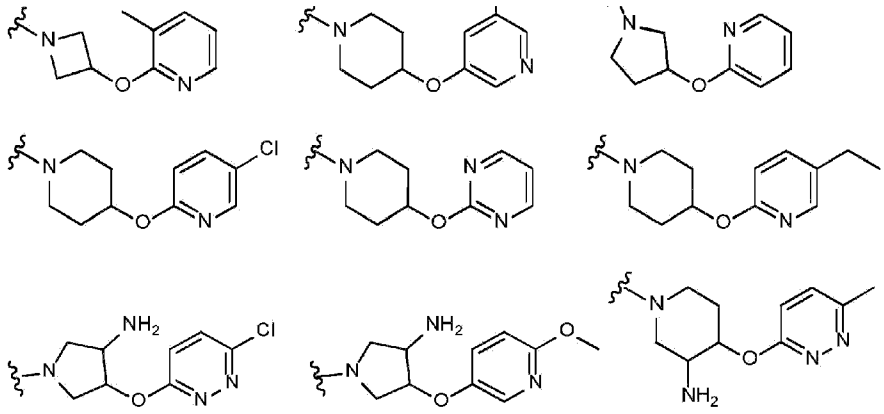


[0083] In one embodiment, Ring D is a saturated 4-6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, Ring D is a saturated 5-6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, n is 0 or 1 and m is 0 or 1. In one embodiment, n is 0 and m is 0. In one embodiment, n is 0 and m is 1. In one embodiment, R^a is C1-C6 alkyl. In one embodiment, R^b is R^cR^dN-. Examples include the structures:

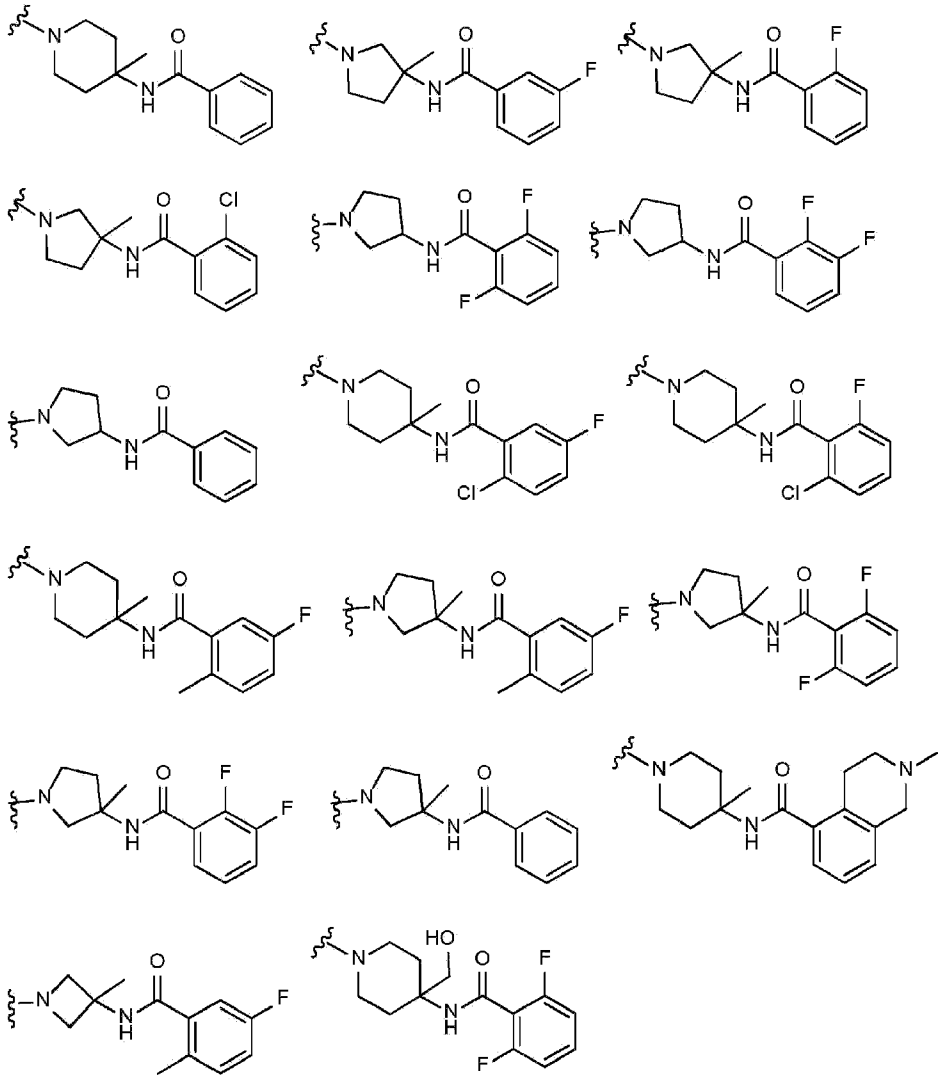


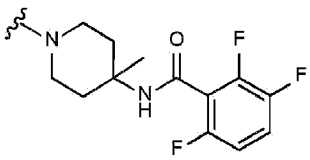
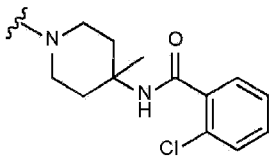
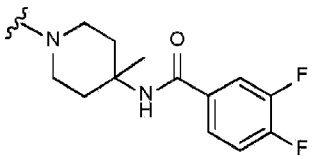
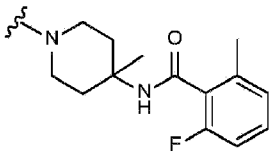
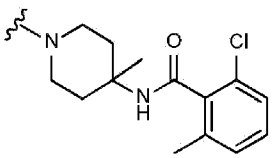
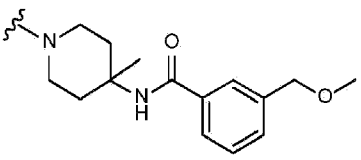
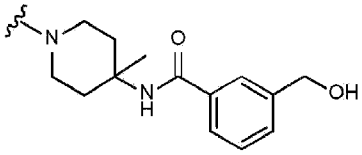
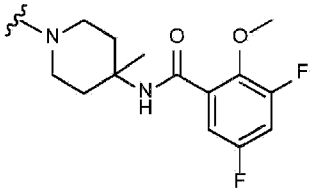
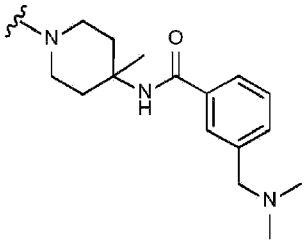
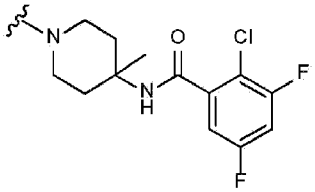
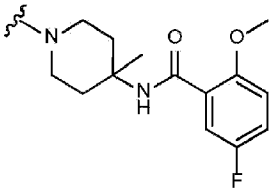
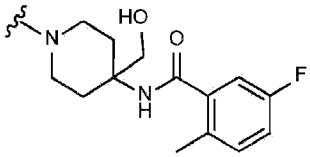
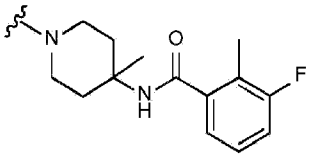
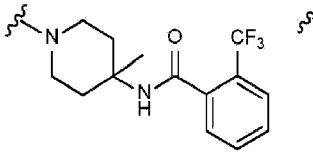
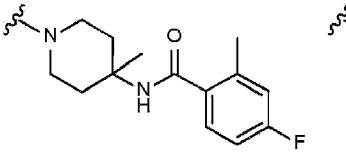


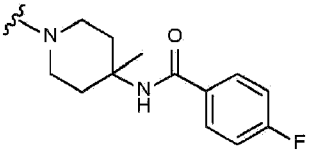
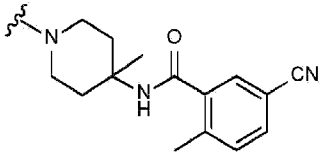
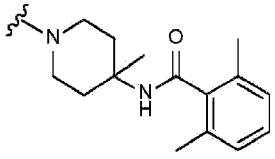
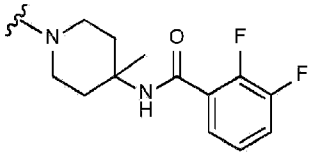
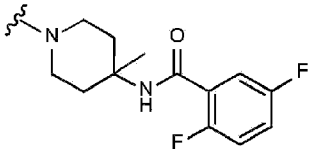
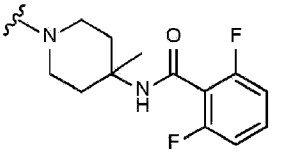
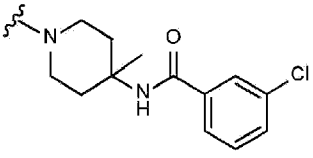
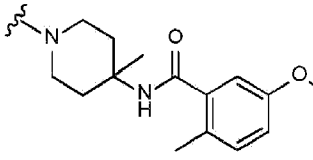
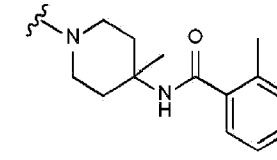


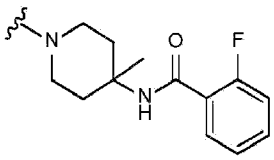


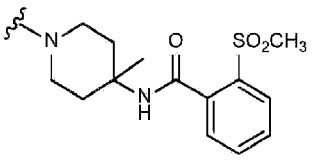
[0084] . In one embodiment, Ring D is a saturated 5-6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, n is 0, 1 or 2 and m is 0 or 1. In one embodiment, n is 0 or 1 and m is 0. In one embodiment, n is 1 and m is 0. In one embodiment, n is 0 and m is 1. In one embodiment, R^a is C1-C6 alkyl (optionally substituted with 1-3 fluoros) or hydroxyC1-C6 alkyl. In one embodiment, R^b is $R^cR^dNCH_2$- where R^c is H or C1-C6 alkyl and R^d is C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl (optionally substituted with 1-3 fluoros). In one embodiment, R^b is hydroxyl. Examples include the structures:

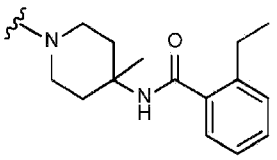


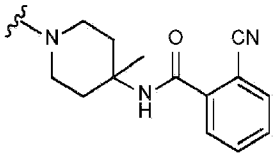
















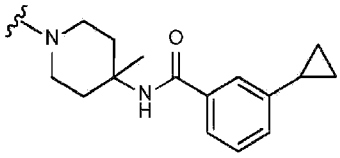










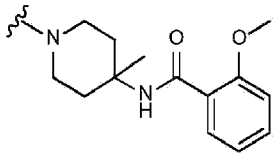



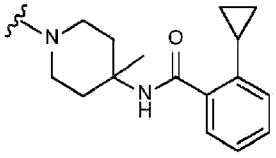


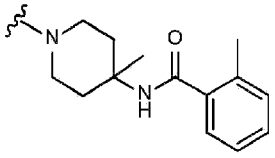


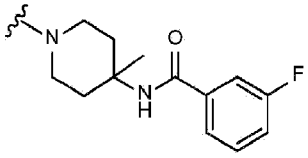


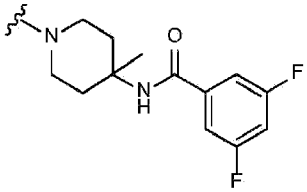


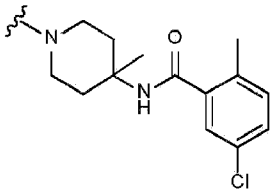


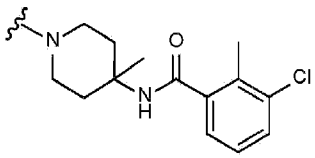


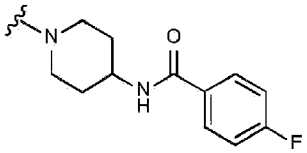


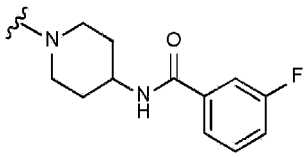


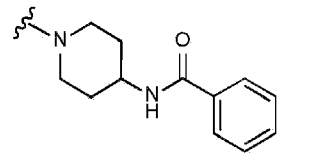


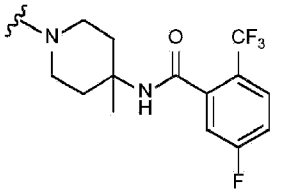


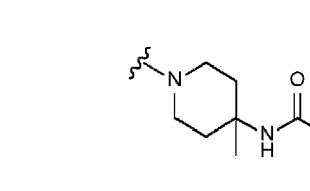


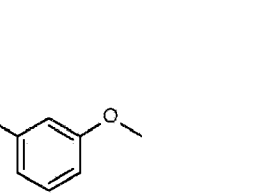


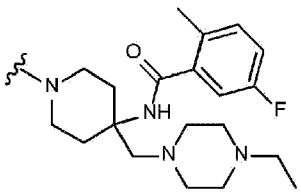


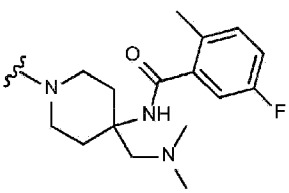


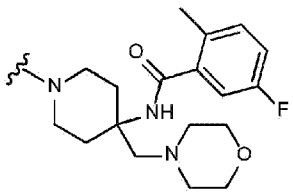


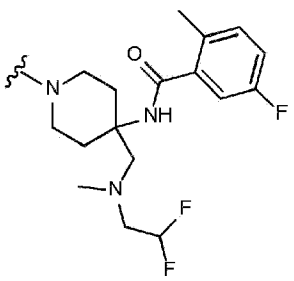


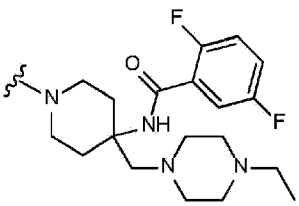


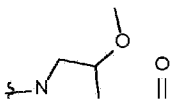


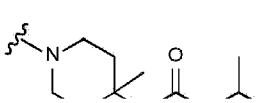












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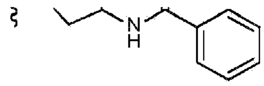
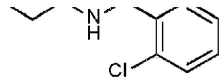
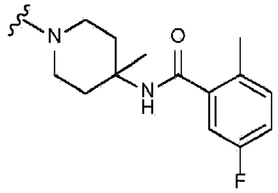
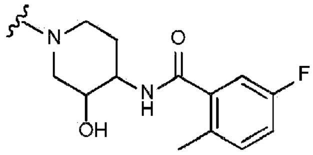
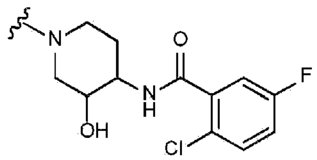
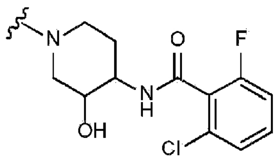
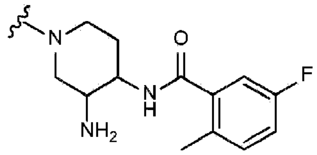
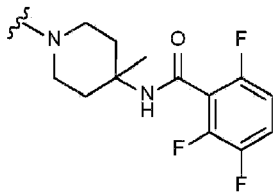
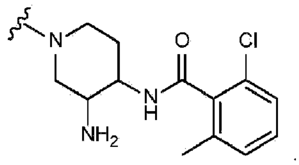
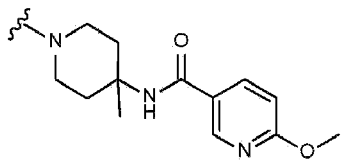
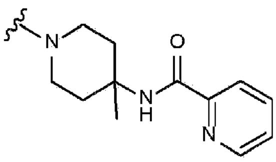
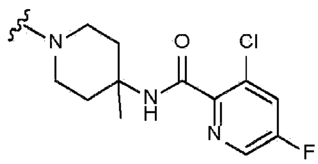
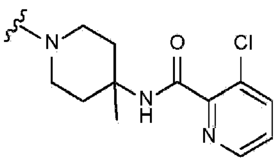
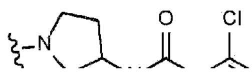
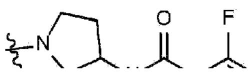
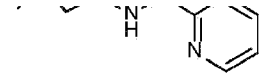
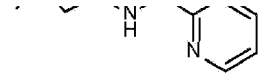
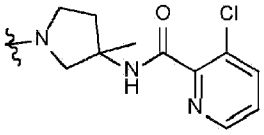










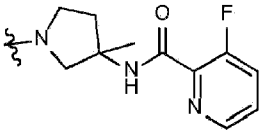
[0085] In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having one ring heteroatom which is nitrogen. In one embodiment, n is 0 or 1 and m is 0. In one embodiment, R^a is C1-C6 alkyl (optionally substituted with 1-3 fluoros) or hydroxyC1-C6 alkyl. In one embodiment, R^b is hydroxy, hetCyc^{b}CH$_2$-, R^cR^dNCH$_2$-, where hetCyc^b, R^c and R^d are as defined for Formula I. In one embodiment, R^b is hetCyc^{b}CH$_2$- where hetCyc^b is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^b is optionally substituted with one or more substituents independently selected from C1-C6 alkyl (optionally substituted with 1-3 fluoros). In one embodiment, R^b is R^cR^dNCH$_2$- where R^c is H or C1-C6 alkyl and R^d is C1-C6 alkyl (optionally substituted with 1-3 fluoros). Examples include the structures:

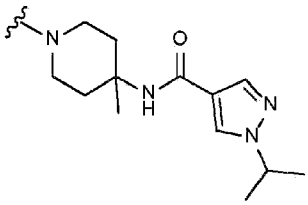







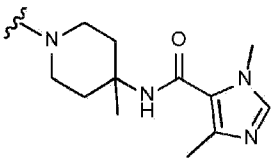


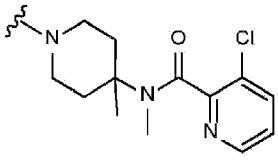


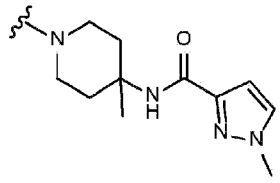


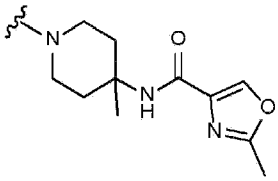


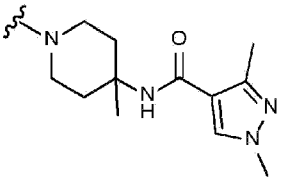


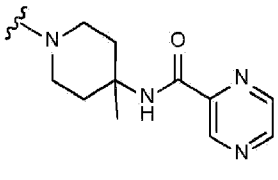


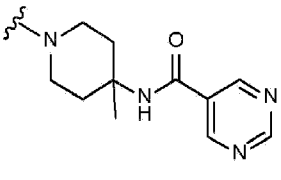


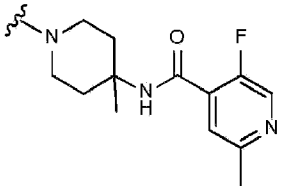


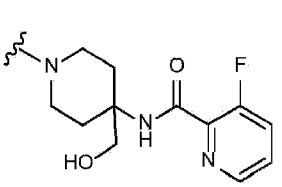


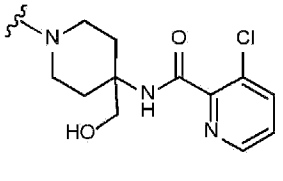


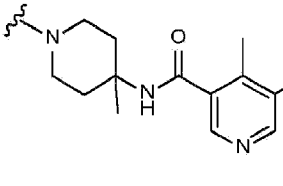


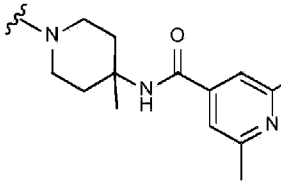


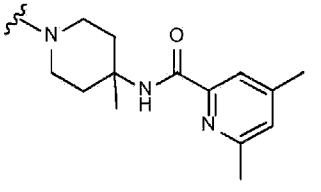


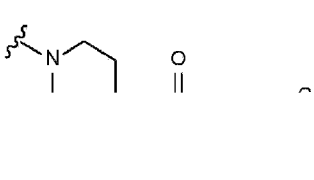


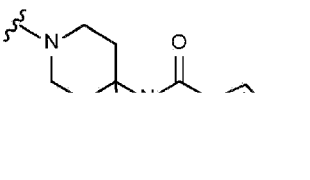












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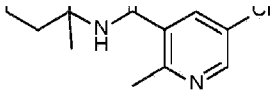
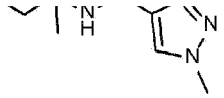
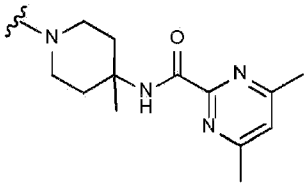
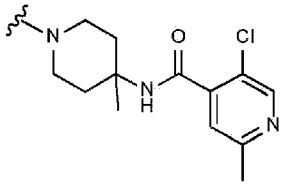
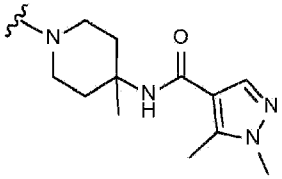
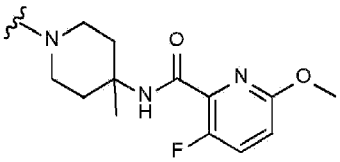


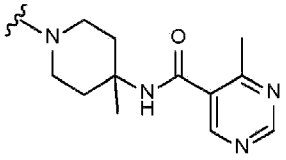


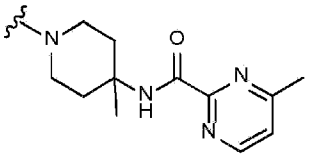


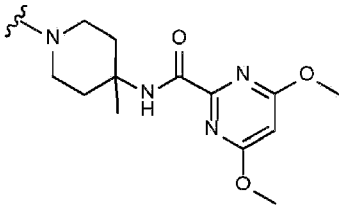


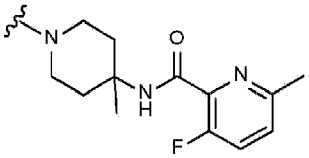


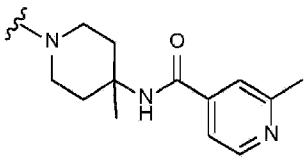


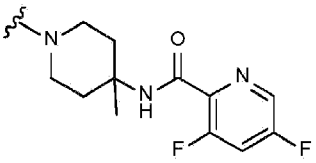


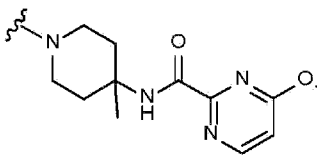


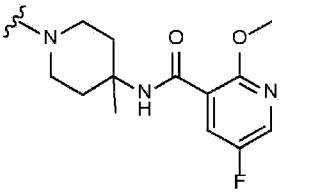


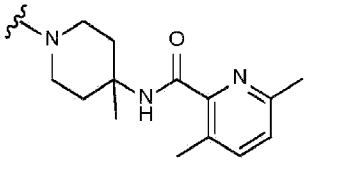


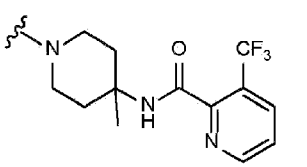


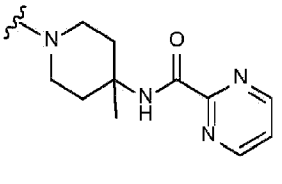


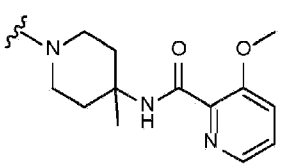


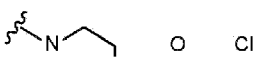


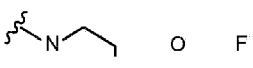


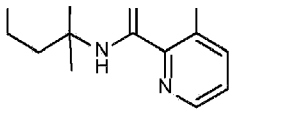
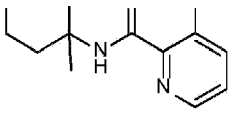
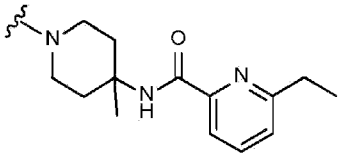
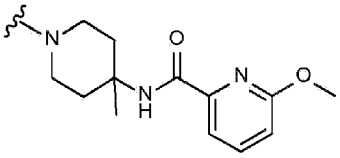
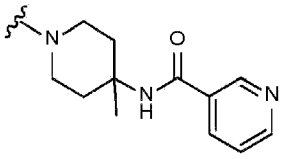
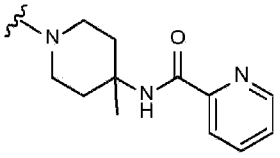
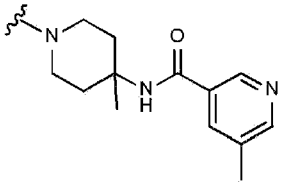
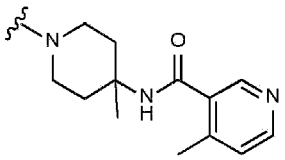
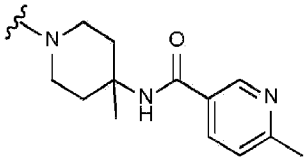
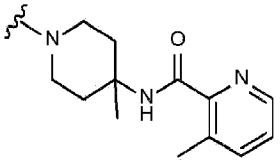
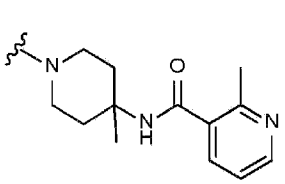
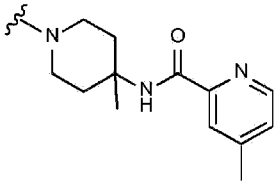
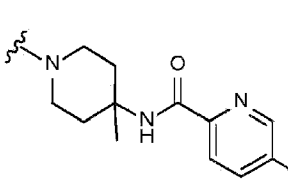
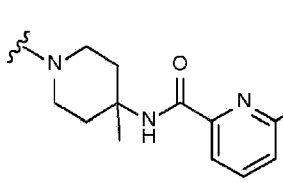
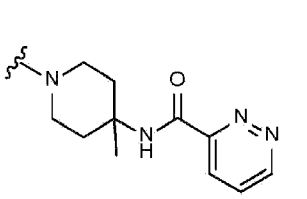
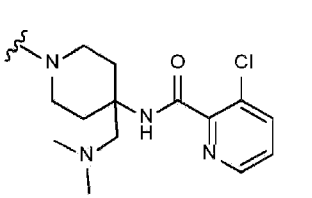
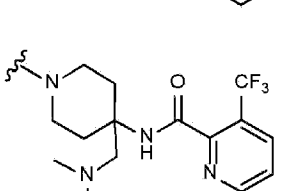
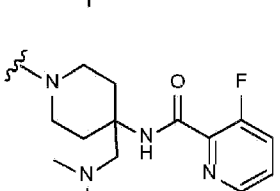
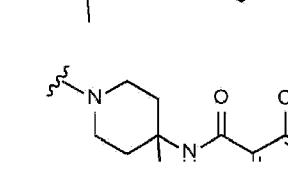
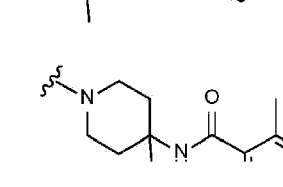


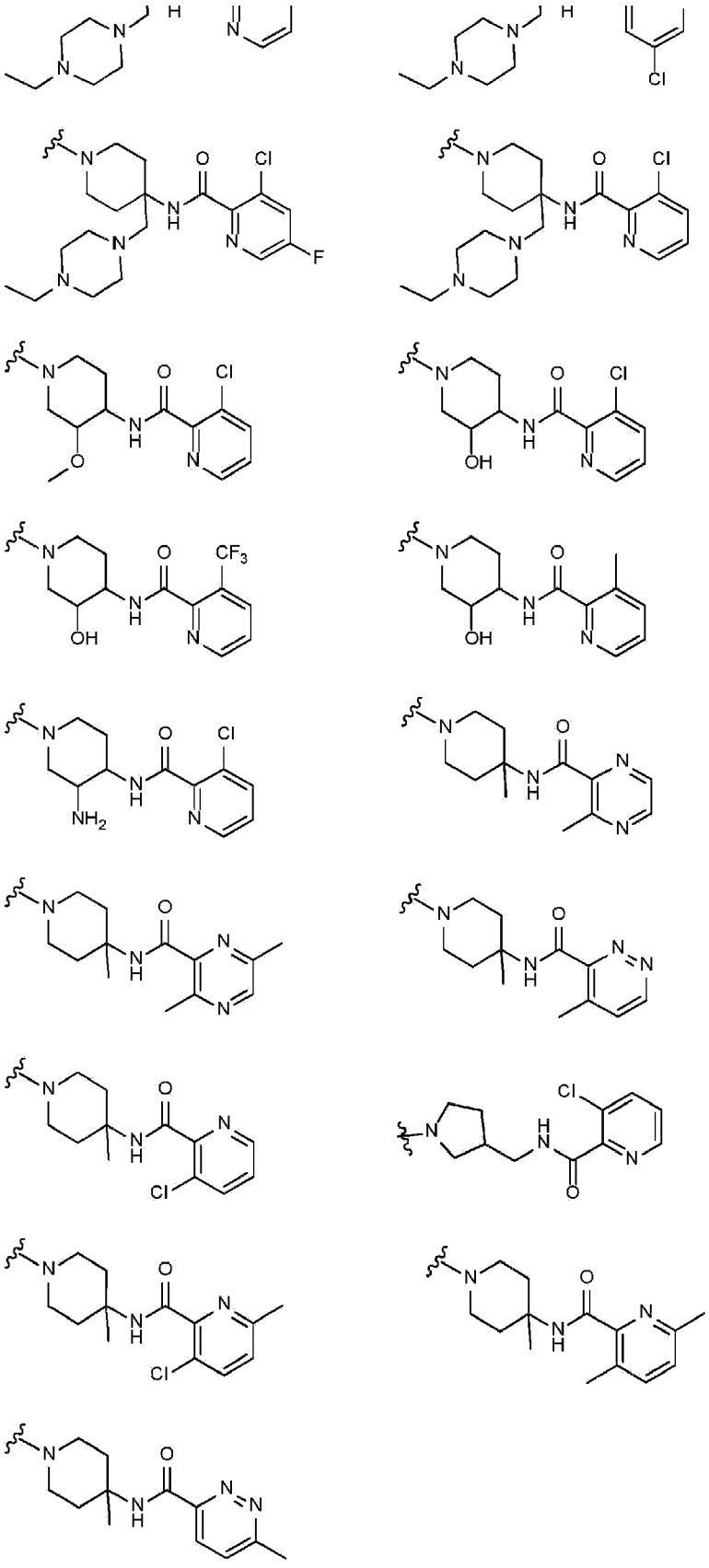










[0086] In one embodiment, Formula I includes compounds of Formula I-D, wherein:

X^1 and X^3 are N, and X^2 and X^4 are CH or CF; and A, B, E, R^a, R^b, m and n are as defined for Formula I.

[0087] In one embodiment of Formula **I-D,** A is CN.

[0088] In one embodiment of Formula **I-D,** B is (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) hetAr^1C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) (hetCyc^a)C1-C3 alkyl-; and hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-.

[0089] In one embodiment of Formula **I-D,** A is CN; B is (c) hydroxyC2-C6 alkyl-wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) hetAr^1C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) (hetCyc^a)C1-C3 alkyl-; and hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-.

[0090] In one embodiment of Formula **I-D,** E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl, or (m) het$Ar^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl.

[0091] In one embodiment of Formula **I-D,** A is CN; B is (c) hydroxyC2-C6 alkyl-wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) hetAr^1C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) (hetCyc^a)C1-C3 alkyl-; hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-; and E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl, or (m) het$Ar^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl.

[0092] In one embodiment of Formula **I-D,** m is 1; and n is 0 or 1.

[0093] In one embodiment of Formula **I-D,** m is 1; and n is 0.

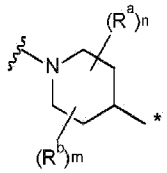
[0094] In one embodiment of Formula **I-D,** m is 1; n is 0; and R^b is hydroxy.

[0095] In one embodiment of Formula **I-D,** m is 0; and n is 0 or 1.

[0096] In one embodiment of Formula **I-D,** m is 0; n is 0 or 1; and R^a is C1-C6 alkyl optionally substituted with 1-3 fluoros.

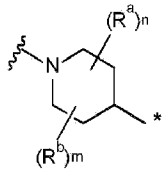
[0097] In one embodiment of Formula **I-D,** A is CN; B is (c) hydroxyC2-C6 alkyl-wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) $hetAr^1$C1-C3 alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) ($hetCyc^a$)C1-C3 alkyl-; $hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-; E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl, or (m) $hetAr^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl; m is 0 or 1; n is 0 or 1; R^a is C1-C6 alkyl optionally substituted with 1-3 fluoros; and R^b is hydroxy. In one embodiment, m is 1, n is 0, and R^b is hydroxy. In one embodiment, m is 0, n is 1, and R^b is C1-C6 alkyl optionally substituted with 1-3 fluoros.

[0098] In one embodiment of Formula **I-D,** Ring D is



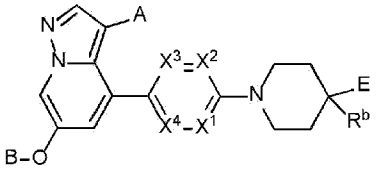
wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group.

[0099] In one embodiment of Formula **I-D,** A is CN; B is (c) hydroxyC2-C6 alkyl-wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) $hetAr^1$C1-C3 alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) ($hetCyc^a$)C1-C3 alkyl-; $hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-; E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl, or (m) $hetAr^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl; m is 0 or 1; n is 0 or 1; R^a is C1-C6 alkyl optionally substituted with 1-3 fluoros; and Ring D is



wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, the asterisk indicates the point of attachment of Ring D to the E group. In one embodiment, m is 1, n is 0, and R^b is hydroxy. In one embodiment, m is 0, n is 1, and R^b is C1-C6 alkyl optionally substituted with 1-3 fluoros.

[0100] In one embodiment, compounds of Formula I include compounds of Formula **I-F**



I-F

where E is (d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros or (e) $hetAr^2$C1-C6 alkyl-; R^b is (a) hydroxy, or (e) R^cR^dN-; and X^1, X^1, X^3, X^4, A, B, Ar^1, $hetAr^2$, R^c and R^d are as defined for Formula **I.**

[0101] In one embodiment of Formula **I-F,** X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, E is (d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) $hetAr^2$C1-C6 alkyl-.

[0102] In one embodiment of Formula **I-F,** A is CN. In one embodiment, E is (d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) $hetAr^2$C1-C6 alkyl-.

[0103] In one embodiment of Formula **I-F,** B is C1-C6 alkyl optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment of Formula **I-F,** B is C1-C6 alkyl or hydroxyC2-C6 alkyl-. In one embodiment, E is (d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) $hetAr^2$C1-C6 alkyl-.

[0104] In one embodiment of Formula **I-F,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is C1-C6 alkyl optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, B is C1-C6 alkyl or hydroxyC2-C6 alkyl-. In one embodiment, E is (d) Ar^1C1-C6 alkyl-wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) $hetAr^2$C1-C6 alkyl-.

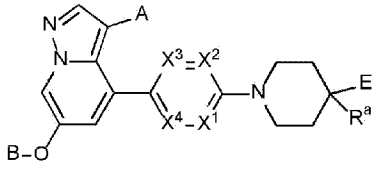
[0105] In one embodiment of Formula **I-F,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and R^b is (a) hydroxy. In one embodiment, E is (d) Ar^1C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) $hetAr^2$C1-C6 alkyl-.

[0106] In one embodiment of Formula **I-F,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and R^b is (e) R^cR^dN-where R^c and R^d are as defined for Formula I. In one embodiment, E is (d) Ar^1C1-C6 alkyl-wherein said alkyl portion is optionally substituted

with 1-3 fluoros. In one embodiment, E is (e) hetAr^{2}C1-C6 alkyl-.

[0107] In one embodiment of Formula **I-F,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and R^b is (e) R^cR^dN-where R^c and R^d are as defined for Formula **I**. In one embodiment, E is (d) Ar^{1}C1-C6 alkyl-wherein said alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, E is (e) hetAr^{2}C1-C6 alkyl-.

[0108] In one embodiment, compounds of Formula I include compounds of Formula **I-G**



I-G

where E is (l) Ar^{1}C(=O)NR^g- where R^g is H or C1-C6 alkyl or (m) hetAr^{2}C(=O)NR^g(CH$_2$)$_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl; R^a is C1-C6 alkyl optionally substituted with 1-3 fluoros; and Ar^1, hetAr^2, X^1, X^1, X^3, X^4, A and B are as defined for Formula **I.**

[0109] In one embodiment of Formula **I-G,** X^1 is N; and X^2, X^3 and X^4 are CH.

[0110] In one embodiment of Formula **I-G,** A is CN.

[0111] In one embodiment of Formula **I-G,** B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros, (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-, (g) hetAr^{1}C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) (hetCyc^a)C1-C3 alkyl-, where hetCyc^a is as defined for Formula **I.**

[0112] In one embodiment of Formula **I-G,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment, B is C1-C6 alkyl.

[0113] In one embodiment of Formula **I-G,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is hydroxyC2-C6 alkyl- optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, B is hydroxyC2-C6 alkyl-.

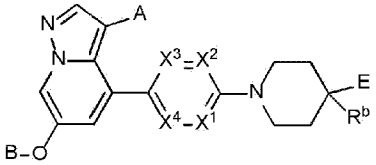
[0114] In one embodiment of Formula **I-G,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-.

[0115] In one embodiment of Formula **I-G,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is hetAr^{1}C1-C3 alkyl-, where hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6

alkyl substituents.

[0116] In one embodiment of Formula **I-G,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (hetCyc^a)C1-C3 alkyl-, where hetCyc^a is as defined for Formula **I.**

[0117] In one embodiment, compounds of Formula I include compounds of Formula **I-H**



I-H

where E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl or (m) $hetAr^2C(=O)NR^g(CH_2)_p$- where p is 0 or 1 and R^g is H or C1-C6 alkyl; R^b is (a) hydroxy, (c) hetCyc^bCH_2-, (f) $R^cR^dNCH_2$-; and Ar^1, $hetAr^2$, X^1, X^1, X^3, X^4, A, B, hetCyc^b, R^c and R^d are as defined for Formula **I.**

[0118] In one embodiment of Formula **I-H,** X^1 is N; and X^2, X^3 and X^4 are CH.

[0119] In one embodiment of Formula **I-H,** A is CN.

[0120] In one embodiment of Formula **I-H,** B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment, B is C1-C6 alkyl.

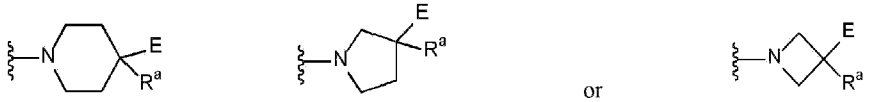
[0121] In one embodiment of Formula **I-H,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment, B is C1-C6 alkyl.

[0122] In one embodiment of Formula **I-H,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; and R^b is (a) hydroxy.

[0123] In one embodiment of Formula **I-H,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; and R^b is (c) hetCyc^bCH_2-.

[0124] In one embodiment of Formula **I-H,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; and R^b is (f) $R^cR^dNCH_2$-.

[0125] In one embodiment, compounds of Formula I include compounds of Formula **I-K** where E is (l) $Ar^1C(=O)NR^g$- where R^g is H or C1-C6 alkyl or (m) $hetAr^2C(=O)NR^g(CH_2)_p$-where p is 0 or 1 and R^g is H or C1-C6 alkyl; Ring D is



or

where the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4; R^a is C1-C6 alkyl optionally substituted with 1-3 fluoros; and X^1, X^1, X^3, X^4, A, B, Ar^1 and $hetAr^2$ are as defined for Formula **I.**

[0126] In one embodiment of Formula **I-K,** X^1 is N; and X^2, X^3 and X^4 are CH.

[0127] In one embodiment of Formula **I-K,** A is CN.

[0128] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; and A is CN.

[0129] In one embodiment of Formula **I-K,** B is (a) hydrogen, (b) C1-C6 alkyl optionally substituted with 1-3 fluoros, (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- and (C1-C6 alkoxy)C(=O)-, (g) $hetAr^1$C1-C3 alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents, or (i) ($hetCyc^a$)C1-C3 alkyl-, where $hetCyc^a$ is as defined for Formula **I.**

[0130] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (a) hydrogen.

[0131] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros.

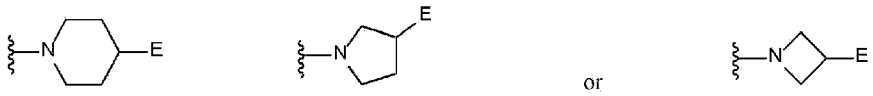
[0132] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[0133] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (f) (R^1R^2N)C1-C6 alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- and (C1-C6 alkoxy)C(=O)-.

[0134] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (g) $hetAr^1$C1-C3 alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents.

[0135] In one embodiment of Formula **I-K,** X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (i) ($hetCyc^a$)C1-C3 alkyl-, where $hetCyc^a$ is as defined for Formula **I.**

[0136] In one embodiment, compounds of Formula I include compounds of Formula **I-L** where E is (g) Ar^1O- or (h) $hetAr^2$-O-; Ring D is



where the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4; and X^1, X^1, X^3, X^4, A, B, Ar^1 and $hetAr^2$ are as defined for Formula **I.**

[0137] In one embodiment of Formula **I-L,** X^1 is N; and X^2, X^3 and X^4 are CH.

[0138] In one embodiment of Formula **I-L,** A is CN.

[0139] In one embodiment of Formula **I-L,** X^1 is N; X^2, X^3 and X^4 are CH; and A is CN.

[0140] In one embodiment of Formula **I-L,** B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros, (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (i) (hetCyc^a)C1-C3 alkyl- or (k) (R^1R^2N)C(=O)C1-C6 alkyl- where R^1 and R^2 are independently selected from H and C1-C6 alkyl.

[0141] In one embodiment of Formula **I-L,** X^1 is N; X^2, X^3 X^4 are CH; and A is CN; and B is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros.

[0142] In one embodiment of Formula **I-L,** X^1 is N; X^2, X^3 X^4 are CH; and A is CN; and B is (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[0143] In one embodiment of Formula **I-L,** X^1 is N; X^2, X^3 X^4 are CH; and A is CN; and B is (i) (hetCyc^a)C1-C3 alkyl- or (k) (R^1R^2N)C(=O)C1-C6 alkyl- where R^1 and R^2 are independently selected from H and C1-C6 alkyl.

[0144] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula **I.** Examples of pharmaceutically acceptable salts of compounds of Formula I include monohydrochloride, dihydrochloride, trifluoroacetic acid, and di-trifluoroacetic acid salts. In one embodiment, compounds of Formula I include trifluoroacetic acid and dihydrochloride salts.

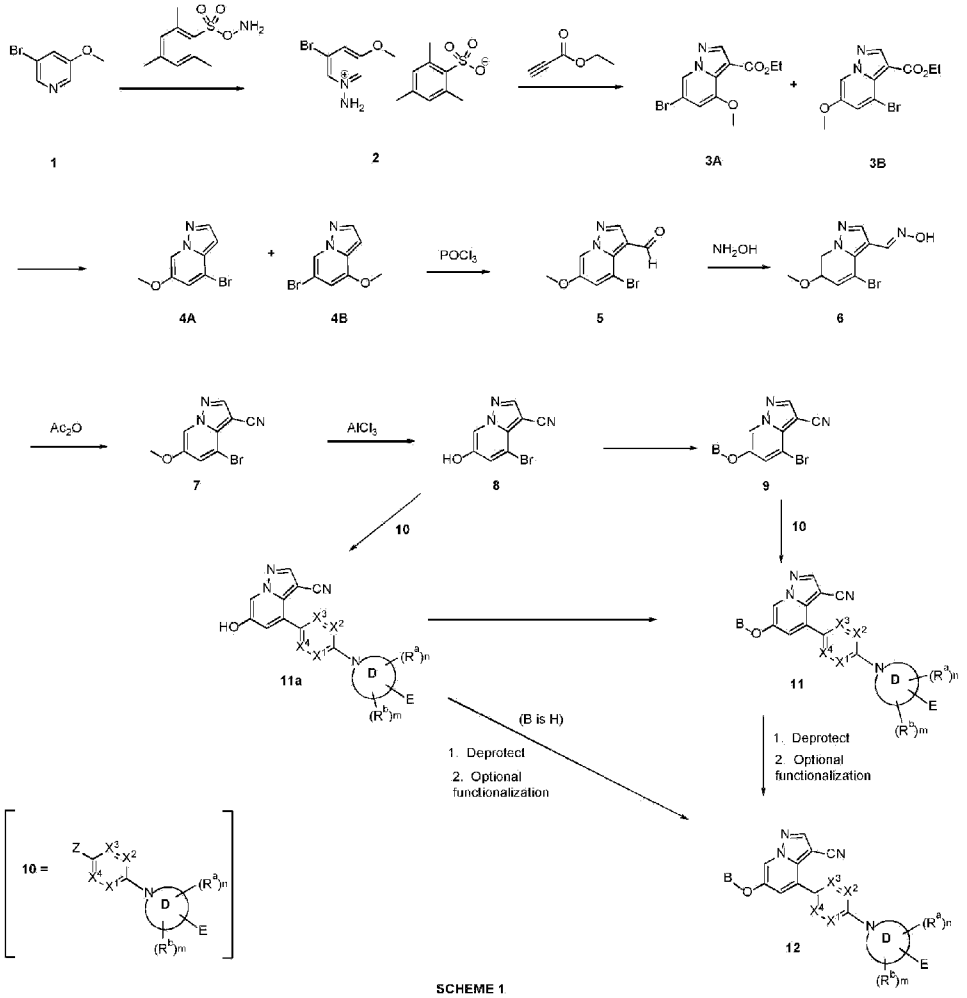
[0145] In one embodiment, the compounds of Formula I include the compounds of Examples 1-819 and stereoisomers and pharmaceutically acceptable salts thereof. In one embodiment, the compounds of Examples 1-819 are in the free base form. In one embodiment, the compounds of Examples 1-819 are dihydrochloride or trifluoroacetic acid salts.

[0146] The term "pharmaceutically acceptable" indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the patient being treated therewith.

[0147] Compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in particular when mentioned in relation to a compound according to Formula **I,** comprises all isotopes and isotopic mixtures of that atom, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H or mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C, ^{12}C, ^{13}C, ^{14}C or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N, ^{14}N, ^{15}N or mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O, ^{15}O, ^{16}O, ^{17}O, ^{18}O or mixtures thereof; and when fluoro is mentioned, it is understood to refer to ^{18}F, ^{19}F or mixtures thereof. The compounds provided herein therefore also comprise compounds with one or more isotopes of one or more atoms, and mixtures thereof, including radioactive compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive enriched isotopes. Radiolabeled compounds are useful as therapeutic

agents, e.g., cancer therapeutic agents, research reagents, e.g., assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0148] For illustrative purposes, Schemes 1-6 show general methods for preparing the compounds provided herein as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.



SCHEME 1

[0149] Scheme 1 shows a general scheme for the synthesis of compound **X** where A is CN, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I.**

[0150] Compound **2** is obtained by treating 3-bromo-5-methoxypyridine (compound 1), which is commercially available, with O-(mesitylsulfonyl)hydroxylamine. The O-mesitylsulfonylhydroxylamine may be prepared as described in Mendiola, J., et al., Org. Process Res. Dev. 2009, 13(2), 263-267. Compound **2** may be reacted with ethyl propiolate to provide a mixture of compounds **3A** and **3B,** which typically are obtained in a ratio of approximately 2:1 to 9:1, respectively. The mixture of compounds **3A**

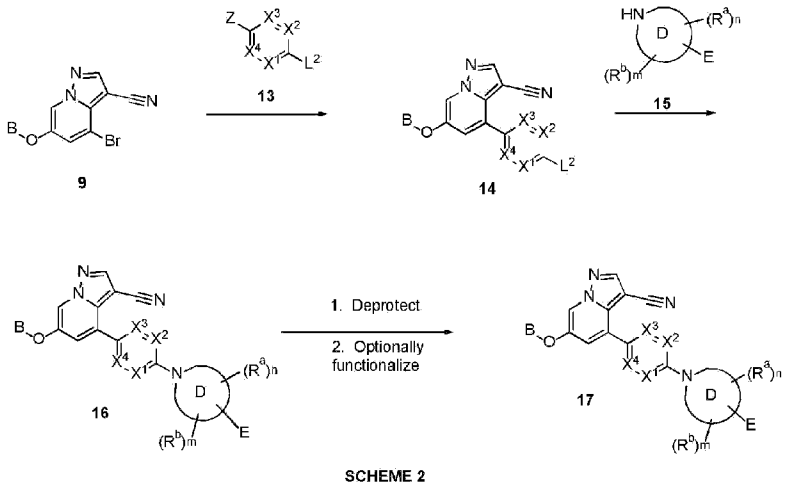
and **3B** may be treated with 48% HBr at elevated temperatures, followed by recrystallization or chromatography purifications, to isolate compound **4A** as the minor isomer and compound **4B** as the major isomer. After isolation, compound **4A** may be treated with $POCl_3$ to provide compound **5.** The formyl group may be converted to an oxime group using NH_2OH to provide compound **6.** The oxime group may be converted to a nitrile group using acetic anhydride to provide compound 7. The methoxy group of compound 7 may be converted to a hydroxy group by treating compound 7 with aluminum trichloride to provide compound **8.**

[0151] When group B is hydrogen, compound **12** may be prepared by coupling compound **8** with the corresponding boronic ester compound **10** (where Ring D, E, X^1, X^2, X^3 and X^4 are as defined for Formula **I;** Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) to provide compound **11a** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures), wherein if Ring D of compound **10** is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. The amino protecting group if present on a substituent of Ring D of compound **11a** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **11a** to acidic conditions, e.g., HCl) to provide compound **12** where B is hydrogen. Alternatively, the E group may be functionalized (i.e., reacted or treated with an appropriate reagent) under standard conditions described below to provide compound **12** where B is hydrogen and E is as defined for Formula I except that E is not hydrogen.

[0152] Alternatively, when group B is as defined for Formula I other than hydrogen, Compound **11a** may be reacted with C1-C6 alkyl-OH, (C1-C6 alkoxy)C1-C6 alkyl-OH optionally substituted with 1-3 fluoros, $hetAr^1$C1-C3 alkyl-OH, (C3-C6 cycloalkyl)C1-C3 alkyl-OH, $(hetCyc^a)$C1-C3 alkyl-OH, $hetCyc^aOH$ or $hetCyc^aC(=O)$C1-C6 alkyl-OH, where $hetAr^1$ and $hetCyc^a$ are as defined for Formula I, under Mitsunobu reaction conditions (PPh_3 and diisopropyl azodicarboxylate) to provide compound **11.** Compound **12** may then be prepared from compound **11** as described above.

[0153] Alternatively, when group B is as defined for Formula I other than hydrogen, compound **9** may be prepared by reacting compound **8** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, $(hetCyc^a)$C1-C3 alkyl-X, $hetCyc^a$-X, or $hetCyc^aC(=O)$C1-C6 alkyl-X, where R^1, R^2, $hetAr^1$, and $hetCyc^a$ are as defined for Formula I and X is a leaving atom or group (halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups), in the presence of a base (for example, potassium carbonate). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **8** with a C1-C6 alkyl-X, where X is Br or Cl, or triflate. Compound **11** may then be prepared by coupling compound **9** with the corresponding boronic ester compound **10** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in

dioxane at elevated temperatures), wherein if Ring D of compound **10** is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. Compound **12** may then be prepared from compound **11** as described above.

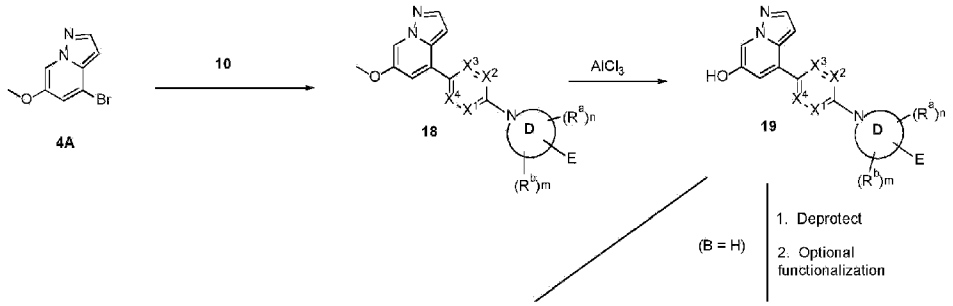


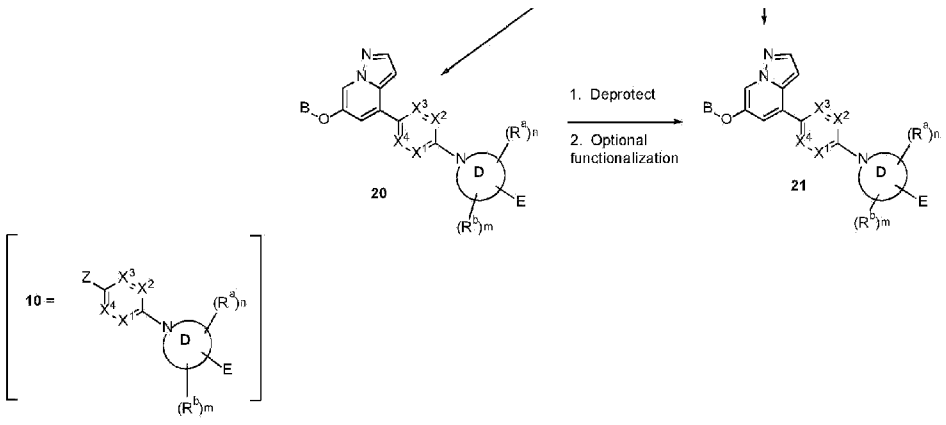
SCHEME 2

[0154] Scheme 2 shows another general scheme for the synthesis of compound **17** where A is CN, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I.**

[0155] Compound **9** (prepared, e.g., as described in Scheme 1) in which B is as defined for Formula **I,** may be coupled with compound **13** (where X^1, X^2, X^3 and X^4 are as defined for Formula I; L^2 is a leaving group such as a triflate or halide); Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)), using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures) to provide compound **14.** Compound **16** may be prepared by coupling compound **14** with compound **15** under appropriate S_NAr conditions (for example, optionally in the presence of K_2CO_3 and at elevated temperature), wherein if Ring D of compound **15** is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. The amino protecting group if present may then be removed under standard conditions (for example, a Boc group may be removed by treating compound **1** to acidic conditions, e.g., HCl) to provide compound **17** where E is H.

[0156] Alternatively, the E group may be functionalized (i.e., reacted or treated with an appropriate reagent) under standard conditions described below to provide compound **17** where E is as defined for Formula I except that E is not H.





SCHEME 3

[0157] Scheme 3 shows a general scheme for the synthesis of Compound **21** where A is H, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I.**

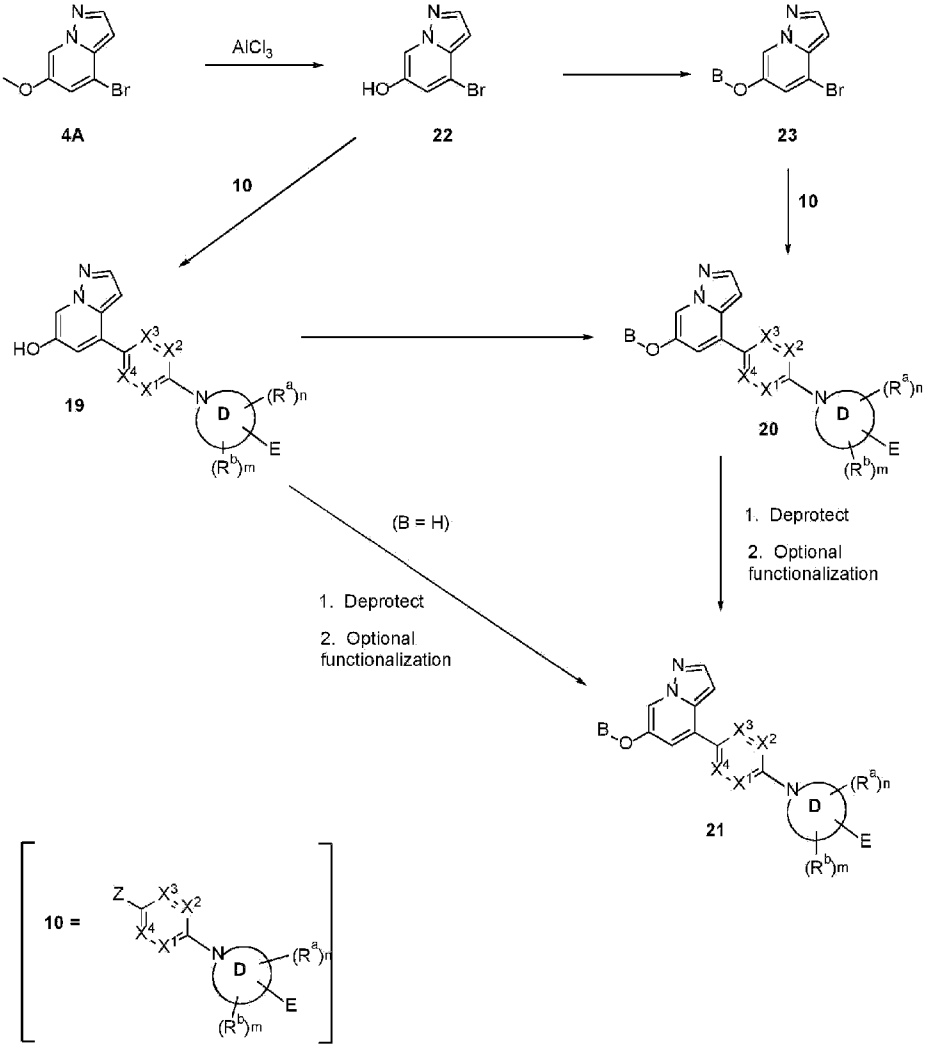
[0158] Compound **18** may be prepared by coupling compound **4A** (prepared e.g., as described in Scheme 1) with the corresponding boronic ester compound **10** (where Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures), wherein if Ring D of compound **10** is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. Compound **19** may be prepared by treating compound **18** with aluminum trichloride.

[0159] When B is as defined for Formula I other than hydrogen, compound **20** may be prepared by reacting compound **19** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, $(hetCyc^a)$C1-C3 alkyl-X, $hetCyc^a$-X or $hetCyc^aC(=O)$C1-C6 alkyl-X, where R^1, R^2, $hetAr^1$, and $hetCyc^a$ are as defined for Formula I and X is a leaving atom or group (halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if B has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **19** with C1-C6 alkyl-X, where X is Br or Cl, or triflate. Compound **21** may then be prepared from compound **20.** If Ring D comprises a substituent having an amino protecting group, the amino protecting group may be removed under standard conditions (for example, a Boc group may be removed by treating compound **20** to acidic conditions, e.g., HCl) to provide compound **21** where E is H.

[0160] Alternatively, the E group of compound **20** may be functionalized (i.e., reacted or treated with an appropriate reagent) under standard conditions described below to provide compound **21** where E is as

defined for Formula I except that E is not H.

[0161] Alternatively, when group B is hydrogen, compound **21** may be prepared from compound **19** according to the deprotection and optional functionalization steps described herein.



SCHEME 4

[0162] Scheme 4 shows an alternative general scheme for the synthesis of Compound **21** where A is H, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I.**

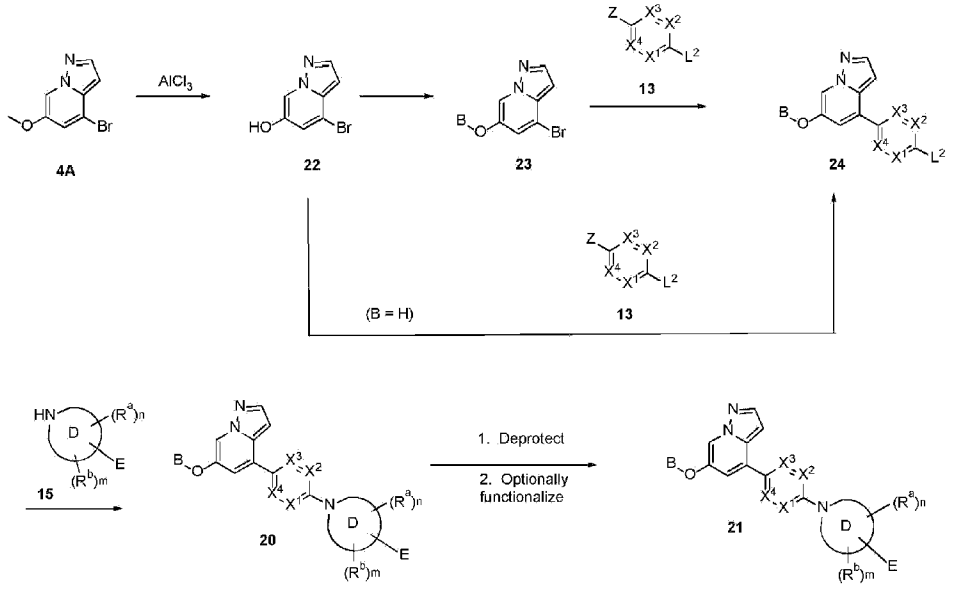
[0163] Compound **22** may be prepared by treating compound **4A** (prepared e.g., as described in Scheme 1) with aluminum trichloride.

[0164] When group B is hydrogen, compound **19** may be prepared by coupling compound **22** with the corresponding boronic ester compound **10** (where Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I;** Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an

inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures), wherein if Ring D of compound **10** is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. Compound **21** may be prepared from compound **19** according to the process described for Scheme 3.

[0165] Alternatively, when group B is as defined for Formula I other than hydrogen, compound **23** may be prepared by reacting compound **22** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, $(hetCyc^a)$C1-C3 alkyl-X, $hetCyc^a$-X or $hetCyc^aC(=O)$C1-C6 alkyl-X, where R^1, R^2, $hetAr^1$, and $hetCyc^a$ are as defined for Formula I and X is a leaving atom or group (halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if B has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **22** with C1-C6 alkyl-X, where X is Br or Cl, or triflate. Compound **20** may be prepared by coupling compound 23 with compound **10** as described in Scheme 3. Compound **21** may be prepared from compound **20** according to the process described for Scheme 3.

[0166] Alternatively, when group B is as defined for Formula I other than hydrogen, compound **20** may be prepared by reacting compound **19** with (C1-C6 alkyl)OH, an appropriately substituted (C1-C3 alkyl)OH, an appropriately substituted (C1-C6 alkyl)OH, or $hetCyc^aOH$ (i.e., where $hetCyc^a$ a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros) or hydroxyC1-C6 alkyl) under Mitsunobu reaction conditions (PPh_3 and diisopropyl azodicarboxylate). Compound **21** may be prepared from compound **20** according to the process described for Scheme 3.



SCHEME 5

[0167] Scheme 5 shows an alternative general scheme for the synthesis of Compound **21** where A is H,

and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I**.

[0168] Compound **22** may be prepared by treating compound **4A** (prepared e.g., as described in Scheme 1) with aluminum trichloride.

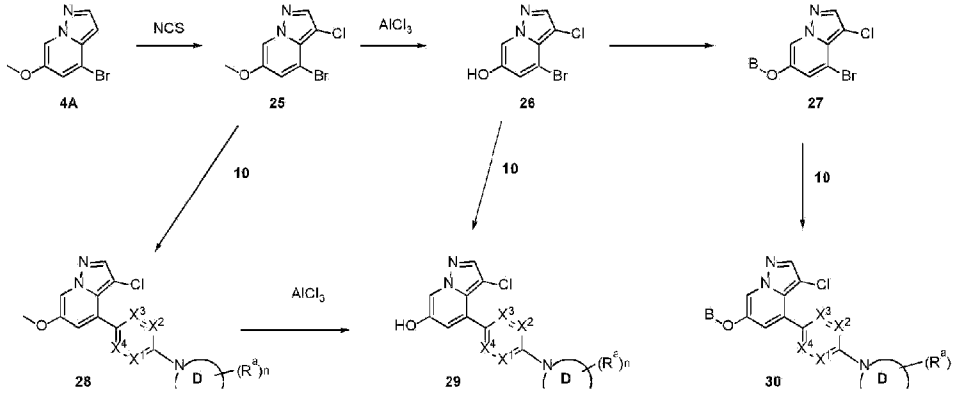
[0169] When group B is as defined for Formula I other than hydrogen, compound **23** may be prepared by reacting compound **22** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, hetAr^1C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, (hetCyc^a)C1-C3 alkyl-X, hetCyc^a-X or hetCyc^aC(=O)C1-C6 alkyl-X, where R^1, R^2, hetAr^1, and hetCyc^a are as defined for Formula I and X is a leaving atom or group (halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if B has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **22** with C1-C6 alkyl-X, where X is Br or Cl, or triflate.

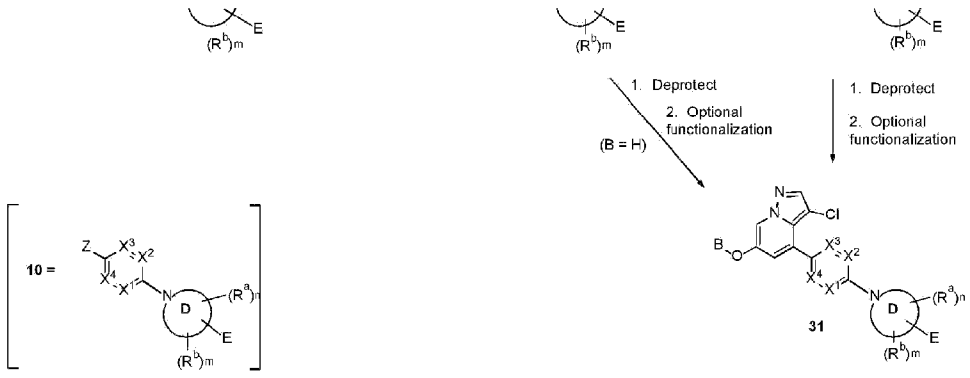
[0170] Compound **24** may be prepared by reacting compound **23** with compound **13** (where X^1, X^2, X^3 and X^4 are as defined for Formula **I**; L^2 is a triflate or halide); Z is -B(OR^x)(OR^y) and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures).

[0171] When group B is hydrogen, compound **24** may be prepared by reacting compound **22** directly with compound **13** as described above.

[0172] Compound **20** may be prepared by coupling compound **24** with compound **15** where Ring D and E are as defined for Formula I under appropriate S_NAr conditions (for example, optionally in the presence of K_2CO_3 and at elevated temperature). If Ring D of compound **15** comprises a substituent having a primary or secondary ring nitrogen atom, the nitrogen atom is protected with an appropriate amino protecting group prior to coupling, and then the amino protecting group may be removed subsequent to coupling as described above.

[0173] Compound **21** may be prepared from compound **20** according to the process described for Scheme 3.





SCHEME 6

[0174] Scheme 6 shows a general scheme for the synthesis of Compound **31** where A is Cl, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, n, m and E are as defined for Formula **I.**

[0175] Compound **25** may be prepared by treating compound 4A (prepared e.g., as described in Scheme 1) with aluminum trichloride.

[0176] Compound **26** may be prepared by treating compound **25** with aluminum trichloride.

[0177] When group B is as defined for Formula I other than hydrogen, compound **27** may be prepared by reacting compound **26** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, ($hetCyc^a$)C1-C3 alkyl-X, $hetCyc^a$-X or $hetCyc^aC(=O)$C1-C6 alkyl-X, where R^1, R^2, $hetAr^1$, and $hetCyc^a$ are as defined for Formula I and X is a leaving atom or group (halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if B has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **26** with C1-C6 alkyl-X, where X is Br or Cl, or triflate.

[0178] Compounds **28** (when group B is methyl), **29** (when group B is hydrogen) and 30 (when group B is other than hydrogen) may be prepared by coupling compounds **25, 26** and **27,** respectively, with the corresponding boronic ester compound **10** (where Ring D, E, X^1, X^2, X^3 and X^4 are as defined for Formula I; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures), wherein if Ring D of is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling. The amino protecting group if present on a substituent of Ring D of compound **29** or **30** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **1** to acidic conditions, e.g., HCl) to provide compound **31** where E is H.

[0179] Alternatively, the E group may be functionalized (i.e., reacted or treated with an appropriate reagent) under standard conditions described below to provide compound **31** where E is as defined for Formula I except that E is not H.

[0180] The E group of compounds **11, 11a, 16, 19, 20, 29** and **30** described in Schemes 1-6 may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce an E group, where E is any of the E groups defined for Formula I with the exception of hydrogen, using standard chemistry well known to persons skilled in the art. As used herein, the term "functionalized" refers to a process step in the E group of a compound of general Formula I is reacted or treated with an appropriate reagent to provide a compound of Formula I where E is as defined for Formula I except that E is other than hydrogen.

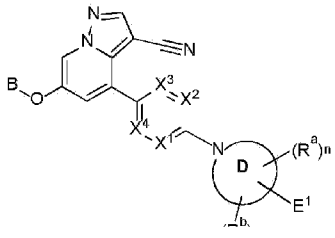
[0181] For example, an amide derivative (e.g., where E is $Ar^1C(=O)NR^g$-, $hetAr^2C(=O)NR^g(CH_2)_p$- p is 0 or 1, or $R^4R^5NC(=O)NR^g$-, may be obtained by reacting compound **11** wherein E is $-NH_2$ with an acid chloride using conventional amide bond formation conditions, for example in the presence of a base (e.g., DIEA) in an appropriate solvent (DCM) to provide a functionalized compound **12.** Alternative, compound **11** wherein E is $-NH_2$ may be reacted with an carboxylic acid using conventional amide bond formation conditions, for example by treating the carboxylic acid with an activating agent (e.g., HATU) followed by addition of compound **11** in the presence of a base ((e.g., DIEA) in an appropriate solvent (DMA) to provide a functionalized compound **12.** The same chemistry may be utilized with compounds **11a, 16, 19, 20, 29** and **30** to prepare functionalized compounds **12, 17, 21** and **31.**

[0182] As another example, a urea derivative, (e.g., where E is $R^4R^5NHC(=O)NR^g$-) may be prepared reacting a compound **11** where E is $-NH_2$ with a compound having the formula $R^4R^5N=C(=O)$ where R^4 and R^5 are as defined for Formula I in the presence of an appropriate base (e.g., DIEA) to provide a functionalized compound **12.** The same chemistry may be utilized with compounds **11a, 16, 19, 20, 29** and **30** to prepare functionalized compounds **12, 17, 21** and **31.**

[0183] As another example, an alkoxy, aryloxy or heteroaryloxy derivative (e.g., where E is (C1-C6 alkoxy)C1-C6 alkoxy, Ar^1O- or $hetAr^2O$-), may be prepared by reacting a compound **11** where E is hydroxy with a compound having the formula (C1-C6 alkoxy)C1-C6 alkyl-X, Ar^1-X or $hetAr^2$-X, where X is a halogen, in the presence of an inorganic base (e.g., sodium hydride or potassium hydride) in an appropriate solvent (e.g., DMA). The same chemistry may be utilized with compounds **11a, 16, 19, 20, 29** and **30** to prepare functionalized compounds **12, 17, 21** and **31.**

[0184] Accordingly, further provided herein is a process for preparing of a compound of Formula I or a pharmaceutically acceptable salt thereof as defined herein which comprises:

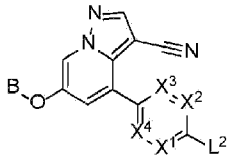
[0185] (b) for a compound of Formula I where A, B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I with the exception that E is not hydrogen, functionalizing a corresponding compound of the formula



$(R^b)_m$

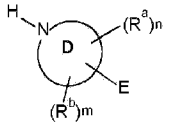
wherein Ring D, B, X^1, X^2, X^3,X^4, R^a, R^b, m and n are as defined for Formula I and E^1 is $-NH_2$ or OH; or

(c) for a compound of Formula I where A is CN and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I, reacting a corresponding compound of the formula **14**



14

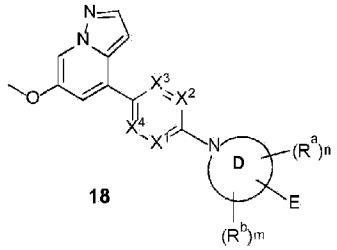
wherein Ring D, B, X^1, X^2, X^3, and X^4 are as defined for Formula I and L^2 is halogen or triflate, with a compound of the formula 15



15

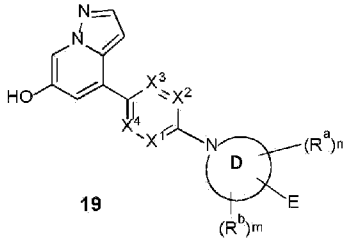
wherein Ring D, R^a, R^b, m, n, and E are as defined for Formula I and wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group prior to coupling, in the presence of a base, optionally followed by removal of the amino protecting group if present; or

(e) for a compound of Formula I where A is H, B is H, and X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula I, treating a corresponding compound of formula **18**



18

where A is H, B is H, and X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an amino protecting group, with aluminum trichloride to provide compound **19**

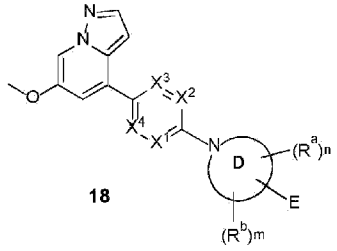


19

optionally followed by removal of the amino protecting group if present; or

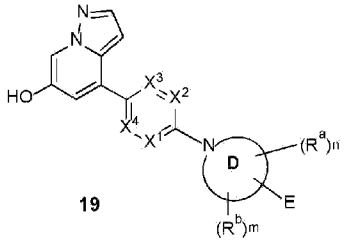
(f) for a compound of Formula I where A is H, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I,

(i) treating a corresponding compound of formula **18**



18

where A is H, and X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula **I**, wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an appropriate amino protecting group, with aluminum trichloride to provide compound **19**

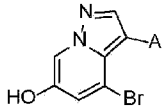


19

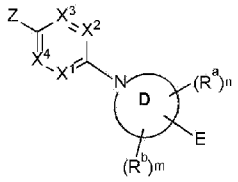
;

(ii) reacting compound **19** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, ($hetCyc^a$)C1-C3 alkyl-X, $hetCyc^a$-X or $hetCyc^aC(=O)$C1-C6 alkyl-X, where R^1, R^2, $hetAr^1$, and $hetCyc^a$ are as defined for Formula I and X is a leaving atom or group, optionally followed by removal of the amino protecting group if present; or

(g) for a compound of Formula **I** where A is H or Cl, B is H, and X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula **I**, coupling a compound of formula



where A is H or Cl with a boronate ester having formula 10

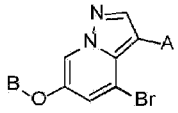


10

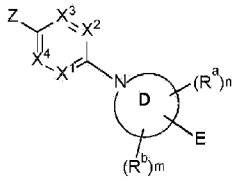
where Z is $-B(OR^x)(OR^y)$ and R^x and R^y are H or (1 -6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl), and Ring D, E, X^1, X^2, X^3, X^4, R^a, R^b, m and n are as defined for Formula **I**, wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an amino protecting group prior to said coupling, in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, optionally followed

by removal of the amino protecting group if present; or

(h) for a compound of Formula I where A is H or Cl, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I, coupling a compound of the formula



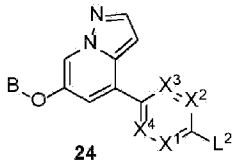
where A is H or Cl, with a corresponding boronate ester compound of formula 10



10

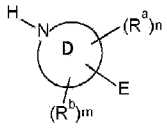
where Z is $-B(OR^x)(OR^y)$ and R^x and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl), and Ring D, E, X^1, X^2, X^3, X^4, R^a, R^b, m and n are as defined for Formula I, wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an amino protecting group prior to said coupling, in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, and optionally followed by removal of the amino protecting group if present; or

(i) for a compound of Formula I where A is H, and B, X^1, X^2, X^3, X^4, Ring D, R^a, R^b, m, n, and E are as defined for Formula I, coupling a compound of formula **24**



24

where B, X^1, X^2, X^3 and X^4, are as defined for Formula I and L^2 is a leaving group or atom, with a corresponding compound of formula **15**



15

where Ring D, R^a, R^b, m, n, and E are as defined for Formula I wherein if Ring D is substituted with an R^b substituent that is R^cR^dN- wherein one or both of R^c and R^d is hydrogen, the nitrogen atom of R^b may be protected with an amino protecting group, optionally followed by removal of the amino protecting group if present; and

removing any additional protecting groups if present and optionally forming a pharmaceutically acceptable salt thereof.

[0186] The term "amino protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on

the compound. Examples of suitable protecting groups for use in any of the processes described herein include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Examples of amino protecting groups are acetyl, trifluoroacetyl, t-butyloxycarbonyl ("Boc"), benzyloxycarbonyl ("CBz") and 9-fluorenylmethyleneoxycarbonyl ("Fmoc"). Further examples of these groups, and other protecting groups, are found in T. W. Greene, et al., Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006.

[0187] Hydroxy groups may be protected with any convenient hydroxy protecting group, for example as described in T. W. Greene, et al., Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006. Examples include benzyl, trityl and silyl ethers.

[0188] Nitrogen atoms in compounds described in any of the above methods may be protected with any convenient nitrogen protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of nitrogen protecting groups include acyl and t-butoxycarbonyl (BOC), phenoxycarbonyl, and [2-(trimethylsilyl)ethoxy]methyl (SEM).

[0189] The ability of test compounds to act as RET inhibitors may be demonstrated by the assay described in Example A. IC_{50} values are shown in **Table 5.**

[0190] In some embodiments, the compounds provided herein exhibit potent and selective RET inhibition. For example, the compounds provided herein exhibit nanomolar potency against wild type RET and select RET mutants, including the KIF5B-RET fusion and V804M gatekeeper mutation, with minimal activity against related kinases.

[0191] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt or solvate thereof, selectively target a RET kinase. For example, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, can selectively target a RET kinase over another kinase or non-kinase target.

[0192] In some embodiments, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibits at least a 30-fold selectivity for a RET kinase over another kinase. For example, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibits at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 200-fold selectivity; at least 300-fold selectivity; at least 400-fold selectivity; at least 500-fold selectivity; at least 600-fold selectivity; at least 700-fold selectivity; at least 800-fold selectivity; at least 900-fold selectivity; or at least 1000-fold selectivity for a RET kinase over another kinase. In some embodiments, selectivity for a RET kinase over another kinase is measured in a cellular assay (e.g., a cellular assay as provided herein).

[0193] In some embodiments, the compounds provided herein can exhibit selectivity for a RET kinase over a KDR kinase (e.g., VEGFR2). In some embodiments, the selectivity for a RET kinase over a KDR kinase is observed without loss of gatekeeper mutant potency. In some embodiments, the selectivity over a KDR kinase is at least 10-fold (e.g., at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 150-fold selectivity; at least 200-fold selectivity; at least 250-fold selectivity; at least 300-fold selectivity; at least 350-fold selectivity; or at least 400-fold selectivity) as compared to the inhibition of KIF5B-RET (i.e. the compounds were more potent against KIF5B-RET than

KDR). In some embodiments, the selectivity for a RET kinase over a KDR kinase is about 30-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 100-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 150-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 400-fold. Without being bound by any theory, potent KDR kinase inhibition is believed to be a common feature among multikinase inhibitors (MKIs) that target RET and may be the source of the dose-limiting toxicities observed with such compounds.

[0194] In some embodiments, inhibition of V804M was similar to that observed for wild-type RET. For example, inhibition of V804M was within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type RET (i.e. the compounds were similarly potent against wild-type RET and V804M). In some embodiments, selectivity for a wildtype or V804M RET kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to RET-mutant cells.

[0195] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor.

[0196] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibit one or more of high GI absorption, low clearance, and low potential for drug-drug interactions.

[0197] Compounds of Formula I are useful for treating diseases and disorders which can be treated with a RET kinase inhibitor, RET-associated diseases and disorders, e.g., proliferative disorders, cancers, including hematological cancers and solid tumors, and gastrointestinal disorders and IBS.

[0198] As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0199] As used herein, the terms "subject," "individual," or "patient," are used interchangeably, refers to any animal, including mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (a RET-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for

a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of a RET gene, a RET protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a RET-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the patient is a pediatric patient.

[0200] The term "pediatric patient" as used herein refers to a patient under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[0201] In certain embodiments, compounds of Formula I are useful for preventing diseases and disorders as defined herein (for example, autoimmune diseases, inflammatory diseases, and cancer). The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[0202] The term "RET-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a RET gene, a RET kinase, a RET kinase domain, or the expression or activity or level of any of the same described herein). Examples of a RET-associated disease or disorder include, for example, cancer and gastrointestinal disorders and irritable bowel syndrome (IBS).

[0203] The term "RET-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or expression or activity, or level of any of the same. Examples of a RET-associated cancer are described herein.

[0204] The phrase "dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a RET gene translocation that results in the expression of a fusion protein, a deletion in a RET gene that results in the expression of a RET protein that includes a deletion of at least one amino acid as compared to the wild-type RET protein, a mutation in a RET gene that results in the expression of a RET protein with one or more point mutations, or an

alternative spliced version of a RET mRNA that results in a RET protein having a deletion of at least one amino acid in the RET protein as compared to the wild-type RET protein) or a RET gene amplification that results in overexpression of a RET protein or an autocrine activity resulting from the overexpression of a RET gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a RET protein (e.g., a constitutively active kinase domain of a RET protein) in a cell. As another example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be a mutation in a RET gene that encodes a RET protein that is constitutively active or has increased activity as compared to a protein encoded by a RET gene that does not include the mutation. For example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of RET that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not RET). In some examples, dysregulation of a RET gene, a RET protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RET gene with another non-RET gene. Examples of fusion proteins are described in Table 1. Examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. Additional examples of RET kinase protein mutations (e.g., point mutations) are RET inhibitor resistance mutations Examples of RET inhibitor resistance mutations are described in Tables 3 and 4.

[0205] The term "wildtype" or "wild-type" describes a nucleic acid (e.g., a RET gene or a RET mRNA) or protein (e.g., a RET protein) that is found in a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease), or is found in a cell or tissue from a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease).

[0206] The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[0207] Provided herein is a method of treating cancer (e.g., a RET-associated cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. For example, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions. Examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of M918T, M918V, C634W, V804L, and V804M.

[0208] In some embodiments of any of the uses described herein, the cancer (e.g., RET-associated cancer) is a hematological cancer. In some embodiments of any of the uses described herein, the cancer

(e.g., RET-associated cancer) is a solid tumor. In some embodiments of any of the uses described herein, the cancer (e.g., RET-associated cancer) is lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, or cervical cancer. In some embodiments of any of the uses described herein, the cancer (e.g., RET-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy and breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[0209] In some embodiments, a hematological cancer (e.g., hematological cancers that are RET-associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL),

myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD), polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In one embodiment, the hematological cancer (e.g., the hematological cancer that is a RET-associated cancer) is AML or CMML

[0210] In some embodiments, the cancer (e.g., the RET-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are RET-associated cancers) include, for example, thyroid cancer (e.g., papillary thyroid carcinoma, medullary thyroid carcinoma), lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, breast cancer, colon cancer, colorectal cancer, prostate cancer, renal cell carcinoma, head and neck tumors, neuroblastoma, and melanoma. See, for example, Nature Reviews Cancer, 2014, 14, 173-186.

[0211] In some embodiments, the cancer is selected from the group consisting of lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

[0212] In some embodiments, the patient is a human.

[0213] Compounds of Formula I and pharmaceutically acceptable salts thereof are also useful for treating a RET-associated cancer.

[0214] Dysregulation of a RET kinase, a RET gene, or the expression or activity or level of any (e.g., one or more) of the same can contribute to tumorigenesis. For example, a dysregulation of a RET kinase, a RET gene, or expression or activity or level of any of the same can be a translocation, overexpression, activation, amplification, or mutation of a RET kinase, a RET gene, or a RET kinase domain. Translocation can include translocations involving the RET kinase domain, mutations can include mutations involving the RET ligand-binding site, and amplification can be of a RET gene. Other dysregulations can include RET mRNA splice variants and RET autocrine/paracrine signaling, which can also contribute to tumorigenesis.

[0215] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes overexpression of wild-type RET kinase (e.g., leading to autocrine activation). In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes overexpression, activation, amplification, or mutation in a chromosomal segment comprising the RET gene or a portion thereof, including, for example, the kinase domain portion, or a portion capable of exhibiting kinase activity.

[0216] In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a RET gene fusion. In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-RET partner protein, and includes a minimum of a functional RET kinase domain.

[0217] Examples of RET fusion proteins are shown in **Table 1.**

Table 1. Exemplary RET Fusion Partners and Cancers

Fusion Partner	Exemplary RET-Associated Cancer(s)
BCR	Chronic Myelomonocytic Leukemia (CMML)
CLIP1	Adenocarcinoma
KIF5B	NSCLC, Ovarian Cancer, Spitzoid Neoplasms; Lung Adenocarcinoma[3, 4, 14, 28]; Adenosquamous Carcinomas[15]
CCDC6 (also called PTC1, D10S170, or H4)	NSCLC, Colon Cancer, Papillary Thyroid Cancer; Adenocarcinomas; Lung Adenocarcinoma; Metastatic Colorectal Cancer[5]; Adenosquamous Carcinomas[15], Breast Cancer[30]
PTC1ex9 (a novel CCDC6 rearrangement)	Metastatic papillary thyroid cancer[2]
NCOA4 (also called PTC3, ELE1, and RFG)	Papillary Thyroid Cancer[21], NSCLC, Colon Cancer, Salivary Gland Cancer, Metastatic Colorectal Cancer[5]; Lung Adenocarcinoma[15]; Adenosquamous Carcinomas[15] Diffuse Sclerosing Variant of Papillary Thyroid Cancer[16] Breast Cancer[30], Acinic Cell Carcinoma[32], Mammary Analog Secretory Carcinoma[33]
TRIM33 (also called PTC7 and RFG7)	NSCLC, Papillary Thyroid Cancer
ERC1 (also called ELKS)	Papillary Thyroid Cancer, Breast Cancer
FGFR1OP	CMML, Primary Myelofibrosis with secondary Acute Myeloid Leukemia
MBD1 (also known as PCM1)	Papillary Thyroid Cancer
RAB61P2	Papillary Thyroid Cancer
PRKAR1A (also called PTC2)	Papillary Thyroid Cancer
TRIM24 (also called PTC6)	Papillary Thyroid Cancer
KTN1 (also called PTC8)	Papillary Thyroid Cancer
GOLGA5 (also called PTC5)	Papillary Thyroid Cancer, Spitzoid Neoplasms
HOOK3	Papillary Thyroid Cancer
KIAA1468 (also called PTC9 and RFG9)	Papillary Thyroid Cancer, Lung Adenocarcinoma[8, 12]
TRIM27 (also called RFP)	Papillary Thyroid Cancer
AKAP13	Papillary Thyroid Cancer
FKBP15	Papillary Thyroid Cancer
SPECC1L	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
TBL1XR1	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
CEP55	Diffuse Gastric Cancer[7]
CUX1	Lung Adenocarcinoma

Fusion Partner	Exemplary RET-Associated Cancer(s)
ACBD5	Papillary Thyroid Carcinoma
MYH13	Medullary Thyroid Carcinoma [1]
Uncharacterized	Inflammatory Myofibroblastic Tumor[6]
PIBF1	Bronchiolus Lung Cell Carcinoma[9]
KIAA1217 (also called SKT)	Papillary Thyroid Cancer[10, 13] Lung Adenocarcinoma[14] NSCLC[14]
MPRIP	NSCLC[11]
HRH4-RET	Thyroid cancer and/or paillary thyroid carcinoma[17]
Ria-RET	Thyroid cancer and/or papillary thyroid carcinoma[17]
RFG8	Papillary thyroid carcinoma[18]
FOXP4	Lung adenocarcinoma[19]
MYH10	Infantile myofibromatosis[20]
HTIF1	Various[22]
TIF1G	Various[22]
H4L	Various[22]
PTC4 (a novel NCO4/ELE1 rearrangement)	Papillary thyroid cancer[23]
FRMD4A	NSCLC[24]
SQSTM1	Papillary thyroid carcinoma[25]
AFAP1L2	Papillary thyroid carcinoma[25]
AFAP1	NSCLC[31]
PPFIBP2	Papillary thyroid carcinoma[25]
EML4	Papillary thyroid cancer[26]
PARD3	NSCLC[27]
UVELD	Papillary thyroid cancer[29]
RASGEF1A	Breast cancer[30]
TEL	*In vitro*[34]
RUFY1	Colorectal Cancer[35]
OLFM4	Small-Bowel Cancer[36]
UEVLD	Papillary Thyroid Carcinoma[37]
DLG5	Non-Anaplastic Thyroid (NAT) Cancer[38]
RRBP1	Colon Cancer[39]

[1] Grubbs et al., J. Clin. Endocrinol. Metab. 100:788-793, 2015.
[2] Halkova et al., Human Pathology 46:1962-1969, 2015.

[3] U.S. Patent No. 9,297,011
[4] U.S. Patent No. 9,216,172
[5] Le Rolle et al., Oncotarget. 6(30):28929-37, 2015.
[6] Antonescu et al., Am J Surg Pathol. 39(7):957-67, 2015.
[7] U.S. Patent Application Publication No. 2015/0177246.
[8] U.S. Patent Application Publication No. 2015/0057335.
[9] Japanese Patent Application Publication No. 2015/109806A.
[10] Chinese Patent Application Publication No. 105255927A.
[11] Fang, et al. Journal of Thoracic Oncology 11.2 (2016): S21-S22.
[12] European Patent Application Publication No. EP3037547A1.
[13] Lee et al., Oncotarget. DOI: 10.18632/oncotarget.9137, e-published ahead of printing, 2016.
[14] Saito et al., Cancer Science 107:713-720, 2016.
[15] Pirker et al., Transl. Lung Cancer Res. 4(6):797-800, 2015.
[16] Joung et al., Histopathology 69(1):45-53, 2016.
[17] PCT Patent Application Publication No. WO 2016/141169.
[18] Klugbauer et al., Cancer Res., 60(24):7028-32, 2000.
[19] Bastien et al., Journal of Molecular Diagnostics, 18(6):1027, Abstract Number: S120, 2016 Annual Meeting of the Association for Molecular Pathology, Charlotte, NC, 2016.
[20] Rosenzweig et al., Pediatr Blood Cancer, doi:10.1002/pbc.26377, 2016.
[21] Su et al., PLoS One, 11(111): e0165596, 2016.
[22] U.S. Patent No. 9,487,491.
[23] Fugazzola et al., Oncogene, 13(5):1093-7, 1996.
[24] Velcheti et al., J Thorac Oncol., 12(2):e15-e16. doi: 10.1016/j.jtho.2016.11.274, 2017.
[25] Iyama et al., Thyroid, doi: 10.1089/thy.2016.0673, 2017.
[26] Demeure et al., World J Surg.. 38(6):1296-305. doi: 10.1007/s00268-014-2485-3, 2014.
[27] Sabari et al., Oncoscience, Advance Publications,www.impactjournals.com/oncoscience/files/papers/1/345/345. pdf, 2017.
[28] U.S. Patent Application Publication No. 2017/0014413.
[29] Lu et al., Oncotarget, doi: 10.18632/oncotarget.17412, [Epub ahead of print], 2017.
[30] Hirshfield et al., Cancer Research, (February 2017) Vol. 77, No. 4, Supp. 1. Abstract Number: P3-07-02. Meeting Info: 39th Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX, United States. 06 Dec 2016-10 Dec 2016.
[31] Morgensztern et al., Journal of Thoracic Oncology, (January 2017) Vol. 12, No. 1, Supp. 1, pp. S717-S718, Abstract Number: P1.07-035, Meeting Info: 17th World Conference of the International Association for the Study of Lung Cancer, IASLC 2016. Vienna, Austria. 04 Dec 2016.
[32] Dogan et al., Laboratory Investigation, (February 2017) Vol. 97, Supp. 1, pp. 323A. Abstract Number: 1298, Meeting Info: 106th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2017. San Antonio, TX, United States.
[33] Dogan et al., MODERN PATHOLOGY, Vol. 30, Supp. [2], pp. 323A-323A. MA 1298, 2017.
[34] PCT Patent Application Publication No. WO 2017/146116.
[35] PCT Patent Application Publication No. WO 2017/122815.
[36] Reeser et al., J. Mol. Diagn., 19(5):682-696, doi: 10.1016/j.jmoldx.2017.05.006, 2017.
[37] Lu et al., Oncotarget, 8(28):45784-45792, doi: 10.18632/oncotarget.17412, 2017.
[38] Ibrahimpasic et al., Clin. Cancer Res., doi: 10.1158/1078-0432.CCR-17-1183, 2017.
[39] Kloosterman et al., Cancer Res., 77(14):3814-3822. doi: 10.1158/0008-5472.CAN-16-3563, 2017.

[0218] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes one or more deletions (e.g., deletion of an amino acid at position 4), insertions, or point mutation(s) in a RET kinase. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the RET kinase, resulting in constitutive activity of the RET kinase domain.

[0219] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2**).

Table 2. Activating RET Kinase Protein Point Mutations/Insertions/Deletions

Exemplary RET Point Mutations
Amino acid position 2
Amino acid position 3
Amino acid position 4
Amino acid position 5
Amino acid position 6
Amino acid position 7
Amino acid position 8
Amino acid position 11
Amino acid position 12
Amino acid position 13
Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 56 (e.g., L56M)[30]
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)
Amino acid position 114 (e.g., R114H)
Amino acid position 136 (e.g., glutamic acid to stop codon)
Amino acid position 145 (e.g., V145G)
Amino acid position 180 (e.g., arginine to stop codon)
Amino acid position 200
Amino acid position 292 (e.g., V292M)
Amino acid position 294
Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 373 (e.g., alanine to frameshift)

Exemplary RET Point Mutations
Amino acid position 393 (e.g., F393L)
Amino acid position 423 (e.g., G423R)[27]
Amino acid position 432
Amino acid position 446 (e.g., G446R)[28]
Δ Amino acid residues 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7)[3]
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D)[7*]
Amino acid position 515 (e.g., C515S, C515W[4])
Amino acid position 525 (e.g., R525W)[7*]
Amino acid position 531 (e.g., C531R, or 9 base pair duplication[2])
Amino acid position 532 (e.g., duplication)[2]
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)
Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A)[18]
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V)[6]
Amino acid position 603 (e.g., K603Q, K603E[2])
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W, C690C[32])
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q)[23]
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618Y, C618G, C618F, C618W)
Amino acid position 619 (e.g., F619F)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F)
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Amino acid position 632 (e.g., E632K, E632G[5, 11])
Δ Amino acid residues 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11)[9]
Amino acid position 633 (e.g., 9 base pair duplication[2])
Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR[2], or a 12 base pair duplication[2]) (e.g., causing MTC)

Exemplary RET Point Mutations
Amino acid position 635 (e.g., R635G)
Amino acid position 636 (e.g., T636P[2], T636M[4])
Amino acid position 640 (e.g., A640G)
Amino acid position 641 (e.g., A641S, A641T[8])
Amino acid position 648 (e.g., V648I)
Amino acid position 649 (e.g., S649L)[28]
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 675 (T675T, silent nucleotide change)[18]
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T)[18]
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)
Amino acid position 713 splice variant (e.g., E713K)[6]
Amino acid position 732 (e.g., E732K)[20]
Amino acid position 736 (e.g., G736R)[6]
Amino acid position 748 (e.g., G748C)
Amino acid position 750 (e.g., A750P)
Amino acid position 765 (e.g., S765P)
Amino acid position 766 (e.g., P766S, P766M[6])
Amino acid position 768 (e.g., E768Q, E768D)
Amino acid position 769 (e.g., L769L)
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 788 (e.g., I788I[32])
Amino acid position 790 (e.g., L790F)
Amino acid position 791 (e.g., Y791F, Y791N[24])
Amino acid position 802
Amino acid position 804 (e.g., V804L[15, 16], V804M[15, 16], V804E[12]) (e.g., causing MTC)
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K)[17]

Exemplary RET Point Mutations
Amino acid position 806 (e.g., Y806F, Y806S[12], Y806G, Y806C[2, 12, 14], Y806E[14], Y806H[12], Y806N[12], Y806Y[32])
Amino acid position 810 (e.g., G810R[12], G810S[12], G810A[13])
Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S)[10]
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S)[19]
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 848 (e.g., M848T)
Amino acid position 852 (e.g., I852M)
Amino acid position 865 (e.g., L865V)[12]
Amino acid position 870 (e.g., L870F)[12]
Amino acid position 873 (e.g., R873W)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T)
Amino acid position 884 (e.g., E884K)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A, S891S[32])
Amino acid position 897 (e.g., R897Q)
Amino acid position 898 (e.g., D898V)
Amino acid position 900 (e.g., Y900F)[22]
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C[2])
Amino acid position 905 (e.g., Y905F)[22]
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T[2], M918V, M918L[6]) (e.g., causing MTC)
Amino acid position 919 (e.g., A919V)
Amino acid position 921 (e.g., E921K)

Exemplary RET Point Mutations
Amino acid position 922 (e.g., S922P, S922Y)
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 981 (e.g., Y981F)[22]
Amino acid position 982 (e.g., R982C)
Amino acid position 1009 (e.g., M1009V)
Amino acid position 1015 (e.g., Y1015F)[22]
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1064 (e.g., M1064T)
Amino acid position 1096 (e.g., Y1096F)[21]
RET+3[1]
(In-Frame Deletion in Exons 6 and 11)[25]
(3bp In-Frame Deletion in Exon 15)[26]
Nucleotide position 2136+2 (e.g., 2136+2T>G)[29]
(del632-636 ins6)[31]
Amino acid positions 791 and 852 (e.g., Y791F + I852M)[31]
Amino acid positions 634 and 852 (e.g., C634R + I852M)[31]

[1] U.S. Patent Application Publication No. 2014/0272951.
[2] Krampitz et al., Cancer 120:1920-1931, 2014.
[3] Latteyer, et al., J. Clin. Endocrinol. Metab. 101(3):1016-22, 2016.
[4] Silva, et al. Endocrine 49.2:366-372, 2015.
[5] Scollo, et al., Endocr. J. 63(1):87-91, 2016.
[6] Jovanovic, et al., Prilozi 36(1):93-107, 2015.
[7] Qi, et al., Oncotarget. 6(32):33993-4003, 2015. *R525W and G513D appear to act in combination with S891A to enchance oncogenic activity.
[8] Kim, et al. ACTA ENDOCRINOLOGICA-BUCHAREST 11.2, 189-194, 2015.
[9] Cecchirini, et al. Oncogene, 14, 2609-2612, 1997.
[10] Karrasch, et al. Eur. Thyroid J., 5(1):73-7, 2016.
[11] Scollo et al., Endocr. J. 63:87-91, 2016.
[12] PCT Patent Application Publication No. WO 2016/127074.
[13] Huang et al., Mol. Cancer Ther., 2016 Aug 5. pii: molcanther.0258.2016. [Epub ahead of print].
[14] Carlomagno, et al., Endocr. Rel. Cancer 16(1):233-41, 2009.
[15] Yoon et al., J. Med. Chem. 59(1):358-73, 2016.
[16] U.S. Patent No. 8,629,135.
[17] Cranston, et al., Cancer Res. 66(20): 10179-87, 2006.
[18] Kheiroddin et al., Clin. Lab. 62(5):871-6, 2016.
[19] Ceolin et al., PLoS One. 11(2): e0147840, doi: 10.1371/journal.pone.0147840, 2016.

[20] Nadezda et al., Summer Undergraduate Research Programs (SURP) Student Abstracts, University of Oklahoma Health Sciences Center, 2016.
[21] Liu et al., J. Biol. Chem., 271(10): 5309-12, 1995.
[22] Kato et al., Cancer Res., 62: 2414-22, 2002.
[23] Grey et al., Endocrine Pathology, doi:10.1007/sl2022-016-9451-6, 2016.
[24] De Almeida et al., Endocrine Reviews, 2016, Vol. 37, No. 2, Supp. Supplement 1. Abstract Number: SUN-068; 98th Annual Meeting and Expo of the Endocrine Society, ENDO 2016. Boston, MA, US. 01 Apr 2016-04 Apr 2016.
[25] Vanden et al., Annals of Oncology, 2016, Vol. 27, Supp. Supplement 6. Abstract Number: 427PD; 41st European Society for Medical Oncology Congress, ESMP 2016. Copenhagen, Denmark. 07 Oct 2016-11 Oct 2016.
[26] Romei et al., European Thyroid Journal (August 2016) Vol. 5, Supp. Supplement 1, pp. 75; 39th Annual Meeting of the European Thyroid Association, ETA 2016. Copenhagen, Denmark. 03 Sep 2016-06 Sep 2016.
[27] Lee et al., Oncotarget, 8(4): 6579-6588, doi: 10.18632/oncotarget.14172, 2017.
[28] Zhang et al., Laboratory Investigation, (February 2017) Vol. 97, Supp. 1, pp. 209A. Abstract Number: 840, Meeting Info: 106th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2017. San Antonio, TX, United States.
[29] Borecka et al., European Journal of Cancer, (July 2016) Vol. 61, No. 1, pp. S26, Abstract Number: 162, Meeting Info: 24th Biennial Congress of the European Association for Cancer Research, EACR 2016. Manchester, United Kingdom.
[30] Corsello et al., Endocrine Reviews, (JUN 2014) Vol. 35, No. 3, Suppl. S, pp. SUN-0322, Meeting Info.: 96th Annual Meeting and Expo of the Endocrine-Society, Chicago, IL, USA, June 21-24, 2014.
[31] Gazizova et al., Endocrine Reviews, (JUN 2014) Vol. 35, No. 3, Suppl. S, pp. SAT-0304, Meeting Info.: 96th Annual Meeting and Expo of the Endocrine-Society, Chicago, IL, USA, June 21-24, 2014.
[32] Sromek et al., *Endocr Pathol.,* doi: 10.1007/s12022-017-9487-2, 2017.

[0220] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2a**).

Exemplary activating RET Kinase Protein Point Mutations/Insertions/Deletions

[0221]

Exemplary RET Point Mutations
Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)
Amino acid position 114 (e.g., R114H)
Amino acid position 145 (e.g., V145G)

Exemplary RET Point Mutations
Amino acid position 200
Amino acid position 292 (e.g., V292M)
Amino acid position 294
Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 393 (e.g., F393L)
Amino acid position 432
Δ Amino acid residues 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7)
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D)
Amino acid position 515 (e.g., C515S, C515W[4])
Amino acid position 525 (e.g., R525W)
Amino acid position 531 (e.g., C531R, or 9 base pair duplication)
Amino acid position 532 (e.g., duplication)
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)
Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A)
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V)
Amino acid position 603 (e.g., K603Q, K603E)
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W)
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q)
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618G, C618F, C618W)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F)
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Amino acid position 632 (e.g., E632K, E632G)
Δ Amino acid residues 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11)
Amino acid position 633 (e.g., 9 base pair duplication)

Exemplary RET Point Mutations
Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR, or a 12 base pair duplication) (e.g., causing MTC)
Amino acid position 635 (e.g., R635G)
Amino acid position 636 (e.g., T636P, T636M)
Amino acid position 640 (e.g., A640G)
Amino acid position 641 (e.g., A641S, A641T)
Amino acid position 648 (e.g., V648I)
Amino acid position 649 (e.g., S649L)
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T)
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)
Amino acid position 713 splice variant (e.g., E713K)
Amino acid position 732 (e.g., E732K)
Amino acid position 736 (e.g., G736R)
Amino acid position 748 (e.g., G748C)
Amino acid position 750 (e.g., A750P)
Amino acid position 765 (e.g., S765P)
Amino acid position 766 (e.g., P766S, P766M)
Amino acid position 768 (e.g., E768Q, E768D)
Amino acid position 769 (e.g., L769L)
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 790 (e.g., L790F)
Amino acid position 791 (e.g., Y791F, Y791N)
Amino acid position 802
Amino acid position 804 (e.g., V804L, V804M, V804E) (e.g., causing MTC)
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K)
Amino acid position 806 (e.g., Y806F, Y806S, Y806G, Y806C, Y806E, Y806H, Y806N)
Amino acid position 810 (e.g., G810R, G810S, G810A)

Exemplary RET Point Mutations
Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S)
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S)
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 848 (e.g., M848T)
Amino acid position 852 (e.g., I852M)
Amino acid position 865 (e.g., L865V)
Amino acid position 870 (e.g., L870F)
Amino acid position 873 (e.g., R873W)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T)
Amino acid position 884 (e.g., E884K)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A)
Amino acid position 897 (e.g., R897Q)
Amino acid position 898 (e.g., D898V)
Amino acid position 900 (e.g., Y900F)
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C)
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T, M918V, M918L) (e.g., causing MTC)
Amino acid position 919 (e.g., A919V)
Amino acid position 921 (e.g., E921K)
Amino acid position 922 (e.g., S922P, S922Y)
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 982 (e.g., R982C)
Amino acid position 1009 (e.g., M1009V)

Exemplary RET Point Mutations
Amino acid position 1015 (e.g., Y1015F)
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1064 (e.g., M1064T)
Amino acid position 1096 (e.g., Y1096F)
RET+3
(In-Frame Deletion in Exons 6 and 11)
(3bp In-Frame Deletion in Exon 15)

[0222] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a splice variation in a RET mRNA which results in an expressed protein that is an alternatively spliced variant of RET having at least one residue deleted (as compared to the wild-type RET kinase) resulting in a constitutive activity of a RET kinase domain.

[0223] A "RET kinase inhibitor" as defined herein includes any compound exhibiting RET inhibition activity. In some embodiments, a RET kinase inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitor can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[0224] As used herein, a "first RET kinase inhibitor" or "first RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. As used herein, a "second RET kinase inhibitor" or a "second RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. When both a first and a second RET inhibitor are present in a method provided herein, the first and second RET kinase inhibitor are different.

[0225] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions or insertions or deletions in a RET gene that results in the production of a RET kinase that has one or more amino acids inserted or removed, as compared to the wild-type RET kinase. In some cases, the resulting RET kinase is more resistant to inhibition of its phosphotransferase activity by one or more first RET kinase inhibitor(s), as compared to a wildtype RET kinase or a RET kinase not including the same mutation. Such mutations, optionally, do not decrease the sensitivity of the cancer cell or tumor having the RET kinase to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof (e.g., as compared to a cancer cell or a tumor that does not include the particular RET inhibitor resistance mutation). In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased V_{max}, a decreased K_m for ATP, and an increased K_D for a first RET kinase inhibitor, when in the presence of a first RET kinase inhibitor, as compared to a wildtype RET kinase or a RET kinase not having the same

mutation in the presence of the same first RET kinase inhibitor.

[0226] In other embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions as compared to the wild-type RET kinase, and which has increased resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype RET kinase or a RET kinase not including the same mutation. In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased V_{max}, a decreased K_m, and a decreased K_D in the presence of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0227] Examples of RET inhibitor resistance mutations can, e.g., include point mutations, insertions, or deletions in and near the ATP binding site in the tertiary structure of RET kinase, including the gatekeeper residue, P-loop residues, residues in or near the DFG motif, and ATP cleft solvent front amino acid residues. Additional examples of these types of mutations include changes in residues that may affect enzyme activity and/or drug binding including residues in the activation loop, residues near or interacting with the activation loop, residues contributing to active or inactive enzyme conformations, changes including mutations, deletions, and insertions in the loop proceeding the C-helix and in the C-helix. Specific residues or residue regions that may be changed (and are RET inhibitor resistance mutations) include those listed in Table 3 based on the human wildtype RET protein sequence (e.g., SEQ ID NO: 1). Additional examples of RET inhibitor resistance mutation positions are shown in Table 4. Changes to these residues may include single or multiple amino acid changes, insertions within or flanking the sequences, and deletions within or flanking the sequences.

[0228] Exemplary Sequence of Mature Human RET Protein (SEQ ID NO: 1)

MAKATSGAAG LRLLLLLLLP LLGKVALGLY FSRDAYWEKL YVDQAAGTPL LYVHALRDAP EEVPSFRLGQ
HLYGTYRTRL HENNWICIQE DTGLLYLNRS LDHSSWEKLS VRNRGFPLLT VYLKVFLSPT SLREGECQWP
GCARVYFSFF NTSFPACSSL KPRELCFPET RPSFRIRENR PPGTFHQFRL LPVQFLCPNI SVAYRLLEGE
GLPFRCAPDS LEVSTRWALD REQREKYELV AVCTVHAGAR EEVVMVPFPV TVYDEDDSAP TFPAGVDTAS
AVVEFKRKED TVVATLRVFD ADVVPASGEL VRRYTSTLLP GDTWAQQTFR VEHWPNETSV QANGSFVRAT
VHDYRLVLNR NLSISENRTM QLAVLVNDSD FQGPGAGVLL LHFNVSVLPV SLHLPSTYSL SVSRRARRFA
QIGKVCVENC QAFSGINVQY KLHSSGANCS TLGVVTSAED TSGILFVNDT KALRRPKCAE LHYMVVATDQ
QTSRQAQAQL LVTVEGSYVA EEAGCPLSCA VSKRRLECEE CGGLGSPTGR CEWRQGDGKG ITRNFSTCSP
STKTCPDGHC DVVETQDINI CPQDCLRGSI VGGHEPGEPR GIKAGYGTCN CFPEEEKCFC EPEDIQDPLC
DELCRTVIAA AVLFSFIVSV LLSAFCIHCY HKFAHKPPIS SAEMTFRRPA QAFPVSYSSS GARRPSLDSM
ENQVSVDAFK ILEDPKWEFP RKNLVLGKTL GEGEFGKVVK ATAFHLKGRA GYTTVAVKML KENASPSELR
DLLSEFNVLK QVNHPHVIKL YGACSQDGPL LLIVEYAKYG SLRGFLRESR KVGPGYLGSG GSRNSSSLDH
PDERALTMGD LISFAWQISQ GMQYLAEMKL VHRDLAARNI LVAEGRKMKI SDFGLSRDVY EEDSYVKRSQ
GRIPVKWMAI ESLFDHIYTT QSDVWSFGVL LWEIVTLGGN PYPGIPPERL FNLLKTGHRM ERPDNCSEEM
YRLMLQCWKQ EPDKRPVFAD ISKDLEKMMV KRRDYLDLAA STPSDSLIYD DGLSEEETPL VDCNNAPLPR
ALPSTWIENK LYGMSDPNWP GESPVPLTRA DGTNTGFPRY PNDSVYANWM LSPSAAKLMD TFDS

[0229] In some embodiments, compounds of Formula I and pharmaceutically acceptable salts are useful in treating patients that develop cancers with RET inhibitor resistance mutations (e.g., that result in an increased resistance to a first RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, and/or one or more RET inhibitor resistance mutations listed in Tables 3 and 4) by either dosing in combination or as a follow-up therapy to existing drug treatments (e.g., other RET kinase inhibitors; e.g., first and/or second RET kinase inhibitors). Exemplary first and second RET kinase

inhibitors are described herein. In some embodiments, a first or second RET kinase inhibitor can be selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[0230] In some embodiments, compounds of Formula I or pharmaceutically acceptable salts thereof are useful for treating a cancer that has been identified as having one or more RET inhibitor resistance mutations (that result in an increased resistance to a first or second RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E). Examples of RET inhibitor resistance mutations are listed in Tables 3 and 4.

Table 3. RET Inhibitor Resistance Mutations

Exemplary RET Resistance Mutations
Amino acid position 732 (e.g., E732K)[7]
Amino acid position 788 (e.g., I788N)[8]
Amino acid position 804 (e.g., V804M[1, 2], V804L[1, 2], V804E[6])
Amino acid position 804/805 (e.g., V804M/E805K)[3]
Amino acid position 806 (e.g., Y806C[4, 6], Y806E[4], Y806S[6], Y806H[6], Y806N[6])
Amino acid position 810 (e.g., G810A[5], G810R[6], G810S[6])
Amino acid position 865 (e.g., L865V[6])
Amino acid position 870 (e.g., L870F[6])
[1] Yoon et al., J. Med. Chem. 59(1):358-73, 2016. [2] U.S. Patent No. 8,629,135. [3] Cranston, et al., Cancer Res. 66(20): 10179-87, 2006. [4] Carlomagno, et al., Endocr. Rel. Cancer 16(1):233-41, 2009. [5] Huang et al., Mol. Cancer Ther., 2016 Aug 5. pii: molcanther.0258.2016. [Epub ahead of print]. [6] PCT Patent Application Publication No. WO 2016/127074. [7] Nadezda et al., Summer Undergraduate Research Programs (SURP) Student Abstracts, University of Oklahoma Health Sciences Center, 2016. [8] Plenker et al., Sci. Transl. Med., 9(394), doi: 10.1126/scitranslmed.aah6144, 2017.

Table 4. Additional Exemplary Amino Acid Positions of RET Inhibitor Resistance Mutations

RET Amino Acid and Position	**Exemplary Mutation**	**Mechanistic Resistance Rationale**
L730	P	Steric hindrance and/or active conformational effect
G731	V	Steric hindrance and/or active conformational effect
E732	K	Steric hindrance and/or active conformational effect
G733	V	Steric hindrance and/or active conformational effect
E734	K	Steric hindrance and/or active conformational effect
L760	M	Active conformational effect
K761	E	Active conformational effect

RET Amino Acid and Position	Exemplary Mutation	Mechanistic Resistance Rationale
E762	K	Active conformational effect
N763	D	Active conformational effect
A764	V	Active conformational effect
S765	N	Active conformational effect
P766	A	Active conformational effect
S767	C	Active conformational effect
E768	K	Active conformational effect
L779	M	Steric hindrance and/or active conformational effect
1788	M	Steric hindrance and/or active conformational effect
M868	R	Steric hindrance and/or active conformational effect
K869	E	Steric hindrance and/or active conformational effect
L870	Q	Steric hindrance and/or active conformational effect
V871	M	Steric hindrance and/or active conformational effect
H872	R	Steric hindrance and/or active conformational effect
R873	P	Steric hindrance and/or active conformational effect
D874	Y	Steric hindrance and/or active conformational effect
L881	R	Steric hindrance and/or active conformational effect
L895	M	Active conformational effect
S896	N	Active conformational effect
R897	C	Active conformational effect
D898	Y	Active conformational effect
V899	G	Active conformational effect
Y900	D	Active conformational effect
E901	K	Active conformational effect
E902	K	Active conformational effect
D903	Y	Active conformational effect
S904	C	Active conformational effect
Y905	D	Active conformational effect
V906	M	Active conformational effect
K907	E	Active conformational effect
R908	P	Active conformational effect

RET Amino Acid and Position	Exemplary Mutation	Mechanistic Resistance Rationale
S909	C	Active conformational effect
Q910	R	Active conformational effect
G911	C	Active conformational effect
R912	P	Active conformational effect

[0231] The oncogenic role of RET was firstly described in papillary thyroid carcinoma (PTC) (Grieco et al., Cell, 1990, 60, 557-63), which arises from follicular thyroid cells and is the most common thyroid malignancy. Approximately 20-30% of PTC harbor somatic chromosomal rearrangements (translocations or inversions) linking the promoter and the 5' portions of constitutively expressed, unrelated genes to the RET tyrosine kinase domain (Greco et al., Q. J. Nucl. Med. Mol. Imaging, 2009, 53, 440-54), therefore driving its ectopic expression in thyroid cells. To date, a variety of fusion partners have been identified, all providing a protein/protein interaction domain that induces ligand-independent RET dimerization and constitutive kinase activity (see, e.g., Table 1). The role of RET-PTC rearrangements in the pathogenesis of PTC has been confirmed in transgenic mice (Santoro et al., Oncogene, 1996, 12, 1821-6). Recently, a 10.6 Mb pericentric inversion in chromosome 10, where RET gene maps, has been identified in about 2% of lung adenocarcinoma patients, generating different variants of the chimeric gene KIF5B-RET (Ju et al., Genome Res., 2012, 22, 436-45; Kohno et al., 2012, Nature Med., 18, 375-7; Takeuchi et al., Nature Med., 2012, 18, 378-81; Lipson et al., 2012, Nature Med., 18, 382-4). The fusion transcripts are highly expressed and all the resulting chimeric proteins contain the N-terminal portion of the coiled-coil region of KIF5B, which mediates homodimerization, and the entire RET kinase domain. None of RET positive patients harbor other known oncogenic alterations (such as EGFR or K-Ras mutation, ALK translocation), supporting the possibility that KIF5B-RET fusion could be a driver mutation of lung adenocarcinoma. The oncogenic potential of KIF5B-RET has been confirmed by transfecting the fusion gene into cultured cell lines: similarly to what has been observed with RET-PTC fusion proteins, KIF5B-RET is constitutively phosphorylated and induces NIH-3T3 transformation and IL-3 independent growth of BA-F3 cells. However, other RET fusion proteins have been identified in lung adenocarcinoma patients, the CCDC6-RET fusion protein, which has been found to play a key role in the proliferation of the human lung adenocarcinoma cell line LC-2/ad (Journal of Thoracic Oncology, 2012, 7(12):1872-1876). RET inhibitors have been shown to be useful in treating lung cancers involving RET rearrangements (Drilon, A.E. et al. J Clin Oncol 33, 2015 (suppl; abstr 8007)). RET fusion proteins have also been identified in patients having colorectal cancer (Song Eun-Kee, et al. International Journal of Cancer, 2015, 136: 1967-1975).

[0232] Besides rearrangements of the RET sequence, gain of function point mutations of RET proto-oncogene are also driving oncogenic events, as shown in medullary thyroid carcinoma (MTC), which arises from parafollicular calcitonin-producing cells (de Groot, et al., Endocrine Rev., 2006, 27, 535-60; Wells and Santoro, Clin. Cancer Res., 2009, 15, 7119-7122). Around 25% of MTC are associated with multiple endocrine neoplasia type 2 (MEN2), a group of inherited cancer syndromes affecting neuroendocrine organs caused by germline activating point mutations of RET. In MEN2 subtypes (MEN2A, MEN2B and Familial MTC/FMTC) RET gene mutations have a strong phenotype-genotype correlation defining different MTC aggressiveness and clinical manifestations of the disease. In MEN2A syndrome mutations involve one of the six cysteine residues (mainly C634) located in the cysteine-rich extracellular region, leading to ligand-independent homodimerization and constitutive RET activation. Patients develop MTC at a young age (onset at 5-25 years) and may also develop pheochromocytoma (50%) and hyperparathyroidism. MEN2B is mainly caused by M918T mutation, which is located in the kinase domain. This mutation constitutively activates RET in its monomeric state and alters substrate

recognition by the kinase. MEN2B syndrome is characterized by an early onset (< 1 year) and very aggressive form of MTC, pheochromocytoma (50% of patients) and ganglioneuromas. In FMTC the only disease manifestation is MTC, usually occurring at an adult age. Many different mutations have been detected, spanning the entire RET gene. The remaining 75% of MTC cases are sporadic and about 50% of them harbor RET somatic mutations: the most frequent mutation is M918T that, as in MEN2B, is associated with the most aggressive phenotype. Somatic point mutations of RET have also been described in colorectal cancer (Wood et al., Science, 2007, 318, 1108-13) and small cell lung carcinoma (Jpn. J. Cancer Res., 1995, 86, 1127-30).

[0233] RET signaling components have been found to be expressed in primary breast tumors and to functionally interact with estrogen receptor-cc pathway in breast tumor cell lines (Boulay et al., Cancer Res. 2008, 68, 3743-51; Plaza-Menacho et al., Oncogene, 2010, 29, 4648-57), while RET expression and activation by GDNF family ligands could play an important role in perineural invasion by different types of cancer cells (Ito et al., Surgery, 2005, 138, 788-94; Gil et al., J. Natl. Cancer Inst., 2010, 102, 107-18; Iwahashi et al., Cancer, 2002, 94, 167-74).

[0234] RET is also expressed in 30-70% of invasive breast cancers, with expression being relatively more frequent in estrogen receptor-positive tumors (Plaza-Menacho, I., et al., Oncogene, 2010, 29, 4648-4657; Esseghir, S., et al., Cancer Res., 2007, 67, 11732-11741; Morandi, A., et al., Cancer Res., 2013, 73, 3783-3795; Gattelli, A., EMBO Mol. Med., 2013, 5, 1335-1350).

[0235] The identification of RET rearrangements has been reported in a subset of (patient-derived xenograft) PDX established from colorectal cancer. Although the frequency of such events in colorectal cancer patients remains to be defined, these data suggest a role of RET as a target in this indication (Gozgit et al., AACR Annual Meeting 2014). Studies have shown that the RET promoter is frequently methylated in colorectal cancers, and heterozygous missense mutations, which are predicted to reduce RET expression, are identified in 5-10% of cases, which suggests that RET might have some features of a tumor suppressor in sporadic colon cancers (Luo, Y., et al., Oncogene, 2013, 32, 2037-2047; Sjoblom, T., et al., Science, 2006, 268-274; Cancer Genome Atlas Network, Nature, 2012, 487, 330-337).

[0236] An increasing number of tumor types are now being shown to express substantial levels of wild-type RET kinase that could have implications for tumor progression and spread. RET is expressed in 50-65% of pancreatic ductal carcinomas, and expression is more frequent in metastatic and higher grade tumors (Ito, Y, et al., Surgery, 2005, 138, 788-794; Zeng, Q., et al., J. Int. Med. Res. 2008, 36, 656-664).

[0237] In neoplasms of hematopoietic lineages, RET is expressed in acute myeloid leukemia (AML) with monocytic differentiation, as well as in CMML (Gattei, V. et al., Blood, 1997, 89, 2925-2937; Gattei, V., et al., Ann. Hematol, 1998, 77, 207-210; Camos, M., Cancer Res. 2006, 66, 6947-6954). Recent studies have identified rare chromosomal rearrangements that involve RET in patients with chronic myelomonocytic leukemia (CMML). CMML is frequently associated with rearrangements of several tyrosine kinases, which result in the expression of chimeric cytosolic oncoproteins that lead to activation of RAS pathways (Kohlmann, A., et al., J. Clin. Oncol. 2010, 28, 2858-2865). In the case of RET, gene fusions that link RET with BCR (BCR-RET) or with fibroblast growth factor receptor 1 oncogene partner (FGFR1OP-RET) were transforming in early hematopoietic progenitor cells and could shift maturation of these cells towards monocytic paths, probably through the initiation of RET-mediated RAS signaling (Ballerini, P., et al., Leukemia, 2012, 26, 2384-2389).

[0238] RET expression has also been shown to occur in several other tumor types, including prostate cancer, small-cell lung carcinoma, melanoma, renal cell carcinoma, and head and neck tumors (Narita,

N., et al., Oncogene, 2009, 28, 3058-3068; Mulligan, L. M., et al., Genes Chromosomes Cancer, 1998, 21, 326-332; Flavin, R., et al., Urol. Oncol., 2012, 30, 900-905; Dawson, D. M., J Natl Cancer Inst, 1998, 90, 519-523).

[0239] In neuroblastoma, RET expression and activation by GFLs has roles in tumor cell differentiation, potentially collaborating with other neurotrophic factor receptors to down regulate N-Myc, the expression of which is a marker of poor prognosis (Hofstra, R. M., W., et al., Hum. Genet. 1996, 97, 362-364; Petersen, S. and Bogenmann, E., Oncogene, 2004, 23, 213-225; Brodeur, G. M., Nature Ref. Cancer, 2003, 3, 203-216).

[0240] Multitargeted inhibitors which cross react with RET are known (Borrello, M.G., et al., Expert Opin. Ther. Targets, 2013, 17(4), 403-419; International Patent Application Nos. WO 2014/141187, WO 2014/184069, and WO 2015/079251).

[0241] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof for use in treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same where the presence of dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Some embodiments of any of the uses described herein further include recording in the patient's clinical record (e.g., a computer readable medium) that the patient is determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[0242] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a cancer in a patient in need thereof or a patient identified or diagnosed as having a RET-associated cancer. Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for use in treating a cancer in a patient identified or diagnosed as having a RET-associated cancer. In some embodiments, the cancer is a RET-associated cancer, for example, a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, a patient is identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the sample. As provided herein, a RET-associated cancer includes those described herein and known in the art.

[0243] In some embodiments of any of the uses described herein, the patient has been identified or diagnosed as having a cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient has a tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the uses described herein, the patient can be a patient with a tumor(s) that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the uses described herein, the patient can be a patient whose tumors have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the uses described herein, the patient is suspected of having a RET-associated cancer (e.g., a cancer having one or more RET inhibitor resistance mutations). In some embodiments, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions/deletions. Examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of M918T, M918V, C634W, V804L, and V804M. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. Examples of RET inhibitor resistance mutations are described in Tables 3 and 4. In some embodiments, the RET inhibitor resistance mutation is V804M. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[0244] In some embodiments of any of the uses described herein, the patient has a clinical record indicating that the patient has a tumor that has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., a tumor having one or more RET inhibitor resistance mutations). In some embodiments, the clinical record indicates that the patient should be treated with one or more of the compounds of Formula I or a pharmaceutically acceptable salts thereof or compositions provided herein. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a cancer having one or more RET inhibitor resistance mutations. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[0245] Also provided is the compound of Formula I or a pharmaceutically acceptable salt thereof for for

use in treating a RET-associated cancer in a patient having a clinical record that indicates that the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Some embodiments of these uses can further include: a step of performing an on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and recording the information in a patient's clinical file (e.g., a computer readable medium) that the patient has been identified to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the dysregulation of a RET gene, RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[0246] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., a RET-associated cancer, a RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas , glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and craniopharyngiomas (see, for example, the tumors listed in Louis, D.N. et al. Acta Neuropathol 131(6), 803-820 (June 2016)). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor. In some embodiments, the brain tumor is a metastatic brain tumor. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor.

[0247] In some embodiments of any of the uses described herein, an assay used to determine whether the patient has a dysregulation of a RET gene, or a RET kinase, or expression or activity or level of any of the same, using a sample from a patient can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a RET gene, a RET kinase, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the dysregulation of the RET gene, the RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the patient. In some embodiments, the patient is a patient suspected of having a RET-associated cancer, a patient having one or more symptoms of a RET-associated cancer, and/or a patient that has an increased risk of developing a RET-associated cancer)

[0248] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint

treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, kinase inhibitors, signal transduction inhibitors and/or monoclonal antibodies. Compounds of Formula I therefore may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example a chemotherapeutic agent that works by the same or by a different mechanism of action.

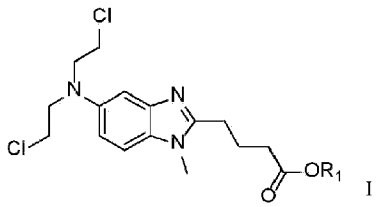
[0249] In some embodiments, the compound of Formula I (or a pharmaceutically acceptable salt or solvate thereof) is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents.

[0250] Examples of additional therapeutic agents include: other RET-targeted therapeutic agents (i.e. a first or second RET kinase inhibitor), receptor tyrosine kinase-targeted therapeutic agents, signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g. obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

[0251] In some embodiments, the other RET-targeted therapeutic is a multikinase inhibitor exhibiting RET inhibition activity. In some embodiments, the other RET-targeted therapeutic inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[0252] Examples of RET-targeted therapeutic agents include alectinib, apatinib, cabozantinib (XL-184), dovitinib, lenvatinib, motesanib, nintedanib, ponatinib, regorafenib, sitravatinib (MGCD516), sunitinib, sorafenib, vatalanib, vandetanib, AUY-922 (5-(2,4-Dihydroxy-5-isopropyl-phenyl)-N-ethyl-4-[4-(morpholinomethyl)phenyl]isoxazole-3-carboxamide), BLU6864, BLU-667, DCC-2157, GSK3179106, NVP-AST487 (1-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-3-[4-[6-(methylamino)pyrimidin-4-yl]oxyphenyl]urea), PZ-1, RPI-1 (1,3-dihydro-5,6-dimethoxy-3-[(4-hydroxyphenyl)methylene]-H-indol-2-one), RXDX-105 (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea), SPP86 (1-Isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), and TG101209 (N-(1,1-dimethylethyl)-3-[[5-methyl-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]amino]-benzenesulfonamide).

[0253] Additional examples of other RET kinase inhibitors include those described in U.S. Patent Nos. 9,150,517 and 9,149,464, and International Publication No. WO 2014075035,. For example, in some embodiments the other RET inhibitor is a compound of formula I:

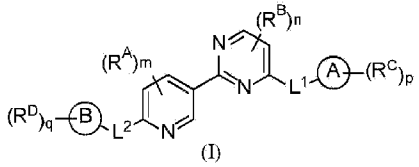


I

wherein R_1 is C_6-C_{24}alkyl or polyethylene glycol; or a pharmaceutically acceptable salt form thereof. In some embodiments, the other RET inhibitor is 4-{5-[bis-(chloroethyl)-amino]-1-methyl-1H-benzimidazol-2-

yl}butyric acid dodecyl ester.

[0254] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2016127074,. For example, in some embodiments, the other RET inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



(I)

wherein Rings A and B are each independently selected from aryl, heteroaryl, cycloalkyl and heterocyclyl;

each L^1 and L^2 is independently selected from a bond, -(C1-C6 alkylene)-, -(C2-C6alkenylene)-, -(C2-C6 alkynylene)-, -(C1-C6 haloalkylene)-, -(C1-C6 heteroalkylene)-, -C(O)-, -O-, -S-, -S(O), $-S(O)_2-$, $-N(R^1)-$, -O-(C1-C6 alkylene)-, -(C1-C6 alkylene)-O-, $-N(R^1)-C(O)-$, $-C(O)N(R^1)-$, -(C1-C6 alkylene)-$N(R^1)-$, $-N(R^1)-$(C1-C6 alkylene)-, $-N(R^1)-C(O)-$(C1-C6 alkylene)-, -(C1-C6 alkylene)-$N(R^1)-C(O)-$, $-C(O)-N(R^1)-$(C1-C6 alkylene)-, -(C1-C6 alkylene)-$C(O)-N(R^1)-$, $-N(R^1)-S(O)_2-$, $-S(O)_2-N(R^1)-$, $-N(R^1)-S(O)_2-$(C1-C6 alkylene)-, and-$S(O)_2-N(R^1)$-(C1-C6 alkylene)-; wherein each alkylene, alkenylene, alkynylene, haloalkylene, and heteroalkylene is independently substituted with 0-5 occurrences of R';

each R^A and R^B is independently selected from C1-C6 alkyl, C1-C6 alkoxy, halo, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl, and $-N(R^1)(R^1)$; wherein each alkyl, alkoxy, haloalkyl, hydroxyalkyl, and hydroxyalkyl is independently substituted with 0-5 occurrences of Ra;

each R^C and R^D is independently selected from C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 alkoxy, halo, C1-C6 heteroalkyl, C1-C6 haloalkyl, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, -(C1-C6 alkylene)-$C(O)R^1$, $-SR^1$,$-S(O)_2R1$, $-S(O)_2-N(R^1)(R^1)$, -(C1-C6 alkylene)-$S(O)_2R^1$, -(C1-C6 alkylene)-$S(O)_2-N(R^1)(R^1)$, $-N(R^1)(R^1)$ $-C(O)-N(R^1)(R^1)-N(R^1)-C(O)R^1$, $-N(R^1)-C(O)OR^1$, -(C1-C6 alkylene)-$N(R^1)-C(O)R^1$, $-N(R^1)S(O)_2R^1$, and $-P(O)(R^1)(R^1)$; wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a; or 2 R^C or 2 R^D together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a;

each R^1 is independently selected from hydrogen, hydroxyl, halo, thiol, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of alkyl, thioalkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b, or 2 R^1 together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b;

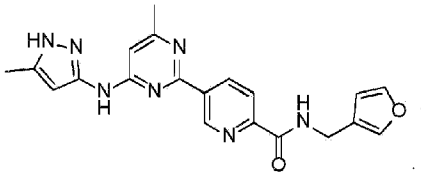
each R^a and R^b is independently C1-C6 alkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 heteroalkyl, C1-C6 hydroxyalkyl, C1-C6 alkoxy, cycloalkyl, heterocyclyl, or cyano, wherein each of alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R';

each R' is C1-C6 alkyl, C1-C6 heteroalkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, cycloalkyl or cyano; or 2 R', together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring;

m is 0, 1, 2, or 3;

n is 0, 1, or 2; and

p and q are each independently 0, 1, 2, 3, or 4. For example, a RET inhibitor can be selected from the group consisting of: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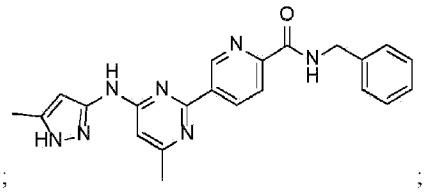
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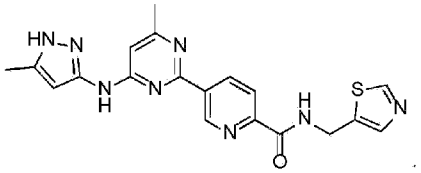
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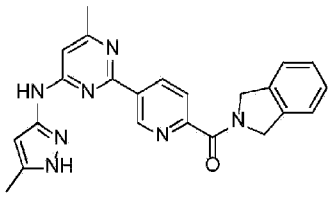
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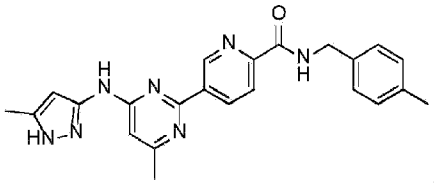
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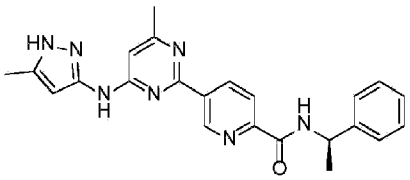
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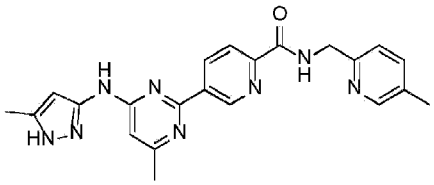
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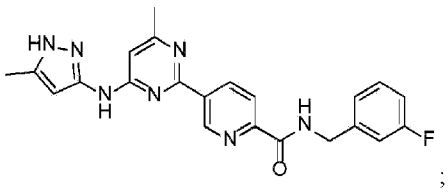
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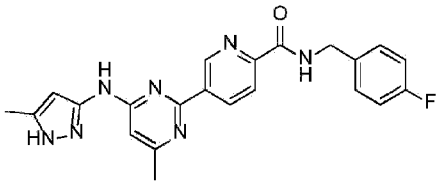
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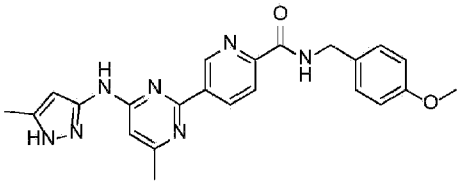
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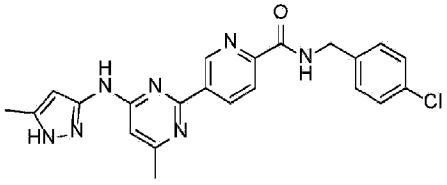
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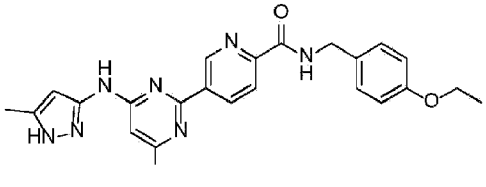

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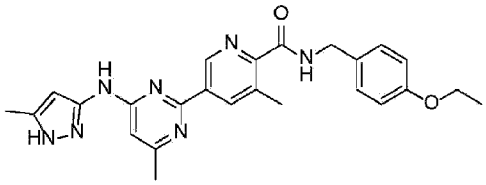
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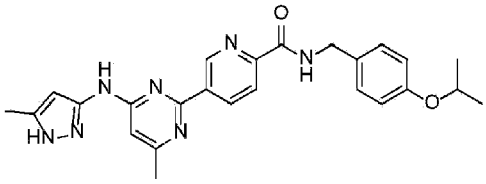
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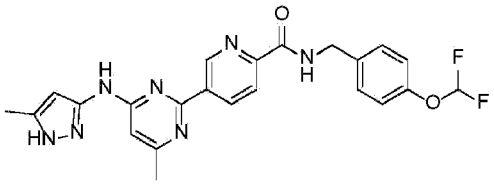
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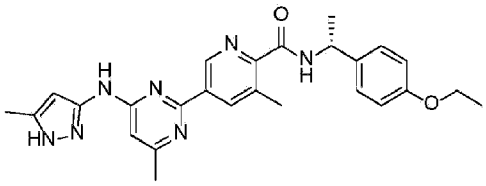
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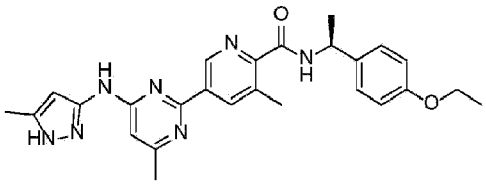
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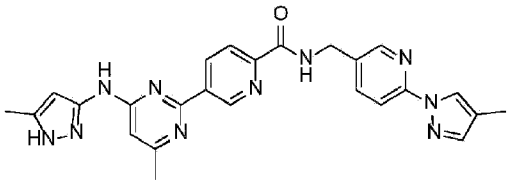
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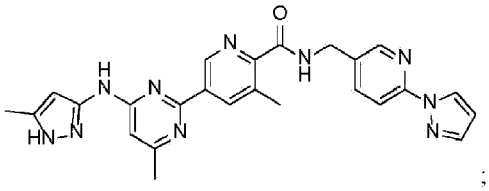
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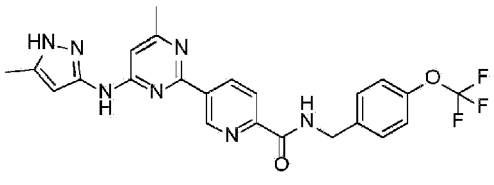
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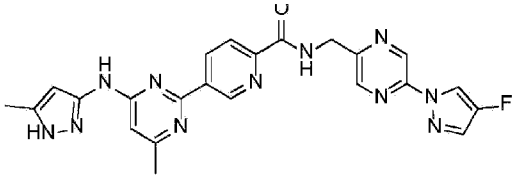
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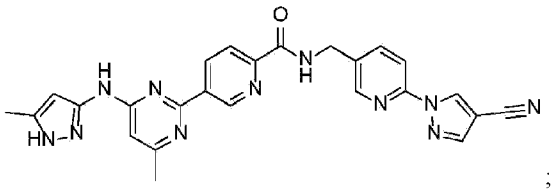
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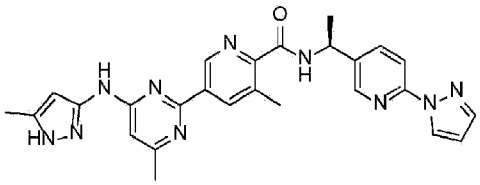
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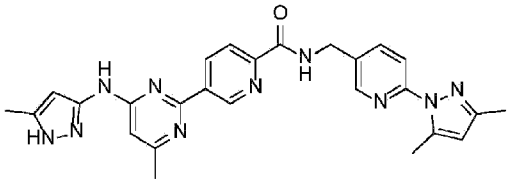
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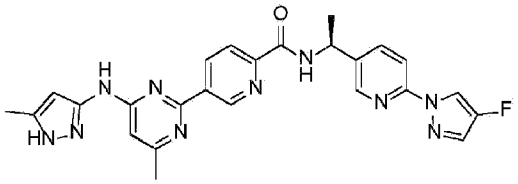
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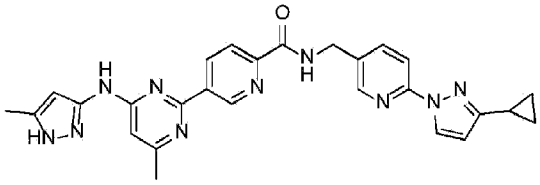
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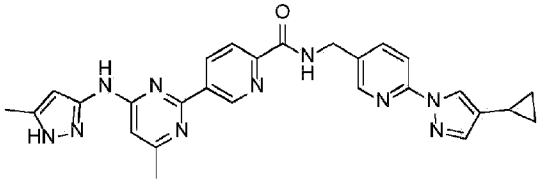
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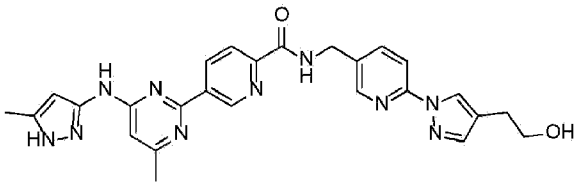
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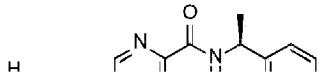

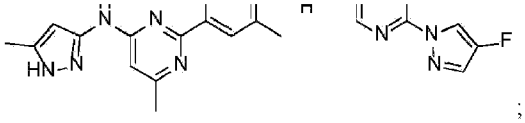
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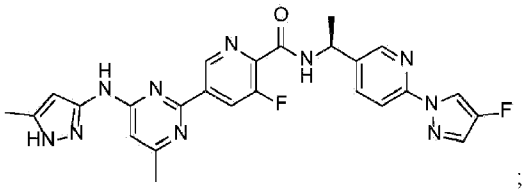
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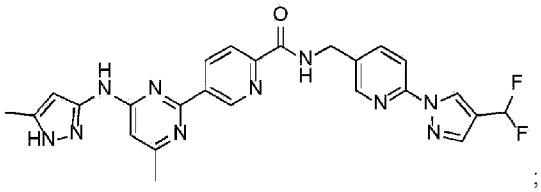
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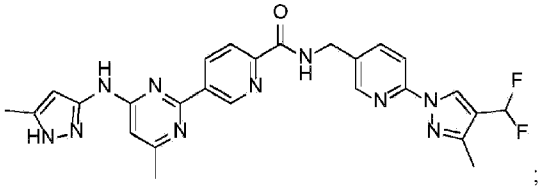
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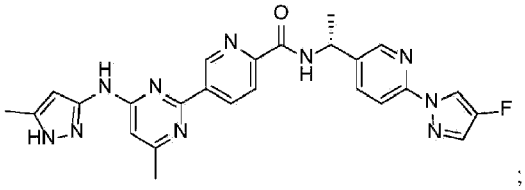
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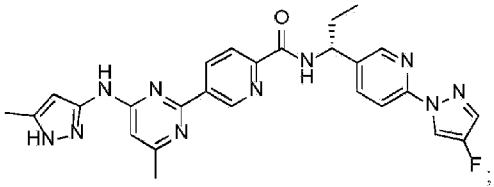
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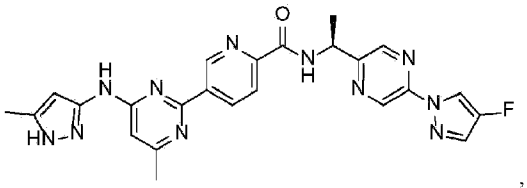
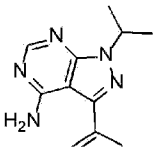
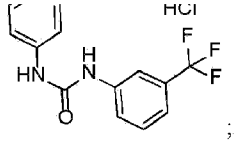

,

or a pharmaceutically acceptable salt thereof.

[0255] In some embodiments, a RET inhibitor is selected from the group consisting of: ABT-348 (N-[4-[4-Amino-7-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]thieno[3,2-c]pyridin-3-yl]phenyl]-N'-(3-fluorophenyl)urea); AD-57, which has the structure:





AD-80 (1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(2-fluoro-5-(trifluoromethyl)phenyl)urea); ALW-II-41-27 (N-(5-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)-2-methylphenyl)-5-(thiophen-2-yl)nicotinamide); Amuvatinib (MP470) (N-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(benzofuro[3,2-d]pyrimidin-4-yl)piperazine-1-carbothioamide); BPR1J373 (a derivative of 5-phenylthhiazol-2-ylamine-pyriminide); CLM3; doramapimod (BIRB-796) (1-(3-(tert-butyl)-1-(p-tolyl)-1H-pyrazol-5-yl)-3-(4-(2-morpholinoethoxy)naphthalen-1-yl)urea); DS-5010; famitinib (5-[2-(diethylamino)ethyl]-2-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-3-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4-one); fedratinib (SAR 302503, TG101348) (N-(tert-butyl)-3-((5-methyl-2-((4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)pyrimidin-4-yl)amino)benzenesulfonamide); GSK3179106; GSK3352589; HG-6-63-01 ((E)-3-(2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)vinyl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide); NVP-BBT594 (5-((6-acetamidopyrimidin-4-yl)oxy)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)indoline-1-carboxamide); PP2 (4-amino-5-(4-chlorophenyl)-7-(dimethylethyl)pyrazolo[3,4-d]pyrimidine); PP242 (2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indol-5-ol); quizartinib (AC220) (1-(5 -(tert-butyl)isoxazol-3 -yl)-3 -(4-(7-(2-morpholinoethoxy)benzo [d]imidazo [2,1 - b]thiazol-2-yl)phenyl)urea); semaxanib (SU5416, VEGFR2 Kinase Inhibitor III) ((Z)-3-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)indolin-2-one); SU4984 (3-[4-(1-formylpiperazin-4-yl)benzylidenyl]-2-indolinone); Withaferin A ((4β,5β,6β,22R)-4,27-Dihydroxy-5,6:22,26-diepoxyergosta-2,24-diene-1,26-dione); XL-999 ((Z)-5-((1-ethylpiperidin-4-yl)amino)-3-((3-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methylene)indolin-2-one); XMD15-44 (N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(pyridin-3-ylethynyl)benzamide); Y078-DM1 (antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine); and Y078-DM1 (antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine).

[0256] Further examples of RET inhibitors include: N-(2-fluoro-5-trifluoromethylphenyl)-N'-{4'-[(2"-benzamido)pyridin-4"-ylamino]phenyl}urea; 1-isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine; 3-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol; N-(5-(tert-butyl)isoxazol-3-yl)-2-(4-(imidazo[1,2-a]pyridin-6-yl)phenyl)acetamide; N-(5-(tert-butyl)isoxazol-3-yl)-2-(3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl)acetamide; 2-amino-6-{[2-(4-chlorophenyl)-2-oxoethyl]sulfanyl}-4-(3-thienyl)pyridine-3,5-dicarbonitrile; and 3-arylureidobenzylidene-indolin-2-ones.

[0257] Yet other therapeutic agents include RET inhibitors described, for example, in U.S. Patent Nos. 7,504,509; 8,012,966; 8,299,057; 8,399,442; 8,067,434; 8,629,135; 8,895,744; 8,937,071; 9,006,256; and 9,035,063; U.S. Publication Nos. 2015/0272958; 2015/0238477; 2014/0121239; 20160176865; 2011/0053934; 2011/0301157; 2010/0324065; 2009/0227556; 2009/0130229; 2009/0099167; 2005/0209195; International Publication Nos. WO 2017/043550; WO 2017/026718; WO 2016/037578; WO 2016/038519; WO 2016/038552; WO 2014/184069; WO 2014/072220; WO 2012/053606; WO 2009/017838; WO 2008/031551; WO 2007/136103; WO 2007/087245; WO 2007/057399; WO 2005/051366; WO 2005/062795; and WO 2005/044835; and J. Med.Chem. 2012, 55 (10), 4872-4876,.

[0258] Examples of receptor tyrosine kinase (e.g., Trk) targeted therapeutic agents, include afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, pazopanib, panitumumab, pertuzumab, sunitinib, trastuzumab, 1-((3S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2- methylpyrimidin-5-yl)-1 -phenyl- 1H-pyrazol-5-yl)urea, AG 879, AR-772, AR-786, AR-256, AR-618, AZ-23, AZ623, DS-6051, Gö 6976, GNF-

5837, GTx-186, GW 441756, LOXO-101, MGCD516, PLX7486, RXDX101, TPX-0005, and TSR-011. Additional Trk targeted therapeutic agents include those described in U.S. Patent No. 8,450,322; 8,513,263; 8,933,084; 8,791,123; 8,946,226; 8,450,322; 8,299,057; and 8,912,194; U.S. Publication No. 2016/0137654; 2015/0166564; 2015/0051222; 2015/0283132; and 2015/0306086; International Publication No. WO 2010/033941; WO 2010/048314; WO 2016/077841; WO 2011/146336; WO 2011/006074; WO 2010/033941; WO 2012/158413; WO 2014078454; WO 2014078417; WO 2014078408; WO 2014078378; WO 2014078372; WO 2014078331; WO 2014078328; WO 2014078325; WO 2014078323; WO 2014078322; WO 2015175788; WO 2009/013126; WO 2013/174876; WO 2015/124697; WO 2010/058006; WO 2015/017533; WO 2015/112806; WO 2013/183578; and WO 2013/074518.

[0259] Further examples of Trk inhibitors can be found in U.S. Patent No. 8,637,516, International Publication No. WO 2012/034091, U.S. Patent No. 9,102,671, International Publication No. WO 2012/116217, U.S. Publication No. 2010/0297115, International Publication No. WO 2009/053442, U.S. Patent No. 8,642,035, International Publication No. WO 2009092049, U.S. Patent No. 8,691,221, International Publication No. WO2006131952. Exemplary Trk inhibitors include GNF-4256, described in Cancer Chemother. Pharmacol. 75(1):131-141, 2015; and GNF-5837 (N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-urea), described in ACS Med. Chem. Lett. 3(2):140-145, 2012.

[0260] Additional examples of Trk inhibitors include those disclosed in U.S. Publication No. 2010/0152219, U.S. Patent No. 8,114,989, and International Publication No. WO 2006/123113,. Exemplary Trk inhibitors include AZ623, described in Cancer 117(6):1321-1391, 2011; AZD6918, described in Cancer Biol Ther. 16(3):477-483, 2015; AZ64, described in Cancer Chemother. Pharmacol. 70:477-486, 2012; AZ-23 ((S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine), described in Mol. Cancer Ther. 8:1818-1827, 2009; and AZD7451.

[0261] A Trk inhibitor can include those described in U.S. Patent Nos. 7,615,383; 7,384,632; 6,153,189; 6,027,927; 6,025,166; 5,910,574; 5,877,016; and 5,844,092.

[0262] Further examples of Trk inhibitors include CEP-751, described in Int. J. Cancer 72:672-679, 1997; CT327, described in Acta Derm. Venereol. 95:542-548, 2015; compounds described in International Publication No. WO 2012/034095; compounds described in U.S. Patent No. 8,673,347 and International Publication No. WO 2007/022999; compounds described in U.S. Patent No. 8,338,417; compounds described in International Publication No. WO 2016/027754; compounds described in U.S. Patent No. 9,242,977; compounds described in U.S. Publication No. 2016/0000783; sunitinib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), as described in PLoS One 9:e95628, 2014; compounds described in International Publication No. WO 2011/133637; compounds described in U.S. Patent No. 8,637,256; compounds described in Expert. Opin. Ther. Pat. 24(7):731-744, 2014; compounds described in Expert Opin. Ther. Pat. 19(3):305-319, 2009; (R)-2-phenylpyrrolidine substituted imidazopyridazines, e.g., GNF-8625, (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-[2,4'-bipyridin]-2'-yl)piperidin-4-ol as described in ACS Med. Chem. Lett. 6(5):562-567, 2015; GTx-186 and others, as described in PLoS One 8(12):e83380, 2013; K252a ((9S-(9α,10β,12α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one), as described in Mol. Cell Biochem. 339(1-2):201-213, 2010; 4-aminopyrazolylpyrimidines, e.g., AZ-23 (((S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine)), as described in J. Med. Chem. 51(15):4672-4684, 2008; PHA-739358 (danusertib), as described in Mol. Cancer Ther. 6:3158, 2007; Gö 6976 (5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-

indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile), as described in J. Neurochem. 72:919-924, 1999; GW441756 ((3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one), as described in IJAE 115:117, 2010; milciclib (PHA-848125AC), described in J. Carcinog. 12:22, 2013; AG-879 ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide); altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); cabozantinib (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); lestaurtinib ((5S,6S,8R)-6-Hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5H-16-oxa-4b,8a,14-triaza-5, 8-methanodibenzo [b,h] cycloocta[jkl] cyclopenta[e] -as-indacen-13(6H)-one); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); ONO-5390556; regorafenib (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); and VSR-902A

[0263] The ability of a Trk inhibitor to act as a TrkA, TrkB, and/or Trk C inhibitor may be tested using the assays described in Examples A and B in U.S. Patent No. 8,513,263

[0264] In some embodiments, signal transduction pathway inhibitors include Ras-Raf-MEK-ERK pathway inhibitors (e.g., binimetinib, selumetinib, encorafinib, sorafenib, trametinib, and vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g. everolimus, rapamycin, perifosine, temsirolimus), and other kinase inhibitors, baricitinib, brigatinib, capmatinib, danusertib, ibrutinib, milciclib, quercetin, regorafenib, ruxolitinib, semaxanib, AP32788, BLU285, BLU554, INCB39110, INCB40093, INCB50465, INCB52793, INCB54828, MGCD265, NMS-088, NMS-1286937, PF 477736 ((R)-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1Hpyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-cyclohexaneacetamide), PLX3397, PLX7486, PLX8394, PLX9486, PRN1008, PRN1371, RXDX103, RXDX106, RXDX108, and TG101209 (N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide).

[0265] Examples of checkpoint inhibitors include ipilimumab, tremelimumab, nivolumab, pidilizumab, MPDL3208A, MEDI4736, MSB0010718C, BMS-936559, BMS-956559, BMS-935559 (MDX-1105), AMP-224, and pembrolizumab.

[0266] In some embodiments, cytotoxic chemotherapeutics are selected from arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

[0267] Examples of angiogenesis-targeted therapies include aflibercept and bevacizumab.

[0268] The term "immunotherapy" refers to an agent that modulates the immune system. In some embodiments, an immunotherapy can increase the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can decrease the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can recruit and/or enhance the activity of an immune cell.

[0269] In some embodiments, the immunotherapy is a cellular immunotherapy (e.g., adoptive T-cell therapy, dendritic cell therapy, natural killer cell therapy). In some embodiments, the cellular immunotherapy is sipuleucel-T (APC8015; Provenge™; Plosker (2011) Drugs 71(1): 101-108). In some

embodiments, the cellular immunotherapy includes cells that express a chimeric antigen receptor (CAR). In some embodiments, the cellular immunotherapy is a CAR-T cell therapy. In some embodiments, the CAR-T cell therapy is tisagenlecleucel (Kymriah™).

[0270] In some embodiments, the immunotherapy is an antibody therapy (e.g., a monoclonal antibody, a conjugated antibody). In some embodiments, the antibody therapy is bevacizumab (Mvasti™, Avastin®), trastuzumab (Herceptin®), avelumab (Bavencio®), rituximab (MabThera™, Rituxan®), edrecolomab (Panorex), daratumuab (Darzalex®), olaratumab (Lartruvo™), ofatumumab (Arzerra®), alemtuzumab (Campath®), cetuximab (Erbitux®), oregovomab, pembrolizumab (Keytruda®), dinutiximab (Unituxin®), obinutuzumab (Gazyva®), tremelimumab (CP-675,206), ramucirumab (Cyramza®), ublituximab (TG-1101), panitumumab (Vectibix®), elotuzumab (Empliciti™), avelumab (Bavencio®), necitumumab (Portrazza™), cirmtuzumab (UC-961), ibritumomab (Zevalin®), isatuximab (SAR650984), nimotuzumab, fresolimumab (GC1008), lirilumab (INN), mogamulizumab (Poteligeo®), ficlatuzumab (AV-299), denosumab (Xgeva®), ganitumab, urelumab, pidilizumab or amatuximab.

[0271] In some embodiments, the immunotherapy is an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate is gemtuzumab ozogamicin (Mylotarg™), inotuzumab ozogamicin (Besponsa®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (TDM-1; Kadcyla®), mirvetuximab soravtansine (IMGN853) or anetumab ravtansine

[0272] In some embodiments, the immunotherapy includes blinatumomab (AMG103; Blincyto®) or midostaurin (Rydapt).

[0273] In some embodiments, the immunotherapy includes a toxin. In some embodiments, the immunotherapy is denileukin diftitox (Ontak®).

[0274] In some embodiments, the immunotherapy is a cytokine therapy. In some embodiments, the cytokine therapy is an interleukin 2 (IL-2) therapy, an interferon alpha (IFNα) therapy, a granulocyte colony stimulating factor (G-CSF) therapy, an interleukin 12 (IL-12) therapy, an interleukin 15 (IL-15) therapy, an interleukin 7 (IL-7) therapy or an erythropoietin-alpha (EPO) therapy. In some embodiments, the IL-2 therapy is aldesleukin (Proleukin®). In some embodiments, the IFNα therapy is IntronA® (Roferon-A®). In some embodiments, the G-CSF therapy is filgrastim (Neupogen®).

[0275] In some embodiments, the immunotherapy is an immune checkpoint inhibitor. In some embodiments, the immunotherapy includes one or more immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the CTLA-4 inhibitor is ipilimumab (Yervoy®) or tremelimumab (CP-675,206). In some embodiments, the PD-1 inhibitor is pembrolizumab (Keytruda®) or nivolumab (Opdivo®). In some embodiments, the PD-L1 inhibitor is atezolizumab (Tecentriq®), avelumab (Bavencio®) or durvalumab (Imfinzi™).

[0276] In some embodiments, the immunotherapy is mRNA-based immunotherapy. In some embodiments, the mRNA-based immunotherapy is CV9104 (see, e.g., Rausch et al. (2014) Human Vaccin Immunother 10(11): 3146-52; and Kubler et al. (2015) J. Immunother Cancer 3:26).

[0277] In some embodiments, the immunotherapy is bacillus Calmette-Guerin (BCG) therapy.

[0278] In some embodiments, the immunotherapy is an oncolytic virus therapy. In some embodiments, the oncolytic virus therapy is talimogene alherparepvec (T-VEC; Imlygic®).

[0279] In some embodiments, the immunotherapy is a cancer vaccine. In some embodiments, the cancer vaccine is a human papillomavirus (HPV) vaccine. In some embodiments, the HPV vaccine is Gardasil®, Gardasil9® or Cervarix®. In some embodiments, the cancer vaccine is a hepatitis B virus (HBV) vaccine. In some embodiments, the HBV vaccine is Engerix-B®, Recombivax HB® or GI-13020 (Tarmogen®). In some embodiments, the cancer vaccine is Twinrix® or Pediarix®. In some embodiments, the cancer vaccine is BiovaxID®, Oncophage®, GVAX, ADXS11-001, ALVAC-CEA, PROSTVAC®, Rindopepimut®, CimaVax-EGF, lapuleucel-T (APC8024; Neuvenge™), GRNVAC1, GRNVAC2, GRN-1201, hepcortespenlisimut-L (Hepko-V5), DCVAX®, SCIB1, BMT CTN 1401, PrCa VBIR, PANVAC, ProstAtak®, DPX-Survivac, or viagenpumatucel-L (HS-110).

[0280] In some embodiments, the immunotherapy is a peptide vaccine. In some embodiments, the peptide vaccine is nelipepimut-S (E75) (NeuVax™), IMA901, or SurVaxM (SVN53-67). In some embodiments, the cancer vaccine is an immunogenic personal neoantigen vaccine (see, e.g., Ott et al. (2017) Nature 547: 217-221; Sahin et al. (2017) Nature 547: 222-226). In some embodiments, the cancer vaccine is RGSH4K, or NEO-PV-01. In some embodiments, the cancer vaccine is a DNA-based vaccine. In some embodiments, the DNA-based vaccine is a mammaglobin-A DNA vaccine (see, e.g., Kim et al. (2016) OncoImmunology 5(2): e1069940).

[0281] In some embodiments, immune-targeted agents are selected from aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, and sipuleucel-T.

[0282] Examples of radiotherapy include radioiodide therapy, external-beam radiation, and radium 223 therapy.

[0283] Additional kinase inhibitors include those described in, for example, U.S. Patent No. 7,514,446; 7,863,289; 8,026,247; 8,501,756; 8,552,002; 8,815,901; 8,912,204; 9,260,437; 9,273,051; U.S. Publication No. US 2015/0018336; International Publication No. WO 2007/002325; WO 2007/002433; WO 2008/080001; WO 2008/079906; WO 2008/079903; WO 2008/079909; WO 2008/080015; WO 2009/007748; WO 2009/012283; WO 2009/143018; WO 2009/143024; WO 2009/014637; 2009/152083; WO 2010/111527; WO 2012/109075; WO 2014/194127; WO 2015/112806; WO 2007/110344; WO 2009/071480; WO 2009/118411; WO 2010/031816; WO 2010/145998; WO 2011/092120; WO 2012/101032; WO 2012/139930; WO 2012/143248; WO 2012/152763; WO 2013/014039; WO 2013/102059; WO 2013/050448; WO 2013/050446; WO 2014/019908; WO 2014/072220; WO 2014/184069.

[0284] Further examples of kinase inhibitors include those described in, for example, WO 2016/081450; WO 2016/022569; WO 2016/011141; WO 2016/011144; WO 2016/011147; WO 2015/191667; WO 2012/101029; WO 2012/113774; WO 2015/191666; WO 2015/161277; WO 2015/161274; WO 2015/108992; WO 2015/061572; WO 2015/058129; WO 2015/057873; WO 2015/017528; WO/2015/017533; WO 2014/160521; and WO 2014/011900.

[0285] Also provided herein is (i) a pharmaceutical combination for treating a cancer in a patient in need thereof, which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a patient in need thereof. In one embodiment the patient is a human. In some embodiments, the cancer is a RET-associated cancer. For example, a RET-associated cancer having one or more RET inhibitor resistance mutations.

[0286] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients

[0287] Although the genetic basis of tumorigenesis may vary between different cancer types, the cellular and molecular mechanisms required for metastasis appear to be similar for all solid tumor types. During a metastatic cascade, the cancer cells lose growth inhibitory responses, undergo alterations in adhesiveness and produce enzymes that can degrade extracellular matrix components. This leads to detachment of tumor cells from the original tumor, infiltration into the circulation through newly formed vasculature, migration and extravasation of the tumor cells at favorable distant sites where they may form colonies. A number of genes have been identified as being promoters or suppressors of metastasis. For example, overexpression of glial cell-derived neurotrophic factor (GDNF) and its RET receptor tyrosine kinase have been correlated with cancer proliferation and metastasis. See, e.g., Zeng, Q. et al. J. Int. Med. Res. (2008) 36(4): 656-64.

[0288] The term "metastasis" is an art known term and means the formation of an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient, where the additional tumor includes the same or similar cancer cells as the primary tumor.

[0289] The phrase "effective amount" means an amount of compound that, when administered to a patient in need of such treatment, is sufficient to (i) treat a RET kinase-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula I that will correspond to such an amount will vary depending upon the particular compound, disease condition and its severity, the identity (e.g., weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in

the art.

[0290] When employed as pharmaceuticals, the compounds of Formula I can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases and thickeners may be necessary

[0291] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semisolid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In one embodiment, the composition is formulated for oral administration. In one embodiment, the composition is formulated as a tablet or capsule.

[0292] The compositions comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other patients, each unit containing a predetermined quantity of active material (i.e., a compound for Formula I as provided herein) calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0293] In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

[0294] In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg,

about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient.

[0295] In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

[0296] In some embodiments, the compounds provided herein can be administered in an amount ranging from about 1 mg/kg to about 100 mg/kg. In some embodiments, the compound provided herein can be administered in an amount of about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 40 mg/kg, about 15 mg/kg to about 45 mg/kg, about 20 mg/kg to about 60 mg/kg, or about 40 mg/kg to about 70 mg/kg. For example, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg. In some embodiments, such administration can be once-daily or twice-daily (BID) administration.

[0297] The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, response of the individual patient, and the severity of the patient's symptoms.

[0298] Provided herein are pharmaceutical kits useful, for example, in the treatment of RET-associated diseases or disorders, cancer or irritable bowel syndrome (IBS), which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

[0299] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[0300] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

Examples

[0301] The following examples illustrate the invention.

Biological Examples

Example A

RET Enzyme Assay

[0302] Compounds of Formula I were screened for their ability to inhibit wildtype and V804M mutant RET kinase using CisBio's HTRF® KinEASE™-TK assay technology. Briefly, N-terminal GST tagged recombinant human RET cytoplasmic domain (aa 658-end) from Eurofins (0.25 nM RET; Catalog No. 14-570M) or N-terminal GST tagged recombinant human V804M mutant RET cytoplasmic domain (aa 658-end) from Millipore (0.25 nM enzyme; Catalog No. 14-760) was incubated with 250 nM TK-substrate biotin (CisBio, part of Catalog No. 62TK0PEC) and 1 mM ATP along with test compound in a buffer consisting of 25 mM HEPES pH 7.4, 10 mM $MgCl_2$, 0.01% Triton X-100, and 2% DMSO in a volume of 8 µL. Compounds were typically prepared in a threefold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 30-minute incubation at 22 °C, the reaction was quenched by adding 8 µL of quench solution containing 31.25 nM Sa-XL665 and IX TK-ab-Cryptate in HTRF detection buffer (all from CisBio, part of Cat. No. 62TK0PEC). After a 1 hour incubation at 22°C, the extent of reaction was determined using a PerkinElmer EnVision multimode plate reader via HTRF dual wavelength detection, and the percent of control (POC) was calculated using a ratiometric emission factor. 100 POC was determined using no test compounds and 0 POC was determined using pre-quenched control reactions. The POC values were fit to a 4 parameter logistic curve, and the IC_{50} is defined as the concentration of inhibitor at which the POC equals 50 for the fitted curve. The IC_{50} values for the compounds tested in this assay are provided in Table 5.

Example B

RET cell assay

[0303] The cellular potency of a compound inhibiting RET kinase was determined in HEK-293 cells expressing a Kif5b-RET fusion protein. Briefly, HEK-293 cells expressing a Kif5b-RET fusion protein were plated at 50K cells /well in 96 well poly-D-Lysine coated plates the day prior to the assay. The cells were incubated for 1 hour with test compound in DMEM (Dulbecco's Modified Eagle Medium) at a final DMSO concentration of 0.5%. Compounds were typically prepared in a three fold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After 1 hour the media was removed, the cells were fixed with 3.8% formaldehyde for 20 min, washed with PBS, and permeabilized for 10 min with 100% methanol. The plates were then washed with PBS-0.05% Tween20, and blocked with LI-COR Blocking solution (LI-COR catalog # 927-40000) for 1 hour. Plates were washed with PBS-0.05% Tween20, then incubated with anti-phospho-RET(Tyr1062) (Santa Cruz catalog #sc-20252-R) antibody and anti-GAPDH (Millipore catalog # MAB374) antibody for 2 hours. The plates were washed with PBS-0.05%Tween20, and incubated with anti-rabbit 680 (Molecular Probes catalog No. A21109) and anti-mouse 800 (LI-COR catalog No. 926-32210) secondary antibodies for 1 hour. All antibodies were diluted

in LI-COR Block containing 0.05% Tween. The plates were washed with PBS-0.05% Tween20, 100 µL PBS was added to each well, and the plates were read on a LI-COR Aerius fluorescent plate reader. The phospho-RET signal was normalized to the GAPDH signal. 100 POC (percent of control) was determined using no test compounds and 0 POC was determined using 1 µM of a control inhibitor. The POC values were fit to a 4 parameter logistic curve. The IC_{50} value is the point where the curve crosses 50 POC. The IC_{50} values for the compounds tested in this assay are provided in Table 5.

Example C

RET G810R mutant assay

[0304] The potency of a compound inhibiting G810R mutant RET kinase was determined using CisBio's HTRF Kinease-TK assay technology. The assays contained G810R mutant RET produced at Array Biopharma, Inc. (1 nM enzyme - p1982 Lot. No. 160713. The kinase was incubated with 250 nM TK-substrate biotin (CisBio, part of Catalog # 62TK0PEC) and 1 mM ATP along with test compound in a buffer consisting of 25 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 0.01% Triton X-100, and 2% DMSO in a volume of 8 µL. Compounds were typically prepared as a three-fold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 60-min incubation at 22 °C, the reaction was quenched by adding 8 µL of quench solution containing 31.25 nM Sa-XL665 and 1x TK-Ab-Cryptate in HTRF detection buffer (all from CisBio, part of cat # 62TK0PEC). After a 1-h incubation at 22 °C, the extent of reaction was determined using a PerkinElmer EnVision multimode plate reader via HTRF dual wavelength detection, and the percent of control (POC) was calculated using a ratiometric emission factor. One hundred POC was determined using no test compounds, and 0 POC was determined using pre-quenched control reactions. A 4-parameter logistic curve was fit to the POC values as a function of the concentration of compound, and the IC_{50} value was the point where the best-fit curve crossed 50 POC.

Table 5. IC_{50}'s of compounds tested in the assay of Examples A,B and C

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
9	18.8	24.6	9.8	128
10	61.2	264.4	163.8	N/A
27	15.3	50.4	8.3	636
29	15.5	54.6	8.4	613
31	75.8	316.4	137.9	N/A
35	8.4	17.3	2.7	133
36	8	20.2	6.3	N/A
37	16	39.3	4.7	N/A
38	13.3	22	3.6	N/A
40	18.5	70	16.8	632
41	80.2	248.9	48	N/A
42	6.7	13.6	1.5	N/A
43	12.2	21	5.4	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
44	20.7	108.2	31.6	195
45	6.3	20.9	2.9	37
46	14.5	44.5	11.2	N/A
47	13.7	34.8	4.2	64
52	20.1	49.7	2	N/A
53	14.4	27.9	1.3	N/A
54	10.8	21.1	1.2	N/A
55	22.9	70.7	3.4	N/A
56	13.9	35.9	1.2	N/A
57	14.8	94.5	12.5	N/A
58	68.6	692.1	153.1	N/A
59	74.3	401.5	170.7	N/A
60	50.5	194.2	93	N/A
61	22.4	97.5	17.8	N/A
62	13.4	31.9	1.7	92
63	66.5	511.9	150.1	N/A
64	19.2	69	10	628
65	9.1	45.7	6.1	N/A
66	9.1	27.5	1.5	N/A
67	21.6	49.9	11.4	N/A
68	19	64.8	13.3	N/A
69	14.9	49.7	11.7	N/A
70	16.4	46.4	10.1	N/A
71	74.6	586.8	80	N/A
72	14.7	46.2	2	N/A
73	16.3	49.1	1.9	N/A
74	11.5	57.4	10.3	N/A
75	24.6	50.2	4.7	N/A
76	23.9	77.6	54.9	N/A
77	16.5	33.3	3	N/A
78	25	34.5	2	280
79	43.3	105.7	6.3	755
80	13.9	25.9	2	N/A
81	11.2	27	2.6	N/A
82	61.3	250.6	58.5	N/A
83	34.2	79.6	6.8	1711
84	25.5	128.8	45.6	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
85	39.8	150.8	91.3	N/A
86	16.7	72.5	20	N/A
87	5.3	30.7	9.7	463
88	26.2	71	4.2	N/A
89	26.9	282.8	38.7	N/A
90	29.3	153.9	30.8	N/A
91	13.3	52.7	7.9	N/A
92	11.3	40.3	6.4	N/A
93	9.4	19	1.8	N/A
94	16.8	28.8	3.7	N/A
100	38	100.5	10.6	N/A
101	12.8	29.7	1.2	N/A
102	11.8	27.5	1	N/A
103	61.8	323.2	57.7	N/A
104	10.7	20.4	3.1	N/A
105	11.2	25	1.2	96
106	24.7	90.3	12.2	N/A
107	12.4	51.6	9.4	N/A
108	12.6	73.9	5.6	N/A
109	18.3	65.2	30	N/A
112	40.4	243.5	48.5	N/A
113	70.5	237.4	168.4	N/A
115	155.9	321.8	N/A	N/A
119	69.9	119.7	34.9	N/A
122	124.3	580.7	N/A	N/A
123	51.1	123.4	73.6	N/A
124	31.3	104.4	8.9	N/A
127	43.2	191.1	26.5	N/A
128	94.8	584.7	113.7	N/A
129	21.7	37.8	3.2	N/A
130	21	40.5	3.5	N/A
131	21	40.7	3.5	N/A
132	24.8	68.4	7.6	N/A
133	16	31.1	2.4	N/A
134	34.5	187.9	68.2	N/A
135	22.1	151.2	41.8	N/A
136	31.9	196.3	130.5	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
137	30.3	242.4	226.8	N/A
139	12.4	22.8	1.4	N/A
140	7.9	47	9.2	N/A
141	48.1	346.6	115.6	N/A
142	56	405.5	169.2	N/A
144	9.8	22.2	1.1	N/A
145	32.3	118.3	9.1	N/A
146	19.1	47.6	1.6	N/A
147	18.5	44.7	5.6	N/A
148	102.7	1153.6	N/A	N/A
149	131.8	1076.2	N/A	N/A
150	133.2	1117.3	N/A	N/A
151	39.5	129.6	77.2	N/A
152	49.9	163.6	106	N/A
153	230.6	2403.5	N/A	N/A
154	142.6	962.4	N/A	N/A
155	21.3	97.2	44.1	N/A
156	28.4	108	31	N/A
157	21.3	47.2	10.2	N/A
159	25.3	181.2	49.7	N/A
160	91	512.3	294.2	N/A
161	8.7	19.2	6.1	N/A
162	17.4	45.7	9.8	N/A
163	28.8	104.4	34.9	N/A
164	358.2	4281.1	N/A	N/A
165	14.6	60.1	37.6	N/A
166	1023.9	10000	N/A	N/A
167	16.7	39.3	9.2	N/A
168	5.8	14.6	5.2	N/A
169	8.2	35.3	13.7	N/A
170	44.3	260.8	162.6	N/A
171	29.3	134.2	89.7	N/A
172	338.7	3403.3	N/A	N/A
174	9.8	17.8	3.2	N/A
175	75.8	417.4	272.4	N/A
176	26.4	77.5	18.4	N/A
177	20.9	46	13.3	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
178	73.2	429.1	354.2	N/A
179	27.1	139	59.6	N/A
180	68.6	328.6	362.8	N/A
181	83.6	478	78.6	N/A
182	191.5	1299.6	N/A	N/A
183	15.4	41.2	23.4	N/A
184	40	379.3	271	N/A
185	10.4	93.9	50	N/A
186	15.5	68.9	25.4	N/A
187	5	15.2	8.3	N/A
188	13.7	75.5	44.6	N/A
189	9.2	35	36.7	N/A
192	12.9	50.5	27.3	N/A
193	21.1	73.8	26.2	N/A
194	70.3	585.5	165.6	N/A
197	45.3	316.2	179.3	N/A
201	10.5	22.7	4.5	165
202	11.6	26.5	18.9	181
203	9.2	68.3	23.3	N/A
204	82.3	813.1	N/A	495
205	10.7	62.1	6.5	275
206	13.8	91.1	44.2	N/A
207	18	92.7	27	496
208	20	87.2	23.9	N/A
209	11	141.8	36.3	N/A
210	19.7	272.8	94.7	1600
211	84	767.9	445.1	8099
212	19.2	69.4	12	286
213	16.3	137.4	34.3	N/A
214	21.4	38.4	14.2	N/A
215	30.2	272	110.6	N/A
224	14.4	84.5	14.5	N/A
226	16.9	152.4	20.9	N/A
227	18	140.5	26.5	N/A
228	33.5	411.4	64.8	N/A
229	10.3	213.5	140.45	N/A
231	12.8	56.9	7.6	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
233	10.5	44	5.3	N/A
234	15.1	49.8	5.2	N/A
235	26.9	155	32.1	N/A
236	30.3	132.7	22.4	N/A
237	23.9	74.7	12.6	1169
239	11.9	33.8	4.6	253
240	15.4	51	4.5	245
241	21.7	131	18.1	834
242	13.2	96.2	18.9	284
243	10.6	69.3	9.4	303
244	19.9	91.1	20.9	353
245	36.1	218.5	56.3	1675
246	38.5	299.6	85	3494
247	55.2	306	145.4	N/A
248	11.3	55.2	25.4	N/A
249	46.4	181.6	27.5	N/A
250	76.5	508.2	98.8	N/A
251	8.4	31.7	16.7	N/A
252	8	16.8	5.4	N/A
253	25.3	61.3	38.8	N/A
254	120.1	298.9	N/A	N/A
255	30.7	69.1	12.4	N/A
256	24.5	86.8	51.2	N/A
257	20.3	88.7	30.6	N/A
258	12.3	19.2	1.2	N/A
259	16.8	39.1	10.8	N/A
264	30.4	118.7	26.8	N/A
265	7.6	19.3	10.8	N/A
266	29.4	182.5	32.5	N/A
267	18.1	67.1	15.9	N/A
268	23.3	128.6	23.1	N/A
269	18.8	70.2	4.9	N/A
270	16.9	44.8	10.5	N/A
271	44.9	137.3	8.6	N/A
272	17.9	55.2	14.7	N/A
273	21.3	41.6	7.9	N/A
274	16.5	64.2	20.2	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
275	39.9	460.1	124.3	N/A
277	29.8	242.6	74.9	779
278	22.7	186.3	108.5	858
289	18	119.4	52.4	N/A
290	17.3	158.3	80.5	N/A
292	14.7	122.6	36.4	N/A
293	106.2	904.7	N/A	N/A
294	15.1	244.4	111.3	N/A
301	6.1	32.6	4.7	52
302	11.8	26.7	13.7	74
303	14.1	28.7	4.6	73
304	22.1	68.3	10.3	136
305	10.7	47.2	5.8	75
306	23.3	95.2	4.3	239
307	25.5	39.8	395.1	N/A
308	11.3	28.8	14.5	329
309	7.6	18.1	18	N/A
310	14.7	30.8	3.2	67
311	8.3	15.4	3.7	28
312	7.7	35.3	10	43
313	52.1	230.2	107.6	N/A
314	14.2	30.7	13.9	66
315	16.5	50.2	12	164
316	18.8	47.5	9.4	165
317	25.9	69.7	6.6	104
318	6.6	15.8	3.5	32
319	17.8	85.6	9.3	160
320	20.6	59.3	3.7	N/A
321	9.8	37.3	14.3	65
322	13.7	27.4	8.9	73
323	16.1	30.5	3.6	69
324	8.7	22	1.4	30
325	17.1	70.9	23.4	255
326	103.9	661.8	203.1	N/A
331	18.9	137.3	34.5	N/A
332	11	48.3	29.8	N/A
333	963.6	6081	N/A	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
336	16.6	88.9	30.8	241
337	391.6	1085.9	N/A	1000
339	726.9	2657.9	N/A	5804
340	12.9	33.5	2.2	92
341	7.6	12	4.4	21
342	12.4	32	7.6	58
343	15.1	50.4	20	80
350	21.7	185.6	43.4	N/A
354	53	542.9	137.6	N/A
358	7.6	41.3	7.6	38
359	10.9	56.9	7	123
360	88.9	833.3	277.9	N/A
361	11.7	74.4	9.2	90
362	4.4	16.9	4.7	19
363	5.5	22.7	3.3	35
364	104.8	972.1	N/A	N/A
373	29.7	233.8	116.5	N/A
379	8.8	21.8	4.8	54
383	21.5	43.4	18.3	62
384	5.7	14	2.6	22
389	13.4	26	1.3	124
390	11.1	37.2	4.3	63
391	6.7	10.6	2	21
398	230.7	2422.2	N/A	8419
399	26.1	56.9	4.1	319
400	13.7	36.6	8.2	189
401	19	33.6	2.9	109
402	11.7	18.5	3.2	71
403	22.3	37.1	2.1	182
404	12.2	31.2	20.7	94
405	8	28.2	12.7	N/A
406	12.2	54.9	19.1	73
407	14	47.5	19.7	42
408	30.2	239.8	72.6	N/A
409	8.9	12.7	3.3	N/A
410	8.7	14.3	3.9	N/A
411	150.2	1078.2	N/A	N/A

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
412	17.3	89.7	13.6	N/A
413	637	3424.7	N/A	5467
414	15.8	50.1	16.5	145
415	6.9	24	5.6	N/A
416	8.6	38.6	8.6	N/A
417	32	58	204.9	89
418	340.2	473.3	N/A	N/A
419	106.5	176.3	N/A	N/A
420	147.4	227.9	N/A	N/A
421	25.7	61.9	70.1	159
422	16.5	30.7	28.9	116
423	23.6	54.1	38.2	144
424	42.2	32.4	137.4	273
425	31.2	70.3	74	195
426	238.4	457	N/A	N/A
427	41.8	72.8	152.3	1122
428	47.5	104.2	141.5	N/A
429	56.2	222.5	745.3	4107
431	38.2	102	47.8	854
432	32.2	81.2	9.5	239
433	20.2	48.5	2.7	90
434	6.2	45.2	7.7	32
435	12.4	35.2	2.7	57
436	19.3	96.2	8.7	182
437	21.8	87.2	9.4	95
438	14.9	92.8	28.2	68
439	22	142.6	16.3	118
440	13.2	30	5	N/A
441	12.4	49.9	13.8	231
442	15	56.2	6.9	70
443	12.6	47.7	6.5	111
444	15.2	60.4	12.7	N/A
445	19.6	161.3	17.2	89
447	24.8	163	98.3	N/A
448	22.9	161.9	80.1	N/A
453	21.4	158.4	24.8	245
454	20.7	189.5	64.3	195

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
455	25.8	83.8	16.6	231
456	17.7	42.9	11.9	75
457	74.8	395	238.5	470
458	35.6	239.4	82.4	414
459	12.7	70	461.8	297
460	12.3	87.4	22.9	401
461	45.9	357.6	65.6	725
462	22.9	93	63.2	283
463	34.6	190.7	36.4	454
464	39.5	211.9	32.7	312
465	28.6	121.4	21.7	383
485	3.7	30.7	32.3	N/A
487	5.5	35.1	88	78
488	8.4	73	23.9	N/A
498	71.9	216.1	171.4	194
523	11.2	39.3	7.4	63
528	6.4	14.7	3	18
529	115.8	1111.9	N/A	698
570	7.2	28.9	6.5	44
571	8.9	55.3	5.3	48
597	6	13.6	2.2	25
598	10.9	59.1	10.2	48
599	17	35.8	4.8	94
616	23.6	67.9	10.9	N/A
625	105.1	718.3	N/A	3513
674	39.3	105.4	3.2	279
675	30.2	91	2.4	249
676	12.9	30.1	8	141
677	13.5	26.8	5	61
678	17.9	38.4	2.3	55
679	18	33.3	2.3	135
680	5.2	28.9	12	88
681	42.9	226.1	25.2	311
682	24.9	53.3	4.9	106
683	16.5	90.2	11.5	196
684	15.2	40.9	4.3	122
685	19.6	53.2	7.7	498

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
686	11	40.7	8.6	174
687	14.8	45.4	13.2	81
688	5	11.5	5.4	109
689	12.7	50.4	9	165
690	3.7	12.6	3.7	42
691	21.9	31.5	3	85
692	9.3	38.9	7.8	128
693	6	63.3	14.1	183
694	27.7	74.2	4.8	161
695	21.8	82.1	28.6	204
696	42.4	61	11.7	277
697	34.7	93	8.4	382
698	6.1	16	81.5	114
699	16	26.5	8.8	153
700	78.7	88.5	N/A	357
701	6.1	21.3	25.1	162
702	10.7	48.3	10.5	130
703	7.2	26.3	14.7	63
704	21.9	87.4	10.9	218
705	4.6	17.8	24.3	131
706	17	121.7	16.5	4540
707	9.1	36.3	11.6	59
709	11	32	8	83
710	53	517	103	467
711	6	11	3	26
712	20	191	29	315
713	17	276	90	284
714	32	303	103	747
715	34	132	66	158
717	23	473	268	1405
718	34	310	85	607
722	2	10	3	15
723	3	10	2	13
724	15	95	11	40
725	4	15	2	16
729	7	21	13	35
730	5	12	5	16

Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
731	5	15	8	27
734	52	321	80	694
735	56	568	N/A	6169
736	53	993	N/A	10000
737	69	295	105	10000
738	40	304	18	10000
739	68	301	96	10000
740	43	320	119	8460
741	217	1315	N/A	5702
742	4	24	5	648
743	12	63	6	1119
744	40	218	36	1109
745	128	966	N/A	10000
746	28	97	15	1283
747	19	66	12	1490
748	14	81	12	1999
749	25	152	15	2584
750	42	212	23	4308
751	48	256	39	1530
752	143	2665	N/A	10000
753	13	72	7	943
754	7	73	16	543
755	143	1197	483	1305
756	6	50	22	81
757	19	537	41	2375
758	29	164	15	570
759	11	137	11	338
760	53	508	76	2594
761	18	134	13	394
762	12	116	11	239
763	22	124	16	3272
764	79	247	418	351
765	578	3799	N/A	10000
766	23	361	54	351
767	23	196	13	592
768	11	118	16	1984
769	12	162	36	6870

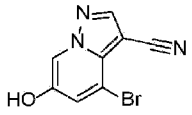
Ex. #	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET Enzyme (G810R) IC50 (nM)
771	9	26	4	52
772	8	24	4	30
773	12	10000	9	10000
774	8	45	6	51
775	3	16	5	26
776	10	46	11	94
777	3	13	3	25
778	23	129	19	192
779	19	66	13	58
780	21	91	15	328
781	41	90	7	154
782	33	221	92	520
783	3	43	62	76
784	24	77	17	796
785	37	142	20	1475
786	48	179	13	965
787	22	60	8	541
788	23	93	9	983
789	23	159	8	1022
790	8	35	34	268
791	16	77	19	107
792	13	106	18	92
793	8	47	11	76
794	5	32	7	29
795	16	245	25	122
796	5	34	7	21
797	10	30	11	423
798	9	9	11	222
799	21	37	28	274
800	9	21	6	86
803	62	213	N/A	384
806	33	180	59	276
N/A = not available				

Synthetic Examples

Synthesis of Synthetic Intermediates

[0305]

Intermediate P1



4-Bromo-6-hydroxypyrazolo[1.5-a]pyridine-3-carbonitrile

Part A: Preparation of O-(mesitylsulfonyl)hydroxylamine

[0306] Step 1: Preparation of tert-butyl (mesitylsulfonyl)oxycarbamate. To a 0 °C solution of 2,4,6-trimethylbenzene-1-sulfonyl chloride (10.0 g, 45.72 mmol) and tert-butyl hydroxycarbamate (6.088 g, 45.72 mmol) in MTBE (100 mL) was added TEA (14.46 mL, 48.01 mmol) drop-wise while stirring. The resulting suspension was stirred at 0 °C for an additional 30 min and then warmed to ambient temperature. The reaction was then diluted with water (100 mL), adjusted to pH 4 with 1 N $HCl_{(aq)}$. The organic layer was dried (Na_2SO_4), filtered and concentrated to yield the title compound initially as a yellowish oil, which upon drying overnight under high vacuum became a white solid (12.89 g, 89% yield). ^1H NMR ($CDCl_3$) δ 7.66 (br s, 1H), 6.98 (s, 2H), 2.67 (s, 6H), 2.32 (s, 3H), 1.31 (s, 9H).

[0307] Step 2: Preparation of O-(mesitylsulfonyl)hydroxylamine. To TFA (117 mL, 1521 mmol) at 0 °C was slowly added tert-butyl (mesitylsulfonyl)oxycarbamate (39.0 g, 124 mmol) over 25 min. The reaction mixture was stirred at 0 °C for 1.5 h and then quenched with the sequential addition of crushed ice and water. The resulting thick suspension was vigorously stirred at ambient temperature for 5 min. Without allowing the filter cake to run dry, the solids were collected by careful vacuum filtration followed by subsequent rinsing with water (4 L) until the filtrate reached pH 6 (Caution: explosion risk exists with dry compound at ambient temperature). The wet filter cake was taken up in DCM (150 mL) and the resulting biphasic solution was separated. The DCM layer was dried over $MgSO_4$ for 30 min and then filtered and rinsed with DCM (420 mL) to provide the title compound as a 0.22 M solution in DCM

Part B: Preparation of 4-Bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0308] Step 1: Preparation of 1-amino-3-bromo-5-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate. To a solution of O-(mesitylsulfonyl)hydroxylamine (Part A, 26.6 g, 117 mmol) in DCM (570 mL) cooled to 0 °C was added 3-bromo-5-methoxypyridine (22.1 g, 117 mmol) in portions. The reaction mixture was stirred for 1 h at 0 °C then treated with additional 3-bromo-5-methoxypyridine (250 mg, 1.39 mmol) and stirred for an additional 2 h at 0 °C. The reaction mixture was diluted with Et_2O (600 mL), stirred at 0 °C for 10 min and then vacuum filtered, rinsed with Et_2O (3 × 250 mL). Upon reduction in volume by about 1/3, the filtrate yielded additional precipitate which was collected by filtration. Both filter cakes were dried *in vacuo* to provide the title compound (39.3 g, 83% yield). ^1H NMR ($CDCl_3$) δ 9.25 (br s, 1H), 8.99 (m,

1H), 8.74 (m, 1H), 7.46 (m, 1H), 6.83 (s, 2H), 3.92 (s, 3H), 2.65 (s, 6H), 2.22 (s, 3H).

[0309] Step 2: Preparation of Ethyl 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and Ethyl 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate. To a magnetically stirred white suspension of 1-amino-3-bromo-5-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate (33.24 g, 82.42 mmol) in DMF (82 mL) at ambient temperature was added TEA (22.98 mL, 164.8 mmol), followed by drop-wise addition of ethyl propiolate (16.71 mL, 164.8 mmol). After vigorous stirring for 2 d, the reaction was slowly quenched via portion-wise addition to rapidly stirring ice water (820 mL). The mixture was stirred at ambient temperature for 10 min and then vacuum filtered. Solids collected were rinsed with water and air-dried, yielding the title compounds as an orange solid in an isomeric ratio of about 4:1 (by ^{1}H NMR) with the 6-Br isomer as the major isomer (21 g). The wet solid isomeric mixture (about 75% w/w) was directly used in Step 3 without further purification. MS (apci) m/z = 298.9, 300.9 (M+H). Regioisomeric ratio was determined by MeO chemical shift in ^{1}H NMR ($CDCl_3$) δ 3.98 (6-Br isomer) vs. 3.83 (4-Br isomer).

[0310] Step 3: Preparation of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (P1) and 4-bromo-6-methoxypyrazolo[1,5-a]pyridine. The isomeric mixture of ethyl 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and ethyl 4-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate from Step 2 (15 g, 50.1 mmol) was added to 48% HBr (114 mL) while stirring, then heated at 80 °C for 90 min followed by stirring at ambient temperature overnight. The resulting suspension was vacuum filtered and rinsed with water. The aqueous filtrate and the filter cake were treated independently. The filter cake was taken up in MTBE and vacuum filtered to remove insoluble impurities. The MTBE filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield 6-bromo-4-methoxypyrazolo[1,5-a]pyridine as a beige solid (about 98:2 6-/4- Br; 5.08 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^{1}H NMR ($CDCl_3$) δ 8.26 (m, 1H), 7.82 (d, 1H), 6.61 (m, 1H), 6.43 (m, 1H), 3.94 (s, 3H). Independently the original aqueous reaction mixture filtrate was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude residue was taken up in DCM (50 mL) and then filtered to remove insoluble solids. Concentration of the DCM filtrate under vacuum followed by silica chromatography (0 to 50% EtOAc/hexanes) yielded a second batch of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate P1) as white solid (upper R_f spot, 2.06 g), as well as the minor isomer title compound 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (Intermediate P2) also as white solid (lower R_f spot, 1.32 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 1H), 7.85 (d, 1H), 7.17 (d, 1H), 6.55 (m, 1H), 3.80 (s, 3H).

[0311] Step 4: Preparation of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde: A solution of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (5.0 g, 22 mmol) in DMF (220 mL) was cooled to 0 °C and then slowly treated with $POCl_3$ (6.2 mL, 66 mmol). The reaction was warmed to ambient temperature and stirred overnight. The reaction mixture was cooled to 0 °C, quenched with water (220 mL), and basified with 6 M $NaOH_{(aq)}$ to pH 9-10. The reaction mixture was stirred for 1 h and then vacuum filtered. The solids were rinsed sequentially with water and MTBE. The collected solid was suspended in DCM (500 mL) and stirred in a sonicating bath for 30 min and then vacuum filtered. The filtrate was retained, while the filter cake was taken up in water (300 mL) and extracted with DCM. The organic extracts, along with the retained DCM filtrate, were combined and dried over anhydrous Na_2SO_4, then filtered and concentrated *in vacuo* to provide the title compound (4.84 g, 86% yield). MS (apci), m/z = 256.9 (M+H).

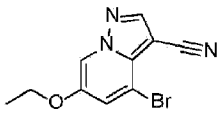
[0312] Step 5: Preparation of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde oxime. To a suspension of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde (4.84 g, 19.0 mmol) in EtOH (253 mL) at ambient temperature was added water (127 mL) and hydroxylamine hydrochloride (1.98 g,

28.5 mmol). After stirring at 50 °C overnight, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo.* The residue was suspended in water (150 mL) and then quenched slowly with saturated $NaHCO_{3(aq)}$ (30 mL). After stirring for 1 hour at ambient temperature the suspension was vacuum filtered and the filter cake rinsed sequentially with H_2O (500 mL) and MTBE (100 mL) to yield the title compound as a 2:1 E/Z mixture (5.13 g, quantitative yield), which was used in the next step without further purification. MS (apci) m/z = 271.9 (M+H).

[0313] Step 6: Preparation of .4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile The E/Z mixture of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde oxime (4.95 g, 18.33 mmol) in acetic anhydride (172.9 mL, 1833 mmol) was stirred at 140 °C for 25 h, and then cooled to ambient temperature. The resulting suspension was further cooled in an ice bath for 15 min and then vacuum filtered and rinsed sequentially with water and MTBE to provide the title compound (3.74 g, 81% yield). ^1H NMR (d^6-DMSO) δ 8.70 (s, 1H), 8.60 (s, 1H), 7.78 (s, 1H), 3.83 (s, 3H).

[0314] Step 7: Preparation of 4-Bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile: A slurry of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (50.0 g, 198.4 mmol) in DCE (500 mL) was treated with $AlCl_3$ (79.34 g, 595.1 mmol). Under a $N_{2(g)}$ atmosphere, the resulting mixture was stirred 19 h at 76 °C, before cooling to room temperature. Using THF (1750 mL) as a rinse solvent, the reaction mixture was poured into a mechanically stirred suspension of sodium sulfate decahydrate (10 eq, 639 g) in THF (1000 mL). After stirring overnight at ambient temperature, the resulting suspension was filtered, and the solids were rinsed with additional THF (2 × 250 mL). The filtrate was concentrated *in vacuo,* and the resulting solid was dried under high vacuum for 3 days to afford the title compound (46.18 g, 98% yield) in sufficient purity for subsequent use. ^1H NMR (d^6-DMSO) δ 10.48 (s, 1H), 8.58 (s, 1H), 8.38 (d, 1H), 7.64 (3, 1H).

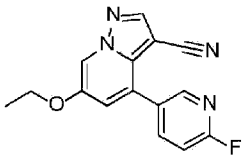
Intermediate P5



4-Bromo-6-ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile

[0315] A solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1;** 4.0 g, 16.80 mmol) in DMA (100 mL) was treated with $K_2CO_{3(s)}$ (7.0 g, 51 mmol) and iodoethane (2.0 mL, 25 mmol) and then stirred for 3 hrs at 60 °C. The reaction mixture was cooled to ambient temperature and then quenched with 1:1 NH_4OH/Water. The resulting suspension was filtered, and the solids were isolated to provide the title compound (4.35 g, 97% yield) in sufficient purity for subsequent use.

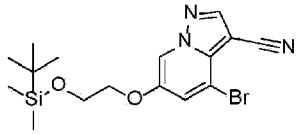
Intermediate P6



6-Ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0316] In a pressure vessel, a solution of 4-bromo-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P5;** 500 mg, 1.88 mmol) in dioxane (9.40 mL) was treated sequentially with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (629 mg, 2.82 mmol), $Pd(PPh_3)_4$ (217 mg, 0.188 mmol) and 2 M $Na_2CO_{3(aq)}$ (4.70 mL, 9.40). The resulting mixture was sparged with $Ar_{(g)}$ and then the vessel was sealed. The mixture was stirred 8 h at 90°C, and then overnight at ambient temperature. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (25-100% EtOAc in hexanes as the gradient eluent) to cleanly provide the title compound (500 mg, 94% yield). MS (apci) m/z = 283.1 (M+H).

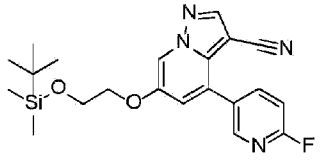
Intermediate P25



4-Bromo-6-(2-((tert-butyldimethylsilyl)oxy)ethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0317] A mixture of (2-bromoethoxy)(tert-butyl)dimethylsilane (451 µL, 2.10 mmol), 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1;** 500 mg, 2.10 mmol) and $K_2CO_{3(s)}$ (871 mg, 6.30 mmol) in DMF (10.5 mL) was stirred for 1 day at 50 °C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water and brine. The resulting organic extracts were directly purified by silica chromatography (0-100% EtOAc/hexanes as the gradient eluent) to cleanly provide the title compound (420 mg, 49% yield).

Intermediate P26

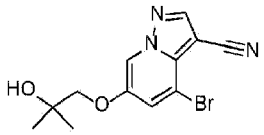


6-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4-('6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile

[0318] In a pressure vessel, a solution of 4-bromo-6-(2-((tertbutyldimethylsilyl)oxy)ethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P25;** 420 mg, 1.06 mmol) in dioxane (10.6 mL) was treated sequentially with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (355 mg, 1.59 mmol), $Pd(PPh_3)_4$ (61.2 mg, 0.530 mmol) and 2 M $Na_2CO_{3(aq)}$ (2.65 mL, 5.30). The resulting mixture was sparged with $Ar_{(g)}$ and the vessel was sealed. The mixture was stirred 8 h at 90°C, and then overnight at ambient temperature. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water (10 mL) and brine (10 mL), then were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-15% MeOH in DCM as the gradient eluent) to afford impure title compound. The impure material was re-subjected to silica chromatography (0-50% EtOAc in Hexanes as the gradient

eluent) to cleanly provide the title compound (351 mg, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6-) δ: 8.81 (d, 1H, J=2.0 Hz), 8.61 (s, 1H), 8.48 (d, 1H, J=2.7 Hz), 8.25 (td, 1H, J=7.8, 2.7 Hz), 7.47 (d, 1H, J=1.9 Hz), 7.38 (dd, 1H, J=7.8, 2.3 Hz), 4.21 (t, 2H, J=4.3 Hz), 3.97 (t, 2H, J=4.7 Hz), 0.86 (s, 9H), 0.08 (s, 6H).

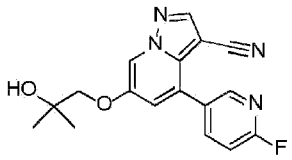
Intermediate P41



4-Bromo-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1.5-a]pyridine-3-carbonitrile

[0319] In a pressure vessel, a mixture of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1;** 10.0 g, 42.0 mmol) and $K_2CO_{3(s)}$ (17.4 g, 126 mmol) in DMF (50 mL) was treated with 2,2-dimethyloxirane (36.9 mL, 420 mmol). After sealing the vessel, the reaction mixture was stirred for 12 h at 60 °C, then for 12 h at 85 °C. The mixture was allowed to cool to ambient temperature. The room temperature mixture was poured into water (400 mL), then stirred for 1 hour at ambient temperature. The resultant suspension was vacuum filtered and the filter cake was rinsed with water. The solids were collected and dried *in vacuo* to cleanly provide the title compound (11 g, 84% yield).

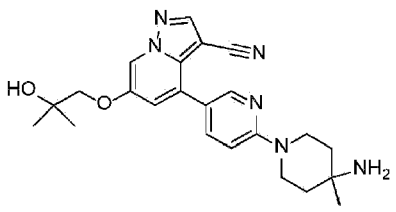
Intermediate P42



4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0320] A mixture of 4-bromo-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P41;** 10.0 g, 32.2 mmol), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (10.8 g, 48.4 mmol) and $Pd(PPh_3)_4$ (1.12 g, 0.967 mmol) in dioxane (200 mL) was treated with 2 M $Na_2CO_{3(aq)}$ (64.5 mL, 129 mmol). The resulting mixture was sparged with $Ar_{(g)}$, then stirred for 12 h at 85 °C under an atmosphere of $N_{2(g)}$. After cooling to ambient temperature, the resultant mixture was poured into cold water (1.5 L). The pH of the mixture was adjusted to about pH 6 with the addition of 10% citric acid. After stirring for 1 hour at ambient temperature, the resultant suspension was vacuum filtered. The solids were collected and dried *in vacuo* to cleanly provide the title compound (10 g, 95% yield).

Intermediate P46

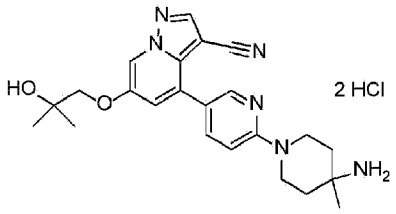


4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0321] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. A solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 100 mg, 0.306 mmol) in DMA (2.04 mL) was treated sequentially with tert-butyl (4-methylpiperidin-4-yl)carbamate (98.5 mg, 0.460 mmol) and DIEA (107 µL, 0.613 mmol). The resulting mixture was sparged with $Ar_{(g)}$, then stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The combined organic extracts were washed with water and brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (22.4 mg, 50% yield) in sufficient purity for step 2. MS (apci) m/z = 521.3 (M+H).

[0322] Step 2: Preparation of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (160 mg, 0.307 mmol) in DCM (1.54 mL) was treated with TFA (1 mL, 13.8 mmol). After stirring for 30 min at ambient temperature, the mixture was treated with additional TFA (1 mL) and stirred an additional 1 hour at ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH_4OH as the gradient eluent) to cleanly provide the title compound (110 mg, 85% yield). MS (apci) m/z = 421.2 (M+H).

Intermediate P48



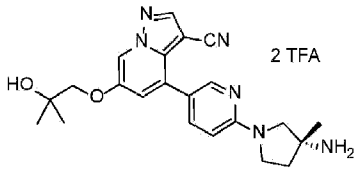
4-(6-(4-amino-4-methylpiperidin-1 -yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0323] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. A solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 2.535 g, 7.768 mmol) in DMSO (6.1 mL) was treated sequentially with tert-butyl (4-methylpiperidin-4-yl)carbamate (1.998 mg, 9.322 mmol) and DIEA (4.06 mL, 23.3 mmol). The resulting mixture stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was poured into 80 mL water and diluted with 80 mL heptane and stirred for 1 hour. The suspension was filtered and the solids were rinsed with 25 mL water then 25 mL heptane. The isolated solids were dried under vacuum for 18 hours to afford the title compound (4.04 g, 99.9% yield) in sufficient purity for step 2. MS (apci) m/z = 521.3 (M+H)

[0324] Step 2: Preparation of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride. A solution of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (4.04 g, 7.76 mmol) in DCM (20 mL) was cooled to 0°C. The reaction was treated with TFA (5.98 mL) and allowed to warm to RT. After stirring for 30 min at ambient the reaction mixture was

concentrated *in vacuo.* The residue was dissolved in MeOH (20 mL) and cooled to 0°C and then treated with Hydrochloric acid, 5 to 6N solution in 2-propanol (15.5 mL, 77.5 mmol) and stirred f0or 15 min at 0°C. The reaction was diluted with 20 mL MTBE, filtered, and solids were rinsed with 20 mL 1:1 MTBE: MeOH. The isolated solids were dried under vacuum to cleanly provide the title compound (3.37 g, 88% yield). MS (apci) m/z = 421.2 (M+H).

Intermediate P49

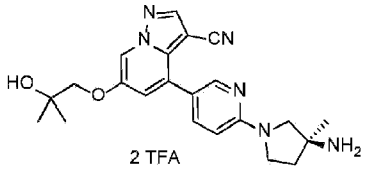


(R)-4-(6-(3-amino-3-methylpyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0325] Step 1: Preparation of tert-butyl (R)-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)carbamate. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 750 mg, 2.30 mmol) and (R)-(3-Methyl-pyrrolidin-3-yl)-carbamic acid tert-butyl ester HCl (644 mg, 3.22 mmol) in DMSO (4.6 mL) was added DIEA (1.2 mL, 6.89 mmol). The reaction mixture was stirred 12 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted into cold water and stirred for 2 h at ambient temperature. The suspension was filtered and the solids were rinsed with water. The isolated solids were dried under vacuum for 48 h to afford the title compound (1.05 g, 90% yield) in sufficient purity for step 2. MS (apci) m/z = 507.3 (M+H)

[0326] Step 2: (R)-4-(6-(3-amino-3-methylpyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate). To a solution of (R)-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)carbamate (1.05 g, 2.07 mmol) in 3 mL DCM was treated with TFA (3 mL, 39 mmol). The reaction mixture was stirred for 4 h at ambient temperature, and then concentrated *in vacuo.* The residue was diluted with DCM (4 mL) and toluene (1 mL) and stirred at ambient temperature for 15 min. The mixture was concentrated *in vacuo* and dried under vacuum for 2 days to afford the title compound with quantitative yield. MS (apci) m/z = 407.3 (M+H).

Intermediate P50



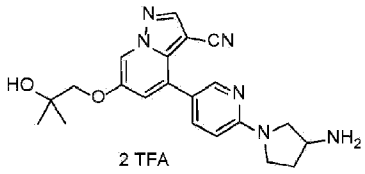
(S)-4-(6-(3 -amino-3 -methylpyrrolidin-1 -yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0327] Step 1: Preparation of tert-butyl (S)-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)carbamate. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 700 mg, 2.15 mmol)

and (S)-(3-Methyl-pyrrolidin-3-yl)-carbamic acid tert-butyl ester HCl (601 mg, 3.0 mmol) in DMSO (4.3 mL) was added DIEA (1.1 mL, 6.44 mmol). The reaction mixture was stirred 12 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted into cold water and stirred for 2 h at ambient temperature. The suspension was filtered and the solids were rinsed with water. The isolated solids were dried under vacuum for 48 h to afford the title compound (950 mg, 87% yield) in sufficient purity for step 2. MS (apci) m/z = 507.3 (M+H)

[0328] Step 2: Preparation of (S)-4-(6-(3-amino-3-methylpyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate). To a solution of tert-butyl (S)-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)carbamate (950 mg, 1.88 mmol) in 3 mL DCM was treated with TFA (3 mL, 39 mmol). The reaction mixture was stirred for 4 h at ambient temperature, and then concentrated *in vacuo.* The residue was diluted with DCM (4 mL) and toluene (1 mL) and stirred at ambient temperature for 15 min. The mixture was concentrated *in vacuo* and dried under vacuum for 2 days afford the title compound with quantitive yield. MS (apci) m/z = 407.2 (M+H).

Intermediate P51

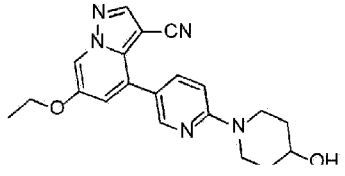


4-(6-(3 -aminopyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0329] Step 1:Preparation of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 850 mg, 2.60 mmol) and 3-(tert-butoxycarbonylamino)pyrrolidine (679 mg, 3.65 mmol) in DMSO (5.2 mL) was added DIEA (1.36 mL, 7.81 mmol). The reaction mixture was stirred 12 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted into cold water and stirred for 2 h at ambient temperature. The suspension was filtered and the solids were rinsed with water. The isolated solids were dried under vacuum for 48 h to afford the title compound (1.26 g, 98% yield) in sufficient purity for step 2. MS (apci) m/z = 493.3 (M+H)

[0330] Step 2: Preparation of 4-(6-(3-aminopyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate). To a solution of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (950 mg, 1.88 mmol) in 3 mL DCM was treated with TFA (3 mL, 39 mmol). The reaction mixture was stirred for 4 h at ambient temperature, and then concentrated *in vacuo.* The residue was diluted with DCM (4 mL) and toluene (1 mL) and stirred at ambient temperature for 15 min. The mixture was concentrated *in vacuo* and dried under vacuum for 2 days afford the title compound with quantative yield. MS (apci) m/z = 393.2 (M+H).

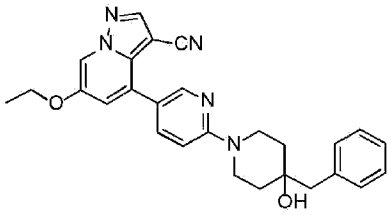
Intermediate P52



6-ethoxy-4-(6-(4-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0331] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.500 g, 1.77 mmol) inDMSO (3.5 mL) was added TEA (0.741 mL, 5.31 mmol) and piperidin-4-ol (269 mg, 2.66 mmol). The reaction mixture was stirred at 70°C for 5 h. After cooling to ambient temperature, the reaction mixture was poured into ice water. The resultant solids were isolated by vacuum filtration to afford the title compound (501 mg, 1.38 mmol, 77.8 % yield). MS (apci) m/z = 364.2 (M+H).

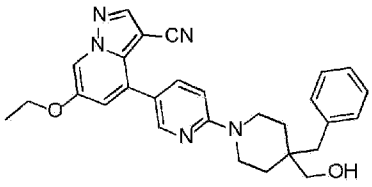
Intermediate P53



4-(6-(4-benzyl-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0332] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 30 mg, 0.106 mmol) in DMA (0.5 mL) was added TEA (0.044 mL, 0.319 mmol) and 4-benzylpiperidin-4-ol (40.7 mg, 0.213 mmol) The reaction mixture was stirred at 90°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NH_4Cl_{(aq)}$ then water. The combined aqueous washes were further extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (30-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (39 mg, 0.0860 mmol, 80.9 % yield). MS (apci) m/z = 454.2 (M+H).

Intermediate P55

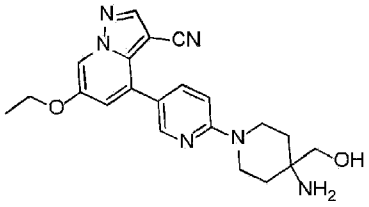


4-(6-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 - carbonitrile

[0333] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 100.5 mg, 0.3560 mmol) in DMSO (3 ml) was added (4-benzylpiperidin-4-yl)methanol hydrochloride (151.5 mg, 0.6267 mmol) and cesium carbonate (812.0 mg, 2.492 mmol). The reaction mixture was stirred at 60°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and saturated $NH_4Cl_{(aq)}$. The combined aqueous layers were

extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated. The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (118.2 mg, 0.2528 mmol, 71.00 % yield). MS (apci) m/z = 468.2 (M+H).

Intermediate P56



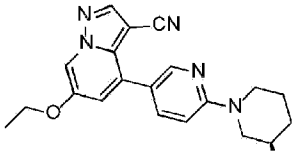
4-(6-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0334] Step 1: Preparation of methyl 4-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 303.4 mg, 1.075 mmol) in DMSO (21.50 mL) was added 4-N-Boc-amino-piperidine-4-carboxylic acid methyl ester (416.5 mg, 1.612 mmol) and potassium carbonate (297.1 mg, 2.150 mmol). The reaction mixture was stirred at 110°C for 72 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_{4(s)}$ and concentrated *in vacuo.* The resultant crude residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (76.7 mg, 13.7% yield) in sufficient purity for step 2. MS (apci) m/z = 521.2 (M+H).

[0335] Step 2: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)carbamate. To a solution of lithium borohydride (0.0120 mL, 0.365 mmol) in THF (0.912 mL) was added methyl 4-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate (47.5 mg, 0.0912 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo,* and the residue was diluted with EtOAc and washed with brine. The organic extract was dried over anhydrous $MgSO_{4(s)}$ and concentrated *in vacuo* to afford the title compound as crude product (65.9 mg), which was used in the next step without further purifications. MS (apci) m/z = 493.2 (M+H).

[0336] Step 3: Preparation of 4-(6-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)carbamate (65.9 mg, 0.134 mmol) in DCM (1 mL) was treated with TFA (0.2 mL, 2.68 mmol). The reaction mixture was stirred at rt 30 min then concentrated *in vacuo.* The residue was taken up in DCM and washed with saturated Na_2CO_3. The aqueous fraction was extracted with DCM, and the combined organic extracts were dried over anhydrous $MgSO_{4(s)}$ and concentrated *in vacuo* to afford the title compound (35.6 mg, 68% yield). MS (apci) m/z = 393.2 (M+H).

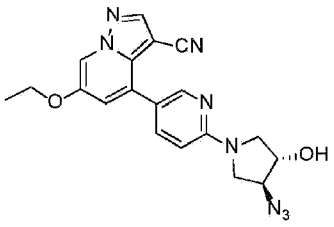
Intermediate P57



tert-butyl (R)-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate

[0337] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.147 g, 0.521 mmol) in DMSO (1 mL) was added tert-butyl (R)-piperidin-3-ylcarbamate (209 mg, 1.04 mmol) and potassium carbonate (216 mg, 1.56 mmol). The reaction mixture was heated to 110°C for 72 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and quenched with saturated NH_4Cl and extracted into additional DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (100 mg, 0.216 mmol, 41.5 % yield). MS (apci) m/z = 463.2 (M+H).

Intermediate P58



4-(6-((3 S,4S)-3 -azido-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

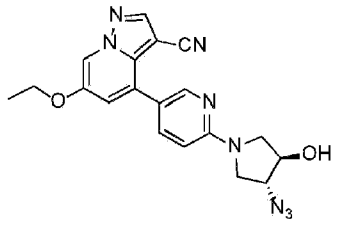
[0338] Step 1: Preparation of (3S,4S)-tert-butyl 3-azido-4-hydroxypyrrolidine-1-carboxylate. A solution of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (15.42 g, 83.25 mmol), (R)-N,N'-Bis(3,5-Di-tert-butylsalicylidene)-1,2-cyclohexanediaminochromium(III) chloride (0.5904 g, 0.8325 mmol), potassium carbonate (13.81 g, 99.90 mmol), and azidotrimethylsilane (12.79 ml, 91.58 mmol) was sparged with nitrogen and stirred at rt for 24 h. The reaction mixture was treated with silica gel (30 g) and water (2 mL) and stirred at rt for an additional 72 h. The solution was filtered through a pad of Celite® and concentrated *in vacuo.* The residue was purified by silica chromatography (20-50% EtOAc in hexanes as the gradient eluent) to afford the title compound (18.5 g, 81.05 mmol, 97.36 % yield) in sufficient purity for step 2.

[0339] Step 2: Preparation of (3S,4S)-4-azidopyrrolidin-3-ol dihydrochloride. A solution of tert-butyl (3S,4S)-3-azido-4-hydroxypyrrolidine-1-carboxylate (0.500 g, 2.19 mmol) in DCM (2.19 mL) was treated with 6M HCl in IPA (4.5 mL, 27 mmol). The reaction mixure was stirred at rt for 4 h, at which time the reaction mixture was concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 0.440 g, 2.19 mmol) in sufficient purity for step 3. MS (apci) m/z = 129.1 (M+H).

[0340] Step 3: Preparation of 4-(6-((3S,4S)-3-azido-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1.5-a]pyridine-3-carbonitrile. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.300 g, 1.06 mmol) in DMSO (2 mL) was added N-ethyl-N-isopropylpropan-2-amine (3.70 mL, 21.3 mmol) and (3S,4S)-4-azidopyrrolidin-3-ol dihydrochloride (0.427

g, 2.13 mmol) The reaction mixture was stirred 100°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.220 g, 0.564 mmol, 53.0 % yield over two steps). MS (apci) m/z = 391.15 (M+H).

Intermediate P59



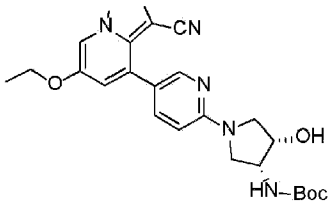
4-(6-((3R,4R)-3-azido-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0341] Step 1: Preparation of (3R,4R)-tert-butyl 3-azido-4-hydroxypyrrolidine-1-carboxylate. A solution of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (15.42 g, 83.25 mmol), (1S,2S)-(-)- [1,2-Cyclohexanediammo-N,N'-bis(3,5-di-t-butylsalicylidene)]chromium (III) chloride (1.181 g, 1.665 mmol), and azidotrimethylsilane (12.79 ml, 91.58 mmol) was sparged with nitrogen and stirred at rt for 24 h. To this was added potassium carbonate (13.81 g, 99.90 mmol) in MeOH (100 mL), and the reaction mixture was stirred an additional 5 h at rt. The solution was filtered through a pad of Celite® and concentrated *in vacuo.* The residue was taken up in EtOAc and water. The aqueous fraction was extracted with EtOAc, and the combined organic extracts were washed successively with saturated $NaHCO_{3(aq)}$, water, and brine. They were dried over anhydrous $MgSO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20% EtOAc in hexanes as the eluent) to afford the title compound (18.5 g, 81.05 mmol, 97.36 % yield) in sufficient purity for step 2.

[0342] Step 2: Preparation of (3R,4R)-4-azidopyrrolidin-3-ol dihydrochloride. A solution of tert-butyl (3R,4R)-3-azido-4-hydroxypyrrolidine-1-carboxylate (0.500 g, 2.19 mmol) in DCM (2.19 mL) was treated with 6M HCl in IPA (4.5 mL, 27 mmol). The reaction mixure was stirred at rt for 4 h, at which time the reaction mixture was concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 0.440 g, 2.19 mmol) in sufficient purity for step 3. MS (apci) m/z = 129.1 (M+H).

[0343] Step 3: Preparation of 4-(6-((3R,4R)-3-azido-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.300 g, 1.06 mmol) in DMSO (2 mL) was added N-ethyl-N-isopropylpropan-2-amine (3.70 mL, 21.3 mmol) and (3R,4R)-4-azidopyrrolidin-3-ol dihydrochloride (0.427 g, 2.13 mmol) The reaction mixture was stirred 100°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.205 g, 0.525 mmol, 49.4 % yield over two steps). MS (apci) m/z = 391.2 (M+H).

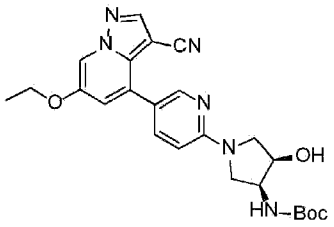
Intermediate P60



tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate

[0344] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.215 g, 0.762 mmol) in DMSO (1.5 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.663 ml, 3.81 mmol) and tert-butyl ((3R,4S)-4-hydroxypyrrolidin-3-yl)carbamate (0.231 g, 1.14 mmol). The reaction mixture was stirred 100°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.347 g, 0.747 mmol, 98.1 % yield). MS (apci) m/z = 465.3 (M+H).

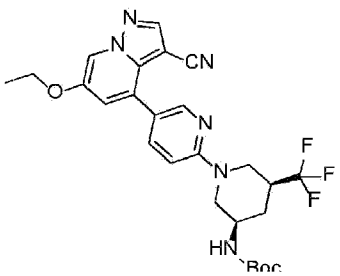
Intermediate P61



tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate

[0345] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.215 g, 0.762 mmol) in DMSO (1.5 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.663 ml, 3.81 mmol) and tert-butyl ((3S,4R)-4-hydroxypyrrolidin-3-yl)carbamate (0.231 g, 1.14 mmol). The reaction mixture was stirred 100°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.284 g, 0.611 mmol, 80.3 % yield). MS (apci) m/z = 465.2 (M+H).

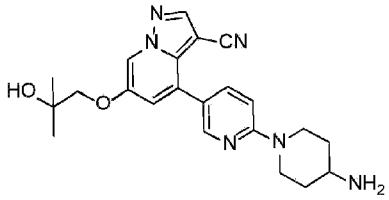
Intermediate P62



tert-butyl ((3R, 5 S)-1 -(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-5-(trifluoromethyl)piperidin-3-yl)carbamate

[0346] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.060 g, 0.21 mmol) in DMSO (0.4 mL) was added potassium carbonate (0.15 g, 1.1 mmol) and tert-butyl ((3R,5S)-5-(trifluoromethyl)piperidin-3-yl)carbamate (0.171 g, 0.638 mmol). The reaction mixture was stirred at 110°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.0538 g47.7 % yield) in sufficient purity for step 2. MS (apci) m/z = 531.2 (M+H).

Intermediate P64

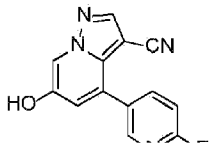


4-(6-(4-aminopiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0347] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)carbamate. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 205 mg, 0.628 mmol) and tert-butyl piperidin-4-ylcarbamate (252 mg, 1.26 mmol) in DMA (2.09 mL) was added DIEA (549 µL, 3.14 mmol). The reaction was stirred 2 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 319 mg) in sufficient purity for step 2. MS (apci) m/z= 507.20 (M+H)

[0348] Step 2: Preparation of 4-(6-(4-aminopiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)carbamate (319 mg, 0.63 mmol) in DCM (3.15 mL) was added TFA (3.14 mL, 40.9 mmol). The reaction was stirred for 30 min at ambient temperature. The reaction was concentrated *in vacuo.* The residue was resuspended in DCM and purified using silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH_4OH as the gradient eluent) to cleanly provide the title compound (37 mg, 53% yield) MS (apci) m/z = 407.2 (M+H).

Intermediate P66

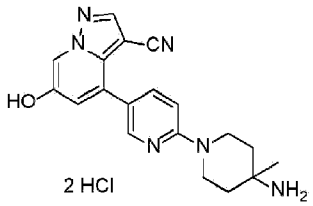


`N` `F`

4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0349] In a pressure vessel, a solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1;** 15.4 g, 64.7 mmol) in dioxane (320 mL) was treated sequentially with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (15.2 g, 67.9 mmol), $Pd(PPh_3)_4$ (3.74 g, 3.23 mmol) and 2 M $Na_2CO_{3(aq)}$ (97 mL, 194 mmol). The resulting mixture was sparged with $Ar_{(g)}$ and then the vessel was sealed. The mixture was stirred 16 h at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with MTBE and extracted with 1 M NaOH. The combined aqueous layers were extracted with MTBE. The combined aqueous layers were acidified to pH 4 with 4 M HCl. The suspension was filtered and washed with water to cleanly provide the title compound (14.8 g, 72% yield). MS (apci) m/z = 253.1 (M-H) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.48-8.47 (d, 1H), 8.41-8.40 (d, 1H), 8.26-8.21 (m, 1H), 7.38-7.36 (m, 1H), 7.31-7.30 (d, 1H).

Intermediate P67

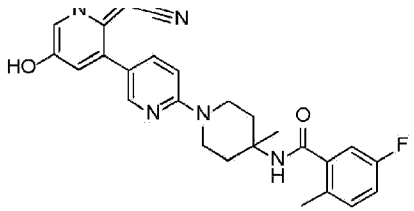


4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0350] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. To a solution of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P66;** 3.0 g, 9.44 mmol) and tert-butyl 4-methylpiperidin-4-ylcarbamate (2.83 mg, 13.2 mmol) in DMSO (12 mL) was added DIEA (4.93 mL, 28.3 mmol). The reaction was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted into water and acidified to pH 5 using a 10% citric acid solution and stirred for 15 min at ambient temperature. The suspension was filtered and the precipitate was rinsed with water. The isolated solids were dissolved in 4:1 DCM:IPA and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography (5-75% EtOAc in DCM) to afford the title compound (assumed theoretical yield, 4.23 g) in sufficient purity for step 2. MS (apci) m/z= 449.3 (M+H)

[0351] Step 2: Preparation of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride To a solution of tert-butyl (1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (assumed 4.23 g, 9.44 mmol) in MeOH (30 mL) was added HCl (5-6 N solution in 2-propanol, 28.3 mL, 142 mmol). The reaction was stirred for 2.5 h at ambient temperature. The reaction was diluted with MTBE (30 mL) and stirred for 30 min at ambient temperature. The suspension was filtered and washed with MTBE (50 mL) to cleanly provide the title compound (2.18 g, 55% yield over two steps) MS (apci) m/z = 349.2 (M+H).

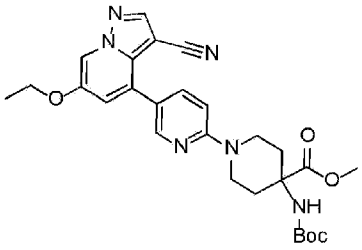
Intermediate P68



N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0352] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P67;** 503 mg, 1.19 mmol), 5-fluoro-2-methylbenzoic acid (552 mg, 3.58 mmol), and HATU (1.36g, 3.58 mmol) in DMSO (5 mL) was added DIEA (1.7 mL, 9.55 mmol). The reaction was stirred 16 h at ambient temperature. The reaction mixture was diluted with THF (4 mL) and treated with NaOH (5.97 mL, 11.9 mmol) and stirred for 4 h at ambient temperature. The reaction was concentrated *in vacuo.* The residue was diluted with EtOAc and washed with water. The pH was adjusted to pH 5 with AcOH and then extracted with EtOAc. The organic extracts were washed with brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography (50-100% Hexanes to EtOAc) to afford the title compound (534 mg, 92% yield) in sufficient purity for step 2. MS (apci) m/z= 485.2 (M+H).

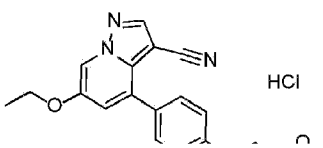
Intermediate P69

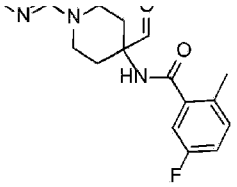


methyl 4-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate

[0353] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.700 g, 2.480 mmol) in DMSO (4.96 mL) was added DIEA (1.296 mL, 7.439 mmol) and methyl 4-((tert-butoxycarbonyl)amino)piperidine-4-carboxylate (0.8968 g, 3.472 mmol). The reaction mixture was stirred 90°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched water and extracted into EtOAc. The combined organic extracts were washed with saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (1.003 g, 1.927 mmol, 77.69 % yield). MS (apci) m/z = 521.3 (M+H).

Intermediate P70





N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0354] Step 1: Preparation of methyl 4-amino-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate. A solution of methyl 4-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate **(Intermediate P69,** 0.8 g, 1.5 mmol) in DCM was treated with TFA. The reaction mixture was stirred at rt for 24 h, then concentrated *in vacuo.* HCl in iPrOH (6N) was added to the mixture to precipitate product. The suspension was stirred at RT for 1h then concentrated, affording the title compound (assumed theoretical yield, 0.65 g, 1.5 mmol) in sufficient purity for step 2. MS (apci) m/z = 421.25 (M+H).

[0355] Step 2: Preparation of methyl 1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(5-fluoro-2-methylbenzamido)piperidine-4-carboxylate. To a solution of methyl 4-amino-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate (0.65 g, 1.5 mmol) in DCM (31 mL) was added 5-fluoro-2-methylbenzoic acid (0.36 g, 2.3 mmol) and HATU (0.88 g, 2.3 mmol). The reaction mixture was stirred at rt for 1 h, at which time a catalytic amount of DMAP was added. The reaction mixture was stirred at 50°C for 1 h, then cooled to RT and purified directly by silica chromatography (0-100% EtOAc in Hexanes then 1-10% MeOH in $CHCl_3$ as the gradient eluent) to afford the title compound (0.8g, 1.4 mmol, 93% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 557.2 (M+H).

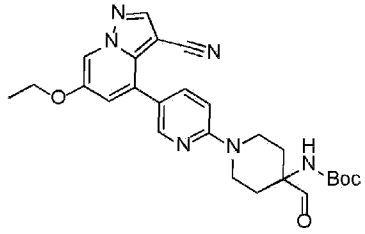
[0356] Step 3: Preparation of N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution of methyl 1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(5-fluoro-2-methylbenzamido)piperidine-4-carboxylate (750 mg, 1.35 mmol) in THF (26.949 mL) at 0°C was added lithium borohydride (117 mg, 5.39 mmol). The reaction mixture was stirred at 0°C for 1h. The reaction mixture was diluted with EtOAc and washed with a 10% aqueous citric acid solution. The organic extract was dried and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in Hexanes then 1-10% MeOH in EtOAc as the gradient eluent) to afford the title compound (700 mg, 1.32 mmol, 98.3% yield) in sufficient purity for step 4. MS (apci) m/z = 529.1 (M+H).

[0357] Step 4: Preparation of N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution of N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide (100 mg, 0.189 mmol) in DCM (0.946 mL) at 0°C was added 3-oxo-1l5-benzo[d][1,2]iodaoxole-1,1,1(3H)-triyltriacetate (201 mg, 0.473 mmol). The reaction mixture was warmed to rt and stirred at that temperature for 1 h, at which time additional 3-oxo-1l5-benzo[d][1,2]iodaoxole-1,1,1(3H)-triyl triacetate (201 mg, 0.473 mmol) was added. The reaction mixture was stirred at rt an additional 15 min, then quenched with EtOAc and saturated $NaHCO_{3(aq)}$ The organic extract was washed with $Na_2S_2O_{3(aq)}$, dried, and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in Hexanes then 1-10% MeOH in EtOAc as the gradient eluent) to afford the title compound (358 mg, 55.3% yield). MS (apci) m/z = 527.15 (M+H).

Intermediate P71

tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)carbamate

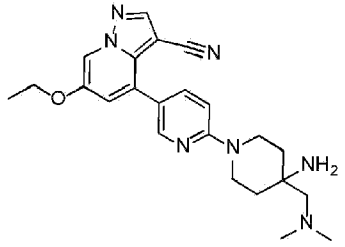
[0358]



[0359] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)carbamate. To a solution of methyl 4-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidine-4-carboxylate **(Intermediate P69,** 1.00 g, 1.92 mmol) in THF (12.8 mL) at 0°C was added lithium borohydride (0.167 g, 7.68 mmol). The reaction mixture was allowed to reach rt and stirred at this temperature for 24 h. The reaction mixture was quenched with water, and the residual solids were removed by filtration. The filtrate was extracted with EtOAc, and the combined organic extracts were washed with saturated $NaCl_{(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.832 g, 1.69 mmol, 87.9 % yield) in sufficient purity for step 2. MS (apci) m/z = 493.3 (M+H).

[0360] Step 2: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)carbamate. To a solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)carbamate (0.832 g, 1.69 mmol) in THF (16.9 mL) was added 3-oxo-1l5-benzo[d][1,2]iodaoxole-1,1,1(3H)-triyl triacetate (0.832 g, 1.69 mmol). The reaction mixture was stirred at rt for 24 h then quenched with water. The mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated $NaCl_{(aq)}$. The organic extracts were concentrated *in vacuo,* and the residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.594 g, 1.21 mmol, 71.7 % yield). MS (apci) m/z = 491.2 (M+H).

Intermediate P72

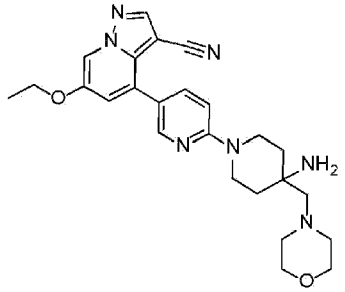


4-(6-(4-amino-4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0361] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)carbamate. To a mixture of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)carbamate (0.594 g, 1.21 mmol) in DCM (0.077 mL) was added dimethylamine hydrochloride (0.197 g, 2.42 mmol) and DIEA (0.443 mL, 2.54 mmol). This mixture was stirred at rt for 15 min, then sodium triacetoxyborohydride (0.385 g, 1.82 mmol) was slowly added. The reaction mixture was stirred at rt for 24 h then quenched with water. The solution was extracted with EtOAc, and the combined organic extracts were washed with saturated $NaCl_{(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo,* and the residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.181 g, 0.348 mmol, 28.8 % yield) in sufficient purity for step 2. MS (apci) m/z = 520.3 (M+H).

[0362] Step 2: Preparation of 4-(6-(4-amino-4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A mixture of tert-butyl (1-(5-(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)carbamate (0.181 g, 0.348 mmol) in DCM (0.02 mL) was treated with TFA (0.0268 mL). The reaction mixture was stirred at rt. The reaction mixture was concentrated *in vacuo,* resuspended in DCM, and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo* to afford the title compound (0.145 g, 0.346 mmol, 99.2 % yield). MS (apci) m/z = 420.3 (M+H).

Intermediate P73

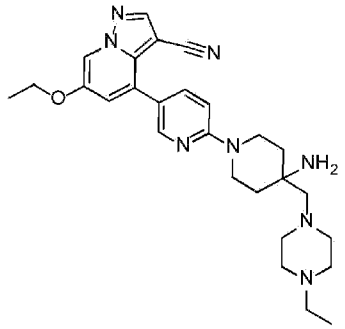


4-(6-(4-amino-4-(morpholinomethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0363] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(morpholinomethyl)piperidin-4-yl)carbamate. To a solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)carbamate **(Intermediate P71,** 400 mg, 0.815 mmol) in DCM (4.077 mL) was added morpholine (0.07703 mL, 0.815 mmol) and sodium triacetoxyborohydride (346 mg, 1.63 mmol). The reaction mixture was stirred at rt for 72 h. The reaction mixture was concentrated *in vacuo,* and the residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 458 mg, 0.815 mmol) in sufficient purity for step 2. MS (apci) m/z = 562.4 (M+H).

[0364] Step 2: Preparation of 4-(6-(4-amino-4-(morr)holinomethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(morpholinomethyl)piperidin-4-yl)carbamate (458 mg, 0.815 mmol) in DCM (0.815 mL) was treated with TFA (0.0628 mL, 0.815 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with 4:1 DCM/IPA and water. The mixture was washed washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (135 mg, 0.292 mmol, 35.9 % yield over two steps). MS (apci) m/z = 462.3 (M+H).

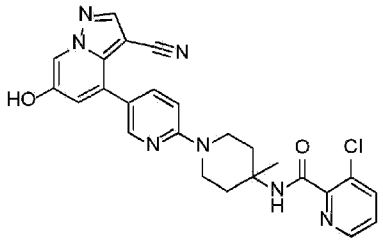
Intermediate P74



4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0365] A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)carbamate **(Example** 379, 0.149 g, 0.253 mmol) in DCM (0.0163 mL) was treated with HCl in IPA (0.00769 mL, 0.253 mmol). The reaction mixture was stirred at rt then quenched with DCM and saturated $Na_2CO_{3(aq)}$. The organic extract was dried over anhydrous $MgSO_{4(s)}$, filtered, then concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 0.124 g, 0.253 mmol). MS (apci) m/z = 489.3 (M+H).

Intermediate P75

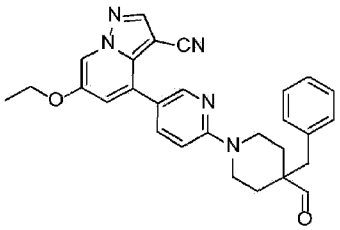


3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0366] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate** P67; 256 mg, 0.608 mmol), 3-Chloropicolinic acid (287 mg, 1.82 mmol), and HATU (294 mg, 1.82 mmol) in DMSO (3 mL) was added DIEA (0.74 mL, 4.25 mmol). The reaction was stirred overnight at ambient temperature. The reaction mixture was diluted with

EtOAc (10 mL) and washed with water (10 mL) and 4:1AcOH:water (10 mL) and then extracted with EtOAc. The organic extracts were washed with 4:1 AcOH:Water and then brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was diluted with THF (4 mL) and 2M NaOH (6 mL). The solution was concentrated *in vacuo.* The residue was resuspended in DCM (2mL) and purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was resuspended in DCM and passed through a PI-HCO_3 resin to elute the free-based product. The organic eluents were concentrated *in vacuo* and recrystallized using DCM/Hexanes to afford the title compound (226 mg, 76% yield). MS (apci) m/z = 488.2 (M+H).

Intermediate P77

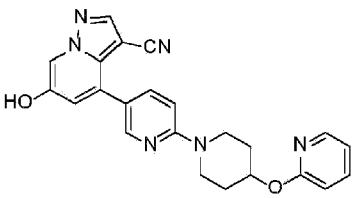


4-(6-(4-benzyl-4-formylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile

[0367] Step 1: Preparation of 4-(6-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 100.5 mg, 0.3560 mmol) in DMSO (3 mL) was added (4-benzylpiperidin-4-yl)methanol hydrochloride (151.5 mg, 0.6267 mmol), and cesium carbonate (812.0 mg, 2.492 mmol). The reaction mixture was stirred at 60°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed successively with water and saturated $NH_4Cl_{(aq)}$. The aqueous fractions were extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ then purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (118.2 mg, 0.2528 mmol, 71.00 % yield) in sufficient purity for step 2. MS (apci) m/z = 468.2 (M+H).

[0368] Step 2: Preparation of 4-(6-(4-benzyl-4-formylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of 4-(6-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (51.3 mg, 0.110 mmol) in DCM (1.5 mL) was treated with 3-oxo-1l5-benzo[d][1,2]iodaoxole-1,1,1(3H)-triyl triacetate (93.1 mg, 0.219 mmol). The reaction mixture was stirred at rt for 1.5 h. The reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (46.7 mg, 0.100 mmol, 91.4 % yield) in sufficient purity for step 2. MS (apci) m/z = 466.3 (M+H).

Intermediate P78

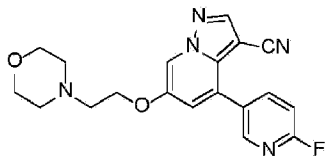


6-hydroxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0369] Step 1: Preparation of 2-(4-(pyridin-2-yloxy)piperidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine. To a solution of 2-Chloropyridine-5-boronic acid, pinacol ester (1.18 g, 4.93 mmol) in DMSO (5.0 mL) was added DIEA (4.29 mL, 24.6 mmol) and 2-(piperidin-4-yloxy)pyridine dihydrochloride (1.55 g, 6.16 mmol). The reaction mixture was stirred at 90°C for 72 h. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were successively washed with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (1.19 g, 3.12 mmol, 63.3 % yield) in sufficient purity for step 2.

[0370] Step 2: Preparation of 6-hydroxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1,** 800.5 mg, 3.363 mmol) in 4:1 dioxane:water (30 mL) was treated with 2-(4-(pyridin-2-yloxy)piperidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1410.406 mg, 3.699 mmol), tetrakis(triphenylphosphine)palladium (0) (388.6035 mg, 0.3363 mmol), and aqueous potassium carbonate (1394.277 mg, 10.088 mmol). The reaction mixture was sparged with argon and stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water and adjusted to pH 7 with 4N HCl. The mixture was extracted with 4:1 DCM:IPA, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% acetone in hexanes as the gradient eluent) to afford the title compound (475.3 mg, 1.152 mmol, 34.3% yield). MS (apci) m/z = 413.2 (M+H).

Intermediate P79



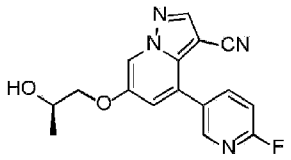
4-(6-fluoropyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0371] Step 1: Preparation of 4-bromo-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1,** 1000 mg, 4.201 mmol) in DMA (21.005 L) was treated with potassium carbonate (1742 mg, 12.60 mmol) and 4-(2-chloroethyl)morpholine (1.132 mL, 8.402 mmol). The reaction mixture was stirred at 50°C for 72 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NaCl_{(aq)}$. The resultant precipitate was isolated by filtration to afford the title compound (1475 mg, 4.200 mmol, 99% yield) in sufficient purity for step 2. MS (apci) m/z = 351 (M^+).

[0372] Step 2: Preparation of 4-(6-fluoropyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of 4-bromo-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (0.83 g, 1.394 mmol) in 1,4-dioxane (1000 mL) was treated with 2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (373.2181 mg, 1.673 mmol), tetrakis(triphenylphosphine)palladium (0) (32.22577 mg, 0.0279 mmol), and aqueous potassium carbonate (2.092 mL, 4.183 mmol). The reaction

mixture was sparged with argon and stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with MTBE and washed with 1N NaOH. The aqueous fractions were extracted with MTBE then adjusted to pH 4 with 4N HCl. Saturated $NaCl_{(aq)}$ was added and the aqueous mixture was extracted with 4:1 DCM/IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (0.341 g, 0.928 mmol, 66.6 % yield). MS (apci) m/z = 368.1 (M+H).

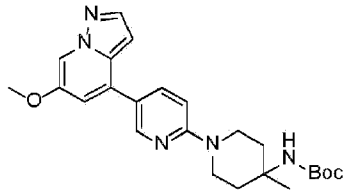
Intermediate P80



(R)-4-(6-fluoropyridin-3 -yl)-6-(2-hydroxypropoxy)pyrazolo [1,5 -a]pyridine-3 - carbonitrile

[0373] To a solution of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P66,** 0.2027 g, 0.78935 mmol) in THF (3.16 mL) was added aqueous sodium hydroxide (2M, 0.40257 mL, 0.80514 mmol) dropwise. The mixture was stirred at rt for 1 h, at which time (R)-2-methyloxirane (0.33181 mL, 4.7361 mmol) was added. The reaction mixture was stirred at 80°C for 16 h. After cooling to ambient temperature, the pH was adjusted to 5 by addition of a 10% aqueous citric acid solution. The mixture was extracted with EtOAc, then the combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.084 g, 0.26897 mmol, 34.074 % yield. MS (apci) m/z = 313.1 (M+H).

Intermediate P81

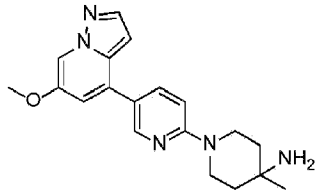


tert-butyl (1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate

[0374] Step 1: Preparation of 4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine. To a solution of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (5.122 g, 22.56 mmol) in 1,4-dioxane (45.12 mL) was added 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.038 g, 27.07 mmol), tetrakis(triphenylphosphine)palladium (0) (1.043 g, 0.9023 mmol), and aqueous sodium carbonate (2M, 23.69 mL, 47.37 mmol). The reaction mixture was stirred at 80°C for 16 h. After cooling to ambient temperature, the reaction mixture was poured onto water and stirred for 4 h. The resultant precipitate was isolated by vacuum filtration then taken up in MTBE and stirred an additional 30 min. The precipitate was isolated by vacuum filtration to afford the title compound (4.616 g, 18.98 mmol, 84.13 % yield) in sufficient purity for step 2. MS (apci) m/z = 244.1 (M+H).

[0375] Step 2: Preparation of tert-butyl (1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. To a solution of 4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine (2.25 g, 9.25 mmol) in DMSO (18.5 mL) was added tert-butyl (4-methylpiperidin-4-yl)carbamate (2.97 g, 13.9 mmol) and DIEA (4.83 mL, 27.8 mmol). The reaction mixture was stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with saturated $NaCl_{(aq}$, dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (3.8 g, 8.68 mmol, 93.9 % yield). MS (apci) m/z = 438.3 (M+H).

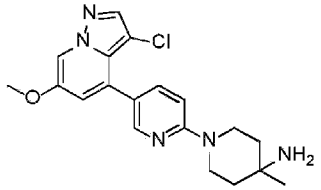
Intermediate P82



1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine

[0376] A solution of tert-butyl (1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate** P81, 0.500 g, 1.14 mmol) in DCM (5 mL) was treated with TFA (5 mL). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo,* and the residue was diluted with EtOAc and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo* to afford the title compound (0.38 g, 1.13 mmol, 98.5 % yield). MS (apci) m/z = 338.2 (M+H).

Intermediate P83



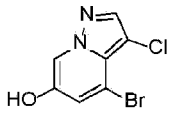
1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine

[0377] Step 1: Preparation of tert-butyl (1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpyperidin-4-yl)carbamate. To a solution of tert-butyl (1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate P81,** 0.800 g, 1.83 mmol) in DCM (12.2 mL) was added NCS (0.293 g, 2.19 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.765 g, 1.62 mmol, 88.6 % yield) in sufficient purity for step 2. MS (apci) m/z = 472.2 (M+H).

[0378] Step 2: Preparation of 1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine. A solution of tert-butyl (1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-

yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (0.765 g, 1.62 mmol) in DCM (12 mL) was treated with TFA (12 mL). The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo* to afford the title compound (0.548 g, 1.47 mmol, 90.9 % yield). MS (apci) m/z = 372.2 (M+H).

Intermediate P84



4-bromo-3 -chloropyrazolo [1,5-a]pyridin-6-ol

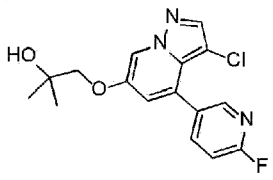
[0379] Step 1: Preparation of 4-bromo-3-chloro-6-methoxypyrazolorl .5-a lpyridine. To a solution of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (15 g, 66.06 mmol) in DCM (100 mL) was added NCS (8.821 g, 66.06 mmol). The reaction mixture was sonicated for 5 min then stirred at rt for 24 h. The reaction mixture was diluted with Et_2O, in which it was stirred for 10 min then sonicated for 2 min. The solid precipitate was isolated by vacuum filtration to afford the title compound (18.69 g, 71.47 mmol, 108.2% yield) in sufficient purity for step 2. MS (apci) m/z = 263.1 (M+H).

[0380] Step 2: Preparation of 4-bromo-3-chloropyrazolo[1,5-a]pyridin-6-ol. A solution of 4-bromo-3-chloro-6-methoxypyrazolo[1,5-a]pyridine (7.59 g, 29.0 mmol) in DCE (290 mL) was sparged with N_2 and treated with aluminum trichloride (11.6 g, 87.1 mmol) over the course of 5 min. The reaction mixture was stirred at 76°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with DMA then concentrated *in vacuo.* The residue was taken up in water and cooled on ice for 30 min. The resultant precipitate was isolated by vacuum filtration then taken up in DMA. The solution was filtered through a plug of silica to afford the title compound as a solution in DMA (assumed quantitative yield, 7.00g, 28.3 mmol).

Intermediate P85

1-((3-chloro-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol

[0381]

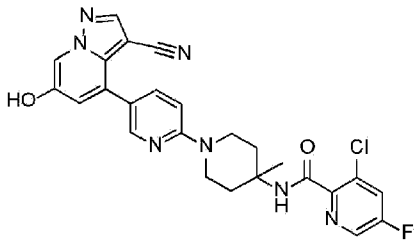


[0382] Step 1: Preparation of 1-((4-bromo-3-chloropyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol. To a solution of 4-bromo-3-chloropyrazolo[1,5-a]pyridin-6-ol **(Intermediate P84**, 4.2 g, 17.0 mmol) in DMA (300 mL) was added potassium carbonate (23.5 g, 170 mmol) and 2,2-dimethyloxirane (14.9 mL,

169.8 mmol). The reaction mixture was stirred at 85°C for 2 h. After cooling to ambient temperature, the reaction mixture was quenched with 1:1 saturated $NH_4Cl_{(aq)}$/water. The solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo* to afford the title compound (2.62 g, 5.74 mmol, 33.8% yield) in sufficient purity for step 2. MS (apci) m/z = 321.0 (M+H).

[0383] Step 2: Preparation of 1-((3-chloro-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol. To a solution of 1-((4-bromo-3-chloropyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol (1.44 g, 4.51 mmol) in 1,4-dioxane was added 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.51 g, 6.76 mmol), tetrakis(triphenylphosphine)palladium(0) (0.260 g, 0.225 mmol), and aqueous sodium carbonate (2M, 50 mL, 100 mmol). The reaction mixture was sparged with N_2 and stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water. The solution was extracted with MTBE, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.37 g, 1.10 mmol, 24.5 % yield). MS (apci) m/z = 336.1 (M+H).

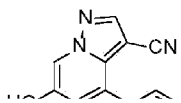
Intermediate P86

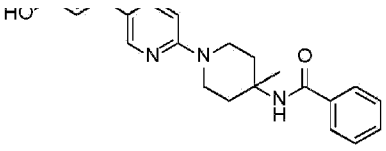


3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide

[0384] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate** P67, 0.253 g, 0.600 mmol) in DCM (3 mL) was added 3-chloro-5-fluoropicolinic acid (0.232 g, 1.32 mmol), HATU (0.502 g, 1.32 mmol), and DIEA (0.524 mL, 3.00 mmol). The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with DCM and washed with aqueous citric acid (adjusted to pH 5). The aqueous mixture was extracted with DCM, and the combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was taken up in THF and 2M NaOH and stirred at rt for 5 min. The mixture was diluted with DCM, washed with aqueous citric acid (adjusted to pH 5), and extracted with 4:1 DCM/IPA. The combined organic extracts were washed with saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (0.325 g, 0.578 mmol, 96.3 % yield). MS (apci) m/z = 506.2 (M+H).

Intermediate P87

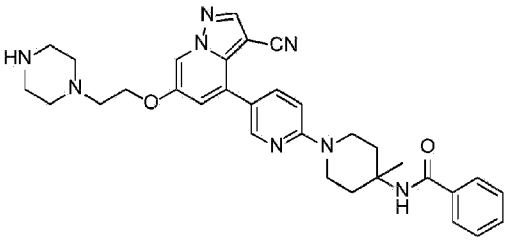




N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0385] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate** P67, 255.4 mg, 0.606 mmol) in DCM (6 mL) was added benzoic acid (185.072 mg, 1.51545 mmol), HATU (576.228 mg, 1.515 mmol), and DIEA (1.056 mL, 6.06 mmol). The reaction mixture was stirred at rt for 16 h then concentrated *in vacuo.* The residue was taken up in THF and treated with 2M $KOH_{(aq)}$. The mixture was stirred at rt for 1 h then adjusted to pH 4 by addition of 2M HCl. The mixture was diluted with water and extracted with 4:1 DCM/IPA. The combined organic extracts were washed with water then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were washed with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM/IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (172.5 mg, 0.381 mmol, 62.9% yield). MS (apci) m/z = 453.2 (M+H).

Intermediate P88



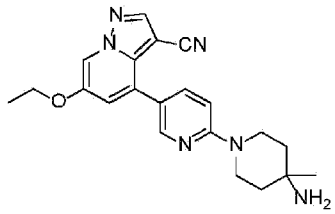
N-(1-(5 -(3 -cyano-6-(2-(piperazin-1 -yl)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0386] Step 1: Preparation of tert-butyl 4-(2-((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide **(Intermediate** P87, 157.2 mg, 0.3474 mmol) in DMA (3.5 mL) was added tert-Butyl 4-(2-chloroethyl)tetrahydro-1(2H)-pyrazinecarboxylate (172.8 mg, 0.6948 mmol) and cesium carbonate (565.9 mg, 1.737 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 231 mg, 0.3474 mmol) in sufficient purity for step 2. MS (apci) m/z = 665.4 (M+H).

[0387] Step 2: Preparation of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-

yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide. A solution of tert-butyl 4-(2-((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate in DCM (1.75 mL) was treated with TFA (1.75 mL, 22.9 mmol). The reaction mixture was stirred at rt for 30 min then concentrated *in vacuo.* The residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water (+ 0.1% TFA) as the gradient eluent). The fractions containing the desired product were washed with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM/IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (111.8 mg, 0.1980 mmol, 56.99% yield over two steps). MS (apci) m/z = 565.3 (M+H).

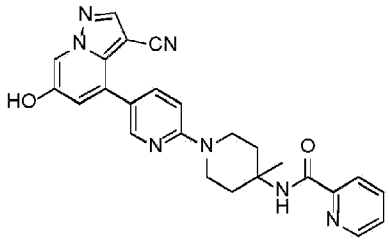
Intermediate P89



4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0388] A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Example 469**, 100 mg, 0.210 mmol) in DCM (2 mL) was treated with TFA (2 mL). The reaction mixture was stirred at rt for 1 h. The crude reaction mixture was directly purified by silica chromatography (5-50% [MeOH + 2% NH_4OH] in DCM as the gradient eluent) to afford the title compound (20 mg, 0.0531 mmol, 25.3% yield). MS (apci) m/z = 377.2 (M+H).

Intermediate P90

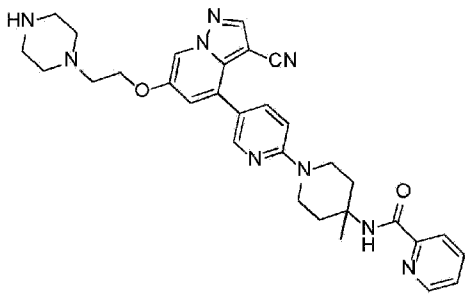


N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0389] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P67**, 1.38 g, 3.2754 mmol) in DCM (6.5507 mL) was added 2-Picolinic acid (1.0081 g, 8.1884 mmol), HATU (3.1135 g, 8.1884 mmol), and DIEA (5.7207 mL, 32.754 mmol). The reaction mixture was stirred at rt for 1 h then concentrated *in vacuo.* The residue was taken up in THF and 2M aqueous KOH and stirred at rt for 30 min. The mixture was adjusted to pH 4 by addition of 1M HCl and extracted with 4:1 DCM/IPA. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water (+ 0.1% TFA) as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic

extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (737 mg, 1.6251 mmol, 49.616% yield). MS (apci) m/z = 454.2 (M+H).

Intermediate P91

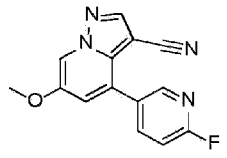


N-(1-(5 -(3 -cyano-6-(2-(piperazin-1 -yl)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0390] Step 1: Preparation of tert-butyl 4-(2-((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Intermediate P90,** 120 mg, 0.265 mmol) in DMA (2.646 mL) was added tert-Butyl 4-(2-chloroethyl)tetrahydro-1(2H)-pyrazinecarboxylate (65.8 mg, 0.265 mmol) and cesium carbonate (431 mg, 1.32 mmol). The reaction mixture was stirred at 60°C for 48 h. After cooling to ambient temperature, the reaction mixture was diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (176 mg, 0.264 mmol, 99.9 % yield) in sufficient purity for step 2. MS (apci) m/z = 666.4 (M+H).

[0391] Step 2: Preparation ofN-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. A solution of tert-butyl 4-(2-((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate (176 mg, 0.264 mmol) in DCM (2.643 mL) was treated with TFA (0.2 mL). The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$, water, and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 150 mg, 0.264 mmol). MS (apci) m/z = 566.4 (M+H).

[00575] Intermediate P93

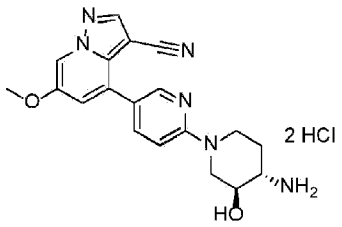


4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0392] In a pressure tube, a mixture of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P1, Step 6**; 1.1854 g, 4.7026 mmol), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)pyridine (1.2587 g, 5.6432 mmol), $Pd(PPh_3)_4$ (0.1087 g, 0.094 mmol) and 2 M $Na_2CO_{3(aq)}$ (15 mL, 30 mmol) in dioxane (15 mL) was sparged with $N_{2(g)}$. The vessel was sealed, and the sparged mixture was stirred for 4 d at 60 °C. After cooling to ambient temperature, the reaction mixture was quenched with water. The resultant precipitate was filtered, washed with water, and then purified by silica chromatography (0-25% MeOH in DCM) to afford the title compound (734.6 mg, 58% yield). MS (apci), m/z = 269.1 (M+H).

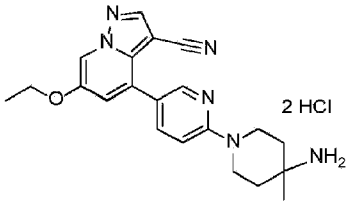
[00578] Intermediate P94



4-(6-((3S,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0393] A solution of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate (**Example 514**, 274.5 mg, 0.5909 mmol) in dioxane (3 mL) was treated with 37% HCl (97 µL, 1.18 mmol), then stirred overnight at ambient temperature. The resulting mixture was concentrated *in vacuo* to afford the title compound (258 mg, 100% yield). MS (apci) m/z = 365.2 (M+H).

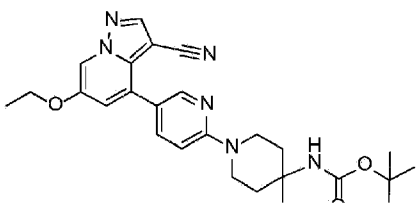
Intermediate P95

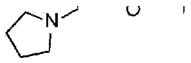


4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0394] A stirring, ambient temperature, solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Example 469,** 807 mg, 1.69 mmol) in MeOH (3387 µL) was treated dropwise with 12 M $HCl_{(aq)}$ (1.41 mL, 16.9 mmol). The resulting mixture was stirred overnight at ambient temperature. The resulting thick slurry was diluted with MeOH (ca. 1 mL), and vacuum filtered. The solids were rinsed with MeOH (3 × 1 mL) and MTBE (3 × 10 mL), then dried *in vacuo* to afford the title compound (690 mg, 91% yield). MS (apci) m/z = 377.2 (M+H).

Intermediate P96

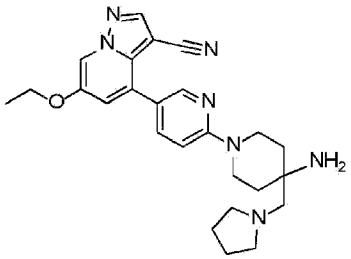




Tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyrrolidin-1-ylmethyl)piperidin-4-yl)carbamate

[0395] Tert-Butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)carbamate **(Intermediate P71,** 100 mg, 0.2038 mmol) was added to solution of pyrrolidine (681 µL, 0.82 mmol) and TEA (142 µL, 1.0 mmol) in DCM (1.0 mL), and the mixture was stirred for 1 h at ambient temperature. Subsequently, $NaBH(AcO)_3$ (86.4 mg, 0.41 mmol) was added, and the resulting mixture was stirred for 2.5 h at ambient temperature then concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN:water with 0.1% TFA). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH, then sequentially extracted with saturated $NaHCO_{3(aq)}$, water and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to cleanly afford the title compound (40 mg, 36% yield). MS (apci) m/z = 546.3 (M+H).

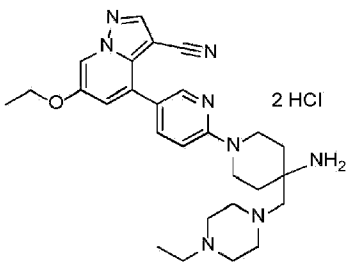
Intermediate P97



4-(6-(4-amino-4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0396] A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyrrolidin-1-ylmethyl)piperidin-4-yl)carbamate **(Intermediate P96;** 40 mg, 0.073 mmol) in DCE (4.7 µL) and TFA (5.6 µE , 0.073 mmol) was stirred for 90 min at ambient temperature. The resulting mixture was diluted with 4:1 DCM:iPrOH, then sequentially extracted with saturated $NaHCO_{3(aq)}$, water and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to cleanly afford the title compound (30 mg, 92% yield). MS (apci) m/z = 446.3 (M+H).

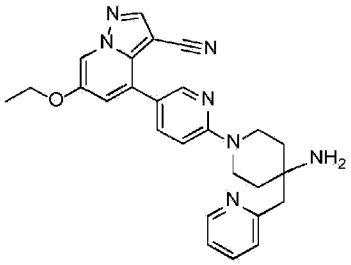
Intermediate P98



4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile dihydrochloride

[0397] A solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)carbamate **(Example 379,** 171.2 mg, 0.2908 mmol) in dioxane (5.0 mL) was treated with 12 M $HCl_{(aq)}$ (23.88 µL, 0.2908 mmol). The resulting mixture was stirred for 45 min at ambient temperature before concentrating the mixture *in vacuo* to cleanly afford the title compound (205.5 mg, quantitative yield). MS (apci) m/z = 489.3 (M+H).

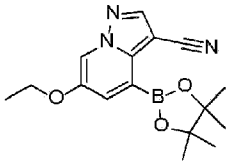
Intermediate P106



4-(6-(4-amino-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5-a]pyridine-3 -carbonitrile

[0398] A solution of 4-(pyridin-2-ylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate) **(Intermediate R41;** 287.5 mg, 0.6856 mmol) in DMF (2 mL) was treated with 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 176 mg, 0.624 mmol), $K_2CO_{3(s)}$ (431 mg, 3.12 mmol) was stirred overnight at 70 °C. The mixture was cooled to ambient temperature, diluted with water (50 mL) and extracted with DCM (3 × 20 mL). The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The crude residue was purified by silica chromatography (0-15% MeOH in DCM) to afford the title compound (73 mg, 26% yield). MS (apci) m/z = 454 (M+H).

Intermediate P110

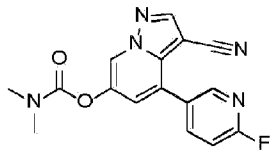


6-ethoxy-4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0399] In a pressure vessel, a solution of 4-bromo-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P5,** 1.37 g, 5.15 mmol) in dioxane (52 mL) was treated with bis(pinacolato)diboron (3.92 g, 15.4 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (0.420 g, 0.515 mmol), and KOAc (1.52 g, 15.4 mmol), then sparged with $Ar_{(g)}$. The vessel was sealed, and the mixture was stirred for 16 h at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, and washed sequentially with water (2x) and brine (1x). The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 5-75% Hexanes-EtOAc as the gradient

eluent) to cleanly afford the title compound (1.31 g, 81% yield). MS (apci) m/z = 314.2 (M+H).

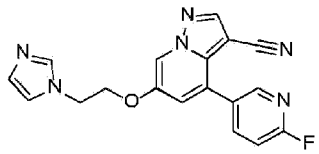
Intermediate P115



3-cyano-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl dimethylcarbamate

[0400] A solution of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P66,** 145.9 mg, 0.5739 mmol) and DIEA (200.5 µL, 1.148 mmol) in DCM (2.0 mL) was treated with dimethylcarbamic chloride (92.57 mg, 0.8609 mmol), then stirred overnight at ambient temperature. The reaction mixture was washed with water. The organic extracts were separated, and purified directly by silica chromatography (using 20-80% Hexanes/ EtOAc as the gradient eluent) to cleanly afford the title compound (158.4 mg, 85% yield). MS (apci) m/z = 326.1 (M+H).

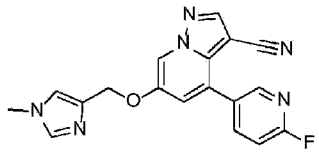
Intermediate P116



6-(2-(1H-imidazol-1-yl)ethoxy)-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0401] A mixture of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P66,** 100.3 mg, 0.3945 mmol), 1-(2-chloroethyl)-1H-imidazole hydrochloride (197.7 mg, 1.184 mmol) and $Cs_2CO_{3(s)}$ (1.285 g, 3.945 mmol) in DMA (2.0 mL) was stirred overnight at 60 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed sequentially with DCM (4x) and 4:1 DCM:iPrOH. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, and filtered. The filtrate was purified directly by silica chromatography (using 0-25% DCM/MeOH with 1% NH_4OH as the gradient eluent) to cleanly afford the title compound (158.4 mg, 85% yield). MS (apci) m/z = 349.10 (M+H).

Intermediate P117

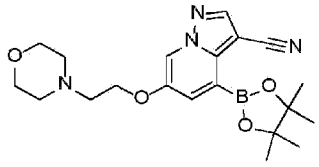


4-(6-fluoropyridin-3-yl)-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridine-3 -carbonitrile

[0402] A mixture of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P66,** 103.6 mg, 0.4075 mmol), 4-(chloromethyl)-1-methyl-1H-imidazole hydrochloride (199.7 mg, 1.196

mmol) and $Cs_2CO_{3(s)}$ (1.328 g, 4.075 mmol) in DMA (2.0 mL) was stirred for 1 d at 60 °C, then for an additional 1 d at 110 °C. After cooling to ambient temperature, the reaction mixture was acidified with 2 M $HCl_{(aq)}$, and purified directly by C18 reverse phase chromatography (using 0-70% water/ACN with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, partially concentrated *in vacuo* to remove the ACN, then partitioned between saturated $NaHCO_{3(aq)}$ and 4:1 DCM:iPrOH. The biphasic mixture was extracted with additional 4:1 DCM:iPrOH (3x). The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (26.0 mg, 18% yield). MS (apci) m/z = 349.10 (M+H).

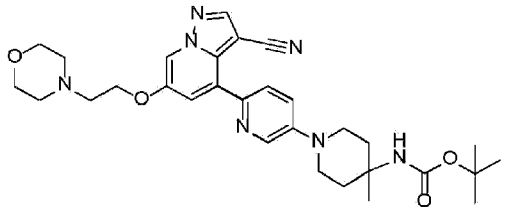
Intermediate P122



6-(2-morpholinoethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile

[0403] In a pressure vessel, a mixture of 4-bromo-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P79, step 1,** 426mg, 1.21mmol), bis(pinacolato)diboron (3.08 g, 12.1 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (89mg, 0.121mmol) and KOAc (595mg, 6.06mmol) in dioxane (10 mL) was sparged with $N_{2(g)}$, for 1 min. The vessel was sealed, and the mixture was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM (15 mL), and filtered through Celite®. The filtrate was concentrated *in vacuo,* and the residue was purified by silica chromatography (using 0-100% Hexanes/Acetone as the gradient eluent) to afford the title compound (185 mg, 38% yield). MS (apci) m/z = 317 (M+H).

Intermediate P123

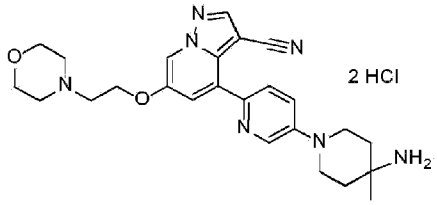


tert-butyl (1-(6-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-3-yl)-4-methylpiperidin-4-yl)carbamate

[0404] In a pressure tube, a suspension of 6-(2-morpholinoethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate** P122; 24 mg, 0.061 mmol) in 3:1 dioxane:water (0.4 mL) was treated with $Cs_2CO_{3(s)}$ (60 mg, 0.18 mmol) and tert-butyl (1-(6-bromopyridin-3-yl)-4-methylpiperidin-4-yl)carbamate (Intermediate **R45;** 25 mg, 0.068 mmol), then sparged with $N_{2(g)}$ for 5 min. The resulting mixture was treated with X-phos (150.9 mg, 0.3165 mmol) and $Pd_2(dba)_3$ (144.9 mg, 0.1582 mmol), then sparged with $N_{2(g)}$. After sealing the vessel, the reaction mixture was stirred for 20 h at 80 °C. After cooling to ambient temperature, the resulting suspension was diluted with water (25

mL) and extracted with DCM (2 × 25 mL). The combined organic extracts were dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-90% Acetone/Hexanes as the gradient eluent) to cleanly afford the title compound (5.4 mg, 16% yield). MS (apci) m/z = 562.3 (M+H).

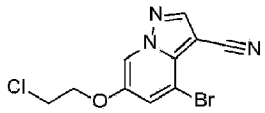
Intermediate P124



4-(5-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0405] A solution of tert-butyl (1-(6-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-3-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate P123;** 5.0 mg, 0.0089 mmol) in DCM (500 µL) was treated with 5-6 N HCl in iPrOH (534 µL, 2.67 mmol), and stirred for 30 min at ambient temperature. The resulting mixture was concentrated *in vacuo,* azeotroping with Et_2O, and then dried under high vacuum to afford the title compound (4.8 mg, quantitative yield). MS (apci) m/z = 462.3 (M+H).

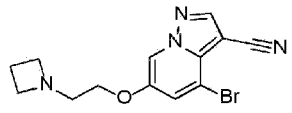
Intermediate P125



4-bromo-6-(2-chloroethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0406] A mixture of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate** P1, 574 mg, 2.41 mmol) in DMF (2.41 mL) was treated sequentially with anhydrous $K_2CO_{3(s)}$ (1.67 g, 12.1 mmol) and 1-chloro-2-iodoethane (221 µL, 2.41 mmol), then stirred for 48 h at ambient temperature. Subsequently, additional 1-chloro-2-iodoethane (221 µL, 2.41 mmol) was introduced, and the mixture was stirred for an additional 60 h at ambient temperature. The reaction mixture was partitioned between DCM and water. The resulting emulsion was filtered, and the biphasic filtrate was separated. After back extracting the aqueous extracts with 4:1 DCM:iPrOH (3x), all organic extracts were combined, dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-100% EtOAc/Hexanes as the gradient eluent) to cleanly afford the title compound (331 mg, 46% yield). ^1H NMR ($CDCl_3$) δ 8.19 (s, 1H), 8.11 (d, 1H), 7.47 (d, 1H), 4.24 (t, 2H), 3.84 (t, 2H).

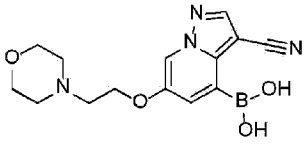
[00620] **Intermediate P126**



6-(2-(azetidin-1-yl)ethoxy)-4-bromopyrazolo[1,5-a]pyridine-3-carbonitrile

[0407] A solution of 4-bromo-6-(2-chloroethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P125**; 77 mg, 0.256 mmol) in DMF (256 µL) was treated sequentially with DIEA (447 µl, 2.56 mmol) and azetidine (43.9 mg, 0.769 mmol). The resulting mixture was stirred overnight at 60 °C. After cooling to ambient temperature, the reaction mixture was diluted with water, and the resultant suspension was filtered. The solids were collected, and dried under high vacuum to cleanly afford the title compound (42 mg, 51% yield). MS (apci) m/z = 321 (M+H).

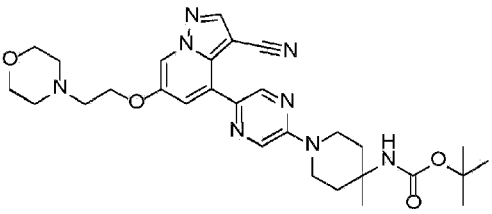
[00623] **Intermediate P127**



(3 -cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)boronic acid

[0408] In a pressure vessel, a mixture of 4-bromo-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P79, step 1,** 200 mg, 0.3360 mmol), bis(pinacolato)diboron (1.446 g, 5.694 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (46.4 mg, 0.0570 mmol) and KOAc (167.7 mg, 1.709 mmol) in dioxane (3.36 mL) was sparged with $Ar_{(g)}$, for 10 min. The vessel was sealed, and the mixture was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM, and filtered through GF/F paper. The filtrate was concentrated *in vacuo,* and the residue was purified by silica chromatography (using 0-20% MeOH in DCM with 2% NH_4OH as the gradient eluent). The purified residue was dissolved in DCM (2 mL) and triturated with Et_2O (5 mL). The resulting suspension was filtered, and the solids were isolated to afford the title compound (60 mg, 56% yield). MS (apci) m/z = 317.1 (M+H).

Intermediate P128

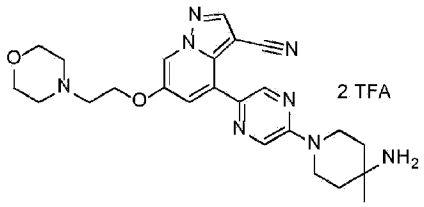


tert-butyl (1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate

[0409] In a pressure tube, a mixture of (3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)boronic acid **(Intermediate P127;** 215 mg, 0.680 mmol), tert-butyl (1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate R46;** 37.6 mg, 0.0991 mmol), X-phos (64.8 mg, 0.136mmol) and $Pd_2(dba)_3$ (31.1 mg, 0.0340 mmol) in dioxane (3.40 mL) was treated with 2 M $K_3PO_{4(aq)}$ (1.02 mL, 2.04 mmol). The mixture was sparged with $Ar_{(g)}$ for 10 min, and then the vessel was sealed. The reaction mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and extracted sequentially with water and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by

silica chromatography (using 0-100% EtOAc/Hexanes followed by 0-10% MeOH in DCM with 0.1% NH_4OH as the gradient eluent) to cleanly afford the title compound (102 mg, 27% yield). MS (apci) m/z = 563.3 (M+H).

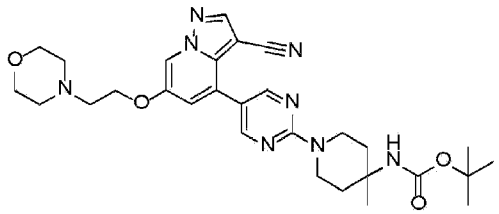
Intermediate P129



4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0410] A solution tert-butyl (1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate** P128; 102 mg, 0.181 mmol) in DCM (1 mL) and TFA (1.4 mL, 18.1 mmol) was stirred for 2.5 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was diluted with DCM, then triturated with Et_2O, and concentrated *in vacuo* (repeat trituration 3x). The solid residue was dried under high vacuum to afford the title compound (125 mg, 100% yield). MS (apci) m/z = 463.3 (M+H).

Intermediate P130



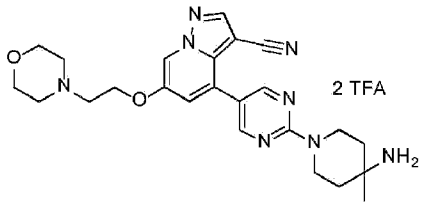
tert-butyl (1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5 -a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)carbamate

[0411] Step 1: Preparation of (2-(4-((tert-butoxycarbonyl)amino)-4-methylpiperidin-1-yl)pyrimidin-5-yl)boronic acid. In a pressure vessel, a mixture of tert-butyl (4-methylpiperidin-4-yl)carbamate (0.23 g, 1.1 mmol), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (0.2 g, 0.89 mmol) and $K_2CO_{3(s)}$ (0.62 g, 4.5 mmol) was combined in dioxane (8.9 mL), and the vessel was sealed. The reaction mixture was stirred overnight at 60 °C. After cooling to ambient temperature, the reaction mixture was directly used for the next step assuming quantitative yield. MS (apci) m/z = 337.2 (M+H).

[0412] Step 2: Preparation of tert-butyl (1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)carbamate. In a sealed vessel, a solution of (2-(4-((tert-butoxycarbonyl)amino)-4-methylpiperidin-1-yl)pyrimidin-5-yl)boronic acid (300 mg, 0.892 mmol) and $K_2CO_{3(s)}$ (617 mg, 4.46 mmol) in dioxane (8.92 mL) was treated with water (0.892 mL), 4-bromo-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P79**, **step 1,** 313 mg, 0.892 mmol) and $Pd(PPh_3)_4$ (103 mg, 0.0892 mmol), then sparged with $Ar_{(g)}$. After sealing the vessel, the reaction mixture was stirred for 16 h at 80 °C. After cooling to ambient temperature, the reaction mixture was

diluted with EtOAc, and washed with brine (3x). The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-20% MeOH in EtOAc as the gradient eluent) to cleanly afford the title compound (243 mg, 36% yield). MS (apci) m/z = 563.4 (M+H).

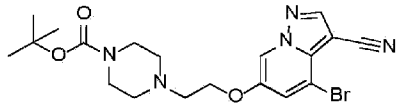
Intermediate P131



4-(2-(4-amino-4-methylpiperidin-1-yl)pyrimidin-5-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0413] A solution tert-butyl (1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate P130**; 91 mg, 0.147 mmol in DCM (2 mL) and TFA (2 mL, 26 mmol) was stirred overnight at ambient temperature, then treated with additional TFA (2 mL). The reaction mixture was stirred for 4 h at 40 °C, and 60 h at ambient temperature before concentrating *in vacuo.* The residue was dried under high vacuum for 3 h to afford the title compound (101.52 mg, quantitative yield). MS (apci) m/z = 463.3 (M+H).

Intermediate P132

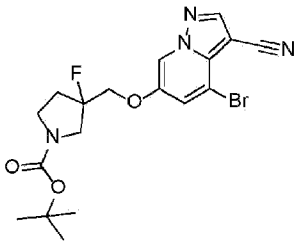
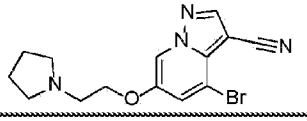
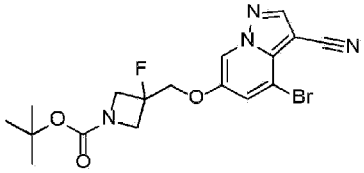
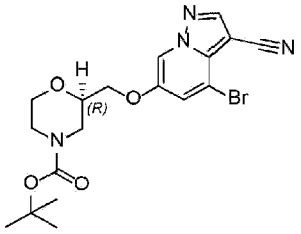
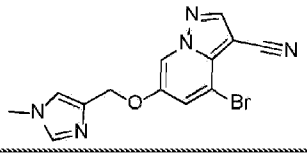
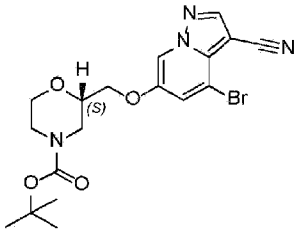
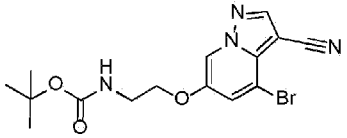


tert-butyl 4-(2-((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate

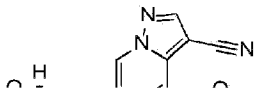
[0414] A mixture of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1,** 200 mg, 0.840 mmol) in DMA (4.20 mL) was treated sequentially with $K_2CO_{3(s)}$ (348 mg, 12.1 mmol) and tert-butyl 4-(2-bromoethyl)piperazine-1-carboxylate (493 mg, 1.68 mmol), then stirred for 3 h at 60 °C. After cooling to ambient temperature, the mixture was diluted with brine. The resulting suspension was filtered, and the solids were rinsed with water (5x). The solids the were collected, dissolved in DCM and concentrated in vacuo to cleanly afford the title compound (239 mg, 63% yield). MS (apci) m/z = 452.0 (M+H).

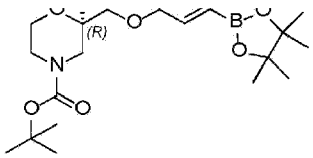
[0415] The compounds in Table **bbb** were prepared using a similar procedure to that used for the synthesis of tert-butyl 4-(2-((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate **(Intermediate P132)** replacing tert-butyl 4-(2-bromoethyl)piperazine-1-carboxylate with (1.0 - 2.0 equivalents) of the appropriate alkyl halide (or alkyl halide salt). Reactions were conducted between 50-60 °C, and monitored for completion by LCMS, and reaction durations were adjusted accordingly. Where noted (*) an additional work up step was required, involving an aqueous work up of the filtrate (or the reaction mixture) using DCM, water and brine, followed by a chromatographic purification of the organics from the extraction using an appropriate gradient eluent.

Table bbb

Intermediate #	Structure	Chemical Name	Analytical
P133		tert-butyl 3-(((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoropyrrolidine-1-carboxylate	^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.14 (d, 1H), 7.49 (br m, 1H), 4.19 m, 2H), 3.46-3.82 (m, 6H), 2.28 (m, 1H), 2.09 (m, 1H) 1.46 (s, 12H).
P134		4-bromo-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridine-3 -carbonitrile	MS (apci) m/z 337 (M+2, with Br pattern)
P135*		tert-butyl 3-(((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate	^{1}H NMR ($CDCl_3$) δ 8.83 (d, 1H), 8.67 (s, 1H), 7.91 (d, 1H), 4.49-4.55 (d, 2H), 3.91-4.15 (m, 4H), 1.39 (s, 9H)
P136*		tert-butyl (R)-2-(((4-bromo-3-cyanopyrazolo [1,5-a]pyridin-6-yl)oxy)methy l)morpholine-4-carboxylate	^{1}H NMR ($CDCl_3$) 8.21 (s, 1H), 8.17(d, 1H), 7.50(d, 1H), 3.78-4.42(m, 9H), 1.48(s, 9H)
P137*		4-bromo-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	MS (apci) m/z 334 (M+2, with Br pattern)
P138*		tert-butyl (S)-2-(((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate	^{1}H NMR ($CDCl_3$)8.23 (d, 1H), 8.21 (s, 1H), 7.51 (d, 1H), 3.52-4.14 (m, 9H), 1.48 (s, 9H)
P139*		tert-butyl (2-((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate	^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H), 8.10 (d, 1H), 7.43 (d, 1H), 4.91 (s, 1H), 4.03 (t, 2H), 3.56 (t, 2H), 1.44 (s, 9H)

Intermediate P140



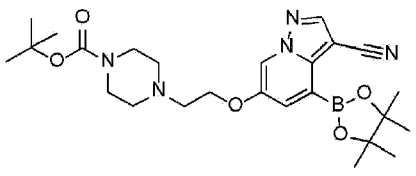


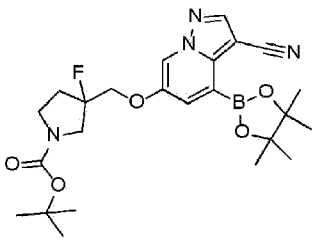
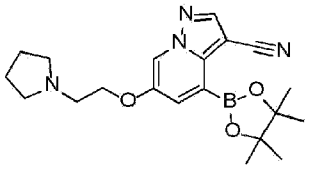
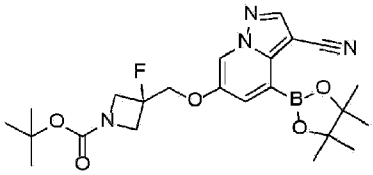
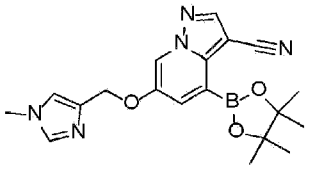
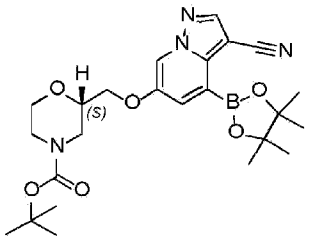
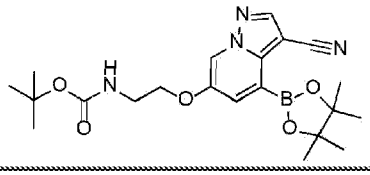
tert-butyl (R)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[0416] In a pressure vessel, a mixture of tert-butyl (R)-2-(((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P136**; 367 mg, 0.839 mmol), bis(pinacolato)diboron (2.131 g, 8.39 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (68.4 mg, 0.0839 mmol) and KOAc (412 mg, 4.20 mmol) in dioxane (8.393 mL) was sparged with $Ar_{(g)}$, for 10 min. The vessel was sealed, and the mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, and filtered through GF/F paper. The filtrate was concentrated *in vacuo,* and the residue was triturated with pentane. The pentane suspension was filtered, and the solids were isolated to afford the title compound (304 mg, 75% yield). ^{1}HNMR ($CDCl_3$) δ 8.19 (s, 1H), 7.70 (s,1H), 7.25 (s, 1H), 3.80-4.12 (m, 6H), 3.52-3.75 (m, 3H), 1.57 (s, 9H), 1.49 (s, 12H).

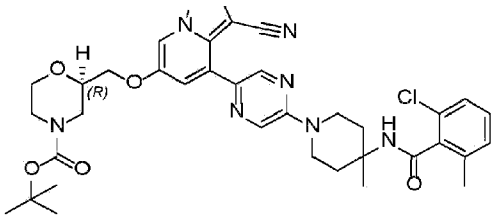
[0417] The compounds in Table ccc were prepared using a similar procedure to that used for the synthesis of tert-butyl (R)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate P140)** replacing tert-butyl (R)-2-(((4-bromo-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate P136)** with the appropriate 4-bromo-6-alkoxypyrazolo[1,5-a]pyridine-3-carbonitrile from **Table bbb** (or the synthetic intermediate referenced therein). Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Work ups were conducted with either DCM or EtOAc, and where noted (*) either a second trituration from pentane or a chromatographic purification using an appropriate gradient eluent (in place of the trituration) was required.

Table ccc

Intermediate #	Structure	Chemical Name	Analytical
P141*		tert-butyl 4-(2-((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate	MS (apci) m/z 416.2 (M-Pinacol) ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H), 8.16 (d, 1H), 7.65 (d, 1H), 4.10 (t, 2H), 3.45 (t, 4H), 2.83 (t, 2H), 2.51 (t, 4H) 1.45 (s, 9H), 1.41 (s, 12H).

Intermediate #	Structure	Chemical Name	Analytical
P142		tert-butyl 3-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoropyrrolidine-1-carboxylate	^{1}H NMR ($CDCl_3$) δ 8.20 (m, 2H), 7.67 (s, 1H), 4.17 (m, 2H), 3.49-3.84 (m, 5H), 2.00-2.35 (m, 3H), 1.45 (s, 9H), 1.42 (s, 12H).
P143*		6-(2-(pyrrolidin-1-yl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	MS (apci) m/z 301.1 (M-Pinacol)
P144		tert-butyl 3-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate	^{1}H NMR ($CDCl_3$) δ 8.21 (d, 1H), 8.19 (s, 1H), 7.69 (d, 1H), 4.11-4.39 (m, 6H), 1.45 (s, 9H), 1.41 (s, 12H)
P145		6-((1-methyl-1H-imidazol-4-yl)methoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.18 (d, 1H), 7.45 (d, 1H), 7.01 (d, 1H), 6.97 (s, 1H), 5.05 (s, 2H), 3.71 (s, 3H), 1.26 (s, 12H)
P146		tert-butyl (S)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate	^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1H), 7.69 (s, 1H), 7.26 (d, 1H), 3.54- 4.25 (m, 9H), 1.48 (s, 9H), !.42 (s, 12H)
P147		tert-butyl (2-((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate	MS (apci) m/z 347.1 (M-pinacol)

Intermediate P148

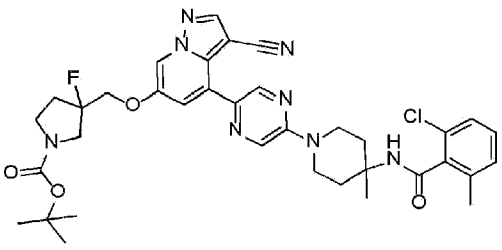
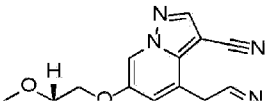


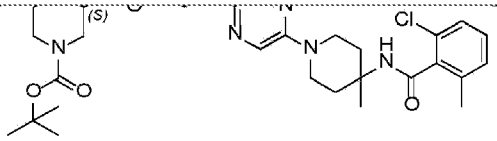
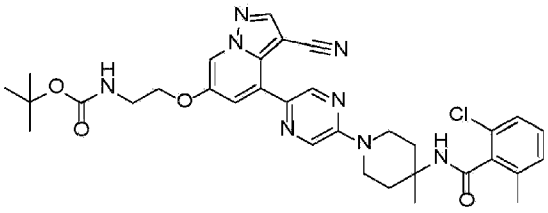
Tert-butyl (R)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[0418] In a pressure tube, a mixture of tert-butyl (R)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P140**; 96 mg, 0.198 mmol), 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide (**Intermediate R48**; 37.6 mg, 0.0991 mmol), 2 M $K_3PO_{4(aq)}$ (149 µL, 0.297 mmol), X-phos (9.45 mg, 0.0198 mmol) and $Pd_2(dba)_3$ (4.54 mg, 0.00495 mmol) in dioxane (1.0 mL) was sparged with $Ar_{(g)}$ for 10 min, and then the vessel was sealed. The reaction mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM, and extracted sequentially with water (3x) and brine (1x). The organic extracts were concentrated *in vacuo*, and purified by silica chromatography (using 0-100% EtOAc/Hexanes as the gradient eluent) to cleanly afford the title compound (40.3 mg, 58% yield). MS (apci) m/z = 701.2 (M+H).

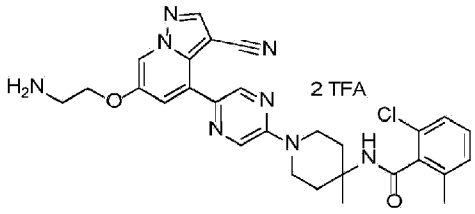
[0419] The compounds in Table **ddd** were prepared using a similar procedure to that used for the synthesis of tert-butyl (R)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P148**) replacing of tert-butyl (R)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate P140)** with the appropriate boronate ester from **Table ccc** (or the synthetic intermediate referenced therein). Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. The title compounds were isolated following a chromatographic purification using an appropriate eluent.

Table ddd

Intermediate #	Structure	Chemical Name	MS (apci) m/z
P149		tert-butyl 3-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoropyrrolidine-1-carboxylate	703.2 (M+H)
P150		tert-butyl (S)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)	701.2 (M+H)

Intermediate #	Structure	Chemical Name	MS (apci) m/z
		-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate	
P151		tert-butyl (2-((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate	645.2 (M+H)

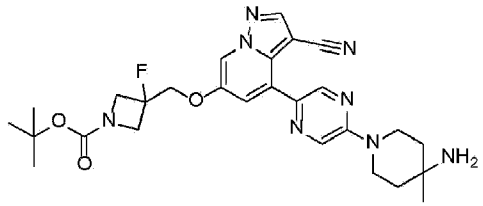
Intermediate P152



N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2-chloro-6-methylbenzamide bis(2,2,2-trifluoroacetate)

[0420] A solution tert-butyl (2-((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate (**Intermediate P151**; 134 mg, 0.208 mmol) in DCM (1 mL) and TFA (0.5 mL, 6.53 mmol) was stirred overnight at ambient temperature. The reaction mixture was concentrated *in vacuo* to afford the title compound (161 mg, quantitative yield). MS (apci) m/z = 545.2 (M+H).

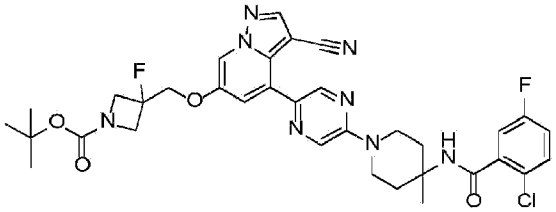
Intermediate P153



Tert-butyl 3 -(((4-(5 -(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3 - cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate

[0421] In a pressure tube, a mixture of tert-butyl 3-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (**Intermediate P144;** 155 mg, 0.328 mmol), 1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-amine bis(2,2,2-trifluoroacetate) (**Intermediate R47**; 149 mg, 0.328 mmol), was treated with 2 M $K_3PO_{4(q)}$ (492 µL, 0.984 mmol), X-phos (31.3 mg, 0.0656 mmol) and $Pd_2(dba)_3$ (15.0 mg, 0.0164 mmol) in dioxane (1.64 mL) was sparged with $Ar_{(g)}$ for 3 min, and then the vessel was sealed. The reaction mixture was stirred for 4 h at 80 °C. After cooling to ambient temperature, the reaction mixture was purified directly, first by silica chromatography (using 0-30% MeOH in DCM as the gradient eluent) then by C18 reverse phase chromatography (using 5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the TFA salt of the title compound. The TFA salt was diluted with DCM, then extracted with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to cleanly afford the title compound (27 mg, 15% yield). MS (apci) m/z = 473.2 (M+H).

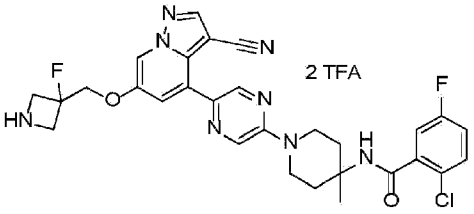
Intermediate P154



Tert-butyl 3-(((4-(5-(4-(2-chloro-5-fluorobenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate

[0422] A solution of 2-chloro-5-fluorobenzoic acid (5.9 mg, 0.034 mmol), tert-butyl 3-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate **(Intermediate P153;** 6 mg, 0.011 mmol), DIEA (20 µL, 0.11 mmol) and HATU (8.5 mg, 0.022 mmol) in DCM (112 µL) was stirred overnight at ambient temperature. The resulting mixture was purified directly by silica chromatography (using 0-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (3 mg, 39% yield). MS (apci) m/z = 693.2 (M+H).

Intermediate P157

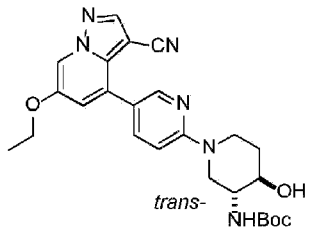


2-chloro-N-(1 -(5 -(3 -cyano-6-((3 -fluoroazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide bis(2,2,2-trifluoroacetate)

[0423] A solution tert-butyl 3-(((4-(5-(4-(2-chloro-5-fluorobenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate **(Intermediate P154;** 19 mg, 0.027 mmol) in DCM (2 mL) and TFA (2 mL, 13 mmol) was stirred for 2 h at ambient temperature.

The reaction mixture was concentrated in vacuo to afford the title compound (16 mg, 73% yield). MS (apci) m/z = 593.2 (M+H).

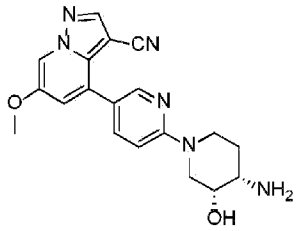
Intermediate P158



tert-butyl ((3r,4r)-1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypiperidin-3-yl)carbamate

[0424] A mixture of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.204 g, 0.723 mmol), tert-butyl ((3r,4r)-4-hydroxypiperidin-3-yl)carbamate (0.313 g, 1.45 mmol) and DIEA (0.378 ml, 2.17 mmol) in DMSO (1.81 mL) was heated at 90 °C overnight. After cooling to RT, the reaction mixture was partitioned between EtOAc and water. After phase-separation, the aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried with Na_2SO_4 and concentrated to yield the title product (0.33 g, 0.69 mmol, 95 % yield). MS (apci) m/z = 479.2 (M+H).

Intermediate P159



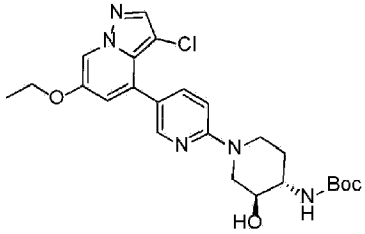
4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3 -carbonitrile

[0425] Step 1: Preparation of tert-butyl ((3R,4S)-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate. A mixture of 4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P93**, 0.206 g, 0.768 mmol), tert-butyl ((3R,4S)-3-hydroxypiperidin-4-yl)carbamate (0.216 g, 0.998 mmol) and DIEA (0.669 mL, 3.84 mmol) in DMSO (1.92 mL) was heated to 90 °C overnight. The reaction mixture was worked up with EtOAc and water. The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated. The crude material was purified by silica chromatography (1-10% MeOH in DCM) to yield the title product (0.223 g, 62.5 % yield). MS (apci) m/z = 465.2 (M+H).

[0426] Step 2: Preparation of 4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile. Tert-butyl ((3R,4S)-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate (0.223 g, 0.480 mmol) was taken up in DCM and TFA (1 mL each) and stirred for 1 h. The mixture was concentrated, taken up in DCM and stirred with MP-carbonate for 20 min. The mixture was filtered and concentrated to give the title product (0.055 g,

31.4 % yield). MS (apci) m/z = 365.1 (M+H).

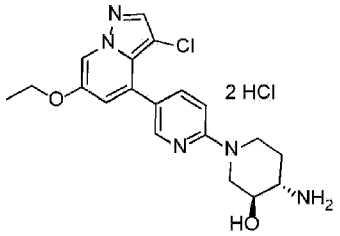
Intermediate P160



tert-butyl ((3S,4S)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate

[0427] A solution of 3-chloro-6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine (**Example 425, Step 2**; 93.1 mg, 0.319 mmol) and tert-butyl ((3S,4S)-3-hydroxypiperidin-4-yl)carbamate (104 mg, 0.479 mmol) in DMSO (2 mL) was treated with DIEA (0.279 mL, 1.60 mmol) and stirred at 115°C overnight. After cooling to RT, the reaction mixture was diluted with water and filtered, yielding the title compound (112 mg, 72 % yield). MS (apci) m/z = 488.2 (M+H).

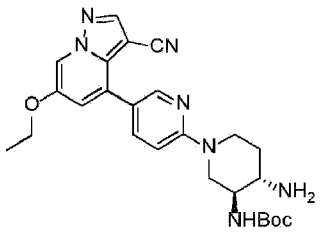
Intermediate P161



(3 S,4S)-4-amino-1-(5-(3-chloro-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)piperidin-3-ol dihydrochloride

[0428] A solution of tert-butyl ((3S,4S)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate **(Intermediate P160,** 110 mg, 0.225 mmol) in 1,4-dioxane (2 mL, 0.225 mmol) was treated with HCl (0.0370 mL, 0.451 mmol) and stirred at RT overnight. Removal of solvent under vacuum yielded the title compound as solid assuming quantitative yield. MS (apci) m/z = 388.2 (M+H).

Intermediate P162



tert-butyl ((3S,4S)-4-amino-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate

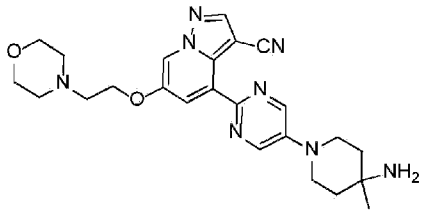
[0429] Step 1: Preparation of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypiperidin-3-yl)carbamate. A mixture of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P6**, 0.270 g, 0.957 mmol), tert-butyl ((3S,4R)-4-hydroxypiperidin-3-yl)carbamate (0.414 g, 1.91 mmol) and Hunig's base (0.500 ml, 2.87 mmol) in DMSO (2.39 mL) was heated to 90 °C overnight. The reaction mixture was worked up with EtOAc and water. The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated to yield the title compound (0.291 g, 63.6 % yield). MS (apci) m/z = 479.2 (M+H).

[0430] Step 2: Preparation of (3S,4R)-3-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl methanesulfonate. A mixture of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypiperidin-3-yl)carbamate (0.291 g, 0.608 mmol), methanesulfonyl chloride (0.0471 ml, 0.608 mmol) and Hunig's base (0.159 ml, 0.912 mmol) in DCM (6.08 mL) was stirred at RT overnight. The mixture was the worked up with DCM and water. The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated to yield the title compound (0.293 g, 86.6 % yield). MS (apci) m/z = 557.2 (M+H).

[0431] Step 3: Preparation of tert-butyl ((3S,4S)-4-azido-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate. (3S,4R)-3-((tert-butoxycarbonyl)amino)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl methanesulfonate (0.293 g, 0.526 mmol) and NaN_3 (0.0513 g, 0.790 mmol) in DMF (2.11 mL) was heated to 90 °C overnight. The mixture was worked up with DCM and water. The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated. The crude material was purified by silica chromatography (1-10% MeOH in DCM) to yield the title compound (0.177 g, 66.8 % yield). MS (apci) m/z = 504.2 (M+H).

[0432] Step 4: Preparation of tert-butyl ((3S,4S)-4-amino-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate. Tert-butyl ((3S,4S)-4-azido-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate (0.177 g, 0.351 mmol) and Pd/C (0.00748 g, 0.0703 mmol) in MeOH (3.51 mL) was stirred under H_2 balloon overnight. This was the filtered and concentrated to give the title compound (0.152 g, 90.6 % yield). MS (apci) m/z = 478.2 (M+H).

Intermediate P163



4-(5-(4-amino-4-methylpiperidin-1-yl)pyrimidin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

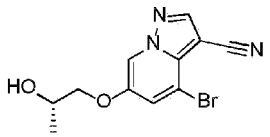
[0433] Step 1: Preparation of 4-(5-bromopyrimidin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of (3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)boronic acid (**Intermediate P127,** 86 mg, 0.27 mmol) and 5-bromo-2-iodopyrimidine (78 mg, 0.27 mmol) in dioxane (2 mL) and water (0.8 mL) was added XPhos (26 mg, 0.054mmol), $Pd_2(dba)_3$ (12mg, 0.014mmol) and 2M

K_3PO_4 (0.4 mL, 0.8 mmol). The reaction was heated to 60 °C for 3 hours. After cooling to RT, the reaction was partitioned between DCM and water (15 mL each), followed by extracting the aqueous with DCM (2 × 15 mL). The organic extracts were combined and concentrated. The crude material was purified by silica chromatography (0 to 100% acetone in hexanes) to yield the title compound (48 mg, 41%). MS (apci) m/z = 429.1, 431.1 (M+H).

[0434] Step 2: Preparation of tert-butyl (1-(2-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-5-yl)-4-methylpiperidin-4-yl)carbamate. A mixture of 4-(5-bromopyrimidin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (48 mg, 0.11 mmol), tert-butyl (4-methylpiperidin-4-yl)carbamate (36 mg, 0.17 mmol), Cs_2CO_3 (73 mg, 0.22 mmol), XPHOS (11 mg, 0.022 mmol) and Pd_2dba_3 (10 mg, 0.011 mmol) in dioxane (1 mL) was heated at 90 °C overnight. The reaction mixture was diluted with water (25 mL) and extracted with DCM (2 × 25 mL). The combined organic extracts were filtered through a Celite® pad and concentrated under reduced pressure. The crude material was purified by silica chromatography (10-100% acetone in hexanes) to yield the title compound (22 mg, 35%). MS (apci) m/z = 563.3 (M+H).

[0435] Step 3: Preparation of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrimidin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. A mixture of tert-butyl (1-(2-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-5-yl)-4-methylpiperidin-4-yl)carbamate (22 mg, 0.04 mmol) in 1:1 DCM:TFA was stirred at RT for 1 h and then concentrated. The crude material was taken up in minimal amount of MeOH and passed thru a P1-HCO_3 resin plug. Removal of solvent under reduced pressure yielded the title compound with quantitative yield. MS (apci) m/z = 463.2 (M+H).

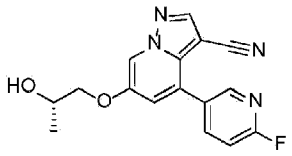
Intermediate P164



(S)-4-bromo-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0436] A mixture of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1;** 500 mg, 2.10 mmol) in DMF (4 mL) was treated sequentially with $K_2CO_{3(s)}$ (1451 mg, 10.5 mmol) and (S)-2-methyloxirane (1830 mg, 31.5 mmol). The reaction mixture was stirred for 3 d at 50 °C in a sealed vessel. After cooling to ambient temperature, the reaction mixture was diluted with water (50 mL) and extracted with DCM (2 × 50 mL). The combined organic extracts were washed with brine (50 mL). The resultant emulsion was filtered through a coarse glass frit, and the biphasic filtrate was separated. The organic extracts were washed again with brine (50 mL), then dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-90% EtOAc/Hexanes as the gradient eluent) to cleanly provide the title compound (357 mg, 57% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.14 (d, 1H), 7.49 (d, 1H), 4.25 (m, 1H), 3.96 (dd, 1H), 3.86 (dd, 1H), 1.33 (d, 3H).

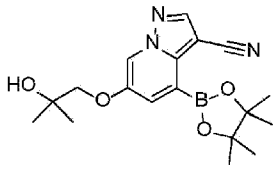
Intermediate P165



(S)-4-(6-fluoropyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3 - carbonitrile

[0437] In a pressure tube, a solution of (S)-4-bromo-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P164;** 357 mg, 1.21 mmol) in dioxane (6 mL) was treated with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (323 mg, 1.45 mmol), and 2 M $Na_2CO_{3(aq)}$ (1808 µL, 3.62 mmol) was sparged with $N_{2(g)}$ for 5 min. The resulting mixture was treated with $Pd(PPh_3)_4$ (34.8 mg, 0.0301 mmol) then sparged again with $N_{2(g)}$ for 5 min, before sealing the vessel. The reaction mixture was stirred for 22 h at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with water (25 mL) and stirred for 1 h. The resulting suspension was vacuum filtered and the solids were collected to cleanly provide the title compound (191 mg, 51% yield). MS (apci) m/z = 313.1 (M+H).

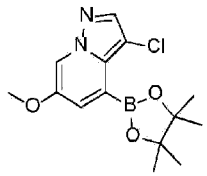
Intermediate P166



6-(2-hydroxy-2-methylpropoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile

[0438] In a pressure vessel, a mixture of 4-bromo-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P41;** 2.0 g, 6.4 mmol), bis(pinacolato)diboron (2.5 g, 9.7 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (0.53 g, 0.64 mmol), and KOAc (1.9 g, 19 mmol) in dioxane (15 mL) was sparged with $Ar_{(g)}$ for 10 min. The vessel was sealed and the mixture was stirred overnight at 90 °C. After cooling to room temperature, the reaction mixture was diluted with EtOAc (100 mL). The resulting suspension was filtered, and the filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo,* and the residue was purified by silica chromatography (25% EtOAc in Hexanes as the eluent) to afford the title compound (2.2 g, 91% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 8.17 (d, J = 2.3 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H), 3.80 (s, 2H), 1.41 (s, 12H), 1.35 (s, 6H).

Intermediate P167

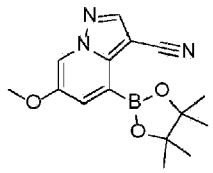


3 -chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine

[0439] A mixture of 4-bromo-3-chloro-6-methoxypyrazolo[1,5-a]pyridine (**Intermediate P84, Step 1**; 152mg, 0.581mmol), $PdCl_2(dppf)•CH_2Cl_2$ (23.7 mg, 0.029 mmol), KOAc (285 mg, 2.91 mmol) and bis(pinacolato)diboron (443 mg, 1.74 mmol) in dioxane (5.8 mL) was sparged with $Ar_{(g)}$. The reaction

vessel was sealed, and the mixture was stirred for 2 h 15 min at 90 °C. After cooling to ambient temperature, the reaction mixture was filtered through Celite®. The filtrate was concentrated in vacuo to afford the title compound (102 mg, 57%). MS (apci) m/z = 309.1 (M+H).

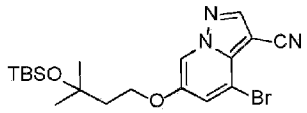
Intermediate P168



6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0440] A mixture of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P1, Step 6;** 150 mg, 0.6 mmol), $PdCl_2$(dppf) (17 mg, 0.02 mmol), KOAc (165 mg, 1.7 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (267 mg, 1.05 mmol) in dioxane (4 mL) was sparged with argon, then heated to 90 °C for 3 h. After cooling to RT, the reaction was filtered through Celite® and concentrated. The crude material was purified by silica chromatography (0-10% MeOH/DCM) to afford the title product (126 mg, 70%).

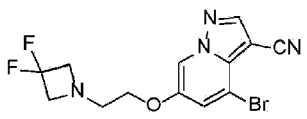
Intermediate P169



4-bromo-6-(3-((tert-butyldimethylsilyl)oxy)-3-methylbutoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0441] To a solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P1;** 194 mg, 0.815 mmol) in DMA (4.0 mL, 0.815 mmol) was added K_2CO_3 (338 mg, 2.44 mmol) then ((4-bromo-2-methylbutan-2-yl)oxy)(tert-butyl)dimethylsilane (459 mg, 1.63 mmol). The reaction was sealed and heated at 60°C overnight. After cooling to RT, the reaction was diluted with brine and filtered, rinsed with water. The solid obtained was dissolved in minimal amount of DCM, followed by addition of Et_2O to induce precipitation. After stirred for 2 h, the suspension was filtered to afford the title product (250 mg, 70%). 1H-NMR (400 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 8.09 (br d,1H), 7.42 (br d, 1H), 4.13 (t, 2H), 1.97 (t, 2H), 1.31 (s, 6H), 0.86 (s, 9H), 0.10 (s, 6H).

Intermediate P170

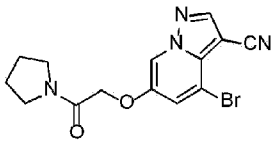


4-bromo-6-(2-(3 ,3-difluoroazetidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0442] To a mixture of 4-bromo-6-(2-chloroethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P125**; 50 mg, 0.17 mmol) in DMF (0.33 mL) were added DIEA (291 µl, 1.7 mmol), followed by 3,3-

difluoroazetidine (46 mg, 0.50 mmol). The reaction was stirred at 60 °C for 4 d, after which additional 3,3-difluoroazetidine (46 mg, 0.50 mmol) was added and heating resumed for another 16 h to reach completion. The reaction was diluted with water and filtered to afford the title product, which was directly used without further purifications (31 mg, 37%). MS (apci) m/z = 357, 359 (M+H).

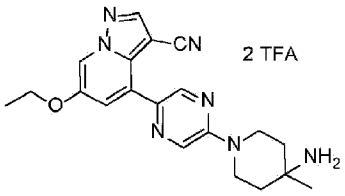
Intermediate P171



4-bromo-6-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0443] To a solution of 4-bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P1;** 100 mg, 0.420 mmol) in DMA (2 mL) were added K_2CO_3 (87.1 mg, 0.63 mmol) then 2-chloro-1-(pyrrolidin-1-yl)ethan-1-one (74.4 mg, 0.504 mmol). The reaction was heated at 50 °C overnight, then poured into water (10 mL) and stirred for 1 h before it was filtered and rinsed with water (5 mL), yielding the title product as beige solid (127 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.19 (d, 1H), 7.50 (d, 1H), 4.66 (s, 2H), 3.54 (t, 2H), 3.47 (t, 2H), 2.04 (m, 2H), 1.90 (m, 2H).

Intermediate P172

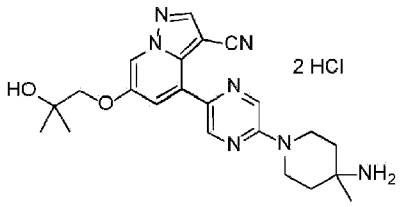


4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[0444] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolor[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate. A mixture of 6-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P110;** 500 mg, 1.60 mmol), tert-butyl (1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate R46;** 521.8 mg, 1.60 mmol), K_3PO_4 (2 M aq, 2.4 mL, 4.79 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (152.2 mg, 0.32 mmol) and $Pd_2(dba)_3$ (73.10 mg, 0.080 mmol) in 1,4-dioxane (8.0 mL) was degassed with argon for 3 min, then sealed and heated to 80°C overnight. After an aqueous workup the crude material was purified using silica chromatography (0-100% EtOAc in hexanes) to afford the title product (338.5 mg, 44%). MS (apci) m/z = 478.2 (M+H).

[0445] Step 2: Preparation of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate). To a solution of tert-butyl (1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate (338.5 mg, 0.71 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (2 mL). After stirred at RT for 1 h, the reaction was diluted with Et_2O (20 mL) and filtered to afford the title product (342 mg, 80%). MS (apci) m/z = 378.1 (M+H).

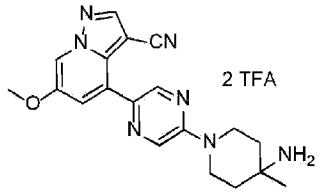
Intermediate P173



4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[0446] The title product was prepared according to the procedure described in **Intermediate P172,** replacing 6-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile with 6-(2-hydroxy-2-methylpropoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P166)** in Step 1. MS (apci) m/z = 422.3 (M+H).

Intermediate P174



4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

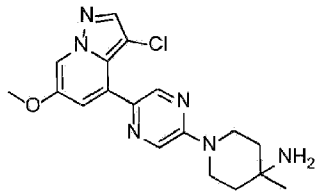
[0447] Step 1: Preparation of tert-butyl (4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)carbamate. In a pressure vessel were combined tert-butyl (1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate R46;** 26 mg, 0.080 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (202 mg, 0.80 mmol), $PdCl_2$(dppf)-DCM (6.5 mg, 0.0080 mmol), KOAc (39 mg, 0.40 mmol) and dioxane (796 µl). The reaction mixture was sparged with argon for 10 min before it was sealed and heated to 90 °C overnight. After cooling to RT, the reaction was partitioned between DCM and water, extracting the aqueous with DCM (3x) after phase-separation. The combined organic extracts were washed with brine, then dried (Na_2SO_4), filtered and concentrated. The crude material was used directly in the next step assuming quantitative yield.

[0448] Step 2: Preparation of tert-butyl (1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate. A mixture of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P1, Step 6;** 300 mg, 1.19 mmol), tert-butyl (4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)carbamate (1158 mg, 1.19 mmol), $Pd(Ph_3P)_4$ (138 mg, 0.119 mmol) and Na_2CO_3 (2 M aq, 3.6 mL, 7.14 mmol) in dioxane (6.0 mL) was sparged with argon for 10 min then heated to 80°C overnight. After cooling to ambient temperature, the reaction was diluted with water (10 mL) and extracted with 4:1 DCM:IPA (5×10 mL). The combined organic extractions was passed through a Phase Separator frit, and the filtrate was concentrated then purified by silica gel chromatography (0-10% MeOH in DCM) to afford the title product as solid (173 mg, 31%). MS (apci) m/z

= 464.2 (M+H).

[0449] Step 3: Preparation of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate). To a solution of tert-butyl (1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate (173 mg, 0.336 mmol) in DCM (2 mL) was added TFA (2 mL). After stirred at RT for 30 min, the reaction was diluted with Et_2O (20 mL) and filtered to yield the title product (163 mg, 78%). MS (apci) m/z = 364.2 (M+H).

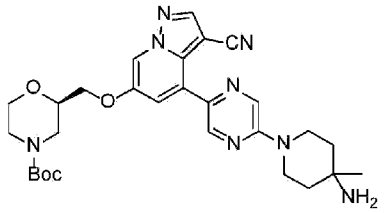
Intermediate P175



1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-amine

[0450] A mixture of 3-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (**P167** 55 mg, 0.18 mmol), 1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-amine (**R47**, 40 mg, 0.18 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (17 mg, 0.036 mmol)), and $Pd_2(dba)_3$ (8.2 mg, 0.0089 mmol) in 1,4-dioxane (891 µL) and K_3PO_4 (2 M aq, 267 µL) was sparged with argon before sealed and heated to 80 °C overnight. After cooling to RT, the reaction was diluted with DCM, washed with water and brine, then dried (Na_2SO_4), filtered and concentrated. The residue was purified using silica chromatography (0-20% MeOH in DCM with 0.2% NH_4OH) to afford the title compound (29 mg, 44%). LCMS m/z = 373.1 (M+H).

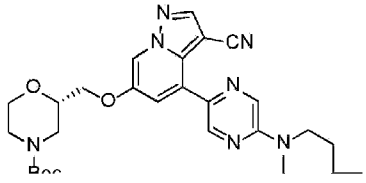
Intermediate P176



tert-butyl (R)-2-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[0451] The title compound (36 mg, 16%) was prepared by a similar method as described in **Intermediate P175**, replacing 3-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine with tert-butyl (R)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5 -a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P140**). LCMS m/z = 549.3 (M+H).

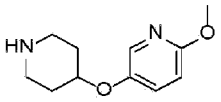
Intermediate P177



tert-butyl (S)-2-(((4-(5 -(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3 - cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[0452] The title compound (36 mg, 16%) was prepared by a similar method as described in **Intermediate P175,** replacing 3-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine with tert-butyl (S)-2-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate P146).** LCMS m/z = 549.3 (M+H).

Intermediate R13

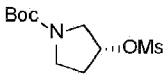


(2-methoxy-5-(piperidin-4-yloxy)pyridine

[0453] Step 1: Preparation of tert-butyl 4-((6-methoxypyridin-3-yl)oxy)piperidine-1-carboxylate. A solution of 6-methoxypyridin-3-ol (100 mg, 0.799 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (161 mg, 0.799 mmol) in THF was treated with PPh_3 (231 mg, 0879 mmol), then sparged with $Ar_{(g)}$ for 5 min. While stirring at ambient temperature, the mixture was treated slowly with DIAD (186 µL, 0.959 mmol). The resulting reaction mixture was stirred for 9 h at ambient temperature, then overnight at 70 °C before introducing additional DIAD (186 µL, 0.959 mmol). The reaction mixture was stirred for 4 h at 70 °C and then allowed to cool to ambient temperature. After concentrating the reaction mixture *in vacuo,* the residue was suspended in DCM and washed with saturated $Na_2CO_{3(aq)}$, water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (246 mg, quantitative yield). MS (apci) m/z = 309.15 (M+H).

[0454] Step 2: Preparation of 2-methoxy-5-(piperidin-4-yloxy)pyridine. A solution of tert-butyl 4-((6-methoxypyridin-3-yl)oxy)piperidine-1-carboxylate (246 mg, 0.80 mmol) in DCM (4.0 mL) was treated with TFA (4.0 mL, 0.80 mmol), then stirred for 5 min at ambient temperature before introducing additional TFA (1 mL). After stirring for 45 min at ambient temperature, the reaction mixture was concentrated *in vacuo.* The crude residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH_4OH as the gradient eluent) to cleanly provide the title compound (127.5 mg, 77% yield). MS (apci) m/z = 209.1 (M+H).

Intermediate R14

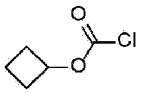


Tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate

[0455] A solution of N-tert-Butoxycarbonyl-(R)-(-)-3-pyrrolidinol (2.0 g, 10.7 mmol) in DCM (28 mL) was treated with TEA (2.9 mL, 21.4 mmol). The solution was cooled to 0°C for 30 minutes. Then

methanesulfonyl chloride (868 µL, 11.2 mmol) was added. The reaction was stirred at 0°C for 30 minutes. The reaction was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (2.83 g, 100% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 5.24 (s, 1H), 3.55-3.38 (m, 3H), 3.31-3.27 (m, 1H), 3.23 (s, 3H), 2.18-2.08 (m, 2H), 1.40 (s, 9H).

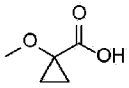
Intermediate R25



cyclobutyl carbonochloridate

[0456] The title compound (93.3 mg, 0.693 mmol, quantitative yield is assumed) was prepared and worked up using a similar procedure to that described for (S)-tetrahydrofuran-3-yl carbonochloridate (**Intermediate** R54), replacing (S)-tetrahydrofuran-3-ol (100 mg, 1.13 mmol) with cyclobutanol (54.3 µl, 0.693 mmol).

Intermediate R26

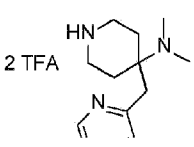


1-methoxycyclopropane-1 -carboxylic acid

[0457] Step 1: Preparation of methyl 1-methoxycyclopropane-1-carboxylate. A solution of 1-hydroxy-1-cyclopropanecarboxylic acid (1.02 g, 9.99 mmol) in DMF (33 mL) was treated sequentially with iodomethane (1.56 mL, 25.0 mmol) and NaH (60 wt.% in mineral oil; 1.00 g, 25.0 mmol), then stirred for 16 h at ambient temperature. The resulting mixture was diluted with water, and then extracted with Et_2O (2x). The combined organic extracts were washed sequentially with water (3x) and brine (1x), and then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound in sufficient purity to carry into step 2 (1.30 g, quantitative yield).

[0458] Step 2: Preparation of 1-methoxycyclopropane-1-carboxylic acid. A solution of crude methyl 1-methoxycyclopropane-1-carboxylate (Step 1; 1.30, 9.99 mmol, assumed) in 1:1 THF:MeOH (60 mL) was treated with 2.0 $MKOH_{(aq)}$. (14.99 mL, 29.97 mmol), then stirred for 60 h at ambient temperature. The resulting mixture was diluted with Et_2O, and extracted with 1.0 M $NaOH_{(aq)}$ (2x). The combined aqueous extracts were acidified to pH ~2 with the addition of 4.0 M $HCl_{(aq)}$, then extracted with DCM (2x). The combined DCM extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (240 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 3.29 (s, 3H), 1.14-1.04 (m, 4H).

Intermediate R29

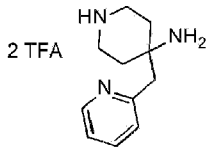


N,N-dimethyl-4-(pyridin-2-ylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate)

[0459] Step 1: Preparation of tert-butyl 4-(dimethylamino)-4-(pyridin-2-ylmethyl)piperidine-1-carboxylate. A solution of tert-Butyl 4-amino-4-(pyridin-2-ylmethyl)piperidine-1-carboxylate (50.2 mg, 0.172 mmol) in DCM (1.15 mL) was treated with formaldehyde (37 wt.% in water with 5-15%MeOH stabilizer; 64.7 µl, 0.861 mmol) and $NaBH(AcO)_3$ (365 mg, 1.72 mmol), and stirred for 1 h at ambient temperature. The reaction mixture was diluted with water and the biphasic mixture was extracted with DCM (3x). The combined organic extracts were washed with brine. After back extracting all aqueous extracts once again with DCM, all DCM extracts were combined and concentrated *in vacuo.* The crude residue was purified by silica chromatography (50-100% EtOAc/Hexanes followed by 0-10% MeOH in EtOAc) to cleanly afford the title compound (55 mg, 100% yield). MS (apci) m/z = 320.2 (M+H).

[0460] Step 2: Preparation of N,N-dimethyl-4-(pyridin-2-ylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate). A mixture of tert-butyl 4-(dimethylamino)-4-(pyridin-2-ylmethyl)piperidine-1-carboxylate (55 mg, 0.172 mmol) in DCM (2 mL) was treated with TFA (1 mL, 6.51 mmol). The resulting mixture was stirred overnight at ambient temperature before concentrating the mixture *in vacuo* to afford the title compound (77.0 mg, quantitative yield). MS (apci) m/z = 220.1 (M+H).

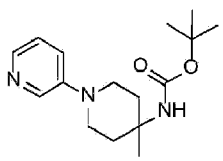
Intermediate R41



4-(pyridin-2-ylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate)

[0461] A mixture of 1 tert-butyl 4-amino-4-(pyridin-2-ylmethyl)piperidine-1-carboxylate (200 mg, 0.686 mmol) in DCM (0.25 mL) was treated with TFA (0.25 mL, 3.27 mmol). The resulting mixture was stirred for 1.75 h at ambient temperature before concentrating the mixture *in vacuo* to afford the title compound (287 mg, 100% yield). MS (apci) m/z = 192.2 (M+H)

Intermediate R44

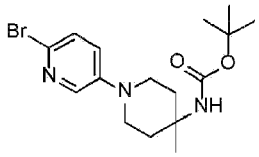


tert-butyl (4-methyl-1-(pyridin-3-yl)piperidin-4-yl)carbamate

[0462] In a pressure tube, a suspension of 3-bromopyridine (304.9 µL, 3.165 mmol), tert-butyl (4-methylpiperidin-4-yl)carbamate (678.2 mg, 3.165 mmol), and $Cs_2CO_{3(s)}$ (2.062 g, 6.329 mmol) in dioxane (15 mL) was sparged with $N_{2(g)}$ for 5 min then treated with X-phos (150.9 mg, 0.3165 mmol) and

$Pd_2(dba)_3$ (144.9 mg, 0.1582 mmol). The resulting mixture was sparged with $N_{2(g)}$. After sealing the vessel, the reaction mixture was stirred for 60 h at 90 °C. After cooling to ambient temperature, the resulting suspension was diluted with water (25 mL) and extracted with DCM (2 x 25 mL). The combined organic extracts were dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by silica chromatography (0-50% acetone/hexanes) to afford the title compound (639.9 mg, 81% yield). MS (apci) m/z = 292.2 (M+H).

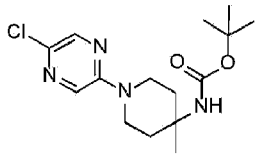
Intermediate R45



tert-butyl (1 -(6-bromopyridin-3 -yl)-4-methylpiperidin-4-yl)carbamate

[0463] A solution of tert-butyl (4-methyl-1-(pyridin-3-yl)piperidin-4-yl)carbamate **(Intermediate R44;** 50 mg, 0.172 mmol) in DCM (0.5 mL) was cooled to 0 °C, then treated with NBS (30.5 mg, 0.172 mmol). The resulting mixture was stirred for 1 h at 0 °C, and then diluted with water. The biphasic mixture was extracted with DCM (2 × 1 mL). The combined organic extracts were partially concentrated then purified directly by silica chromatography (0-90% acetone/hexanes) to afford the title compound (50.2 mg, 79% yield). MS (apci) m/z = 372.2 (M+H).

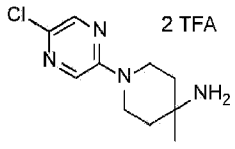
Intermediate R46



tert-butyl (1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate

[0464] In a sealed vessel, a mixture of tert-butyl (4-methylpiperidin-4-yl)carbamate (1.44 g, 6.71 mmol), 2,5-dichloropyrazine (1.00 g, 6.71 mmol) and $K_2CO_{3(s)}$ (4.64 g, 33.6 mmol) in dioxane (67.1 mL) was stirred for 60 h at 60 °C. After cooling to ambient temperature, the resulting suspension was diluted with EtOAc, filtered through Celite ® then concentrated *in vacuo.* The crude residue was purified by silica chromatography (0-100% EtOAc in hexanes) to afford the title compound (657 mg, 30% yield). MS (apci) m/z = 327.1 (M+H).

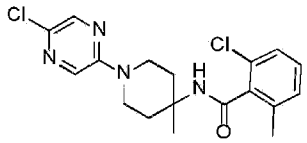
Intermediate R47



1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-amine bis(2,2,2-trifluoroacetate)

[0465] A mixture of tert-butyl (1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate** R46; 500 mg, 1.53 mmol) in DCM (0.5 mL) was treated with TFA (0.25 mL, 3.27 mmol). The resulting mixture was stirred for 2 h at ambient temperature before concentrating the mixture *in vacuo* to afford the title compound (696 mg, quantitative yield). MS (apci) m/z = 227.1 (M+H).

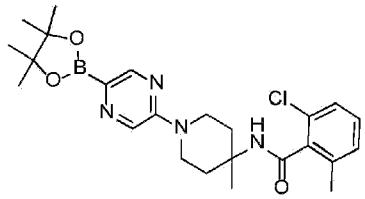
Intermediate R48



2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[0466] A solution of 1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-amine bis(2,2,2-trifluoroacetate) **(Intermediate** R47; 596 mg, 1.31 mmol) in DCM (26 mL) was treated sequentially with 2-chloro-6-methylbenzoic acid (1.345 g, 7.89 mmol), HATU (1.999 g, 5.26 mmol) and DIEA (4.6 mL 26.3 mmol). The resulting mixture was stirred overnight at ambient temperature, before concentrating the mixture *in vacuo.* The crude residue was purified by silica chromatography (0-60% EtOAc in hexanes) to afford the title compound (360 mg, 72% yield). MS (apci) m/z = 379 (M+H).

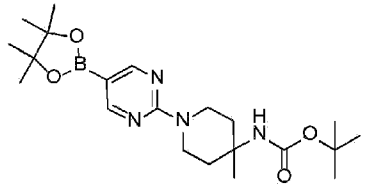
Intermediate R49



2-chloro-6-methyl-N-(4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)benzamide

[0467] In a pressure vessel, a mixture of 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Intermediate R48;** 730 mg, 1.92 mmol), bis(pinacolato)diboron (4.888 g, 19.2 mmol), KOAc (944 mg, 9.62 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (157 mg, 0.192 mmol), in dioxane (19.25 mL) was sparged with $Ar_{(g)}$. The vessel was sealed, and the mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM, and filtered through a GF/F filter. The filtrate was concentrated *in vacuo,* and the residue was triturated with pentane (50 mL). The resulting suspension was sonicated for 4 min, and then filtered. The solids were collected to afford the title compound (980 mg, 54% yield). MS (apci) m/z = 389.1 (M+H).

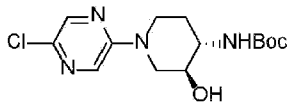
Intermediate R50



tert-butyl (4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)piperidin-4-yl)carbamate

[0468] In a pressure vessel, a mixture of tert-butyl (4-methylpiperidin-4-yl)carbamate (0.23 g, 1.1 mmol), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (0.2 g, 0.89 mmol) and $K_2CO_{3(s)}$ (944 mg, 9.62 mmol) was combined in dioxane (8.9 mL). The vessel was sealed, and the reaction mixture was stirred overnight at 60 °C. After cooling to ambient temperature, the reaction mixture was preserved as a suspension (i.e. without further work up, purification or isolation) containing the title compound (assumed 370 mg, quantitative yield. MS (apci) m/z = 419.3 (M+H).

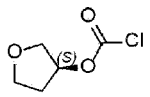
Intermediate R53



Tert-butyl ((3S,4S)-1-(5-chloropyrazin-2-yl)-3-hydroxypiperidin-4-yl)carbamate

[0469] A solution of 2,5-dichloropyrazine (217 mg, 1.46 mmol), tert-butyl ((3S,4S)-3-hydroxypiperidin-4-yl)carbamate (300 mg, 1.387 mmol) and K_2CO_3 (575 mg, 2.25 mmol) in DMSO (2.3 mL) was stirred at 90 °C for 12 h, then at room temperature overnight. The reaction was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic extracts was washed with brine (15 mL), dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The crude was purified by silica chromatography (0-15% MeOH/DCM) followed by reverse phase chromatography (0 to 98% MeCN/water). The fractions containing product were combined, concentrated to remove most ACN, diluted with sat. $NaHCO_3$ (15 mL) and extracted with DCM (3 × 15 mL). The combined organic extracts was washed with brine (15 mL) and dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (180.7 mg, 40% yield). MS (apci) m/z = 329.2 (M+H).

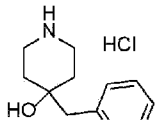
Intermediate R54



(S)-tetrahydrofuran-3-yl carbonochloridate

[0470] A solution of triphosgene (111 mg, 0.375 mmol) in DCM (284 µL) was stirred at 0 °C, while sequentially adding dropwise (S)-tetrahydrofuran-3-ol (100 mg, 1.13 mmol) and a solution of pyridine (91.8 µL, 1.13 mmol) in DCM (0.15 mL). The resulting mixture was stirred for 1.5 h at 0 °C, then for an additional 0.5 h at ambient temperature. The resulting mixture was filtered to remove pyridinium solids. The filtrate containing the title compound in DCM was collected and used as is in subsequent steps assuming quantitative yield.

Intermediate R55

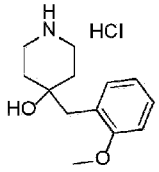


4-(2-fluorobenzyl)piperidin-4-ol hydrochloride

[0471] Step 1: Preparation of tert-butyl 4-(2-fluorobenzyl)-4-hydroxypiperidine-1-carboxylate. To a solution of (2-fluorobenzyl)magnesium chloride (0.5 M in Et_2O, 2.4 mL, 1.227 mmol) cooled to -78 °C was added tert-butyl 4-oxopiperidine-1-carboxylate (203.7 mg, 1.022 mmol) portionwise. The reaction mixture was allowed to gradually warm up to RT and stirred overnight. After removal of solvent under reduced pressure, the residue was taken up in DCM and washed with water and brine. The organic layer was concentrated and the crude material was treated with silica chromatography (0-70% EtOAc in hexanes) to yield the title compound as colorless oil (143.9 mg, 45.5%). MS (apci) m/z = 210.2 (M+H-Boc).

[0472] Step 2: Preparation of 4-(2-fluorobenzyl)piperidin-4-ol hydrochloride. A solution of tert-butyl 4-(2-fluorobenzyl)-4-hydroxypiperidine-1-carboxylate (143.9 mg, 0.4651 mmol) in 1,4-dioxane (0.5 mL) was treated with conc. HCl (0.038 mL, 0.46 mmol) and stirred at RT for 1 h. Removal of solvent under reduced pressure gave the title product as colorless oil (114 mg, 99 % yield). MS (apci) m/z = 210.1 (M+H).

Intermediate R56

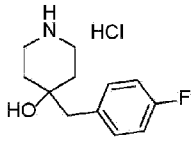


4-(2-methoxybenzyl)piperidin-4-ol hydrochloride

[0473] Step 1: Preparation of tert-butyl 4-hydroxy-4-(2-methoxybenzyl)piperidine-1-carboxylate. To a solution of (2-methoxybenzyl)magnesium chloride (0.25 M in 2-methyltetrahydrofuran, 4.8 mL, 1.2 mmol) cooled to -78 °C was added tert-butyl 4-oxopiperidine-1-carboxylate (207.0 mg, 1.04 mmol) portionwise. The reaction was stirred at - 78°C for 2 h before it was quenched with sat. NH_4Cl (aq.). After phase-separation, the aqueous was extracted with EtOAc (3x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica chromatography (0-70% EtOAc in hexanes) to afford the title compound as a colorless oil (64.1mg, 19 %). MS (apci) m/z = 222.2 (M+H-Boc).

[0474] Step 2: Preparation of 4-(2-methoxybenzyl)piperidin-4-ol hydrochloride. The title product (51 mg, 99%) was prepared according to the procedure described for the preparation of **Intermediate R55,** Step 2. MS (apci) m/z = 222.2 (M+H).

Intermediate R57

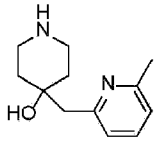


4-(4-fluorobenzyl)piperidin-4-ol hydrochloride

[0475] Step 1: Preparation of tert-butyl 4-(4-fluorobenzyl)-4-hydroxypiperidine-1-carboxylate. To a solution of (4-fluorobenzyl)magnesium chloride (0.5 M in 2-methyltetrahydrofuran, 7.5 mL, 3.75 mmol) cooled to 0°C was added tert-butyl 4-oxopiperidine-1-carboxylate (496.4 mg, 2.49 mmol) portionwise. The mixture was stirred at 0°C for 30 min before it was quenched with sat. NH_4Cl (aq). After phase-separation, the aqueous was extracted with EtOAc (3x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica chromatography (0-70% EtOAc in hexanes) to afford the title compound as a colorless oil (950.5 mg, 73%). MS (apci) m/z = 210.2 (M+H-Boc).

[0476] Step 2: Preparation of 4-(2-methoxybenzyl)piperidin-4-ol hydrochloride. The title product (51 mg, 99%) was prepared according to the procedure described for the preparation of Intermediate R55, Step 2. MS (apci) m/z = 210.1 (M+H).

Intermediate R58

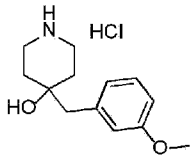


4-((6-methylpyridin-2-yl)methyl)piperidin-4-ol

[0477] Step 1: Preparation of tert-butyl 4-hydroxy-4-((6-methylpyridin-2-yl)methyl)piperidine-1-carboxylate. To a flask that was dried under vacuum with heat was added 2,6-dimethylpyridine (0.06 mL, 0.5 mmol) and dry THF (1.1 mL) under argon. After cooling to -78 °C, n-BuLi (2.5 M in THF, 0.17 mL, 0.43mmol) was introduced. The reaction was allowed to warm up to 0°C, then cooled to -78°C again, and 1-benzylpiperidin-4-one (66 mg, 0.33mmol) was added. The reaction was allowed to slowly warm up to RT and stirred for 3 h before it was partitioned between DCM and water. After phase-separation and extracting the aqueous with DCM (2 x), the organic extracts were combined, dried (Na_2SO_4), filtered and concentrated. The crude was purified by silica chromatography (0-20% MeOH in DCM) to afford the title compound (73 mg, 71%). MS (apci) m/z = 307.2 (M+H).

[0478] Step 2: Preparation of 4-((6-methylpyridin-2-yl)methyl)piperidin-4-ol. A mixture of tert-butyl 4-hydroxy-4-((6-methylpyridin-2-yl)methyl)piperidine-1-carboxylate (73 mg, 0.24 mmol) in DCM (3 mL) and TFA (2 mL) was stirred at RT for 2 h before it was concentrated. The residue was taken up in minimal amount of MeOH and passed thru a P1-HCO_3 resin plug. Removal of solvent under reduced pressure yielded the title compound with quantitative yield. MS (apci) m/z = 207.1 (M+H).

Intermediate R59

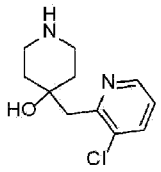


4-(3-methoxybenzyl)piperidin-4-ol hydrochloride

[0479] Step 1: Preparation of tert-butyl 4-hydroxy-4-(3-methoxybenzyl)piperidine-1-carboxylate. To a solution of (3-methoxybenzyl)magnesium chloride (0.25 M in 2-methyltetrahydrofuran, 15 mL, 3.75 mmol) cooled to 0 °C was added tert-butyl 4-oxopiperidine-1-carboxylate (678 mg, 3.40 mmol) portionwise. The reaction mixture was allowed to slowly warm up to RT and stirred overnight before quenched with sat. NH_4Cl (aq.). After phase-separation, the aqueous was extracted with EtOAc (3x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica chromatography (0-70% EtOAc in hexanes) to afford the title compound as a colorless oil (1.09 g). MS (apci) m/z = 222.2 (M+H-Boc).

[0480] Step 2: Preparation of 4-(3-methoxybenzyl)piperidin-4-ol hydrochloride. The title product was prepared according to the procedure described for the preparation of Intermediate R55, Step 2. MS (apci) m/z = 222.1 (M+H).

[0481] RE23649-093

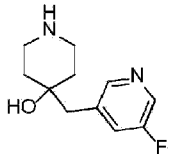


4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol

[0482] Step 1: Preparation of tert-butyl 4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate. A solution of 3-chloro-2-methylpyridine (64.2 mg, 0.50 mmol) in THF (1 mL) was sparged with N_2 and cooled to -78 °C before n-butyllithium (2.5 M THF, 0.16 mL, 0.41 mmol) was added dropwise. After stirred at -78 °C for 45 min, the mixture was warmed to RT and stirred for 2 h before cooled again to -78 °C. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (74.2 mg, 0.37 mmol) in THF (1.5 mL) was added dropwise. After stirring for 2 hr at -78 °C, the mixture was warmed to rt and stirred for 2 d. The reaction was then partitioned between EtOAc and sat. NH_4Cl (aq). After phase-separation, the aqueous was extracted with EtOAc (3x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica chromatography (10-90% EtOAc in hexanes) to afford the title compound as a colorless oil (103.5 mg, 85%). MS (apci) m/z = 227.1 (M+H-Boc).

[0483] Step 2: Preparation of 4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol. A solution of tert-butyl 4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate (103.5 mg, 0.32 mmol) in DCM (1.5 mL) was treated with TFA (1.5 mL) and stirred at RT overnight. After removal of solvent under reduced pressure, the residue was treated with $NaHCO_3$ (sat.) and extracted with 4:1 DCM/IPA (4x). The combined organic extracts were passed through a phase-separator frit and concentrated to afford the title product as a colorless oil (71.1 mg, 99%). MS (apci) m/z = 227.1 (M+H).

Intermediate R61



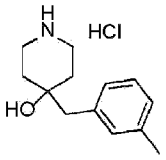
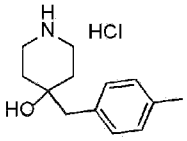
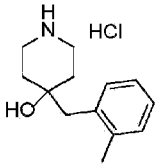
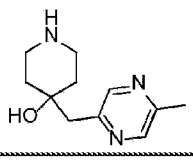
4-((5-fluoropyridin-3-yl)methyl)piperidin-4-ol

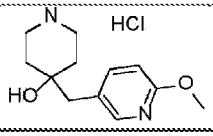
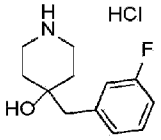
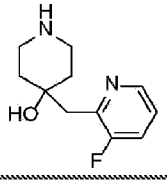
[0484] Step 1: Preparation of tert-butyl 4-((5-fluoropyridin-3-yl)methyl)-4-hydroxypiperidine-1-carboxylate. A solution of 3-fluoro-5-methylpyridine (279 mg, 2.51 mmol) in THF (1.5 mL) was sparged with N_2 and cooled to -78 °C before butyllithium (2.5 M THF, 0.79 mL, 1.99 mmol) was added dropwise. After 5 min stirring, a solution of tert-butyl 4-oxopiperidine-1-carboxylate (359.7 mg, 1.805 mmol) in THF (1.5mL) was added dropwise, and stirring continued for another 5 min.. The reaction was then quenched with sat. NH_4Cl (aq) and filtered. After phase-separation, the organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica chromatography (10-90% EtOAc in hexanes) to afford the title product as a colorless oil (104.9 mg, 18.7%). MS (apci) m/z = 211.1 (M+H-Boc).

[0485] Step 2: Preparation of 4-((5-fluoropyridin-3-yl)methyl)piperidin-4-ol. The title product was prepared according to the procedure described for the preparation of Intermediate **R60,** Step 2. MS (apci) m/z = 211.2 (M+H).

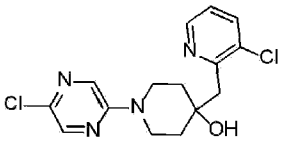
[0486] The compounds in Table **R1** were prepared using similar methods as described for the preparation of **Intermediate R56** (Method A), **Intermediate R57** (Method B), **Intermediate R60** (Method C), **Intermediate R55** (Method D) or **Intermediate R58** (Method E), using the appropriate reagent and chromatography conditions for Step 1.

Table **R1**

Intermediate	Method	Structure	Chemical Name	LCMS m/z
R62	A		4-(3-methylbenzyl)piperidin-4-ol hydrochloride	206.2 (M+H)
R63	A		4-(4-methylbenzyl)piperidin-4-ol hydrochloride	206.3 (M+H)
R64	B		4-(2-methylbenzyl)piperidin-4-ol hydrochloride	206.2 (M+H)
R65	C		4-((5-methylpyrazin-2-yl)methyl)piperidin-4-ol	208.2 (M+H)
R66				

Intermediate	Method	Structure	Chemical Name	LCMS m/z
	C		4-((6-methoxypyridin-3 -yl)methyl)piperidin-4-ol hydrochloride	223.1 (M+H)
R67	D		4-(3-fluorobenzyl)piperidin-4-ol hydrochloride	210.2 (M+H)
R68	E		4-((3-fluoropyridin-2-yl)methyl)piperidin-4-ol	211.2 (M+H)

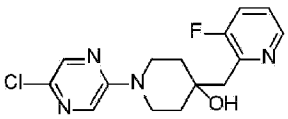
Intermediate R69



1-(5-chloropyrazin-2-yl)-4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol

[0487] A solution of 4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol (R60, 222.0 mg, 0.98 mmol) and 2,5-dichloropyrazine (145.9 mg, 0.98 mmol) in DMSO (2 mL) was treated with DIEA (0.86 mL, 4.90 mmol) and stirred at 100°C overnight. After cooling to RT the reaction was diluted with H_2O and extracted with 4:1 DCM/IPA (3x). The organic extracts were combined and concentrated. The crude residue was purified by silica chromatography (20-80% EtOAc in hexanes) to afford the title product as a colorless oil (206.7 mg, 62% yield). MS (apci) m/z = 339.1 (M+H).

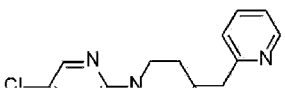
Intermediate R70

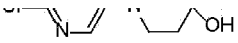


1-(5-chloropyrazin-2-yl)-4-((3-fluoropyridin-2-yl)methyl)piperidin-4-ol

[0488] The title product (460 mg, 59%) was prepared according to the procedure described for the preparation of **Intermediate R69,** replacing 4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol with 4-((3-fluoropyridin-2-yl)methyl)piperidin-4-ol **(Intermediate R68).** MS (apci) m/z = 323.1 (M+H).

Intermediate R71

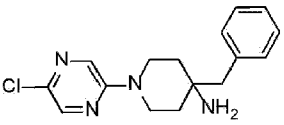




1-(5-chloropyrazin-2-yl)-4-(pyridin-2-ylmethyl)piperidin-4-ol

[0489] The title product (550 mg, 96%) was prepared according to the procedure described for the preparation of **Intermediate R69,** replacing 4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol with 4-(pyridin-2-ylmethyl)piperidin-4-ol dihydrochloride. MS (apci) m/z = 305.1 (M+H).

Intermediate R72



4-benzyl-1-(5-chloropyrazin-2-yl)piperidin-4-amine

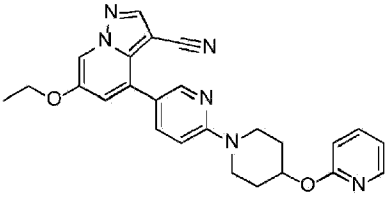
[0490] Step 1: Preparation of 4-benzylpiperidin-4-amine bis(2,2,2-trifluoroacetate). A mixture of tert-butyl 4-amino-4-benzylpiperidine-1-carboxylate (210 mg, 0.723 mmol) in DCM (2 mL) and TFA (1 mL) was stirred at RT for ~3 h before it was concentrated to yield the title compound assuming quantitative yield. MS (apci) m/z = 191.2 (M+H).

[0491] Step 2: Preparation of 4-benzyl-1-(5-chloropyrazin-2-yl)piperidin-4-amine. To a solution of 2,5-dichloropyrazine (0.1316 mL, 0.7243 mmol) in DMSO (10 mL) were added K_2CO_3 (300.3 mg, 2.173 mmol) followed by 4-benzylpiperidin-4-amine bis(2,2,2-trifluoroacetate) (303 mg, 0.72 mmol). The reaction was sealed and heated at 75 °C overnight. After cooling to RT, the reaction was diluted with EtOAc (10 mL) and water (20 mL). After phase-separation, the aqueous was extracted with EtOAc (2x). The combined organic extracts were concentrated and used directly in the next step. MS (apci) m/z = 303.1 (M+H).

Synthetic examples

Example 9

[0492]

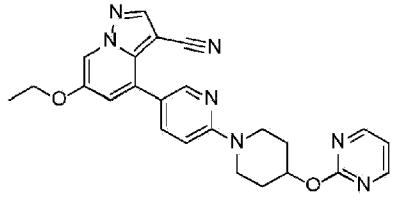


6-ethoxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3 -yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile

[0493] A suspension of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6;** 30 mg, 0.11 mmol), 2-(piperidin-4-yloxy)pyridine (28.4 mg, 0.159 mmol), and TEA (44 µL, 0.319 mmol) in DMA (500 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and quenched with water. The resulting biphasic mixture was extracted with DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The crude residue was purified by silica chromatography (40-100% EtOAc/ Hexanes as the gradient eluent) to afford the title compound (23.6 mg, 50% yield). MS (apci) m/z = 441.2 (M+H).

Example 10

[0494]

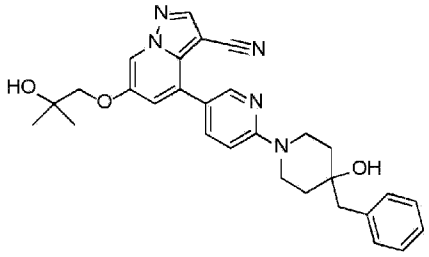


6-ethoxy-4-(6-(4-(pyrimidin-2-yloxy)piperidin-1-yl)pyridin-3 -yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile

[0495] The title compound (18.6 mg, 40% yield) was prepared and purified using a similar procedure to that described for **Example 9,** replacing 2-(piperidin-4-yloxy)pyridine with 2-(piperidin-4-yloxy)pyrimidine. MS (apci) m/z = 442.3 (M+H).

Example 27

[0496]



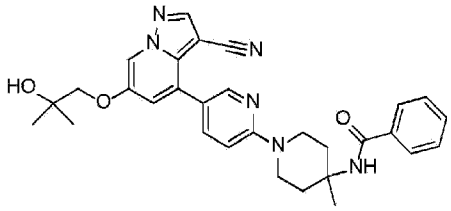
4-(6-(4-benzyl-4-hydroxypiperidin-1-yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0497] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 29.3 mg, 0.0898 mmol), 4-benzylpiperidin-4-ol (25.8 mg, 0.135 mmol)

and TEA (37.5 µL, 0.269 mmol) in DMA (599 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% water:ACN with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated $Na_2CO_{3(aq)}$. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to cleanly provide the title compound (22.4 mg, 50% yield). MS (apci) m/z = 498.2 (M+H).

Example 29

[0498]

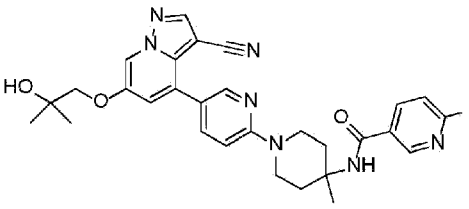


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0499] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 36 mg, 0.0856 mmol), benzoic acid (20.9 mg, 0.171 mmol) and HATU (35.8 mg, 0.0942 mmol) in DCM (856 µL) was treated with DIEA (74.8 µL, 0.428 mmol) and then stirred for 2 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA, then filtered through a syringe filter. The filtrate was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (33.2 mg, 74% yield). MS (apci) m/z = 525.25 (M+H).

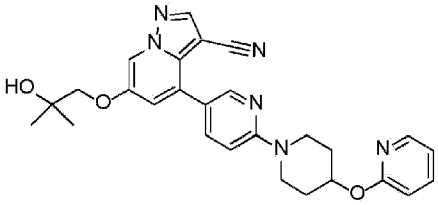
[0500] The compounds in Table N were prepared using a similar method to that described for the synthesis of **Example 29,** replacing benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table N

Ex #	Structure	Chemical Name	MS (apci) m/z
31		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-methoxynicotinamide	556.3 (M+H)

Example 35

[0501]

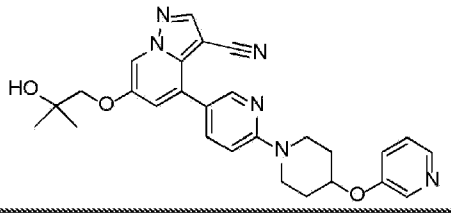
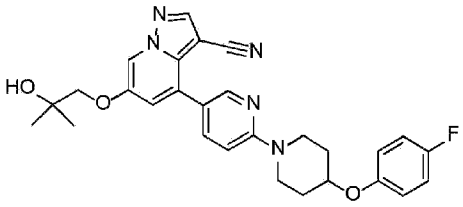
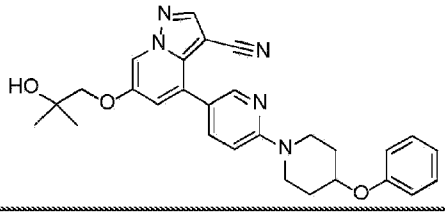
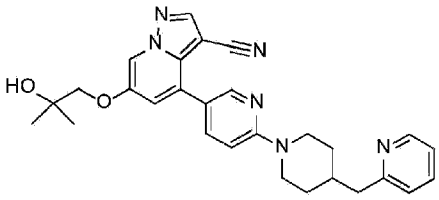
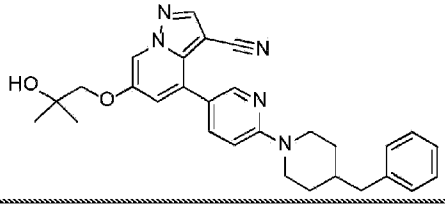


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0502] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 29.7 mg, 0.0910 mmol), 2-(piperidin-4-yloxy)pyridine (24.3 mg, 0.137 mmol) and TEA (38.1 µL, 0.273 mmol) in DMA (607 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated $Na_2CO_{3(aq)}$. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to cleanly provide the title compound (12.1 mg, 27% yield). MS (apci) m/z = 485.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$)δ: 8.34(d, 1H), 8.20(s, 1H), 8.15(m, 2H), 7.71(dd, 1H), 7.58(m, 1H), 7.15(d, 1H), 6.86(m, 1H), 6.81(d, 1H), 6.74(d, 1H), 5.35(m, 1H), 4.06(m, 2H), 3.86(s, 2H), 3.55(m, 2H), 2.15(m, 2H), 1.88(m, 2H), 1.40(s, 6H).

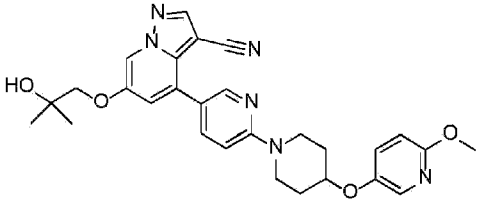
[0503] The compounds in Table **P** were prepared using a similar method to that described for the synthesis of **Example 35,** replacing 2-(piperidin-4-yloxy)pyridine with the appropriate piperidine. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly.

Table P

Ex #	Structure	Chemical Name	MS (apci) m/z
36		6-(2-hydroxy-2-methy lpropoxy)-4-(6-(4-(pyridin-3-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	485.2 (M+H)
37		4-(6-(4-(4-fluorophenoxy)piperid in-1-yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazo lo[1,5-a]pyridine-3-carbonitrile	502.2 (M+H)
38		6-(2-hydroxy-2-methy lpropoxy)-4-(6-(4-phenoxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	484.2 (M+H)
40		6-(2-hydroxy-2-methy lpropoxy)-4-(6-(4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	483.2 (M+H)
41		4-(6-(4-benzylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methy lpropoxy)pyrazo lo[1,5-a]pyridine-3-carbonitrile	482.2 (M+H)

Example 42

[0504]

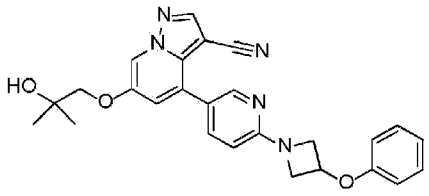


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methoxypyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0505] A solution of 2-methoxy-5-(piperidin-4-yloxy)pyridine **(Intermediate R13;** 66.1 mg, 0.317 mmol) in DMA (794 µL) was treated with 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 51.8 mg, 0.159 mmol), and TEA (43.4 µL, 0.317 mmol). The resulting mixture was sparged with $Ar_{(g)}$ then stirred overnight at 110 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated $NaHCO_{3(aq)}$. The aqueous extracts were back extracted with DCM. The combined organic extracts were washed with brine, and subsequently dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to cleanly provide the title compound (41 mg, 50% yield). MS (apci) m/z = 515.2 (M+H).

Example 43

[0506]

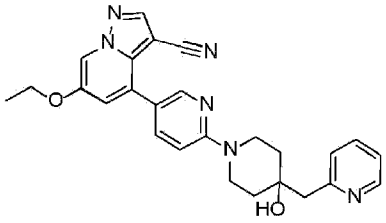


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-phenoxyazetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0507] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 42.7 mg, 0.131 mmol), 3-phenoxyazetidine (23.4 mg, 0.157 mmol) and TEA (54.7 µL, 0.393 mmol) in DMA (872 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated $Na_2CO_{3(aq)}$. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to cleanly provide the title compound (14.1 mg, 24% yield). MS (apci) m/z = 456.2 (M+H).

Example 44

[0508]

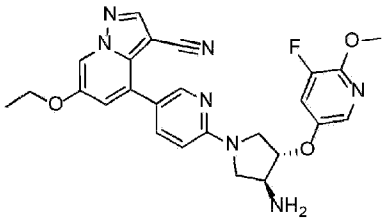


6-ethoxy-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 - a]pyridine-3 -carbonitrile

[0509] 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.030 g, 0.11 mmol), triethylamine (0.044 mL, 0.32 mmol) and 4-(pyridin-2-ylmethyl)piperidin-4-ol (0.041 g, 0.21 mmol) were combined in DMA (0.5 mL) and stirred at 90°C for 5 h. The reaction mixture was diluted with DCM (5 mL), sat. NH_4Cl (aq., 5 mL) and water (20 mL). After phase-separation, the aqueous layer was extracted with DCM. The combined organic extracts were dried (Na_2SO_4), filtered, concentrated and purified by silica chromatography (30-100% EtOAc/hexanes) to provide the title product as solid (0.022 g, 46 % yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.5 (dq, 1H), 8.3 (d, 1H), 8.15 (s, 1H), 8.05 (d, 1H), 7.65 (qd, 2H), 7.15 (qd, 1H), 7.1 (d, 1H), 7.05 (d, 1H), 6.75 (d, 1H), 6.05 (br s, 1H), 4.1 (q, 2H), 3.45 (m, 2H), 2.9 (s, 2H), 1.6 (m, 4H), 1.5 (t, 3H). LCMS (apci) m/z = 455.2 (M+H).

Example 45

[0510]



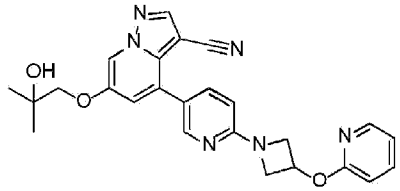
4-(6-((3S,4S)-3-amino-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0511] Step 1: Preparation of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate. 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 0.22 g, 0.76 mmol), N-ethyl-N-isopropylpropan-2-amine (0.66 mL, 3.81 mmol), and tert-butyl ((3S,4R)-4-hydroxypyrrolidin-3-yl)carbamate (0.23 g, 1.14 mmol) were combined in DMSO (1.5 mL) and stirred at 100 °C for 60 h. The reaction mixture was diluted with sat. NH_4Cl and extracted into DCM. The combined organic extracts were dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by silica chromatography (0-100% EtOAc/hexanes) to provide the product as solid (0.28 g, 80% yield).

[0512] Step 2: Preparation of 4-(6-((3S,4S)-3-amino-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A mixture of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (0.030 g, 0.07 mmol), 5-fluoro-6-methoxypyridin-3-ol (0.037 g, 0.26 mmol), and triphenylphosphine (0.068 g, 0.26 mmol) was combined in 1:1 DCM/THF (0.7 mL). The reaction vessel was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.035 mL, 0.26 mmol) was added. The reaction was stirred at room temperature for 48 h. The reaction mixture was diluted with DCM and H_2O, filtered through phase separating paper, and extracted into DCM. The combined organic extracts were dried (Na_2SO_4),filtered, concentrated *in vacuo* and purified by silica chromatography (0-100% EtOAc/hexanes). The fractions containing the Boc-protected title compound were concentrated, and the residue was diluted with 6 mL 1:1 DCM/5N HCl in isopropyl alcohol. This mixture was stirred at room temperature 24 h. The combined organic extracts were washed with 2M NaOH and purified by reverse phase chromatography (0-80% ACN/Water [0.1% Formic Acid]) to provide the title compound (2.2 mg, 7.0 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.4 (d, 1H), 8.3 (s, 1H), 8.25 (dd, 1H), 7.75 (dd, 1H), 7.7 (d, 1H), 7.3 (dd, 1H), 7.2 (d, 1H), 6.7 (dd, 1H), 4.1 (m, 2H), 3.95 (s, 3H), 3.9 (m, 2H), 3.7 (dd, 1H), 3.6 (dd, 1H), 3.3 (s, 2H), 1.45 (t, 3H). LCMS (apci) m/z = 490.1 (M+H).

Example 46

[0513]

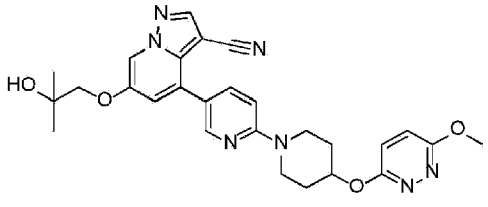


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0514] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (0.040 g, 0.12 mmol) **(Intermediate P42),** 2-(azetidin-3-yloxy)pyridine dihydrochloride (0.055 g, 0.24 mmol) and triethylamine (0.10 mL, 0.74 mmol) in DMA (0.82 mL) was heated in a sealed vial to 90 °C overnight. After cooling to ambient temperature, the reaction was partitioned between DCM and water (10 mL each). After phase-separation, the aqueous was extracted with DCM (2 × 10 mL). The combined organic extracts was washed with brine, dried (Na_2SO_4),filtered and concentrated. The crude was purified by preparative HPLC (5-95% ACN in water with 0.1% TFA) to yield the title product as a TFA salt, which was then converted to the free base by partitioning in DCM and Na_2CO_3 (sat. aq). The combined organic extracts were washed with brine, dried (Na_2SO_4),filtered and concentrated to yield the title product (4.7 mg, 8.4 % yield). ^{1}H NMR ($CDCl_3$) δ 8.31 (dd, 1H), 8.19 (s, 1H), 8.14 (m, 2H), 7.68 (dd, 1H), 7.61 (m, 1H), 7.13 (d, 1H), 6.91 (m, 1H), 6.80 (m, 1H), 6.44 (dd, 1H), 5.57 (m, 1H), 4.55 (m, 2H), 4.15 (m, 2H), 3.86 (s, 2H), 1.39 (s, 6H). LCMS (apci) m/z = 457.2 (M+H).

Example 47

[0515]

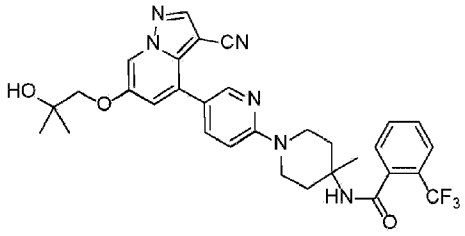


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methoxypyridazin-3-yl)oxy)piperidin-1 -yl)pyridin-3 -yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile

[0516] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (0.031 g, 0.095 mmol) **(Intermediate P42),** 3-methoxy-6-(piperidin-4-yloxy)pyridazine dihydrochloride (0.090 g, 0.32 mmol), triethylamine (0.10 mL, 0.76 mmol) in DMA (0.32 mL) was heated in a sealed vial to 95 °C overnight. After cooling to ambient temperature, the reaction mixture was diluted with DCM (10 mL) and sequentially washed with sat. $NaHCO_3$ (15 mL), water (2 x 15 mL) and brine (15 mL), then dried (Na_2SO_4), filtered and concentrated. The crude material was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.01% TFA) and the combined product fractions was concentrated and converted to the free base with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4),filtered and concentrated to afford the title compound as a white solid (22.5 mg, 46 % yield). ^1H NMR ($CDCl_3$) δ 8.32 (dd, 1H), 8.19 (s, 1H), 8.13 (d, 1H), 7.68 (dd, 1H), 7.13 (d, 1H), 6.92 (m, 2H), 6.80 (m, 1H), 5.42 (m, 1H), 4.10 (m, 2H), 4.04 (s, 3H), 3.84 (s, 2H), 3.46 (m, 2H), 2.22 (m, 2H), 1.88 (m, 2H), 1.39 (s, 6H). LCMS (apci) m/z = 516.2 (M+H).

Example 52

[0517]



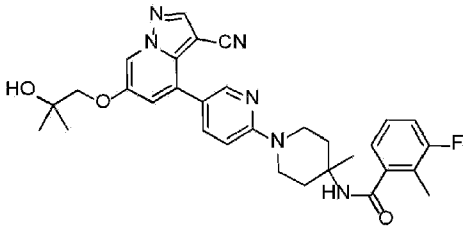
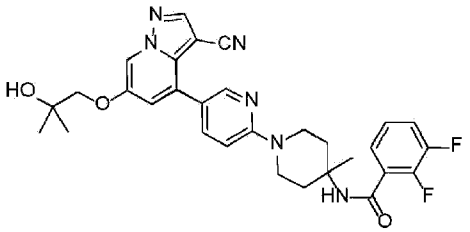
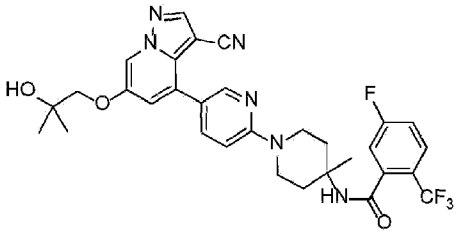
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-(trifluoromethyl)benzamide

[0518] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (50 mg, 0.13 mmol), and 2-(trifluoromethyl)benzoic acid (25 mg, 0.13 mmol) in DMSO (1 mL) was treated with DIEA (83 µL, 0.48 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was

concentrated *in vacuo.* The reaction mixture was diluted with EtOAc and washed with water. The organic extracts then dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (1-10% MeOH in DCM with 0.1-1% NH_4OH as the gradient eluent) to cleanly provide the title compound (37 mg, 53% yield) MS (apci) m/z=593.3 (M+H).

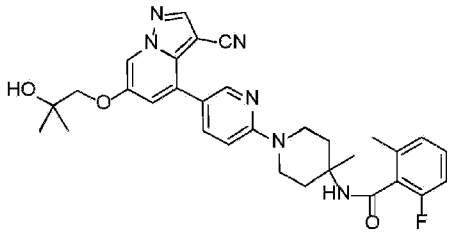
[0519] The compounds in Table Q were prepared using a similar method to that described for the synthesis of Example **52,** replacing 2-(trifluoromethyl)benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table Q

Ex. #	Structure	Chemical Name	LCMS m/z
53		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-fluoro-2-methylbenzamide	557.3 (M+H)
54		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,3-difluoro benzamide	561.3 (M+H)
55		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-5-fluoro-2-(trifl uoromethy l)benzamid e	611.3 (M+H)

Example 56

[0520]

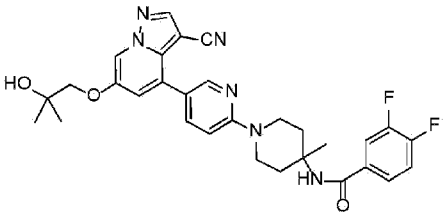
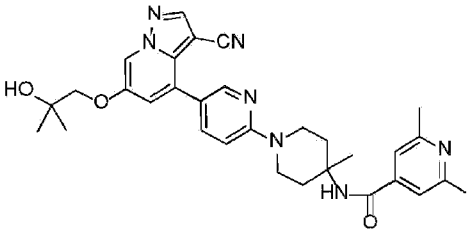


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-fluoro-6-methylbenzamide

[0521] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (90 mg, 0.24 mmol), and 2-Fluoro-6-methylbenzoic acid (37 mg, 0.24 mmol) in DMSO (1 mL) was treated with DIEA (93 µL, 0.54 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (1-10% MeOH in DCM with 0.1-1% NH_4OH as the gradient eluent) to cleanly provide the title compound (35 mg, 53% yield) MS (apci) m/z= 557.3 (M+H).

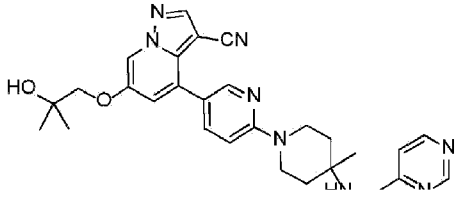
[0522] The compounds in Table R were prepared using a similar method to that described for the synthesis of Example 56, replacing 2-Fluoro-6-methylbenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table R

Ex. #	Structure	Chemical Name	LCMS m/z
57		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,4-difluorobenzamide	561.3 (M+H)
58		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,6-dimethy lisonicotinamide	554.3 (M+H)

Example 59

[0523]

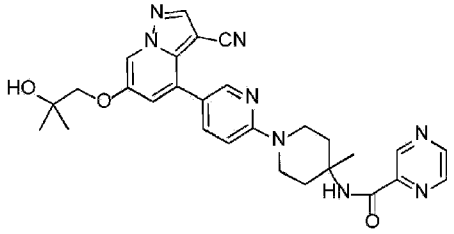


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)pyrimidine-4-carboxamide

[0524] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 43 mg, 0.10 mmol), HATU (77.8 mg, 0.21 mmol), and pyrimidine-4-carboxylic acid (12.7 mg, 0.10 mmol) in DMSO (600 µL) was treated with DIEA (80 µL, 0.46 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts then dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (1-10% MeOH in DCM with 0.1-1% NH_4OH as the gradient eluent) to cleanly provide the title compound (35 mg, 53% yield). MS (apci) m/z= 527.3 (M+H).

Example 60

[0525]

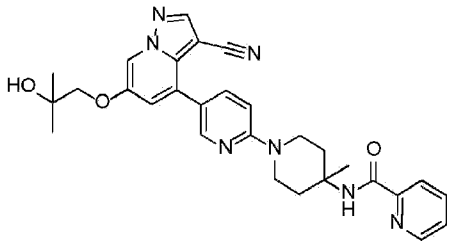


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,4-difluorobenzamide

[0526] The compound was prepared using a similar method to that described for the synthesis of **Example 59,** replacing pyrimidine-4-carboxylic acid with pyrazine-2-carboxylic acid. MS (apci) m/z= 527.2 (M+H).

Example 61

[0527]

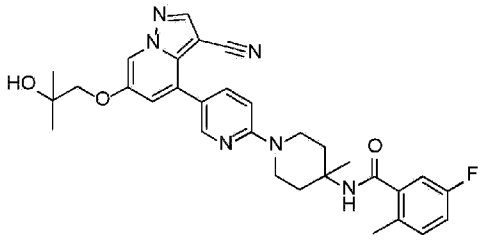


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0528] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 35 mg, 0.08 mmol), HATU (34.8 mg, 0.09 mmol), and picolinic acid (22.6 mg, 0.18 mmol) in DCM (832 µL) was treated with DIEA (47 µL, 0.35 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (43.7 mg, 49.3% yield). MS (apci) m/z = 526.20 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (m, 1H), 8.33 (d, 1H), 8.19 (s, 1H), 8.18 (dt, 1H), 8.16 (s, br, 1H), 8.14 (d, 1H), 7.85 (td, 1H). 7.70 (dd, 1H), 7.43 (m, 1H), 7.13 (d, 1H), 6.80 (d, 1H), 4.08 (m, 2H), 3.85 (s, 2H), 3.37 (m, 2H), 2.42 (m, 2H), 1.82 (m, 2H), 1.59 (s, 3H), 1.39 (s, 6H)

Example 62

[0529]



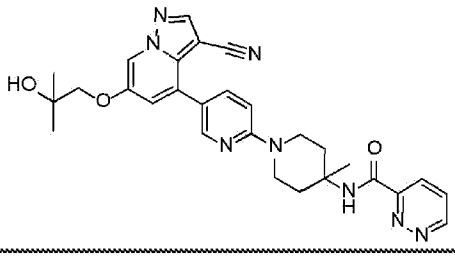
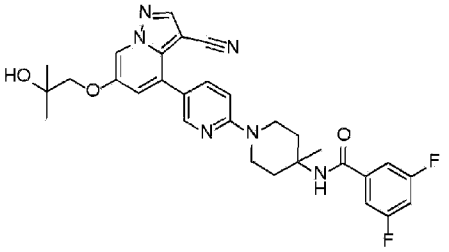
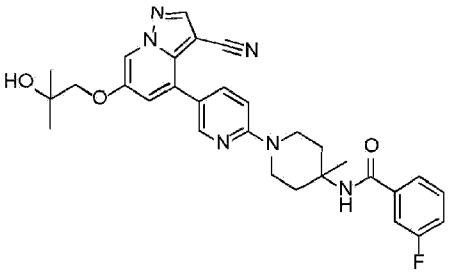
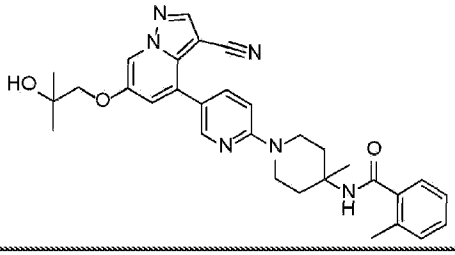
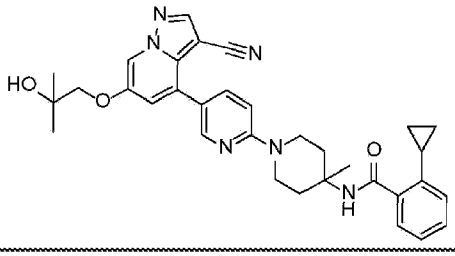
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

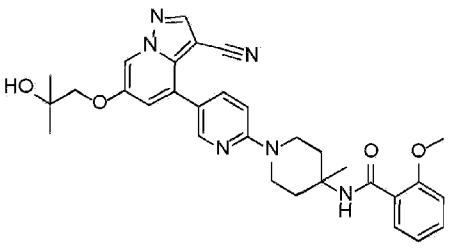
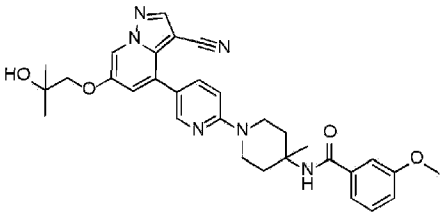
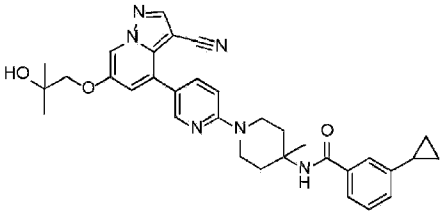
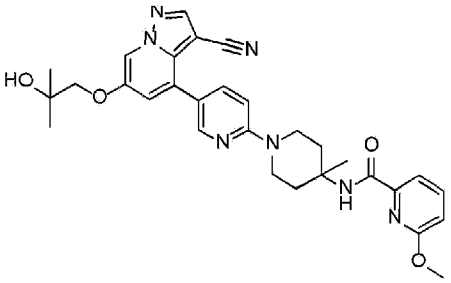
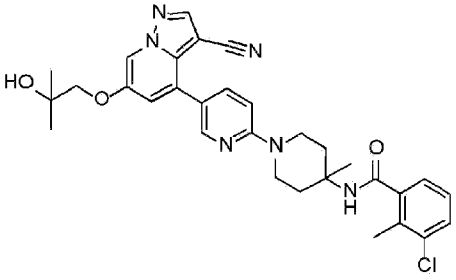
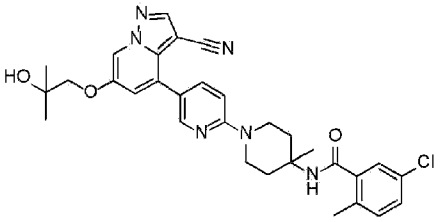
[0530] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 15.8 mg, 0.038 mmol), HATU (15.7 mg, 0.041 mmol), and 5-Fluoro-2-methylbenzoic acid (11.6 mg, 0.075 mmol) in DCM (1.07 mL) was treated with DIEA (33 µL, 0.19 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (11.2 mg, 53.6% yield). MS (apci) m/z = 557.3 (M+H).^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (d, 1H), 8.20 (s, 1H), 8.15 (d, 1H), 7.71 (dd, 1H), 7.17 (dd, 1H). 7.14 (d, 1H), 7.06 (dd, 1H), 7.00 (td, 1H), 6.81 (d, 1H), 5.50 (s, br, 1H), 4.01 (m, 2H), 3.86 (s, 2H), 3.41 (m, 2H), 2.41 (s, 3H), 2.30 (m, 2H), 1.84 (m, 2H), 1.61

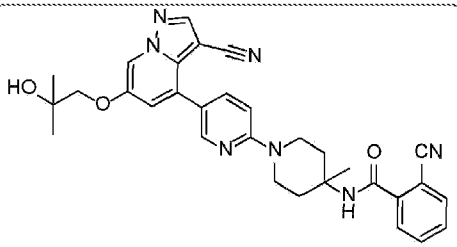
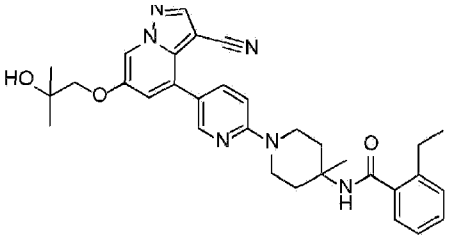
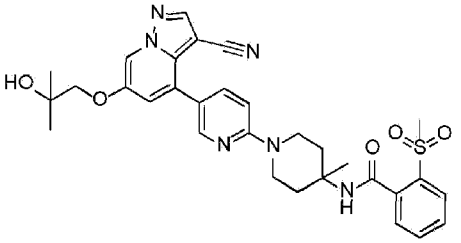
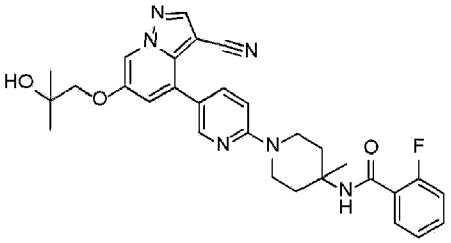
(s, 3H), 1.39 (s, 6H)

[0531] The compounds in Table S were prepared using a similar method to that described for the synthesis of **Example 62,** replacing 5-Fluoro-2-methylbenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table S

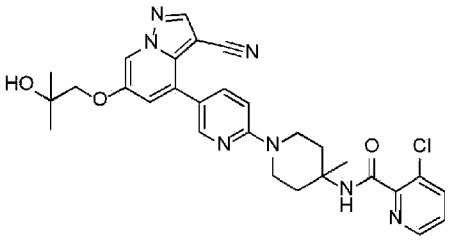
Ex. #	Structure	Chemical Name	LCMS m/z
63		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)pyridazine-3-carboxamide	**527.20 (M+H)**
64		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,5-difluorobenzamide	**561.2 (M+H)**
65		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-fluorobenzamide	**543.2 (M+H)**
66		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylbenzamide	**539.3 (M+H)**
67		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-cyclopropy lbenzamide	**565.3 (M+H)**

Ex. #	Structure	Chemical Name	LCMS m/z
68		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methoxybenzamide	555.3 (M+H)
69		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-methoxybenzamide	555.3 (M+H)
70		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-cyclopropy lbenzamide	565.3 (M+H)
71		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-6-methoxypicolinamide	556.3 (M+H)
72		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy -2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylbenzamide	573.3 (M+H)
73		5-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy -2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylbenzamide	573.3 (M+H)
74		2-cyano-N-(1-(5-(3-cyano-6-	550.3

Ex. #	Structure	Chemical Name	LCMS m/z
		(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	(M+H)
75		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-ethylbenzamide	553.3 (M+H)
76		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-(methylsulfonyl)benzamid e	603.3 (M+H)
77		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-fluorobenzamide	543.3 (M+H)

Example 78

[0532]

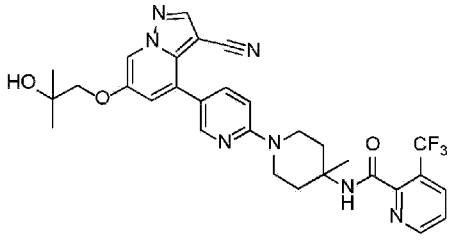


3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0533] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (50 mg, 0.13 mmol), and 3-chloropicolinic acid (37 mg, 0.24 mmol) in DMSO (1.2 mL, 0.1 M) was treated with DIEA (100 µL, 0.59 mmol) and then stirred for 1h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (45 mg, 68% yield). MS (apci) m/z = 560.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, 1H), 8.32 (d, 1H), 8.18 (s, 1H), 8.12 (d, 1H), 7.88 (s, br, 1H), 7.81 (dd, 1H). 7.68 (dd, 1H), 7.35 (dd, 1H), 7.11 (d, 1H), 6.78 (d, 1H), 4.06 (m, 2H), 3.85 (s, 2H), 3.36 (m, 2H), 2.38 (m, 2H), 1.79 (m, 2H), 1.60 (s, 3H), 1.38 (s, 6H).

Example 79

[0534]

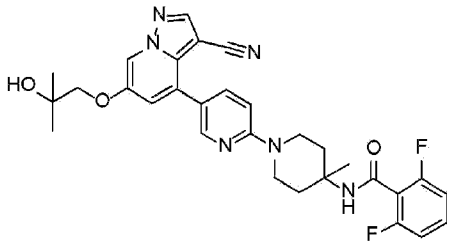


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-(trifluoromethyl)picolinamide

[0535] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (50 mg, 0.13 mmol), and 3-(trifluoromethyl)picolinic acid (45.4mg, 0.24 mmol) in DMSO (1.19 mL, 0.1 M) was treated with DIEA (104 µL, 0.60 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (46.5 mg, 66% yield). MS (apci) m/z = 594.3 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.8.71 (d, 1H), 8.34 (d, 1H), 8.19 (s, 1H), 8.16 (d, 1H), 8.14 (d, 1H), 7.70 (dd, 1H). 7.56 (dd, 1H), 7.52 (s, br, 1H), 7.13 (d, 1H), 6.80 (d, 1H), 4.06 (m, 2H), 3.85 (s, 2H), 3.36 (m, 2H), 2.40 (m, 2H), 1.82 (m, 2H), 1.60 (s, 3H), 1.39 (s, 6H).

Example 80

[0536]

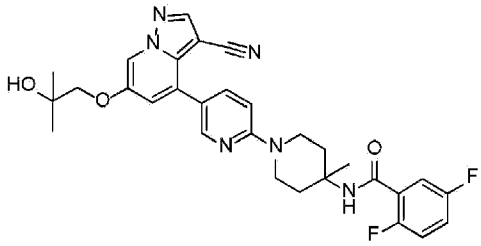


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,6-difluorobenzamide

[0537] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (50 mg, 0.13 mmol), and 2,6-difluorobenzoic acid (37.6 mg, 0.24 mmol) in DMSO (1.19 mL, 0.1 M) was treated with DIEA (104 µL, 0.60 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (46.5 mg, 66% yield). MS (apci) m/z = 561.2 (M+H).

Example 81

[0538]



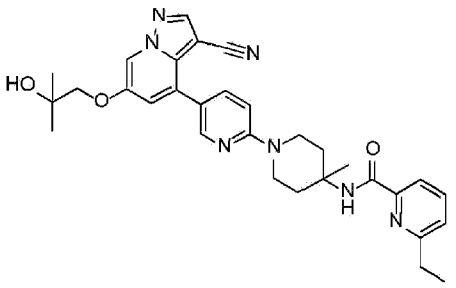
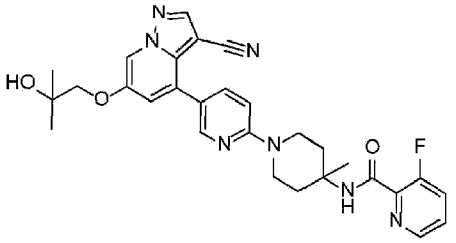
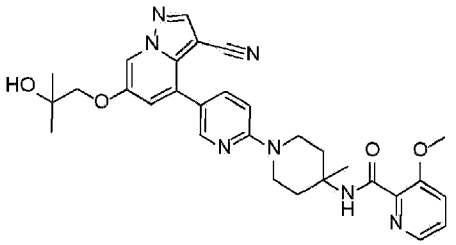
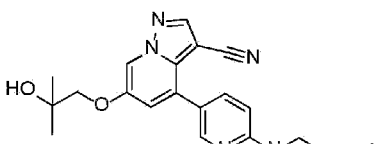
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,5-difluorobenzamide

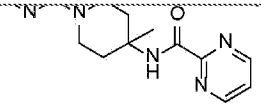
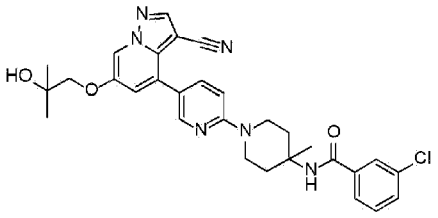
[0539] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 67 mg, 0.16 mmol), HATU (67

mg, 0.18 mmol), and 2,5-difluorobenzoic acid (50 mg, 0.32 mmol) in DMSO (1.6 mL, 0.1 M) was treated with DIEA (0.14 mL, 0.80 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (57 mg, 64% yield). MS (apci) m/z = 561.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H), 8.20 (s, 1H), 8.14 (d, 1H), 7.76 (m, 1H). 7.70 (dd, 1H), 7.14 (m, 3H), 6.80 (d, 1H), 6.62 (d, 1H), 4.06 (m, 2H), 3.86 (s, 2H), 3.34 (m, 2H), 2.31 (m, 2H), 1.81 (m, 2H), 1.59 (s, 3H), 1.39 (s, 6H).

[0540] The compounds in Table T were prepared using a similar method to that described for the synthesis of **Example 81,** replacing 2,5-difluorobenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

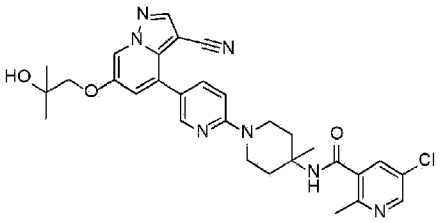
Table T

Ex. #	Structure	Chemical Name	LCMS m/z
82		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-ethylpicolinamide	554.3 (M+H)
83		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-fluoropicolinamide	**544.3 (M+H)**
84		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-methoxypicolinamide	**556.3 (M+H)**
85		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)pyrimidine-2-carboxamide	**527.2 (M+H)**

Ex. #	Structure	Chemical Name	LCMS m/z
			
86		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy -2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	**559.2 (M+H)**

Example 87

[0541]

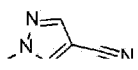


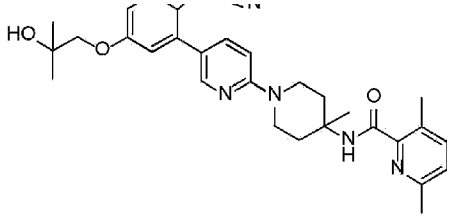
5-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylnicotinamide

[0542] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 53 mg, 0.107 mmol), HATU (44.9mg, 0.118 mmol), and 5-Chloro-2-methyl-3-pyridinecarboxylic acid (36.9 mg, 0.107 mmol) in DMSO (1.28 mL, 0.1 M) was treated with DIEA (0.09 mL, 0.54 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (26.1 mg, 42% yield). MS (apci) m/z = 574.2 (M+H).

Example 88

[0543]



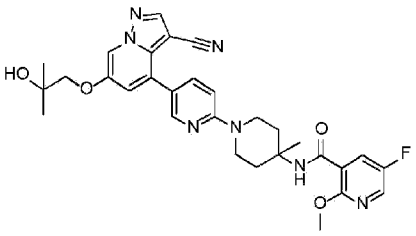
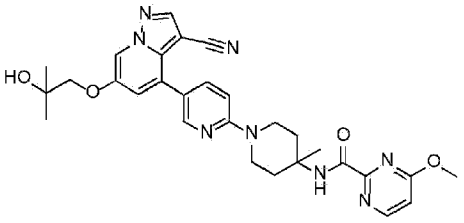


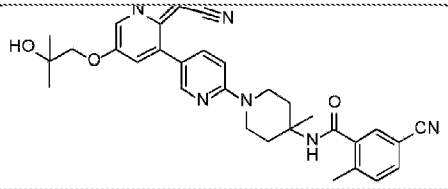
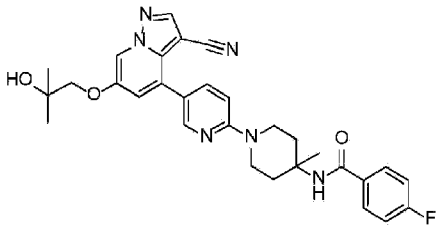
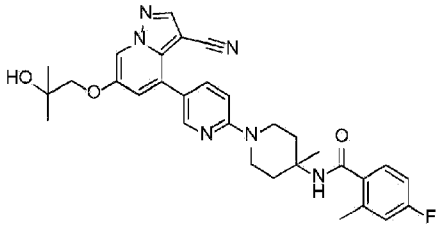
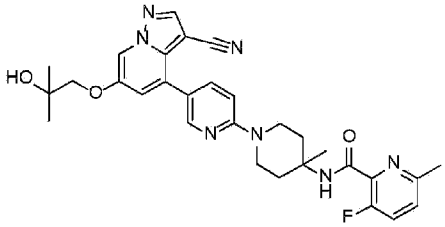
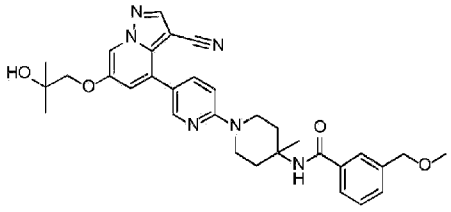
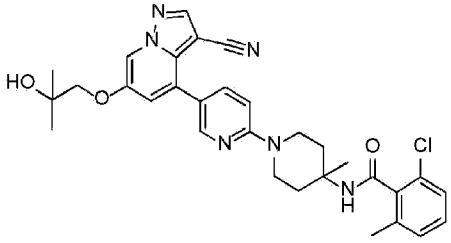
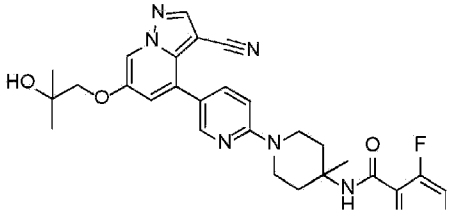
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,6-dimethylpicolinamide

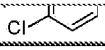
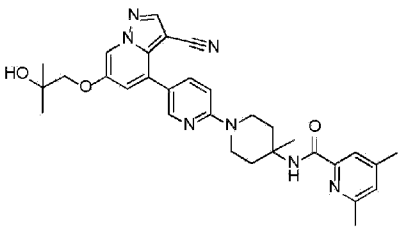
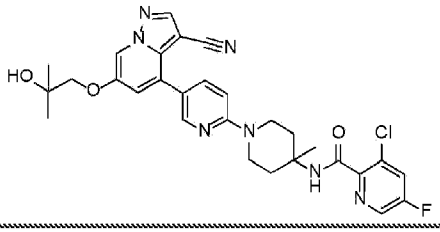
[0544] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 63 mg, 0.128 mmol), HATU (67 mg, 0.18 mmol), and 3,6-Dimethylpicolinic acid (38.6 mg, 0.26 mmol) in DMSO (1.28 mL, 0.1 M) was treated with DIEA (0.11 mL, 0.64 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (57 mg, 64% yield). MS (apci) m/z = 554.3 (M+H).

[0545] The compounds in Table U were prepared using a similar method to that described for the synthesis of **Example 88,** replacing 3,6-Dimethylpicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table U

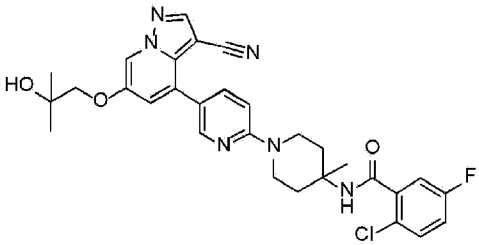
Ex. #	Structure	Chemical Name	LCMS m/z
89		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-5-fluoro-2-methoxynicotinamide	**574.3 (M+H)**
90		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-4-methoxypyrimidine- 2-carboxamide	**557.3 (M+H)**
91		5-cyano-N-(1-(5-(3-cyano-6-(2-hydroxy-2-	**564.3 (M+H)**

Ex. #	Structure	Chemical Name	LCMS m/z
		methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-2-methylbenzamide	
92		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-4-fluoro benzamide	**543.2 (M+H)**
93		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-4-fluoro- 2-methy lbenzamide	**557.3 (M+H)**
94		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-3-fluoro-6-methy lpicolinamide	**558.3 (M+H)**
100		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-3-(methoxymethyl)benzamide	**569.3 (M+H)**
101		2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-6-methylbenzamide	**573.2 (M+H)**
102		2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-6-fluoro benzamide	**577.2 (M+H)**

Ex. #	Structure	Chemical Name	LCMS m/z
			
103		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4,6-dimethylpicolinamide	**554.3 (M+H)**
104		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-5-fluoropicolinamide	**578.2 (M+H)**

Example 105

[0546]

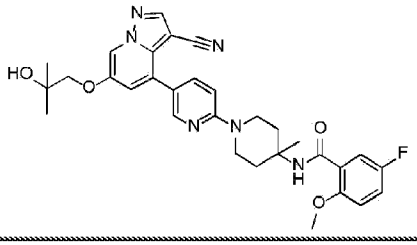
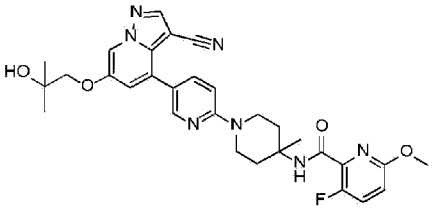


[0547] 2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamideA mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 56 mg, 0.11 mmol), HATU (47.5 mg, 0.125 mmol), and 2-Chloro-5-fluorobenzoic acid (39.6 mg, 0.23 mmol) in DMSO (1.13 mL, 0.1 M) was treated with DIEA (0.06 mL, 0.125 mmol) and then stirred for 4h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (34.3 mg, 52% yield). MS (apci) m/z = 577.2 (M+H).

[0548] The compounds in Table V were prepared using a similar method to that described for the synthesis of **Example 105,** replacing 2-Chloro-5-fluorobenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly.

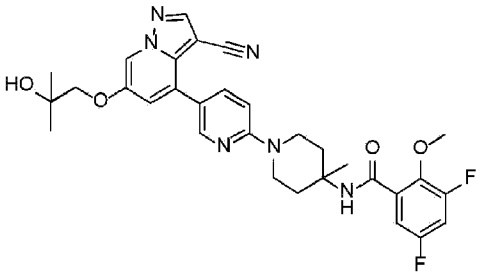
Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table V

Ex. #	Structure	Chemical Name	LCMS m/z
106		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methoxybenzamide	573.3 (M+H)
107		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-3-fluoro-6-methoxypicolinamide	574.2 (M+H)

Example 108

[0549]



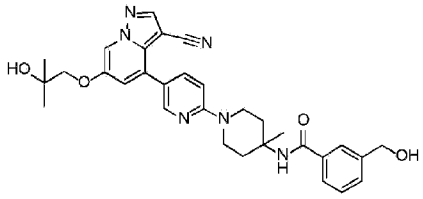
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,5-difluoro-2-methoxybenzamide

[0550] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 52 mg, 0.105 mmol), HATU (44.1 mg, 0.116 mmol), 3,5-difluoro-2-methoxybenzoic acid (19.8 mg, 0.105 mmol) in DMSO (1.05 mL, 0.1 M) was treated with DIEA (0.09 mL, 0.527 mmol) and then stirred for 2h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$,

filtered and concentrated *in vacuo* to afford the title compound (41.6 mg, 66.8% yield). MS (apci) m/z = 591.3 (M+H).

Example 109

[0551]

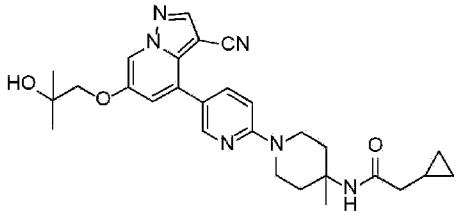


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-(hydroxymethyl)benzamide

[0552] Prepared using a similar method to that described for the synthesis of **Example 108,** replacing 3,5-difluoro-2-methoxybenzoic acid with the appropriate carboxylic acid. The reaction was monitored for completion by LCMS, and reaction duration was adjusted accordingly. The title compound was cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base). MS (apci) m/z = 555.3 (M+H).

Example 111 reference

[0553]

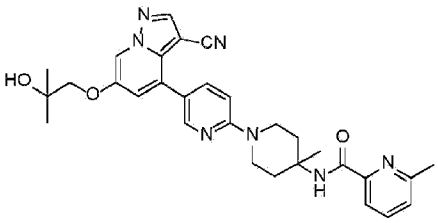
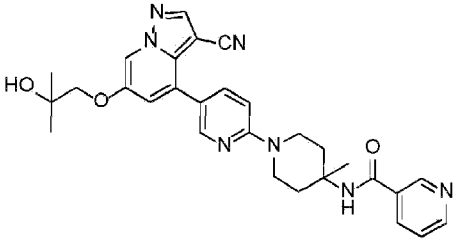
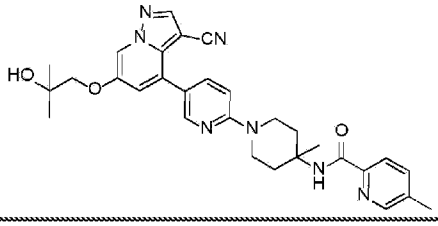


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-cyclopropylacetamide

[0554] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 21 mg, 0.05 mmol), HATU (23 mg, 0.06 mmol), Cyclopropylacetic acid (5 mg, 0.05 mmol) in DCM (100 µL) was treated with DIEA (35 µL, 0.2 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (50-100% EtOAc in Hexanes then 0-20% MeOH in EtOAc as the gradient eluent) to cleanly provide the title compound (17 mg, 67.5% yield) MS (apci) m/z= 503.30 (M+H).

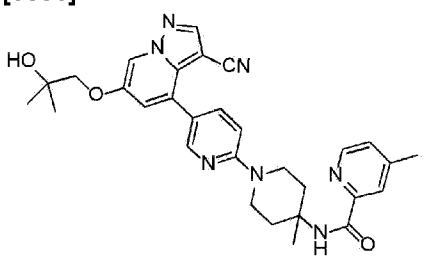
[0555] The compounds in Table W were prepared using a similar method to that described for the synthesis of **Example 111,** replacing cyclopropylacetic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table W

Ex. #	Structure	Chemical Name	LCMS m/z
112		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-methylpicolinamide	540.30 (M+H)
113		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)nicotinamide	526.25 (M+H)
115		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-methylpicolinamide	540.30 (M+H)

Example 119

[0556]

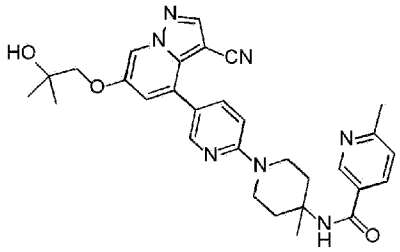


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4-methylpicolinamide 2,2,2-trifluoroacetate

[0557] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 20 mg, 0.048 mmol), HATU (54 mg, 0.14 mmol), 4-methylpicolinic acid (6.52 mg, 0.048 mmol) in DCM (238 µL) was treated with DIEA (33 µL, 0.19 mmol) and then stirred for 1 h at ambient temperature. The reaction mixture was filtered to remove solids, then the filtrate was concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt (14.2 mg, 55.3% yield). MS (apci) m/z = 540.3 (M+H).

Example 122

[0558]

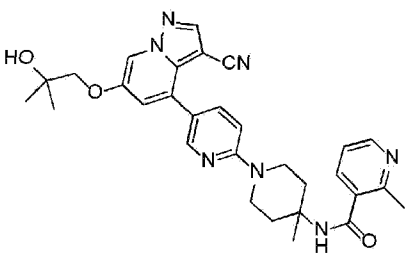


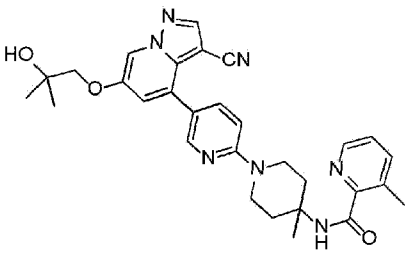
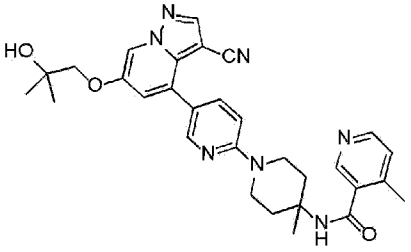
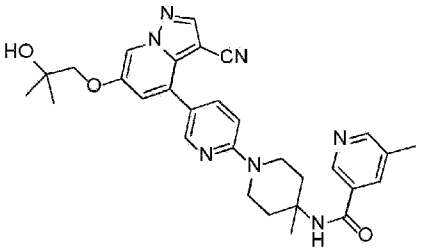
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-methylnicotinamide

[0559] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 20 mg, 0.048 mmol), HATU (54 mg, 0.14 mmol), 6-methylnicotinic acid (6.52 mg, 0.048 mmol) in DCM (238 µL) was treated with DIEA (33 µL, 0.19 mmol) and then stirred for 4 h at ambient temperature. The reaction was purified directly by silica chromatography (1-10% MeOH in $CHCl_3$ with 0.1-1% NH_4OH as the gradient eluent) to cleanly provide the title compound (10 mg, 39% yield) MS (apci) m/z= 540.3 (M+H).

[0560] The compounds in Table Z were prepared using a similar method to that described for the synthesis of **Example 122,** replacing 6-methylnicotinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base)

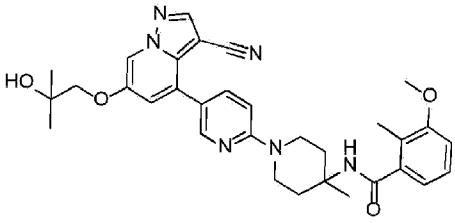
Table Z

Ex. #	Structure	Chemical Name	LCMS m/z
123		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methy lnicotinamide	540.3 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
124		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-methy lpicolinamide	540.3 (M+H)
127		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-4-methy lnicotinamide	540.3 (M+H)
128		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-methy lnicotinamide	540.3 (M+H)

Example 129

[0561]



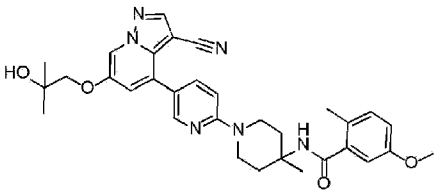
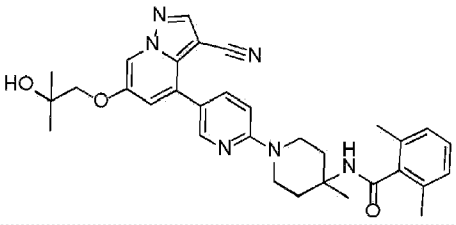
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-methoxy-2-methylbenzamide

[0562] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P46;** 50 mg, 0.12 mmol), HATU (54 mg, 0.14 mmol), 3-methoxy-2-methylbenzoic acid (24 mg, 0.14 mmol) in DMSO (793 µL) was treated with DIEA (25 µL, 0.14 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over

anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (25 mg, 37% yield). MS (apci) m/z = 569.3 (M+H).

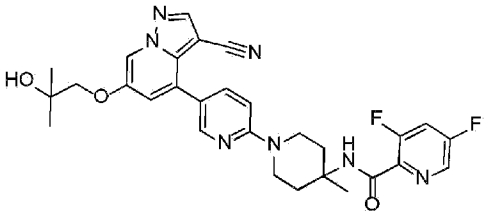
[0563] The compounds in Table AA were prepared using a similar method to that described for the synthesis of **Example 129,** replacing 3-methoxy-2-methylbenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table AA

Ex. #	Structure	Chemical Name	MS (apci) m/z
130		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-methoxy-2-methylbenzamide	569.3 (M+H)
131		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,6-dimethylbenzamide	553.3 (M+H)

Example 132

[0564]



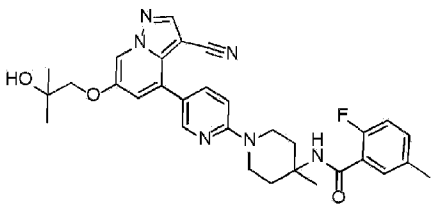
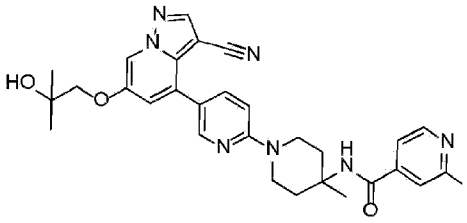
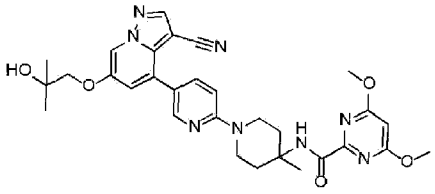
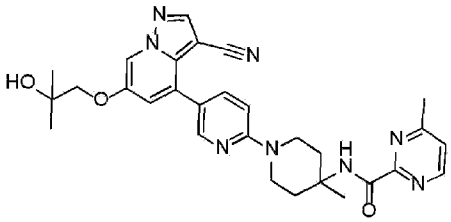
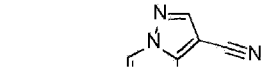
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,5-difluoropicolinamide

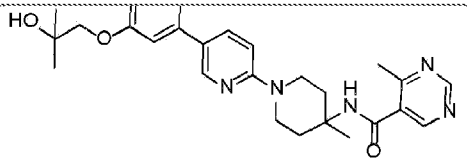
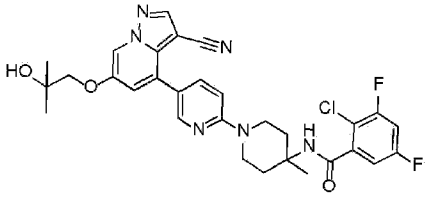
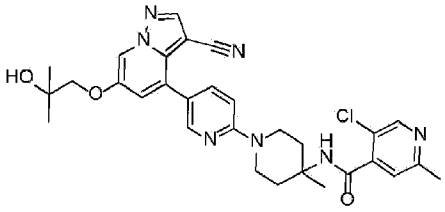
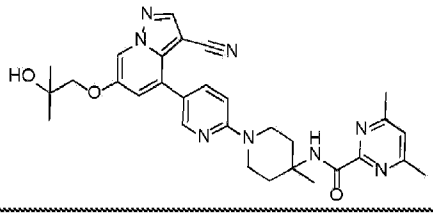
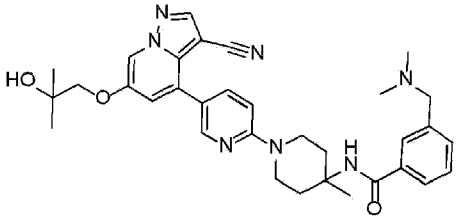
[0565] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-

methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 50 mg, 0.10 mmol), HATU (59 mg, 0.16 mmol), 3,5-difluoropicolinic acid (25 mg, 0.16 mmol) in DMSO (793 µL) was treated with DIEA (73 µL, 0.42 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (29.7 mg, 44.5% yield). MS (apci) m/z = 562.2 (M+H).

[0566] The compounds in Table BB were prepared using a similar method to that described for the synthesis of **Example 132,** replacing 3,5-difluoropicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

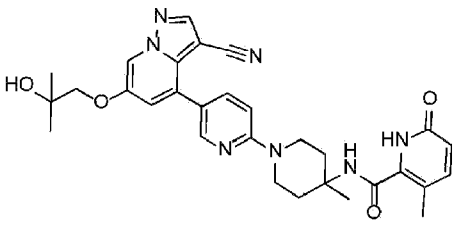
Table BB

Ex. #	Structure	Chemical Name	LCMS m/z
133		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-fluoro-5-methylbenzamide	557.3 (M+H)
134		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylisonicotinamide	540.3 (M+H)
135		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methy lpiperidin-4-yl)-4,6-dimethoxypyrimidine-2-carboxamide	587.3 (M+H)
136		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4-methylpyrimidine-2-carboxamide	541.3 (M+H)
137		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-	541.3 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
		a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4-methylpyrimidine-5-carboxamide	
139		2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3,5-difluorobenzamide	595.2 (M+H)
140		5-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methylisonicotinamide	561.3 (M+H)
141		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4,6-dimethy lpyrimidine-2-carboxamide	555.3 (M+H)
142		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-((dimethylamino)methyl)benzamide	582.3 (M+H)

Example 143 reference

[0567]



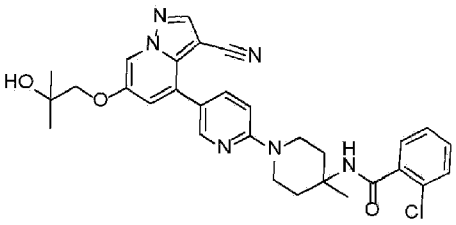
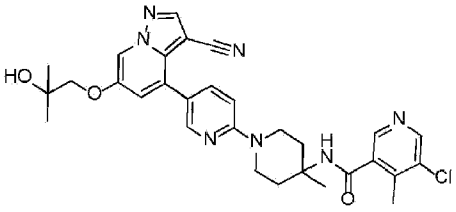
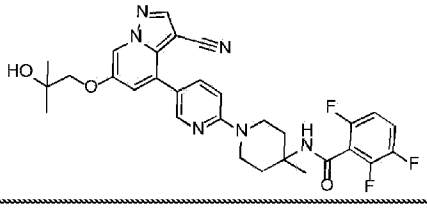
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-

methylpiperidin-4-yl)-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide

[0568] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 50 mg, 0.10 mmol), HATU (90 mg, 0.238 mmol), 6-hydroxy-3-methylpicolinic acid (36 mg, 0.238 mmol) in DMSO (793 µL) was treated with DIEA (93 µL, 0.535 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (10 mg, 15.1% yield). MS (apci) m/z = 556.3 (M+H).

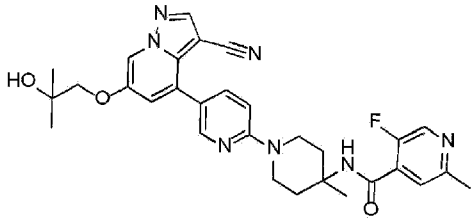
[0569] The compounds in Table CC were prepared using a similar method to that described for the synthesis of **Example 143,** replacing 6-Hydroxy-3-methylpicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table CC

Ex. #	Structure	Chemical Name	LCMS m/z
144		2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	559.2 (M+H)
145		5-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4-methylnicotinamide	574.3 (M+H)
146		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2,3,6-trifluorobenzamide	579.3 (M+H)

Example 147

[0570]

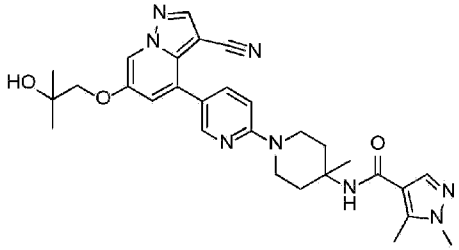


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylisonicotinamide

[0571] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P48;** 50 mg, 0.10 mmol), HATU (90 mg, 0.238 mmol), 5-Fluoro-2-methylisonicotinic acid (18 mg, 0.12 mmol) in DMSO (793 µL) was treated with DIEA (93 µL, 0.535 mmol) and then stirred for 18 h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The reaction was purified directly by silica chromatography (1-10% MeOH in DCM as the gradient eluent) to cleanly provide the title compound (41.9 mg, 63.2% yield) MS (apci) m/z= 558.3 (M+H).

Example 148

[0572]

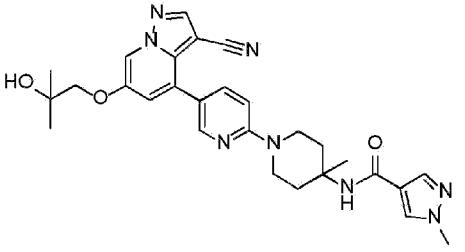
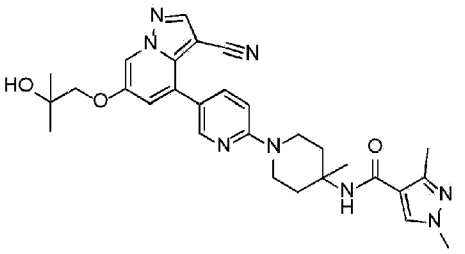


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1,5-dimethyl-1H-pyrazole-4-carboxamide

[0573] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (Intermediate P46; 50 mg, 0.12 mmol), HATU (54 mg, 0.14 mmol), 1,5-dimethyl-1H-pyrazole-4-carboxylic acid (25 mg, 0.18 mmol) in DCM(2.4 mL) was treated with DIEA (104 µL, 0.59 mmol) and then stirred for 16 h at ambient temperature. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$. The organic extracts were dried over anhydrous $Na_2SO4(s)$, filtered and concentrated *in vacuo.* The reaction was purified by silica chromatography (1-10% MeOH in EtOAc as the gradient eluent) to cleanly provide the title compound (41.9 mg, 63.2% yield) MS (apci) m/z= 543.20 (M+H).

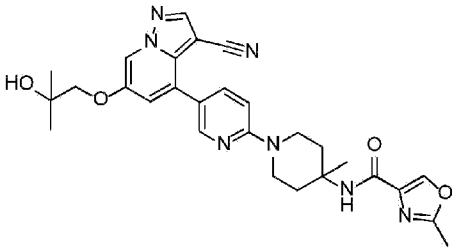
[0574] The compounds in Table DD were prepared using a similar method to that described for the synthesis of **Example 148,** replacing 1,5-dimethyl-1H-pyrazole-4-carboxylic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table DD

Ex. #	Structure	Chemical Name	LCMS m/z
149		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1-methyl-1H-pyrazole-4-carboxamide	528.6 (M+H)
150		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1,3-dimethyl-1H-pyrazole-4-carboxamide	543.2 (M+H)

Example 151

[0575]



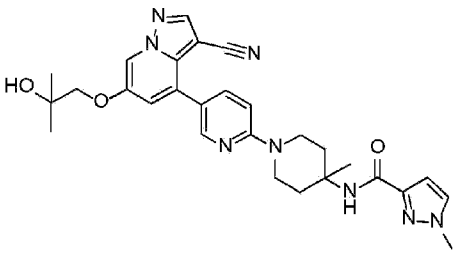
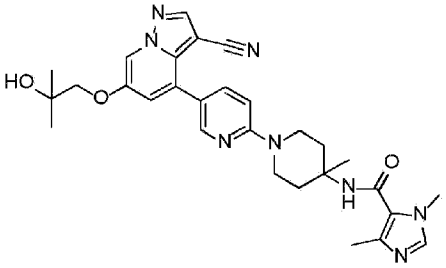
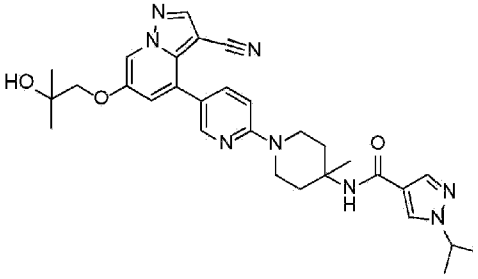
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-2-methyloxazole-4-carboxamide

[0576] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (Intermediate P46; 50 mg, 0.12 mmol), HATU (54 mg, 0.14 mmol), 2-methyloxazole-4-carboxylic acid (18 mg, 0.14 mmol) in DCM (2.4 mL) was treated with DIEA (104 µL, 0.59 mmol) and then stirred for 20 h at ambient temperature. The reaction mixture was diluted with DCM (5 mL) and washed with 0.1M NaOH. The organic extracts were dried over anhydrous Na_2SO4(s), filtered and concentrated *in vacuo.* The residue was triturated with

MTBE to cleanly provide the title compound (15 mg, 23.8% yield) MS (apci) m/z= 543.20 (M+H).

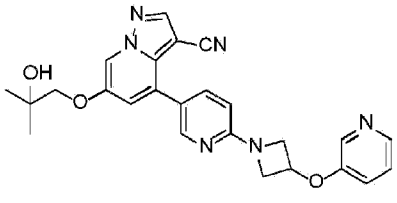
[0577] The compounds in Table EE were prepared using a similar method to that described for the synthesis of **Example 151,** replacing 2-methyloxazole-4-carboxylic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following the same a basic workup and trituration purification.

Table EE

Ex. #	Structure	Chemical Name	LCMS m/z
152		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1-methyl-1H-pyrazole-3-carboxamide	528.2 (M+H)
153		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1,4-dimethyl-1H-imidazole-5-carboxamide	543.20 (M+H)
154		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-1-isopropyl-1H-pyrazole-4-carboxamide	557.20 (M+H)

Example 155

[0578]



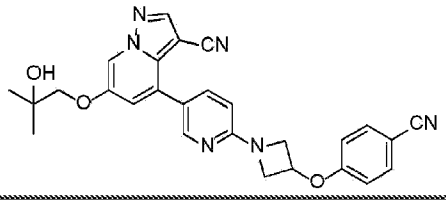
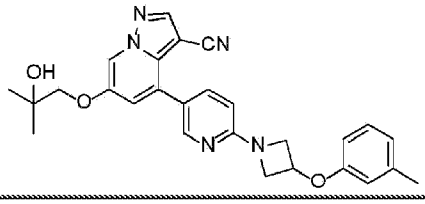
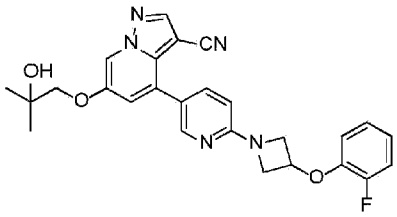
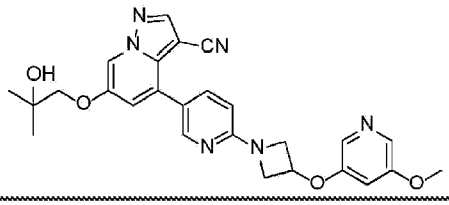
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-3-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo [1,5-

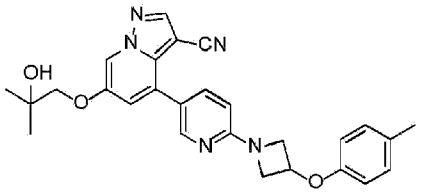
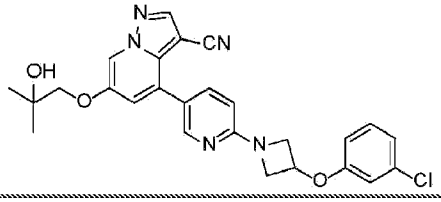
a]pyridine-3 -carbonitrile

[0579] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (Intermediate P42; 30.7 mg, 0.0941 mmol), 3-(azetidin-3-yloxy)pyridine (28.3 mg, 0.188 mmol) and TEA (78.7 µL, 0.564 mmol) in DMA (627 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated Na_2CO_3(aq). The combined organic extracts were washed with brine, then dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo* to cleanly provide the title compound (17 mg, 39.6% yield). MS (apci) m/z = 457.2 (M+H).

[0580] The compounds in Table FF were prepared using a similar method to that described for the synthesis of **Example 155**, replacing 3-(azetidin-3-yloxy)pyridine with the appropriate azetidine nucleophile. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

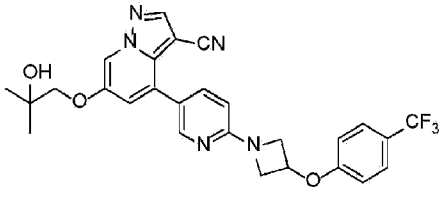
Table FF

Ex. #	Structure	Chemical Name	LCMS m/z
156		4-(6-(3-(4-cyanophenoxy)azetidin-1 -yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	481.1 (M+H)
157		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(m-tolyloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	470.2 (M+H)
159		4-(6-(3-(2-fluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	474.1 (M+H)
160		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methoxypyridin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	487.1 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
161		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(p-tolyloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	470.2 (M+H)
162		4-(6-(3-(3-chlorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	490.1 (M+H)

Example 163

[0581]

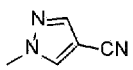


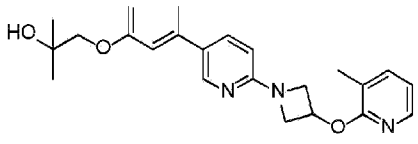
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0582] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 36.4 mg, 0.112 mmol), 3-(4-(trifluoromethyl)phenoxy)azetidine hydrochloride (70.7 mg, 0.279 mmol) and TEA (93.3 µL, 0.669 mmol) in DMA (372 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was diluted with water and washed with DCM. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM and washed with saturated Na_2CO_3(aq). The combined organic extracts were washed with brine, then dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo* to cleanly provide the title compound (15 mg, 25.7% yield). MS (apci) m/z = 524.1 (M+H).

Example 164

[0583]



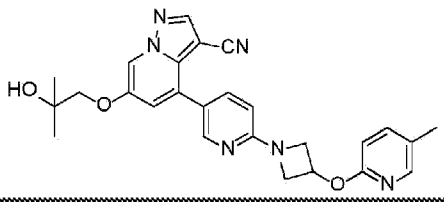
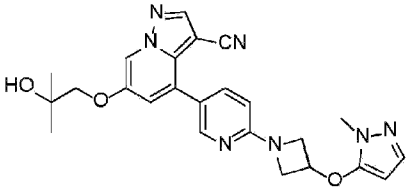
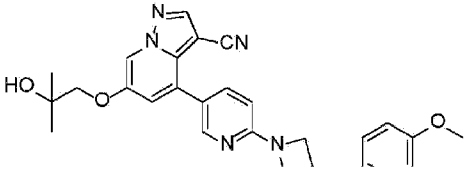


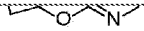
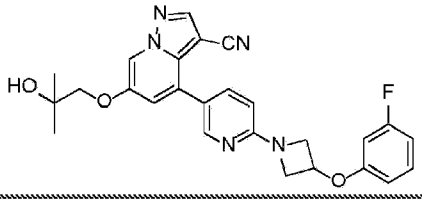
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((3-methylpyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0584] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35 mg, 0.107 mmol), 2-(azetidin-3-yloxy)-3-methylpyridine dihydrochloride (76.3 mg, 0.322 mmol) and TEA (117 µL, 0.858 mmol) in DMA (358 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated Na_2CO_3(aq). The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (9.4 mg, 18.6% yield). MS (apci) m/z = 471.10 (M+H).

[0585] The compounds in Table GG were prepared using a similar method to that described for the synthesis of **Example 164**, replacing 2-(azetidin-3-yloxy)-3-methylpyridine dihydrochloride with the appropriate azetidine nucleophile. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

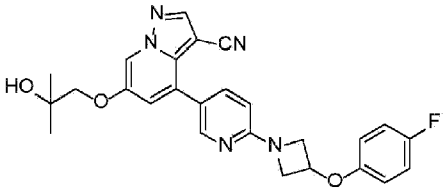
Table GG

Ex. #	Structure	Chemical Name	LCMS m/z
165		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methylpyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	471.20 (M+H)
166		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((1-methyl-1H-pyrazol-5-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	460.20 (M+H)
167		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methoxypyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	487.20 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
			
168		4-(6-(3-(3-fluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	474.20 (M+H)

Example 169

[0586]

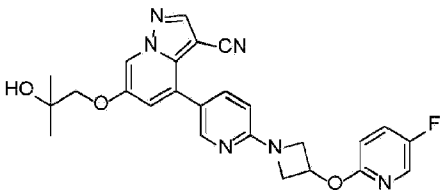


4-(6-(3-(4-fluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0587] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 36.5 mg, 0.112 mmol), 3-(4-fluorophenoxy)azetidine hydrochloride (68.3 mg, 0.336 mmol) and TEA (91.8 µL, 0.671 mmol) in DMA (358 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (23.5 mg, 44.4% yield). MS (apci) m/z = 474.20 (M+H).

Example 170

[0588]

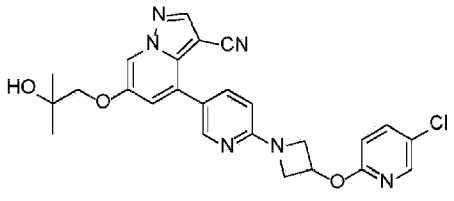


4-(6-(3-((5-fluoropyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0589] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35 mg, 0.107 mmol), 2-(azetidin-3-yloxy)-5-fluoropyridine dihydrochloride (51.7 mg, 0.215 mmol) and TEA (65.1 µL, 0.644 mmol) in DMA (358 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (8.3 mg, 16.3% yield). MS (apci) m/z = 475.20 (M+H).

Example 171

[0590]

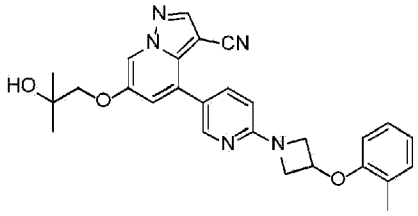


4-(6-(3-((5-chloropyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0591] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 35 mg, 0.107 mmol), 2-(azetidin-3-yloxy)-5-chloropyridine dihydrochloride (94.7 mg, 0.368 mmol) and TEA (117 µL, 0.858 mmol) in DMA (358 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. Then the organic extracts were washed with brine, dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (19.1 mg, 36.3% yield). MS (apci) m/z = 491.10 (M+H).

Example 172

[0592]

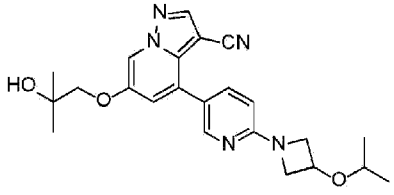


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(o-tolyloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0593] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35 mg, 0.107 mmol), 3-(2-Methylphenoxy)azetidine (52.2 mg, 0.322 mmol) and TEA (44 µL, 0.322 mmol) in DMA (358 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by silica chromatography (40-90% EtOAc in Hexanes as the gradient eluent). Impurities remained and product-containing fractions were concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (21.6 mg, 42.9% yield). MS (apci) m/z = 470.20 (M+H).

Example 173 reference

[0594]



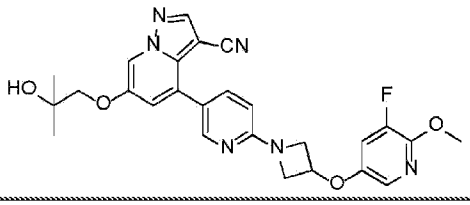
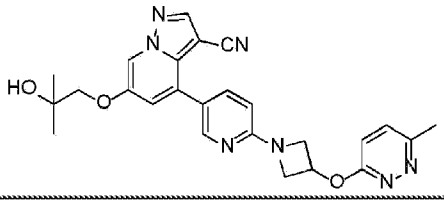
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-isopropoxyazetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0595] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35 mg, 0.107 mmol), 3-(1-methylethoxy)-azetidine hydrochloride (48.8 mg, 0.322 mmol) and TEA (73 µL, 0.536 mmol) in DMA (358 µL) was stirred overnight at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN: water containing 2% TFA. The solution was purified

directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16.8 mg, 37.2% yield). MS (apci) m/z = 422.20 (M+H).

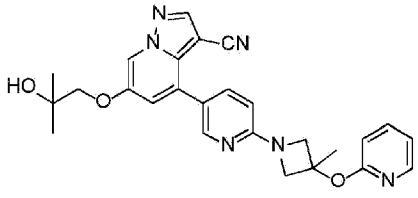
[0596] The compounds in Table HH were prepared using a similar method to that described for the synthesis of **173**, replacing 3-(1-methylethoxy)-azetidine hydrochloride with the appropriate azetidine nucleophile. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table HH

Ex. #	Structure	Chemical Name	LCMS m/z
174		4-(6-(3-((5-fluoro-6-methoxypyridin-3-yl)oxy)azetidin-1-yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	505.20 (M+H)
175		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methylpyridazin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	472.20 (M+H)

Example 176

[0597]



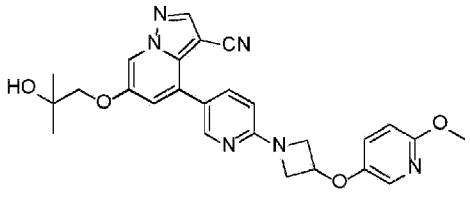
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-methyl-3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0598] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 76.1mg, 0.233 mmol), 2-((3-methylazetidin-3-yl)oxy)pyridine (95 mg, 0.579 mmol) and TEA (159 µL, 1.17 mmol) in DMA (777 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic

extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (33 mg, 30.1% yield). MS (apci) m/z = 471.20 (M+H).

Example 177

[0599]

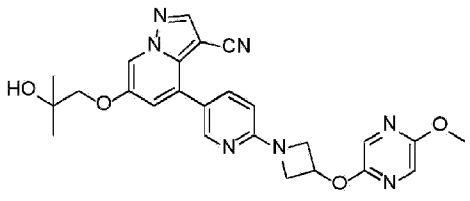


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0600] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 75.8 mg, 0.232 mmol), 5-(azetidin-3-yloxy)-2-methoxypyridine (93 mg, 0.516 mmol) and TEA (118 µL, 1.16 mmol) in DMA (774 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (65.6 mg, 58% yield). MS (apci) m/z = 487.15 (M+H).

Example 178

[0601]

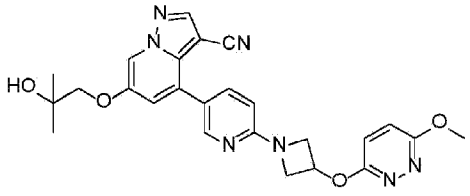


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methoxypyrazin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0602] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 32.2 mg, 0.0987 mmol), 2-(azetidin-3-yloxy)-5-methoxypyrazine (41.7 mg, 0.230 mmol) and TEA (67.5 µL, 0.493 mmol) in DMA (329 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN: water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (14.8 mg, 30.8% yield). MS (apci) m/z = 488.20 (M+H).

Example 179

[0603]

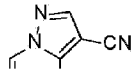


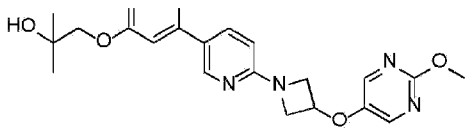
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridazin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0604] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 32.2 mg, 0.0987 mmol), 3-(azetidin-3-yloxy)-6-methoxypyridazine (51 mg, 0.281 mmol) and TEA (67.5 µL, 0.493 mmol) in DMA (329 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN: water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (28.6 mg, 59.5% yield). MS (apci) m/z = 488.20 (M+H).

Example 180

[0605]



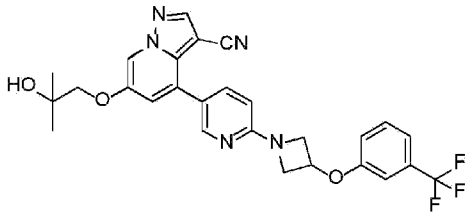


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((2-methoxypyrimidin-5-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0606] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 30.0 mg, 0.0919 mmol), 5-(azetidin-3-yloxy)-2-methoxypyrimidine (56 mg, 0.309 mmol) and TEA (101 µL, 0.735 mmol) in DMA (306 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (14.9 mg, 33.2% yield). MS (apci) m/z = 488.20 (M+H).

Example 181

[0607]



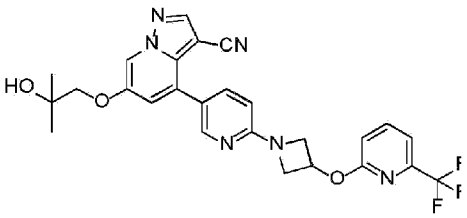
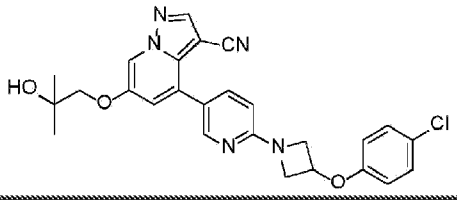
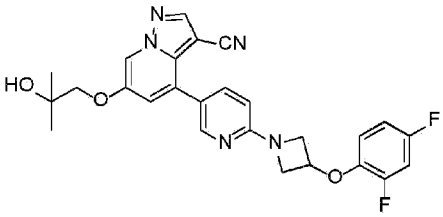
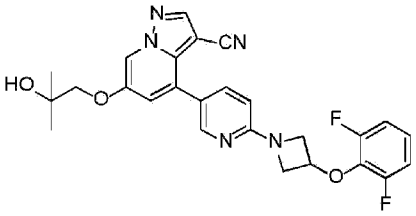
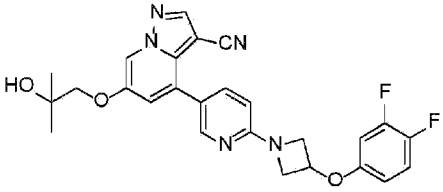
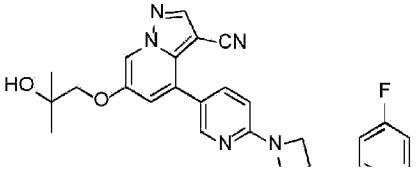
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(3-(trifluoromethyl)phenoxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

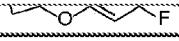
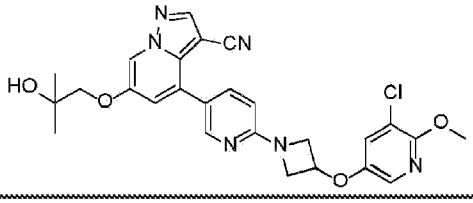
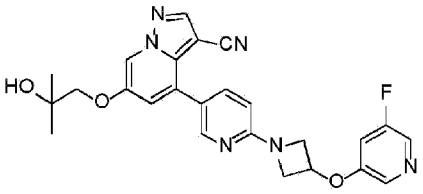
[0608] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 31.9 mg, 0.0978 mmol), 3-[3-(trifluoromethyl)phenoxy]azetidine hydrochloride (74.4 mg, 0.293 mmol) and TEA (93.6 µL, 0.684 mmol) in DMA (326 µL) was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$,

filtered and concentrated *in vacuo* to afford the title compound (36.6 mg, 71.5% yield). MS (apci) m/z = 524.10 (M+H).

[0609] The compounds in Table II were prepared using a similar method to that described for the synthesis of **Example 181,** replacing 3-[3-(trifluoromethyl)phenoxy]azetidine hydrochloride with the appropriate azetidine nucleophile. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification.

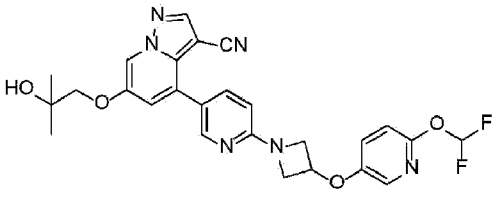
Table II

Ex. #	Structure	Chemical Name	LCMS m/z
182		6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-(trifluoromethyl)pyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	525.10 (M+H)
183		4-(6-(3-(4-chlorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	490.10 (M+H)
184		4-(6-(3-(2,4-difluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	492.15 (M+H)
185		4-(6-(3-(2,6-difluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	492.10 (M+H)
186		4-(6-(3-(3,4-difluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	492.10 (M+H)
187		4-(6-(3-(3,5-difluorophenoxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	492.15 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
			
188		4-(6-(3 -((5-chloro-6-methoxypyridin-3 -yl)oxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	521.10 (M+H)
189		4-(6-(3-((5-fluoropyridin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3-carbonitrile	475.10 (M+H)

Example 192

[0610]

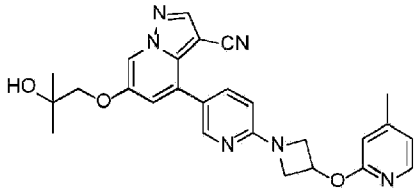


4-(6-(3-((6-(difluoromethoxy)pyridin-3-yl)oxy)azetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0611] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 30.7 mg, 0.0941 mmol), 5-(azetidin-3-yloxy)-2-(difluoromethoxy)pyridine (55 mg, 0.254 mmol) and TEA (64.3 µL, 0.470 mmol) in DMA (314 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (39.9 mg, 81.2% yield). MS (apci) m/z = 523.20 (M+H).

Example 193

[0612]

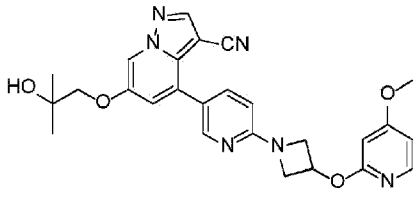


6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((4-methylpyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0613] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 25.5 mg, 0.0781 mmol), 2-(azetidin-3-yloxy)-4-methylpyridine (50 mg, 0.304 mmol) and TEA (74.8 µL, 0.547 mmol) in DMA (391 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (19.3 mg, 52.5% yield). MS (apci) m/z = 471.3 (M+H).

Example 194

[0614]



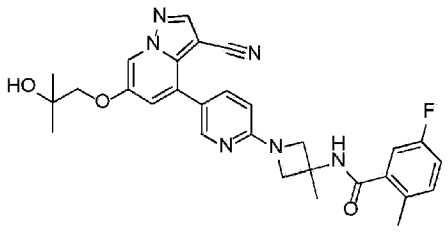
6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((4-methoxypyridin-2-yl)oxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0615] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 28 mg, 0.0858 mmol), 2-(azetidin-3-yloxy)-4-methoxypyridine (15.5 mg, 0.858 mmol) and TEA (82.1 µL, 0.601 mmol) in DMA (286 µL) was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt.

The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16.9 mg, 40.5% yield). MS (apci) m/z = 487.20 (M+H).

Example 197

[0616]



N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylazetidin-3-yl)-5-fluoro-2-methylbenzamide

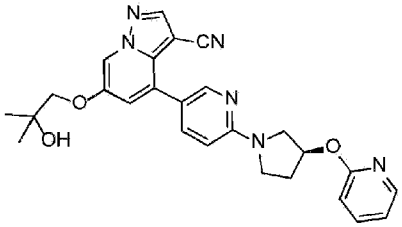
[0617] Step 1: Preparation of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylazetidin-3-yl)carbamate. A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 753 mg, 2.307 mmol), tert-butyl (3-methylazetidin-3-yl)carbamate hydrochloride (770.9 mg, 3.461 mmol) and DIEA (1.809 mL, 10.38 mmol) in DMSO (4.615 mL) was stirred overnight at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (1-10% MeOH in DCM as the gradient eluent) to afford the title compound (1.089 g, 95.81% yield) in sufficient purity for step 2. MS (apci) m/z = 493.3 (M+H).

[0618] Step 2: Preparation of 4-(6-(3-amino-3-methylazetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile.A solution of tert-butyl (1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylazetidin-3-yl)carbamate (1.089g, 2.211 mmol) in DCM (5.527 mL) was treated with TFA (10 mL, 130 mmol). After stirring for 1 h at ambient temperature the mixture was concentrated *in vacuo* and the residue diluted with EtOAc and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were washed with brine and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to cleanly provide the title compound (800 mg, 92.2% yield) in sufficient purity for step 3. MS (apci) m/z = 393.2 (M+H).

[0619] Step 3: Preparation of N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylazetidin-3-yl)-5-fluoro-2-methylbenzamide. A mixture of 4-(6-(3-amino-3-methylazetidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (54 mg, 0.138 mmol), HATU (57.5 mg, 0.151 mmol), 5-Fluoro-2-methylbenzoic acid (42.4 mg, 0.275 mmol) in DMSO (1.38 mL) was treated with DIEA (120 µL, 0.688 mmol) and then stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (0.5-10% MeOH in DCM with 0.05-1% NH_4OH as the gradient eluent) to cleanly provide the title compound (48.2 mg, 66.3% yield) MS (apci) m/z=529.2 (M+H)

Example 201

[0620]

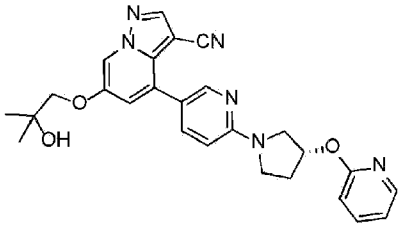


(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0621] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 394 mg, 1.208 mmol, (S)-2-(pyrrolidin-3-yloxy)-pyridine dihydrochloride (1.146 g, 4.833 mmol) and TEA (1.639 mL, 12.08 mmol) in DMA (12 mL) was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (400 mg, 70% yield). MS (apci) m/z = 471.2 (M+H). ^{1}H NMR (400 MHz, DMSO) δ 8.65-8.64 (d, 1H), 8.56 (s, 1H), 8.31-8.30 (dd, 1H), 8.22-8.20 (m, 1H), 7.76-7.69 (m, 2H), 7.26-7.25 (d, 1H), 7.01-6.98 (m, 1H), 6.85-6.83 (m, 1H), 6.61-6.59 (d, 1H), 5.69-5.67 (m, 1H), 4.69 (s, 1H), 3.86-3.81 (m, 3H), 3.70-3.65 (m, 2H), 3.60-3.53 (m, 1H), 2.42-2.22 (m, 2H), 1.22 (s, 6H)

Example 202

[0622]

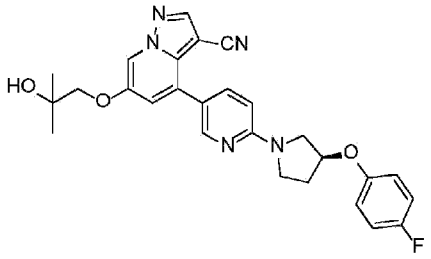


(R)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0623] A solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 25 mg, 0.077 mmol) in DMA (100 µL) was treated with TEA (27 µL, 0.192 mmol) and (R)-2-(pyrrolidin-3-yloxy)pyridine hydrochloride (15.4 mg, 0.077 mmol) and was stirred overnight at 110°C. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 × 10 mL) using a phase separator frit. The organic extracts were concentrated *in vacuo.* The residue was purified directly by C18 reverse phase chromatography (0-60% ACN in water as the gradient eluent) to cleanly provide the title compound (16 mg, 44% yield). MS (apci) m/z = 471.2 (M+H).

Example 203

[0624]

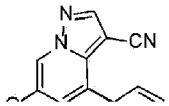


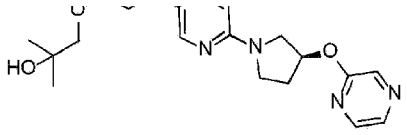
(S)-4-(6-(3-(4-fluorophenoxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0625] A solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 31.6 mg, 0.097 mmol) in DMA (1 mL) was treated with (S)-3-(4-fluorophenoxy)pyrrolidine hydrochloride (22.1 mg, 0.102 mmol) followed by TEA (65.7 µL, 0.484 mmol) and was stirred overnight at 90°C. Additional (S)-3-(4-fluorophenoxy)pyrrolidine hydrochloride (8.8 mg, 0.48 mmol) was added to the reaction and reaction continued to stir for an additional 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-50% Acetone in DCM as the gradient eluent). An impurity remained so product-containing fractions were concentrated *in vacuo.* The residue was repurified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (9.8 mg, 20.8% yield). MS (apci) m/z = 488.2 (M+H).

Example 204

[0626]





(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyrazin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

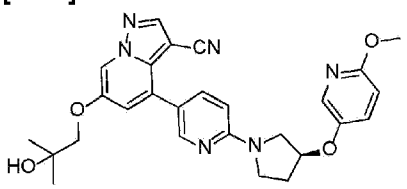
[0627] Step 1: Preparation of tert-butyl (S)-3-(pyrazin-2-yloxy)pyrrolidine-1-carboxylate. To a solution of tert-butyl (S)-3-(phenylcarbamoyl)pyrrolidine-1-carboxylate (264.5 mg, 1.413 mmol) in DMF (7.1 mL) was added 2-chloropyrazine (192.2 mg, 1.695 mmol) followed by sodium hydride (60% w/w, 113 mg, 2.825 mmol) and then the reaction mixture was stirred for 16 hours at 80°C After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-60% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 374.9 mg, 1.413 mmol) in sufficient purity for step 2. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1H), 8.22 (s, 2H), 5.49 (s, 1H), 3.64-3.57 (m, 1H), 3.48-3.31 (m, 3H), 2.23-2.04 (m, 2H), 1.40-1.39 (d, 9H).

[0628] Step 2: Preparation of (S)-2-(pyrrolidin-3-yloxy)pyrazine. To a solution of tert-butyl (S)-3-(pyrazin-2-yloxy)pyrrolidine-1-carboxylate (assumed 374.9 mg, 1.413 mmol) in 3mL DCM was treated with TFA (3 mL, 39 mmol). The reaction mixture was stirred for 0.5 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (72.1 mg, 31 % yield over two steps) in sufficient purity for step 3. 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 8.21 (s, 2H), 5.46-5.42 (m, 1H), 3.25-3.21 (m, 1H), 3.09-2.95 (m, 3H), 2.17-2.08 (m, 1H), 1.96-1.89 (m, 1H).

[0629] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyrazin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 30.8 mg, 0.094 mmol) in DMA (2 mL) was added TEA (64 µL, 0.472 mmol) followed by (S)-2-(pyrrolidin-3-yloxy)pyrazine (71.7mg, 0.434 mmol). The reaction mixture was stirred overnight at 90°C. After cooling to ambient temperature, the reaction was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). An impurity remained and product-containing fractions were concentrated *in vacuo.* The residue was repurified by silica chromatography (5-95% Acetone in DCM as the gradient eluent) to afford the title compound (36.2 mg, 81% yield). MS (apci) m/z = 472.2 (M+H).

Example 205

[0630]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

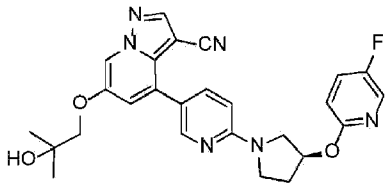
[0631] Step 1: Preparation of tert-butyl (S)-3-((6-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate. To a solution of tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate **(Intermediate R14;** 208.7 mg, 0.787 mmol) in DMF (8 mL) was added 5-hydroxy-2-methoxylpyridine (118.1 mg, 0.944 mmol) followed by potassium carbonate (217.4 mg, 1.573 mmol) and then the reaction mixture was stirred for 16 hours at 90°C After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-75% Acetone in DCM as the gradient eluent) to afford the title compound (assume theoretical yield, 231 mg, 0.787 mmol) in sufficient purity for step 2. MS (apci) m/z = 295.1 (M+H).

[0632] Step 2: Preparation of (S)-2-methoxy-5-(pyrrolidin-3-yloxy)pyridine. To a solution of tert-butyl (S)-3-((6-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate (assumed 231 mg, 0.787 mmol) in 2mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (54.6 mg, 36% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 195.1 (M+H).

[0633] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 60.8 mg, 0.186 mmol) in DMA (2 mL) was added TEA (126µL, 0.932 mmol) followed by (S)-2-methoxy-5-(pyrrolidin-3-yloxy)pyridine (54.3 mg, 0.279 mmol). The reaction mixture was stirred overnight at 90°C. After cooling to ambient temperature, the reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (39.5 mg, 42% yield). MS (apci) m/z = 501.2 (M+H).

Example 206

[0634]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-

yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

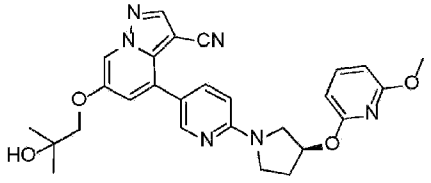
[0635] Step 1: Preparation of tert-butyl (S)-3-((5-fluoropyridin-2-yl)oxy)pyrrolidine-1-carboxylate. To a solution of tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate **(Intermediate R14;** 200.8 mg, 0.757 mmol) in DMF (8 mL) was added 5-fluoro-2-hydroxypyridine (102.7 mg, 0.908 mmol) followed by potassium carbonate (209.2 mg, 1.514 mmol) and then the reaction mixture was stirred for 60 hours at 90°C After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-75% Acetone in DCM as the gradient eluent) to afford the title compound (assume theoretical yield, 213.5 mg, 0.757 mmol) in sufficient purity for step 2. MS (apci) m/z = 183.1 (M-Boc).

[0636] Step 2: Preparation of (S)-5-fluoro-2-(pyrrolidin-3-yloxy)pyridine. To a solution tert-butyl (S)-3-((5-fluoropyridin-2-yl)oxy)pyrrolidine-1-carboxylate (assumed 213.5 mg, 0.75 mmol) in 2mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (57.2 mg, 41% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 183.1 (M+H).

[0637] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 30.3 mg, 0.093 mmol) and (S)-5-fluoro-2-(pyrrolidin-3-yloxy)pyridine (55.8 mg, 0.31 mmol) in DMA (2 mL) was added TEA (63µL, 0.464 mmol). The reaction mixture was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (29.6 mg, 65% yield). MS (apci) m/z = 489.2 (M+H).

Example 207

[0638]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

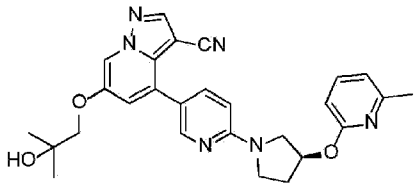
[0639] Step 1: Preparation of tert-butyl (S)-3-((6-methoxypyridin-2-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of (S)-1-Boc-3-hydroxypyrrolidine(112.5 mg, 0.601 mmol) and 2-Chloro-6-methoxypyridine (86 µL, 0.721 mmol) in DMF (6 mL) was added sodium hydride (60% w/w, 48.1 mg, 1.20 mmol) and then the reaction mixture was stirred for 16 hours at 80°C. Additional sodium hydride (60% w/w, 48.1 mg, 1.20 mmol) was added and the reaction mixture was stirred for an additional 16 hours at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound as crude product that was directly used in the next step, assuming quantitative yield. MS (apci) m/z = 195.1 (M-Boc).

[0640] Step 2: Preparation of (S)-2-methoxy-6-(pyrrolidin-3-yloxy)pyridine. To a solution of tert-butyl (S)-3-((6-methoxypyridin-2-yl)oxy)pyrrolidine-1-carboxylate (assumed 176.8 mg, 0.601 mmol) in 2mL DCM was treated with TFA (2 mL). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (81.6 mg, 70% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 195.1 (M+H).

[0641] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 57.2 mg, 0.175 mmol) and (S)-2-methoxy-6-(pyrrolidin-3-yloxy)pyridine (71.5 mg, 0.368 mmol) in DMA (3 mL) was added TEA (64 µL, 0.472 mmol) . The reaction mixture was stirred overnight at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (56.6 mg, 65% yield). MS (apci) m/z = 501.2 (M+H).

Example 208

[0642]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methylpyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

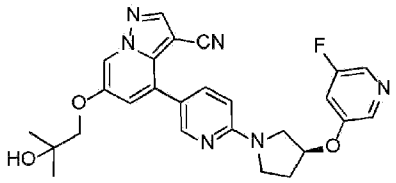
[0643] Step 1: Preparation of tert-butyl (S)-3-((6-methylpyridin-2-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of (S)-1-Boc-3-hydroxypyrrolidine (112.5 mg, 0.601 mmol) and 2-chloro-6-methylpyridine (74 µL, 0.669 mmol) in DMF (6 mL) was added sodium hydride (60% w/w, 44.6 mg, 1.11 mmol) and then the reaction mixture was stirred for 16 hours at 80°C. Additional sodium hydride (60% w/w, 44.6 mg, 1.11 mmol) was added and the reaction mixture was stirred for an additional 16 hours at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 155 mg, 0.557 mmol) in sufficient purity for step 2. MS (apci) m/z = 279.1 (M+H).

[0644] Step 2: Preparation of (S)-2-methyl-6-(pyrrolidin-3-yloxy)pyridine. To a solution of tert-butyl (S)-3-((6-methylpyridin-2-yl)oxy)pyrrolidine-1-carboxylate (assumed 155 mg, 0.557 mmol) in 2mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (81.6 mg, 70 % yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 179.1(M+H).

[0645] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methylpyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 53.3 mg, 0.163 mmol) and (S)-2-methyl-6-(pyrrolidin-3-yloxy)pyridine (69.9 mg, 0.392 mmol) in DMA (2 mL) was added TEA (111 µL, 0.817mmol). The reaction mixture was stirred overnight at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography 1-30% MeOH in EtOAc with 0.1-2% NH_4OH as the gradient eluent) to cleanly provide the title compound (60.8 mg, 76.8% yield) MS (apci) m/z=485.2 (M+H)

Example 209

[0646]



(S)-4-(6-(3-((5-fluoropyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0647] Step 1: Preparation of tert-butyl (S)-3-((5-fluoropyridin-3-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate **(Intermediate R14;** 301.5 mg, 1.136 mmol) and 5-fluoropyridin-3-ol (154.2 mg, 1.364 mmol) in DMF (11 mL) was added potassium carbonate (314.1 mg, 2.273 mmol) and then the reaction mixture was stirred for 16 hours at 80°C After

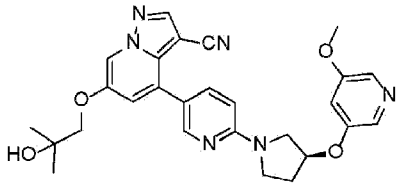
cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 320.7 mg, 1.136 mmol) in sufficient purity for step 2. MS (apci) m/z = 183.1 (M-Boc).

[0648] Step 2: Preparation of (S)-3-fluoro-5-(pyrrolidin-3-yloxy)pyridine. To a solution tert-butyl (S)-3-((5-fluoropyridin-3-yl)oxy)pyrrolidine-1-carboxylate (assumed 320.7 mg, 1.136 mmol) in 2.5 mL DCM was treated with TFA (2.5 mL, 32.7 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (57.2 mg, 41% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 183.1 (M+H).

[0649] Step 3: Preparation of (S)-4-(6-(3-((5-fluoropyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 32.7 mg, 0.10 mmol) and (S)-3-fluoro-5-(pyrrolidin-3-yloxy)pyridine (48.4 mg, 0.266 mmol) in DMA (2 mL) was added TEA (68µL, 0.501 mmol). The reaction mixture was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography 1-30% MeOH in EtOAc with 0.1-2% NH_4OH as the gradient eluent) to cleanly provide the title compound (23 mg, 47% yield) MS (apci) m/z=489.2 (M+H)

Example 210

[0650]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

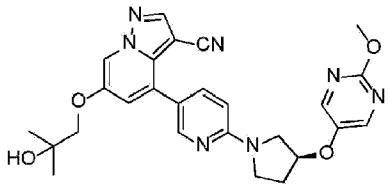
[0651] Step 1: Preparation of tert-butyl (S)-3-((5-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate **(Intermediate R14;** 301.6 mg, 1.137 mmol) and 5-methoxypyridin-3-ol (170.7 mg, 1.364 mmol) in DMF (11 mL) was added potassium carbonate (314 mg, 2.273 mmol) and then the reaction mixture was stirred for 16 hours at 80°C After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 334.7 mg, 1.137 mmol) in sufficient purity for step 2. MS (apci) m/z = 239.1 (M- *t*-Bu fragment).

[0652] Step 2: Preparation of (S)-3-methoxy-5-(pyrrolidin-3-yloxy)pyridine. To a solution of tert-butyl (S)-3-((5-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate (assumed 334.7 mg, 1.137 mmol) in 2.5 mL DCM was treated with TFA (2.5 mL, 32.7 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (59.4 mg, 26.9% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 195.1 (M+H).

[0653] Step 3: Preparation of ((S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((5-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 30 mg, 0.092 mmol) and (S)-3-methoxy-5-(pyrrolidin-3-yloxy)pyridine (59.4 mg, 0.306 mmol) in DMA (2 mL) was added TEA (62µL, 0.46 mmol). The reaction mixture was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography 1-30% MeOH in EtOAc with 0.1-2% NH_4OH as the gradient eluent) to cleanly provide the title compound (32.6 mg, 71 % yield) MS (apci) m/z=501.2 (M+H)

Example 211

[0654]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((2-methoxypyrimidin-5-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0655] Step 1: Preparation oftert-butyl (S)-3-((2-methoxypyrimidin-5-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of tert-butyl (R)-3-((methylsulfonyl)oxypyrrolidine-1-carboxylate **(Intermediate R14;** 374.0 mg, 1.410 mmol) and 2-methoxypyrimidine-5-ol (213.3 mg, 1.692 mmol) in DMF (14 mL) was added potassium carbonate (390 mg, 2.819 mmol) and then the reaction mixture was stirred for 60 hours at 80°C After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 416.4 mg, 1.410 mmol) in sufficient purity for step 2. MS (apci) m/z = 196.1 (M-Boc).

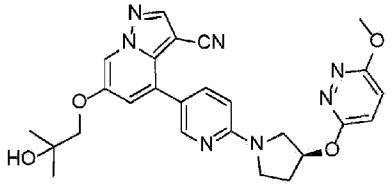
[0656] Step 2: Preparation of and (S)-2-methoxy-5-(pyrrolidin-3-yloxy)pyrimidine. To a solution of tert-butyl (S)-3-((2-methoxypyrimidin-5-yl)oxy)pyrrolidine-1-carboxylate (assumed 416.4 mg, 1.410 mmol) in 2 mL DCM was treated with TFA (2 mL, 26mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and

washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (61.7 mg, 20% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 196.1 (M+H).

[0657] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((2-methoxypyrimidin-5-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 31.7 mg, 0.097 mmol) and (S)-2-methoxy-5-(pyrrolidin-3-yloxy)pyrimidine (60.7 mg, 0.311 mmol) in DMA (2 mL) was added TEA (79µL, 0.58 mmol). The reaction mixture was stirred 16 h at 80°C. The reaction mixture was stirred at 80°C for 16 hours. The reaction was heated to 100°C for 60 hours. The reaction was heated to 150°C for 2 hours in a microwave reactor. The reaction was heated to 150°C for 8 hours in a microwave reactor. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16.6 mg, 34% yield). MS (apci) m/z = 502.3 (M+H).

Example 212

[0658]



(S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0659] Step 1: Preparation of tert-butyl (S)-3-((6-methoxypyridazin-3-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of (S)-1-Boc-3-hydroxypyrrolidine (83.9 mg, 0.448 mmol) 3-Chloro-6-methoxypyridazine (77.7 mg, 0.538 mmol) in DMF (4.5 mL) was added sodium hydride (60% w/w, 35.8 mg, 0.896 mmol) and then the reaction mixture was stirred for 60 hours at 80°C. Additional sodium hydride (60% w/w, 35.8 mg, 0.896 mmol) was added and the reaction mixture was stirred for an additional 16 hours at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 132 mg, 0.448 mmol) in sufficient purity for step 2. MS (apci) m/z = 295.1 (M+H).

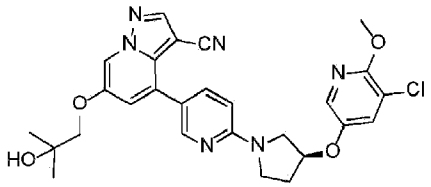
[0660] Step 2: Preparation of (S)-3-methoxy-6-(pyrrolidin-3-yloxy)pyridazine. To a solution of tert-butyl (S)-3-((6-methoxypyridazin-3-yl)oxy)pyrrolidine-1-carboxylate (assumed 132 mg, 0.448 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient

temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (17.6 mg, 20.1% yield over two steps) in sufficient purity for step 3.

[0661] Step 3: Preparation of (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-((6-methoxypyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42**; 22.4 mg, 0.069 mmol) and (S)-3-methoxy-6-(pyrrolidin-3-yloxy)pyridazine (17.4 mg, 0.892 mmol) in DMA (3 mL) was added TEA (46µL, 0.343 mmol). The reaction mixture was stirred 16 h at 80°C. The reaction mixture was stirred for 60 h at 100°C. The reaction mixture was then stirred for 2 h at 150°C in a microwave reactor. The reaction was heated for an additional 8 h at 150°C in a microwave reactor. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO4(s)$, filtered and concentrated *in vacuo* to afford the title compound (6.3 mg, 18.3% yield). MS (apci) m/z = 502.2 (M+H).

Example 213

[0662]



(S)-4-(6-(3-((5-chloro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0663] Step 1: Preparation of tert-butyl (S)-3-((5-chloro-6-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate. To a mixture of tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate **(Intermediate R14;** 602.2 mg, 2.27 mmol) and 3-Chloro-5-hydroxy-2-methoxypyridine (301.8 mg, 1.891 mmol) in DMF (22 mL) was added potassium carbonate (522.8 mg, 3.783 mmol) and then the reaction mixture was stirred for 60 hours at 80°C After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-95% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 621.7 mg, 1.891 mmol) in sufficient purity for step 2. MS (apci) m/z = 229.1 (M-Boc).

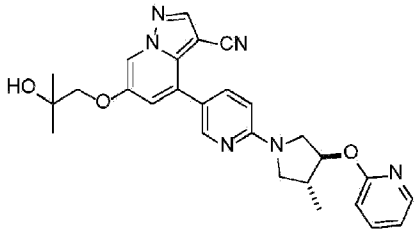
[0664] Step 2: Preparation of (S)-3-chloro-2-methoxy-5-(pyrrolidin-3-yloxy)pyridine. To a solution tert-butyl (S)-3-((5-chloro-6-methoxypyridin-3-yl)oxy)pyrrolidine-1-carboxylate (assumed 621.7 mg, 1.891 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min

at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (140.6 mg, 32.5% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 229.10 (M+H).

[0665] Step 3: Preparation of (S)-4-(6-(3-((5-chloro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 26.4 mg, 0.081 mmol) and (S)-3-chloro-2-methoxy-5-(pyrrolidin-3-yloxy)pyridine (64.7 mg, 0.283 mmol) in DMA (1 mL) was added TEA (66 µL, 0.49 mmol). The reaction mixture was stirred 16 h at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (27.2 mg, 63% yield). MS (apci) m/z = 535.2 (M+H).

Example 214

[0666]



6-(2-hydroxy-2-methylpropoxy)-4-(6-((trans)-3-methyl-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0667] Step 1: Preparation of tert-butyl (trans)-3-methyl-4-(pyridin-2-yloxy)pyrrolidine-1-carboxylate. To a mixture of tert-butyl (trans)-3-hydroxy-4-methylpyrrolidine-1-carboxylate (303.8 mg, 1.509 mmol) and 2-fluoropyridine (259 µL, 3.019 mmol) in DMA (7.5 mL) was added sodium hydride (60% w/w, 120.7 mg, 3.019 mmol). The reaction mixture was stirred for 16 h at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-50% EtOAc in hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 420 mg, 1.509 mmol) in sufficient purity for step 2. MS (apci) m/z = 279.1 (M+H).

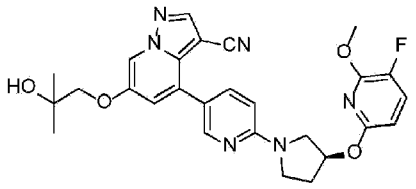
[0668] Step 2: Preparation of 2-(((trans)-4-methylpyrrolidin-3-yl)oxy)pyridine. To a solution of tert-butyl (trans)-3-hydroxy-4-methylpyrrolidine-1-carboxylate (assumed 420 mg, 1.509 mmol) in 3 mL DCM was treated with TFA (3 mL, 39.2 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with

saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (178.6 mg, 66% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 179.1 (M+H).

[0669] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-((trans)-3-methyl-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35 mg, 0.107 mmol) and 2-(((trans)-4-methylpyrrolidin-3-yl)oxy)pyridine (76.5 mg, 0.428 mmol) in DMA (1.1 mL) was added TEA (145µL, 1.07 mmol). The reaction mixture was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_3$(aq) and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous Na_2SO4(s), filtered and concentrated *in vacuo* to afford the title compound (38.2 mg, 73.5% yield). MS (apci) m/z = 485.2 (M+H).

Example 215

[0670]



(S)-4-(6-(3-((5-fluoro-6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0671] Step 1: Preparation of 3,6-difluoro-2-methoxypyridine. To a solution of 2,3,6-Trifluoropyridine (1.00 mL, 11.27 mmol) in MeOH (11 mL) was added sodium methoxide (30% solution in MeOH, 2.5 mL), 13.5 mmol). The reaction solution was stirred for 2 h at 70°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo* to afford the title compound (257 mg, 16% yield) in sufficient purity for step 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90-7.84 (m, 1H), 6.75-6.72 (m, 1H), 3.92 (s, 3H).

[0672] Step 2: Preparation of tert-butyl (S)-3-((5-fluoro-6-methoxypyridin-2-yl)oxy)pyrrolidine-1-carboxylate. A solution of (S)-1-Boc-3-hydroxypyrrolidine (255 mg, 1.362 mmol) in 13.6 mL DMF was treated with 3,6-difluoro-2-methoxypyridine (256.9 mg, 1.77 mmol) followed by sodium hydride (60% w/w, 163.4 mg, 4.086 mmol). The reaction mixture was stirred for 16 h at 80°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-40%

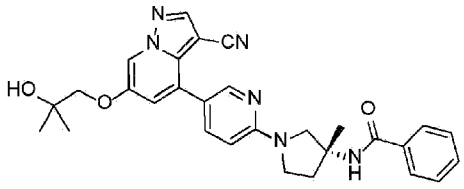
EtOAc in Hexanes as the gradient eluent) to afford the title compound (assume theoretical yield, 425 mg, 1.362 mmol) in sufficient purity for step 3. MS (apci) m/z = 213.1 (M-Boc).

[0673] Step 3: Preparation of (S)-3-fluoro-2-methoxy-6-(pyrrolidin-3-yloxy)pyridine. To a solution of tert-butyl (S)-3-((5-fluoro-6-methoxypyridin-2-yl)oxy)pyrrolidine-1-carboxylate (assumed 425 mg, 1.362 mmol) in 3 mL DCM was treated with TFA (3 mL, 39 mmol). The reaction mixture was stirred for 30 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was diluted with 4:1 DCM: IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo to* afford the title compound (222.2 mg, 77% yield over two steps) in sufficient purity for step 4. MS (apci) m/z = 213.1 (M+H).

[0674] Step 4: Preparation of (S)-4-(6-(3-((5-fluoro-6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 35.2 mg, 0.108 mmol) in DMA (1.1 mL) was added (S)-3-fluoro-2-methoxy-6-(pyrrolidin-3-yloxy)pyridine (91.6 mg, 0.431 mmol) followed by TEA (145µL, 1.07 mmol). The reaction mixture was stirred 16 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated NaHCO3(aq) and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous Na_2SO4(s), filtered and concentrated *in vacuo* to afford the title compound (44.8 mg, 80.1% yield). MS (apci) m/z = 519.2 (M+H).

Example 224

[0675]



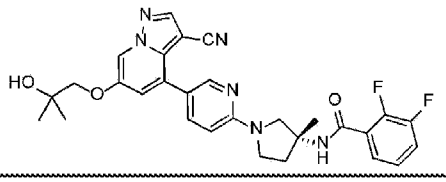
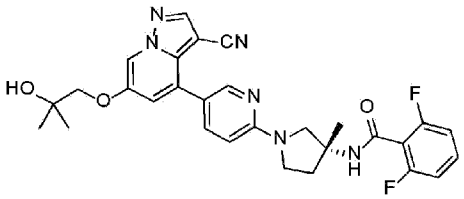
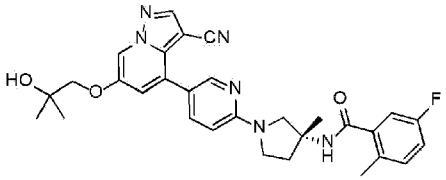
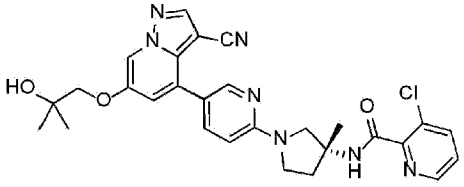
(R)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)benzamide.

[0676] A mixture of (R)-4-(6-(3-amino-3-methylpyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)(**Intermediate P49**; 40 mg, 0.098 mmol), HATU (75 mg, 0.20 mmol), and benzoic acid (24 mg, 0.20 mmol) in ACN (600 µL) was treated with DIEA (86 µL, 0.49 mmol) and then stirred for 12 h at ambient temperature. The reaction mixture was diluted with 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic extracts were washed with brine, then dried over anhydrous $MgSO_{4(s)}$,

filtered and concentrated *in vacuo* to afford the title compound (15 mg, 46% yield). MS (apci) m/z = 511.3 (M+H).

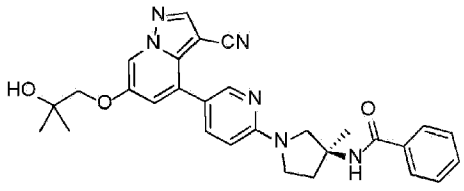
[0677] The compounds in Table JJ were prepared using a similar method to that described for the synthesis of **Example 224**, replacing benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table JJ

Ex. #	Structure	Chemical Name	LCMS m/z
226		(R)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-2,3-difluorobenzamide	547.3 (M+H)
227		(R)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-2,6-difluorobenzamide	547.3 (M+H)
228		(R)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-5-fluoro-2-methylbenzamide	543.3 (M+H)
229		(R)-3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3 -yl)picolinamide	546.3 (M+H)

Example 231

[0678]



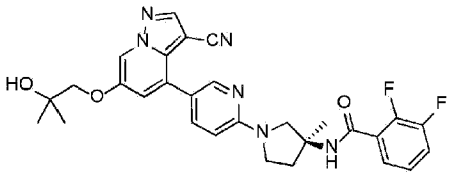
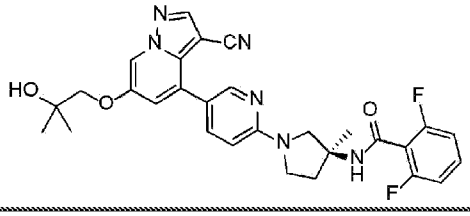
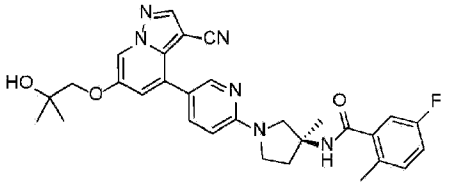
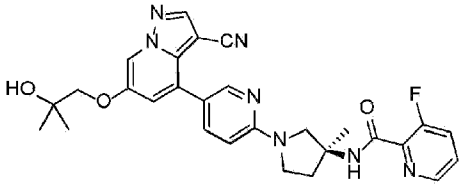
(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-

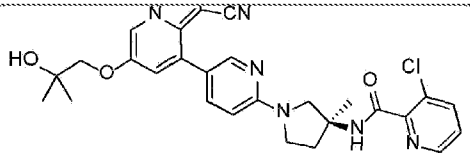
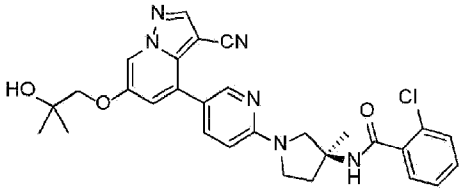
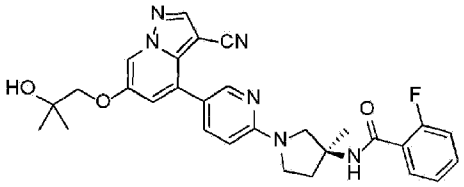
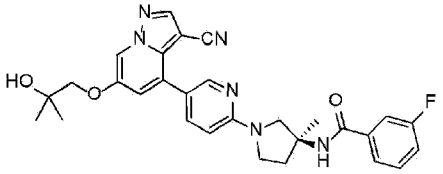
methylpyrrolidin-3-yl)benzamide

[0679] A mixture of (S)-4-(6-(3-amino-3-methylpyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate** P50; 30 mg, 0.047 mmol), HATU (56 mg, 0.15 mmol), and benzoic acid (18 mg, 0.15 mmol) in ACN (600 µL) was treated with DIEA (64 µL, 0.37 mmol) and then stirred for 12 h at ambient temperature. The reaction mixture was diluted with 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic extracts were washed with brine, then dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (12 mg, 51% yield). MS (apci) m/z = 511.3 (M+H).

[0680] The compounds in Table KK were prepared using a similar method to that described for the synthesis of **Example 231**, replacing benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

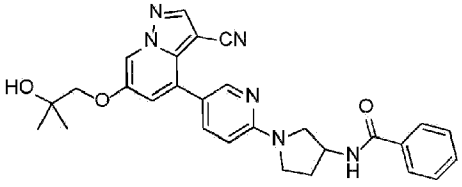
Table KK

Ex. #	Structure	Chemical Name	LCMS m/z
233		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-2,3-difluorobenzamide	547.3 (M+H)
234		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-2,6-difluorobenzamide	547.2 (M+H)
235		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-5-fluoro-2-methylbenzamide	543.3 (M+H)
236		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-3-fluoropicolinamide	530.2 (M+H)
237		(S)-3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-	546.2 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
		methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)picolinamide	
239		(S)-2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)benzamide	545.2 (M+H)
240		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3-yl)-2-fluorobenzamide	529.3 (M+H)
241		(S)-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)-3-methylpyrrolidin-3 -yl)-3-fluorobenzamide	529.2 (M+H)

Example 242

[0681]



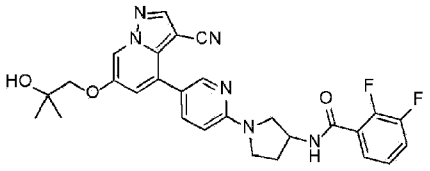
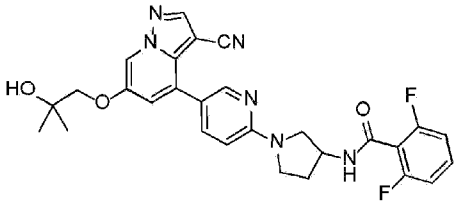
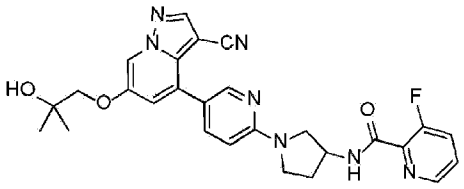
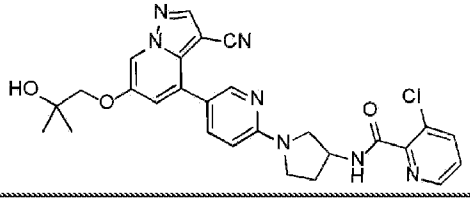
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)benzamide

[0682] A mixture of 4-(6-(3-aminopyrrolidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P51**; 40 mg, 0.064 mmol), HATU (78 mg, 0.20 mmol), and benzoic acid (25 mg, 0.20 mmol) in ACN (600 µL) was treated with DIEA (89 µL, 0.51 mmol) and then stirred for 12 h at ambient temperature. The reaction mixture was diluted with 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic

extracts were washed with brine, then dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (15 mg, 47% yield). MS (apci) m/z = 497.2 (M+H).

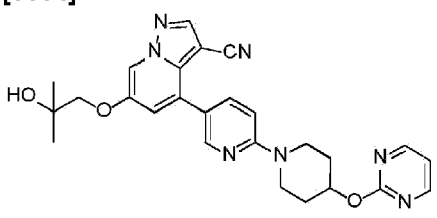
[0683] The compounds in Table LL were prepared using a similar method to that described for the synthesis of **Example 242,** replacing benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table LL

Ex. #	Structure	Chemical Name	LCMS m/z
243		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)-2,3-difluorobenzamide	533.2 (M+H)
244		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)-2,6-difluorobenzamide	533.2 (M+H)
245		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)-3-fluoropicolinamide	516.3 (M+H)
246		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)picolinamide	532.2 (M+H)

Example 247

[0684]

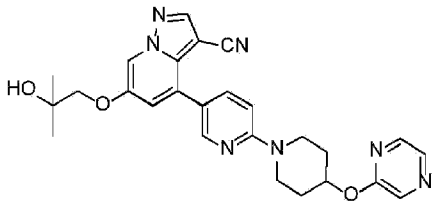


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(pyrimidin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0685] To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 40 mg, 0.123 mmol) in DMA (1.2 mL) was added 2-(piperidin-4-yloxy)pyrimidine (242 mg, 0.135 mmol) followed by TEA (33.5µL, 0.245 mmol). The reaction mixture was sparged with argon and stirred overnight at 90°C. Then additional 2-(piperidin-4-yloxy)pyrimidine (242 mg, 0.135 mmol) and TEA (33.5µL, 0.245 mmol) and the reaction was stirred for 8 h at 110°C and then the reaction temperature was lowered to 90°C where it was stirred at for 60 h. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The reaction was purified by silica chromatography (40-99% EtOAc in hexanes as the gradient eluent) to afford the title compound (20.8 mg, 35% yield). MS (apci) m/z = 486.2 (M+H).

Example 248

[0686]

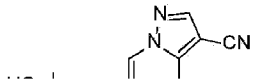


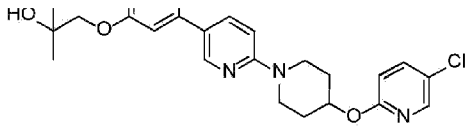
6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(pyrazin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0687] To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 25 mg, 0.077 mmol) in DMA (38 mL) was added 2-(piperidin-4-yloxy)pyrazine (13.7 mg, 0.077 mmol) followed by TEA (21 µL, 0.153 mmol). The reaction mixture was sparged with argon and stirred for 60 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM the organic extracts were washed with saturated $NaHCO_{3(aq)}$ and then water. Then the organic extracts were washed with brine and dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was resuspended in 1 mL DCM and was purified by silica chromatography (40-99% EtOAc in hexanes as the gradient eluent) to afford the title compound (12.3 mg, 33.1% yield). MS (apci) m/z = 486.2 (M+H).

Example 249

[0688]



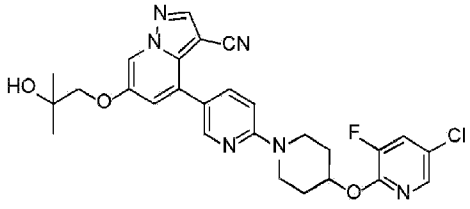


4-(6-(4-((5-chloropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0689] To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 51.1 mg, 0.157 mmol) in DMA (78 mL) was added 5-chloro-2-(piperidin-4-yloxy)pyridine (40 mg, 0.188 mmol) followed by TEA (43µL, 0.313 mmol). The reaction mixture was stirred for 48 h at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM the organic extracts were washed with saturated $NaHCO_{3(aq)}$ and then water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The reaction was purified by silica chromatography (40-75% EtOAc in hexanes as the gradient eluent) to afford the title compound (16.1 mg, 20% yield). MS (apci) m/z = 519.2 (M+H).

Example 250

[0690]



4-(6-(4-((5 -chloro-3 -fluoropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0691] Step 1: Preparation of tert-butyl 4-((5-chloro-3-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl-4-hydroxy-1-piperidinecarboxylate (135 mg, 0.67 mmol) in DMF (2.2 mL) was added sodium hydride (60% w/w, 113 mg, 2.825 mmol). The mixture stirred at ambient temperature for 30 minutes and then 5-chloro-2,3-difluoropyridine (100 mg, 0.67 mmol) was added. The reaction mixture was stirred for 60 h at 60°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$ and then water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assume theoretical yield, 222 mg, 0.671 mmol) in sufficient purity for step 2. MS (apci) m/z = 213.1 (M-Boc).

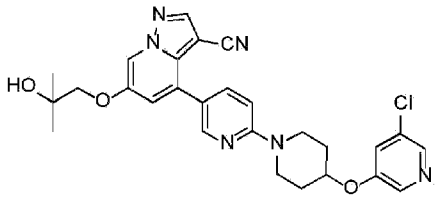
[0692] Step 2: Preparation of 5-chloro-3-fluoro-2-(piperidin-4-yloxy)pyridine. To a solution of tert-butyl 4-((5-chloro-3-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 222 mg, 0.671 mmol) in 3.4 mL DCM was treated with TFA (3.4 mL, 43.6 mmol). The reaction mixture was stirred for 16 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM (1 mL). The

solution was purified by silica chromatography 1-10% MeOH in DCM with 0.1-1% NH_4OH as the gradient eluent) to provide the title compound (56 mg, 36% yield) in sufficient purity for step 3. MS (apci) m/z=231.1 (M+H).

[0693] Step 3: Preparation of 4-(6-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 25 mg, 0.77 mmol) and 5-chloro-3-fluoro-2-(piperidin-4-yloxy)pyridine (35 mg, 0.153 mmol) in DMA (0.4 mL) was added TEA (52 µL, 0.383 mmol). The reaction mixture was stirred overnight at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$ and then water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (25-99% EtOAc in hexanes as the gradient eluent) to afford the title compound (8.2 mg, 20% yield). MS (apci) m/z = 357.1 (M+H).

Example 251

[0694]



4-(6-(4-((5-chloropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0695] Step 1: Preparation of tert-butyl 4-((5-chloropyridin-3-yl)oxy)piperidine-1-carboxylate. A solution of 5-Chloro-3-pyridinol (1.018 g, 0.786 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (1.582 mg, 0.786 mmol) in THF was treated with PPh_3 (227 mg, 0.864 mmol), then sparged with $Ar_{(g)}$ for 5 min. While stirring at ambient temperature, the mixture was treated slowly with DIAD (186 µL, 0.959 mmol). The resulting reaction mixture was stirred for 5 h at 70°C and then allowed to cool to ambient temperature. The reaction was diluted with DCM and washed with saturated $Na_2CO_{3(aq)}$, water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (246 mg, assumed quantitative yield). MS (apci) m/z = 213.1 (M-Boc).

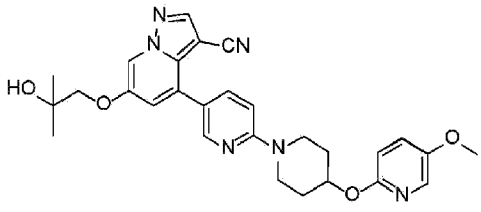
[0696] Step 2: Preparation of 3-chloro-5-(piperidin-4-yloxy)pyridine dihydrochloride. To a solution of tert-butyl 4-((5-chloropyridin-3-yl)oxy)piperidine-1-carboxylate (264 mg, 0.844 mmol) in 4.2 mL DCM was treated with TFA (4.2 mL, 54.5 mmol). The reaction mixture was stirred for 16 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in MeOH and treated with then treated with 4 N HCl in dioxanes (5 mL). The solution was stirred at ambient temperature and concentrated *in vacuo* to provide the title compound as a dihydrochloride salt, which was used in the next step without further purifications. MS (apci) m/z=213.1(M+H).

[0697] Step 3: Preparation of 4-(6-(4-((5-chloropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-

methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 40 mg, 0.123 mmol) and 3-chloro-5-(piperidin-4-yloxy)pyridine dihydrochloride (35 mg, 0.123 mmol) in DMA (0.6 mL) was added TEA (84 µL, 0.613 mmol). The reaction mixture was stirred overnight at 105°C. The reaction was maintained at 90 °C for 60 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water. Then the organic extracts were washed with brine and dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (8.1 mg, 13% yield). MS (apci) m/z = 519.20 (M+H).

Example 252

[0698]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((5-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

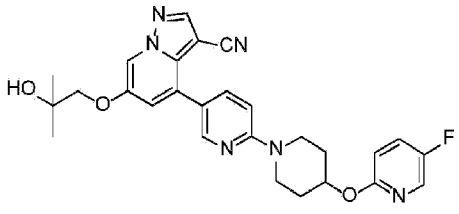
[0699] Step 1: Preparation of tert-butyl 4-((5-methoxypyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (158 mg, 0.787 mmol) in DMF (2 mL) was added sodium hydride (60% w/w, 38 mg, 0.944 mmol). The reaction was stirred for 10 min at ambient temperature. Then 2-fluoro-5-methoxypyridine (100 mg, 0.787 mmol) was added and reaction stirred overnight at 60°C. The reaction was heated to 70°C for an additional overnight. The reaction was cooled to ambient temperature and additional of tert-butyl 4-hydroxypiperidine-1-carboxylate (316 mg, 1.574 mmol) and sodium hydride (60% w/w, 76 mg, 1.888 mmol) was added and reaction was stirred for 60 h at 70°C. The reaction was cooled to ambient temperature and diluted with DCM and washed water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (243 mg, assumed quantitative yield). MS (apci) m/z = 253.1 (M-Bu^t).

[0700] Step 2: Preparation of 5-methoxy-2-(piperidin-4-yloxy)pyridine dihydrochloride. To a solution of tert-butyl 4-((5-methoxypyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 243 mg, 0.786 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in MeOH and treated with then treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature and concentrated *in vacuo* to provide the title compound as a dihydrochloride salt (221 mg, 100% yield), which was used in the next step without further purifications.

[0701] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((5-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 25 mg, 0.077 mmol) and 5-methoxy-2-(piperidin-4-yloxy)pyridine dihydrochloride (43 mg, 0.153 mmol) in DMA (0.4 mL) was added TEA (52 µL, 0.383 mmol). The reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (4.3 mg, 11% yield). MS (apci) m/z = 515.30 (M+H). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.34 (m, 1 H), 8.20 (s, 1 H), 8.14 (d, 1 H), 7.81 (d, 1 H), 7.69-7.72 (m, 1 H), 7.20-7.24 (m, 1 H), 7.14 (m, 1 H), 6.81 (d, 1 H), 6.68 (m, 1 H), 5.20-5.26 (m, 1 H), 4.03-4.08 (m, 2 H), 3.86 (s, 2 H), 3.82 (s, 3 H), 3.50-3.56 (m, 2 H), 2.09-2.14 (m, 2 H), 2.04 (s, 1 H), 1.82-1.89 (m, 2 H), 1.40 (s, 6 H).

Example 253

[0702]



4-(6-(4-((5 -fluoropyridin-2-yl)oxy)piperidin-1 -yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0703] Step 1: Preparation of tert-butyl 4-((5-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (175 mg, 0.869 mmol) in DMF (2.9 mL) was added sodium hydride (60% w/w, 41.7 mg, 1.043 mmol). The reaction was stirred for 10 min at ambient temperature. 2,5-Difluoropyridine (100 mg, 0.869 mmol) was added and reaction stirred overnight at 60°C. The reaction was heated to 70°C for an additional overnight. The reaction was cooled to ambient temperature and additional of tert-butyl 4-hydroxypiperidine-1-carboxylate (316 mg, 1.574 mmol) and sodium hydride (60% w/w, 76 mg, 1.888 mmol) was added and reaction was stirred for 4 h at 70°C. The reaction was cooled to ambient temperature and diluted with DCM and washed water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (257.5 mg, assumed quantitative yield). MS (apci) m/z = 197.10 (M-Boc).

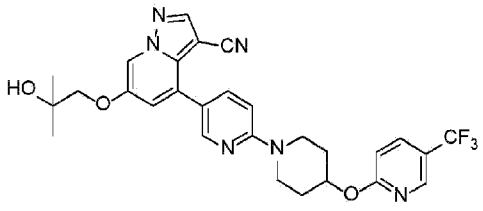
[0704] Step 2: Preparation of 5-methoxy-2-(piperidin-4-yloxy)pyridine dihydrochloride. To a solution of tert-butyl 4-((5-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 257.5 mg, 0.869 mmol) in 2 mL DCM was treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature for 15 min and concentrated *in vacuo* to provide the title compound as a dihydrochloride salt (202 mg, 100%

yield) in sufficient purity for step 3 MS (apci) m/z = 197.10 (M+H).

[0705] Step 3: Preparation of 4-(6-(4-((5-fluoropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 35 mg, 0.107 mmol) and 5-methoxy-2-(piperidin-4-yloxy)pyridine dihydrochloride (87 mg, 0.322 mmol) in DMA (0.4 mL) was added TEA (117 µL, 0.858 mmol). The reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (7.7 mg, 14% yield). MS (apci) m/z = 503.20 (M+H).

Example 254

[0706]

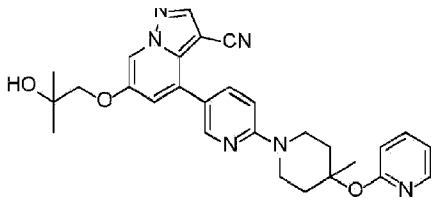


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0707] To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 35 mg, 0.107 mmol) and 2-(piperidin-4-yloxy)-5-(trifluoromethyl)pyridine dihydrochloride (79 mg, 0.322 mmol) in DMA (0.4 mL) was added TEA (117 µL, 0.858 mmol). The reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (14.6 mg, 25% yield). MS (apci) m/z = 553.20 (M+H).

Example 255

[0708]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-methyl-4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

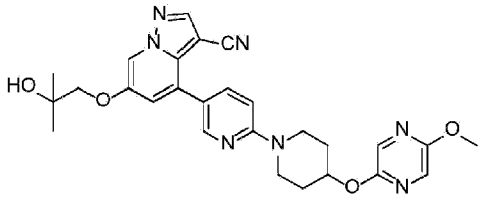
[0709] Step 1: Preparation of tert-butyl 4-methyl-4-(pyridin-2-yloxy)piperidine-1-carboxylate. To a solution of tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (266 mg, 1.24 mmol) in DMF (2.6 mL) was added sodium hydride (60% w/w, 91 mg, 2.27 mmol). The reaction was stirred for 5 min at ambient temperature. Then 2-Fluoropyridine (100 mg, 1.03 mmol) was added and reaction stirred overnight at 70°C. The reaction was cooled to ambient temperature and diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-50% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed quantative yield, 301 mg) in sufficient purity for step 2. MS (apci) m/z = 293.3 (M+H).

[0710] Step 2: Preparation of 2-((4-methylpiperidin-4-yl)oxy)pyridine dihydrochloride. To a solution of tert-butyl 4-methyl-4-(pyridin-2-yloxy)piperidine-1-carboxylate (assumed 301 mg, 1.03 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in MeOH and treated with then treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature for 5 min. The reaction was concentrated *in vacuo* to provide the title compound as a dihydrochloride salt (221 mg, 100% yield) in sufficient purity for step 3. ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.12 (d, 1H), 7.69 (dd, 1H), 6.97 (dd, 1H), 6.84 (d, 1H), 3.26 (m, 4H), 2.74 (m, 2H), 1.89 (m, 2H), 1.64 (s,3H).

[0711] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-methyl-4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 25 mg, 0.077 mmol) and 2-((4-methylpiperidin-4-yl)oxy)pyridine dihydrochloride (44 mg, 0.17 mmol) in DMA (0.3 mL) was added TEA (84 µL, 0.61 mmol). The reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (5.6mg, 15% yield). (400 MHz, CDCl3) δ 8.32 (d, 1H), 8.19 (s, 1H), 8.12 (m, 2H), 7.69 (dd, 1H), 7.54 (m, 1H). 7.13 (d, 1H), 6.83 (m, 1H), 6.78 (d, 1H), 6.72 (d, 1H), 4.08 (m, 2H), 3.85 (s, 3H), 3.36 (m, 2H), 2.57 (m, 2H), 1.79 (m, 2H), 1.70 (s, 3H), 1.39 (s, 6H).

Example 256

[0712]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((5-methoxypyrazin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

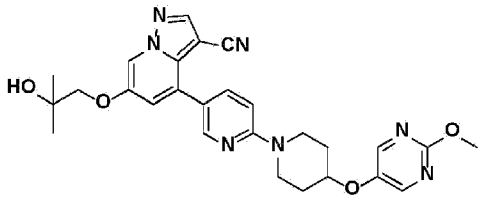
[0713] Step 1: Preparation of tert-butyl 4-((5-methoxypyrazin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (278 mg, 1.38 mmol) in DMF (1.7 mL) was added sodium hydride (60% w/w, 61 mg, 1.52 mmol). The reaction was stirred for 5 min at ambient temperature. Then 2-chloro-5-methoxypyrazine (100 mg, 0.692 mmol) was added and reaction stirred overnight at 95°C. The reaction was cooled to ambient temperature and diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by silica chromatography (5-40% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed quantative yield, 214 mg) in sufficient purity for step 2. MS (apci) m/z = 210.1 (M-Boc).

[0714] Step 2: Preparation of 2-methoxy-5-(piperidin-4-yloxy)pyrazine dihydrochloride. To a solution of tert-butyl 4-((5-methoxypyrazin-2-yl)oxy)piperidine-1-carboxylate (assumed 214 mg, 0.692 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in MeOH and treated with treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature for 5 min. The reaction was concentrated *in vacuo* to provide the title compound as a dihydrochloride salt (61.3 mg, 21.7% yield) in sufficient purity for step 3. MS (apci) m/z = 210.1 (M+H).

[0715] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((5-methoxypyrazin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 32 mg, 0.098 mmol) and 2-methoxy-5-(piperidin-4-yloxy)pyrazine dihydrochloride (61 mg, 0.216 mmol) in DMA (0.3 mL) was added TEA (107 µL, 0.784 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16.7 mg, 33% yield). MS (apci) m/z = 516.25 (M+H).

Example 257

[0716]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((2-methoxypyrimidin-5-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

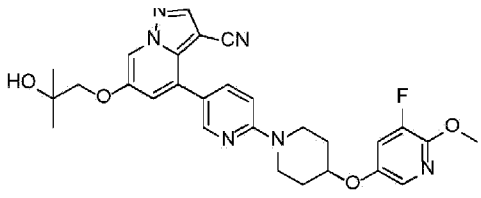
[0717] Step 1: Preparation of tert-butyl 4-((2-methoxypyrimidin-5-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (222 mg, 0.793 mmol) and 2-methoxypyrimidin-5-ol (100 mg, 0.793 mmol) in DMF (2 mL) was added potassium carbonate (219 mg, 1.59 mmol) and then the reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 245 mg) in sufficient purity for step 2. MS (apci) m/z = 254.1 (M-*t*-bu).

[0718] Step 2: Preparation of 2-methoxy-5-(piperidin-4-yloxy)pyrimidine dihydrochloride. To a solution of tert-butyl 4-((2-methoxypyrimidin-5-yl)oxy)piperidine-1-carboxylate (assumed 245 mg, 0.793 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 45 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature for 5 min. The reaction was concentrated *in vacuo* to provide the title compound as a dihydrochloride salt (166 mg, 74.2% yield) in sufficient purity for step 3. MS (apci) m/z = 210.2 (M+H).

[0719] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((2-methoxypyrimidin-5-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 31 mg, 0.096 mmol) 2-methoxy-5-(piperidin-4-yloxy)pyrimidine dihydrochloride (81 mg, 0.287 mmol) in DMA (0.3 mL) was added TEA (105 µL, 0.765 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (9.6 mg, 20% yield).

Example 258

[0720]



4-(6-(4-((5-fluoro-6-methoxypyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

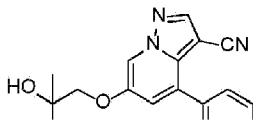
[0721] Step 1: Preparation of tert-butyl 4-((5-fluoro-6-methoxypyridin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (197 mg, 0.706 mmol) and 5-fluoro-6-methoxypyridin-3-ol (101 mg, 0.706 mmol) in DMF (1.8 mL) was added potassium carbonate (195 mg, 1.41 mmol) and then the reaction mixture was stirred for 60 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic extracts were washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 230 mg) in sufficient purity for step 2. MS (apci) m/z = 227.1 (M-Boc).

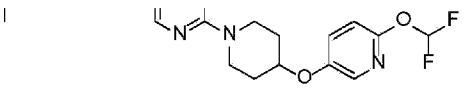
[0722] Step 2: Preparation of 3-fluoro-2-methoxy-5-(piperidin-4-yloxy)pyridine. To a solution of tert-butyl 4-((5-fluoro-6-methoxypyridin-3-yl)oxy)piperidine-1-carboxylate (assumed 230 mg, 0.706 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 45 min at ambient temperature, and then concentrated *in vacuo.* The residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (86 mg, 54% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 227.10 (M+H).

[0723] Step 3: Preparation of 4-(6-(4-((5-fluoro-6-methoxypyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 33 mg, 0.102 mmol) and 3-fluoro-2-methoxy-5-(piperidin-4-yloxy)pyridine (86 mg, 0.380 mmol) in DMA (0.3 mL) was added TEA (97 µL, 0.712 mmol). The reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (36 mg, 67% yield). MS (apci) m/z = 533.20 (M+H).

Example 259

[0724]





4-(6-(4-((6-(difluoromethoxy)pyridin-3 -yl)oxy)piperidin-1 -yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

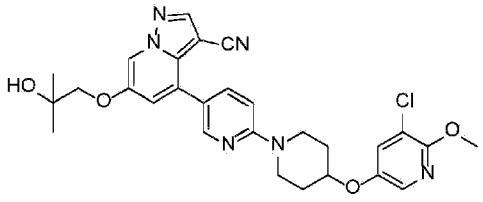
[0725] Step 1: Preparation of tert-butyl 4-((6-(difluoromethoxy)pyridin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (133 mg, 0.475 mmol) and 6-(difluoromethoxy)pyridin-3-ol (76.5 mg, 0.475 mmol) in DMF (1.2 mL) was added potassium carbonate (197 mg, 1.42 mmol) and then the reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic extracts were washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 164 mg) in sufficient purity for step 2. MS (apci) m/z = 245.10 (M-Boc).

[0726] Step 2: Preparation of 2-(difluoromethoxy)-5-(piperidin-4-yloxy)pyridine. To a solution tert-butyl 4-((6-(difluoromethoxy)pyridin-3 -yl)oxy)piperidine-1-carboxylate (assumed 164 mg, 0.706 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 45 min at ambient temperature, and then concentrated *in vacuo.* The residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (61 mg, 53% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 245.10 (M+H).

[0727] Step 3: Preparation of 4-(6-(4-((6-(difluoromethoxy)pyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 31 mg, 0.095 mmol) and 2-(difluoromethoxy)-5-(piperidin-4-yloxy)pyridine (61 mg, 0.25 mmol) in DMA (0.32 mL) was added TEA (65 µL, 0.477 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (21 mg, 41% yield). MS (apci) m/z = 551.20 (M+H).

Example 264

[0728]



4-(6-(4-((5 -chloro-6-methoxypyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

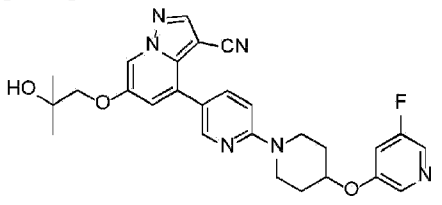
[0729] Step 1: Preparation of tert-butyl 4-((5-chloro-6-methoxypyridin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (186 mg, 0.664 mmol) and 5-chloro-6-methoxypyridin-3-ol (106 mg, 0.664 mmol) in DMF (1.7 mL) was added potassium carbonate (275mg, 1.99 mmol) and then the reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic extracts were washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 228 mg) in sufficient purity for step 2. MS (apci) m/z = 243.10 (M-Boc).

[0730] Step 2: Preparation 3-chloro-2-methoxy-5-(piperidin-4-yloxy)pyridine. To a solution tert-butyl 4-((5 -chloro-6-methoxypyridin-3 -yl)oxy)piperidine-1-carboxylate (assumed 228 mg, 0.664 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (65 mg, 40% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 243.10 (M+H).

[0731] Step 3: Preparation of 4-(6-(4-((5-chloro-6-methoxypyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 26 mg, 0.079 mmol) and 3-chloro-2-methoxy-5-(piperidin-4-yloxy)pyridine (82 mg, 0.338 mmol) in DMA (0.26 mL) was added TEA (76 µL, 0.553 mmol). The reaction mixture was stirred 1 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with 60:40 ACN: water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (12 mg, 28% yield). MS (apci) m/z = 549.15 (M+H).

Example 265

[0732]



4-(6-(4-((5-fluoropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

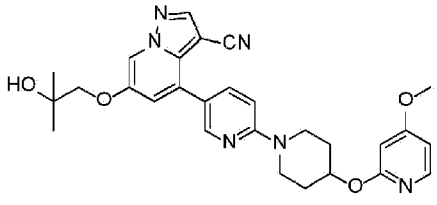
[0733] Step 1: Preparation of tert-butyl 4-((5-fluoropyridin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (257 mg, 0.920 mmol) and 3-fluoro-5-hydroxypyridine (104 mg, 0.920 mmol) in DMF (2.3 mL) was added potassium carbonate (381 mg, 2.76 mmol) and then the reaction mixture was stirred overnight at 105°C. After cooling to ambient temperature, the reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic extracts were washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 273 mg) in sufficient purity for step 2. MS (apci) m/z = 297.2 (M+H).

[0734] Step 2: Preparation 3-fluoro-5-(piperidin-4-yloxy)pyridine. To a solution tert-butyl 4-((5-fluoropyridin-3-yl)oxy)piperidine-1-carboxylate (assumed 273 mg, 0.920 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The residue was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (89 mg, 49% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 197.10 (M+H).

[0735] Step 3: Preparation of 4-(6-(4-((5-fluoropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 25.5 mg, 0.078 mmol) and 3-fluoro-5-(piperidin-4-yloxy)pyridine (15.3 mg, 0.781 mmol) in DMA (0.26 mL) was added TEA (75 µL, 0.547 mmol). The reaction mixture was stirred 1 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (12 mg, 31% yield). MS (apci) m/z = 503.25 (M+H).

Example 266

[0736]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((4-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0737] Step 1: Preparation of tert-butyl 4-((4-methoxypyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (146 mg, 0.725 mmol) in DMF (2.4 mL) was added sodium hydride (60% w/w, 37.7 mg, 0.943 mmol). The reaction was stirred for 10 min at ambient temperature. Then 2-chloro-4-methoxypyridine (104 mg, 0.725 mmol) was added and reaction

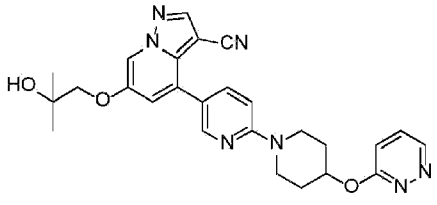
stirred 92 h at 95°C. The reaction was cooled to ambient temperature and diluted with water and extracted with EtOAc. Combined organics were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 224 mg) in sufficient purity for step 2. MS (apci) m/z = 309.1 (M+H).

[0738] Step 2: Preparation of 4-methoxy-2-(piperidin-4-yloxy)pyridine. To a solution tert-butyl 4-((4-methoxypyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 224 mg, 0.725 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 20 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH_4OH as the gradient eluent) to afford the title compound (54 mg, 36% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 209.1 (M+H).

[0739] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((4-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42**; 25 mg, 0.077 mmol) and 4-methoxy-2-(piperidin-4-yloxy)pyridine (16 mg, 0.077mmol) in DMA (0.3 mL) was added TEA (73 µL, 0.54 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16.7 mg, 33% yield). MS (apci) m/z = 515.20 (M+H).

Example 267

[0740]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(pyridazin-3-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0741] Step 1: Preparation of tert-butyl 4-(pyridazin-3-yloxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (140 mg, 0.696 mmol) in DMF (2.3 mL) was added sodium hydride (60% w/w, 56 mg, 1.39 mmol). The reaction was stirred for 10 min at ambient

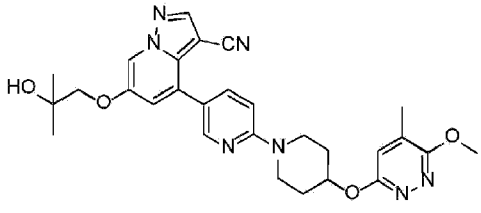
temperature. Then 3-chloropyridazine (159 mg, 1.39 mmol) was added and reaction stirred 3 h at 95°C. The reaction was cooled to ambient temperature and diluted with water and extracted with EtOAc. Combined organics were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 194 mg) in sufficient purity for step 2. MS (apci) m/z = 280.2 (M+H).

[0742] Step 2: Preparation of 3-(piperidin-4-yloxy)pyridazine. To a solution of tert-butyl 4-(pyridazin-3-yloxy)piperidine-1-carboxylate (assumed 194 mg, 0.696 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 20 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (111 mg, 89% yield over two steps) in sufficient purity for the next step. MS (apci) m/z = 180.1 (M+H).

[0743] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(pyridazin-3-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 28 mg, 0.086 mmol) and 3-(piperidin-4-yloxy)pyridazine (46 mg, 0.257 mmol) in DMA (0.3 mL) was added TEA (82 µL, 0.601 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (23.5 mg, 56% yield). MS (apci) m/z = 486.20 (M+H).

Example 268

[0744]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methoxy-5-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0745] Step 1: Preparation of tert-butyl 4-((6-methoxy-5-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (761 mg, 3.78 mmol) in DMF (7.9 mL) was added sodium hydride (60% w/w, 164 mg, 4.10 mmol). The reaction was stirred for

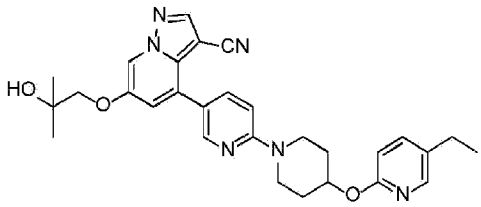
5 min at ambient temperature. Then 6-chloro-3-methoxy-4-methylpyridazine (500 mg, 3.15 mmol) was added and reaction stirred overnight at 95°C. The reaction was cooled to ambient temperature and diluted with water and extracted with EtOAc. Combined organics were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 1.019 g) in sufficient purity for step 2. MS (apci) m/z = 324.1 (M+H).

[0746] Step 2: Preparation of 3-methoxy-4-methyl-6-(piperidin-4-yloxy)pyridazine. To a solution of tert-butyl 4-((6-methoxy-5-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate (assumed 1.019 g, 3.15 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 20 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (70 mg, 10% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 224.15 (M+H).

[0747] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methoxy-5-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 51 mg, 0.156 mmol) and 3-methoxy-4-methyl-6-(piperidin-4-yloxy)pyridazine (70 mg, 0.314 mmol) in DMA (0.8 mL) was added TEA (150 µL, 1.09 mmol). The reaction mixture was stirred 40 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (26.5 mg, 32% yield). MS (apci) m/z = 530.30 (M+H).

Example 269

[0748]



4-(6-(4-((5-ethylpyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0749] Step 1: Preparation of tert-butyl 4-((5-ethylpyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (1.42 g, 7.06 mmol) in DMF (11.8 mL) was added

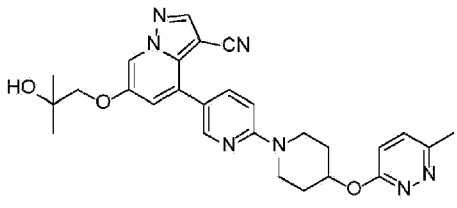
sodium hydride (60% w/w, 311 mg, 7.77mmol). The reaction was stirred for 15 min at ambient temperature. Then 2-chloro-5-ethylpyridine (1.00 g, 3.15 mmol) was added and reaction stirred 48 h at 90°C. The reaction was cooled to ambient temperature and additional tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (1.42 g, 7.06 mmol) and sodium hydride (60% w/w, 311 mg, 7.77 mmol) were added. The reaction was stirred for 60 h at 90°C. The reaction was cooled to ambient temperature and additional tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (1.42 g, 7.06 mmol) and sodium hydride (60% w/w, 311 mg, 7.77 mmol) were added. The reaction was stirred for 4 h at 90°C The reaction was cooled to ambient temperature and diluted with water and saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. Combined organics were washed with water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (5-50% EtOAc in Hexanes as the gradient eluent) to afford the title compound (assumed quantative yield, 2.163g) in sufficient purity for step 2. MS (apci) m/z = 307.2 (M+H).

[0750] Step 2: Preparation of 5-ethyl-2-(piperidin-4-yloxy)pyridine. To a solution of tert-butyl 4-((5-ethylpyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 2.163 g, 7.06 mmol) in 5 mL DCM was treated with TFA (10 mL, 130 mmol). The reaction mixture was stirred for 20 min at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (835 mg, 57% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 207.20 (M+H).

[0751] Step 3: Preparation of 4-(6-(4-((5-ethylpyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 25 mg, 0.077 mmol) and 5-ethyl-2-(piperidin-4-yloxy)pyridine (55 mg, 0.27 mmol) in DMA (0.8 mL) was added TEA (73 µL, 0.54 mmol). The reaction mixture was stirred 40 h at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (6.7 mg, 17% yield). MS (apci) m/z = 513.30 (M+H).

Example 270

[0752]



6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-

yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

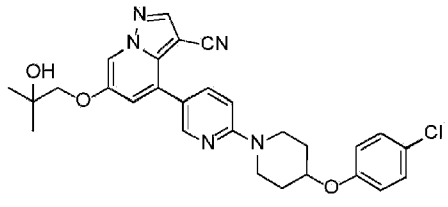
[0753] Step 1: Preparation of tert-butyl 4-((6-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (313 mg, 1.56 mmol) in DMF (1.94 mL) was added sodium hydride (60% w/w, 68.4 mg, 1.71mmol). The reaction was stirred for 5 min at ambient temperature. Then 3-chloro-6-methylpyridazine (100 mg, 0.778 mmol) was added and reaction stirred overnight at 95°C. The reaction was cooled to ambient temperature and diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. Combined organics were washed with water and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 228 mg) in sufficient purity for step 2. MS (apci) m/z = 294.20 (M+H).

[0754] Step 2: 3-methyl-6-(piperidin-4-yloxy)pyridazine. To a solution of tert-butyl 4-((6-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate (assumed 228 mg, 0.778 mmol) in 2 mL DCM was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then concentrated *in vacuo.* The crude residue was resuspended in DCM and the solution was purified by silica chromatography (1-9% MeOH in DCM with 0.1-0.9% NH4OH as the gradient eluent) to afford the title compound (104 mg, 69% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 194.1 (M+H).

[0755] Step 3: Preparation of 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 32mg, 0.098 mmol) and 3-methyl-6-(piperidin-4-yloxy)pyridazine (57 mg, 0.29 mmol) in DMA (0.3 mL) was added TEA (67 µL, 0.49 mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (25 mg, 51% yield). MS (apci) m/z = 500.20 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H), 8.20 (s, 1H), 8.15 (d, 1H), 7.72 (dd, 1H), 7.24 (d, 1H). 7.15 (d, 1H), 6.87 (d, 1H), 6.82 (d, 1H), 5.56 (m, 1H), 4.10 (m, 2H), 3.86 (s, 2H), 3.51 (m, 2H), 2.61 (s, 3H), 2.23 (m, 2H), 1.91 (m, 2H), 1.39 (s, 6H).

Example 271

[0756]

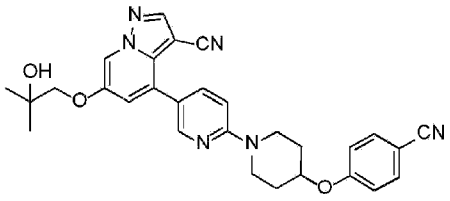


4-(6-(4-(4-chlorophenoxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0757] To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 25.5 mg, 0.078 mmol) and 4-(4-chlorophenoxy)piperidine hydrochloride (38.8 mg, 0.156 mmol) in DMA (0.5 mL) was added TEA (33 µL, 0.234 mmol). The reaction mixture was stirred overnight at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $Na_2CO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (28 mg, 70% yield). MS (apci) m/z = 518.1 (M+H).

Example 272

[0758]

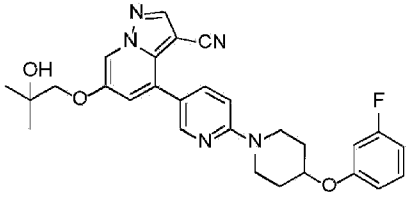


4-(6-(4-(4-cyanophenoxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0759] The title compound was prepared using a similar method to that described for the synthesis of Example 271, replacing 4-(4-chlorophenoxy)piperidine hydrochloride with 4-(piperidin-4-yloxy)benzonitrile. MS (apci) m/z = 509.2 (M+H).

Example 273

[0760]

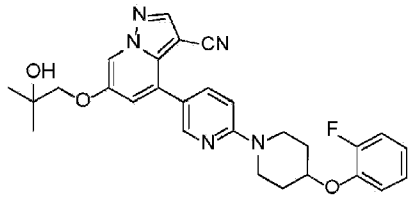


4-(6-(4-(3-fluorophenoxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0761] To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 28 mg, 0.085 mmol) and 4-(3-fluorophenoxy)piperidine hydrochloride (39 mg, 0.170 mmol) in DMA (0.6 mL) was added TEA (47 µL, 0.34 mmol). The reaction mixture was stirred overnight at 90°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $Na_2CO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (25.5 mg, 60% yield). MS (apci) m/z = 502.2 (M+H).

Example 274

[0762]

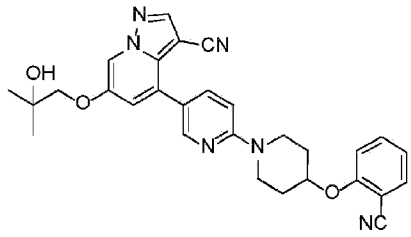


4-(6-(4-(2-fluorophenoxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0763] The title compound was prepared using a similar method to that described for the synthesis of **Example 273,** replacing 4-(3-fluorophenoxy)piperidine hydrochloride with 4-(2-fluorophenoxy)piperidine. MS (apci) m/z = 502.2 (M+H).

Example 275

[0764]

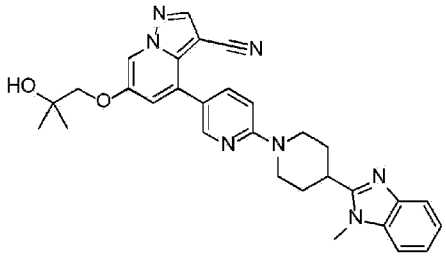


4-(6-(4-(2-cyanophenoxy)piperidin-l-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0765] To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 27 mg, 0.083 mmol) and 2-(piperidin-4-yloxy)benzonitrile (34 mg, 0.166 mmol) in DMA (0.42 mL) was added TEA (70 µL, 0.498mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $Na_2CO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (23 mg, 55% yield). MS (apci) m/z = 509.2 (M+H).

Example 277

[0766]

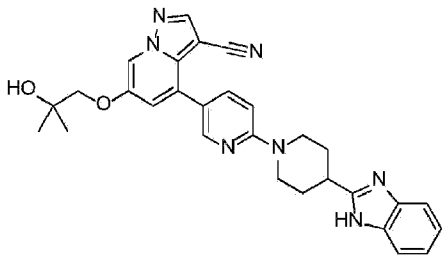


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0767] A mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42;** 50 mg, 0.15 mmol) and 1-methyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride (66 mg, 0.23 mmol) and DIEA (133µL, 0.77 mmol) were combined in DMSO (306 µL). The reaction mixture was stirred 72 h at 90°C. After cooling to ambient temperature, the reaction mixture was purified directly by C18 reverse phase chromatography (5-45% ACN in water as the gradient eluent) to afford the title compound (38 mg, 47% yield). MS (apci) m/z = 522.2 (M+H).

Example 278

[0768]

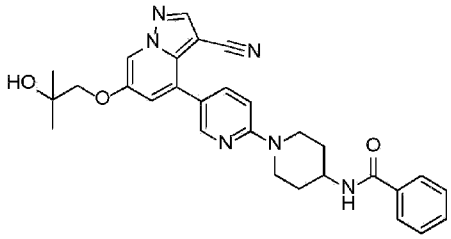


4-(6-(4-(1H-benzo[d] imidazol-2-yl)piperidin-1 -yl)pyridin-3 -yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0769] The title compound was prepared using a similar method to that described for the synthesis of **Example 277,** replacing 1-methyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride with 2-(piperidin-4-yl)-1H-benzo[d]imidazole. MS (apci) m/z = 508.2 (M+H).

Example 289

[0770]

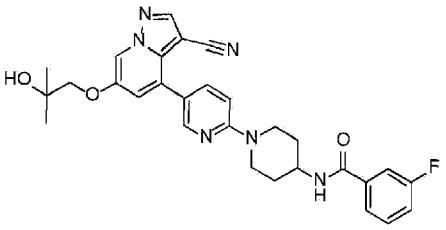
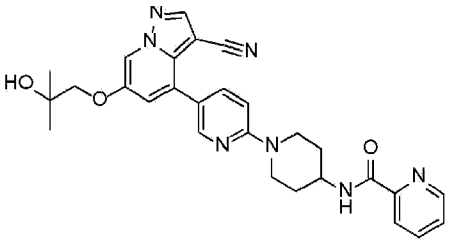
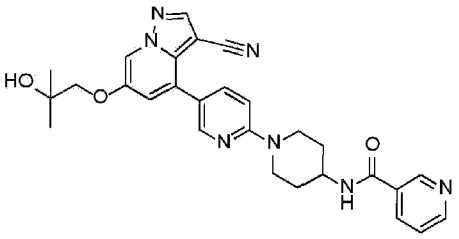


N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)benzamide

[0771] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P64;** 20 mg, 0.049 mmol), HATU (21 mg, 0.054 mmol), and benzoic acid (9 mg, 0.24 mmol) in DCM (0.5 mL) was treated with DIEA (43 µL, 0.054 mmol) and then stirred for 1 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_4(s)$, filtered and concentrated *in vacuo* to afford the title compound (43.7 mg, 49.3% yield). MS (apci) m/z = 511.20 (M+H).

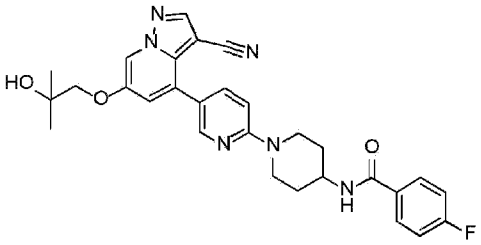
[0772] The compounds in Table OO were prepared using a similar method to that described for the synthesis of **Example 289,** replacing benzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table OO

Ex. #	Structure	Chemical Name	MS m/z
290		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)-3 -fluorobenzamide	529.20 (M+H)
292		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)picolinamide	512.20 (M+H)
293		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)nicotinamide	512.20 (M+H)

Example 294

[0773]



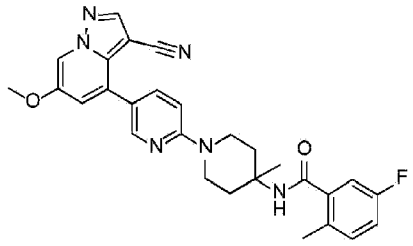
N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)-4-fluorobenzamide

[0774] A mixture of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P64;** 20 mg, 0.049 mmol), HATU (21 mg, 0.054 mmol), and 4-fluorobenzoic acid (69 mg, 0.049 mmol) in DCM (0.5 mL) was treated with DIEA (43 µL, 0.049 mmol) and then stirred for 2.5 h at ambient temperature. The reaction mixture was concentrated *in vacuo.* The residue was suspended in 60:40 ACN:water containing 2% TFA. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the

gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16 mg, 60% yield). MS (apci) m/z = 529.20 (M+H).

Example 301

[0775]

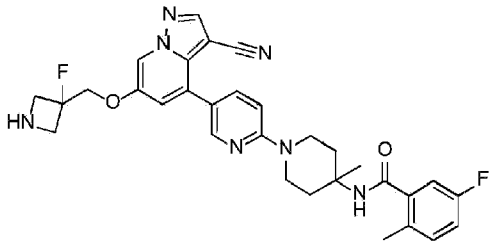


N-(1-(5 -(3 -cyano-6-methoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0776] To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide **(P68,** 30 mg, 0.619 mmol) in DMF (0.6 mL) was added potassium carbonate (26 mg, 0.186 mmol), followed by iodomethane (6 µL, 0.09 mmol) and was stirred for 1 h at 60°C. The reaction was diluted with EtOAc and washed with water and brine and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was resuspended in DCM (2 mL) and purified using silica chromatography 10-90% EtOAc in Hexanes to afford the title compound (9 mg, 29% yield) MS (apci) m/z=499.2 (M+H).

Example 302

[0777]



N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

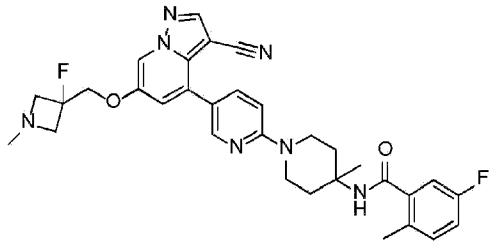
[0778] Step 1: Preparation of tert-butyl 3-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-

methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. To a mixture of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P68**; 47 mg, 0.097 mmol) and tert-butyl 3-(bromomethyl)-3-fluoroazetidine-1-carboxylate (39 mg, 0.146 mmol) was added cesium carbonate (126 mg, 0.388 mmol) in DMA (1 mL) and was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography 25-50% EtOAc in Hexanes to afford the title compound (62 mg, 95% yield) MS (apci) m/z=672.3 (M+H).

[0779] Step 2: Preparation of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution of tert-butyl 3-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (62 mg, 0.09 mmol) in DCM (4 mL) was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 2 h at ambient temperature, and then concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH and washed sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts then were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound. (42 mg, 80% yield) MS (apci) m/z=572.3 (M+H).

Example 303

[0780]



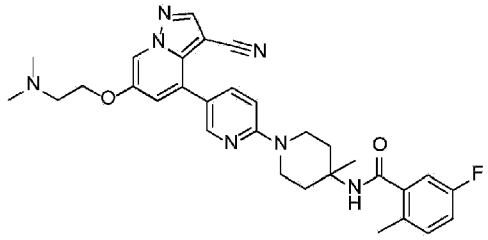
N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0781] A mixture of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (Example 302; 30 mg, 0.053 mmol), formaldehyde (20 µL, 0.26 mmol), and $NaBH(AcO)_3$ (56 mg, 0.26 mmol) were dissolved in DMA (2 mL). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH and washed sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts then were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (27 mg, 87% yield) MS (apci) m/z = 586.3 (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ 8.32-8.30 (m, 1H), 8.19-8.15 (m, 2H), 7.71-7.66 (m, 1H), 7.17-7.13 (m, 2H), 7.06-7.02 (m, 1H), 7.00-6.94

(m, 1H), 6.80-6.77 (m, 1H), 5.50 (br s, 1H), 4.36-4.29 (m, 2H), 4.05-3.92 (m, 2H), 3.75-3.57 (m, 2H), 3.43-3.32 (m, 2H), 3.26-3.13 (m, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 2.33-2.21 (m, 2H), 1.90-1.75 (m, 2H), 1.58 (s, 3H).

Example 304

[0782]

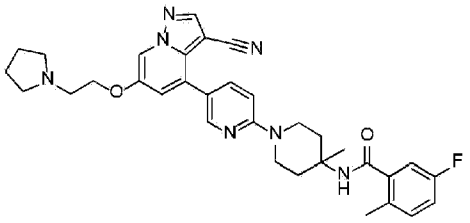
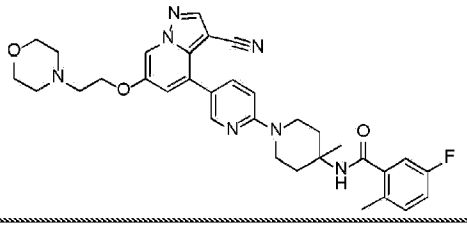


N-(1-(5-(3-cyano-6-(2-(dimethylamino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0783] To a mixture of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P68;** 39 mg, 0.08 mmol) and 2-bromo-N,N-dimethylethan-1-amine hydrobromide (37 mg, 0.16 mmol) was added cesium carbonate (105 mg, 0.32 mmol) in DMA (1 mL) and was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography 2-4% MeOH in DCM. Fractions containing the product were concentrated *in vacuo.* The residue was repurified was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH and washed sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts then were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (8 mg, 18% yield) MS (apci) m/z = 556.3 (M+H).

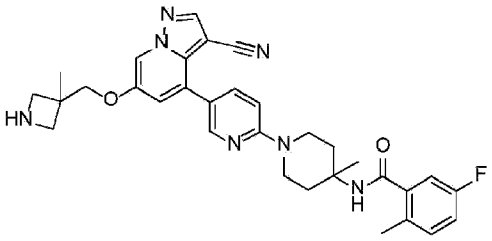
[0784] The compounds in Table QQ were prepared using a similar method to that described for the synthesis of **Example 304,** replacing 2-bromo-N,N-dimethylethan-1-amine hydrobromide with the appropriate alkyl halide. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table QQ

Ex. #	Structure	Chemical Name	MS m/z
305		N-(1-(5-(3-cyano-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide	582.3 (M+H)
306		N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide	598.3 (M+H)

Example 307

[0785]



N-(1-(5-(3-cyano-6-((3 -methylazetidin-3-yl)methoxy)pyrazolo[1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

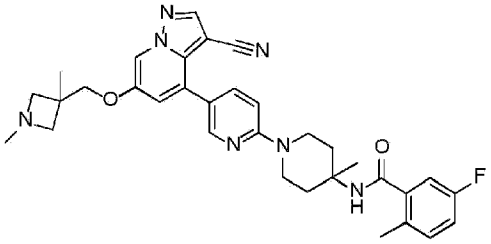
[0786] Step 1: Preparation of tert-butyl 3-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-methylazetidine-1-carboxylate. To a mixture of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P68**; 42 mg, 0.087 mmol) and tert-butyl 3-(bromomethyl)-3-methylazetidine-1-carboxylate (34 mg, 0.13 mmol) was added cesium carbonate (113 mg, 0.347 mmol) in DMA (1 mL) and was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and the organic extracts were dried over anhydrous Na_2SO_4(s), filtered and concentrated *in vacuo.* The residue was purified using silica chromatography 50-100% EtOAc in Hexanes to afford the title compound (21 mg, 36% yield) MS (apci) m/z=668.4 (M+H).

[0787] Step 2: Preparation of N-(1-(5-(3-cyano-6-((3-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution of tert-butyl 3-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-

yl)oxy)methyl)-3-methylazetidine-1-carboxylate (21 mg, 0.03 mmol) in DCM (4 mL) was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 2 h at ambient temperature, and then concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH and washed sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts then were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound. (13 mg, 73% yield) MS (apci) m/z=568.3 (M+H).

Example 308

[0788]

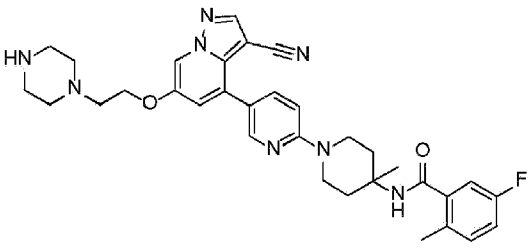


N-(1-(5-(3-cyano-6-((1,3-dimethylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0789] A mixture of N-(1-(5-(3-cyano-6-((3-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Example 307;** 12 mg, 0.021 mmol), formaldehyde (8 µL, 0.106 mmol), and $NaBH(AcO)_3$ (22mg, 0.106 mmol) were dissolved in DCM (4 mL). The resulting reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with EtOAc and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, diluted with 4:1 DCM:iPrOH and washed sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts then were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (10 mg, 81% yield) MS (apci) m/z = 582.3 (M+H).

Example 309

[0790]



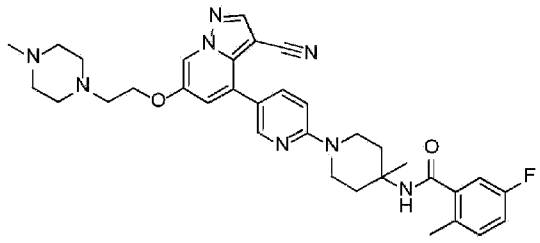
N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0791] Step 1: Preparation of tert-butyl 4-(2-((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate. To a mixture of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P68;** 55 mg, 0.114 mmol), tert-Butyl 4-(2-chloroethyl)tetrahydro-1(2H)-pyrazine carboxylate (57 mg, 0.227 mmol) was added cesium carbonate (148 mg, 0.454 mmol) in DMA (1 mL) and was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and the organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography (50-100% EtOAc in Hexanes) to afford the title compound (49 mg, 62% yield) MS (apci) m/z=697.4 (M+H).

[0792] Step 2: Preparation of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution of tert-butyl 4-(2-((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate (49 mg, 0.070 mmol) in DCM (4 mL) was treated with TFA (2 mL, 26 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent). Fractions containing the product were concentrated *in vacuo.* The residue was repurified using silica chromatography (4% MeOH in DCM with 1% TEA as the eluent) to afford the title compound. (33 mg, 79% yield) MS (apci) m/z=597.3 (M+H).

Example 310

[0793]



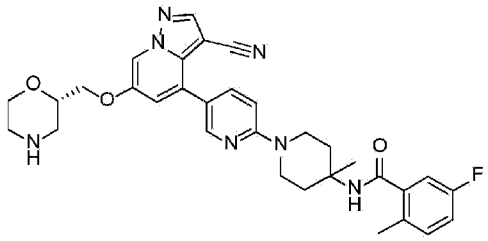
N-(1-(5-(3-cyano-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0794] To a solution of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Example** 309; 27 mg, 0.045 mmol) in DCM (0.25 mL) and MeOH (0.25 mL) was added formaldehyde (17 µL, 0.226 mmol) and $NaBH(AcO)_3$ (48 mg, 0.226 mmol) The resulting reaction mixture was allowed to stir overnight at room temperature. The reaction was directly purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous

$Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was triturated with DCM/Hexanes and concentrated *in vacuo* to afford the title compound (12.5 mg, 45% yield) MS (apci) m/z=611.4 (M+H).

Example 311

[0795]



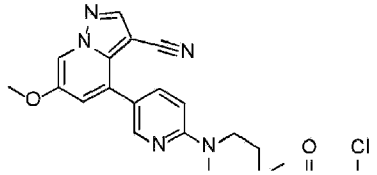
(S)-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

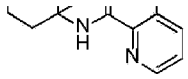
[0796] Step 1: Preparation of tert-butyl (S)-2-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate. To N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide **(Intermediate P68;** 30 mg, 0.062 mmol) was added cesium carbonate (22 mg, 0.068 mmol) in DMA (1.2 mL). The resulting mixture was sparged with $Ar_{(g)}$ and stirred for 10 min. (S)-tert-butyl 2-(bromomethyl)morpholine-4-carboxylate (26 mg, 0.093 mmol) was added to the reaction mixture. The resulting mixture was sparged with $Ar_{(g)}$ and stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and brine and the organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (42 mg, 99% yield) MS (apci) m/z=684.3(M+H).

[0797] Step 2: Preparation of (S)-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide. To a solution tert-butyl (S)-2-(((3-cyano-4-(6-(4-(5-fluoro-2-methylbenzamido)-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (42 mg, 0.061 mmol) in DCM (2 mL) was treated with TFA (0.31 mL). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The residue was resuspended in DCM (2 mL). The solution was purified by by silica chromatography (0.5-10% MeOH in DCM with 0.05-1% NH_4OH as the gradient eluent) to afford the title compound (6 mg, 16% yield) MS (apci) m/z=584.3 (M+H).

Example 312

[0798]



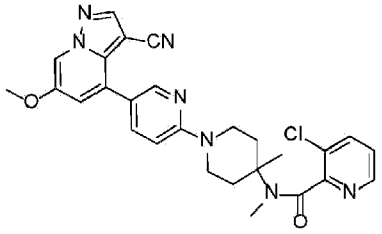


3-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0799] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Intermediate P75;** 34 mg, 0.070 mmol) in DMF (0.7 mL) was added potassium carbonate (29 mg, 0.209 mmol) and then iodomethane (7 µL, 0.105 mmol) was added to the reaction mixture. The resulting mixture was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with DCM and purified directly using silica chromatography (0.5-10% MeOH in DCM with 0.1-2% NH_4OH as the gradient eluent). Fractions containing the product were concentrated *in vacuo.* The residue was diluted with EtOAc and washed with water and brine and then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16 mg, 45% yield) MS (apci) m/z=502.2 (M+H).

Example 313

[0800]

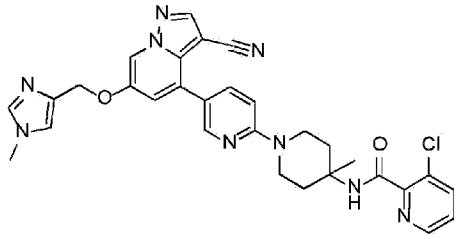


3-chloro-N-(1-(5-(3 -cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-N-methylpicolinamide

[0801] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Example 312;** 10 mg, 0.020 mmol) in ACN (0.3 mL) was added iodomethane (4 µL, 0.06 mmol) followed by sodium hydride (1.4 mg, 0.06 mmol) and then the reaction mixture was stirred for 1 hour at ambient temperature. The reaction was stirred for 1 hour at 85°C. After cooling to ambient temperature, the reaction mixture was directly purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (6.5 mg, 63% yield). MS (apci) m/z= 516.2 (M+H).

Example 314

[0802]

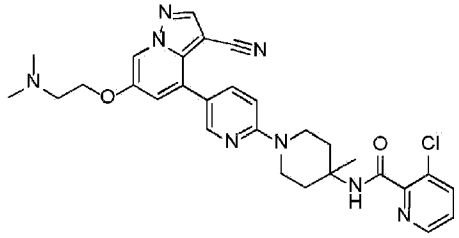


3-chloro-N-(1-(5-(3-cyano-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0803] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 25 mg, 0.051 mmol) in DMF (0.5 mL) was added potassium carbonate (22 mg, 0.159 mmol) then 4-(Chloromethyl)-1-methyl-1H-imidazole (13 mg, 0.102 mmol). The resulting mixture was stirred 2 h at 60°C. After cooling to ambient temperature, reaction was diluted with 60:40 ACN:water. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM (10 mL) and MeOH (1 mL) and eluted through a PI-HCO_3 resin. The organic eluent concentrated *in vacuo* to afford the title compound (14 mg, 45% yield). MS (apci) m/z = 582.2 (M+H).

Example 315

[0804]

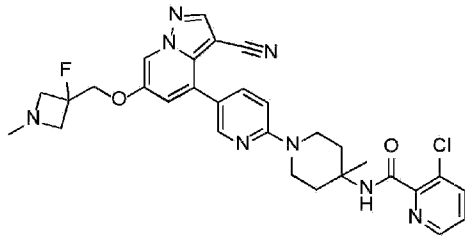


3 -chloro-N-(1 -(5 -(3 -cyano-6-(2-(dimethylamino)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0805] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 25 mg, 0.051 mmol) in DMA (0.5 mL) was added cesium carbonate (52 mg, 0.159 mmol) then 2-dimethylaminoethyl chloride hydrochloride (15 mg, 0.102 mmol). The resulting mixture was stirred 1 h at 60°C. After cooling to ambient temperature, potassium carbonate was added. The resulting mixture was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with DCM and purified directly by silica chromatography (0.5-10% MeOH in DCM with 0.1-2% NH_4OH as the gradient eluent) to afford the title compound (14 mg, 47% yield). MS (apci) m/z = 559.2 (M+H).

Example 316

[0806]



3 -chloro-N-(1 -(5 -(3 -cyano-6-((3 -fluoro-1 -methylazetidin-3 - yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

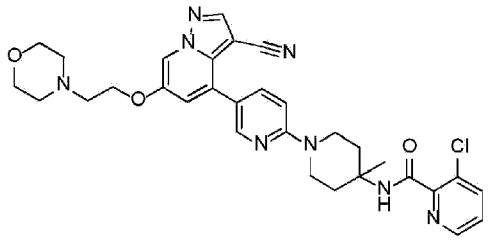
[0807] Step 1: Preparation of tert-butyl 3-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 37 mg, 0.076 mmol) in DMF (0.76 mL) was added cesium carbonate (27 mg, 0.083 mmol) then tert-butyl 3-(bromomethyl)-3-fluoroazetidine-1-carboxylate (41 mg, 0.15 mmol). The resulting mixture was stirred 3 h at 60°C. After cooling to ambient temperature, reaction was diluted with EtOAc and washed with water and brine and the organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (Assumed quantative yield, 51 mg) MS (apci) m/z=675.3 (M+H).

[0808] Step 2: Preparation of 3-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. To a solution of tert-butyl 3-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methy1)-3-fluoroazetidine-1-carboxylate (62 mg, 0.092 mmol) in DCM (0.46 mL) was treated with TFA (0.46 mL, 6 mmol). The reaction mixture was stirred for 15 min at ambient temperature, and then concentrated *in vacuo.* The residue was resuspended in DCM (3 mL). The solution was passed through two PI-HCO_3 resins and eluted with additional DCM. The eluent was concentrated *in vacuo* to afford the title compound (30 mg, 57% yield) MS (apci) m/z=575.2 (M+H).

[0809] Step 3: Preparation of 3-chloro-N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. To a solution of 3-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (35 mg, 0.061 mmol) in DMA (0.61 mL) was added formaldehyde (8 µL, 0.304 mmol) and $NaBH(AcO)_3$ (116 mg, 0.547 mmol) The resulting reaction mixture was allowed to stir overnight at room temperature. The reaction was directly purified by C18 reverse phase chromatography (5-75% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was diluted with DCM and passed through a PI-HCO_3 resin and eluted with additional DCM. The eluent was concentrated *in vacuo.* The residue was dissolved in DCM and treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (7 mg, 19% yield) MS (apci) m/z=589.3 (M+H).

Example 317

[0810]

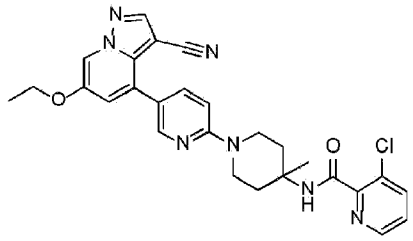


3-chloro-N-(1 -(5 -(3 -cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0811] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 36 mg, 0.074 mmol) in DMA (0.74 mL) was added cesium carbonate (26 mg, 0.081 mmol) followed by 4-(2-chloroethyl)morpholine (44 mg, 0.295 mmol) was added to the reaction mixture. The resulting mixture was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with 60:40 ACN:water. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (9 mg, 20% yield) MS (apci) m/z=601.3 (M+H).

Example 318

[0812]



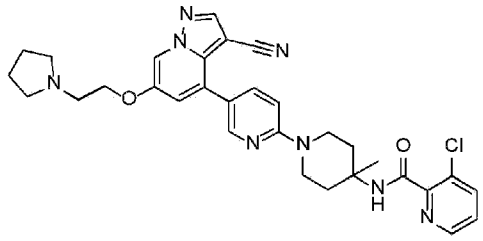
3 -chloro-N-(1 -(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0813] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 36 mg, 0.074 mmol) in DMF (0.74 mL) was added potassium carbonate (31 mg, 0.221 mmol) followed by iodoethane (17 mg, 0.111 mmol). The resulting

mixture was stirred overnight at 60°C. After cooling to ambient temperature, reaction was diluted with 60:40 ACN: water. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (19 mg, 50% yield) MS (apci) m/z=516.2 (M+H).

Example 319

[0814]

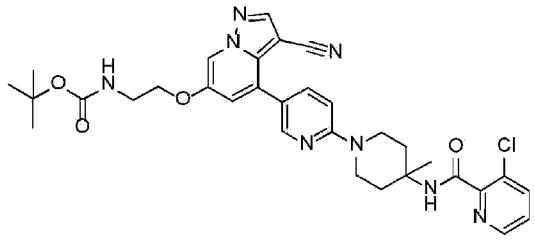


3-chloro-N-(1-(5-(3-cyano-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0815] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 31 mg, 0.063 mmol) in DMA (0.63 mL) was added potassium carbonate (10 mg, 0.69 mmol) followed by 1-(2-Chloroethyl)-pyrrolidine (25 mg, 0.189 mmol). The resulting mixture was stirred overnight at 60°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. The water layer was further extracted using 4:1 DCM:IPA. The organic extracts were seperately washed with brine, then combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was resuspended with 60:40 ACN:water. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (16 mg, 42% yield) MS (apci) m/z=585.3 (M+H).

Example 320

[0816]

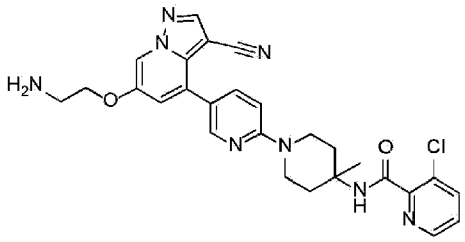


tert-butyl (2-((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate

[0817] To a mixture of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75;** 150 mg, 0.307 mmol) and potassium carbonate (47 mg, 0.34 mmol) in DMA (3.07 mL) was added 2-(bocamino)ethyl bromide (138 mg, 0.615 mmol). The resulting mixture was stirred overnight at 60°C. After cooling to ambient temperature, addional 2-(bocamino)ethyl bromide (69 mg, 0.307 mmol) was added and reaction stirred for 1 h at ambient temperature. Then additional potassium carbonate (42 mg, 0.31 mmol) was added and reaction stirred for two overnights at 60°C. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed with water. The organic extracts were washed with brine, then combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound in sufficient purity for the next step. 10 mg of the title compound was repurified using C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound. (169 mg, 87% yield) MS (apci) m/z=631.3 (M+H).

Example 321

[0818]

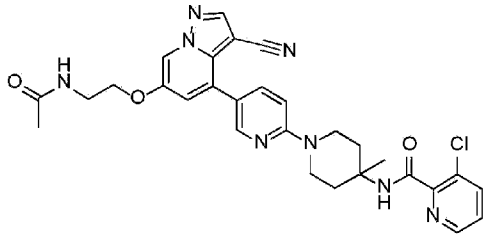


N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-chloropicolinamide

[0819] To a solution tert-butyl (2-((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate (**Example 320,** 158 mg, 0.250 mmol) in DCM (2.5 mL) was treated with TFA (2.5 mL, 32 mmol). The reaction mixture was stirred for 10 min at ambient temperature, and then concentrated *in vacuo.* The residue was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (130 mg, 98% yield) MS (apci) m/z=531.2 (M+H)

Example 322

[0820]

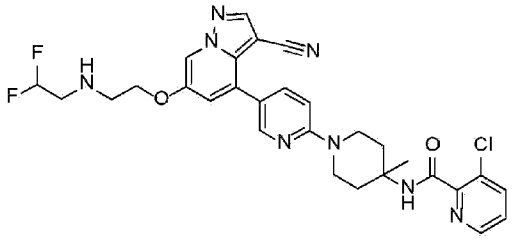


N-(1-(5-(6-(2-acetamidoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-chloropicolinamide

[0821] To a solution of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-chloropicolinamide (**Example 321**; 27 mg, 0.51 mmol) in DCM (0.5 mL) was added acetic anhydride (5 µL, 0.51 mmol) followed by TEA (14 µL, 0.102 mmol). The reaction solution was stirred for 1 h at ambient temperature. The reaction was concentrated *in vacuo.* The residue was resuspended with 60:40 ACN:water. The solution was purified directly by C18 reverse phase chromatography (5-75% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (20 mg, 67% yield) MS (apci) m/z=573.2 (M+H).

Example 323

[0822]



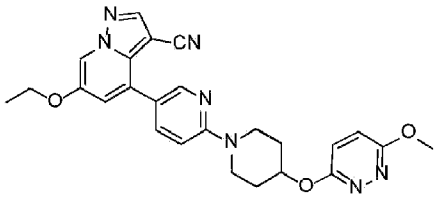
3-chloro-N-(1-(5-(3-cyano-6-(2-((2,2-difluoroethyl)amino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0823] To a solution of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-chloropicolinamide (**Example 321,** 27 mg, 0.051 mmol) in DMA (0.5 mL) was added potassium carbonate (35 mg, 0.254 mmol). The suspension was sparged with argon and stirred for 10 min at ambient temperature. Then 2,2-difluoroethyl trifluoromethanesulfonate (11 mg, 0.51 mmol). The resulting mixture was sparged with argon and stirred 60 h at 60°C. After cooling to ambient temperature, reaction was diluted with 60:40 ACN:water. The solution was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1

DCM:IPA and then washed with brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (4 mg, 13% yield) MS (apci) m/z=595.2 (M+H).

Example 324

[0824]



6-ethoxy-4-(6-(4-((6-methoxypyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

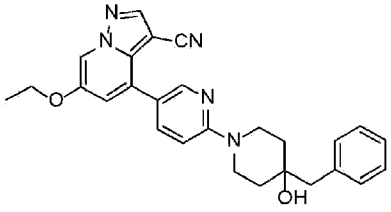
[0825] Step 1: Preparation of tert-butyl 4-((6-methoxypyridazin-3-yl)oxy)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (10.0 g, 49.7 mmol) in DMF (82.8 mL) was added sodium hydride (2.19 g, 54.7 mmol). The mixture was stirred at rt for 15 mins, after which 3-chloro-6-methoxypyridazine (7.18 g, 49.7 mmol) was added. The reaction mixture was stirred at 90°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (5-50% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 15.4 g, 49.8 mmol) in sufficient purity for Step 2. MS (apci) m/z = 310.1 (M+H).

[0826] Step 2: Preparation of 3-methoxy-6-(piperidin-4-yloxy)pyridazine. To a solution of tert-butyl 4-((6-methoxypyridazin-3-yl)oxy)piperidine-1-carboxylate (assumed 15.4 g, 49.8 mol) in DCM (16 mL) was added TFA (19.2 mL, 250.9 mmol). The reaction mixture was stirred at rt 15 min, at which time it was concentrated *in vacuo.* The residue was resuspended in 20 mL DCM and purified by silica chromatography (1-9% MeOH in DCM with 1% NH_4OH as the gradient eluent) to afford the title compound (6.0 g, 28.7 mmol, 57.6 % yield over two steps) in sufficient purity for Step 3. MS (apci) m/z = 210.1 (M+H).

[0827] Step 3: Preparation of 6-ethoxy-4-(6-(4-((6-methoxypyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P6,** 0.012 g, 0.0425 mmol) in DMSO (0.1 mL) was added 3-methoxy-6-(piperidin-4-yloxy)pyridazine (0.0133 g, 0.0638 mmol) and DIEA (37 µL, 0.213 mmol). The reaction mixture was stirred at 110°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NH_4Cl_{(aq)}$. The combined aqueous washes were were further extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (6 mg, 0.0127 mmol, 30 % yield). MS (apci) m/z = 472.2 (M+H).

Example 325

[0828]

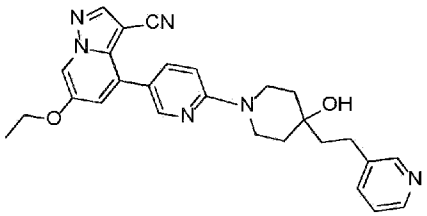


4-(6-(4-benzyl-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0829] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P6,** 30 mg, 0.106 mmol) in DMA (0.5 mL) was added TEA (0.044 mL, 0.319 mmol) and 4-benzylpiperidin-4-ol (40.7 mg, 0.213 mmol) The reaction mixture was stirred at 90°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with saturated $NH_4Cl_{(aq)}$ then water. The combined aqueous washes were further extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (30-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (39 mg, 0.0860 mmol, 80.9 % yield). MS (apci) m/z = 454.2 (M+H).

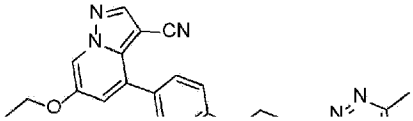
[0830] The compounds in Table RR were prepared using a similar method to that described for the synthesis of **Example 325,** replacing 4-benzylpiperidin-4-ol with the appropriate piperidine nucleophile. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

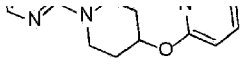
Table RR

Ex. #	Structure	Chemical Name	MS m/z
326		6-ethoxy-4-(6-(4-hydroxy-4-(2-(pyridin-3-yl)ethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	469.15 (M+H)

Example 331

[0831]



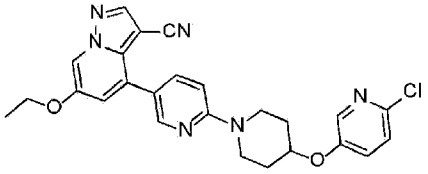


6-ethoxy-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0832] To a solution of 6-ethoxy-4-(6-(4-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P52**, 30 mg, 0.0825 mmol) in 1:1 DCM/THF (0.7 mL) was added 6-methylpyridazin-3-ol (18.2 mg, 0.165 mmol) and triphenylphosphane (43.3 mg, 0.165 mmol). The reaction vessel was sparged with argon, at which time diisopropyl (E)-diazene-1,2-dicarboxylate (0.0235 ml, 0.165 mmol) was added, and the reaction mixture was stirred at rt 24 h. The reaction mixture was diluted with DCM and washed with water. The aqueous fraction was extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (50-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (15 mg, 0.0329 mmol, 39.9 % yield). MS (apci) m/z = 456.2 (M+H).

Example 332

[0833]

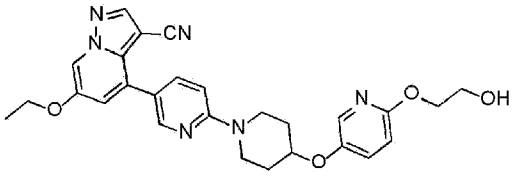


4-(6-(4-((6-chloropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0834] The title compound was prepared using a similar method to that described for the synthesis of **Example 331**, replacing 6-methylpyridazin-3-ol with 6-chloropyridin-3-ol. MS (apci) m/z = 475.2 (M+H).

Example 333

[0835]

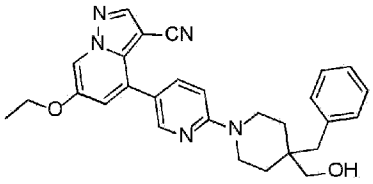


6-ethoxy-4-(6-(4-((6-(2-hydroxyethoxy)pyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0836] To a solution of ethane-1,2-diol (9.8 mg, 0.16 mmol) in DMF (0.2 mL) was added sodium hydride (60% w/w, 2.3 mg, 0.095 mmol) and stirred at rt for 5 min, at which time 4-(6-(4-((6-chloropyridin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Example 332**, 15 mg, 0.032 mmol) in an additional 0.3 mL of DMF was added. The reaction mixture was stirred at 110°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (10-90% ACN in water with 0.1% formic acid as the gradient eluent) to afford the title compound (2.2 mg, 0.0044 mmol, 14 % yield). MS (apci) m/z = 501.25 (M+H).

Example 336

[0837]

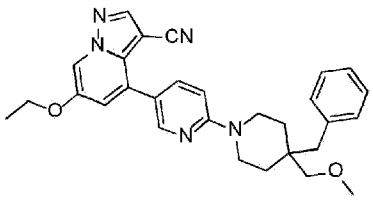


4-(6-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0838] To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (100.5 mg, 0.3560 mmol) in DMSO (3 ml) was added (4-benzylpiperidin-4-yl)methanol hydrochloride (151.5 mg, 0.6267 mmol) and cesium carbonate (812.0 mg, 2.492 mmol). The reaction mixture was stirred at 60°C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and saturated $NH_4Cl_{(aq)}$. The combined aqueous layers were extracted with DCM, then the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (118.2 mg, 0.2528 mmol, 71.00 % yield). MS (apci) m/z = 468.2 (M+H).

Example 337

[0839]



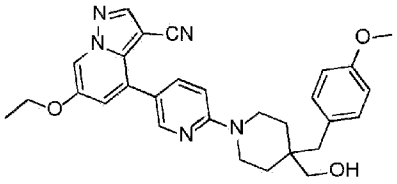
4-(6-(4-benzyl-4-(methoxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -

carbonitrile

[0840] To a solution of 4-(6-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P55**, 9.0 mg, 0.019 mmol) in DMF (0.4 mL) was added sodium hydride (60% w/w, 2.8 mg, 0.070 mmol). This mixture was stirred at rt 1 h, at which time methyl iodide (0.021 ml, 0.34 mmol) was added. The reaction mixture was stirred at rt for 72 h. The reaction mixture was diluted with DCM and washed with water. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (4.0 mg, 0.0083 mmol, 43 % yield). MS (apci) m/z = 482.25 (M+H).

Example 339

[0841]



6-ethoxy-4-(6-(4-(hydroxymethyl)-4-(4-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0842] Step 1: Preparation of tert-butyl 4-formyl-4-(4-methoxybenzyl)piperidine-1-carboxylate. To a sealed 3-neck flask that had been sparged with N_2 was added tert-butyl 4-formylpiperidine-1-carboxylate (201.8 mg, 0.9462 mmol) in THF (2 mL). The mixture was cooled to -78°C and stirred at this temperature for 10 min, at which time lithium bis(trimethylsilyl)amide (3 mL, 3 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 40 min then warmed to rt. After 16 h, 1-(bromomethyl)-4-methoxybenzene (0.3 mL, 2.058 mmol) was added, and the reaction mixture was stirred an additional 24 h at rt. The reaction was quenched with water, extracted into EtOAc, and the organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 315 mg, 0.946 mmol) in sufficient purity for Step 2. MS (apci) m/z = 234.2 (M+H-Boc).

[0843] Step 2: Preparation of 4-(4-methoxybenzyl)piperidine-4-carbaldehyde.To a solution of tert-butyl 4-formyl-4-(4-methoxybenzyl)piperidine-1-carboxylate (assumed 315 mg, 0.946 mmol) in DCM (2 mL) was added TFA (2 mL, 26 mmol). The reaction mixture was stirred at rt 30 min then concentrated *in vacuo.* The residue was diluted in DCM and 10% NH_4OH in MeOH and stirred for 15 min. The mixture was concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 220.8 mg, 0.9462 mmol) in sufficient purity for Step 3. MS (apci) m/z = 234.2 (M+H).

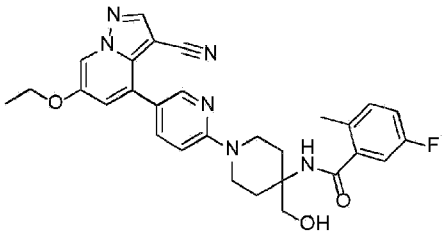
[0844] Step 3: Preparation of 6-ethoxy-4-(6-(4-formyl-4-(4-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P6**, 40.3 mg, 0.143 mmol) in DMSO (0.5 mL) was added 4-(4-

methoxybenzyl)piperidine-4-carbaldehyde (66.6 mg, 0.286 mmol) and cesium carbonate (465 mg, 1.43 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted with DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 70.8 mg, 0.143 mmol) in sufficient purity for Step 4. MS (apci) m/z = 496.2 (M+H).

[0845] Step 4: Preparation of 6-ethoxy-4-(6-(4-(hydroxymethyl)-4-(4-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. MeOH (0.5 mL) was added to 6-ethoxy-4-(6-(4-formyl-4-(4-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (assumed 70.8 mg, 0.143 mmol) and stirred at rt 10 min, at which time sodium borohydride (103.5 mg, 2.736 mmol) was added. The reaction mixture was stirred at rt 1.5 h then quenched with water and 2M HCl. The pH of the mixture was adjusted to 12 with 2M NaOH, and the mixture was extracted with 4:1 DCM/IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (0-70% ACN in water with 0.1% TFA). The fractions containing the desired product were free-based with saturated $NaHCO_{3(aq)}$ to afford the title compound (1.1 mg, 0.00221 mmol, 1.57 % yield over four steps). MS (apci) m/z = 498.3 (M+H).

Example 340

[0846]

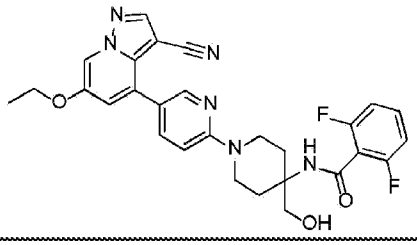
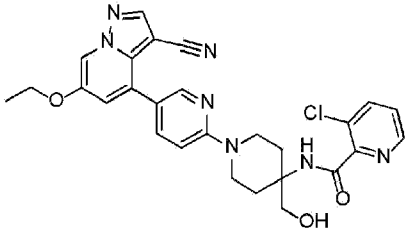
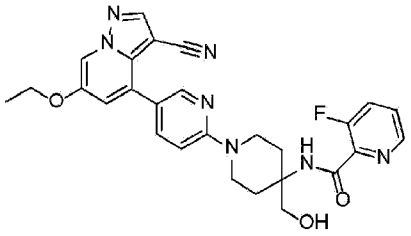


N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[0847] To a solution of 4-(6-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P56**, 30 mg, 0.0764 mmol) in DCM (0.005 mL) was added 5-fluoro-2-methylbenzoic acid (11.8 mg, 0.0764 mmol), DIEA (13.4 µl, 0.0764 mmol), and HATU (29.1 mg, 0.0764 mmol). The reaction mixture was stirred at rt 24 h then purified by C18 prep HPLC eluting with a 5-95% acetonitrile/water + 0.1% TFA gradient then silica chromaography eluting with (0-100% EtOAc in Hexanes then 0-10% MeOH in EtOAc as the gradient eluent) followed by trituration with 1:3 DCM/MTBE to afford the title compound (23.8 mg, 0.045 mmol, 59% yield). MS (apci) m/z = 529.2 (M+H).

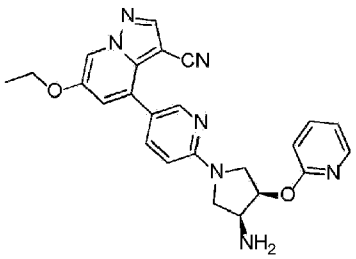
[0848] The compounds in Table SS were prepared using a similar method to that described for the synthesis of **Example 340**, replacing 5-fluoro-2-methylbenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table SS

Ex. #	Structure	Chemical Name	MS m/z
341		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl)-2,6-difluorobenzamide	533.20 (M+H)
342		3-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperi din-4-yl)picolinamide	532.20 (M^+)
343		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(hydroxymethyl)piperi din-4-yl)-3-fluoropicolinamide	516.20 (M+H)

Example 350

[0849]



4-(6-((3S,4R)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

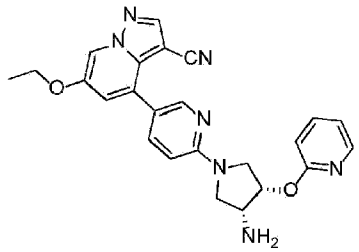
[0850] Step 1: Preparation of 4-(6-((3S,4R)-3-azido-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-((3 S,4S)-3 -azido-4-hydroxypyrrolidin-1 -yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 - carbonitrile (**Intermediate P58**, 0.050 g, 0.128 mmol) in 1:1 DCM/THF (0.7 mL) was added pyridin-2-ol (0.0244 g, 0.256 mmol) and triphenylphosphane (0.0672 g, 0.256 mmol). The reaction mixture was sparged with argon, diisopropyl (E)-diazene-1,2-dicarboxylate (0.0350 mL, 0.256 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was

quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.014 g, 0.0299 mmol, 23.4 % yield) in sufficient purity for step 2. MS (apci) m/z = 468.1 (M+H).

[0851] Step 2: Preparation of 4-(6-((3S,4R)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-((3 S,4R)-3 -azido-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5-a]pyridine-3-carbonitrile (0.013 g, 0.028 mmol) in 1:1 MeOH/EtOAc (2 mL) was added 10% palladium on carbon (0.33 mg, 0.0028 mmol). The reaction mixture was sparged with H_2 and stirred at rt for 24 h. The solids were removed by filtration, and the filtrate was concentrated *in vacuo.* The residue was purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (7 mg, 56 % yield). MS (apci) m/z = 442.2 (M+H).

Example 354

[0852]



4-(6-((3R,4S)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

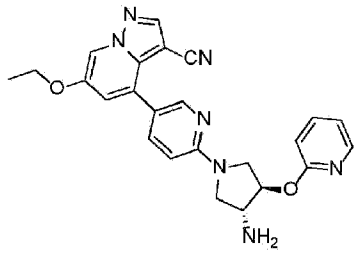
[0853] Step 1: Preparation of 4-(6-((3R,4S)-3-azido-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-((3R,4R)-3-azido-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P59**, 0.050 g, 0.128 mmol) in 1:1 DCM/THF (0.7 mL) was added pyridin-2-ol (0.0244 g, 0.256 mmol) and triphenylphosphane (0.0672 g, 0.256 mmol). The reaction mixture was sparged with argon, diisopropyl (E)-diazene-1,2-dicarboxylate (0.0350 mL, 0.256 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.025 g, 0.0535 mmol, 41.8% yield) in sufficient purity for step 2. MS (apci) m/z = 468.1 (M+H).

[0854] Step 2: Preparation of 4-(6-((3R,4S)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-((3R,4S)-3-azido-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (0.022 g, 0.0471 mmol) in 1:1 MeOH/EtOAc (2 mL) was added 10% palladium on carbon (0.56 mg, 0.0047 mmol). The reaction mixture was sparged with H_2 and stirred at rt for 24 h. The solids were removed by vacuum filtration, and the filtrate was concentrated *in vacuo.* The residue was purified by silica chromatography (0-40% [9:1

MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (13 mg, 0.0297 mmol, 63.1 % yield). MS (apci) m/z = 442.2 (M+H).

Example 358

[0855]



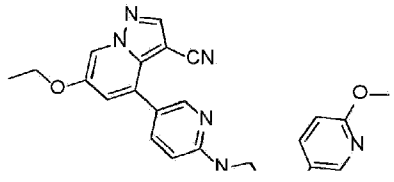
4-(6-((3R,4R)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

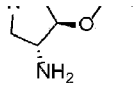
[0856] Step 1: Preparation of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate. To a solution of tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P60**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.75 mL) was added pyridin-2-ol (0.0123 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.035 g, 0.0646 mmol) in sufficient purity for step 2.

[0857] Step 2: Preparation of 4-(6-((3R,4R)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate (0.035 g, 0.0646 mmol) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0073 g, 0.0165 mmol, 25.6% yield over two steps). MS (apci) m/z = 442.2 (M+H).

Example 359

[0858]





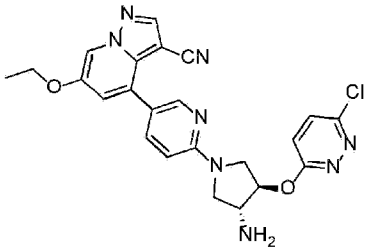
4-(6-((3R,4R)-3-amino-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0859] Step 1: Preparation of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate. To a solution of tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P60**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.75 mL) was added 5-methoxypyridin-2-ol (0.0162 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.037 g, 0.0646 mmol) in sufficient purity for step 2.

[0860] Step 2: Preparation of 4-(6-((3R,4R)-3-amino-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate (0.037 g, 0.0646) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0065 g, 0.0138 mmol, 21.3% yield over two steps). MS (apci) m/z = 472.2 (M+H).

Example 360

[0861]



4-(6-((3R,4R)-3-amino-4-((6-chloropyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

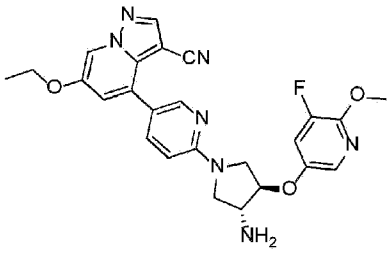
[0862] Step 1: Preparation of tert-butyl ((3R,4R)-4-((6-chloropyridazin-3-yl)oxy)-1-(5-(3-cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3 -yl)carbamate. To a solution of tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-

yl)carbamate (**Intermediate P60**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.7 mL) was added 6-chloropyridazin-3-ol (0.0169 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.031 g, 0.0646 mmol) in sufficient purity for step 2.

[0863] Step 2: Preparation of 4-(6-((3R,4R)-3-amino-4-((6-chloropyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3R,4R)-4-((6-chloropyridazin-3-yl)oxy)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (0.031 g, 0.0646) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.013 g, 0.0273 mmol, 42.2% yield over two steps). MS (apci) m/z = 477.1 (M+H).

Example 361

[0864]



4-(6-((3R,4R)-3-amino-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile

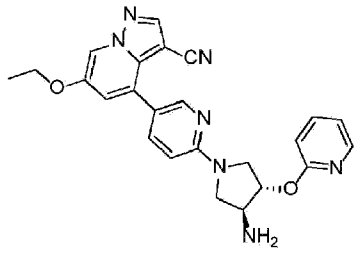
[0865] Step 1: Preparation of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-3-yl)carbamate. To a solution of tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P60**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.7 mL) was added 5-fluoro-6-methoxypyridin-3-ol (0.0185 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.038 g, 0.0646 mmol) in sufficient purity for step 2.

[0866] Step 2: Preparation of 4-(6-((3R,4R)-3-amino-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-1-

yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((5-fluoro-6-methoxypyridin-3-yl)oxy)pyrrolidin-3-yl)carbamate (0.038 g, 0.0646) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0014 g, 0.00286 mmol, 4.43% yield over two steps). MS (apci) m/z = 490.2 (M+H).

Example 362

[0867]



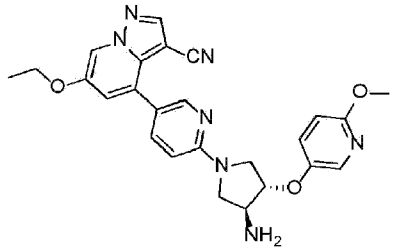
4-(6-((3S,4S)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0868] Step 1: Preparation of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate. To a solution of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P61**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.75 mL) was added pyridin-2-ol (0.0123 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.035 g, 0.0646 mmol) in sufficient purity for step 2. MS (apci) m/z = 542.3 (M+H).

[0869] Step 2: Preparation of 4-(6-((3S,4S)-3-amino-4-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate (0.035 g, 0.0646 mmol) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0101 g, 0.0229 mmol, 35.4% yield over two steps). MS (apci) m/z = 442.2 (M+H).

Example 363

[0870]



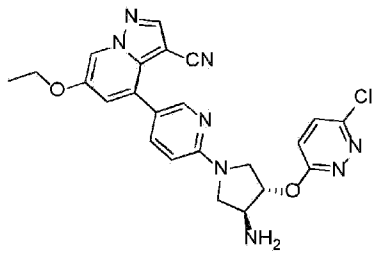
4-(6-((3S,4S)-3-amino-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0871] Step 1: Preparation of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate. To a solution of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P61**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.75 mL) was added 5-methoxypyridin-2-ol (0.0162 g, 0.129 mmol) and triphenylphosphane (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 48 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.037 g, 0.0646 mmol) in sufficient purity for step 2. MS (apci) m/z = 572.3 (M+H).

[0872] Step 2: Preparation of 4-(6-((3S,4S)-3-amino-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-(pyridin-2-yloxy)pyrrolidin-3-yl)carbamate (0.037 g, 0.0646) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0112 g, 0.0238 mmol, 36.8% yield over two steps). MS (apci) m/z = 472.2 (M+H).

Example 364

[0873]



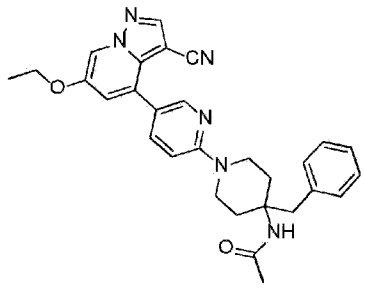
4-(6-((3S,4S)-3-amino-4-((6-chloropyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0874] Step 1: Preparation of tert-butyl ((3S,4S)-4-((6-chloropyridazin-3-yl)oxy)-1-(5-(3-cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3 -yl)carbamate. To a solution of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (**Intermediate P61**, 0.030 g, 0.0646 mmol) in 1:1 DCM/THF (0.7 mL) was added 6-chloropyridazin-3-ol (0.0169 g, 0.129 mmol) and triphenylphosphine (0.0339 g, 0.129 mmol). The reaction mixture was sparged with argon, and diisopropyl (E)-diazene-1,2-dicarboxylate (0.0176 mL, 0.129 mmol) was added. The reaction mixture was stirred at rt for 24 h. It was quenched with water and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (20-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (assumed theoretical yield, 0.031 g, 0.0646 mmol) in sufficient purity for step 2. MS (apci) m/z = 577.2 (M+H).

[0875] Step 2: Preparation of 4-(6-((3S,4S)-3-amino-4-((6-chloropyridazin-3-yl)oxy)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3S,4S)-4-((6-chloropyridazin-3-yl)oxy)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (0.031 g, 0.0646) in DCM (2 mL) was treated with 6M HCl in IPA (2 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo,* and the residue was taken up in water. 2M NaOH was added and extracted with DCM. The combined organic extracts were passed through a phase separator frit then purified by silica chromatography (0-40% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent) to afford the title compound (0.0096 g, 0.0201 mmol, 31.2% yield over two steps). MS (apci) m/z = 477.2 (M+H).

Example 372 reference

[0876]



N-(4-benzyl-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)acetamide

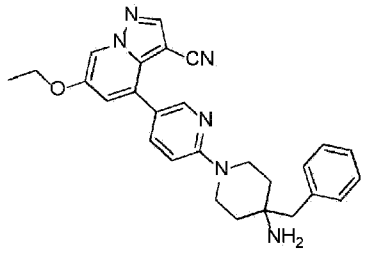
[0877] Step 1: Preparation of N-(4-benzylpiperidin-4-yl)acetamide. A solution of 4-benzylpiperidin-4-ol (0.100 g, 0.523 mmol) in ACN (0.5 mL) was cooled to 0°C and then treated with dropwise addition of sulfuric acid (98%, 0.418 mL, 7.84 mmol). The reaction mixture was warmed to rt and stirred at the same temperature for 24 h. The reaction mixture was cooled to 0°C and treated with slow addition of 2M NaOH until basic. The solution was extracted with DCM, and the combined organic extracts were passed

through a phase separation frit then concentrated *in vacuo* to afford the title compound (0.102 g, 0.439 mmol, 84% yield) in sufficient purity for step 2. MS (apci) m/z = 233.2 (M+H).

[0878] Step 2: Preparation of N-(4-benzyl-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)acetamide. To a solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P6**, 0.060 g, 0.213 mmol) in DMSO (1 mL) was added DIEA (0.184 mL, 1.06 mmol) and N-(4-benzylpiperidin-4-yl)acetamide (0.0988 g, 0.425 mmol). The reaction mixture was stirred at 100°C for 24 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$. and extracted into DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.072 g, 0.146 mmol, 68.5 % yield). MS (apci) m/z = 495.2 (M+H).

Example 373

[0879]

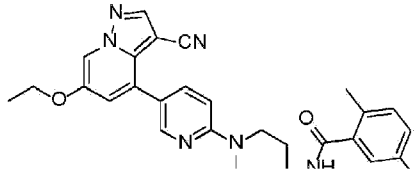


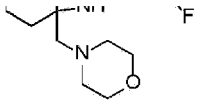
4-(6-(4-amino-4-benzylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[0880] To a solution of N-(4-benzyl-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)acetamide (**Example 372**, 0.020 g, 0.040 mmol) in 1:1 THF/DCM (0.7 mL) was added titanium(IV) propan-2-olate (0.048 mL, 0.16 mmol) and diphenylsilane (0.030 g, 0.16 mmol). The reaction mixture was stirred at rt for 24 h then quenched with water. The mixture was extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$ and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were combined and washed with 2M NaOH and extracted into DCM. The combined organic extracts were were passed through a phase separation frit then concentrated *in vacuo* to afford the title compound (0.0030 g, 0.0066 mmol, 16 % yield). MS (apci) m/z = 453.3 (M+H).

Example 379

[0881]





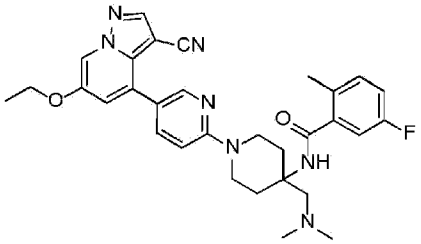
N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-(morpholinomethyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[0882] To a solution of N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P70**, 0.0196 g, 0.03722 mmol) in DCE (0.1861 mL) was added morpholine (0.009661 mL, 0.1117 mmol) and sodium triacetoxyborohydride (0.01183 g, 0.05583 mmol). The reaction mixture was stirred at rt for 16 h. The crude reaction mixture was directly purified by silica chromatography (0-100% EtOAc in Hexanes then 0-10% MeOH in $CHCl_3$ as the gradient eluent) to afford the title compound (0.0172 g, 0.02878 mmol, 77% yield). MS (apci) m/z = 598.3 (M+H).

[0883] The compounds in Table TT were prepared using a similar method to that described for the synthesis of **Example 379**, replacing morpholine with the appropriate amine. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Example 383

[0884]

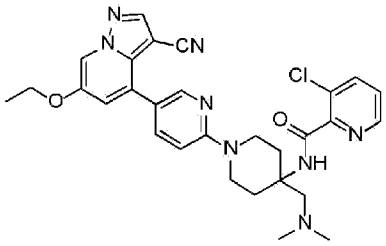


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[0885] To a solution of 4-(6-(4-amino-4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P72**, 7 mg, 0.017 mmol) in DMF (0.334 mL) was added 5-fluoro-2-methylbenzoic acid (5.1 mg, 0.033 mmol), HATU (13 mg, 0.033 mmol), and DIEA (0.015 mL, 0.083 mmol). The reaction mixture was stirred at rt for 1 h. The crude reaction mixture was directly purified by silica chromatography (0-100% EtOAc in Hexanes then 1-10% MeOH in EtOAc with 0.1-1% NH_4OH as the gradient eluent) to afford the title compound (5 mg, 0.0090 mmol, 54% yield). MS (apci) m/z = 556.2 (M+H).

Example 384

[0886]

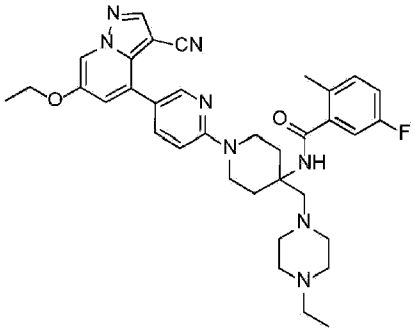


3-chloro-N-(1 -(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)picolinamide

[0887] To a mixture of 4-(6-(4-amino-4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P72**, 0.050 g, 0.119 mmol) in DMSO (0.795 mL) was added 3-chloropicolinic acid (0.0282 g, 0.179 mmol) followed by Hunig's base (0.0934 mL, 0.536 mmol) and HATU (0.0906 g, 0.238 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The organic extract was washed with saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were combined and washed with saturated $NaHCO_{3(aq)}$ and extracted into DCM. The combined organic extracts were washed with saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo* to afford the title compound (0.0108 g, 0.0193 mmol, 16.2% yield). MS (apci) m/z = 559.3 (M+H).

Example 389

[0888]



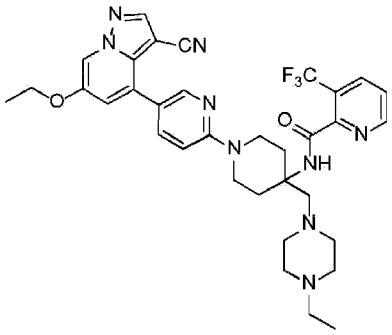
N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[0889] To a solution of 4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-

ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile dihydrochloride (**Intermediate P74**. 20 mg, 0.0356 mmol) in DMF (0.356 mL) was added 5-fluoro-2-methylbenzoic acid (6.86 mg, 0.0445 mmol), DIEA (0.0311 mL, 0.178 mmol), and HATU (16.9 mg, 0.0445 mmol). The reaction mixture was stirred at rt for 5 min. The crude reaction mixture was directly purified by silica chromatography (0-100% EtOAc in Hexanes then 1-10% MeOH in EtOAc with 0.1-1% NH_4OH as the gradient eluent) to afford the title compound (7 mg, 0.0112 mmol, 31.5% yield). MS (apci) m/z = 625.4 (M+H).

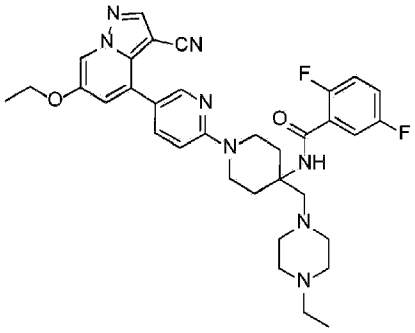
[0890] The compounds in Table UU were prepared using a similar method to that described for the synthesis of **Example 389**, replacing 5-fluoro-2-methylbenzoic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table UU

Ex. #	Structure	Chemical Name	MS (apci) m/z
390		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-3-(trifluoromethyl)picolinam ide	662.20 (M+H)

Example 391

[0891]



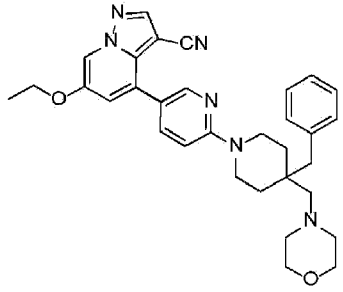
N-(1-(5 -(3 -cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-2,5-difluorobenzamide

[0892] To a solution of 4-(6-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P74**, 0.0238 g, 0.0606 mmol) in DMSO (0.606 mL) was added

DIEA (0.0530 ml, 0.303 mmol), 2,6-difluorobenzoic acid (0.0192 g, 0.121 mmol), HATU (0.0461 g, 0.121 mmol). The reaction mixture was stirred at rt for 16 h. The crude reaction mixture was directly purified by silica chromatography (1-10% MeOH in DCM with 0.1-1% NH_4OH as the gradient eluent) to afford the title compound (29 mg, 0.023 mmol, 49.5% yield). MS (apci) m/z = 629.4 (M+H).

Example 398

[0893]

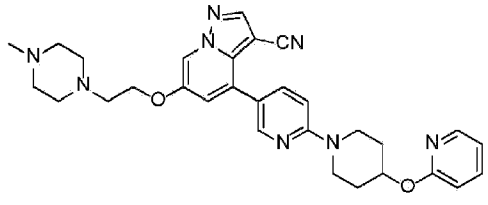


4-(6-(4-benzyl-4-(morpholinomethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0894] To a solution of 4-(6-(4-benzyl-4-formylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P77**, 10.4 mg, 0.0223 mmol) in DCE (0.75 mL) was added morpholine (9.1 mg, 0.104 mmol). The mixture was stirred at rt for 1 hr then was treated with sodium triacetoxyborohydride (34.0 mg, 0.160 mmol). The reaction mixture was stirred at rt for 96 h. The reaction mixture was diluted with DCM and washed with water. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$ and purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent to afford the title compound (1.6 mg, 0.00295 mmol, 13.2 % yield). MS (apci) m/z = 537.3 (M+H).

Example 399

[0895]



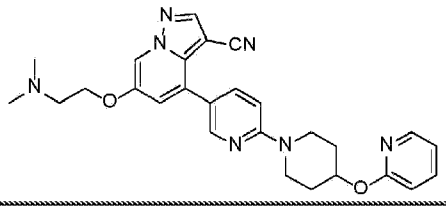
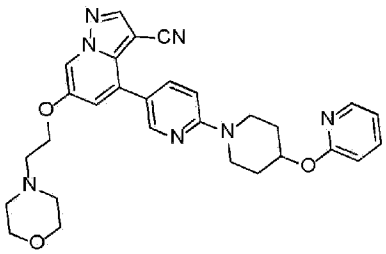
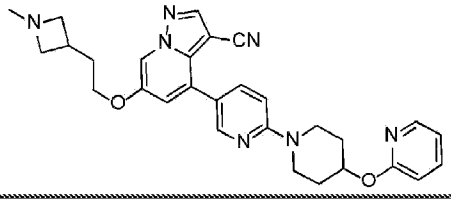
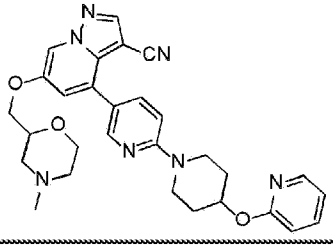
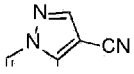
6-(2-(4-methylpiperazin-1-yl)ethoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

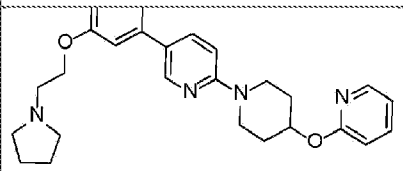
[0896] A solution of triphenylphosphane (31.7966 mg, 0.121 mmol) in 1:1 DCM:THF (0.6 mL) was cooled to 0°C and treated with diisopropyl azodicarboxylate (0.023 mL, 0.121 mmol) and stirred at 0°C for 15

min. The reaction mixture was treated with 6-hydroxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P78,** 25.0 mg, 0.0606 mmol) in a 1:1 DCM:THF (0.6 mL) and 1-(N-hydroxyethyl)-4-methyl piperazine (13.1 mg, 0.0909 mmol). The reaction mixture was allowed to warm to rt and was stirred at this temperature for 30 min. The reaction mixture was concentrated *in vacuo,* and the resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM:IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (31.5 mg, 0.0526 mmol, 86.8% yield). MS (apci) m/z = 539.2 (M+H).

[0897] The compounds in Table VV were prepared using a similar method to that described for the synthesis of **Example 399**, replacing 1-(N-hydroxyethyl)-4-methyl piperazine with the appropriate alcohol. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

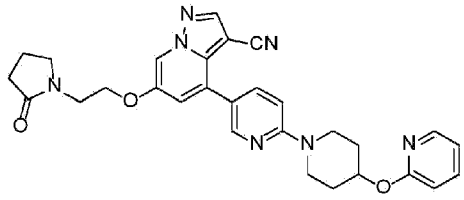
Table VV

Ex. #	Structure	Chemical Name	MS m/z
400		6-(2-(dimethylamino)ethoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	484.20 (M+H)
401		6-(2-morpholinoethoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	526.20 (M+H)
402		6-(2-(1-methylazetidin-3-yl)ethoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	510.20 (M+H)
403		6-((4-methylmorpholin-2-yl)methoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	526.20 (M+H)
404		4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3 -yl)-6-(2-(pyrrolidin-1-	510.30 (M+H)

Ex. #	Structure	Chemical Name	MS m/z
		yl)ethoxy)pyrazolo [1,5-a]pyridine-3 -carbonitrile	

Example 405

[0898]

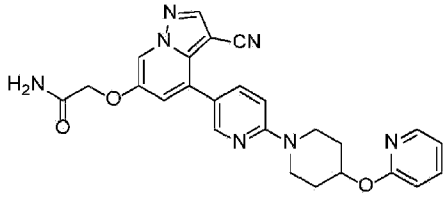


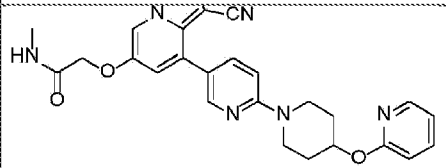
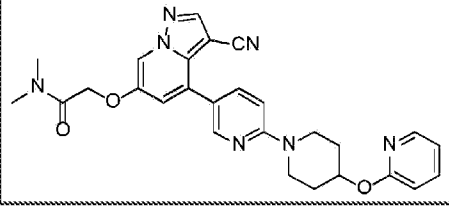
6-(2-(2-oxopyrrolidin-1-yl)ethoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0899] To a solution of 6-hydroxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P78**, 0.010 g, 0.0242 mmol) in DMF (0.8 mL) was added 1-(2-chloroethyl)pyrrolidin-2-one (7.16 mg, 0.0485 mmol), potassium carbonate (6.7 mg, 0.0485 mmol), and sodium bromide (3.24 mg, 0.0315 mmol). The reaction mixture was stirred at 100°C for 72 h. After cooling to ambient temperature, the crude reaction mixture purified by C-18 reverse phase chromatography (0-70% ACN in water as the gradient eluent) to afford the title compound (8 mg, 0.0153 mmol, 63% yield). MS (apci) m/z = 524.2 (M+H).

[0900] The compounds in Table WW were prepared using a similar method to that described for the synthesis of **Example 405**, replacing 1-(2-chloroethyl)pyrrolidin-2-one with the appropriate alkyl halide. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

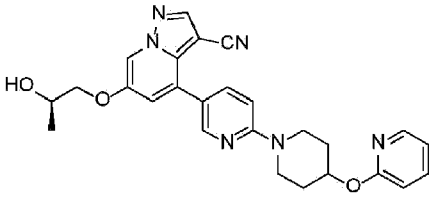
Table WW

Ex. #	Structure	Chemical Name	MS m/z
406		2-((3-cyano-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)acetamide	470.10 (M+H)
407		2-((3-cyano-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-	484.10 (M+H)

Ex. #	Structure	Chemical Name	MS m/z
		yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-N-methylacetamide	
408		2-((3-cyano-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-N,N-dimethylacetamide	498.15 (M+H)

Example 409

[0901]

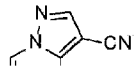


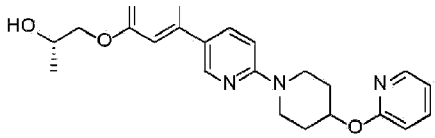
(R)-6-(2-hydroxypropoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 - a]pyridine-3 -carbonitrile

[0902] To a solution of 6-hydroxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P78**, 1.023 mL, 0.0512 mmol) in DMF (1.0 mL) was added aqueous sodium hydroxide (1M, 0.0563 mL, 0.0563 mmol). The mixture was stirred at rt for 5 min, at which time R-(+)-propylene oxide (35.8 µL, 0.512 mmol) was added. The reaction mixture was stirred at 80°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc then washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (8.5 mg, 0.0181 mmol, 35.3% yield). MS (apci) m/z = 471.2 (M+H).

Example 410

[0903]



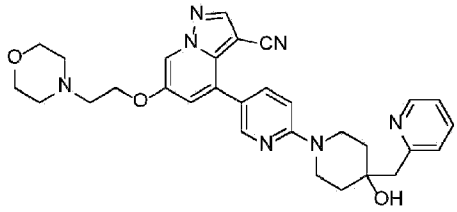


(S)-6-(2-hydroxypropoxy)-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0904] The title compound was prepared using a similar method to that described for the synthesis of **Example 409**, replacing R-(+)-propylene oxide with S-(-)-propylene oxide. MS (apci) m/z = 471.2 (M+H).

Example 411

[0905]

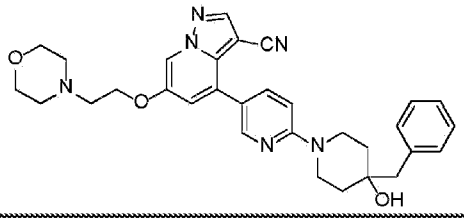
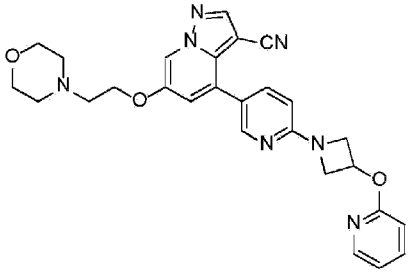


4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0906] To a solution of 4-(6-fluoropyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P79**, 19.7 mg, 0.05362 mmol) in DMSO (1 mL) was added 4-(pyridin-2-ylmethyl)piperidin-4-ol hydrochloride (39.3 mg, 0.1718 mmol) and cesium carbonate (157.2 mg, 0.4826 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed successively with water and saturated $NH_4Cl_{(aq)}$. The aqueous fraction was extracted with DCM, and the combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$. The mixture was purified by silica chromatography (0-100% MeOH in DCM as the gradient eluent) to afford the title compound (16.9 mg, 0.02505 mmol, 46.72 % yield). MS (apci) m/z = 540.2 (M+H).

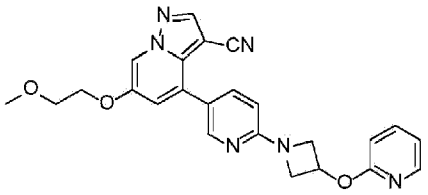
[0907] The compounds in Table XX were prepared using a similar method to that described for the synthesis of **Example 411**, replacing 4-(pyridin-2-ylmethyl)piperidin-4-ol hydrochloride with the appropriate amine. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table XX

Ex. #	Structure	Chemical Name	MS m/z
412		4-(6-(4-benzyl-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	539.20 (M+H)
413		6-(2-morpholinoethoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	498.20 (M+H)

Example 414

[0908]



6-(2-methoxyethoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

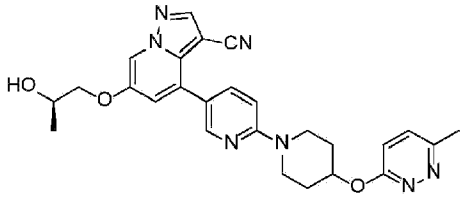
[0909] Step 1: Preparation of 6-hydroxy-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 4-(6-fluoropyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P66**, 0.250 g, 0.9834 mmol) in DMA (2.458 mL) was added 2-(azetidin-3-yloxy)pyridine (0.452 g, 3.010 mmol) and TEA (0.9413 mL, 6.884 mmol). The reaction mixture was stirred at 95°C for 72 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (1-9% MeOH in DCM as the gradient eluent) to afford the title compound (0.1557 g, 0.4050 mmol, 41.19% yield) in sufficient purity for step 2. MS (apci) m/z = 385.1 (M+H).

[0910] Step 2: Preparation of 6-(2-methoxyethoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1.5-a]pyridine-3-carbonitrile. To a solution of 6-hydroxy-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (0.030 g, 0.07804 mmol) in DMF (0.3902 mL) was

added potassium carbonate (0.02157 g, 0.1561 mmol) and 2-bromoethyl methyl ether (0.01467 mL, 0.1561 mmol). The reaction mixture was stirred at 95°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were washed with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (0.0108 g, 0.02441 mmol, 31.27% yield). MS (apci) m/z = 443.2 (M+H).

Example 415

[0911]

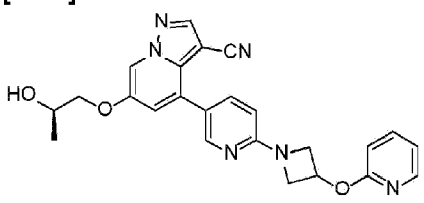


(R)-6-(2-hydroxypropoxy)-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0912] To a solution of (R)-4-(6-fluoropyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P80**, 0.020 g, 0.0640 mmol) in DMA (0.640 mL) was added 3-methyl-6-(piperidin-4-yloxy)pyridazine (0.039 g, 0.202 mmol) and TEA (0.0613 ml, 0.448 mmol). The reaction mixture was stirred at 90°C for 48 h. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were washed with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed successively with water and saturated $NaCl_{(aq)}$ then dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (11 mg, 0.022 mmol, 34 % yield). MS (apci) m/z = 486.2 (M+H).

Example 416

[0913]

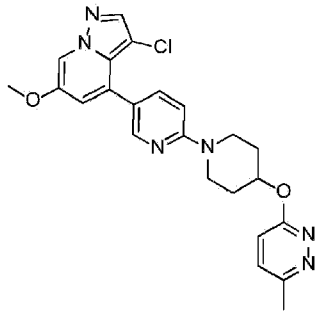


(R)-6-(2-hydroxypropoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-yl)pyridin-3-yl)pyrazolo [1,5 -a]pyridine-3 -carbonitrile

[0914] The compound was prepared using a similar method to that described for the synthesis of **Example 415**, replacing 3-methyl-6-(piperidin-4-yloxy)pyridazine with 2-(azetidin-3-yloxy)pyridine. MS (apci) m/z = 443.1 (M+H).

Example 417

[0915]



3-chloro-6-methoxy-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine

[0916] Step 1: Preparation of 4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine. To a mixture of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (10.0 g, 44.04 mmol) in 1,4-dioxane (88.08 mL) was added 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (11.79 g, 52.85 mmol), tetrakis(triphenylphosphine)palladium(0) (1.018 g, 0.8808 mmol) and aqueous sodium carbonate (2M, 46.24 mL, 92.49 mmol). The reaction mixture was stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was poured onto water and stirred for 4 h. The resultant precipitate was isolated by vacuum filtration then taken up in MTBE and stirred an additional 30 min. The precipitate was isolated by vacuum filtration to afford the title compound (4.616 g, 18.98 mmol, 43.09% yield) in sufficient yield for step 2. MS (apci) m/z = 244.0 (M+H).

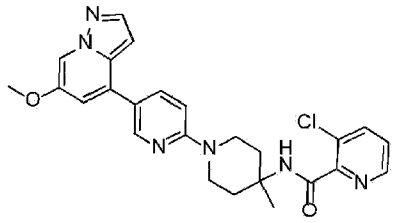
[0917] Step 2: Preparation of 3-chloro-4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine. A solution of 4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine (1.00 g, 4.11 mmol) in DCM (27.4 mL) was treated with NCS (0.549 g, 4.11 mmol). The reaction mixture was stirred at rt for 16 h. The mixture was poured into 2M NaOH and extracted with 10% IPA in DCM in a PS frit. The organic extract was concentrated *in vacuo,* and the residue was triturated with Et_2O. The solid was isolated on a glass frit to afford the title compound (0.98 g, 3.53 mmol, 85.8% yield) in sufficient purity for step 3. MS (apci) m/z = 278.0 (M+H).

[0918] Step 3: Preparation of 3-chloro-6-methoxy-4-(6-(4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine. To a solution of 3-chloro-4-(6-fluoropyridin-3-yl)-6-

methoxypyrazolo[1,5-a]pyridine (30 mg, 0.11 mmol) in DMSO (0.2 mL) was added 3-methyl-6-(piperidin-4-yloxy)pyridazine (31 mg, 0.16 mmol) and cesium carbonate (176 mg, 0.54 mmol). The reaction mixture was stirred at 90°C for 16 h. After cooling to ambient temperature, the mixture was poured into 2M NaOH and extracted with 10% IPA in DCM in a PS frit. The organic extract was concentrated *in vacuo,* and the residue was purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (14 mg, 0.031 mmol, 29% yield). MS (apci) m/z = 451.2 (M+H).

Example 418

[0919]

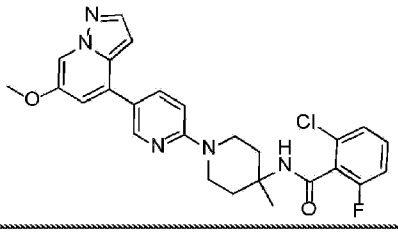
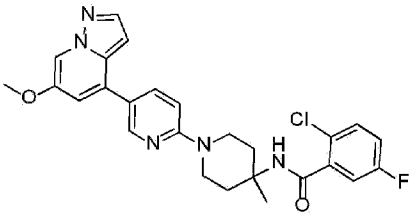


3-chloro-N-(1 -(5 -(6-methoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0920] To a mixture of 1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine (0.057 g, 0.169 mmol) in DMSO (1.13 mL) was added 3-chloropicolinic acid (0.0399 g, 0.253 mmol), DIEA (0.132 mL, 0.760 mmol), and HATU (0.128 g, 0.338 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with DCM and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (0.0501 g, 0.105 mmol, 62.2% yield). MS (apci) m/z = 477.2 (M+H).

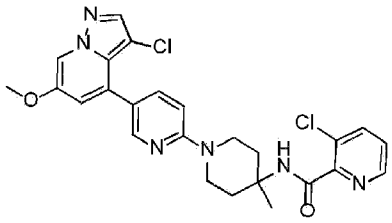
[0921] The compounds in Table YY were prepared using a similar method to that described for the synthesis of **Example 418**, replacing 3-chloropicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table YY

Ex. #	Structure	Chemical Name	MS (apci) m/z
419		2-chloro-6-fluoro-N-(1-(5-(6-methoxypyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	494.20 (M+H)
420		2-chloro-5-fluoro-N-(1-(5-(6-methoxypyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	494.20 (M+H)

Example 421

[0922]

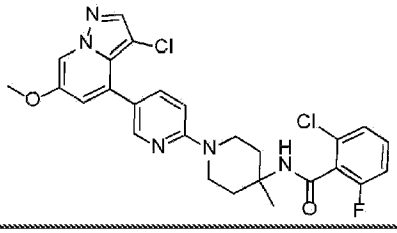
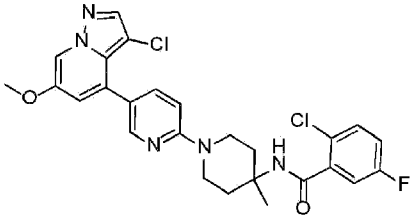


3-chloro-N-(1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0923] To a mixture of 1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine (0.057 g, 0.153 mmol) in DMSO (1.02 mL) was added 3-chloropicolinic acid (0.0362 g, 0.230 mmol), DIEA (0.120 mL, 0.690 mmol), and HATU (0.117 g, 0.307 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-99% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.0415 g, 0.0811 mmol, 52.9% yield). MS (apci) m/z = 511.2 (M^+).

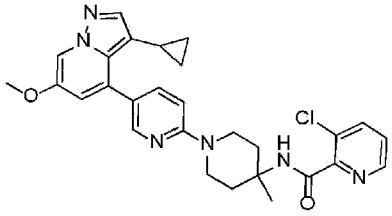
[0924] The compounds in Table ZZ were prepared using a similar method to that described for the synthesis of **Example 421**, replacing 3-chloropicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table ZZ

Ex. #	Structure	Chemical Name	MS m/z
422		2-chloro-N-(1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-fluorobenzamide	528.20 (M^+)
423		2-chloro-N-(1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide	528.20 (M^+)

Example 424

[0925]



3-chloro-N-(1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0926] Step 1: Preparation of tert-butyl (1-(5-(3-bromo-6-methoxypyrazolo[1.5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. To a solution of tert-butyl (1-(5-(6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate **(Intermediate P81,** 0.806 g, 1.84 mmol) in DCM (12.3 mL) was added NBS (0.328 g, 1.84 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.839 g, 1.62 mmol, 88% yield) in sufficient purity for step 2. MS (apci) m/z = 518.1 (M+H+1).

[0927] Step 2: Preparation of tert-butyl (1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate. To a mixture of tert-butyl (1-(5-(3-bromo-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (0.250 g, 0.484 mmol) in a biphasic mixture of toluene (2.42 mL) and water (0.4 mL) was added cyclopropylboronic acid (0.0832 g, 0.968 mmol),

potassium phosphate (0.308 g, 1.45 mmol), palladium(II) acetate (0.0109 g, 0.0484 mmol) and tricyclopentylphosphine (0.0272 g, 0.0968 mmol). The reaction mixture was stirred at 90°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by silica chromatography (10-90% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.061 g, 0.128 mmol, 26% yield) in sufficient purity for step 3. MS (apci) m/z = 478.3 (M+H).

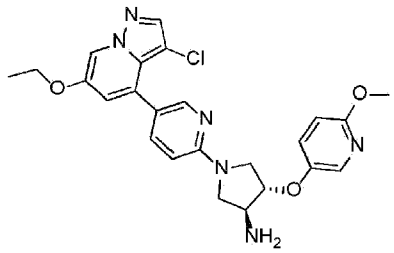
[0928] Step 3: Preparation of 1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine

[0929] A solution of tert-butyl (1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)carbamate (0.060 g, 0.13 mmol) in DCM (12 mL) was treated with TFA (12 mL). The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo* to afford the title compound (0.047 g, 0.12 mmol, 99% yield) in sufficient purity for step 4. MS (apci) m/z = 378.2 (M+H).

[0930] Step 4: Preparation of 3-chloro-N-(1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. To a mixture of 1-(5-(3-cyclopropyl-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-amine (0.047 g, 0.125 mmol) inDMSO (0.830 mL) was added 3-chloropicolinic acid (0.0294 g, 0.187 mmol), DIEA (0.0976 mL, 0.560 mmol), and HATU (0.0947 g, 0.249 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo.* The residue was purified by preparative HPLC (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with DCM and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (0.0441 g, 0.0853 mmol, 68.5% yield). MS (apci) m/z = 517.2 (M^+).

Example 425

[0931]



(3 S,4S)-1-(5-(3 -chloro-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-3-amine

[0932] Step 1: Preparation of 4-bromo-3-chloro-6-ethoxypyrazolo[1,5-a]pyridine. To a solution of 4-

bromo-3-chloropyrazolo[1,5-a]pyridin-6-ol (**Intermediate P84**, 2.5 g, 10.1 mmol) in DMA (150 mL) was added potassium carbonate (14.0 g, 101 mmol) and iodoethane (2.45 mL, 30.3 mmol). The reaction mixture was stirred at 65°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, and concentrated *in vacuo* to afford the title compound (2.00 g, 7.26 mmol, 72% yield) in sufficient purity for step 2. MS (apci) m/z = 277.0 (M+H).

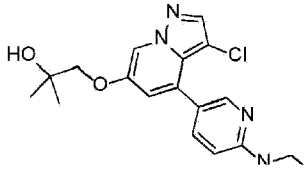
[0933] Step 2: Preparation of 3-chloro-6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolor[1.5-a]pyridine. To a solution of 4-bromo-3-chloro-6-ethoxypyrazolo[1,5-a]pyridine (1.0 g, 3.6 mmol) in 1,4-dioxane (18 mL) was added 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.1 g, 4.7 mmol), tetrakis(triphenylphosphine)palladium (0) (0.21 g, 0.18 mmol), and aqueous sodium carbonate (2M, 9.1 mL, 18 mmol). The reaction mixture was sparged with N_2 and stirred at 90°C for 4 h. After cooling to ambient temperature, the reaction mixture was quenched with water and sonicated for 5 min. The resultant precipitate was isolated by vacuum filtration and washed on the filter with Et_2O to afford the title compound (0.4 g, 1.4 mmol, 38% yield) in sufficient purity for step 3. MS (apci) m/z = 292.1 (M+H).

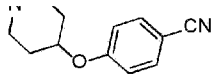
[0934] Step 3: Preparation of tert-butyl ((3S,4R)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate. To a solution of 3-chloro-6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine (0.100 g, 0.343 mmol) in DMSO (1 mL) was added DIEA (0.296 mL, 1.71 mmol) and tert-butyl ((3S,4R)-4-hydroxypyrrolidin-3-yl)carbamate (0.139 g, 0.686 mmol). The reaction mixture was stirred at 95°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water and cooled to 0°C. The resultant precipitate was isolated by vacuum filtration then taken up in 1:1 MTBE/pentane. The slurry was sonicated for 20 min, and the solids were isolated by vacuum filtration to afford the title compound (0.148 g, 0.312 mmol, 91.1% yield) in sufficient purity for step 4. MS (apci) m/z = 474.15 (M+H).

[0935] Step 4: Preparation of (3S,4S)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((6-methoxypyridin-3-yl)oxy)pyrrolidin-3-amine. To a solution of tert-butyl ((3S,4R)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypyrrolidin-3-yl)carbamate (0.040 g, 0.0844 mmol) in 1:1 THF/DCM (0.8 mL) was added 6-methoxypyridin-3-ol (0.0211 g, 0.169 mmol) and triphenylphosphane (0.0443 g, 0.169 mmol). The reaction mixture was sparged with argon and stirred at rt for 16 h. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$. and extracted with DCM. The combined organic extracts were dried using a PS frit, concentrated *in vacuo,* and purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent). The fractions containing the desired product were concentrated *in vacuo,* and the residue was taken up in 6M HCl in IPA and stirred for 2 h. The mixture was concentrated *in vacuo,* taken up in water and 2M NaOH, then extracted with DCM. The combined organic extracts were dried using a PS frit, concentrated *in vacuo,* and purified by silica chromatography (0-35% [9:1 MeOH/NH_4OH] in EtOAc as the gradient eluent to afford the title compound (0.004 g, 0.00832 mmol, 9.85% yield). MS (apci) m/z = 481.2 (M+H).

Example 426

[0936]



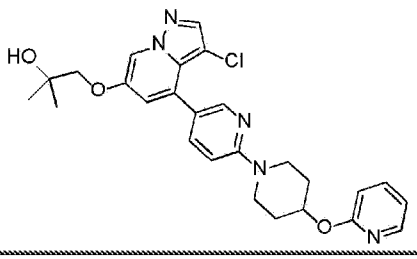
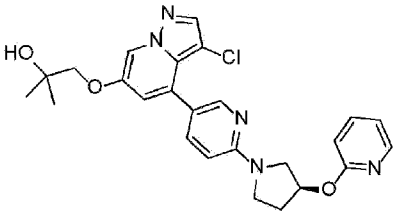
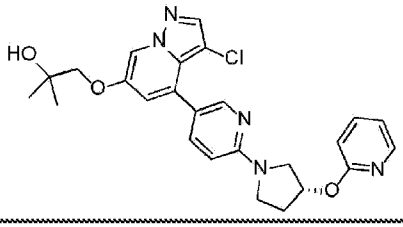
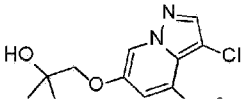


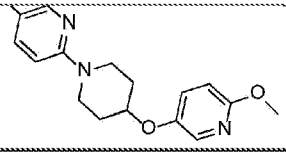
4-((1-(5-(3-chloro-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)oxy)benzonitrile

[0937] To a solution of 1-((3-chloro-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol (**Intermediate P85**, 0.026 g, 0.077 mmol) in DMA (0.5 mL) was added TEA (0.024 g, 0.23 mmol) and 4-(piperidin-4-yloxy)benzonitrile (0.023 g, 0.12 mmol). The reaction mixture was stirred at 105°C for 16 h. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with DCM. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, concentrated *in vacuo,* and purified by silica chromatography (0-100% EtOAc in hexanes as the gradient eluent) to afford the title compound (0.012 g, 0.023 mmol, 30% yield). MS (apci) m/z = 518.2 (M+H).

[0938] The compounds in Table AAA were prepared using a similar method to that described for the synthesis of **Example 426**, replacing 4-(piperidin-4-yloxy)benzonitrile with the appropriate amine reagent. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

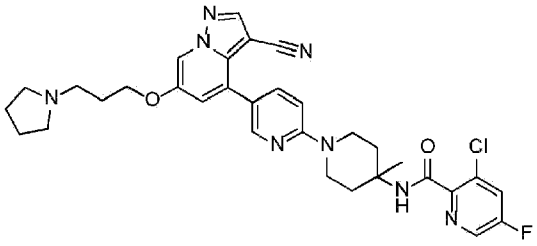
Table AAA

Ex. #	Structure	Chemical Name	MS m/z
427		1-((3-chloro-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol	494.20 (M+H)
428		(S)-1-((3-chloro-4-(6-(3-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol	480.20 (M+H)
429		(R)-1-((3-chloro-4-(6-(3-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-ol	480.20 (M+H)
431		1-((3-chloro-4-(6-(4-((6-methoxypyridin-3 -yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-	524.20 (M+H)

Ex. #	Structure	Chemical Name	MS m/z
		yl)oxy)-2-methylpropan-2-ol	

Example 432

[0939]

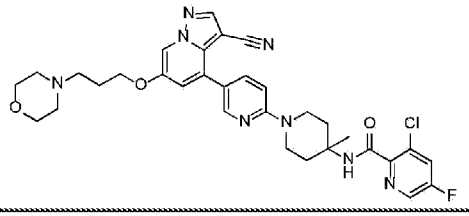
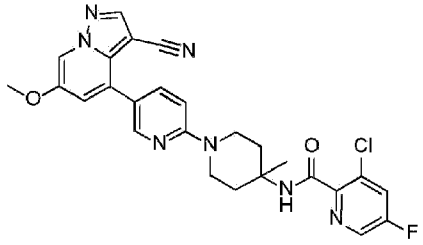
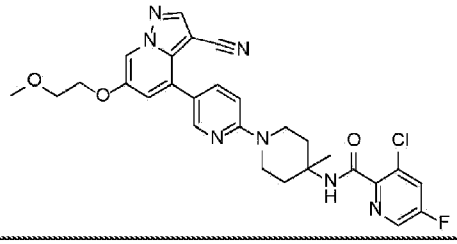
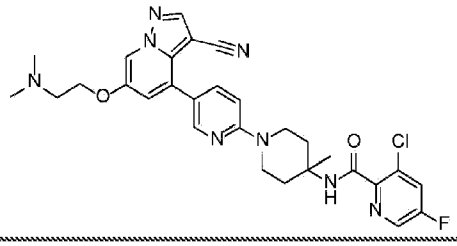


3-chloro-N-(1 -(5 -(3 -cyano-6-(3 -(pyrrolidin-1-yl)propoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide

[0940] To a solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide (**Intermediate P86**, 0.035 g, 0.0692 mmol) in DMA (0.692 mL) was added potassium carbonate (0.0478 g, 0.346 mmol). The reaction mixture was sparged with argon, then 1-(3-chloropropyl)-pyrrolidine (0.0204 g, 0.138 mmol) was added, and the reaction mixture was stirred at 60°C for 5 h. After cooling to ambient temperature, the reaction mixture was directly purified by preparative HPLC (5-75% ACN in water [+ 2% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (0.0186 g, 0.0301 mmol, 43.6% yield). MS (apci) m/z = 617.3 (M+H).

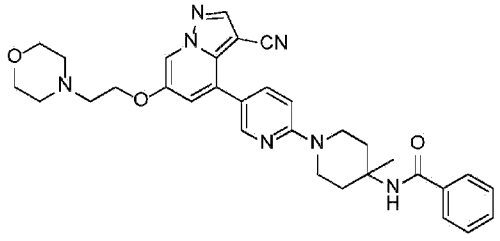
[0941] The compounds in Table BBB were prepared using a similar method to that described for the synthesis of **Example 432**, replacing 1-(3-chloropropyl)-pyrrolidine with the appropriate alkyl halide. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table BBB

Ex. #	Structure	Chemical Name	MS m/z
433		3-chloro-N-(1-(5-(3-cyano-6-(3-morpholinopropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	633.30 (M+H)
434		3-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	520.2 (M+H)
435		3-chloro-N-(1-(5-(3-cyano-6-(2-methoxyethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	564.20 (M+H)
436		3-chloro-N-(1-(5-(3-cyano-6-(2-(dimethylamino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	577.20 (M+H)

Example 437

[0942]

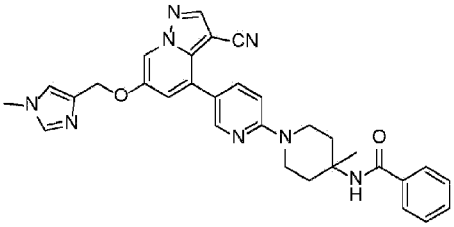
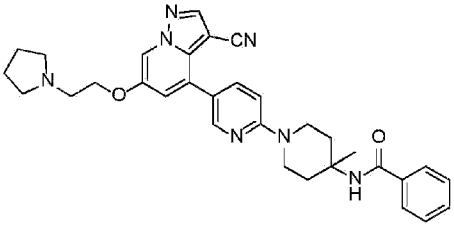
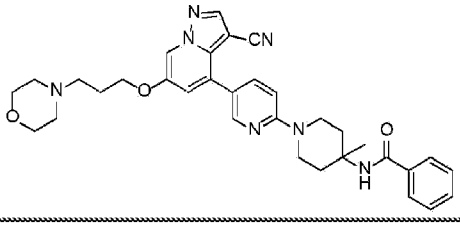


N-(1-(5 -(3 -cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0943] To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (**Intermediate P87**, 30.3 mg, 0.0670 mmol) in DMA (0.7 mL) was added 4-(2-chloroethyl)morpholine hydrochloride (24.9 mg, 0.134 mmol) and cesium carbonate (109 mg, 0.335 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (22.3 mg, 0.0394 mmol, 58.9% yield). MS (apci) m/z = 566.3 (M+H).

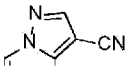
[0944] The compounds in Table CCC were prepared using a similar method to that described for the synthesis of **Example 437**, replacing 4-(2-chloroethyl)morpholine hydrochloride with the appropriate alkyl halide. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

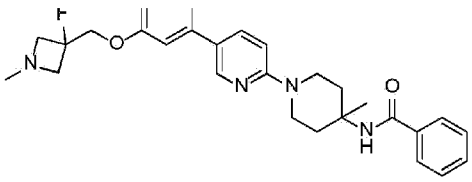
Table CCC

Ex. #	Structure	Chemical Name	MS m/z
438		N-(1-(5-(3-cyano-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	547.30 (M+H)
439		N-(1-(5-(3-cyano-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	550.30 (M+H)
440		N-(1-(5-(3-cyano-6-(3-morpholinopropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide	580.30 (M+H)

Example 441

[0945]





N-(1-(5 -(3 -cyano-6-((3 -fluoro-1-methylazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

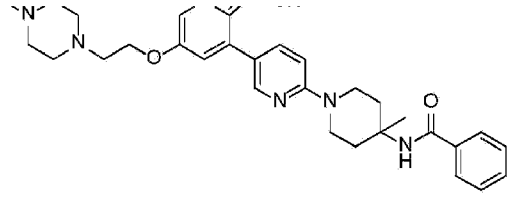
[0946] Step 1: Preparation of tert-butyl 3-(((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (**Intermediate P87**, 44.8 mg, 0.0990 mmol) in DMA (1 mL) was added tert-butyl 3-(bromomethyl)-3-fluoroazetidine-1-carboxylate (53.1 mg, 0.198 mmol) and cesium carbonate (161 mg, 0.495 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 63 mg, 0.099 mmol) in sufficient purity for step 2. MS (apci) m/z = 640.25 (M+H).

[0947] Step 2: Preparation of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide. A solution of tert-butyl 3-(((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate in DCM (0.5 mL) was treated with TFA (0.5 mL, 6.5 mmol). The reaction mixture was stirred at rt for 30 min then concentrated *in vacuo.* The resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (29.5 mg, 0.055 mmol, 55.2% yield over two steps). MS (apci) m/z = 540.3 (M+H).

[0948] Step 3: Preparation of N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide. To a solution of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (29.5 mg, 0.055 mmol) in 1:1 DCM:MeOH (1.1 mL) was added formaldehyde (21 µL, 0.273 mmol) was added, followed by $NaBH(AcO)_3$ (58 mg, 0.273 mmol) The resulting reaction mixture was allowed to stir 30 min at ambient temperature. The reaction was concentrated *in vacuo.* The residue was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (24 mg, 78% yield). MS (apci) m/z = 554.3 (M+H).

Example 442

[0949]

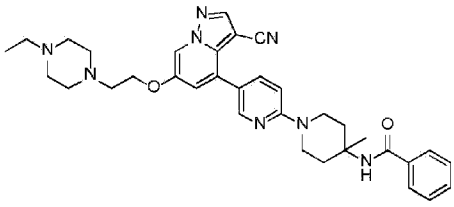


N-(1-(5-(3-cyano-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0950] To a solution of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (**Intermediate P88**, 32.7 mg, 0.0579 mmol) in 1:1 DCM/MeOH (1 mL) was added formaldehyde (0.0218 mL, 0.290 mmol) and sodium triacetoxyborohydride (61.4 mg, 0.290 mmol). The reaction mixture was stirred at rt for 16 h then concentrated *in vacuo*. The residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (21.4 mg, 0.0370 mmol, 63.9% yield). MS (apci) m/z = 579.4 (M+H).

Example 443

[0951]

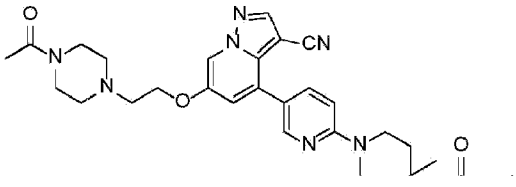


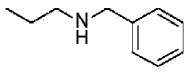
N-(1-(5-(3-cyano-6-(2-(4-ethylpiperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0952] The compound was prepared using a similar method to that described for the synthesis of **Example 442**, replacing formaldehyde with acetaldehyde. MS (apci) m/z = 593.4 (M+H).

Example 444

[0953]



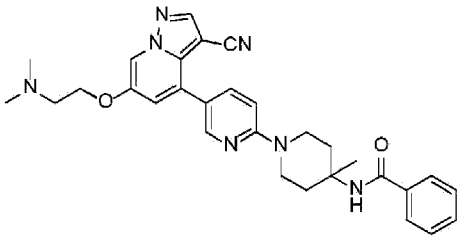


N-(1-(5-(6-(2-(4-acetylpiperazin-1-yl)ethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0954] To a solution of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (**Intermediate P88**, 46.4 mg, 0.0822 mmol) in DCM (1 mL) was added TEA (0.0557 mL, 0.411 mmol) then acetyl chloride (0.164 mL, 0.164 mmol). The reaction mixture was stirred at rt for 16 h then concentrated *in vacuo.* The residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (1-30% [MeOH + 2% NH_4OH] in DCM as the gradient eluent) to afford the title compound (24.7 mg, 0.0407 mmol, 49.5% yield). MS (apci) m/z = 607.4 (M+H).

Example 445

[0955]



N-(1-(5-(3-cyano-6-(2-(dimethylamino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide

[0956] Step 1: Preparation of tert-butyl (2-((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (**Intermediate P87**, 64.2 mg, 0.142 mmol) in DMA (1.5 mL) was added 2-(Boc-amino)ethyl bromide (63.6 mg, 0.284 mmol) and cesium carbonate (231 mg, 0.709 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and washed successively with water and saturated $NaCl_{(aq)}$, dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed theoretical yield, 84.6 mg, 0.142 mmol) in sufficient purity for step 2. MS (apci) m/z = 596.3 (M+H).

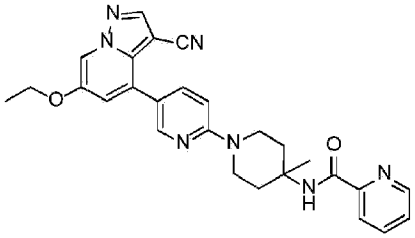
[0957] Step 2: Preparation of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1.5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide. A solution of tert-butyl (2-((4-(6-(4-benzamido-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate (84.6 mg, 0.142 mmol) in DCM (0.75 mL) was treated with TFA (0.75 mL, 9.8 mmol). The reaction mixture was stirred at rt for 30 min

then concentrated *in vacuo.* The residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (17.9 mg, 0.0361 mmol, 25.5% yield over two steps). MS (apci) m/z = 496.2 (M+H).

[0958] Step 3: Preparation of N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide. To a solution of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide (18 mg, 0.036 mmol) in 1:1 DCM:MeOH (0.5 mL) was added formaldehyde (27 µL, 0.36 mmol) was added, followed by $NaBH(AcO)_3$ (77 mg, 0.36 mmol) The resulting reaction mixture was allowed to stir 16 h at ambient temperature. The reaction was concentrated *in vacuo.* The residue was purified directly by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $NaHCO_{3(aq)}$ and extracted with 4:1 DCM:IPA. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (9 mg, 49% yield). MS (apci) m/z = 524.3 (M+H).

Example 447

[0959]

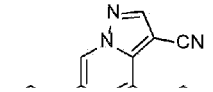


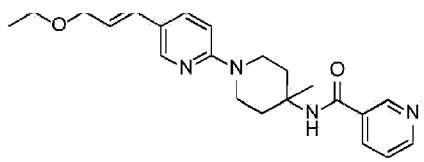
N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0960] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P89**, 25.6 mg, 0.0680 mmol) in DCM (0.136 mL) was added 2-picolinic acid (10.9 mg, 0.0884 mmol), HATU (31.0 mg, 0.0816 mmol), and DIEA (0.0474 mL, 0.272 mmol). The reaction mixture was stirred at rt for 72 h. After cooling to ambient temperature, the reaction mixture was washed with water and concentrated *in vacuo.* The residue was purified by silica chromatography (50-100% EtOAc in hexanes then 0-10% MeOH in EtOAc as the gradient eluent) to afford the title compound (23 mg, 0.0473 mmol, 70% yield). MS (apci) m/z = 482.2 (M+H).

Example 448

[0961]



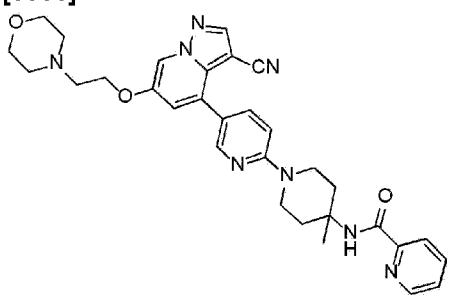


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)nicotinamide

[0962] The title compound was prepared using a similar method to that described for the synthesis of **Example 447**, replacing 2-picolinic acid with nicotinic acid. MS (apci) m/z = 482.2 (M+H).

Example 453

[0963]

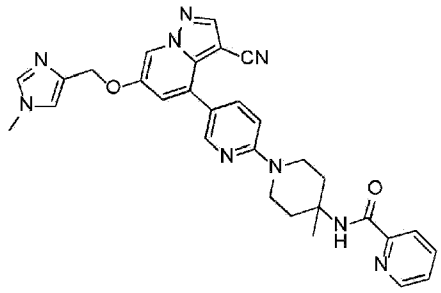
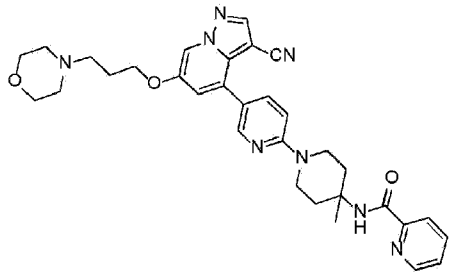
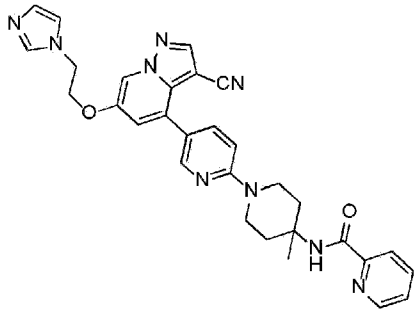
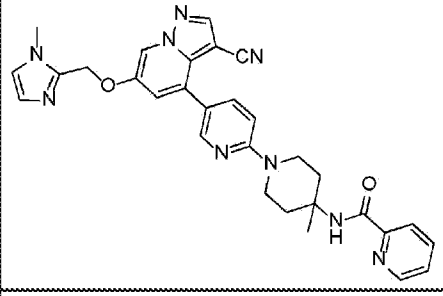
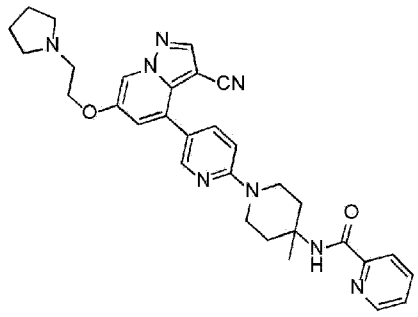


N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0964] To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P90**, 40 mg, 0.0882 mmol) in DMA (0.882 mL) was added 4-(2-chloroethyl)morpholine hydrochloride (32.8 mg, 0.176 mmol) and cesium carbonate (144 mg, 0.441 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with 4:1 DCM/IPA and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, concentrated *in vacuo,* and purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (15.0 mg, 0.0265 mmol, 30.0% yield). MS (apci) m/z = 567.3 (M+H).

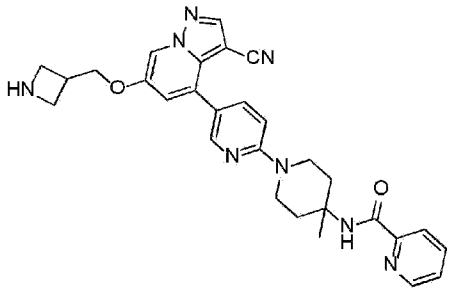
[0965] The compounds in Table EEE were prepared using a similar method to that described for the synthesis of **Example 453**, replacing 4-(2-chloroethyl)morpholine hydrochloride with the appropriate alkyl halide. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Table EEE

Ex. #	Structure	Chemical Name	MS m/z
454		N-(1-(5-(3-cyano-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide	548.30 (M+H)
455		N-(1-(5-(3-cyano-6-(3-morpholinopropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide	581.30 (M+H)
456		N-(1-(5-(6-(2-(1H-imidazol-1-yl)ethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide	548.30 (M+H)
457		N-(1-(5-(3-cyano-6-((1-methyl-1H-imidazol-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide	548.30 (M+H)
458		N-(1-(5-(3-cyano-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide	551.30 (M+H)

Example 459

[0966]



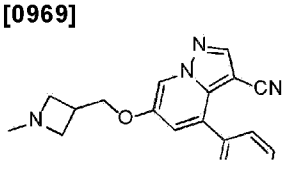
N-(1-(5 -(6-(azetidin-3-ylmethoxy)-3-cyanopyrazolo[1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

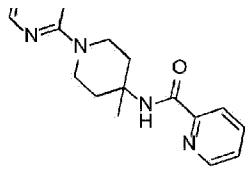
[0967] Step 1: Preparation of tert-butyl 3-(((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)azetidine-1-carboxylate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P90,** 40 mg, 0.088 mmol) in DMA (0.882 mL) was added 3-bromomethyl-azetidine-1-carboxylic acid tert-butyl ester (22 mg, 0.088 mmol) and cesium carbonate (144 mg, 0.44 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature the reaction mixture was diluted with 4:1 DCM/IPA and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, concentrated *in vacuo,* and purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (15.0 mg, 0.0265 mmol, 30.0% yield) in sufficient purity for step 2. MS (apci) m/z = 623.3 (M+H).

[0968] Step 2: Preparation of N-(1-(5-(6-(azetidin-3-ylmethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. A solution of tert-butyl 3-(((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)azetidine-1-carboxylate (55 mg, 0.088 mmol) in 1:1 (v/v) mixture of DCM:TFA (883 µL) was stirred at rt for 16 h. The reaction mixture was diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and brine. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (46 mg, 0.088 mmol, 100% yield). MS (apci) m/z = 523.3 (M+H).

Example 460

[0969]



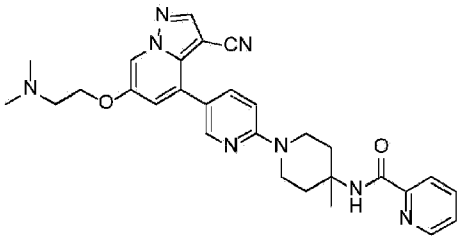


N-(1-(5-(3-cyano-6-((1 -methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0970] To a solution of N-(1-(5-(6-(azetidin-3-ylmethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Example 459,** 46 mg, 0.088 mmol) in DCM (1.760 mL) was added formaldehyde (0.066 mL, 0.88 mmol) and sodium triacetoxyborohydride (93 mg, 0.44 mmol). The reaction mixture was stirred at rt for 1 h then concentrated *in vacuo.* The resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (9.4 mg, 0.017 mmol, 20% yield) in sufficient purity for step 2. MS (apci) m/z = 537.3 (M+H).

Example 461

[0971]



N-(1-(5-(3-cyano-6-(2-(dimethylamino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0972] Step 1: Preparation of tert-butyl (2-((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P90,** 40 mg, 0.088 mmol) in DMA (0.882 mL) was added 2-(Boc-amino)ethyl bromide (20 mg, 0.088 mmol) and cesium carbonate (144 mg, 0.44 mmol). The reaction mixture was stirred at 70°C for 3 h. After cooling to ambient temperature, the reaction mixture was diluted with 4:1 DCM/IPA and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, concentrated *in vacuo,* and purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (assumed

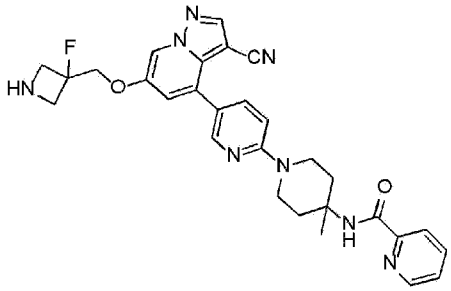
theoretical yield, 53 mg, 0.088 mmol) in sufficient purity for step 2. MS (apci) m/z = 597.3 (M+H).

[0973] Step 2: Preparation of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. A solution of tert-butyl (2-((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)carbamate (53 mg, 0.089 mmol) in 1:1 (v/v) mixture of DCM:TFA (0.89 mL) was stirred at rt for 16 h. The reaction mixture was diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and brine. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (34 mg, 0.068 mmol, 77% yield over two steps) in sufficient purity for step 3. MS (apci) m/z = 497.2 (M+H).

[0974] Step 3: Preparation of N-(1-(5-(3-cyano-6-(2-(dimethylamino)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. To a solution of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (34 mg, 0.0685 mmol) in DCM (1.369 mL) was added formaldehyde (0.051 mL, 0.685 mmol) and sodium triacetoxyborohydride (72.6 mg, 0.342 mmol). The reaction mixture was stirred at rt for 1 h then concentrated *in vacuo.* The resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The resultant film was triturated with DCM/hexanes and concentrated *in vacuo* to afford the title compound (10.5 mg, 0.0198 mmol, 29% yield). MS (apci) m/z = 525.3 (M+H).

Example 462

[0975]



N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

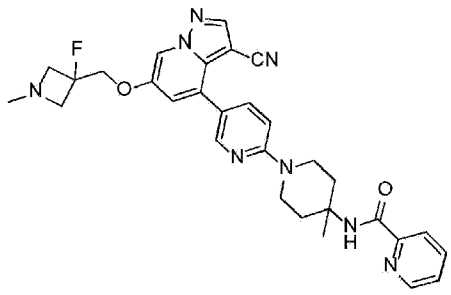
[0976] Step 1: Preparation of tert-butyl 3-(((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. To a solution of N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Intermediate P90,** 40 mg, 0.088 mmol) in DMA (0.882 mL) was added 1-boc-3-bromomethyl-azetidine (24 mg, 0.088 mmol) and cesium carbonate (144 mg, 0.44 mmol). The reaction mixture was stirred at 60°C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with 4:1 DCM/IPA and washed successively with water and saturated $NaCl_{(aq)}$. The organic extract was dried over

anhydrous $Na_2SO_{4(s)}$, filtered, concentrated *in vacuo,* and purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (54 mg, 0.084 mmol, 96% yield) in sufficient purity for step 2. MS (apci) m/z = 641.3 (M+H).

[0977] Step 2: Preparation of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide. A solution of tert-butyl 3-(((3-cyano-4-(6-(4-methyl-4-(picolinamido)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (54 mg, 0.084 mmol) in 1:1 (v/v) mixture of DCM:TFA (0.84 mL) was stirred at rt for 1 h. The reaction mixture was diluted with 4:1 DCM/IPA and washed successively with saturated $NaHCO_{3(aq)}$ and brine. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (5.0 mg, 11% yield). MS (apci) m/z = 541.2 (M+H).

Example 463

[0978]

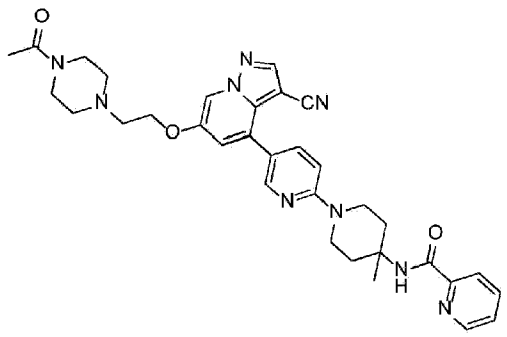


N-(1-(5 -(3 -cyano-6-((3 -fluoro-1-methylazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0979] To a solution of N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Example 462**, 35 mg, 0.065 mmol) in DCM (1.295 mL) was added formaldehyde (0.048 mL, 0.65 mmol) and sodium triacetoxyborohydride (69 mg, 0.32 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo,* and the resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (19 mg, 0.034 mmol, 53% yield). MS (apci) m/z = 555.3 (M+H).

Example 464

[0980]

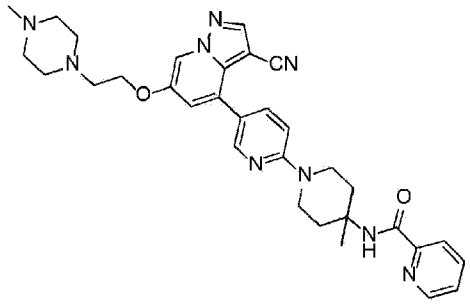


N-(1-(5-(6-(2-(4-acetylpiperazin-1-yl)ethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0981] To a solution of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P91,** 35 mg, 0.0619 mmol) in DCM (0.619 mL) was added TEA (0.00862 mL, 0.0619 mmol) and acetyl chloride (0.124 mL, 0.124 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 4:1 DCM/IPA and washed successively with water and brine. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (27.7 mg, 0.0456 mmol, 73.7% yield). MS (apci) m/z = 608.3 (M+H).

Example 465

[0982]

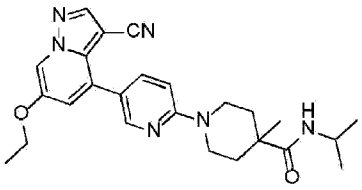


N-(1-(5-(3-cyano-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0983] To a solution of N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P91,** 40 mg, 0.0707 mmol) in DCM (1.414 mL) was added formaldehyde (0.0526 mL, 0.707 mmol) and sodium triacetoxyborohydride (74.9 mg, 0.354 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo,* and the resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 0.1% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ and saturated $NaCl_{(aq)}$. The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (0-10% MeOH in DCM as the gradient eluent) to afford the title compound (15.4 mg, 37.6% yield). MS (apci) m/z = 580.3 (M+H).

Example 466 reference

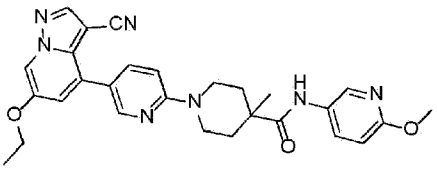
[0984]



1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-N-isopropyl-4-methylpiperidine-4-carboxamide

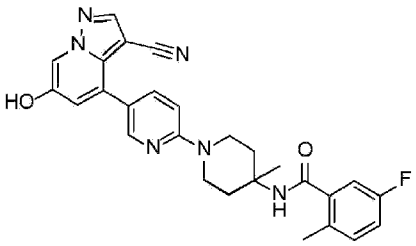
[0985] To a solution of 1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidine-4-carboxylic acid **(Intermediate P92,** 38.2 mg, 0.0942 mmol) in DCM (0.942 mL) was added HATU (43.0 mg, 0.113 mmol), DIEA (0.033 mL, 0.188 mmol), and propan-2-amine (0.009 mL, 0.104 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo,* and the resultant crude residue was directly purified by C-18 reverse phase chromatography (5-95% ACN in water [+ 2% TFA] as the gradient eluent). The fractions containing the desired product were diluted with 4:1 DCM/IPA and washed with saturated $NaHCO_{3(aq)}$ The organic extract was dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (32.4 mg, 0.0726 mmol, 77% yield). MS (apci) m/z = 447.2 (M+H).

[0986] The compounds in Table FFF were prepared using a similar method to that described for the synthesis of **Example 466**, replacing propan-2-amine with the appropriate amine coupling partner. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. Title compounds were cleanly isolated following chromatographic purification using an appropriate gradient eluent (and if necessary converted to the free base).

Ex. #	Structure	Chemical Name	MS m/z
469# Ref		1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-N-(6-methoxypyridin-3-yl)-4-methylpiperidine-4-carboxamide	512.20 (M+H)

Example 485

[0987]

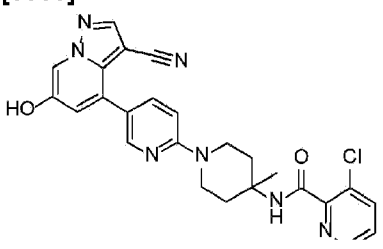


N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[0988] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P67;** 503 mg, 1.19 mmol), 5-fluoro-2-methylbenzoic acid (552 mg, 3.58 mmol), and HATU (1.36g, 3.58 mmol) in DMSO (5 mL) was added DIEA (1.7 mL, 9.55 mmol). The reaction was stirred 16 h at ambient temperature. The reaction mixture was diluted with THF (4 mL) and treated with NaOH (5.97 mL, 11.9 mmol) and stirred for 4 h at ambient temperature. The reaction was concentrated *in vacuo.* The residue was diluted with EtOAc and washed with water. The pH was adjusted to pH 5 with AcOH and then extracted with EtOAc. The organic extracts were washed with brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified using silica chromatography (50-100% Hexanes to EtOAc) to afford the title compound (534 mg, 92% yield) in sufficient purity for step 2. MS (apci) m/z= 485.2 (M+H).

Example 487

[0989]

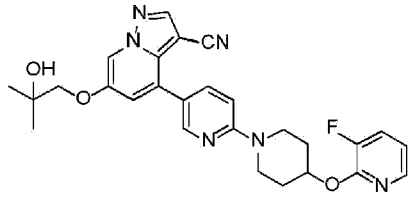


3 -chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[0990] To a solution of 4-(6-(4-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P67;** 256 mg, 0.608 mmol), 3-Chloropicolinic acid (287 mg, 1.82 mmol), and HATU (294 mg, 1.82 mmol) in DMSO (3 mL) was added DIEA (0.74 mL, 4.25 mmol). The reaction was stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL) and 4:1 AcOH: water (10 mL) and then extracted with EtOAc. The organic extracts were washed with 4:1 AcOH:Water and then brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was diluted with THF (4 mL) and 2M NaOH (6 mL). The solution was concentrated *in vacuo.* The residue was resuspended in DCM (2mL) and purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was resuspended in DCM and passed through a PI-HCO_3 resin to elute the free-based product. The organic eluents were concentrated *in vacuo* and recrystallized using DCM/Hexanes to afford the title compound (226 mg, 76% yield). MS (apci) m/z = 488.2 (M+H).

Example 488

[0991]



4-(6-(4-((3-fluoropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[0992] Step 1: Preparation of tert-butyl 4-((3-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate. To a solution of tert-Butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (175 mg, 0.869 mmol) in DMF (2.2 mL) was added sodium hydride (60% w/w, 41.7 mg, 1.04 mmol). The reaction was stirred for 10 min at ambient temperature. 2,3-Difluoropyridine (100 mg, 0.869 mmol) was added and reaction stirred overnight at 60°C. The reaction was cooled to ambient temperature and diluted with DCM and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (assumed quantative yield, 258 mg) in sufficient purity for step 2. MS (apci) m/z = 197.2 (M-Boc).

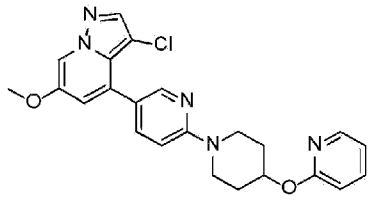
[0993] Step 2: Preparation of 3-fluoro-2-(piperidin-4-yloxy)pyridine hydrochloride. To a solution of tert-butyl 4-((3-fluoropyridin-2-yl)oxy)piperidine-1-carboxylate (assumed 258mg, 0.869 mmol) in 4.3 mL DCM was treated with TFA (4.3 mL, 55.8 mmol). The reaction mixture was stirred for 1 h at ambient

temperature, and then concentrated *in vacuo.* The crude residue was resuspended in MeOH and treated with treated with 4 N HCl in dioxanes (4 mL). The solution was stirred at ambient temperature for 15 min. The reaction was concentrated *in vacuo* to provide the title compound as a dihydrochloride salt, which was used in the next step without further purifications.. MS (apci) m/z = 197.1 (M+H).

[0994] Step 3: Preparation of 4-(6-(4-((3-fluoropyridin-2-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a mixture of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P42;** 40 mg, 0.123 mmol) and 3-fluoro-2-(piperidin-4-yloxy)pyridine dihydrochloride (66 mg, 0.245 mmol) in DMA (0.817 mL) was added TEA (103 µL, 0.735mmol). The reaction mixture was stirred overnight at 95°C. After cooling to ambient temperature, the reaction mixture was diluted with DCM and washed with water and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was treated with saturated $Na_2CO_{3(aq)}$ and extracted with DCM. The combined organic extracts were washed with brine, then dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo* to afford the title compound (17 mg, 28% yield). MS (apci) m/z = 503.2 (M+H).

Example 498

[0995]

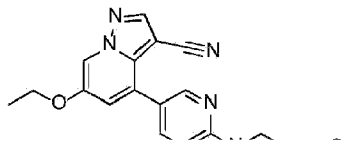


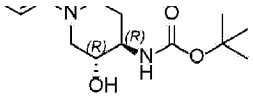
3-chloro-6-methoxy-4-(6-(4-(pyridin-2-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine

[0996] In a pressure vessel, a mixture of 3-chloro-4-(6-fluoropyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine (**Example 417, Step 2;** 30 mg, 0.11 mmol), 2-(piperidin-4-yloxy)pyridine (29 mg, 0.16 mmol) and $Cs_2CO_{3(s)}$ (176 mg, 0.54 mmol) in DMSO (200 µL) was stirred overnight at 90 °C. After cooling to ambient temperature, the reaction mixture was poured into 2N $NaOH_{(aq)}$ (2 mL), and extracted with 10% iPrOH in DCM (2 × 3 mL) in a PS Frit. The combined organic extracts were concentrated *in vacuo.* The resulting crude residue was purified by silica chromatography (using 0-100% EtOAc / Hexanes as the gradient eluent) to cleanly afford the title compound (22 mg, 47% yield). MS (apci) m/z = 436.1 (M+H).

Example 512 reference

[0997]



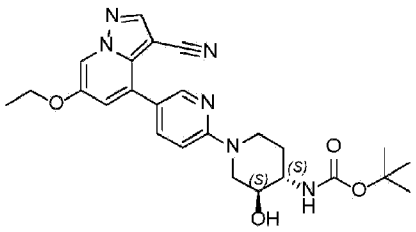
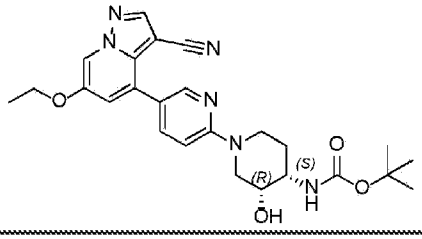
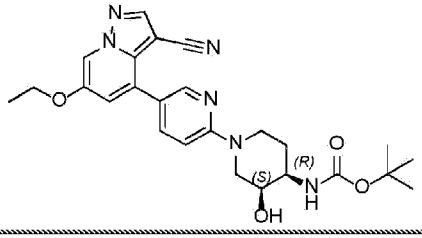


tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate

[0998] A solution of 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 177.8 mg, 0.6299 mmol) and tert-butyl ((3R,4R)-3-hydroxypiperidin-4-yl)carbamate (199 mg, 0.9201 mmol) in DMSO (1.5 mL) was treated with DIEA (55.01 µL, 3.149 mmol), and stirred for 2 d at 90 °C. After cooling to ambient temperature, the mixture was diluted with water, and the resultant suspension was filtered. The solids were rinsed with water (3x), then dried *in vacuo* to afford the title compound (255.2 mg, 81% yield). MS (apci) m/z = 479.2 (M+H).

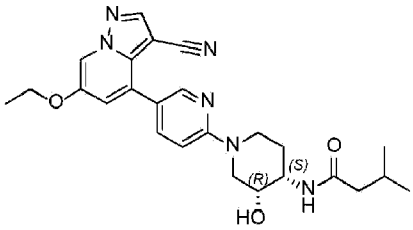
[0999] The compounds in Table **III** were prepared using a similar method to that described for the preparation, isolation and purification of tert-butyl ((3R,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate **(Example 512),** replacing the tert-butyl ((3R,4R)-3-hydroxypiperidin-4-yl)carbamate with the appropriate commercial piperidine. Reactions were conducted at 90-95 °C, and monitored for completion by LCMS. And reaction durations were adjusted accordingly.

Table III

Ex #	Structure	Chemical Name	MS (apci) m/z
513 ref		tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate	479.2 (M+H)
514 ref		tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate	479.2 (M+H)
515 ref		tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate	479.2 (M+H)

Example 520 reference

[1000]



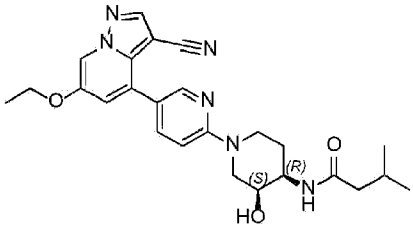
N-((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide

[1001] Step 1: Preparation of 4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride. A solution tert-butyl ((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate **(Example 514;** 293.5 mg, 0.6133 mmol) in dioxane (2.0 mL) was treated with 12 M $HCl_{(aq)}$ (100.7 µL, 1.227 mmol). The resulting mixture was stirred overnight at ambient temperature, then concentrated *in vacuo* to cleanly afford the title compound (276 mg, 100% yield). MS (apci) m/z = 379.2 (M+H).

[1002] Step 2: Preparation of N-((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide. A solution of 4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (112 mg, 0.2481 mmol) in DCM (2 mL) was treated with DIEA (433.4 µL, 2.481 mmol), and then stirred for 5 min at 0 °C. The cold solution was treated dropwise with isovaleryl chloride (60.51 µL, 0.4963 mmol). The cooling bath was removed, and the resulting mixture was stirred for 1h at ambient temperature. The reaction mixture was directly purified by silica chromatography (using 20-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (115.7 mg, quantitative yield). MS (apci) m/z = 463.2 (M+H).

Example 521 reference

[1003]



N-((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide

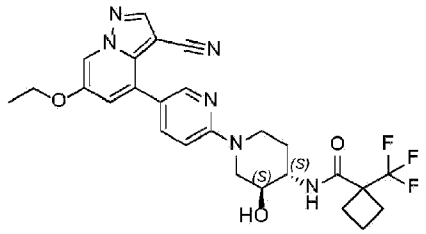
[1004] Step 1: Preparation of 4-(6-((3S,4R)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-

ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride. A solution of tert-butyl ((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate **(Example** 515; 341.5 mg, 0.7136 mmol) in dioxane (2.0 mL) was treated with 12 M $HCl_{(aq)}$ (117.2 µL, 1.427 mmol). The resulting mixture was stirred overnight at ambient temperature, then concentrated *in vacuo* to cleanly afford the title compound (322 mg, 100% yield). MS (apci) m/z = 379.2 (M+H).

[1005] Step 2: Preparation of N-((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide. A solution of 4-(6-((3S,4R)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (160.4 mg, 0.3554 mmol) in DCM (2 mL) was treated with DIEA (620.7 µL, 3.554 mmol), and then stirred for 5 min at 0 °C. The cold solution was treated dropwise with isovaleryl chloride (86.65 µL, 0.7108 mmol). The cooling bath was removed, and the resulting mixture was stirred for 1h at ambient temperature. The reaction mixture was directly purified by silica chromatography (using 30-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (63.4 mg, 39% yield). MS (apci) m/z = 463.2 (M+H).

Example 522 reference

[1006]



N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-1-(trifluoromethyl)cyclobutane-1-carboxamide

[1007] Step 1: Preparation of 4-(6-((3S,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride. A solution of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)carbamate (**Example 513;** 845.1 mg, 1.766 mmol) in dioxane (3.0 mL) was treated with 12 M $HCl_{(aq)}$ (290.0 µL, 3.532 mmol). The resulting mixture was stirred overnight at ambient temperature then concentrated *in vacuo* to cleanly afford the title compound (797 mg, 100% yield). MS (apci) m/z = 379.3 (M+H).

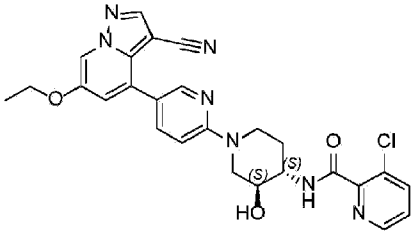
[1008] Step 2: Preparation of N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-1-(trifluoromethyl)cyclobutane-1-carboxamide. A solution of 4-(6-((3S,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (61.6 mg, 0.136 mmol) and 1-(trifluoromethyl)cyclobutane-1-carboxylic acid (45.9 mg, 0.273 mmol) in DCM (1 mL) was treated sequentially with DIEA (119 µL, 0.682 mmol) and HATU (104 mg, 0.273 mmol), then stirred for 1 h at ambient temperature. The resulting mixture was purified directly by silica chromatography (using 20-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (45.5 mg, 63% yield). MS (apci) m/z = 529.25 (M+H).

[1009] The compounds in Table **JJJ** were prepared using a similar method to that described in Step 2 in

the synthesis of N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-1-(trifluoromethyl)cyclobutane-1-carboxamide (**Example 522**), replacing 1-(trifluoromethyl)cyclobutane-1-carboxylic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. The title compounds were isolated following a chromatographic purification utilizing an appropriate gradient eluent.

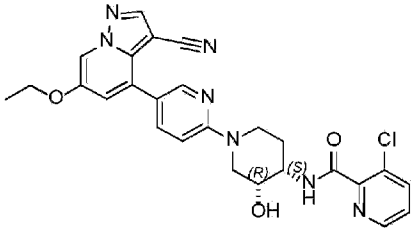
Where noted (*) an aqueous work up, consisting of dilution of the reaction mixture with DCM and water wash preceded the chromatographic purification.

Table JJJ

Ex #	Structure	Chemical Name	MS (apci) m/z
523*		3-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3 -hydroxypiperidin-4-yl)picolinamide	518.15 (M+H)

Example 528

[1010]

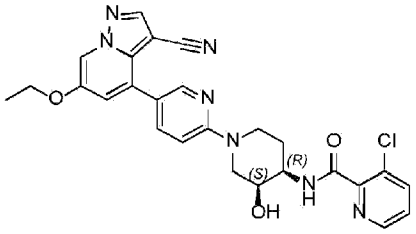


3-chloro-N-((3R,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)picolinamide

[1011] A solution of 4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (**Example 520,** Step 1; 164 mg, 0.3634 mmol) in DCM (2 mL) was treated sequentially with DIEA (634.6 µL, 3.634 mmol), 3-chloropicolinic acid (229.0 mg, 1.453 mmol) and HATU (276.3 mg, 0.7267 mmol). The resulting mixture was stirred for 3 h at ambient temperature, and washed with water. The organic extracts were purified directly by silica chromatography (using 30-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (241.1 mg, quantitative yield). MS (apci) m/z = 518.1 (M+H).

Example 529

[1012]

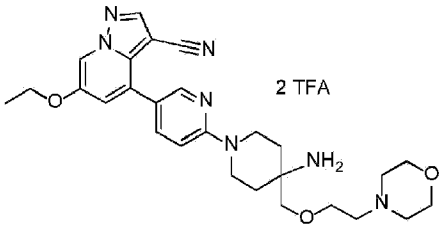


3-chloro-N-((3S,4R)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)picolinamide

[1013] A solution of 4-(6-((3S,4R)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (**Example 521,** Step 1; 161.6 mg, 0.3580 mmol) in DCM (2 mL) was treated sequentially with DIEA (625.3 µL, 3.580 mmol), 3-chloropicolinic acid (225.6 mg, 1.432 mmol) and HATU (272.3 mg, 0.7161 mmol). The resulting mixture was stirred for 3 h at ambient temperature, and washed with water. The organic extracts were purified directly by silica chromatography (using 30-100% EtOAc in Hexanes as the gradient eluent) to cleanly provide the title compound (241.1 mg, quantitative yield). MS (apci) m/z = 518.1 (M+H).

Example 561 reference

[1014]

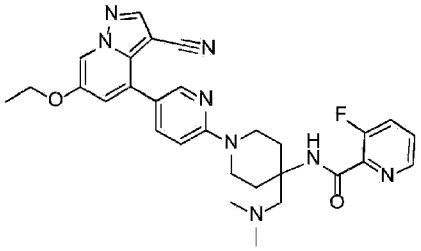


4-(6-(4-amino-4-((2-morpholinoethoxy)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate)

[1015] A suspension of 4-(6-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P56**, 40 mg, 0.10 mmol) in DMF (2 mL) was treated sequentially with NaH (60 wt.% in mineral oil; 41 mg, 1.0 mmol) and 4-(2-chloroethyl)morpholine (76 mg, 0.51 mmol). After stirring for 4 h at 50 °C, the reaction mixture was cooled to ambient temperature, and quenched with water (2 mL). The quenched mixture was concentrated to dryness *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA) to afford the title compound (40 mg, 55% yield). MS (apci) m/z = 506.3 (M+H).

Example 570

[1016]

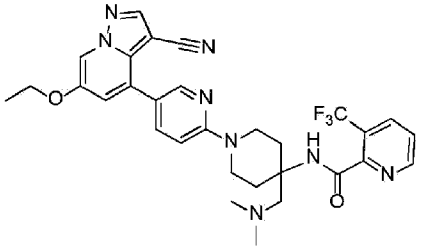


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)-3-fluoropicolinamide

[1017] A solution of 4-(6-(4-amino-4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P72,** 50 mg, 0.119 mmol) in DMSO (795 µL) was treated sequentially with 3-fluoropicolinic acid (0.0252 g, 0.179 mmol), DIEA (93.4 µL, 0.536 mmol) and HATU (90.6 mg, 0.238 mmol). The resulting mixture was stirred overnight at ambient temperature, and then partitioned between EtOAc and water. The organic extracts were washed with brine, dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The crude residue was purified by C18 reverse phase chromatography (using 5-95% water: ACN with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was dissolved in DCM, and extracted sequentially with saturated $NaHCO_{3(aq)}$ and brine. The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (40.1 mg, 62% yield). MS (apci) m/z = 543.3 (M+H).

Example 571

[1018]

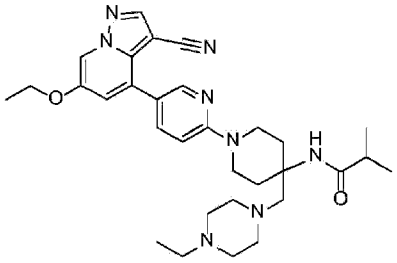


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)-3-(trifluoromethyl)picolinamide

[1019] The title compound (24 mg, 34% yield) was prepared, worked up and purified using a similar procedure to that described for N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((dimethylamino)methyl)piperidin-4-yl)-3-fluoropicolinamide (**Example** 570), replacing 3-fluoropicolinic acid with 3-(trifluoromethyl)picolinic acid. MS (apci) m/z = 593.3 (M+H).

Example 595 reference

[1020]

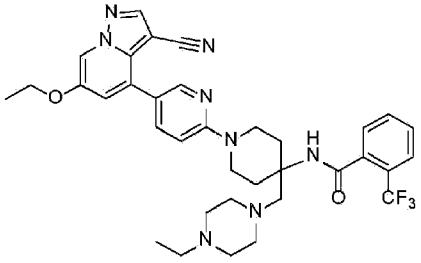


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)isobutyramide

[1021] A solution of 4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile dihydrochloride **(Intermediate P98;** 9.5 mg, 0.0169 mmol), isobutyric acid (1.86 mg, 0.0211 mmol) and DIEA (14.8 µL, 0.0846 mmol) in DMF (169 µL) was treated with HATU (8.04 mg, 0.0211 mmol). The resulting mixture was stirred for 5 min at ambient temperature, and then purified by silica chromatography (using 0-10% [MeOH with 1% NH_4OH] in EtOAc as the gradient eluent). The purified residue was triturated with MTBE then concentrated *in vacuo* to cleanly afford the title compound (9 mg, 95% yield). MS (apci) m/z = 559.3 (M+H).

Example 596

[1022]

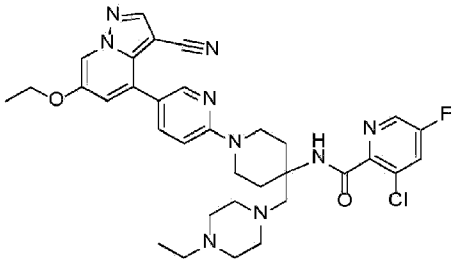


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-2-(trifluoromethyl)benzamide

[1023] The title compound can be prepared in a similar fashion as described for N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)isobutyramide (**Example 595**), replacing isobutyric acid with 2-(trifluoromethyl)benzoic acid.

Example 597

[1024]

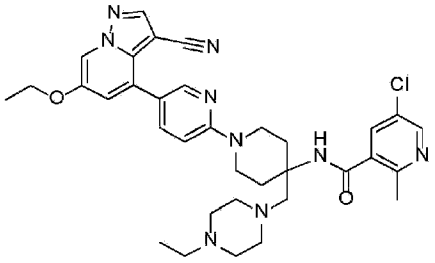


3-chloro-N-(1 -(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-5-fluoropicolinamide

[1025] A solution of 4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P74,** 23.5 mg, 0.0481 mmol) in DMSO (481 µL) was treated with DIEA (42.0 µL, 0.240 mmol), 3-chloro-5-fluoropicolinic acid (16.9 mg, 0.0962 mmol) and HATU (36.6 mg, 0.0962 mmol). The resulting mixture was stirred overnight at ambient temperature, and then purified directly by silica chromatography (using 0-10% [MeOH with 1% NH_4OH] in DCM as the gradient eluent) to cleanly afford the title compound (20.6 mg, 66% yield). MS (apci) m/z = 646.3 (M+H).

Example 598

[1026]

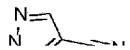


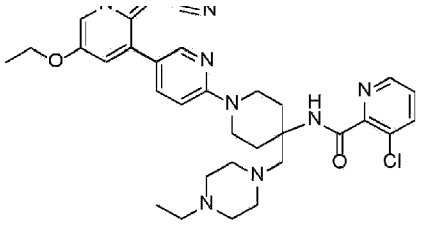
5-chloro-N-(1-(5-(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-2-methylnicotinamide

[1027] The title compound (17.2 mg, 56% yield) was prepared, worked up and purified using a similar procedure to that described for 3-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)-5-fluoropicolinamide **(Example 597**), replacing 3-chloro-5-fluoropicolinic acid (2 equivalents) with 5-chloro-2-methyl-3-pyridinecarboxylic acid (1 equivalent). MS (apci) m/z = 642.4 (M+H).

Example 599

[1028]



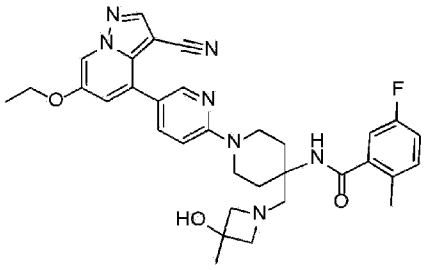


3-chloro-N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((4-ethylpiperazin-1-yl)methyl)piperidin-4-yl)picolinamide

[1029] A solution of 4-(6-(4-amino-4-((4-ethylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3 -yl)-6-ethoxypyrazolo[1,5-a]pyridine-3 -carbonitrile dihydrochloride **(Intermediate P98;** 31.9 mg, 0.0568 mmol) in DMF (169 µL) was treated with DIEA (9.2 µL, 0.0568 mmol), 3-chloropicolinic acid (26.9 mg, 0.170 mmol) and HATU (43.2 mg, 0.114 mmol). The resulting mixture was stirred for 30 min at ambient temperature, and then purified directly by silica chromatography (using 10-25% [MeOH with 1% NH_4OH] in DCM as the gradient eluent) to cleanly afford the title compound (23.4 mg, 66% yield). MS (apci) m/z = 628.3 (M+H).

Example 615 reference

[1030]

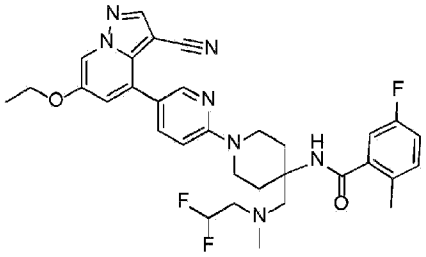


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-((3 - hydroxy-3-methylazetidin-1-yl)methyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[1031] A solution of N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-formylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Intermediate P70,** 44.3 mg, 0.0841 mmol), 3-hydroxy-3-methylazetidine hydrochloride (31.2 mg, 0.252 mmol) and DIEA (44.1 µL, 0.252 mmol) in DCM (421 µL) was stirred for 30 min at ambient temperature. The resulting mixture was treated with $NaBH(AcO)_3$ (26.7 mg, 0.126 mmol), and stirred overnight at room temperature. The resulting mixture was directly purified by silica chromatography (using 0-10% [9:1 DCM:MeOH with 1% NH_4OH] in DCM as the gradient eluent) to afford the title compound (42.2 mg, 84% yield). MS (apci) m/z = 598.3 (M+H).

Example 616

[1032]

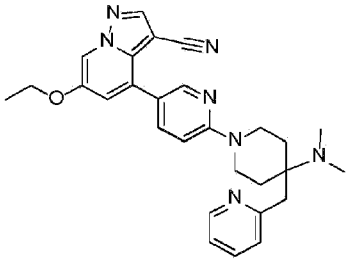


N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)-4-(((2,2-difluoroethyl) (methyl)amino)methyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide

[1033] The title compound (17.5 mg, 35% yield) was prepared, worked up and purified using a similar procedure to that described for N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-((3-hydroxy-3-methylazetidin-1-yl)methyl)piperidin-4-yl)-5-fluoro-2-methylbenzamide **(Example 615)**, replacing 3-hydroxy-3-methylazetidine hydrochloride with 2,2-difluoro-N-methylethanamine hydrochloride. MS (apci) m/z = 606.3 (M+H).

Example 625

[1034]

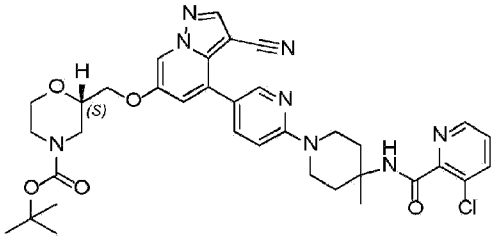


4-(6-(4-(dimethylamino)-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[1035] A solution of N,N-dimethyl-4-(pyridin-2-ylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate) **(Intermediate R29;** 71 mg, 0.16 mmol), 6-ethoxy-4-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P6,** 30 mg, 0.11 mmol) and $K_2CO_{3(s)}$ (73 mg, 0.53 mmol) in DMSO (1063 µL) was stirred for 1 h at 100 °C. After cooling to ambient temperature, the mixture was filtered, and the filtrate was purified directly by C18 reverse phase chromatography (using 5-95% ACN/ water with 0.1% TFA as the gradient eluent) to afford the title compound as the TFA salt. The TFA salt was suspended in MeOH (5 mL), eluted through a basic resin (Stratospheres PI-HCO3) to cleanly afford the title compound (15 mg, 29% yield). MS (apci) m/z = 482.3 (M+H).

Example 674

[1036]

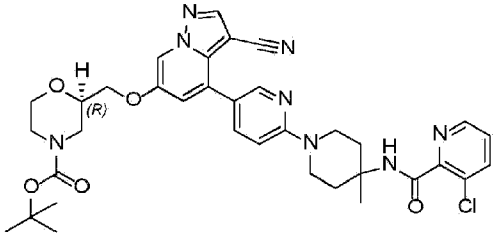


tert-butyl (S)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[1037] A solution of 3-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide (**Intermediate P75**, 100 mg, 0.205 mmol) and $Cs_2CO_{3(s)}$ (134 mg, 0.410 mmol) in DMF (1366 µL) was treated with tert-butyl (S)-2-(bromomethyl)morpholine-4-carboxylate (57.4 mg 0.205 mmol) was stirred overnight at 60 °C. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL), and extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed sequentially with water (3 × 10 mL) and brine (10 mL). The organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated *in vacuo.* The residue was purified twice by silica chromatography (first using 0-100% [10% MeOH with 1% NH_4OH in DCM]/DCM, and again using a stepped gradient of 0-100% EtOAc/Hexanes followed by 0-10% EtOAc/MeOH as the gradient eluent) to afford the title compound (130 mg, 84% yield). MS (apci) m/z = 687.2(M+H).

Example 675

[1038]

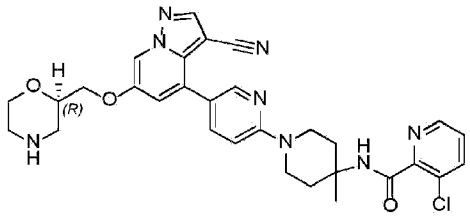


tert-butyl (R)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate

[1039] The title compound (110 mg, 78% yield) was prepared, worked up and purified using a similar procedure to that described for tert-butyl (S)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Example 674)**, replacing tert-butyl (S)-2-(bromomethyl)morpholine-4-carboxylate with tert-butyl (R)-2-(bromomethyl)morpholine-4-carboxylate. MS (apci) m/z = 687.2(M+H).

Example 676

[1040]

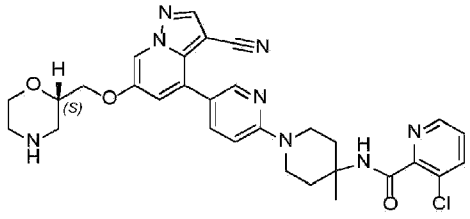


(R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1041] A solution of tert-butyl (R)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Example 675;** 110 mg, 0.160 mmol) in DCM (10.2 µL) and TFA (12.2 µL, 0.160 mmol) was stirred for 1 h at ambient temperature. The reaction mixture was concentrated *in vacuo,* and the residue was dissolved in MeOH (3 mL). A portion of the methanolic solution (2 mL) was concentrated *in vacuo* to afford the TFA salt of the title compound, (R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide bis(2,2,2-trifluoroacetate) (63 mg, 48% yield; MS (apci) m/z = 587.2 (M+H)). The remaining portion of the methanolic solution (1 mL) was purified by C18 reverse phase chromatography (using 5-95% ACN in water with 0.2% TFA as the gradient eluent). Fractions containing the desired compound were combined, then sequentially, concentrated *in vacuo,* dissolved in MeOH (5 mL), and eluted through a basic resin (Stratospheres MP-HCO3) to cleanly afford the title compound (9.3 mg, 10% yield). MS (apci) m/z = 587.2 (M+H).

Example 677

[1042]



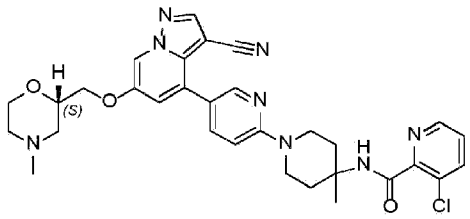
(S)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1043] The title compound (8.2 mg, 7% yield), along with the TFA salt of the title compound (S)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide bis(2,2,2-trifluoroacetate) (78 mg, 51% yield) were prepared, separated and purified using a similar procedure to that described for (R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-

ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Example 676),** replacing tert-butyl (R)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Example 675;** with tert-butyl (S)-2-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Example 674).** MS (apci) m/z = 587.2 (M+H).

Example 678

[1044]

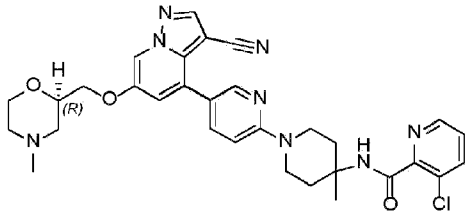


(S)-3-chloro-N-(1-(5-(3-cyano-6-((4-methylmorpholin-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1045] A solution of (S)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide bis(2,2,2-trifluoroacetate) **(Example 677,** TFA salt; 78 mg, 0.0957 mmol) in DCM (957 µL) was treated with formaldehyde (35 wt.% in water with 5-15% MeOH stabilizer; 38 µL, 0.478), and $NaBH(AcO)_3$ (203 mg, 0.957 mmol), and stirred for 1 h at room temperature. The reaction mixture was purified directly by C18 reverse phase chromatography (using 5-95% ACN in water with 0.2% TFA as the gradient eluent). Fractions containing the desired compound were combined, then sequentially, concentrated *in vacuo,* dissolved in MeOH (5 mL), and eluted through a basic resin (Stratospheres MP-HCO3) to cleanly afford the title compound (31 mg, 54% yield). MS (apci) m/z = 601.2 (M+H).

Example 679

[1046]

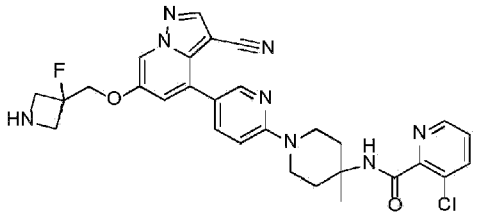


(R)-3-chloro-N-(1-(5-(3-cyano-6-((4-methylmorpholin-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1047] The title compound (21 mg, 45% yield) was prepared and purified using a similar procedure to that described for (S)-3-chloro-N-(1-(5-(3-cyano-6-((4-methylmorpholin-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Example 678),** replacing (S)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide bis(2,2,2-trifluoroacetate) (**Example 677**) with (R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide bis(2,2,2-trifluoroacetate) **(Example 676).** MS (apci) m/z = 601.2 (M+H).

Example 680

[1048]



3-chloro-N-(1-(5-(3-cyano-6-((3 -fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide

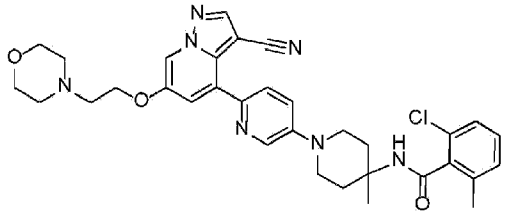
[1049] Step 1: Preparation of tert-butyl 3-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. A mixture of 3 -chloro-N-(1-(5 -(3 -cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide **(Intermediate P75,** 200 mg, 0.410 mmol), tert-butyl 3-(bromomethyl)-3-fluoroazetidine-1-carboxylate (220 mg, 0.820 mmol) and $Cs_2CO_{3(s)}$ (160 mg, 0.492 mmol) in DMA (4099 µL) was stirred overnight at 60 °C. Subsequently, additional $Cs_2CO_{3(s)}$ (160 mg, 0.492 mmol) was introduced, and the reaction mixture was stirred overnight again at 60 °C. After cooling to ambient temperature, the reaction mixture was partitioned between 4:1 DCM:IPA and water through a PS Frit rinsing with 4:1 DCM:IPA (3x). The combined organic extracts were concentrated *in vacuo,* and purified by silica chromatography (using a stepped gradient of 0-100% EtOAc/Hexanes as the gradient eluent) to afford the title compound contaminated with DMA (277 mg, quantitative yield assumed). MS (apci) m/z = 675.3 (M+H).

[1050] Step 2: Preparation of 3-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide.

[1051] A solution of tert-butyl 3-(((4-(6-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyridin-3-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (277 mg, 0.410 mmol) in DMA (~0.5 mL; a solution that carried through the column) was treated with TFA (1106 µL, 14.4 mmol) and stirred for 60 h at ambient temperature. The reaction mixture was diluted with DCM and brine, then neutralized to pH 7 with 2 N $NaOH_{(aq)}$. The resulting biphasic mixture was passed through a PS Frit, and the organics were concentrated *in vacuo.* The crude residue was purified by silica chromatography (using 0-15% MeOH in EtOAc with 0.2% NH_4OH as the gradient eluent) to cleanly afford the title compound (79 mg, 34% yield, over 2 steps). MS (apci) m/z = 575.2 (M+H).

Example 681

[1052]

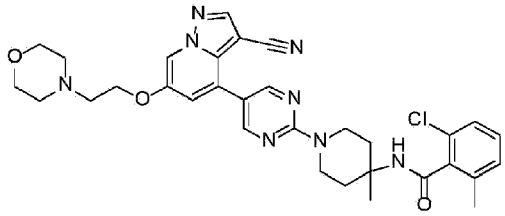


2-chloro-N-(1-(6-(3 -cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyridin-3-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1053] A solution of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (**Intermediate P124;** 4.8 mg, 0.010 mmol) in DCM (0.2 mL) was treated sequentially with 2-chloro-6-methylbenzoic acid (3.5 mg, 0.021 mmol), DIEA (27 µL, 0.16 mmol), HATU (7.9 mg, 0.021 mmol). The resulting mixture was stirred for 17 h at ambient temperature, before diluting with water (10 mL) and extracting with DCM (2 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by C18 reverse phase chromatography (using 5-95% ACN in water with 0.2% TFA as the gradient eluent) to afford the TFA salt of the title compound. The TFA salt was dissolved in MeOH (1 mL), and eluted through a basic resin (Stratospheres SPE MP-HCO3) to cleanly afford the title compound (3.5 mg, 55% yield). MS (apci) m/z = 614.2 (M+H).

Example 682

[1054]



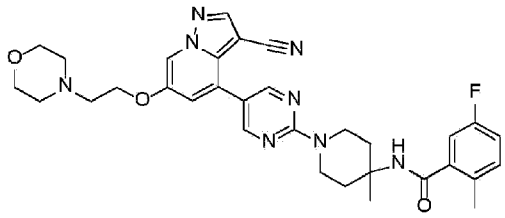
2-chloro-N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1055] A solution of 4-(2-(4-amino-4-methylpiperidin-1-yl)pyrimidin-5-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P131;** 22.7 mg, 0.0329 mmol) in DCM (579 µL) was treated with 2-chloro-6-methylbenzoic acid (25.1 mg, 0.147 mmol), DIEA (15 µL, 0.087 mmol) and HATU (13 mg, 0.035 mmol). The resulting mixture was stirred for 3 h at ambient temperature, was concentrated *in vacuo.* The residue was purified directly by silica chromatography (0-100% EtOAc in Hexanes followed by 0-10% MeOH in DCM). Persistent impurities

required a second silica chromatography (0-10% MeOH in DCM with 0-0.1% NH_4OH) to cleanly afford the title compound (2.8 mg, 9% yield). MS (apci) m/z = 615.2 (M+H).

Example 683

[1056]

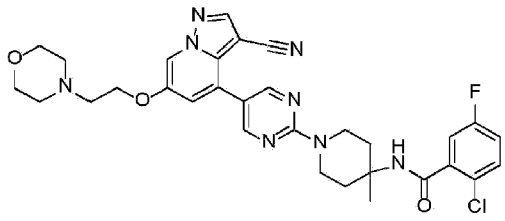


N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[1057] The title compound (12.34 mg, 42% yield) was prepared and purified using a similar procedure to that described for N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide **(Example 682),** replacing 2-chloro-6-methylbenzoic acid with 5-fluoro-2-methylbenzoic acid. MS (apci) m/z = 599.3 (M+H).

Example 684

[1058]

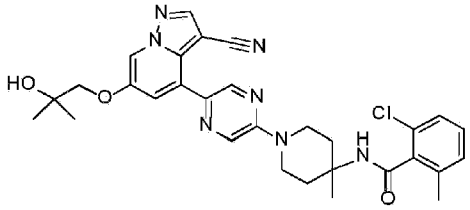


2-chloro-N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide

[1059] The title compound (14 mg, 46% yield) was prepared and purified using a similar procedure to that described for N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide (**Example 682),** except 2-chloro-6-methylbenzoic acid was replaced with 2-chloro-5-fluorobenzoic acid and the reaction was allowed to stir overnight at ambient temperature before the work up and purification required only a single silica chromatographic separation (using 0-100% EtOAc in Hex then 0-10% MeOH in EtOAc as the gradient eluent). MS (apci) m/z = 619.2 (M+H).

Example 685

[1060]

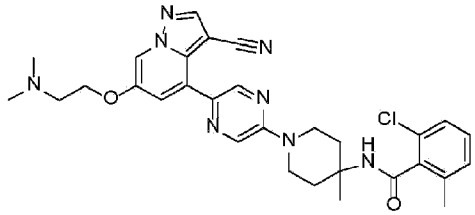


2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1061] In a sealed vessel, a solution of 4-bromo-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P41,** 18 mg, 0.058 mmol) in dioxane (0.5 mL) was treated sequentially with water (0.15 mL), $Cs_2CO_{3(s)}$ (57 mg, 0.17 mmol), and 2-chloro-6-methyl-N-(4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)benzamide **(Intermediate P125;** 38 mg, 0.058 mmol). The resulting mixture was sparged with $N_{2(g)}$ for 5 min then treated with X-phos (11 mg, 0.023 mmol) and $Pd_2(dba)_3$ (5.3 mg, 0.0058 mmol). After sparging with $N_{2(g)}$ for 5 min, the vessel was sealed, and the resulting mixture was stirred for 17 h at 80 °C. After cooling to ambient temperature, the resulting suspension was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_{4(s)}$, filtered and concentrated *in vacuo.* The crude residue was purified by C18 reverse phase chromatography (using 5-95% ACN in water with 0.1% TFA as the gradient eluent) to afford the TFA salt of the title compound. The TFA salt was dissolved in MeOH (1 mL), and eluted through a basic resin (Stratospheres SPE MP-HCO3) to cleanly afford the title compound (3.6 mg, 11% yield). MS (apci) m/z = 574.2 (M+H); 596.2 (M+Na).

Example 686

[1062]



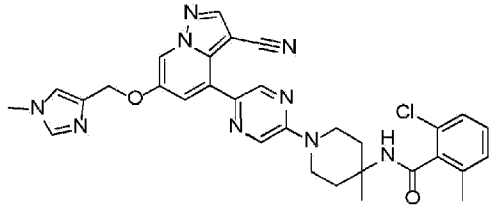
2-chloro-N-(1 -(5 -(3 -cyano-6-(2-(dimethylamino)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1063] A solution of N-(1-(5-(6-(2-aminoethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2-chloro-6-methylbenzamide bis(2,2,2-trifluoroacetate) (**Intermediate P152;** 80 mg, 0.103 mmol) in DCM (66 µL) was treated with formaldehyde (37% aq, 19.3 µL, 0.517 mmol) and

$NaBH(AcO)_3$ (110 mg, 0.517 mmol), then stirred overnight at ambient temperature. The resulting mixture was partitioned between 4:1 DCM:iPrOH and saturated $NaHCO_{3(aq)}$, and eluted through a PS Frit. The organic filtrate was concentrated *in vacuo* to cleanly afford the title compound (12.6 mg, 21% yield). MS (apci) m/z = 573.3 (M+H).

Example 687

[1064]

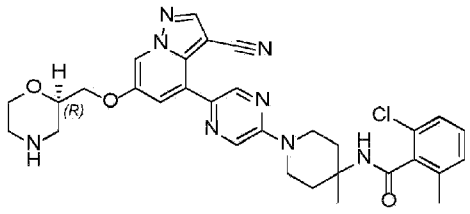


2-chloro-N-(1-(5-(3-cyano-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1065] In a pressure tube, a mixture of 6-((1-methyl-1H-imidazol-4-yl)methoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P145;** 54 mg, 0.142 mmol), 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Intermediate R48;** 54.0 mg, 0.142 mmol), 2 M $K_3PO_{4(aq)}$ (214 µL, 0.427 mmol), X-phos (13.6 mg, 0.0285 mmol) and $Pd_2(dba)_3$ (6.52 mg, 0.00712 mmol) in dioxane (1.0 mL) was sparged with $Ar_{(g)}$ for 10 min, and then the vessel was sealed. The reaction mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM, and extracted sequentially with water (3x) and brine (1x). The organic extracts were purified directly by silica chromatography (0-100% EtOAc/Hexanes), and then by C18 reverse phase chromatography (5-95% ACN in water with 0.1% TFA) to cleanly provide the title compound (12.5 mg, 14.7% yield). MS (apci) m/z = 596.2 (M+H).

Example 688

[1066]

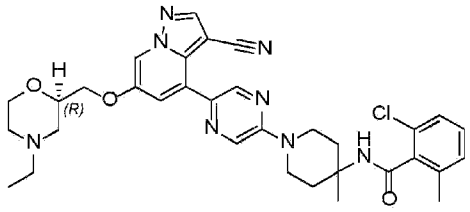


(R)-2-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1067] A solution of tert-butyl (R)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P148;** 40.3 mg, 0.0575 mmol) in DCM (1 mL) and TFA (500 µL, 6.53 mmol) was stirred for 2 h at ambient temperature. Reaction was then concentrated down and purified by silica chromatography (using 0-100% [10% MeOH in DCM WITH 1% NH_4OH]/ DCM as the gradient eluent) to cleanly afford the title compound (21.3 mg, 10% yield). MS (apci) m/z = 601.2 (M+H).

Example 689

[1068]

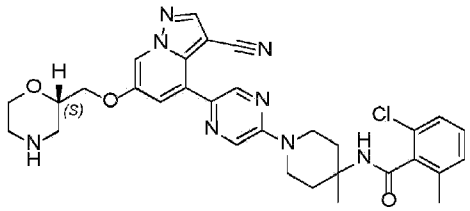


(R)-2-chloro-N-(1-(5-(3-cyano-6-((4-ethylmorpholin-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1069] A solution of (R)-2-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Example 688;** 12 mg, 0.02 mmol) in DCM (100 µL) was treated with acetaldehyde (1 µL, 0.02 mmol) and $NaBH(AcO)_3$ (4 mg, 0.02 mmol), and stirred for 20 h at ambient temperature. The resulting mixture was concentrated in vacuo, and the residue was purified by C18 reverse phase chromatography (using 5-95% water-ACN with 0.1% TFA as the gradient eluent) to afford the TFA salt of the title compound. The TFA salt was partitioned between 4:1 DCM:iPrOH and saturated $NaHCO_{3(aq)}$. The organic extracts were separated, dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated in vacuo to cleanly afford the title compound (2.25 mg, 18% yield). MS (apci) m/z = 629.2 (M+H).

Example 690

[1070]

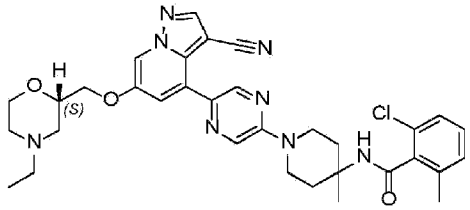


(S)-2-chloro-N-(1-(5-(3 -cyano-6-(morpholin-2-ylmethoxy)pyrazolo [1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1071] The title compound (26.2 mg, quantitative yield) was prepared and purified using a similar procedure to that described for (R)-2-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Example 688),** replacing tert-butyl (R)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P148;** 0.0575 mmol) with of tert-butyl (S)-2-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (**Intermediate P150;** 0.164 mmol) and using 1 mL TFA. MS (apci) m/z = 601.2 (M+H).

Example 691

[1072]

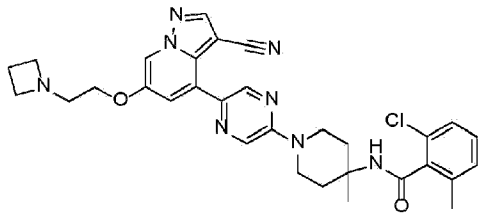


(S)-2-chloro-N-(1-(5-(3-cyano-6-((4-ethylmorpholin-2-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1073] A solution of (S)-2-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Example 690;** 19.5 mg, 0.0324 mmol) in DCM (200 µL) was treated with acetaldehyde (1.88 µL, 0.0649 mmol) and $NaBH(AcO)_3$ (13.8 mg, 0.0649 mmol), and stirred overnight at ambient temperature. The resulting mixture was partitioned between 4:1 DCM:iPrOH and saturated $NaHCO_{3(aq)}$, and eluted through a PS Frit. The combined organic filtrates were concentrated *in vacuo* to cleanly afford the title compound (9.4 mg, 46% yield). MS (apci) m/z = 629.3 (M+H).

Example 692

[1074]

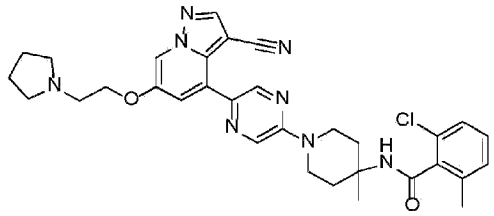


N-(1-(5-(6-(2-(azetidin-1-yl)ethoxy)-3-cyanopyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2-chloro-6-methylbenzamide

[1075] In a pressure tube, a mixture of 6-(2-(azetidin-1-yl)ethoxy)-4-bromopyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P126;** 26.4 mg, 0.0822 mmol), 2-chloro-6-methyl-N-(4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)benzamide **(Intermediate R49;** 53 mg, 0.0822 mmol), $Pd(PPh_3)_4$ (2.85 mg, 0.00247 mmol) and 2 M $Na_2CO_{3(aq)}$ (247 µL, 0.493 mmol) in dioxane (2 mL) was sparged with $Ar_{(g)}$. The vessel was sealed, and the mixture was stirred for 2 h at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL) and extracted with 4:1 DCM:iPrOH (5 × 10 mL). The combined organic extracts were concentrated *in vacuo,* and the residue was purified by silica chromatography (using 0-10% MeOH in DCM as the gradient eluent) to cleanly afford the title compound (17 mg, 35% yield). MS (apci), m/z = 585.3 (M+H).

Example 693

[1076]

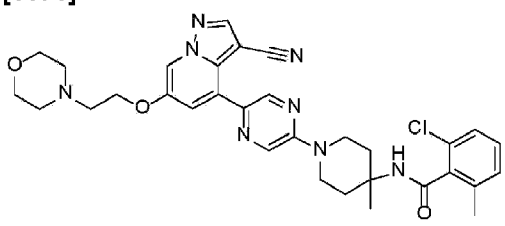


2-chloro-N-(1 -(5 -(3 -cyano-6-(2-(pyrrolidin-1-yl)ethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1077] In a pressure tube, a mixture of 6-(2-(pyrrolidin-1-yl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P143;** 68 mg, 0.178 mmol), 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide (**Intermediate R48;** 67.5 mg, 0.178 mmol), 2 M $K_3PO_{4(aq)}$ (267 µL, 0.534 mmol), X-phos (17.0 mg, 0.0356 mmol) and $Pd_2(dba)_3$ (8.14 mg, 0.00889 mmol) in dioxane (889 µL) was sparged with $Ar_{(g)}$ for 3 min, and then the vessel was sealed. The reaction mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with water, and extracted with DCM (4x). The combined organic extracts were washed with brine (1x), dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified by silica chromatography (using 0-20% MeOH in DCM as the gradient eluent) to cleanly afford the title compound (2.04 mg, 2% yield). MS (apci), m/z = 599.2 (M+H).

Example 694

[1078]

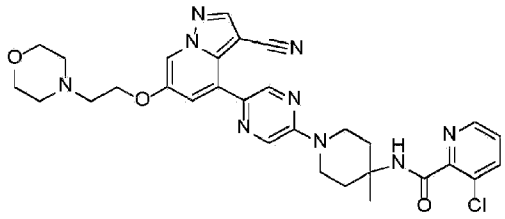


2-chloro-N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1079] A solution of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P129;** 20 mg, 0.0290 mmol), HATU (13.2 mg, 0.0348 mmol) and 2-chloro-6-methylbenzoic acid (5.43 mg, 0.0319 mmol) in DCM (579 µL) was treated with DIEA (15.2 µL, 0.0869 mmol). The resulting mixture was stirred overnight at ambient temperature, before introducing additional HATU (3.4 mg, 0.015 mmol) and DIEA (5 µL, 0.029 mmol). The resulting mixture was stirred for 60 h at ambient temperature. The reaction mixture was purified directly by silica chromatography (using 0-10% MeOH in EtOAc with 0.2% NH_4OH as the gradient eluent) to cleanly afford the title compound (2.87 mg, 16% yield). MS (apci) m/z = 615.4 (M+H).

Example 695

[1080]

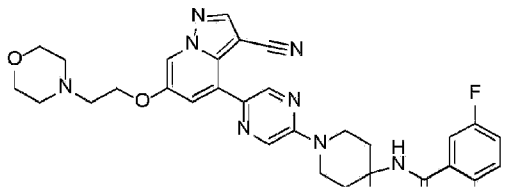


3-chloro-N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1081] A solution of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P129;** 20 mg, 0.0290 mmol), HATU (13 mg, 0.035 mmol) and 3-chloropicolinic acid (5.0 mg, 0.032 mmol) in DCM (579 µL) was treated with DIEA (15 µL, 0.087 mmol). The resulting mixture was stirred overnight at ambient temperature, was purified directly by silica chromatography (using 0-10% MeOH in EtOAc with 0.2% NH_4OH as the gradient eluent) to cleanly afford the title compound (4 mg, 22% yield). MS (apci) m/z = 602.3 (M+H).

Example 696

[1082]

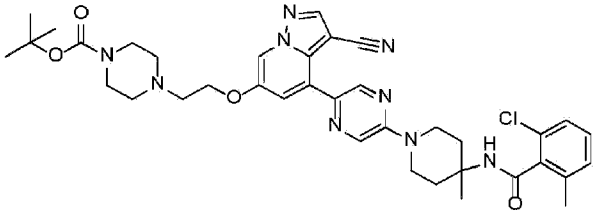


N-(1-(5-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide

[1083] A solution of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P129;** 20 mg, 0.0290 mmol), HATU (13 mg, 0.035 mmol) and 5-fluoro-2-methylbenzoic acid (4.9 mg, 0.032 mmol) in DCM (579 µL) was treated with DIEA (15 µL, 0.087 mmol). The resulting mixture was stirred overnight at ambient temperature, was purified directly by silica chromatography (using 0-10% MeOH in EtOAc with 0.2% NH_4OH as the gradient eluent) to cleanly afford the title compound (4 mg, 22% yield). MS (apci) m/z = 599.3 (M+H).

Example 697

[1084]

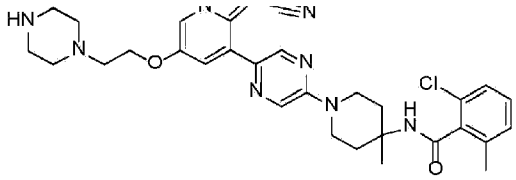


tert-butyl 4-(2-((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate

[1085] In a pressure tube, a mixture of tert-butyl 4-(2-((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate (**Intermediate P141**; 50 mg, 0.10 mmol), 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Intermediate R48;** 38 mg, 0.10 mmol), 2 M $K_3PO_{4(aq)}$ (151 µL, 0.30 mmol), X-phos (9.6 mg, 0.02 mmol) and $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) in dioxane (503 µL) was sparged with $Ar_{(g)}$ for 3 min, and then the vessel was sealed. The reaction mixture was stirred for 4 h at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with water, and extracted with DCM (4x). The combined organic extracts were washed with brine (1x), dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The residue was purified twice by silica chromatography (using 0-100% EtOAc in Hexanes then with 0-20% MeOH in DCM as the gradient eluent) to cleanly afford the title compound (2.04 mg, 2% yield). MS (apci), m/z = 714.3 (M+H).

Example 698

[1086]

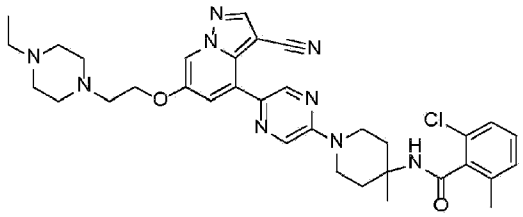


2-chloro-N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1087] A solution of tert-butyl 4-(2-((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)ethyl)piperazine-1-carboxylate **(Example 697;** 26 mg, 0.036 mmol) in DCM (1 mL) and TFA (1 mL, 13 mmol) was stirred for 45 min at ambient temperature. The reaction mixture was treated with saturated $NaHCO_{3(aq)}$ (20 mL), extracted with 4:1 DCM:iPrOH (3x) and eluted through a PS Frit. The organics were concentrated *in vacuo,* and the residue was purified by silica chromatography (using 0-100% DCM in Hexanes then 0-10% MeOH in DCM with 0.1% NH_4OH as the gradient eluent) to cleanly afford the title compound (7 mg, 31% yield). MS (apci) m/z = 614.2 (M+H).

Example 699

[1088]

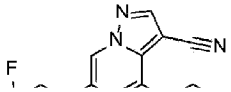


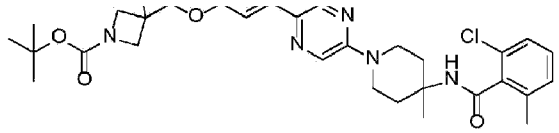
2-chloro-N-(1-(5-(3-cyano-6-(2-(4-ethylpiperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1089] A solution of 2-chloro-N-(1-(5-(3-cyano-6-(2-(piperazin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide (**Example 698;** 6 mg, 0.01mmol) in DCM (488 µL) was treated with acetaldehyde (2.74 µL, 0.0488 mmol) and $NaBH(AcO)_3$ (20.7 mg, 0.10 mmol), then stirred for 2 d at ambient temperature. The resulting mixture was purified directly by silica chromatography (using 0-20% MeOH in DCM with 0.1% NH_4OH as the gradient eluent) to cleanly afford the title compound (1.33 mg, 20% yield). MS (apci) m/z = 642.3 (M+H).

Example 700

[1090]



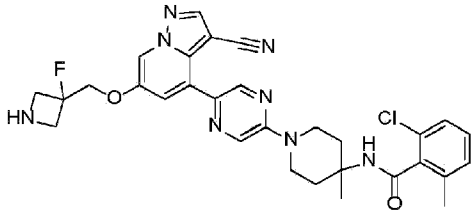


tert-butyl 3-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate

[1091] In a pressure tube, a mixture tert-butyl 3-(((3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate **(Intermediate P144;** 125 mg, 0.264 mmol), 2-chloro-N-(1-(5-chloropyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Intermediate R48;** 50 mg, 0.132 mmol), 2 M $K_3PO_{4(aq)}$ (198 µL, 0.395 mmol), X-phos (12.6 mg, 0.0264 mmol) and $Pd_2(dba)_3$ (6.04 mg, 0.00659 mmol) in dioxane (659 µL) was sparged with $Ar_{(g)}$ for 10 min, and then the vessel was sealed. The reaction mixture was stirred overnight at 80 °C. After cooling to ambient temperature, the reaction mixture was diluted with DCM, and extracted with water (3x) and brine (1x). The organic extracts were concentrated *in vacuo.* The residue was purified by silica chromatography (using 0-100% EtOAc in Hexanes as the gradient eluent) to cleanly afford the title compound (28.2 mg, 31% yield). MS (apci), m/z = 689.3 (M+H).

Example 701

[1092]

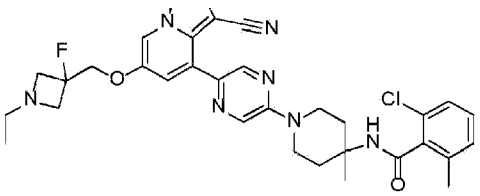


2-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1093] A solution tert-butyl 3-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate **(Example 700;** 27 mg, 0.039 mmol) in DCM (1 mL) and TFA (0.2 mL, 2.6 mmol) was stirred overnight at ambient temperature. The reaction mixture was concentrated *in vacuo,* and the residue was purified by silica chromatography (using 0-100% DCM/10% MeOH/1% NH_4OH as the gradient eluent) to cleanly afford the title compound (19 mg, 82% yield). MS (apci) m/z = 589.2 (M+H).

Example 702

[1094]

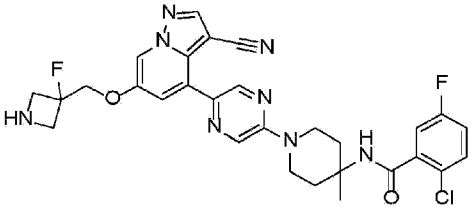


2-chloro-N-(1-(5-(3-cyano-6-((1-ethyl-3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1095] A solution of 2-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide **(Example** 701; 16 mg, 0.0270 mmol) in DCM (0.15 mL) was treated with acetaldehyde (7.6 µL, 0.136 mmol) and $NaBH(AcO)_3$ (29 mg, 0.136 mmol), then stirred for 15 h at ambient temperature. The resulting mixture was concentrated *in vacuo.* The residue was purified by C18 reverse phase chromatography (5-95% acetonitrile in water with 0.1% TFA) to cleanly afford the title compound (10 mg, 60% yield). MS (apci) m/z = 617.2 (M+H).

Example 703

[1096]

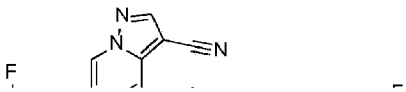


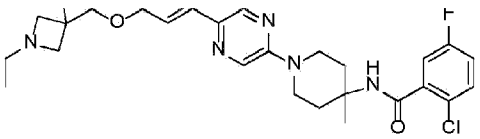
2-chloro-N-(1 -(5 -(3 -cyano-6-((3 -fluoroazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide

[1097] A solution of tert-butyl 3-(((4-(5-(4-(2-chloro-5-fluorobenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (**Intermediate P154;** 3 mg, 0.0043 mmol) in DCM (0.25 mL) and TFA (0.05 mL, 0.65 mmol) was stirred overnight at ambient temperature. The reaction mixture was diluted with DCM, treated with saturated $NaHCO_{3(aq)}$, and the biphasic mixture was extracted with DCM (3x). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_{4(s)}$, filtered and concentrated in vacuo to afford the title compound (1.79 mg, 70% yield). MS (apci) m/z = 593.2 (M+H).

Example 704

[1098]



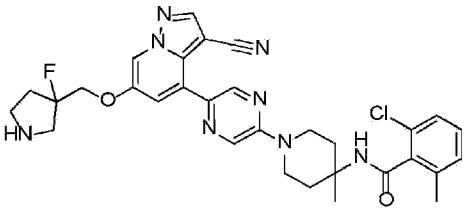


2-chloro-N-(1-(5-(3-cyano-6-((1-ethyl-3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide

[1099] A solution of 2-chloro-N-(1-(5-(3-cyano-6-((3-fluoroazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide **(Example 703;** 16 mg, 0.0270 mmol) in DCM (1.72 mL) was treated with acetaldehyde (7.57 µL, 0.135 mmol) and $NaBH(AcO)_3$ (57.2 mg, 0.270 mmol), then stirred for 1 h at ambient temperature. The resulting mixture was purified directly by silica chromatography (using 0-20% MeOH in DCM with 0.1% NH_4OH as the gradient eluent) to cleanly afford the title compound (2 mg, 12% yield). MS (apci) m/z = 521.2 (M+H).

Example 705

[1100]

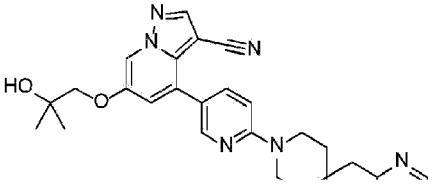


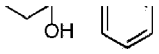
2-chloro-N-(1 -(5 -(3 -cyano-6-((3-fluoropyrrolidin-3-yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1101] A solution of tert-butyl 3-(((4-(5-(4-(2-chloro-6-methylbenzamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoropyrrolidine-1-carboxylate (**Intermediate P149;** 15 mg, 0.019 mmol) in DCM (1 mL) and TFA (1 mL, 13 mmol) was stirred overnight at ambient temperature. The reaction mixture was concentrated *in vacuo,* and the residue was purified directly by silica chromatography (using 0-100% DCM in Hexanes then 0-10% MeOH in DCM with 0.1% NH_4OH as the gradient eluent to cleanly afford the title compound (7 mg, 60% yield). MS (apci) m/z = 603.2 (M+H).

Example 706

[1102]



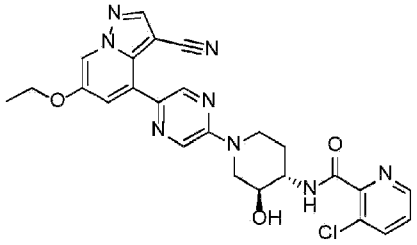


6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

[1103] To a suspension of 4-(6-fluoropyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P42,** 90 mg, 0.276 mmol) in DMSO (2 mL) was added DIEA (193 µL, 1.10 mmol), followed by the addition of 4-(pyridin-2-ylmethyl)piperidin-4-ol hydrochloride (69 mg, 0.303 mmol). The reaction mixture was stirred at 90 °C for 60 h, then purified directly by C18 reverse phase chromatography (using 5-95% acetonitrile in water with 0.1% TFA as the gradient eluent). Fractions containing the desired product were combined, partially concentrated in vacuo to remove the ACN, then partitioned between saturated $NaHCO_3$(aq) and DCM. The biphasic mixture was extracted with additional DCM (2x). The combined organic extracts were dried over anhydrous $MgSO_4$(s), filtered and concentrated in vacuo. The residue was sonicated in Et_2O (2 mL) and then concentrated in vacuo to afford the title compound (48 mg, 35% yield). MS (apci) m/z = 499.2 (M+H).

Example 707

[1104]



3 -chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)picolinamide

[1105] Step 1: Preparation of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)carbamate. To a mixture of 6-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P110,** 296 mg, 0.782 mmol) and tert-butyl ((3S,4S)-1-(5-chloropyrazin-2-yl)-3-hydroxypiperidin-4-yl)carbamate (**Intermediate R53,** 181 mg, 0.55 mmol) in dioxane (2.7 mL) was added XPhos (52 mg, 0.11 mmol), $Pd_2(dba)_3$ (25 mg, 0.028 mmol), and K_3PO_4 (2 M aq., 0.82 mL). The reaction was sparged with Argon for one minute before heating to 85 °C and stirring overnight. After cooling to RT, the reaction was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo.* The crude material was purified by silica chromatography (0-15% MeOH/DCM) to afford the title compound (147 mg, 56% yield). MS (apci) m/z = 480.2 (M+H).

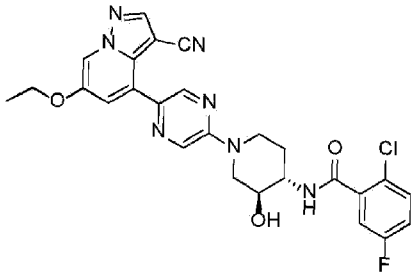
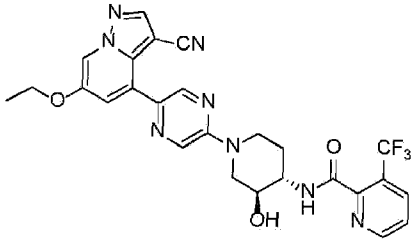
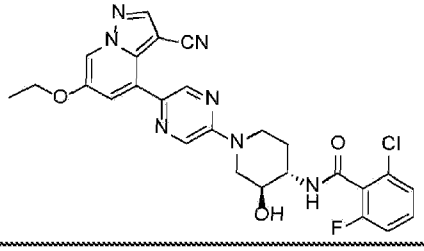
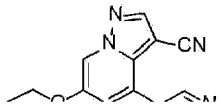
[1106] Step 2: Preparation of 4-(5-((3S,4S)-4-amino-3-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-

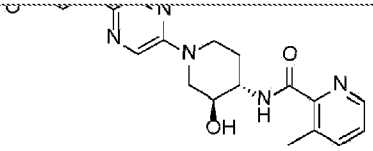
ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of tert-butyl ((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)carbamate (147 mg, 0.31 mmol) in DCM (3 mL) and TFA (2 mL) was stirred for 30 minutes at RT. The solution was concentrated *in vacuo,* then diluted with saturated $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (58 mg, 50% yield). MS (apci) m/z = 380.2 (M+H).

[1107] Step 3: Preparation of 3-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)picolinamide. To a solution of 4-(5-((3S,4S)-4-amino-3-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (21.2 mg, 0.056 mmol) in DMSO (0.6 mL) was added 3-chloropicolinic acid (8.8 mg, 0.056 mmol) and DIEA (0.1 mL, 0.56 mmol), followed by the addition of HATU (23.4 mg, 0.061 mmol). After stirring for 80 minutes at RT, the reaction mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous $Na_2SO_{4(s)}$, filtered, and concentrated *in vacuo* to afford the title compound (29 mg, 99% yield). MS (apci) m/z = 519.1 (M+H).

[1108] The compounds in **Table ZZZ** were prepared using a similar method as described in **Example 707 Step 3,** replacing 3-chloropicolinic acid with the appropriate carboxylic acid.

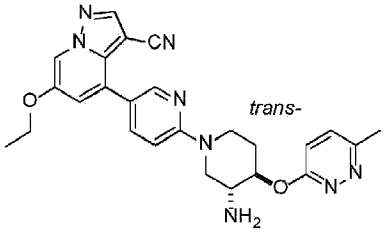
Table ZZZ

Ex. #	Structure	Chemical Name	LCMS m/z
709		2-chloro-N-((3 S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)-5-fluorobenzamide	536.1 (M+H)
710		N-((3 S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)-3-(trifluoromethyl)picolinamide	553.1 (M+H)
711		2-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)-6-fluoro benzamide	536.1 (M+H)
712		N-((3 S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-	499.2, 521.2 (M+H, M+Na)

Ex. #	Structure	Chemical Name	LCMS m/z
		yl)-3-methylpicolinamide	

Example 713

[1109]

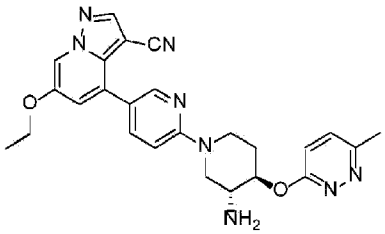


4-(6-((3r,4r)-3 -amino-4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3 - yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[1110] A mixture of tert-butyl ((3r,4r)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-hydroxypiperidin-3-yl)carbamate (**Intermediate P158,** 0.025 g, 0.052 mmol), 3-chloro-6-methylpyridazine (0.010 g, 0.078 mmol) and NaH (0.0042 g, 0.10 mmol) in DMF (0.26 mL) was heated to 90 °C overnight. The mixture was then concentrated down and purified by preparative HPLC (5-95% ACN in water with 1% TFA). The mixture was then worked up with DCM and sat. NaHCO3. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated to yield the title product (6.4 mg, 26 % yield). MS (apci) m/z = 471.2 (M+H).

Example 714

[1111]

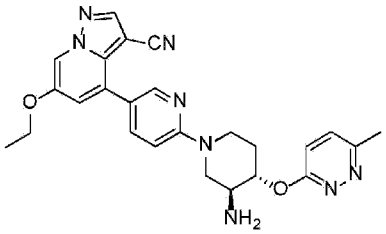


4-(6-((3R,4R)-3-amino-4-((6-methylpyridazin-3 -yl)oxy)piperidin-1-yl)pyridin-3 - yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[1112] 4-(6-((3r,4r)-3 -amino-4-((6-methylpyridazin-3 -yl)oxy)piperidin-1-yl)pyridin-3 - yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Example 713,** 65 mg, 0.138 mmol) was treated with SFC chiral chromatography (5-70% MeOH:IPA:DEA 80:20:0.1) to yield two products. The desired product was isolated from fractions containing peak 1 and was arbitrarily assigned as the (R,R) isomer (6.6 mg). MS (apci) m/z = 471.2 (M+H).

Example 715

[1113]

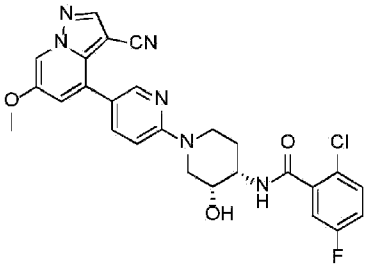


4-(6-((3S,4S)-3-amino-4-((6-methylpyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo [1,5 -a]pyridine-3 -carbonitrile

[1114] The title compound was prepared and purified by chiral chromatography according to the procedure described in **Example 714.** The desired product was isolated from fractions containing peak 2 and was arbitrarily assigned as the (S,S) isomer (9.1 mg). MS (apci) m/z = 471.2 (M+H).

Example 717

[1115]



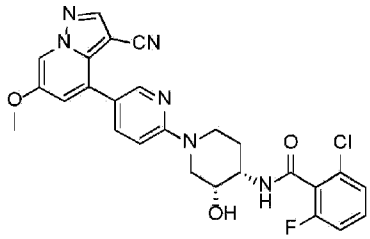
2-chloro-N-((3R4S)-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-5-fluorobenzamide

[1116] A mixture of 4-(6-((3R,4S)-4-amino-3-hydroxypiperidin-1-yl)pyridin-3-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (**Intermediate P159,** 0.025 g, 0.0686 mmol), 2-chloro-5-fluorobenzoic acid (0.0180 g, 0.103 mmol), HATU (0.0522 g, 0.137 mmol) and Hunig's base (0.0358 ml, 0.206 mmol) in DMSO (0.686 mL) was stirred at RT overnight. The mixture was worked up with DCM and water. The

organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated. The crude material was purified by preparative HPLC (5-95% ACN in water with 1% TFA). The combined fractions containing the product were worked up with DCM and sat. $NaHCO_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated to yield the title product (0.0198 g, 55.4 % yield). MS (apci) m/z = 521.1 (M+H).

Example 718

[1117]

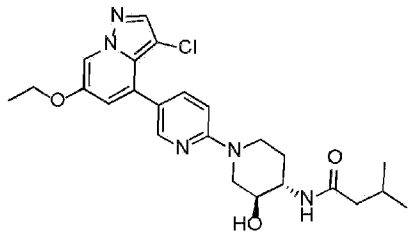


2-chloro-N-((3R4S)-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-6-fluorobenzamide

[1118] The title product was prepared according to the procedure described in **Example 717,** replacing 2-chloro-5-fluorobenzoic acid with 2-chloro-6-fluorobenzoic acid. MS (apci) m/z = 521.1 (M+H).

Example 721 reference

[1119]

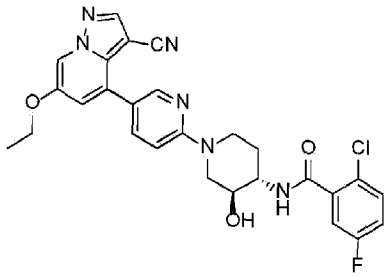
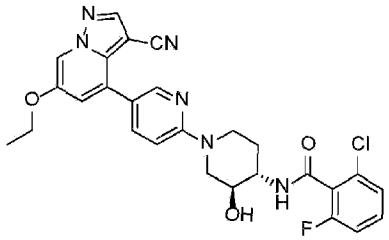
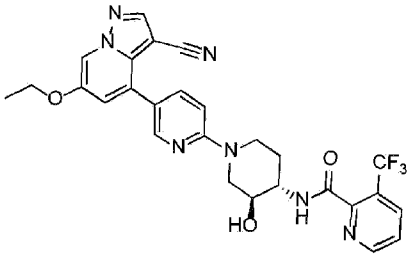
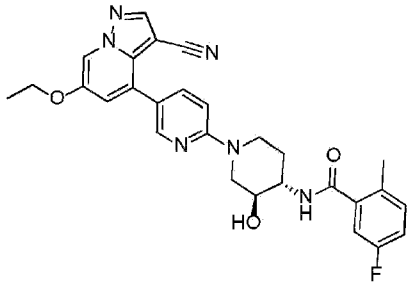


N-((3S,4S)-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide

[1120] A solution of (3S,4S)-4-amino-1-(5-(3-chloro-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-ol dihydrochloride (**Intermediate P161;** 50 mg, 0.109 mmol) in DCM (1 mL, 0.109 mmol) was treated with DIEA (0.190 mL, 1.09 mmol) and 3-methylbutanoyl chloride (19.6 mg, 0.163 mmol). The reaction mixture was stirred at rt for 1 h, then purified by silica chromatography (20-100% EtOAc in hexanes) to yield the title product as white solid (14.6 mg, 28 % yield). MS (apci) m/z = 472.2 (M+H).

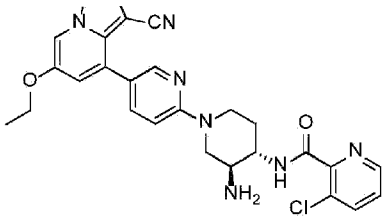
[1121] The compounds in Table **X1** were prepared using a similar method to that described in Step 2 in the synthesis of N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-1-(trifluoromethyl)cyclobutane-1-carboxamide **(Example 522),** replacing 1-(trifluoromethyl)cyclobutane-1-carboxylic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. The title compounds were isolated following a chromatographic purification utilizing an appropriate gradient eluent.

Table X1

Ex #	Structure	Chemical Name	MS (apci) m/z
722		2-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3 -hydroxypiperidin-4-yl)-5-fluorobenzamide	535.2 (M+H)
723		2-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3 -hydroxypiperidin-4-yl)-6-fluorobenzamide	535.1 (M+H)
724		N-((3 S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-(trifluoromethyl)picolinam ide	552.1 (M+H)
725		N-((3 S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3 -hydroxypiperidin-4-yl)-5-fluoro-2-methylbenzamide	515.2, 557.2 (M+H, M+Na)

Example 729

[1122]

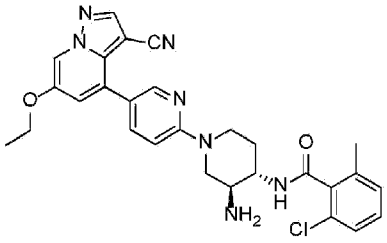
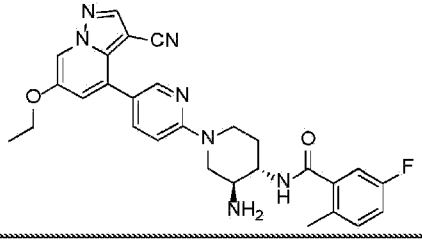


N-((3 S,4S)-3 -amino-1 -(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)-3-chloropicolinamide

[1123] A mixture of tert-butyl ((3S,4S)-4-amino-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-3-yl)carbamate **(Intermediate P162;** 0.026 g, 0.0544 mmol), 3-chloropicolinic acid (0.00944 g, 0.0599 mmol), HATU (0.0414 g, 0.109 mmol) and Hunig's base (0.0123 ml, 0.0708 mmol) in DMSO (0.544 mL) was stirred at room temp overnight. The mixture was worked up with DCM and water. The organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated. The concentrated material was stirred in DCM (1 mL) and TFA (1 mL) for 1 h, then concentrated and purified by preparative HPLC (5-95% acetonitrile in water with 1% TFA). The fractions containing the product were combined and partitioned between DCM and saturated $NaHCO_3$ The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated to yield the title product (0.008 g, 28.4 % yield). MS (apci) m/z = 517.2 (M+H).

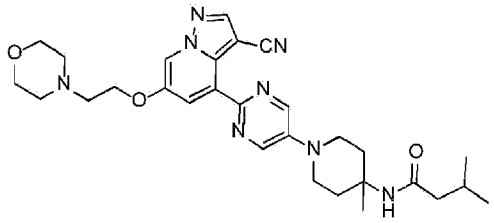
[1124] The compounds in Table **X2** were prepared using a similar method to that described in **Example 729,** replacing 3-chloropicolinic acid with the appropriate carboxylic acid. Reactions were monitored for completion by LCMS, and reaction durations were adjusted accordingly. The title compounds were isolated following a chromatographic purification utilizing an appropriate gradient eluent.

Table X2

Ex #	Structure	Chemical Name	MS (apci) m/z
730		N-((3S,4S)-3-ammo-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)-2-chloro-6-methy lbenzamide	530.2 (M+H)
731		N-((3S,4S)-3-ammo-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperidin-4-yl)-5-fluoro-2-methy lbenzamide	514.2 (M+H)

Example 733 reference

[1125]

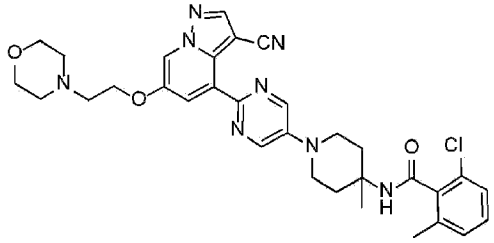


N-(1-(2-(3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrimidin-5-yl)-4-methylpiperidin-4-yl)-3-methylbutanamide

[1126] To a solution of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrimidin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile (**P163**, 4 mg, 0.00865 mmol) in DCM (0.3 mL) was added 3-methylbutanoic acid (0.001mL, 0.013 mmol), N-ethyl-N-isopropylpropan-2-amine (0.009 mL, 0.052 mmol) and HATU (4.3mg, 0.0112 mmol). After stirred at RT overnight, the reaction was partitioned between DCM and saturated $NaHCO_3$. After phase-separation, the aqueous was extracted with DCM (3 × 10 mL). The organic extracts were combined and concentrated. The crude material was purified by preparative HPLC (5-95% acetonitrile in water with 1% TFA) to yield the title product (1.7 mg, 36%). MS (apci) m/z = 547.3 (M+H).

Example 734

[1127]

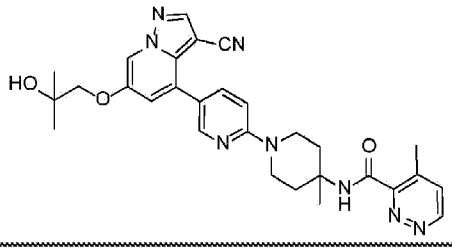
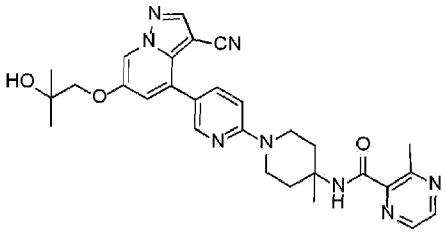
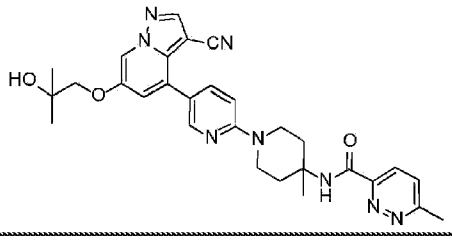
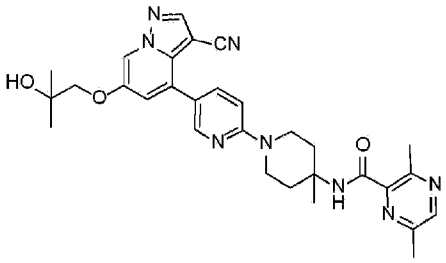


2-chloro-N-(1-(2-(3 -cyano-6-(2-morpholinoethoxy)pyrazolo [1,5 -a]pyridin-4-yl)pyrimidin-5-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1128] The title compound was prepared using a similar method to that described in **Example 733,** replacing 3-methylbutanoic acid with the 2-chloro-6-methylbenzoic acid. MS (apci) m/z = 615.2 (M+H).

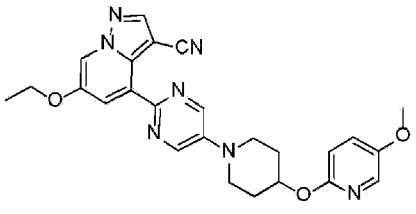
[1129] The compounds in **Table X**3 were prepared using a similar method as described in **Example 88,** replacing 3,6-dimethylpicolinic acid with the appropriate carboxylic acid.

Table X3

Ex. #	Structure	Chemical Name	LCMS m/z
735		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-4-methylpyridazine-3-carboxamide	541.2 (M+H)
736		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-3-methylpyrazine-2-carboxamide	541.2 (M+H)
737		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-6-methylpyridazine-3 -carboxamide	541.2 (M+H)
738		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-y1)-3,6-dimethylpyrazine-2-carboxamide	555.3 (M+H)

Example 739

[1130]



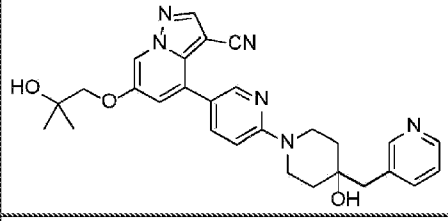
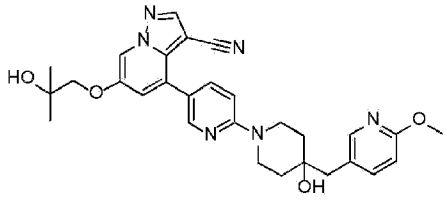
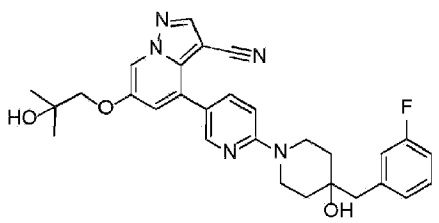
6-ethoxy-4-(5-(4-((5-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyrimidin-2-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile

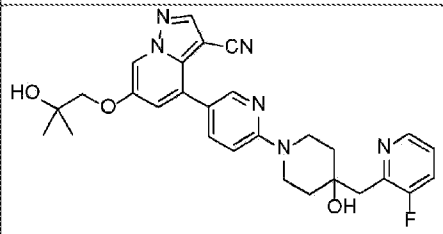
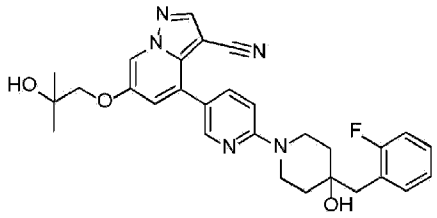
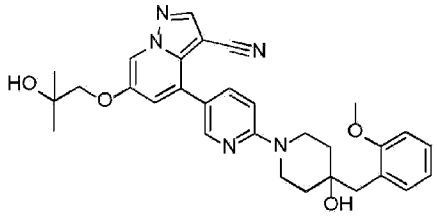
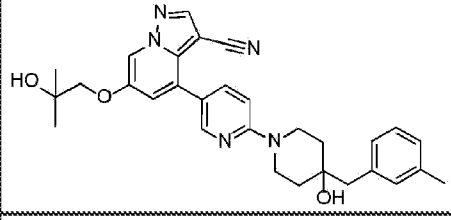
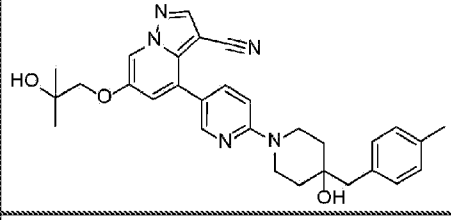
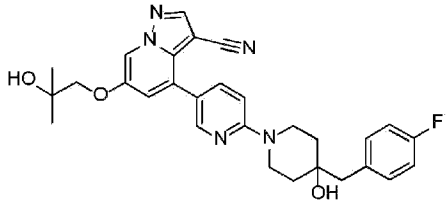
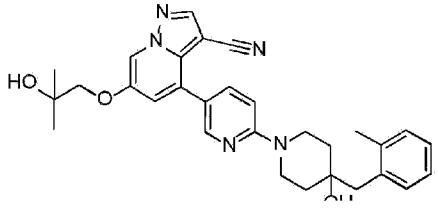
[1131] Step 1: Preparation of 4-(5-bromopyrimidin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile. To (3-cyano-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridin-4-yl)boronic acid **(Intermediate P110,** 190 mg, 0.61mmol) and 5-bromo-2-iodopyrimidine (225mg, 0.789mmol) in dioxane (2 mL) was added XPhos (58 mg, 0.121 mmol), $Pd_2(dba)_3$ (3.3 mg, 0.03 mmol) and K_3PO_4 (2 M aq, 0.9 mL, 1.8 mmol). The reaction mixture was sparged with argon and heated at 85 °C overnight. After cooling to RT, the reaction was partitioned in 1:1 DCM:water (30 mL). After phase-separation, the aqueous was extracted with DCM (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica chromatography (0-60% EtOAc/hexanes) to afford the title compound (30 mg, 14%).

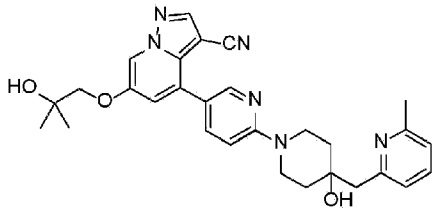
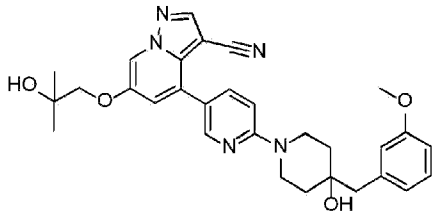
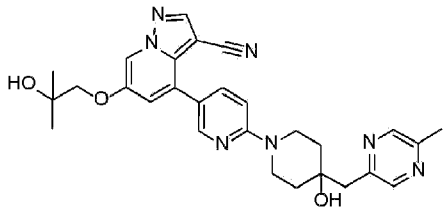
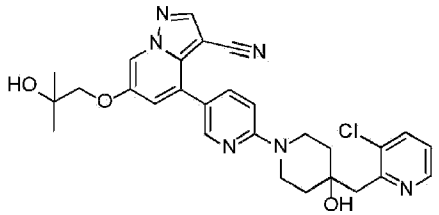
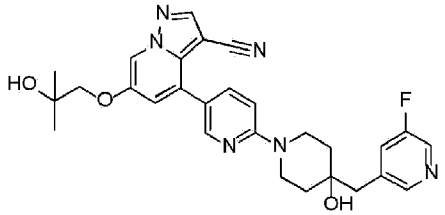
[1132] Step 2: Preparation of 6-ethoxy-4-(5-(4-((5-methoxypyridin-2-yl)oxy)piperidin-1-yl)pyrimidin-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. A mixture of 4-(5-bromopyrimidin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile (30 mg, 0.087 mmol), 5-methoxy-2-(piperidin-4-yloxy)pyridine (37 mg, 0.18mmol), Cs_2CO_3 (57 mg, 0.17 mmol), XPhos (4 mg, 0.0087 mmol) and $Pd_2(dba)_3$ (4 mg, 0.0044 mmol) in dioxane (0.44 mL) was sparged with argon, and stirred at 90 °C overnight. After cooling to RT, the reaction was partitioned in 1:1 DCM:water (20 mL). After phase-separation, the aqueous was extracted with DCM (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by preparative TLC (10% MeOH in DCM) to afford the title product (1.4 mg, 3%). MS (apci) m/z = 472.2 (M+H).

[1133] The compounds in **Table X4** were prepared using a similar method as described in **Example 706,** replacing 4-(pyridin-2-ylmethyl)piperidin-4-ol hydrochloride with the appropriate piperidine intermediate.

Table X4

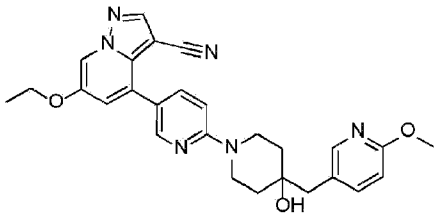
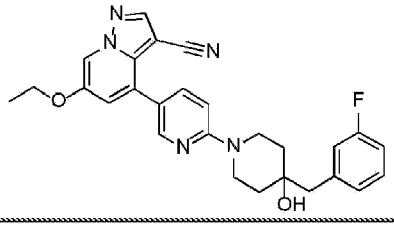
Ex. #	Structure	Chemical Name	LCMS m/z	Intermediate
740		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(pyridin-3-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	499.2 (M+H)	4-(pyridin - 3-ylmethyl)piperidi hydrochloride (commercially available)
741		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-((6-methoxypyridin-3-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	529.2 (M+H)	**R66**
742		4-(6-(4-(3-fluorobenzyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3 -carbonitrile	516.2 (M+H)	**R67**
743		4-(6-(4-((3-fluoropyridin-	517.2	**R68**

Ex. #	Structure	Chemical Name	LCMS m/z	Intermediate
		2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3 -carbonitrile	(M+H)	
744		4-(6-(4-(2-fluorobenzyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5 -a]pyridine-3 -carbonitrile	516.3 (M+H)	**R55**
745		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(2-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile	528.3 (M+H)	**R56**
746		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(3-methylbenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile	512.3 (M+H)	**R62**
747		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(4-methylbenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 -carbonitrile	512.2 (M+H)	**R63**
748		4-(6-(4-(4-fluorobenzyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3 -carbonitrile	516.2 (M+H)	**R57**
749		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(2-methylbenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	512.3 (M+H)	**R64**

Ex. #	Structure	Chemical Name	LCMS m/z	Intermediate
	OH			
750		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-((6-methylpyridin-2-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 - carbonitrile	513.2 (M+H)	**R58**
751		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(3-methoxybenzyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 - carbonitrile	528.3 (M+H)	**R59**
752		6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-((5-methylpyrazin-2-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo [1,5-a]pyridine-3 - carbonitrile	514.3 (M+H)	**R65**
753		4-(6-(4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3 - carbonitrile	533.2 (M+H)	**R60**
754		4-(6-(4-((5-fluoropyridin-3-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridine-3 - carbonitrile	517.3 (M+H)	**R61**

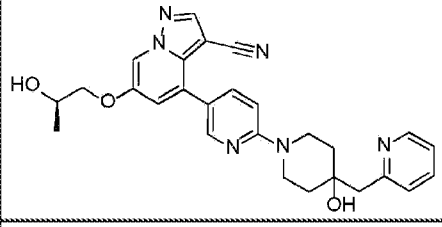
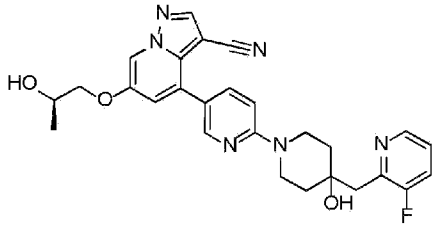
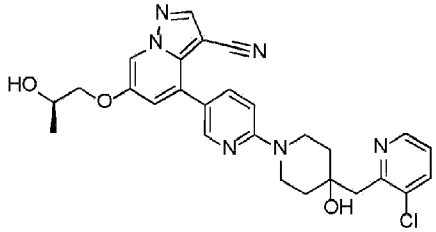
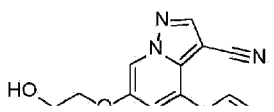
[1134] The compounds in **Table X5** were prepared using a similar method as described in **Example 325,** replacing 4-benzylpiperidin-4-ol with the appropriate piperidine intermediate.

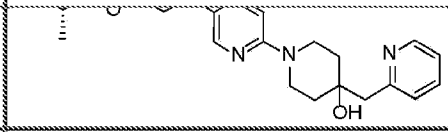
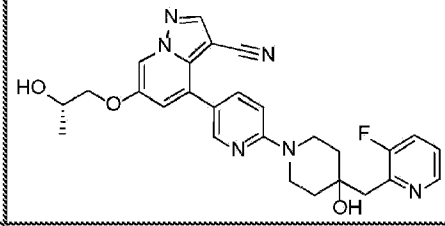
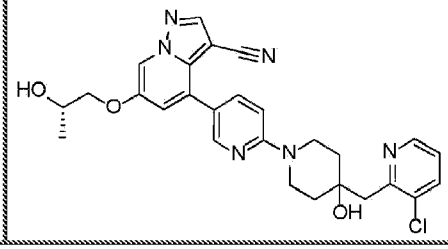
Table X5

Ex. #	Structure	Chemical Name	MS m/z	Intermediate
755		6-ethoxy-4-(6-(4-hydroxy-4-((6-methoxypyridin-3-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	485.2 (M+H)	**R66**
756		6-ethoxy-4-(6-(4-(3-fluorobenzyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	472.2 (M+H)	**R67**

[1135] The compounds in **Table X6** were prepared according to the procedure described in **Example 415,** reacting either **Intermediate P80** (Method A) or **Intermediate P165** (Method B) with an appropriate piperidine intermediate.

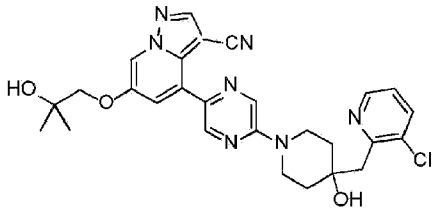
Table X6

Ex. #	Structure	Chemical Name	MS m/z	Intermediate (Method)
757		(R)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	485.3 (M+H)	4-(pyridin- 2-ylmethyl)piperidin-4-ol hydrochloride (Commercially available) (Method A)
758		(R)-4-(6-(4-((3-fluoropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	503.2 (M+H)	**R68** (Method A)
759		(R)-4-(6-(4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	519.1 (M+H)	**R60** (Method A)
760		(S)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[	485.2 (M+H)	4-(pyridin-2-ylmethyl)piperidin-4-ol hydrochloride

Ex. #	Structure	Chemical Name	MS m/z	Intermediate (Method)
		1,5-a]pyridine-3-carbonitrile		(Commercially available) (Method B)
761		(S)-4-(6-(4-((3-fluoropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	503.2 (M+H)	**R68** (Method B)
762		(S)-4-(6-(4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxypropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	519.2 (M+H)	**R60** (Method B)

Example 763

[1136]



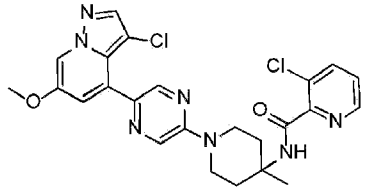
4-(5-(4-((3-chloropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[1137] A pressure vessel was charged with 6-(2-hydroxy-2-methylpropoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(P166** 76.0 mg, 0.213 mmol), 1-(5-chloropyrazin-2-yl)-4-((3-chloropyridin-2-yl)methyl)piperidin-4-ol **(R69,** 65.6 mg, 0.193 mmol), and K_3PO_4 (123 mg, 0.580 mmol), followed by 1,4-dioxane (1.5 mL) and water (0.2 mL). The reaction mixture was sparged with N_2 for 10 min before $Pd_2(dba)_3$ (8.85 mg, 0.00967 mmol) and XPhos (18.4 mg, 0.0387 mmol) were introduced. The reaction was sparged with N_2 for an additional 3 min before it was sealed and heated to 100°C for 3 d to reach ~79% conversion (LCMS). After cooling to RT, the reaction was diluted with 60/40 ACN:H_2O with 2% TFA and filtered through a Pall Acrodisc to remove solids. The filtrate was concentrated and purified by preparative HPLC (40-60% ACN/H_2O with 0.1% TFA). The combined fractions containing the product were concentrated, and the residue was taken up in MeOH and filtered through MP-HCO_3 resin. The filtrate was concentrated to yield the title product as yellow powder (2.0 mg, 1.9%). MS (apci)

m/z = 534.2 (M+H).

Example 764

[1138]

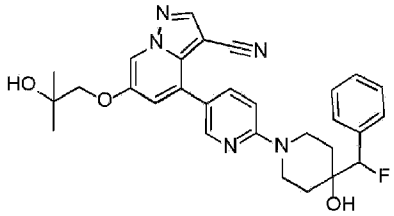


3-chloro-N-(1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1139] To a mixture of 3-chloropicolinic acid (23 mg, 0.14 mmol) and HATU (37 mg, 0.097 mmol) in DCM (2.4 mL) was added DIEA (84 µL, 0.48 mmol). After 30-min stirring at RT, 1-(5-(3-chloro-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-amine **(Intermediate P175,** 29 mg, 0.078 mmol) was added in one portion. The reaction was stirred for 3 h at ambient temperature, then partitioned in sat. NH_4Cl and DCM. After phase-separation, the organic layer was concentrated and purified by silica chromatography (0-100% EtOAc in hexanes) to afford the title product (20 mg, 50%). MS (apci) m/z = 512.2 (M+H).

Example 765

[1140]



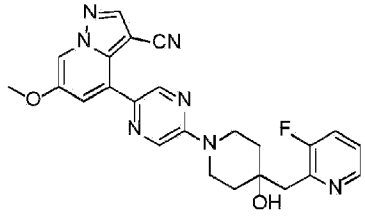
4-(6-(4-(fluoro(phenyl)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile

[1141] To a solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (115 mg, 0.325 mmol) and V_2O_3 (2.87 mg, 0.0192 mmol) in CH_3CN (2 mL) was added 4-(6-(4-benzyl-4-hydroxypiperidin-1-yl)pyridin-3-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Example 27,** 95.3 mg, 0.192 mmol). The reaction mixture was frozen at -78°C, and purged of air. The mixture was slowly warmed up to RT and stirred overnight. After diluting the reaction with H_2O, the mixture was extracted with EtOAc (3 x). The combined organic extracts were concentrated and purified by

preparative HPLC (20-80% ACN in H_2O with 0.1% TFA). The combined fractions containing the product were concentrated, dissolved in minimal amount of MeOH, and passed through PL-HCO3 resin. The filtrate was concentrated to afford the title product as a pale yellow solid (4.2 mg, 4%). MS (apci) m/z = 516.2 (M+H).

Example 766

[1142]

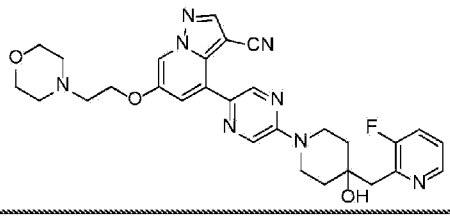
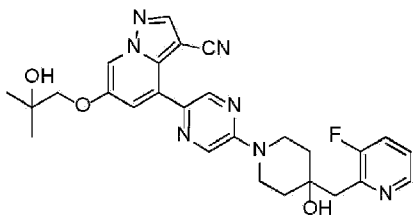


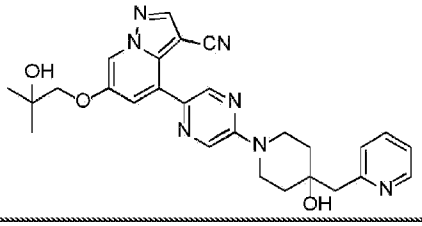
4-(5-(4-((3-fluoropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile

[1143] To 6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P168,** 126 mg, 0.211mmol) and 1-(5-chloropyrazin-2-yl)-4-((3-fluoropyridin-2-yl)methyl)piperidin-4-ol **(Intermediate R70,** 68 mg, 0.211mmol) in dioxane (1.5 mL) were added XPhos (20 mg, 0.04 mmol), $Pd_2(dba)_3$ (10 mg, 0.011mmol) and K_3PO_4 (2 M aq, 0.3 mL, 0.3 mmol). The mixture was sparged with Ar and heated to 90 °C for 17 h. After cooling to RT, the reaction was partitioned in 1:1 DCM/water (30 mL). After phase-separation, the organic layer was washed with water and brine and concentrated. The crude material was purified by preparative HPLC (5 to 95% acetonitrile in water with 1% TFA) to afford the title product (3.4 mg, 2.8%). MS (apci) m/z = 460.2 (M+H).

[1144] The compounds in **Table X7** were prepared according to the procedure described in **Example 766,** coupling the appropriate boronate and halide intermediates.

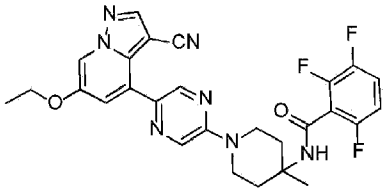
Table X7

Ex. #	Structure	Chemical Name	LCMS m/z	Reactant Intermediates
767		4-(5-(4-((3-fluoropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	559.2 (M+H)	P12 and R70
768		4-(5-(4-((3-fluoropyridin-2-yl)methyl)-4-hydroxypiperidin-1-yl)pyrazin-2-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile	518.2 (M+H)	P166 and R70

Ex. #	Structure	Chemical Name	LCMS m/z	Reactant Intermediates
769		6-(2-hydroxy-2-methylpropoxy)-4-(5-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyrazin-2-yl)pyrazolo[1,5-a]pyridine-3 -carbonitrile	500.2 (M+H)	P166 and R71

Example 771

[1145]

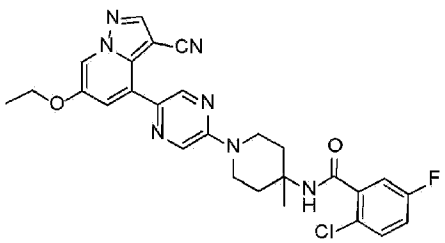


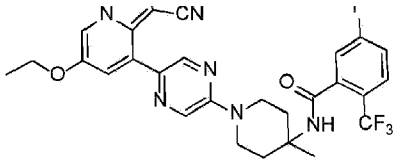
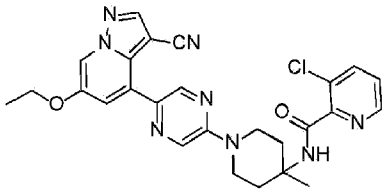
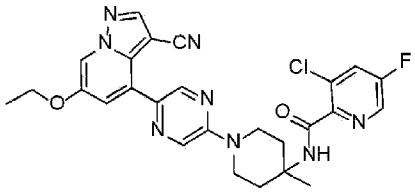
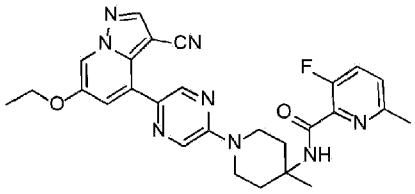
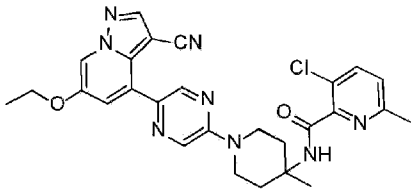
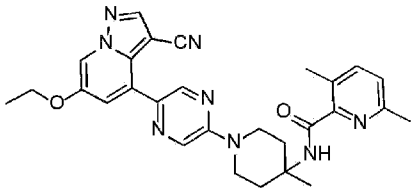
N-(1-(5-(3-cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2,3,6-trifluorobenzamide

[1146] To a mixture of 2,3,6-trifluorobenzoic acid (22 mg, 0.12 mmol) and HATU (31 mg, 0.083 mmol) in DCM (2.1 mL) was added DIEA (72 µl, 0.41 mmol) and stirred for 30 min at RT, followed by addition of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P172;** 25 mg, 0.041 mmol) in one portion. After stirred for another 2 h, the reaction was diluted with sat. NH_4Cl (2 mL) and passed through a Phase Separator frit. The organic filtrate was purified by silica chromatography (0-100% EtOAc in hexanes) to afford the title compound (17 mg, 77%). MS (apci) m/z = 536.1 (M+H).

[1147] The compounds in **Table X8** were prepared using a similar method as described in **Example 771,** replacing 2,3,6-trifluorobenzoic acid with the appropriate carboxylic acid.

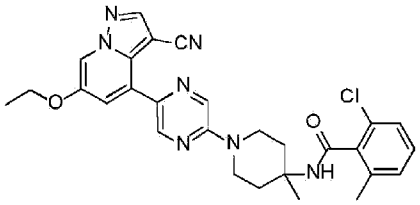
Table X8

Ex. #	Structure	Chemical Name	LCMS m/z
772		2-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide	534.2 (M+H)
773		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-	568.2 (M+H)

		4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-(trifluoromethyl)benzamid e	
774		3-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide	517.1 (M+H)
775		3-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	535.1 (M+H)
776		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-3-fluoro-6-methylpicolinamide	515.2 (M+H)
777		3-chloro-N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylpicolinamide	531.2, 553.2 (M+H, M+Na)
778		N-(1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-3,6-dimethylpicolinamide	511.2 (M+H)

Example 779

[1148]

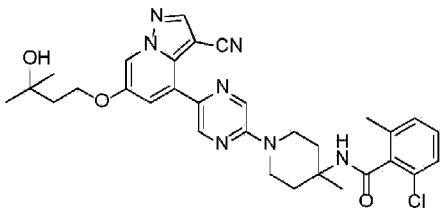
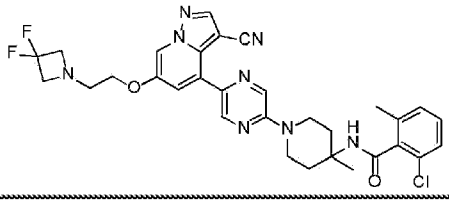
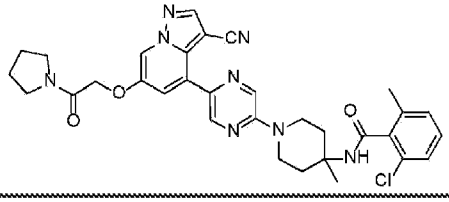
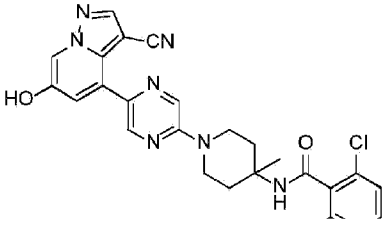


2-chloro-N-(1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide

[1149] In a 15-mL pressure tube was charged 4-bromo-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Intermediate P5;** 15 mg, 0.056 mmol) and dioxane (0.5 mL) to form a suspension, followed by addition of water (0.15 mL), Cs_2CO_3 (55 mg, 0.17 mmol) and 2-chloro-6-methyl-N-(4-methyl-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)piperidin-4-yl)benzamide **(Intermediate R49;** 37 mg, 0.056 mmol). The mixture was sparged with N_2 for 5 min before XPHOS (11 mg, 0.023 mmol) and Pd_2dba_3 (5.2 mg, 0.0056 mmol) were added, followed by an additional 5 min of sparging with N_2 before the reaction was sealed and heated at 80°C for 17 h. Once cooled to RT, the reaction was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified first by preparative HPLC (5-95% MeCN/H_2O with 0.2% TFA), followed by silica chromatography (0-100% acetone/hexanes) to afford the title product (2.1 mg, 7%). MS (apci) m/z = 530.2 (M+H).

[1150] The compounds in **Table X9** were prepared according to the procedure described in **Example 779,** replacing 4-bromo-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile with the appropriate bromide intermediate.

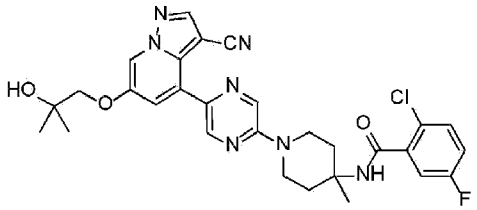
Table X9

Ex. #	Structure	Chemical Name	LCMS m/z	Bromide Intermediate
780*		2-chloro-N-(1-(5-(3-cyano-6-(3-hydroxy-3-methylbutoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide	588.2 (M+H)	**P169**
781		2-chloro-N-(1-(5-(3-cyano-6-(2-(3,3-difluoroazetidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide	621.2 (M+H)	**P170**
782		2-chloro-N-(1-(5-(3-cyano-6-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide	613.2 (M+H)	**P171**
783		2-chloro-N-(1-(5-(3-cyano-6-hydroxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylbenzamide	502.1 (M+H)	**P1**

Ex. #	Structure	Chemical Name	LCMS m/z	Bromide Intermediate
*Note: TBS protective group was removed during preparative HPLC purification (5-95% ACN in water with 0.1% TFA).				

Example 784

[1151]

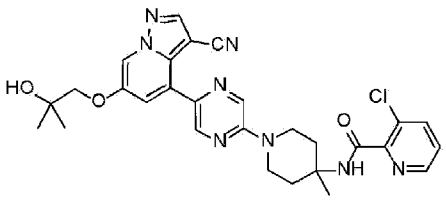
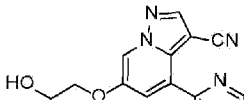


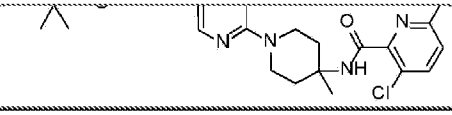
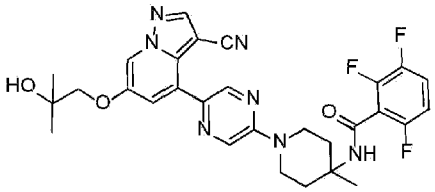
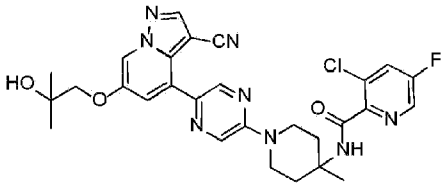
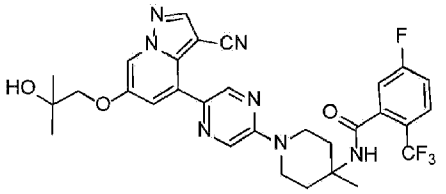
2-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide

[1152] To a suspension of 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride **(Intermediate P173;** 10 mg, 0.020 mmol) in DCM (0.2 mL) were added 2-chloro-5-fluorobenzoic acid (4.2 mg, 0.024 mmol) , DIEA (14 µl, 0.081 mmol) and HATU (12 mg, 0.030 mmol). The reaction was stirred at RT for 2 d, then diluted with H_2O (10 mL), extracted with DCM (3 x 10 mL), and the combined organic phases were concentrated. The crude material was purified by preparative HPLC (5-95% MeCN/H_2O with 0.1% TFA). The combined fractions containing the product were diluted with sat. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to afford the title product (1.2 mg, 10%). MS (apci) m/z = 578.2 (M+H).

[1153] The compounds in **Table X10** were prepared using a similar method as described in **Example 784,** replacing 2-chloro-5-fluorobenzoic acid with the appropriate carboxylic acid.

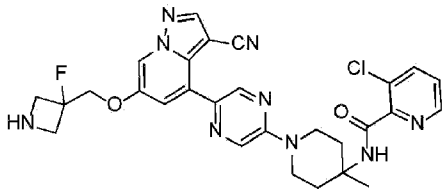
Table X10

Ex. #	Structure	Chemical Name	LCMS m/z
785		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide	561.2, 583.2 (M+H, M+Na)
786		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyrazin-2-yl)-4-	575.2, 597.2 (M+H, M+Na)

Ex. #	Structure	Chemical Name	LCMS m/z
		methylpiperidin-4-yl)-6-methylpicolinamide	
787		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2,3,6-trifluorobenzamide	580.2 (M+H)
788		3-chloro-N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	579.2 (M+H)
789		N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1 ,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-(trifluoromethyl)benzamid e	612.2, 634.2 (M+H, M+Na)

Example 790

[1154]



3-chloro-N-(1-(5 -(3 -cyano-6-((3 -fluoroazetidin-3 -yl)methoxy)pyrazolo [1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

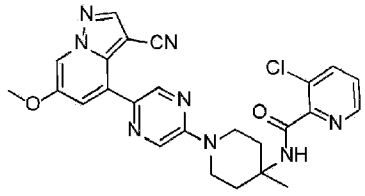
[1155] Step 1: Preparation of tert-butyl 3-(((4-(5-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate. A mixture of 3-chloropicolinic acid (24 mg, 0.15 mmol) and HATU (38 mg, 0.10 mmol) in DCM (2.5 mL) was treated with DIEA (88 µL, 0.50 mmol), then stirred for 30 min at RT before tert-butyl 3-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazm-2-yl)-3-cyanopyrazolo[1,5-a]pyridm-6-yl)oxy)methyl)-3-fluoroazetidme-1-carboxylate **(Intermediate P153;** 27 mg, 0.050 mmol) was added in one portion. After overnight stirring, the reaction was diluted with sat. NH_4Cl (aq) (2 mL) and passed through a Phase Separator frit. The filtrate was purified by silica chromatography (0-100% EtOAc in hexanes) to afford the title compound (34

mg, quantitative yield). LCMS m/z = 676.2 (M+H).

[1156] Step 2: Preparation of (R)-N-(4-benzyl-1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)piperidin-4-yl)-2,3-dihydroxypropanamide. A solution of tert-butyl 3-(((4-(5-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)-3-fluoroazetidine-1-carboxylate (34 mg, 0.050 mmol) in DCM (2 mL) was treated with TFA (2 mL). The reaction was stirred for 20 min at ambient temperature before it was concentrated in vacuo and purified by silica chromatography (0-10% MeOH in DCM with 0.1% NH_4OH) to afford the title product (12 mg, 41%). MS (apci) m/z = 576.2 (M+H).

Example 791

[1157]

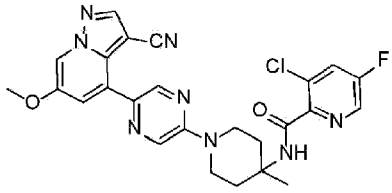
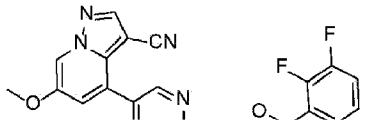


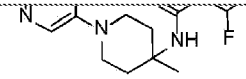
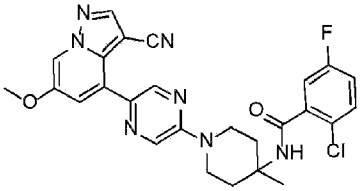
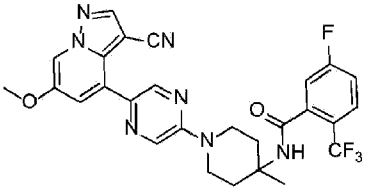
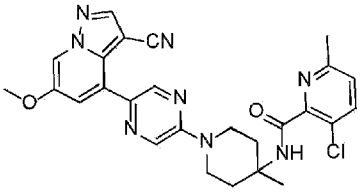
3-chloro-N-(1 -(5 -(3 -cyano-6-methoxypyrazolo [1,5 -a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1158] To a mixture of 3-chloropicolinic acid (15 mg, 0.096 mmol) and HATU (24 mg, 0.064 mmol) in DCM (1.6 mL) was added DIEA (56 µl, 0.32 mmol), then stirred for 30 min before 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) **(Intermediate P174;** 20 mg, 0.032 mmol) was added in one portion. The reaction was stirred for 1 h at RT, then diluted with sat. NH_4Cl (aq) (2 mL) and passed through a Phase Separator frit. The organic filtrate was purified by silica chromatography (0-100% EtOAc in hexanes) to yield the title product as solid (14 mg, 87%). MS (apci) m/z = 503.2 (M+H).

[1159] The compounds in **Table X11** were prepared using a similar method as described in **Example 791,** replacing 3-chloropicolinic acid with the appropriate carboxylic acid.

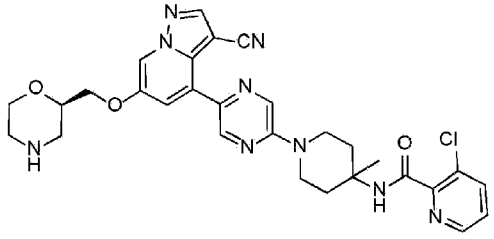
Table **X11**

Ex. #	Structure	Chemical Name	LCMS m/z
792		3-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	521.1 (M+H)
793		N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-2,3,6-trifluorobenzamide	522.1 (M+H)

Ex. #	Structure	Chemical Name	LCMS m/z
			
794		2-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluorobenzamide	520.1 (M+H)
795		N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-(trifluoromethyl)benzamid e	554.2 (M+H)
796		3-chloro-N-(1-(5-(3-cyano-6-methoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-6-methylpicolinamide	517.2 (M+H)

Example 797

[1160]



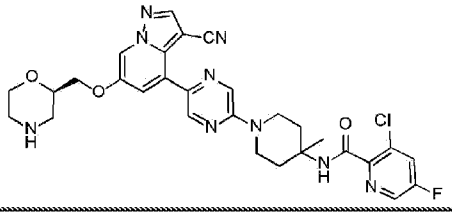
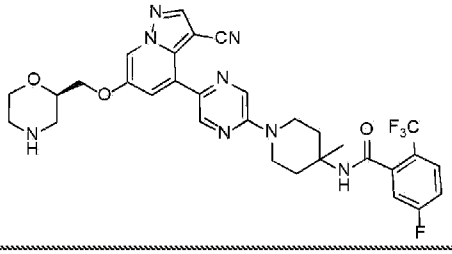
(R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1161] Step 1: Preparation of tert-butyl (R)-2-(((4-(5-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate. The title compound (30 mg, 67%) was prepared according to the procedure described in **Example 791,** replacing 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) with tert-butyl (R)-2-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate P176).** LCMS m/z = 688.2 (M+H).

[1162] Step 2: Preparation of (R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide. To a solution of tert-butyl (R)-2-(((4-(5-(4-(3-chloropicolinamido)-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate (30.2 mg, 0.044 mmol) in DCM (2 mL) was added TFA (1 mL), then stirred for 2 h at RT and then concentrated and redissolved in 4:1 DCM/IPA. The mixture was washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to yield the title product (21.5 mg, 83% yield). MS (apci) m/z = 588.3 (M+H).

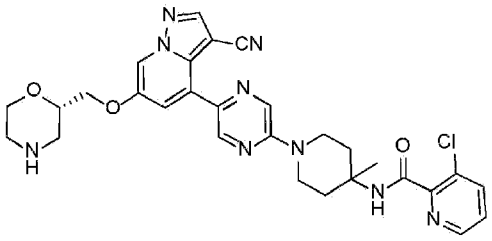
[1163] The compounds in **Table X12** were prepared using a similar method as described in **Example 797,** replacing 3-chloropicolinic acid with the appropriate carboxylic acid in Step 1.

Table X12

Ex. #	Structure	Chemical Name	LCMS m/z
798		(R)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoropicolinamide	606.2 (M+H)
799		(R)-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-(trifluoromethyl)benzamid e	639.2 (M+H)

Example 800

[1164]



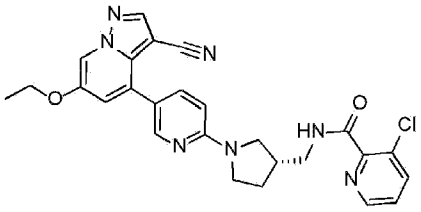
(S)-3-chloro-N-(1-(5-(3-cyano-6-(morpholin-2-ylmethoxy)pyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-4-methylpiperidin-4-yl)picolinamide

[1165] The title compound (50 mg, 74%) was prepared according to the procedure described in **Example 797,** replacing tert-butyl (R)-2-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-

a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate with tert-butyl (S)-2-(((4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-3-cyanopyrazolo[1,5-a]pyridin-6-yl)oxy)methyl)morpholine-4-carboxylate **(Intermediate 177).** LCMS m/z = 688.2 (M+H).

Example 803

[1166]

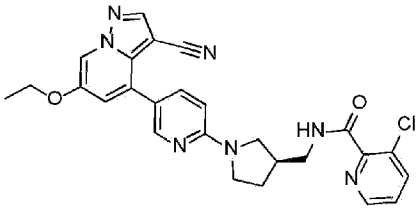


(S)-3-chloro-N-((1-(5 -(3 -cyano-6-ethoxypyrazolo [1,5 -a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)methyl)picolinamide

[1167] The title compound (32.6 mg, 71%) was prepared according to the procedure described in **Example 791,** replacing 4-(5-(4-amino-4-methylpiperidin-1-yl)pyrazin-2-yl)-6-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile bis(2,2,2-trifluoroacetate) with (S)-4-(6-(3-(aminomethyl)pyrrolidin-1-yl)pyridin-3-yl)-6-ethoxypyrazolo[1,5-a]pyridine-3-carbonitrile **(Example 801).** LCMS m/z = 502.2 (M+H).

[1168] The compounds in **Table X13** were prepared according to the procedure described in **Example 803,** coupling the appropriate amine intermediate the corresponding carboxylic acid.

Table X13

Ex. #	Structure	Chemical Name	LCMS m/z	Amine intermediate
806		(R)-3-chloro-N-((1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)pyrrolidin-3-yl)methyl)picolinamide	502.1 (M+H)	**Example 802**

Abbreviations:

18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
ACN	Acetonitrile
AcOH	Acetic Acid
(±)-BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Bis(pinacolato)diboron	4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)
Boc	tert-butyl carboxylate group
Boc-anhydride	di-tert-butyl dicarbonate
Boc-Inp-OH	1-Boc-piperidine-4-carboxylic acid; or Boc-isonipecotic acid
n-BuLi	n-butyllithium or 1-butyllithium

s-BuOH	Sec-Butanol or 2-Butanol
t-BuOH	tert-Butanol or 2-Methylpropan-2-ol
Celite®	Diatomaceous earth; SiO_2
CuI	Copper (I) iodide
$Cu(OAc)_2$	Copper (II) diacetate
d	day, days
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIEA	N,N-Diisopropylethylamine
DI water	Deionized water
dioxane	1,4-dioxane
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DMP	Dess-MartinPeriodinane; 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
EDC-HCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
eq	equivalent
GF/F paper	GF/F glass microfiber filter paper
h	hour, hours
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate or 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	3-[Bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAc	Acetic Acid
isobutyl chloroformate	isobutyl carbonochloridate
isovaleryl chloride	3-methylbutanoyl chloride
iPrOH	Isopropanol
i-PrMgCl	Isopropyl magnesium chloride
KOAc	Potassium Acetate
KOtBu	Potassium tert-Butoxide
K_2HPO_4	Potassium Phosphate, Dibasic
LCMS	Liquid chromatography-mass spectrometry

LiHMDS	Lithium Hexamethyldisilazide; or Lithium bis(trimethylsilyl)amide
MeOH	Methanol
$Me_4N(AcO)_3BH$	Tetramethylammonium Triacetoxyborohydride
min	minute, minutes
MSH	o-(mesitylsulfonyl)hydroxylamine
MTBE	Methyl tert-Butyl Ether
NCS	N-Chlorosuccinimide
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
$NaBH(AcO)_3$	Sodium Triacetoxyborohydride
NH_4OAc	Ammonium Acetate
P1-HCO_3 resin	Stratospheres MP-HCO3
10% Pd/C	Palladium 10 wt. % (dry basis), active carbon, wet, Degussa
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium (0)
$PdCl_2(dppf)•CH_2Cl_2$	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride
	dichloromethane complex
$Pd_2(dba)_3•CHCl_3$	tris(dibenzylideneacetone)dipalladium (0) chloroform complex
$PdCl_2(PPh_3)_2$	Palladium(II)bis(triphenylphosphine) dichloride,
PPh_3	Triphenylphosphine
PPTS	Pyridinium p-toluenesulfonate
PS frit	Biotage® "Isolute® Phase Separators"
PS paper	Whatman® silicone treated Phase Separators filter paper
PVDF (0.45 µm) disc	polyvinylidene difluoride membrane with a 0.45-micron pore size
rt	Room temperature
TBAF	Tetra-n-butylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
Triphosgene	(bis(trichloromethyl) carbonate
Tf-O-Tf	trifluoromethanesulfonic anhydride
TsCl	4-Toluenesulfonyl chloride
X-Phos	dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine

SEQUENCE LISTING

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Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro Glu Glu Val Pro
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Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr Arg Thr Arg Leu
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Val Gln Phe Leu Cys Pro Asn Ile Ser Val Ala Tyr Arg Leu Leu Glu
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Thr Arg Trp Ala Leu Asp Arg Glu Gln Arg Glu Lys Tyr Glu Leu Val
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Ala Val Cys Thr Val His Ala Gly Ala Arg Glu Glu Val Val Met Val
                245                 250                 255

Pro Phe Pro Val Thr Val Tyr Asp Glu Asp Asp Ser Ala Pro Thr Phe
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Glu Asp Thr Val Val Ala Thr Leu Arg Val Phe Asp Ala Asp Val Val
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Cys Asn Cys Phe Pro Glu Glu Glu Lys Cys Phe Cys Glu Pro Glu Asp
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Ile His Cys Tyr His Lys Phe Ala His Lys Pro Pro Ile Ser Ser Ala
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REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- US20120277247A [0001]
- US9297011B [0217]
- US9216172B [0217]
- US20150177246 [0217]
- US20150057335 [0217]
- JP2015109806A [0217]
- CN105255927A [0217]
- EP3037547A1 [0217]
- WO2016141169A [0217]
- US9487491B [0217]
- US20170014413 [0217]
- WO2017146116A [0217]
- WO2017122815A [0217]
- US20140272951 [0219]
- WO2016127074A [0219] [0230] [0254]
- US8629135B [0219] [0230] [0257]
- WO2014141187A [0240]
- WO2014184069A [0240] [0257] [0283]
- WO2015079251A [0240]
- US9150517B [0253]
- US9149464B [0253]
- WO2014075035A [0253]
- US7504509B [0257]
- US8012966B [0257]
- US8299057B [0257] [0258]
- US8399442B [0257]
- US8067434B [0257]
- US8895744B [0257]
- US8937071B [0257]
- US9006256B [0257]
- US9035063B [0257]
- US20150272958A [0257]

- US20150238477A [0257]
- US20140121239A [0257]
- US20160176865A [0257]
- US20110053934A [0257]
- US20110301157A [0257]
- US20100324065A [0257]
- US20090227556A [0257]
- US20090130229A [0257]
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- US20050209195A [0257]
- WO2017043550A [0257]
- WO2017026718A [0257]
- WO2016037578A [0257]
- WO2016038519A [0257]
- WO2016038552A [0257]
- WO2014072220A [0257] [0283]
- WO2012053606A [0257]
- WO2009017838A [0257]
- WO2008031551A [0257]
- WO2007136103A [0257]
- WO2007087245A [0257]
- WO2007057399A [0257]
- WO2005051366A [0257]
- WO2005062795A [0257]
- WO2005044835A [0257]
- US8450322B [0258] [0258]
- US8513263B [0258] [0263]
- US8933084B [0258]
- US8791123B [0258]
- US8946226B [0258]
- US8912194B [0258]
- US20160137654A [0258]
- US20150166564A [0258]
- US20150051222A [0258]
- US20150283132A [0258]
- US20150306086A [0258]
- WO2010033941A [0258] [0258]
- WO2010048314A [0258]
- WO2016077841A [0258]
- WO2011146336A [0258]
- WO2011006074A [0258]
- WO2012158413A [0258]
- WO2014078454A [0258]
- WO2014078417A [0258]
- WO2014078408A [0258]
- WO2014078378A [0258]
- WO2014078372A [0258]
- WO2014078331A [0258]
- WO2014078328A [0258]

- WO2014078325A [0258]
- WO2014078323A [0258]
- WO2014078322A [0258]
- WO2015175788A [0258]
- WO2009013126A [0258]
- WO2013174876A [0258]
- WO2015124697A [0258]
- WO2010058006A [0258]
- WO2015017533A [0258] [0284]
- WO2015112806A [0258] [0283]
- WO2013183578A [0258]
- WO2013074518A [0258]
- US8637516B [0259]
- WO2012034091A [0259]
- US9102671B [0259]
- WO2012116217A [0259]
- US20100297115A [0259]
- WO2009053442A [0259]
- US8642035B [0259]
- WO2009092049A [0259]
- US8691221B [0259]
- WO2006131952A [0259]
- US20100152219A [0260]
- US8114989B [0260]
- WO2006123113A [0260]
- US7615383B [0261]
- US7384632B [0261]
- US6153189A [0261]
- US6027927A [0261]
- US6025166A [0261]
- US5910574A [0261]
- US5877016A [0261]
- US5844092A [0261]
- WO2012034095A [0262]
- US8673347B [0262]
- WO2007022999A [0262]
- US8338417B [0262]
- WO2016027754A [0262]
- US9242977B [0262]
- US20160000783A [0262]
- WO2011133637A [0262]
- US8637256B [0262]
- US7514446B [0283]
- US7863289B [0283]
- US8026247B [0283]
- US8501756B [0283]
- US8552002B [0283]
- US8815901B [0283]
- US8912204B [0283]

- US9260437B [0283]
- US9273051B [0283]
- US20150018336A [0283]
- WO2007002325A [0283]
- WO2007002433A [0283]
- WO2008080001A [0283]
- WO2008079906A [0283]
- WO2008079903A [0283]
- WO2008079909A [0283]
- WO2008080015A [0283]
- WO2009007748A [0283]
- WO2009012283A [0283]
- WO2009143018A [0283]
- WO2009143024A [0283]
- WO2009014637A [0283]
- WO2009152083A [0283]
- WO2010111527A [0283]
- WO2012109075A [0283]
- WO2014194127A [0283]
- WO2007110344A [0283]
- WO2009071480A [0283]
- WO2009118411A [0283]
- WO2010031816A [0283]
- WO2010145998A [0283]
- WO2011092120A [0283]
- WO2012101032A [0283]
- WO2012139930A [0283]
- WO2012143248A [0283]
- WO2012152763A [0283]
- WO2013014039A [0283]
- WO2013102059A [0283]
- WO2013050448A [0283]
- WO2013050446A [0283]
- WO2014019908A [0283]
- WO2016081450A [0284]
- WO2016022569A [0284]
- WO2016011141A [0284]
- WO2016011144A [0284]
- WO2016011147A [0284]
- WO2015191667A [0284]
- WO2012101029A [0284]
- WO2012113774A [0284]
- WO2015191666A [0284]
- WO2015161277A [0284]
- WO2015161274A [0284]
- WO2015108992A [0284]
- WO2015061572A [0284]
- WO2015058129A [0284]
- WO2015057873A [0284]

- WO2015017528A [0284]
- WO2014160521A [0284]
- WO2014011900A [0284]
- WO404490063A [1169]
- WO62406275A [1169]
- WO62447849A [1169]
- WO62491180A [1169]
- WO62531690A [1169]
- WO62566030A [1169]

Non-patent literature cited in the description

- **MULLIGAN, L. M.**Nature Reviews Cancer, 2014, vol. 14, 173-186 [0002]
- **ARIGHI et al.**Cytokine Growth Factor Rev., 2005, vol. 16, 441-67 [0003]
- **MENDIOLA, J. et al.**Org. Process Res. Dev., 2009, vol. 13, 2263-267 [0150]
- **T. W. GREENE et al.**Greene's Protective Groups in Organic SynthesisWiley Interscience20060000 [0186] [0187]
- Protecting Groups in Organic SynthesisJohn Wiley & Sons, Inc.19910000 [0188]
- **BERHMAN REKLIEGMAN RARVIN AMNELSON WE**Nelson Textbook of PediatricsW.B. Saunders Company19960000 [0200]
- **RUDOLPH AM et al.**Rudolph's PediatricsMcGraw-Hill20020000 [0200]
- **AVERY MDFIRST LR**Pediatric MedicineWilliams & Wilkins19940000 [0200]
- Nature Reviews Cancer, 2014, vol. 14, 173-186 [0210]
- **GRUBBS et al.**J. Clin. Endocrinol. Metab., 2015, vol. 100, 788-793 [0217]
- **HALKOVA et al.**Human Pathology, 2015, vol. 46, 1962-1969 [0217]
- **LE ROLLE et al.**Oncotarget, 2015, vol. 6, 3028929-37 [0217]
- **ANTONESCU et al.**Am J Surg Pathol, 2015, vol. 39, 7957-67 [0217]
- **FANG et al.**Journal of Thoracic Oncology, 2016, vol. 11, 2S21-S22 [0217]
- **LEE et al.**Oncotarget, 2016, [0217]
- **SAITO et al.**Cancer Science, 2016, vol. 107, 713-720 [0217]
- **PIRKER et al.**Transl. Lung Cancer Res., 2015, vol. 4, 6797-800 [0217]
- **JOUNG et al.**Histopathology, 2016, vol. 69, 145-53 [0217]
- **KLUGBAUER et al.**Cancer Res., 2000, vol. 60, 247028-32 [0217]
- Journal of Molecular Diagnostics**BASTIEN et al.**Annual Meeting of the Association for Molecular Pathology, Charlotte, NCAnnual Meeting of the Association for Molecular Pathology20160000vol. 18, 1027- [0217]
- **ROSENZWEIG et al.**Pediatr Blood Cancer, 2016, [0217]
- **SU et al.**PLoS One, 2016, vol. 11, 111e0165596- [0217]
- **FUGAZZOLA et al.**Oncogene, 1996, vol. 13, 51093-7 [0217]
- **VELCHETI et al.**J Thorac Oncol., 2017, vol. 12, 2e15-e16 [0217]
- **IYAMA et al.**Thyroid, 2017, [0217]
- **DEMEURE et al.**World J Surg., 2014, vol. 38, 61296-305 [0217]
- **SABARI et al.**OncoscienceAdvance Publications20170000 [0217]
- **LU et al.**Oncotarget, 2017, [0217]
- **HIRSHFIELD et al.**Cancer ResearchMeeting Info: 39th Annual CTRC-AACR San Antonio Breast

Cancer Symposium. San Antonio, TX, United States, 2016, vol. 77, 4 [0217]

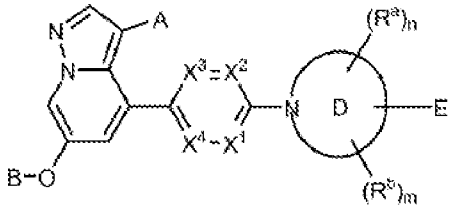
- **MORGENSZTERN et al.**Journal of Thoracic OncologyMeeting Info: 17th World Conference of the International Association for the Study of Lung Cancer, IASLC 2016. Vienna, Austria, 2016, vol. 12, 1S717-S718 [0217]
- **DOGAN et al.**Laboratory InvestigationMeeting Info: 106th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2017. San Antonio, TX, United States, vol. 97, [0217]
- **DOGAN et al.**MODERN PATHOLOGY, 2017, vol. 30, 2323A-323A [0217]
- **REESER et al.**J. Mol. Diagn., 2017, vol. 19, 5682-696 [0217]
- **LU et al.**Oncotarget, 2017, vol. 8, 2845784-45792 [0217]
- **IBRAHIMPASIC et al.**Clin. Cancer Res., 2017, [0217]
- **KLOOSTERMAN et al.**Cancer Res., 2017, vol. 77, 143814-3822 [0217]
- **KRAMPITZ et al.**Cancer, 2014, vol. 120, 1920-1931 [0219]
- **LATTEYER et al.**J. Clin. Endocrinol. Metab., 2016, vol. 101, 31016-22 [0219]
- **SILVA et al.**Endocrine, 2015, vol. 49.2, 366-372 [0219]
- **SCOLLO et al.**Endocr. J., 2016, vol. 63, 187-91 [0219]
- **JOVANOVIC et al.**Prilozi, 2015, vol. 36, 193-107 [0219]
- **QI et al.**Oncotarget, 2015, vol. 6, 3233993-4003 [0219]
- **KIM et al.**ACTA ENDOCRINOLOGICA-BUCHAREST, 2015, vol. 11.2, 189-194 [0219]
- **CECCHIRINI et al.**Oncogene, 1997, vol. 14, 2609-2612 [0219]
- **KARRASCH et al.**Eur. Thyroid J., 2016, vol. 5, 173-7 [0219]
- **SCOLLO et al.**Endocr. J., 2016, vol. 63, 87-91 [0219]
- **HUANG et al.**Mol. Cancer Ther., 2016, [0219] [0230]
- **CARLOMAGNO et al.**Endocr. Rel. Cancer, 2009, vol. 16, 1233-41 [0219] [0230]
- **YOON et al.**J. Med. Chem., 2016, vol. 59, 1358-73 [0219] [0230]
- **CRANSTON et al.**Cancer Res., 2006, vol. 66, 2010179-87 [0219] [0230]
- **KHEIRODDIN et al.**Clin. Lab., 2016, vol. 62, 5871-6 [0219]
- **CEOLIN et al.**PLoS One, 2016, vol. 11, 2e0147840- [0219]
- **NADEZDA et al.**Summer Undergraduate Research Programs (SURP) Student AbstractsUniversity of Oklahoma Health Sciences Center20160000 [0219] [0230]
- **LIU et al.**J. Biol. Chem., 1995, vol. 271, 105309-12 [0219]
- **KATO et al.**Cancer Res., 2002, vol. 62, 2414-22 [0219]
- **GREY et al.**Endocrine Pathology, 2016, [0219]
- **DE ALMEIDA et al.**Endocrine Reviews98th Annual Meeting and Expo of the Endocrine Society, ENDO 2016. Boston, MA, US, 2016, vol. 37, 2 [0219]
- **VANDEN et al.**Annals of Oncology41st European Society for Medical Oncology Congress, ESMP 2016. Copenhagen, Denmark, 2016, vol. 27, [0219]
- **ROMEI et al.**European Thyroid Journal39th Annual Meeting of the European Thyroid Association, ETA 2016. Copenhagen, Denmark, 2016, vol. 5, 175- [0219]
- **LEE et al.**Oncotarget, 2017, vol. 8, 46579-6588 [0219]
- **ZHANG et al.**Laboratory InvestigationMeeting Info: 106th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2017. San Antonio, TX, United States, 2017, vol. 97, 1 [0219]
- **BORECKA et al.**European Journal of CancerMeeting Info: 24th Biennial Congress of the European Association for Cancer Research, EACR 2016. Manchester, United Kingdom, 2016, vol. 61, 1S26- [0219]
- **CORSELLO et al.**Endocrine ReviewsMeeting Info.: 96th Annual Meeting and Expo of the Endocrine-Society, Chicago, IL, USA, June 21-24, 2014, vol. 35, 3 [0219]
- **GAZIZOVA et al.**Endocrine ReviewsMeeting Info.: 96th Annual Meeting and Expo of the Endocrine-Society, Chicago, IL, USA, vol. 35, 3SAT-0304- [0219]

- **PLENKER et al.**Sci. Transl. Med., 2017, vol. 9, 394 [0230]
- **GRIECO et al.**Cell, 1990, vol. 60, 557-63 [0231]
- **GRECO et al.**Q. J. Nucl. Med. Mol. Imaging, 2009, vol. 53, 440-54 [0231]
- **SANTORO et al.**Oncogene, 1996, vol. 12, 1821-6 [0231]
- **JU et al.**Genome Res., 2012, vol. 22, 436-45 [0231]
- **KOHNO et al.**Nature Med., vol. 18, 375-7 [0231]
- **TAKEUCHI et al.**Nature Med., 2012, vol. 18, 378-81 [0231]
- **LIPSON et al.**Nature Med., vol. 18, 382-4 [0231]
- Journal of Thoracic Oncology, 2012, vol. 7, 121872-1876 [0231]
- **DRILON, A.E. et al.**J Clin Oncol, 2015, vol. 33, [0231]
- **SONG EUN-KEE et al.**International Journal of Cancer, 2015, vol. 136, 1967-1975 [0231]
- **DE GROOT et al.**Endocrine Rev., 2006, vol. 27, 535-60 [0232]
- **WELLSSANTORO**Clin. Cancer Res., 2009, vol. 15, 7119-7122 [0232]
- **WOOD et al.**Science, 2007, vol. 318, 1108-13 [0232]
- Jpn. J. Cancer Res., 1995, vol. 86, 1127-30 [0232]
- **BOULAY et al.**Cancer Res., 2008, vol. 68, 3743-51 [0233]
- **PLAZA-MENACHO et al.**Oncogene, 2010, vol. 29, 4648-57 [0233]
- **ITO et al.**Surgery, 2005, vol. 138, 788-94 [0233]
- **GIL et al.**J. Natl. Cancer Inst., 2010, vol. 102, 107-18 [0233]
- **IWAHASHI et al.**Cancer, 2002, vol. 94, 167-74 [0233]
- **PLAZA-MENACHO, I. et al.**Oncogene, 2010, vol. 29, 4648-4657 [0234]
- **ESSEGHIR, S. et al.**Cancer Res., 2007, vol. 67, 11732-11741 [0234]
- **MORANDI, A. et al.**Cancer Res., 2013, vol. 73, 3783-3795 [0234]
- **GATTELLI, A.**EMBO Mol. Med., 2013, vol. 5, 1335-1350 [0234]
- **GOZGIT et al.**AACR Annual Meeting, 2014, [0235]
- **LUO, Y. et al.**Oncogene, 2013, vol. 32, 2037-2047 [0235]
- **SJOBLOM, T. et al.**Science, 2006, 268-274 [0235]
- Cancer Genome Atlas NetworkNature, 2012, vol. 487, 330-337 [0235]
- **ITO, Y et al.**Surgery, 2005, vol. 138, 788-794 [0236]
- **ZENG, Q. et al.**J. Int. Med. Res., 2008, vol. 36, 656-664 [0236]
- **GATTEI, V. et al.**Blood, 1997, vol. 89, 2925-2937 [0237]
- **GATTEI, V. et al.**Ann. Hematol, 1998, vol. 77, 207-210 [0237]
- **CAMOS, M.**Cancer Res., 2006, vol. 66, 6947-6954 [0237]
- **KOHLMANN, A. et al.**J. Clin. Oncol., 2010, vol. 28, 2858-2865 [0237]
- **BALLERINI, P. et al.**Leukemia, 2012, vol. 26, 2384-2389 [0237]
- **NARITA, N. et al.**Oncogene, 2009, vol. 28, 3058-3068 [0238]
- **MULLIGAN, L. M. et al.**Genes Chromosomes Cancer, 1998, vol. 21, 326-332 [0238]
- **FLAVIN, R. et al.**Urol. Oncol., 2012, vol. 30, 900-905 [0238]
- **DAWSON, D. M.**J Natl Cancer Inst, 1998, vol. 90, 519-523 [0238]
- **HOFSTRA, R. M., W. et al.**Hum. Genet., 1996, vol. 97, 362-364 [0239]
- **PETERSEN, S.BOGENMANN, E.**Oncogene, 2004, vol. 23, 213-225 [0239]
- **BRODEUR, G. M.**Nature Ref. Cancer, 2003, vol. 3, 203-216 [0239]
- **BORRELLO, M.G. et al.**Expert Opin. Ther. Targets, 2013, vol. 17, 4403-419 [0240]
- **LOUIS, D.N. et al.**Acta Neuropathol, 2016, vol. 131, 6803-820 [0246]
- J. Med.Chem., 2012, vol. 55, 104872-4876 [0257]
- Cancer Chemother. Pharmacol., 2015, vol. 75, 1131-141 [0259]
- ACS Med. Chem. Lett., 2012, vol. 3, 2140-145 [0259]
- Cancer, 2011, vol. 117, 61321-1391 [0260]
- Cancer Biol Ther, 2015, vol. 16, 3477-483 [0260]

- Cancer Chemother. Pharmacol., 2012, vol. 70, 477-486 [0260]
- Mol. Cancer Ther., 2009, vol. 8, 1818-1827 [0260]
- Int. J. Cancer, 1997, vol. 72, 672-679 [0262]
- Acta Derm. Venereol., 2015, vol. 95, 542-548 [0262]
- PLoS One, 2014, vol. 9, e95628- [0262]
- Expert. Opin. Ther. Pat., 2014, vol. 24, 7731-744 [0262]
- Expert Opin. Ther. Pat., 2009, vol. 19, 3305-319 [0262]
- ACS Med. Chem. Lett., 2015, vol. 6, 5562-567 [0262]
- PLoS One, 2013, vol. 8, 12e83380- [0262]
- Mol. Cell Biochem., 2010, vol. 339, 1-2201-213 [0262]
- J. Med. Chem., 2008, vol. 51, 154672-4684 [0262]
- Mol. Cancer Ther., 2007, vol. 6, 3158- [0262]
- J. Neurochem., 1999, vol. 72, 919-924 [0262]
- IJAE, 2010, vol. 115, 117- [0262]
- J. Carcinog., 2013, vol. 12, 22- [0262]
- **PLOSKER**Drugs, 2011, vol. 71, 1101-108 [0269]
- **RAUSCH et al.**Human Vaccin Immunother, 2014, vol. 10, 113146-52 [0276]
- **KUBLER et al.**J. Immunother Cancer, 2015, vol. 3, 26- [0276]
- **OTT et al.**Nature, 2017, vol. 547, 217-221 [0280]
- **SAHIN et al.**Nature, 2017, vol. 547, 222-226 [0280]
- **KIM et al.**OncoImmunology, 2016, vol. 5, 2e1069940- [0280]
- **ZENG, Q. et al.**J. Int. Med. Res., 2008, vol. 36, 4656-64 [0287]

Patentkrav

1. Forbindelse med formlen I:



I

og farmaceutisk acceptable salte deraf deraf, hvor:

X^1, X^2, X^3 og X^4 uafhængigt er CH, CCH_3, CF eller N, hvor nul, et eller to af X^1, X^2, X^3 og X^4 er N;

A er H, CN, Cl, methyl, ethyl eller cyclopropyl;

B er:

(a) hydrogen,

(b) C1-C6-alkyl eventuelt substitueret med 1-3 fluoros,

(c) hydroxyC2-C6-alkyl-, hvor alkyldelen eventuelt er substitueret med en C3-C6-cycloalkylidenring,

(d) dihydroxy-C3-C6-alkyl-, hvor alkyldelen eventuelt er substitueret med en C3-C6-cycloalkylidenring,

(e) (C1-C6-alkoxy)C1-C6-alkyl- eventuelt substitueret med 1-3 fluoros,

(f) (R^1R^2N)C1-C6-alkyl-, hvor R^1 og R^2 uafhængigt er valgt blandt H, C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros), (C1-C6-alkoxy)C1-C6-alkyl- og (C1-C6-alkoxy)C(=O)-;

(g) $hetAr^1$C1-C3-alkyl-, hvor $hetAr^1$ er en 5-6-leddet heteroarylring med 1-3 ringheteroatomer, uafhængigt valgt blandt N, O og S, og eventuelt er substitueret med en eller flere uafhængigt valgte C1-C6-alkylsubstituenter;

(h) (C3-C6-cycloalkyl)C1-C3 alkyl-,

(i) ($hetCyc^a$)C1-C3-alkyl-,

(j) $hetCyc^a$,

(k) (R^1R^2N)C(=O)C1-C6-alkyl-, hvor R^1 og R^2 uafhængigt er valgt blandt H og C1-C6-alkyl,

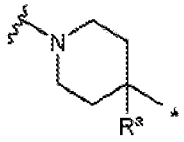
(l) (R^1R^2N)C(=O)-, hvor R^1 og R^2 uafhængigt er valgt blandt H og C1-C6-alkyl, eller

(m) hetCyc^{a}C(=O)C1-C6-alkyl-;
hetCyc^a er en 4-6-leddet heterocyklisk ring med 1-2 ringheteroatomer, uafhængigt valgt blandt N og O og eventuelt substitueret med en eller flere substituenter, der uafhængigt er valgt blandt OH, C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros), hydroxyC1-C6-alkyl, halogen, (C1-C6-alkyl)C(=O)-, C1-C6-alkoxy, oxo og (C1-C6-alkoxy)C(=O)-;
Ring D er
(i) en mættet monocyklisk 4-7-leddet heterocyklisk ring med et ringheteroatom, der er nitrogen,
hvert R^a uafhængigt er C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros), hydroxyC1-C6-alkyl eller (C1-C6-alkoxy)C1-C6-alkyl-;
R^b er (a) hydroxy,
(c) hetCyc^{b}CH$_2$-, hvor hetCyc^b er en 4-6-leddet heterocyklisk ring med 1-2 ringheteroatomer, der uafhængigt er valgt blandt N og O, og hvor hetCyc^b eventuelt er substitueret med C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros),
(e) R^cR^dN- eller
(f) $R^cR^dNCH_2$-;
R^c er hydrogen eller C1-C6-alkyl; og
R^d er hydrogen eller C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros);
n er 0 eller 1;
m er 0 eller 1;
E er:
(d) Ar^{1}C1-C6 alkyl-, hvor alkyldelen eventuelt er substitueret med 1-3 fluoros,
(e) hetAr^{2}C1-C6-alkyl-,
(g) Ar^{1}O-,
(h) hetAr^{2}O-,
(l) Ar^{1}C(=O)NR^g-, hvor R^g er H eller C1-C6-alkyl, eller
(m) hetAr^{2}C(=O)NR^g(CH$_2$)$_p$-, hvor p er 0 eller 1;
Ar^1 er phenyl, eventuelt substitueret med en eller flere substituenter, der uafhængigt er valgt fra gruppen bestående af halogen, CN, C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros), C1-C6-alkoxy (eventuelt substitueret med 1-3 fluoros), (C1-C6-alkoxy)C1-C6-alkyl- (eventuelt substitueret med 1-3 fluoros), C3-C6-cycloalkyl, hydroxyC1-C6-alkyl, (C1-C6-alkyl)SO$_2$-, R^eR^fN- og (R^eR^fN)C1-C6-alkyl-, hvor hvert R^e og R^f uafhængigt er H eller C1-C6-alkyl;

hetAr^2 er en 5-6-leddet heteroarylring med 1-3 ringheteroatomer, der uafhængigt er valgt blandt N, O og S, eller et 9-10-leddet bicyklisk heteroaryl med 1-2 ringnitrogenatomer, hvor hetAr^2 eventuelt er substitueret med en eller flere substituenter, der uafhængigt er valgt fra gruppen bestående af halogen, CN, C1-C6-alkyl (eventuelt substitueret med 1-3 fluoros), C1-C6-alkoxy (eventuelt substitueret med 1-3 fluoros), (C1-C6- alkoxy)C1-C6-alkyl- (eventuelt substitueret med 1-3 fluoros) og hydroxyC1-C6-alkoxy.

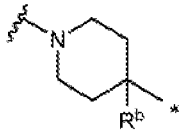
2. Forbindelse ifølge krav 1, hvor hvert R^a er en uafhængigt valgt C1-C6-alkylgruppe.

3. Forbindelse ifølge krav 2, hvor D er



hvor den bølgede linje angiver fastgørelsespunktet mellem Ring D og ringen, der omfatter X^1, X^2, X^3 og X^4, og stjernen angiver fastgørelsespunktet mellem Ring D og E-gruppen.

4. Forbindelse ifølge krav 1, hvor D er



hvor den bølgede linje angiver fastgørelsespunktet mellem Ring D og ringen, der omfatter X^1, X^2, X^3 og X^4, og stjernen angiver fastgørelsespunktet til E-gruppen.

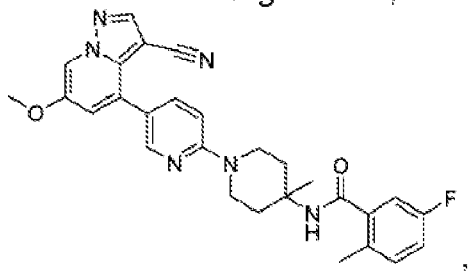
5. Forbindelse ifølge krav 4, hvor E er (d) Ar^1C1-C6-alkyl-, hvor alkyldelen eventuelt er substitueret med 1-3 fluoros, (e) hetAr^{2}C1-C6-alkyl-, (g) Ar^1O-, (h) hetAr^{2}O-, (1) $Ar^1C(=O)NR^g$-, hvor R^g er H eller C1-C6-alkyl, eller (m) hetAr$^2C(=O)NR^g(CH_2)_p$-, hvor p er 0 eller 1.

6. Forbindelse ifølge et af kravene 1-5, hvor B er C1-C6-alkyl, eventuelt substitueret med 1-3 fluoros.

7. Forbindelse ifølge et af kravene 1-6, hvor X^1 er N, og X^2, X^3 og X^4 er CH.

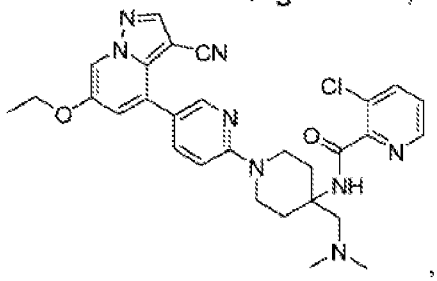
8. Forbindelse ifølge et af kravene 1-7, hvor A er CN.

9. Forbindelse ifølge krav 1, som er



eller et farmaceutisk acceptabelt salt deraf.

10. Forbindelse ifølge krav 1, som er:



eller et farmaceutisk acceptabelt salt deraf.

11. Farmaceutisk sammensætning, omfattende en forbindelse ifølge et af kravene 1-10, eller et farmaceutisk acceptabelt salt deraf, blandet med et farmaceutisk acceptabelt fortyndingsmiddel eller bærestof.

12. Forbindelse ifølge et af kravene 1-10 eller et farmaceutisk acceptabelt salt deraf til anvendelse inden for behandlingen af kræft.

13. Forbindelse eller farmaceutisk acceptabelt salt deraf til anvendelse ifølge krav 12, hvor kræften er en RET-associeret kræft.

14. Forbindelse eller farmaceutisk acceptabelt salt deraf til anvendelse ifølge krav 13, hvor den RET-associerede kræft er en kræft, som har en dysregulering i et RET-gen, et RET-kinase-protein, eller ekspression eller aktivitet eller niveau af en hvilken som helst af de samme, forårsaget af en eller flere punktmutationer i RET-genet.

15. Forbindelse eller farmaceutisk acceptabelt salt deraf til anvendelse ifølge enten krav 13 eller 14, hvor den RET-associerede kræft er valgt fra gruppen bestående af: lungekræft, papillær skjoldbruskkirtelkræft, medullær skjoldbruskkirtelkræft, differentieret skjoldbruskkirtelkræft, tilbagevendende skjoldbruskkirtelkræft, refraktær differentieret skjoldbruskkirtelkræft, multipel endokrin neoplasi type 2A eller 2B (respektivt MEN2A eller MEN2B), phæochromocytom, biskjoldbruskkirtel-hyperplasi, brystkræft, kolorektalkræft, papillært nyrecellekarcinom, ganglioneuromatose af den gastroenteriske slimhinde og livmoderhalskræft.

16. Forbindelse eller farmaceutisk acceptabelt salt deraf til anvendelse ifølge et af kravene 12-15, hvor medikamentet er formuleret til oral indgivelse.