(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2023 (29.06.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/115149 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *A61P 21/00* (2006.01)
C07D 417/14 (2006.01) *A61P 25/00* (2006.01)
A61K 31/437 (2006.01) *A61P 29/00* (2006.01)
A61K 31/4545 (2006.01) *A61P 31/00* (2006.01)
A61K 31/513 (2006.01) *A61P 35/00* (2006.01)
A61K 47/55 (2017.01) *A61P 37/00* (2006.01)
A61P 1/00 (2006.01) *A61P 43/00* (2006.01)
A61P 11/00 (2006.01) *A61P 9/00* (2006.01)
A61P 19/00 (2006.01)

(21) International Application Number:
PCT/AU2022/051575

(22) International Filing Date:
22 December 2022 (22.12.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2021904204 22 December 2021 (22.12.2021) AU

(71) Applicant: **ANAXIS PHARMA PTY LTD** [AU/AU]; Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU).

(72) Inventors: **BRZOZOWSKI, Martin**; c/- Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU). **GARNIER, Jean-Marc Daniel**; c/- Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU). **GARDNER, Christopher**; c/- Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU). **LESSENE, Guillaume Laurent**; c/- Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU). **KERSTEN, Wilco**; c/- Bio21 Institute, 30 Flemington Road, Parkville, Victoria 3052 (AU).

(74) Agent: **FPA PATENT ATTORNEYS PTY LTD**; Level 19, South Tower, 80 Collins Street, Melbourne, Victoria 3000 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: BIFUNCTIONAL SULPHONAMIDE COMPOUNDS

(57) Abstract: This invention relates to compounds of formula (X) and salts, solvates, tautomers, N-oxides, stereoisomers, polymorphs and/or prodrugs thereof. Also disclosed is the use of the compounds of formula (X) to treat necroptosis, and/or inhibit and/or degrade MLKL.

WO 2023/115149 A1

Bifunctional sulphonamide compounds

Cross reference

This application claims priority to Australian provisional patent application no. 2021904204 (filed on 22 December 2021), the entire contents of which are incorporated herein by reference.

Field

The present disclosure relates to bifunctional sulphonamide compounds which treat necroptosis, and/or inhibit and/or degrade mixed lineage kinase domain-like protein (MLKL), and methods for their use.

Background

In many diseases, cell death is mediated through apoptotic and/or necrotic pathways. While much is known about the mechanisms of action that control apoptosis, control of necrosis is not as well understood. Understanding the mechanisms in respect of both necrosis and apoptosis in cells is essential to being able to treat conditions, such as neurodegenerative diseases, stroke, coronary heart disease, kidney disease, liver disease, AIDS and the conditions associated with AIDS.

Cell death has traditionally been categorized as either apoptotic or necrotic based on morphological characteristics (Wyllie *et al.*, *Int. Rev. Cytol*. 68:251, 1980). These two modes of cell death were also initially thought to occur *via* regulated (caspase-dependent) and non-regulated processes, respectively. More recent studies, however, demonstrate that the underlying cell death mechanisms resulting in these two phenotypes are much more complicated and under some circumstances interrelated. Furthermore, conditions that lead to necrosis can occur by either regulated caspase-independent or non-regulated processes.

One regulated caspase-independent cell death pathway with morphological features resembling necrosis, called necroptosis, has been described (Degterev *et al., Nat. Chem. Biol.* 1:112, 2005). This cell death modality can be initiated with various stimuli (e.g., TNF-[alpha] and Fas ligand) and in an array of cell types (e.g., monocytes, fibroblasts, lymphocytes, macrophages, epithelial cells and neurons). Necroptosis may represent a significant contributor to and in some cases predominant mode of cellular demise under pathological conditions involving excessive cell stress, rapid energy loss and massive oxidative species generation, where the highly energy-dependent apoptosis process is not operative.

In WO2015/172203, we reported that particular compounds described in US2005/0085637 have been found to be suitable for inhibiting necroptosis. We also discussed particularly suitable compounds for inhibiting necroptosis in WO2016/127213.

All publications, patents and patent applications that may be cited herein are hereby incorporated by reference in their entirety.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

Summary

As discussed above, certain compounds described in WO2016/127213, US2005/0085637 and WO2015/172203 have been found to be suitable for treating necroptosis-associated diseases. Surprisingly, the inventors of this invention have now discovered that other types of compounds are also suitable for treating necroptosis-associated diseases. Further, and equally surprisingly, the inventors of this invention have now discovered that compounds that degrade mixed lineage kinase domain-like protein (MLKL) can also inhibit necroptosis. The inventors have also found that the compounds described in this invention target and degrade human MLKL.

In one aspect, there is provided a compound according to Formula (X):

MLKLi-L-E3L

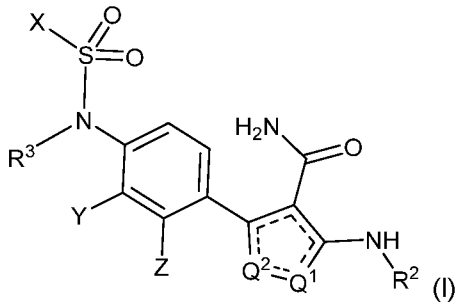
(X)

wherein:

E3L is an E3 ligase binding moiety

L is a linker covalently linking E3L to MLKLi

MLKLi is a radical of formula (I):



(I)

wherein

Q^1 and Q^2 are selected from N and NR^1, wherein when Q^1 is N, Q^2 is NR^1 and when Q^2 is N, Q^1 is NR^1;

R^1 and R^3 are independently selected from H and an optionally substituted C_{1-6}-alkyl;

R^2 is an optionally substituted C_1-C_6-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted C_{1-6}alkyl, optionally substituted haloC_{1-6}alkyl, optionally substituted C_{2-6}alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted C_{1-6}alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, R^4, $-OR^4$ and $-NR^4R^5$ and halo;

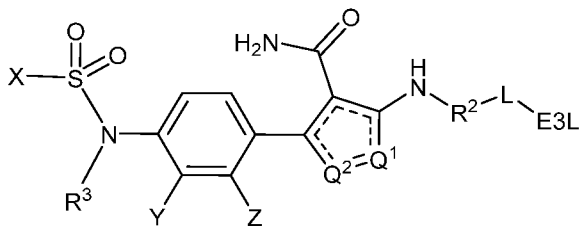
wherein at least one of Y and Z is H;

R^4 is independently selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted C_{1-6}alkylaryl, optionally substituted heterocyclyl, C_{1-6}alkylheterocyclyl, optionally substituted cycloalkyl, optionally

substituted C_{1-6}alkylC_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkylaryl, optionally substituted C_{3-10}cycloalkylheterocyclyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic heterocyclylC_{3-10}cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

R^5 is H or optionally substituted C_{1-6}alkyl.

In some embodiments, the compound of formula (X) is provided as the compound of formula (XI):



E3L is an E3 ligase binding moiety

L is a linker covalently linking E3L to MLKLi

Q^1 and Q^2 are selected from N and NR^1, wherein when Q^1 is N, Q^2 is NR^1 and when Q^2 is N, Q^1 is NR^1;

R^1 and R^3 are independently selected from H and an optionally substituted C_{1-6}-alkyl;

R^2 is an optionally substituted C_1-C_6-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted C_{1-6}alkyl, optionally substituted haloC_{1-6}alkyl, optionally substituted C_{2-6}alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted C_{1-6}alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, R^4, $-OR^4$ and $-NR^4R^5$ and halo;

wherein at least one of Y and Z is H;

R^4 is independently selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted C_{1-6}alkylaryl, optionally substituted heterocyclyl, C_{1-6}alkylheterocyclyl, optionally substituted cycloalkyl, optionally

substituted C_{1-6}alkylC_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkylaryl, optionally substituted C_{3-10}cycloalkylheterocyclyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic heterocyclylC_{3-10}cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

R^5 is H or optionally substituted C_{1-6}alkyl.

In any aspect or embodiment described herein, the compound of the invention may be provided in the form of a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

The inventors have found that compounds of Formula (I) are selective degraders of MLKL. Degradation of MLKL may be preferred to inhibition of MLKL in some instances as degradation results in a loss of function of the degraded protein, while the effects of inhibition last only as long as the inhibitor interacts with the protein.

In some embodiments, the compound of the invention is selected from any of compounds 1001-1014, 1016-1037, 1039-1053 and 1055-1060.

In some embodiments, the compound of the invention is selected from any of compounds 1001-1014 and 1016-1036 described herein, preferably from any of compounds 1001-1014, 1016-1030, 1032-1033 and 1036, more preferably from any one of compounds 1001, 1005, 1007, 1013, 1016, 1019-1021 and 1023-1030.

In some embodiments, the compound of the invention comprises a radical of compounds 1-320 described herein, preferably a radical of any of compounds 9, 14, 21-22, 24-25, 34, 39, 41-43, 53, 62-63, 66, 68, 71, 84, 88, 90, 92-93, 101-102, 108, 113, 115, 123-124, 127-128, 139-140, 143-144, 146, 150, 152-158, 160-166, 169-171, 175-176, 181, 188, 190-191, 194, 196, 198-199, 202, 208, 222-223, 229, 233-235, 238, 242, 245-246, 248-249, 251-253, 256, 259-260, 262, 264-266, 271, 273-279, 281-286, 288-299, 301-312, 314 and 316-320.

In another aspect, there is provided a medicament comprising a compound of the invention, and the use of the compound of the invention in the preparation of a medicament. That medicament may be for treating necroptosis; the medicament may also be for degrading MLKL.

In another aspect, there is provided a pharmaceutical composition comprising a compound of the invention and optionally a pharmaceutically acceptable excipient.

In another aspect, there is provided a method of treating necroptosis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

In another aspect, there is provided a method of degrading MLKL, comprising contacting a cell with a compound of the invention.

In another aspect, there is provided a compound of the invention for use in treating necroptosis, and for use in degrading MLKL.

Any embodiment herein shall be taken to apply *mutatis mutandis* to any other embodiment unless specifically stated otherwise.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

Definitions

Unless otherwise herein defined, the following terms will be understood to have the general meanings which follow.

The term "C_{1-6} alkyl" refers to optionally substituted straight chain or branched chain hydrocarbon groups having from 1 to 6 carbon atoms. Examples include methyl (Me), ethyl (Et), propyl (Pr), isopropyl (i-Pr), butyl (Bu), isobutyl (i-Bu), sec-butyl (s-Bu), tert-butyl (t-Bu), pentyl, neopentyl, hexyl and the like. Unless the context requires otherwise, the term "C_{1-6}alkyl" also encompasses alkyl groups containing one less hydrogen atom such that the group is attached *via* two positions i.e. divalent. "C_{1-4}alkyl" and "C_{1-3}alkyl" including methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and tert-butyl are preferred with methyl being particularly preferred.

The term "C_{2-6}alkenyl" refers to optionally substituted straight chain or branched chain hydrocarbon groups having at least one double bond of either *E* or *Z* stereochemistry where applicable and 2 to 6 carbon atoms. Examples include vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl. Unless the context requires otherwise, the

term "C_{2-6}alkenyl" also encompasses alkenyl groups containing one less hydrogen atom such that the group is attached *via* two positions i.e. divalent. "C_{2-4}alkenyl" and "C_{2-3}alkenyl" including ethenyl, propenyl and butenyl are preferred with ethenyl being particularly preferred.

The term "C_{2-6}alkynyl" refers to optionally substituted straight chain or branched chain hydrocarbon groups having at least one triple bond and 2 to 6 carbon atoms. Examples include ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl and the like. Unless the context indicates otherwise, the term "C_{2-6}alkynyl" also encompasses alkynyl groups containing one less hydrogen atom such that the group is attached *via* two positions i.e. divalent. C_{2-3}alkynyl is preferred.

The term "C_{3-10}cycloalkyl" refers to non-aromatic cyclic groups having from 3 to 10 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. It will be understood that cycloalkyl groups may be saturated such as cyclohexyl or unsaturated such as cyclohexenyl. C_{3-6}cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl are preferred. Cycloalkyl groups also include polycyclic carbocycles and include fused, bridged and spirocyclic systems.

The terms "hydroxy" and "hydroxyl" refer to the group -OH.

The term "oxo" refers to the group =O.

The term "C_{1-6}alkoxy" refers to an alkyl group as defined above covalently bound *via* an O linkage containing 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy and pentoxy. "C_{1-4}alkoxy" and "C_{1-3}alkoxy" including methoxy, ethoxy, propoxy and butoxy are preferred with methoxy being particularly preferred.

The terms "haloC_{1-6}alkyl" and "C_{1-6}alkylhalo" refer to a C_{1-6}alkyl which is substituted with one or more halogens. HaloC_{1-3}alkyl groups are preferred, such as for example, $-CH_2CF_3$, and $-CF_3$.

The terms "haloC_{1-6}alkoxy" and "C_{1-6}alkoxyhalo" refer to a C_{1-6}alkoxy which is substituted with one or more halogens. C_{1-3}alkoxyhalo groups are preferred, such as for example, $-OCF_3$.

The term "carboxylate" or "carboxyl" refers to the group -COO- or -COOH.

The term “ester” refers to a carboxyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group (“carboxylC_{1-6}alkyl” or “alkylester”), an aryl or aralkyl group (“arylester” or “aralkylester”) and so on. CO_2C_{1-3}alkyl groups are preferred, such as for example, methylester (CO_2Me), ethylester (CO_2Et) and propylester (CO_2Pr) and includes reverse esters thereof (e.g. -OC(O)Me, -OC(O)Et and -OC(O)Pr).

The terms “cyano” and “nitrile” refer to the group -CN.

The term “nitro” refers to the group -NO_2.

The term “amino” refers to the group -NH_2.

The term “substituted amino” refers to an amino group having at least one hydrogen replaced with, for example a C_{1-6}alkyl group (“C_{1-6}alkylamino”), an aryl or aralkyl group (“arylamino”, “aralkylamino”) and so on. Substituted amino groups include “monosubstituted amino” (or “secondary amino”) groups, which refer to an amino group having a single hydrogen replaced with, for example a C_{1-6}alkyl group, an aryl or aralkyl group and so on. Preferred secondary amino groups include C_{1-3}alkylamino groups, such as for example, methylamino (NHMe), ethylamino (NHEt) and propylamino (NHPr). Substituted amino groups also include “disubstituted amino” (or “tertiary amino”) groups, which refer to amino groups having both hydrogens replaced with, for example C_{1-6}alkyl groups, which may be the same or different (“dialkylamino”), aryl and alkyl groups (“aryl(alkyl)amino”) and so on. Preferred tertiary amino groups include di(C_{1-3}alkyl)amino groups, such as for example, dimethylamino (NMe_2), diethylamino (NEt_2), dipropylamino (NPr_2) and variations thereof (e.g. N(Me)(Et) and so on).

The term “aldehyde” refers to the group -C(=O)H.

The terms “acyl” and “acetyl” refers to the group –C(O)CH_3.

The term “ketone” refers to a carbonyl group which may be represented by –C(O)-.

The term “substituted ketone” refers to a ketone group covalently linked to at least one further group, for example, a C_{1-6}alkyl group (“C_{1-6}alkylacyl” or “alkylketone” or “ketoalkyl”), an aryl group (“arylketone”), an aralkyl group (“aralkylketone) and so on. C_{1-3}alkylacyl groups are preferred.

The term “amido” or “amide” refers to the group -C(O)NH_2.

The term “substituted amido” or “substituted amide” refers to an amido group having a hydrogen replaced with, for example a C_{1-6}alkyl group (“C_{1-6}alkylamido” or

"C_{1-6}alkylamide"), an aryl ("arylamido"), aralkyl group ("aralkylamido") and so on. C_{1-3}alkylamide groups are preferred, such as for example, methylamide (-C(O)NHMe), ethylamide (-C(O)NHEt) and propylamide (-C(O)NHPr) and includes reverse amides thereof (e.g. -NHMeC(O)-, -NHEtC(O)- and –NHPrC(O)-).

The term "disubstituted amido" or "disubstituted amide" refers to an amido group having the two hydrogens replaced with, for example a C_{1-6}alkyl group ("di(C_{1-6}alkyl)amido" or "di(C_{1-6}alkyl)amide"), an aralkyl and alkyl group ("alkyl(aralkyl)amido") and so on. Di(C_{1-3}alkyl)amide groups are preferred, such as for example, dimethylamide (-C(O)NMe_2), diethylamide (-C(O)NEt_2) and dipropylamide ((-C(O)NPr_2) and variations thereof (e.g. -C(O)N(Me)Et and so on) and includes reverse amides thereof (e.g. –N(Me)C(O)Me, -N(Et)C(O)Et, -N(Pr)C(O)Pr and –N(Me)C(O)Et).

The term "thiol" refers to the group -SH.

The term "C_{1-6}alkylthio" refers to a thiol group having the hydrogen replaced with a C_{1-6}alkyl group. C_{1-3}alkylthio groups are preferred, such as for example, thiolmethyl, thiolethyl and thiolpropyl.

The terms "thioxo" refer to the group =S.

The term "sulfinyl" refers to the group -S(=O)H.

The term "substituted sulfinyl" or "sulfoxide" refers to a sulfinyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group ("C_{1-6}alkylsulfinyl" or "C_{1-6}alkylsulfoxide"), an aryl ("arylsulfinyl"), an aralkyl ("aralkyl sulfinyl") and so on. C_{1-3}alkylsulfinyl groups are preferred, such as for example, -SOmethyl, -SOethyl and -SOpropyl.

The term "sulfonyl" refers to the group -SO_2H.

The term "substituted sulfonyl" refers to a sulfonyl group having the hydrogen replaced with, for example a C_{1-6}alkyl group ("sulfonylC_{1-6}alkyl"), an aryl ("arylsulfonyl"), an aralkyl ("aralkylsulfonyl") and so on. SulfonylC_{1-3}alkyl groups are preferred, such as for example, -SO_2Me, -SO_2Et and -SO_2Pr.

The terms "sulfonylamido", "sulfonamido", "sulfonamide", "sulphonylamido", "sulphonamido", "sulphonylamide" or "sulphonamide" refer to the group -SO_2NH_2.

The terms "substituted sulfonamido", "substituted sulfonamide", "substituted sulphonamido" or "substituted sulphonamide" refer to an sulfonylamido group having

a hydrogen replaced with, for example a C_{1-6}alkyl group (e.g. "sulfonylamidoC_{1-6}alkyl"), an aryl ("arylsulfonamide"), aralkyl ("aralkylsulfonamide") and so on. SulfonylamidoC_{1-3}alkyl groups are preferred, such as for example, $-SO_2NHMe$, $-SO_2NHEt$ and $-SO_2NHPr$ and includes reverse sulfonamides thereof (e.g. $-NHSO_2Me$, $-NHSO_2Et$ and $-NHSO_2Pr$). In some embodiments, the alkylsulfonamides may be optionally substituted, for example with a halo group.

The terms "disubstituted sulfonamido", "disubstituted sulfonamide", "disubstituted sulphonamido" or "disubstituted sulphonamide" refers to an sulfonylamido group having the two hydrogens replaced with, for example a C_{1-6}alkyl group, which may be the same or different ("sulfonylamidodi(C_{1-6}alkyl)"), an aralkyl and alkyl group ("sulfonamido(aralkyl)alkyl") and so on. Sulfonylamidodi(C_{1-3}alkyl) groups are preferred, such as for example, $-SO_2NMe_2$, $-SO_2NEt_2$ and $-SO_2NPr_2$ and variations thereof (e.g. $-SO_2N(Me)Et$ and so on) and includes reserve sulfonamides thereof (e.g. $–N(Me)SO_2Me$ and so on).

The term "sulfate" refers to the group $OS(O)_2OH$ and includes groups having the hydrogen replaced with, for example a C_{1-6}alkyl group ("alkylsulfates"), an aryl ("arylsulfate"), an aralkyl ("aralkylsulfate") and so on. C_{1-3}sulfates are preferred, such as for example, $OS(O)_2OMe$, $OS(O)_2OEt$ and $OS(O)_2OPr$.

The term "sulfonate" refers to the group SO_3H and includes groups having the hydrogen replaced with, for example a C_{1-6}alkyl group ("alkylsulfonate"), an aryl ("arylsulfonate"), an aralkyl ("aralkylsulfonate") and so on. C_{1-3}sulfonates are preferred, such as for example, SO_3Me, SO_3Et and SO_3Pr.

The term "aryl" refers to a carbocyclic (non-heterocyclic) aromatic ring or mono-, bi- or tri-cyclic ring system. Poly-cyclic ring systems may be referred to as "aryl" provided at least 1 of the rings within the system is aromatic. The aromatic ring or ring system is generally composed of 6 to 10 carbon atoms. Examples of aryl groups include but are not limited to phenyl, biphenyl, naphthyl and tetrahydronaphthyl. 6-membered aryls such as phenyl are preferred. The term "alkylaryl" refers to C_{1-6}alkylaryl such as benzyl.

The term "alkoxyaryl" refers to C_{1-6}alkyloxyaryl such as benzyloxy.

The term "heterocyclyl" refers to a moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound which moiety has from 3 to 10 ring atoms (unless otherwise specified), of which 1, 2, 3 or 4 are ring heteroatoms with each heteroatom being independently selected from O, S and N. Heterocyclyl groups

include monocyclic and polycyclic (such as bicyclic) ring systems, such as fused, bridged and spirocyclic systems, provided at least one of the rings of the ring system contains at least one heteroatom.

In this context, the prefixes 3-, 4-, 5-, 6-, 7-, 8-, 9- and 10- membered denote the number of ring atoms, or range of ring atoms, whether carbon atoms or heteroatoms. For example, the term "3-10 membered heterocylyl", as used herein, pertains to a heterocyclyl group having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms. Examples of heterocylyl groups include 5-6-membered monocyclic heterocyclyls and 9-10 membered fused bicyclic heterocyclyls.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those containing one nitrogen atom such as aziridine (3-membered ring), azetidine (4-membered ring), pyrrolidine (tetrahydropyrrole), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) or pyrrolidinone (5-membered rings) , piperidine, dihydropyridine, tetrahydropyridine (6-membered rings), and azepine (7-membered ring); those containing two nitrogen atoms such as imidazoline, pyrazolidine (diazolidine), imidazoline, pyrazoline (dihydropyrazole) (5-membered rings), piperazine (6-membered ring); those containing one oxygen atom such as oxirane (3-membered ring), oxetane (4-membered ring), oxolane (tetrahydrofuran), oxole (dihydrofuran) (5-membered rings), oxane (tetrahydropyran), dihydropyran, pyran (6-membered rings), oxepin (7-membered ring); those containing two oxygen atoms such as dioxolane (5-membered ring), dioxane (6-membered ring), and dioxepane (7-membered ring); those containing three oxygen atoms such as trioxane (6-membered ring); those containing one sulfur atom such as thiirane (3-membered ring), thietane (4-membered ring), thiolane (tetrahydrothiophene) (5-membered ring), thiane (tetrahydrothiopyran) (6-membered ring), thiepane (7-membered ring); those containing one nitrogen and one oxygen atom such as tetrahydrooxazole, dihydrooxazole, tetrahydroisoxazole, dihydroisoxazole (5-membered rings), morpholine, tetrahydrooxazine, dihydrooxazine, oxazine (6-membered rings); those containing one nitrogen and one sulfur atom such as thiazoline, thiazolidine (5-membered rings), thiomorpholine (6-membered ring); those containing two nitrogen and one oxygen atom such as oxadiazine (6-membered ring); those containing one oxygen and one sulfur such as: oxathiole (5-membered ring) and oxathiane (thioxane) (6-membered ring); and those containing one nitrogen, one oxygen and one sulfur atom such as oxathiazine (6-membered ring).

Heterocyclyls encompass aromatic heterocyclyls and non-aromatic heterocyclyls. Such groups may be substituted or unsubstituted.

The term “aromatic heterocyclyl” may be used interchangeably with the term “heteroaromatic” or the term “heteroaryl” or “hetaryl”. The heteroatoms in the aromatic heterocyclyl group may be independently selected from N, S and O. The aromatic heterocyclyl groups may comprise 1, 2, 3, 4 or more ring heteroatoms. In the case of fused aromatic heterocyclyl groups, only one of the rings must contain a heteroatom and not all rings must be aromatic.

“Heteroaryl” is used herein to denote a heterocyclic group having aromatic character and embraces aromatic monocyclic ring systems and polycyclic (e.g. bicyclic) ring systems containing one or more aromatic rings. The term aromatic heterocyclyl also encompasses pseudoaromatic heterocyclyls. The term “pseudoaromatic” refers to a ring system which is not strictly aromatic, but which is stabilized by means of delocalization of electrons and behaves in a similar manner to aromatic rings. The term aromatic heterocyclyl therefore covers polycyclic ring systems in which all of the fused rings are aromatic as well as ring systems where one or more rings are non-aromatic, provided that at least one ring is aromatic. In polycyclic systems containing both aromatic and non-aromatic rings fused together, the group may be attached to another moiety by the aromatic ring or by a non-aromatic ring.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or two fused five membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. The heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Aromatic heterocyclyl groups may be 5-membered or 6-membered mono-cyclic aromatic ring systems.

Examples of 5-membered monocyclic heteroaryl groups include but are not limited to furanyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl (including 1,2,3 and 1,2,4 oxadiazolyls and furazanyl i.e. 1,2,5-oxadiazolyl), thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl (including 1,2,3, 1,2,4 and 1,3,4 triazolyls), oxatriazolyl, tetrazolyl, thiadiazolyl (including 1,2,3 and 1,3,4 thiadiazolyls) and the like.

Examples of 6-membered monocyclic heteroaryl groups include but are not limited to pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, oxazinyl, dioxinyl, thiazinyl, thiadiazinyl and the like. Examples of 6-membered aromatic heterocyclyls containing nitrogen include pyridyl (1 nitrogen), pyrazinyl, pyrimidinyl and pyridazinyl (2 nitrogens).

Aromatic heterocyclyl groups may also be bicyclic or polycyclic heteroaromatic ring systems such as fused ring systems (including purine, pteridinyl, napthyridinyl, 1H thieno[2,3-c]pyrazolyl, thieno[2,3-b]furyl and the like) or linked ring systems (such as oligothiophene, polypyrrole and the like). Fused ring systems may also include aromatic 5-membered or 6-membered heterocyclyls fused to carbocyclic aromatic rings such as phenyl, naphtyl, indenyl, azulenyl, fluorenyl, anthracenyl and the like, such as 5-membered aromatic heterocyclyls containing nitrogen fused to phenyl rings, 5-membered aromatic heterocyclyls containing 1 or 2 nitrogens fused to phenyl ring.

A bicyclic heteroaryl group may be, for example, a group selected from: a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; b) a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; c) a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; d) a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; e) a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; f) an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; g) an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; h) an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; i) a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; j) an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms; k) a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; l) a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; m) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and n) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole (e.g. imidazo[2,1-b]thiazole) and imidazoimidazole (e.g. imidazo[1,2-a]imidazole).

Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzothiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine (e.g. pyrazolo[1 ,5-a]pyrimidine), benzodioxole and pyrazolopyridine (e.g. pyrazolo[1,5-a]pyridine) groups. A further example of a six membered ring fused to a five membered ring is a pyrrolopyridine group such as a pyrrolo[2,3-b]pyridine group.

Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzothiophene, dihydrobenzofuran, 2,3-dihydro- benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline, isoindoline and indane groups.

Examples of aromatic heterocyclyls fused to carbocyclic aromatic rings may therefore include but are not limited to benzothiophenyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzimidazolyl, indazolyl, benzoxazolyl, benzisoxazolyl, isobenzoxazoyl, benzothiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzotriazinyl, phthalazinyl, carbolinyl and the like.

The term “non-aromatic heterocyclyl” encompasses optionally substituted saturated and unsaturated rings which contain at least one heteroatom selected from the group consisting of N, S and O. The ring may contain 1, 2 or 3 heteroatoms. The ring may be a monocyclic ring or part of a polycyclic ring system. Polycyclic ring systems include fused rings and spirocycles. Not every ring in a non-aromatic heterocyclic polycyclic ring system must contain a heteroatom, provided at least one ring contains one or more heteroatoms.

Non-aromatic heterocyclyls may be 3-7 membered mono-cyclic rings.

Examples of 5-membered non-aromatic heterocyclyl rings include 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyrazolidinyl, 2-pyrazolidinyl, 3-pyrazolidinyl, imidazolidinyl, 3-dioxalanyl, thiazolidinyl, isoxazolidinyl, 2-imidazolinyl and the like.

Examples of 6-membered non-aromatic heterocyclyls include piperidinyl, piperidinonyl, pyranyl, dihyrdopyranyl, tetrahydropyranyl, 2H pyranyl, 4H pyranyl, thianyl, thianyl oxide, thianyl dioxide, piperazinyl, diozanyl, 1,4-dioxinyl, 1,4-dithianyl, 1,3,5-triozalanyl, 1,3,5-trithianyl, 1,4-morpholinyl, thiomorpholinyl, 1,4-oxathianyl, triazinyl, 1,4-thiazinyl and the like.

Examples of 7-membered non-aromatic heterocyclyls include azepanyl, oxepanyl, thiepanyl and the like.

Non-aromatic heterocyclyl rings may also be bicyclic heterocyclyl rings such as linked ring systems (for example uridinyl and the like) or fused ring systems. Fused ring systems include non-aromatic 5-membered, 6-membered or 7-membered heterocyclyls fused to carbocyclic aromatic rings such as phenyl, napthyl, indenyl, azulenyl, fluorenyl, anthracenyl and the like. Examples of non-aromatic 5-membered, 6-membered or 7-membered heterocyclyls fused to carbocyclic aromatic rings include indolinyl, benzodiazepinyl, benzazepinyl, dihydrobenzofuranyl and the like.

The term “halo” refers to fluoro, chloro, bromo or iodo.

Unless otherwise defined, the term “optionally substituted” or “optional substituent” as used herein refers to a group which may or may not be further substituted with 1, 2, 3, 4 or more groups, preferably 1, 2 or 3, more preferably 1 or 2 groups selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, hydroxyl, oxo, C_{1-6}alkoxy, aryloxy, C_{1-6}alkoxyaryl, halo, C_{1-6}alkylhalo (such as CF_3), C_{1-6}alkoxyhalo (such as OCF_3), carboxyl, esters, cyano, nitro, amino, substituted amino, disubstituted amino, acyl, ketones, substituted ketones, amides, aminoacyl, substituted amides, disubstituted amides, thiol, alkylthio, thioxo, sulfates, sulfonates, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfonylamides, substituted sulfonamides, disubstituted sulfonamides, aryl, arC_{1-6}alkyl, heterocyclyl and heteroaryl wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclyl and groups containing them may be further optionally substituted. Optional substituents in

the case of heterocycles containing N may also include but are not limited to C_{1-6}alkyl i.e. N-C_{1-3}alkyl, more preferably methyl particularly N-methyl.

For optionally substituted "C_{1-6}alkyl", "C_{2-6}alkenyl" and "C_{2-6}alkynyl", the optional substituent or substituents are preferably selected from halo, aryl, heterocyclyl, C_{3-8}cycloalkyl, C_{1-6}alkoxy, hydroxyl, oxo, aryloxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxyl and carboxyl. Each of these optional substituents may also be optionally substituted with any of the optional substituents referred to above, where nitro, amino, substituted amino, cyano, heterocyclyl (including non-aromatic heterocyclyl and heteroaryl), C_{1-6}alkyl, C_{2-6}akenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, halo, hydroxyl and carboxyl are preferred.

It will be understood that suitable derivatives of aromatic heterocyclyls containing nitrogen include N-oxides thereof.

In the case of hybrid naming of substituent radicals describing two moieties that may both form a bond attaching the radical to the rest of the compound, such as alkylamino and alkylaryl, no direction in the order of groups is intended, so the point of attachment may be to any of the moieties included in the hybrid radical. For example, the terms "alkylaryl" and "arylalkyl", are intended to refer to the same group and the point of attachment may be *via* the alkyl or the aryl moiety (or both in the case of diradical species). The direction of attachment of such a hybrid radical may be denoted by inclusion of a bond, for example, "-alkylaryl" or "arylalkyl-" denotes that the point of attachment of the radical to the rest of the compound is *via* the alkyl moiety, and "alkylaryl-" or "-arylalkyl" denotes that the point of attachment is *via* the aryl moiety.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a salt" may include a plurality of salts and a reference to "at least one heteroatom" may include one or more heteroatoms, and so forth.

The term "and/or" can mean "and" or "or".

The term "(s)" following a noun contemplates the singular or plural form, or both.

Various features of the invention are described with reference to a certain value, or range of values. These values are intended to relate to the results of the various appropriate measurement techniques, and therefore should be interpreted as including a margin of error inherent in any particular measurement technique. Some of the values referred to herein are denoted by the term "about" to at least in part account for this variability. The term "about", when used to describe a value, may mean an amount within ±25%, ±10%, ±5%, ±1% or ±0.1% of that value.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Detailed description of embodiments

The invention provides a compound of formula (X):

MLKLi–L–E3L

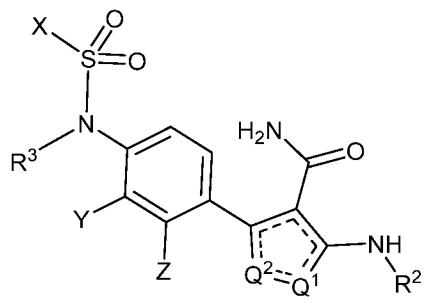
(X)

wherein

E3L is an E3 ligase binding moiety;

L is a linker covalently linking MLKLi to E3L; and

MLKLi is a radical of formula (I)



(I)

wherein

Q^1 and Q^2 are selected from N and NR^1, wherein when Q^1 is N, Q^2 is NR^1 and when Q^2 is N, Q^1 is NR^1;

R^1 and R^3 are independently selected from H and an optionally substituted C_{1-6}-alkyl;

R^2 is an optionally substituted C_{1-6}-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted C_{1-6}alkyl, optionally substituted haloC_{1-6}alkyl, optionally substituted C_{2-6}alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted C_{1-6}alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, R^4, $-OR^4$, $-NR^4R^5$ and halo;

wherein at least one of Y and Z is H;

R^4 is selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted C_{1-6}alkylaryl, optionally substituted heterocyclyl, optionally substituted C_{1-6}alkylheterocyclyl, optionally substituted cycloalkyl, optionally substituted C_{1-6}alkylC_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkylaryl, optionally substituted C_{3-10}cycloalkylheterocyclyl, optionally substituted C_{3-10}cycloalkylC_{3-10}cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic heterocyclylC_{3-10}cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

R^5 is H or optionally substituted C_{1-6}alkyl,

or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

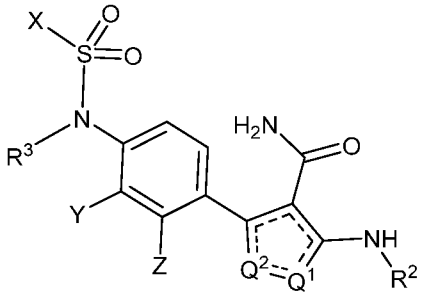
MLKLi

In the compounds of the invention, the MLKLi is a radical of a compound of Formula (I).

Various embodiments of the compound of formula (I) are described below. It will be appreciated that in the compound of formula (X) of the invention, any of the

compounds described herein capable of MLKL binding may be included as the MLKLi moiety.

In some embodiments, there is provided a compound of formula (I)



(I)

wherein

Q^1 and Q^2 are selected from N and NR^1, wherein when Q^1 is N, Q^2 is NR^1 and when Q^2 is N, Q^1 is NR^1;

R^1 and R^3 are independently selected from H and an optionally substituted $C_{1\text{-}6}$-alkyl;

R^2 is an optionally substituted C_1-C_6-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted halo$C_{1\text{-}6}$alkyl, optionally substituted $C_{2\text{-}6}$alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted $C_{1\text{-}6}$alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, R^4, $-OR^4$, $-NR^4R^5$ and halo;

wherein at least one of Y and Z is H;

R^4 is independently selected from optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted aryl, optionally substituted $C_{1\text{-}6}$alkylaryl, optionally substituted heterocyclyl, optionally substituted $C_{1\text{-}6}$alkylheterocyclyl, optionally substituted cycloalkyl, optionally substituted $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, optionally substituted $C_{3\text{-}10}$cycloalkylaryl, optionally substituted $C_{3\text{-}10}$cycloalkylheterocyclyl, optionally substituted $C_{3\text{-}10}$cycloalkyl$C_{3\text{-}10}$cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic

heterocyclylC_{3-10}cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

R^5 is H or optionally substituted C_{1-6}alkyl.

In some embodiments, X is selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, -$(CH_2)_n$aryl, -$(CH_2)_n$cycloalkyl, and -$N(C_{1-4}alkyl)_2$;

wherein

n is 1 or 2, and

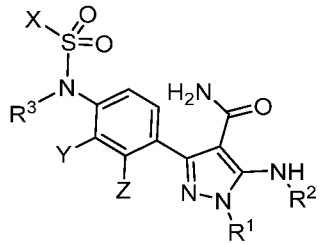
each alkyl and alkynyl is optionally substituted with one or more groups selected from halo, nitrile, -OR^6, -$N(R^7)R^8$;

R^6, R^7 and R^8 are independently selected from H, C_{1-6}alkyl and haloC_{1-6}alkyl, and

wherein each aryl and cycloalkyl is optionally substituted with one or more groups that are independently selected from halo, nitrile, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl and haloC_{1-4}alkoxy.

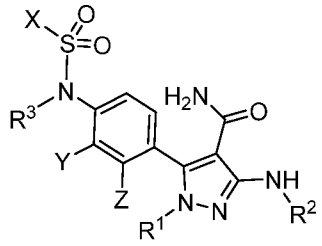
It will be appreciated that ≡ denotes a single or a double bond. For example, the 5-membered heterocyclyl depicted in formula (I) with ≡ is a pyrazole that may adopt one of two isomeric forms.

In some embodiments, Q^2 is N and Q^1 is NR^1. In these embodiments, the compound of formula (I) may be a compound of formula (1A):



(1A)

In some embodiments, Q^2 is NR^1 and Q^1 is N. In these embodiments, the compound of formula (I) may be a compound of formula (1B):



(1B)

In the compounds of formula (1A) and/or (1B), R^1, R^2, R^3, X, Y and Z are as defined in formula (I) or any embodiment thereof as described herein.

In some embodiments, X is selected from optionally substituted C_{1-4}alkyl, optionally substituted C_{2-4}alkynyl, optionally substituted C_{1-4}alkylnitrile, optionally substituted haloC_{1-4}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_1alkylC_{3-6}cycloalkyl, optionally substituted aryl, optionally substituted haloaryl, optionally substituted C_1alkylaryl, optionally substituted haloC_1alkylaryl, optionally substituted haloC_1alkoxyaryl, optionally substituted benzyl, optionally substituted halobenzyl, optionally substituted C_1alkylbenzyl, optionally substituted C_1alkoybenzyl and optionally substituted haloC_1alkoybenzyl.

In some embodiments, X is selected from an optionally substituted C_{1-4}alkyl, an optionally substituted haloC_{1-4}alkyl and a C_{3-6}cycloalkyl.

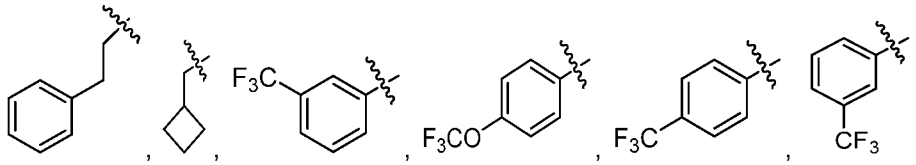
In some embodiments, X is selected from an optionally substituted C_{1-2}alkyl, an optionally substituted haloC_{1-2}alkyl and a C_3cycloalkyl.

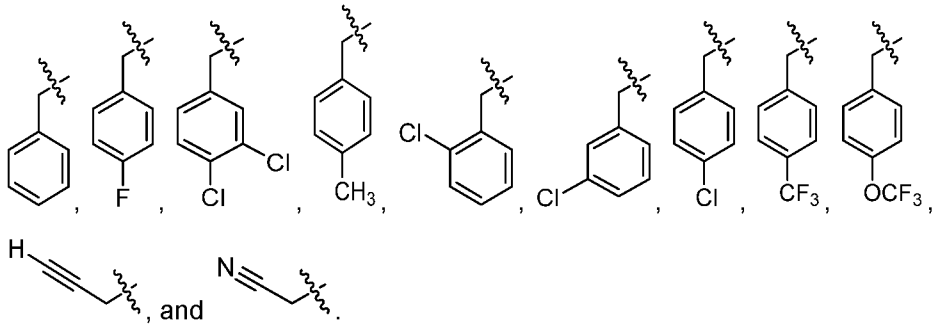
In some embodiments, X is an optionally substituted haloC_{1-4}alkyl selected from $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$ and $-CH_2CH_2CF_3$.

In some embodiments, X is an optionally substituted amino preferably disubstituted amino, such as $-N(C_{1-4}alkyl)_2$. In some embodiments, X is $–N(CH_3)_2$.

In some embodiments, X is selected from any one of the following groups:

methyl, ethyl, isopropyl, *tert*-butyl, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, cyclohexyl, cyclopropyl, $-N(CH_3)_2$





In some embodiments, X is selected from any one of the following groups: ethyl, difluoromethyl, trifluoroethyl and cyclopropyl.

In some embodiments, X is selected from C_{1-4}alkyl and C_{1-4}fluroalkyl, preferably $-CHF_2$, $-CH_2CF_3$ and $-CH_2CH_3$.

In some embodiments, X is difluoromethyl.

In some embodiments, X is a group that has a longest linear chain extending from the sulfur atom depicted in formula (I) by not more than 6, 5, 4, 3 or 2 atoms, preferably 3-6 atoms. By "longest linear chain" it is meant the number of atoms from the point of attachment not including any branching or rings. For example, when X is benzyl, the longest linear chain is 6 atoms which includes the methylene carbon atom, four ring atoms and the hydrogen atom attached to the carbon at the 4-position of the benzyl, and when X is $-CH_2CF_3$, the longest linear chain is 3. The longest linear chain in each of these exemplary X-substituents is numbered in the partial formulas shown below:



In some embodiments, Y and Z are independently selected from H, R^4, $-OR^4$, $-NR^4R^5$, and halo, wherein at least one of Y and Z is H; and R^4 is selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted C_{1-6}alkylaryl, optionally substituted heterocyclyl, optionally substituted C_{1-6}alkylheterocyclyl, optionally substituted cycloalkyl, optionally substituted C_{1-6}alkylC_{3-10}cycloalkyl.

In some embodiments, the halo at Y or Z is fluoro.

In some embodiments, Y and Z are independently selected from H, R^4, -OR^4, -NR^4R^5, and fluoro, wherein at least one of Y and Z is H

In some embodiments, Y and Z are independently selected from H, R^4, -OR^4, -NR^4R^5, wherein at least one of Y and Z is H; and

R^4 is selected from C_{1-6}alkyl, aryl, cycloalkyl, heterocyclyl, C_{1-6}alkylcycloalkyl, C_{1-6}alkylaryl and C_{1-6}alkylheterocyclyl,

wherein each alkyl (including when present as an optional substituent) is optionally substituted with one or more groups independently selected from halo, C_{1-4}alkoxy, hydroxy, nitrile, amino, C_{1-4}alkylamino, $(C_{1-4}alkyl)_2$amino, aryl, cycloalkyl and heterocyclyl;

wherein each aryl (including when present as an optional substituent) is optionally substituted with one or more groups independently selected from halo, hydroxy, nitrile, amino, C_{1-4}alkylamino and $(C_{1-4}alkyl)_2$amino, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, aryl, cycloalkyl and heterocyclyl;

wherein each cycloalkyl (including when present as an optional substituent) is optionally substituted with one or more groups independently selected from halo, hydroxy, nitrile, amino, C_{1-4}alkylamino and $(C_{1-4}alkyl)_2$amino, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, aryl, cycloalkyl and heterocyclyl; and

wherein each heterocyclyl (including when present as an optional substituent) is optionally substituted with one or more groups independently selected from halo, hydroxy, nitrile, amino, C_{1-4}alkylamino and $(C_{1-4}alkyl)_2$amino, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, cycloalkyl, heterocyclyl and aryl.

In some embodiments, R^4 is selected from C_{1-6}alkyl, aryl, cycloalkyl, heterocyclyl, C_{1-6}alkylcycloalkyl, C_{1-6}alkylaryl, C_{1-6}alkylheterocyclyl, C_{3-10}cycloalkylaryl, C_{3-10}cycloalkylheterocyclyl, C_{3-10}cycloalkylC_{3-10}cycloalkyl, 3-6 membered non-aromatic heterocyclyl-aryl, 3-6 membered non-aromatic heterocyclyl-C_{3-10}cycloalkyl and 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl and wherein each cycloalkyl, aryl and heterocyclyl are optionally substituted with one or more groups independently selected from halo, hydroxy, nitrile, amino, C_{1-4}alkylamino and $(C_{1-4}alkyl)_2$amino, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl and haloC_{1-4}alkoxy.

In some embodiments, Y and Z are independently selected from H, R^4, -OR^4, -NR^4R^5, wherein at least one of Y and Z is H; and

R^4 is selected from C_{1-6}alkyl, aryl, cycloalkyl, heterocyclyl and -$(CH_2)_mR^9$,

R^9 is selected from C_{3-10}cycloalkyl, aryl, heterocyclyl, and

m is an integer selected from 1 to 6;

wherein each cycloalkyl, aryl and heterocyclyl are optionally substituted with one or more groups independently selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl and haloC_{1-4}alkoxy.

In some embodiments, Y and Z are independently selected from H, R^4, -OR^4, -NR^4R^5, wherein at least one of Y and Z is H; and

R^4 is selected from C_{1-4}alkyl, cycloalkyl, haloaryl, -C_{1-2}alkylaryl, -C_{1-2}alkylarylhalo, -C_{1-2}alkylC_{3-6}cycloalkyl, -C_{1-2}alkylheterocyclyl, -C_{1-2}alkylarylC_1alkylhalo, -C_{1-2}alkylarylhaloC_1alkyl, -C_{1-2}alkylarylhaloalkoxy, cycloalkylaryl, cycloalkylheterocyclyl, cycloalkylcycloalkyl, 3-6 membered non-aromatic heterocyclyl-aryl, 3-6 membered non-aromatic heterocyclylcycloalkyl, 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl, 3-6 membered heteroaryl-aryl, 3-6 membered heteroarylcycloalkyl, 3-6 membered heteroaryl-3-10 membered heteroaryl, C_{1-2}alkyl-3-6 membered non-aromatic hereocyclyl and C_{1-2}alkyl-3-6 membered heteroaryl;

wherein each alkyl, cycloalkyl, aryl, aralkyl, non-aromatic heterocyclyl, heteroaryl and alkoxy is optionally substituted with a group selected from halo, hydroxy, nitrile, amino, C_{1-4}alkylamino and $(C_{1-4}alkyl)_2$amino, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy and acyl.

In some embodiments, Y and Z are independently selected from H and -OR^4.

In some embodiments, Z is H.

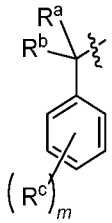
In some embodiments, Y is selected from H, R^4, -OR^4, -NR^4R^5.

In some embodiments, Z is H and Y is selected from R^4, -OR^4, -NR^4R^5.

In some embodiments, Z is H and Y is -OR^4.

In some embodiments, R^4 is an optionally substituted C_1alkylC_6aryl or an optionally substituted C_1alkylheteroaryl. In some embodiments, the C_1alkyl moiety is substituted. In some embodiments, the aryl or heteroaryl moiety is substituted.

In some embodiments, R^4 is an optionally substituted C_1alkylC_6aryl moiety represented by the following partial formula:



wherein

R^a and R^b are independently selected from H, optionally substituted C_{1-4}alkyl, optionally substituted C_{1-4}alkoxy, optionally substituted C_{1-4}alkylhydroxy, optionally substituted C_{1-4}alkylnitrile, optionally substituted amino, optionally substituted C_{1-4}alkylamino and optionally substituted $(C_{1-4}alkyl)_2$amino, or

R^a and R^b together with the carbon atom to which they are attached form an optionally substituted C_{3-6}cycloalkyl or a 3-6 membered non-aromatic heterocyclyl;

R^c is selected from halo and an optionally substituted C_{1-4}alkyl; and

m is 0, 1 or 2.

In some embodiments, R^a and R^b are independently selected from H, optionally substituted C_{1-4}alkyl, optionally substituted C_{1-4}alkoxy, optionally substituted $C_{1-4}alkoxyC_{1-2}$alkyl, optionally substituted C_{1-4}alkylhydroxy, optionally substituted C_{1-4}alkylnitrile, optionally substituted C_{1-4}alkylamino and optionally substituted $(C_{1-4}alkyl)_2$amino. When R^a and/or R^b are an optionally substituted C_{1-4}alkylamino, either the C_{1-4}alkyl or amino moiety may be optionally substituted.

In some embodiments, R^a and R^b together with the carbon atom to which they are attached form an optionally substituted C_{3-6}cycloalkyl or a 3-6 membered non-aromatic heterocyclyl selected from an optionally substituted cyclopropyl, an optionally substituted cyclobutyl, an optionally substituted cyclopentyl, an optionally substituted cyclohexyl, an optionally substituted oxetane and an optionally substituted azetidine.

In some embodiments, R^a and R^b together with the carbon atom to which they are attached form a 3-6 membered non-aromatic heterocyclyl comprising 1 or 2, preferably 1 heteroatom, preferably selected from O and N.

In some embodiments, *m* is 0 or 1.

In some embodiments, *m* is 1 or 2.

In some embodiments, at least one R^c is in the para position relative to the benzyl carbon atom.

In some embodiments, R^c is selected from methyl, fluoro and chloro.

In some embodiments, R^a is selected from H and methyl, and R^b is H.

In some embodiments, R^a and R^b together with the carbon atom to which they are attached are cyclopropyl.

In some embodiments, R^4 is -CR^aR^bheteroaryl, wherein the heteroaryl moiety is optionally substituted by 1 or 2 R^c groups. R^a, R^b and R^c may be as defined for any embodiment described herein. In some embodiments, the heteroaryl moiety of the -CR^aR^bheteroaryl group is a 5- or 6- membered heteroaryl comprising 1 or 2 heteroatoms selected from N, S and O. In some embodiments, the heteroaryl moiety is selected from an optionally substituted oxazolyl and an optionally substituted thiazolyl.

In some embodiments, Y is selected from -OR^4, -NR^4R^5.

In some embodiments, wherein Y is selected from -OR^4, -NR^4R^5, R^4 has partial structure (A):



(A)

wherein

R^d is selected from H, optionally substituted C_{1-4}alkyl, optionally substituted C_{1-4}alkoxy, optionally substituted C_{1-4}alkoxyC_{1-4}alkyl, optionally substituted C_{1-4}alkylhydroxy, optionally substituted C_{1-4}alkylnitrile, optionally substituted C_{1-4}alkylamino and optionally substituted $(C_{1-4}alkyl)_2$amino, optionally substituted cycloalkyl and optionally substituted C_{1-4}alkylcycloalkyl; and

R^e is selected from optionally substituted aryl, optionally substituted C_{1-5}alkylaryl, optionally substituted heterocyclyl, optionally substituted C_{1-5}alkylheterocyclyl, optionally substituted cycloalkyl, and optionally substituted C_{1-5}alkylC_{3-10}cycloalkyl.

In some embodiments, R^d is methyl.

In some embodiments, R^e is selected from optionally substituted aryl, optionally substituted C_{1-5}alkylaryl, optionally substituted heterocyclyl, optionally substituted C_{1-4}alkylheterocyclyl, optionally substituted cycloalkyl, and optionally substituted C_{1-4}alkylC_{3-10}cycloalkyl.

In some embodiments, R^e is selected from optionally substituted aryl, optionally substituted cycloalkyl and optionally substituted heterocyclyl.

In some embodiments, R^e is selected from optionally substituted aryl and optionally substituted heteroaryl.

In some embodiments, R^d is selected from optionally substituted C_{1-4}alkyl, optionally substituted C_{1-4}alkoxy, optionally substituted C_{1-4}alkoxyC_{1-4}alkyl, optionally substituted cycloalkyl and optionally substituted C_{1-4}alkylcycloalkyl. In these embodiments, where R^d and R^e are not the same group, the partial structure (A) may contain a chiral centre at the carbon to which R^d and R^e are attached. Therefore, the carbon atom to which R^d and R^e are attached may be enantiomerically enriched. In some embodiments, the carbon atom to which R^d and R^e is attached is enriched as the (S) stereoisomer, for example when R^e has a higher ranking than R^d in the Cahn-Ingold-Prelog rules for stereochemical assignment. In some embodiments, the carbon atom to which R^d and R^e is attached is enriched as the (R) stereoisomer, for example when R^e has a lower ranking than R^d the Cahn-Ingold-Prelog rules for stereochemical assignment. In some embodiments, R^d is selected from optionally substituted C_{1-4}alkyl, and the carbon atom to which R^d and R^e are attached is enriched in the (S) stereoisomer. The inventors have surprisingly found that compounds with the (S) configuration at this position possess greater MLKL activity than those with the (R) configuration at the same position. In some cases, the S-stereoisomer is greater than 2-fold more active than the corresponding R-steroisomer, and in some embodiments, the S-stereoisomer may be at least about 5-fold or about 10-fold more active than the corresponding R-stereoisomer for MLKL inhibition.

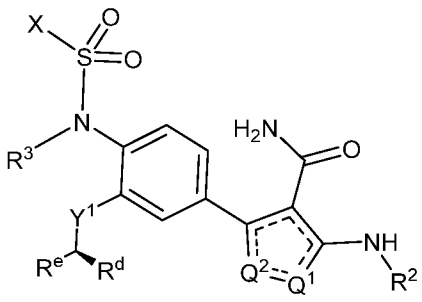
In some embodiments, partial structure (A) may have the stereochemical configuration shown in by partial structure (A1):



(A1)

wherein R^e has a higher ranking than R^d in the Cahn-Ingold-Prelog rules for stereochemical assignment.

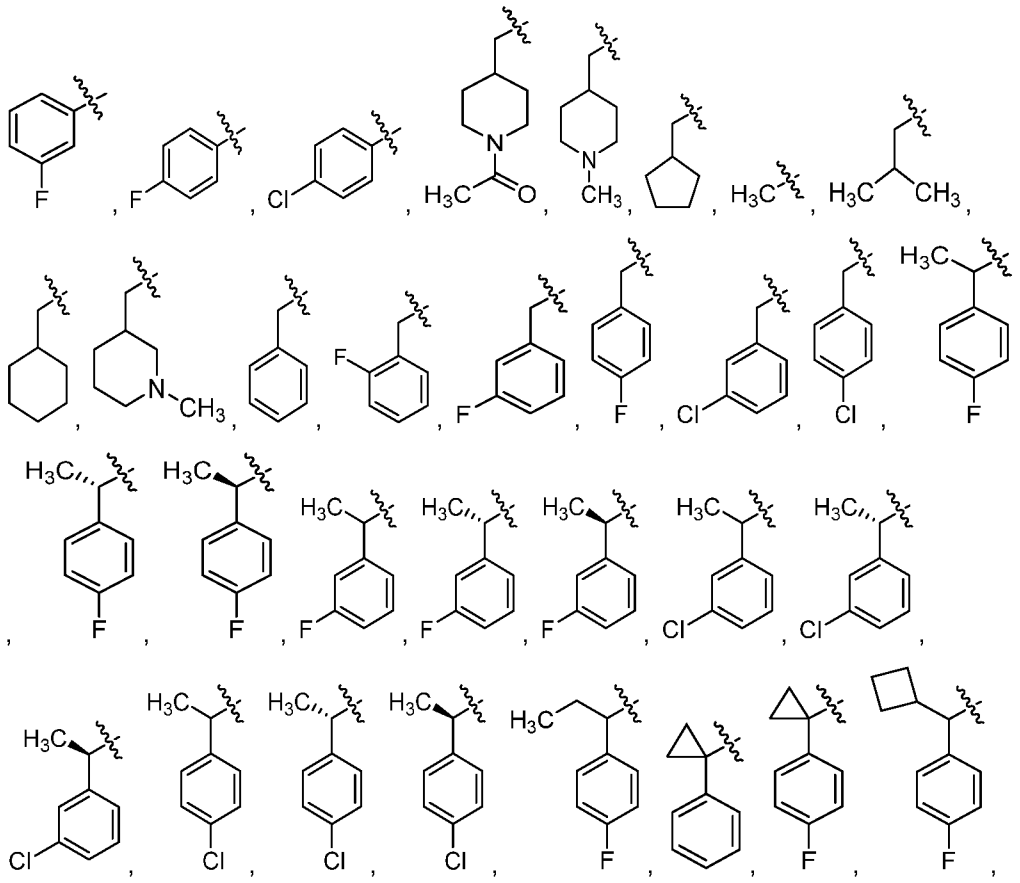
In some embodiments, the compound of formula (I) is provided as a compound of formula (SI):

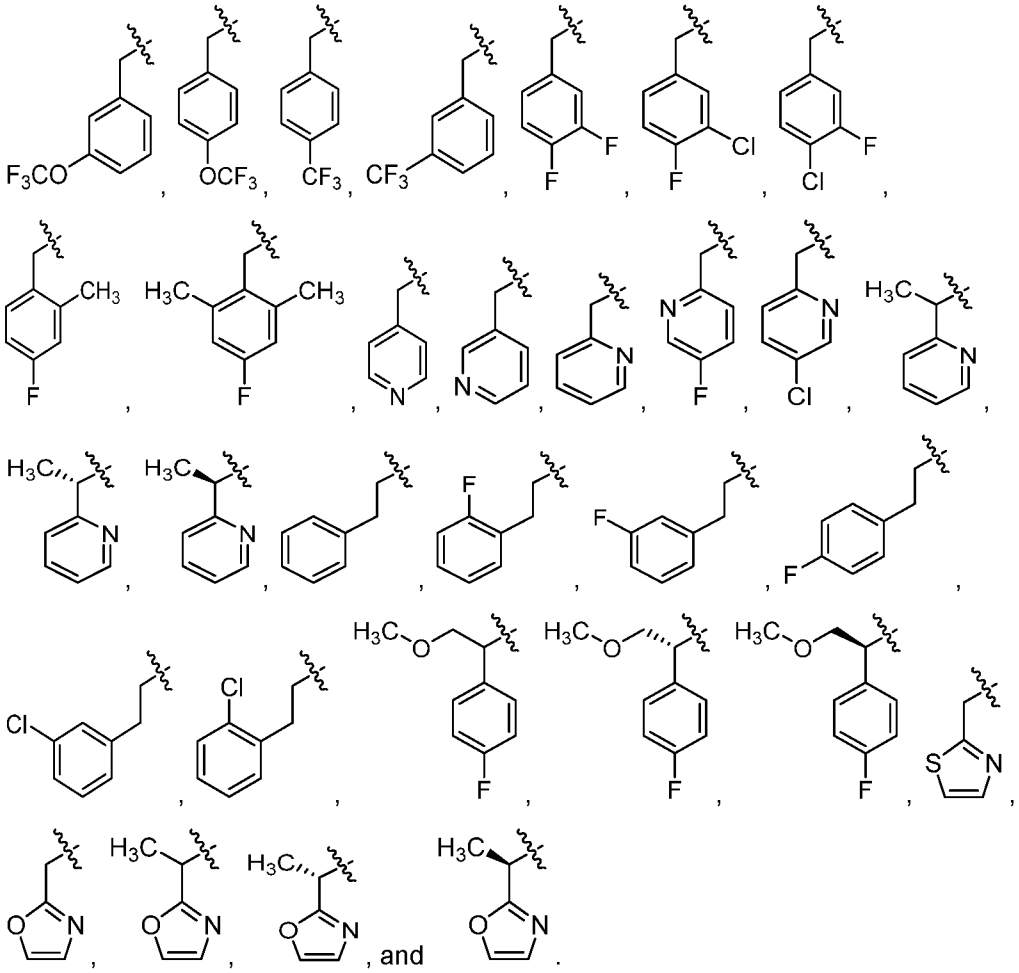


(SI)

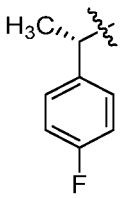
wherein X, Q^1, Q^2, R^2 and R^3 are as defined for formula (I), R^e and R^d are as defined for partial formula (A) and Y^1 is selected from O and NR^5.

In some embodiments, R^4 is selected from any one of the following groups:





and



In some embodiments, R^4 is .

In some embodiments, R^5 is selected from H and methyl.

In some embodiments, R^5 is H.

In some embodiments, Y is H.

In some embodiments, Z is H.

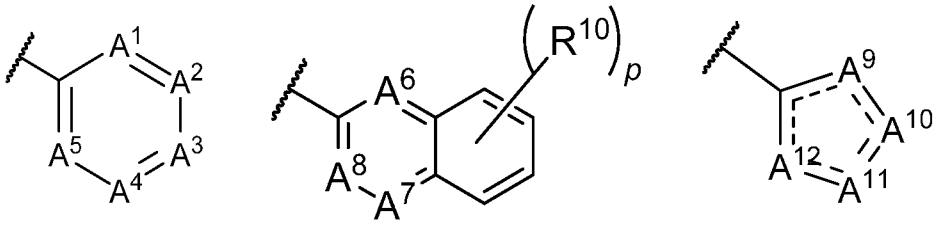
In some embodiments, both Y and Z are H.

In some embodiments, R^1 and R^3 are H.

In some embodiments, R^2 is selected from an optionally substituted phenyl, an optionally substituted 5-membered heteroaryl, an optionally substituted 6-membered heteroaryl, an optionally substituted 8-membered heteroaryl, an optionally substituted 9-membered heteroaryl and an optionally substituted 10-membered heteroaryl.

In some embodiments, R^2 is selected from an optionally substituted phenyl, an optionally substituted 5-membered monocyclic heteroaryl, an optionally substituted 6-membered monocyclic heteroaryl and an optionally substituted 10-membered bicyclic heteroaryl.

In some embodiments, R^2 is represented by any one of partial formulas Ar1-Ar3:



Ar1 Ar2 Ar3

wherein

A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are independently selected from CR^{11} and N;

A^9, A^{10}, A^{11} and A^{12} are independently selected from $C(R^{11})_q$, O, S, N and NR^{12};

wherein not more than 2 of A^1, A^2, A^3, A^4 and A^5 are N

wherein not more than 2 of A^6, A^7 and A^8 are N

wherein at least 1 of A^9, A^{10}, A^{11} and A^{12} is selected from $C(R^{11})_q$, O, S and NR^{12};

each R^{11} is independently selected from H and R^{10};

each R^{10} is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}4}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, $C_{3\text{-}10}$cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

each R^{12} is independently selected from H, C_{1-6}alkyl, haloC_{1-4}alkyl, C_{1-6}alkylacyl and haloC_{1-6}alkylacyl;

or when two adjacent groups selected from A^1, A^2, A^3, A^4, A^5, A^7, A^8 A^9, A^{10}, A^{11} and A^{12} (e.g. A^1 and A^2, A^2 and A^3, A^3 and A^4, A^4 and A^5, A^8 and A^7, A^9 and A^{10}, A^{10} and A^{11}, A^{11} and A^{12}) are selected from CR^{11} and NR^{12}, two R^{11}, two R^{12} or one R^{11} and one R^{12} may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl;

p is an integer from 0 to 4; and

q is 1 or 2.

In some embodiments, 0, 1 or 2 of A^1, A^2, A^3, A^4 and A^5 are N.

In some embodiments, 0, 1 or 2 of A^6, A^7 and A^8 are N.

In some embodiments, R^{10} is selected from fluoro, chloro, methyl, isopropyl, tert-butyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, difluoroethoxy, nitrile, amido, trifluoromethoxy, $-OCH_2CH_2OCH_3$, cyclopropyl and morpholino.

In some embodiments, the compound comprises not more than 1, 2, 3 or 4 instances of R^{10}.

In some embodiments, R^2 is represented by partial formula Ar1.

In some embodiments, R^2 is represented by partial formula Ar3.

In some embodiments, A^{10} is NR^{12} and A^{12} is CR^{11}.

In some embodiments, A^9 and A^{11} may be independently selected from CR^{11}, N, O and S. In some embodiments, when A^9 is CR^{11}, A^{11} is N, O or S and when A^9 is N, O or S, A^{11} is CR^{11}.

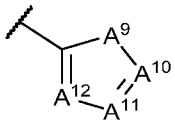
In some embodiments, A^9 and A^{11} are each CR^{11}.

In some embodiments, A^{10} and A^{12} are each CR^{11}.

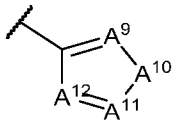
In some embodiments, at least one of A^9, A^{10}, A^{11} and A^{12} is selected from O, S, N and NR^{12}.

In some embodiments, one of A^9, A^{10}, A^{11} and A^{12} is selected from O, S and NR^{12}.

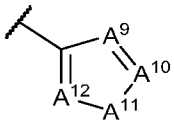
In some embodiments, partial formula Ar3 is provided by any one of the partial formulas Ar3-I, Ar3-II, Ar3-III and Ar3-IV



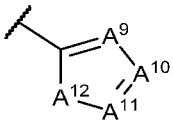
Ar3-I



Ar3-II



Ar3-III



Ar3-IV

wherein

in Ar3-I, A^9 is selected from $C(R^{11})_2$, O, S and NR^{12}, preferably O, S and NR^{12};

in Ar3-II, A^{10} is selected from $C(R^{11})_2$, O, S and NR^{12}, preferably O, S and NR^{12};

in Ar3-III, A^{11} is selected from $C(R^{11})_2$, O, S and NR^{12}, preferably O, S and NR^{12}; and

in Ar3-IV, A^{12} is selected from $C(R^{11})_2$, O, S and NR^{12}, preferably O, S and NR^{12}.

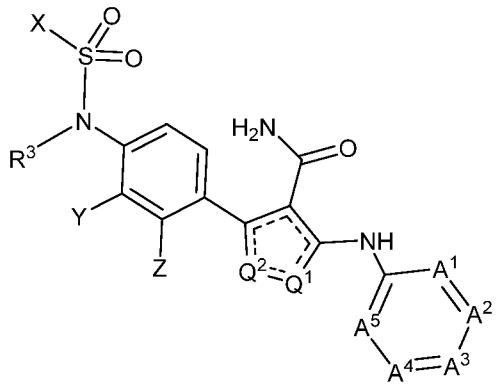
In some embodiments, A^{10} and A^{11} are independently selected from CR^{11} and NR^{12} such that two R^{11}, two R^{12} or R^{11} and R^{12} together form a 5-10 membered cycloalkyl, aryl or heterocyclyl ring.

In some embodiments, A^{10} is CR^{11} and A^{11} is NR^{12}, and R^{11} and R^{12} together form a 5-10 membered cycloalkyl, aryl or heterocyclyl ring. In these embodiments, A^{12} may be N and/or A^9 may be CR^{11}. In some embodiments, when A^{10} is CR^{11} and A^{11} is NR^{12}, and R^{11} and R^{12} together form a 5-10 membered heterocyclyl ring, preferably a non-aromatic heterocyclyl ring. In some embodiments, when A^{10} is CR^{11} and A^{11} is NR^{12}, R^{11} and R^{12} together form a 5-8 membered cycloalkyl, aryl or heterocyclyl ring, preferably a 6 or 7 membered ring, more preferably a 6 or 7 membered heterocyclyl ring.

When two R^{11}, two R^{12} or one R^{11} and R^{12} on adjacent ring atoms form a fused ring, the fused ring may be optionally substituted by 1-3 R^{10} groups. Any R^{10} group described herein may be suitable.

In some embodiments, R^{12} is methyl.

In some embodiments, the compound of formula (I) is a compound of formula (II)



(II)

wherein Q^1, Q^2, X, Y, Z and R^3 are as defined in formula (I) and A^1-A^5 are as defined for partial formula Ar1.

In some embodiments, A^1 is N.

In some embodiments, A^4 is N.

In some embodiments, A^1 and A^4 are N.

In some embodiments, A^2 is N.

In some embodiments, A^1 and A^3 are N.

In some embodiments, A^2 is CR^{10}.

In some embodiments, A^6 is N.

In some embodiments, A^7 is N.

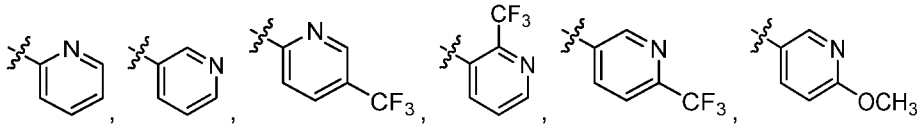
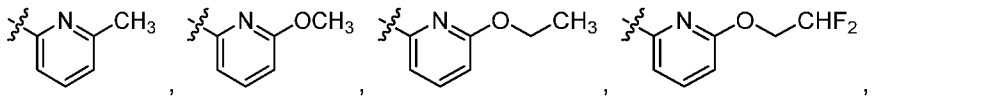
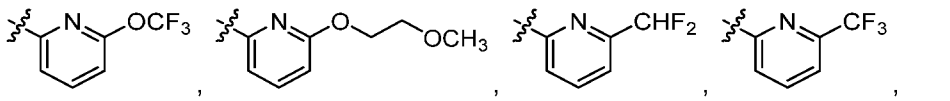
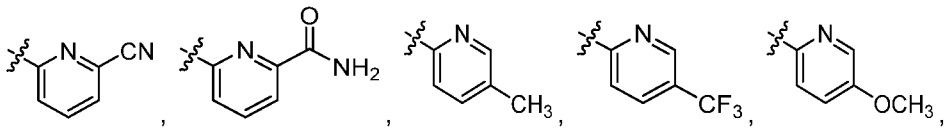
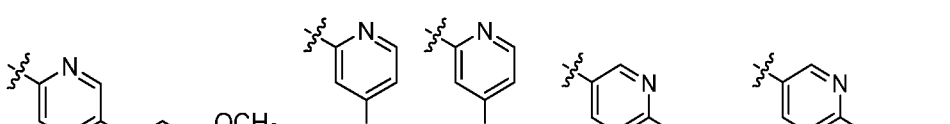
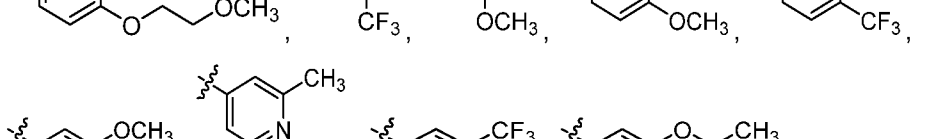
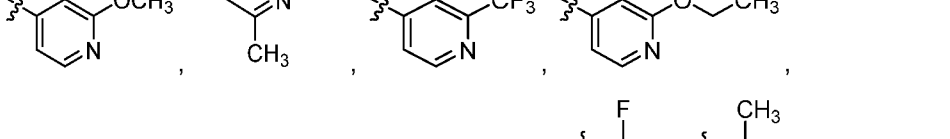
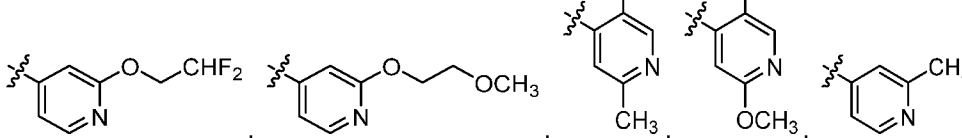
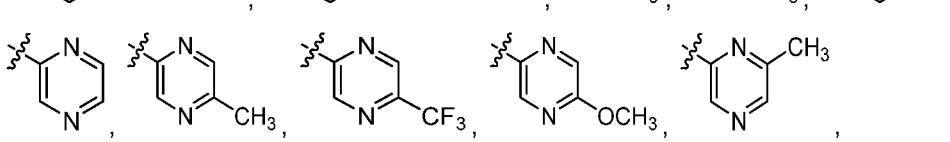
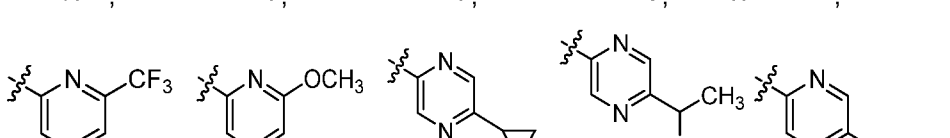
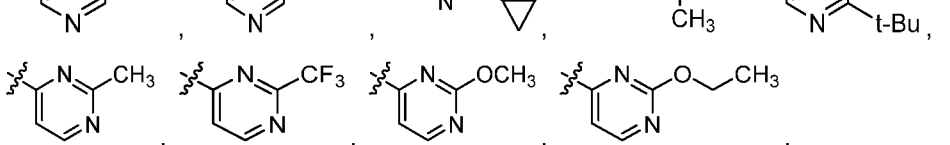
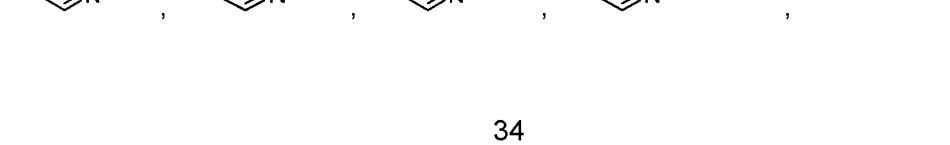
In some embodiments, A^6 and A^7 are N.

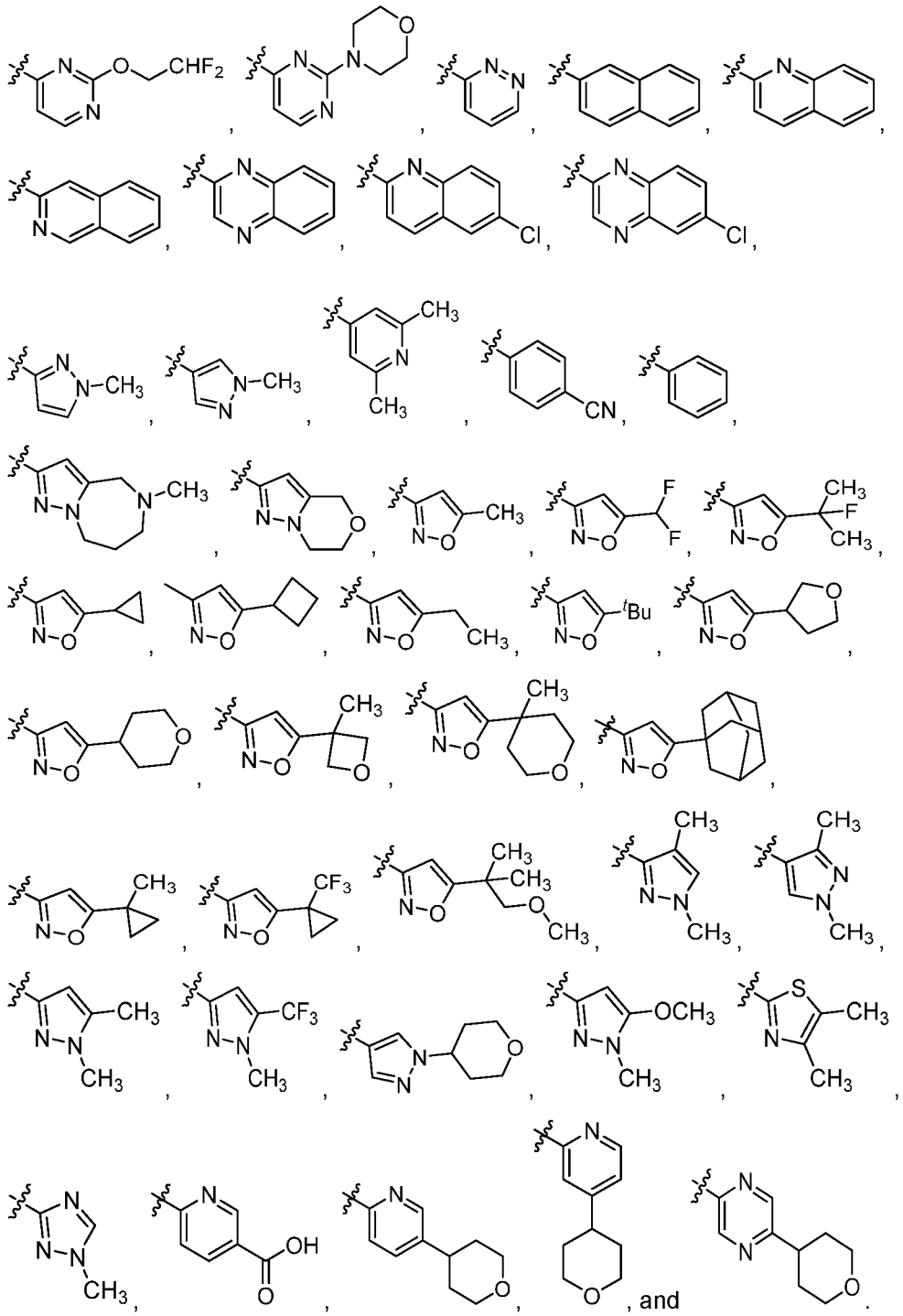
In some embodiments, R^2 is a 5-, 6- or 10-membered heteroaryl comprising 0, 1 or 2 substituents selected from fluoro, chloro, methyl, isopropyl, *tert*-butyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, difluoroethoxy, trifluoromethoxy, $-OCH_2CH_2OCH_3$, cyclopropyl, nitrile, amido and morpholino. Preferably, the substituents are selected from methyl, trifluoromethyl and methoxy. Preferably, when R^2 is a 10-membered heteroaryl, it is a fused bicyclic ring system.

In some embodiments, R^2 is a 5-, 6- or 10-membered heteroaryl comprising 1 or 2 nitrogen atoms, which is substituted by 0, 1 or 2 substituents.

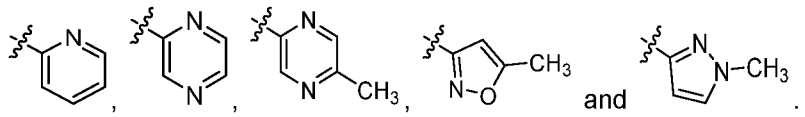
In some embodiments, R^2 is a 6-membered heteroaryl comprising 1 or 2 nitrogen atoms, which is substituted by 0 or 1 substituents selected from methyl, trifluoromethyl and methoxy. Typically, if present, the substituent is in the meta or para position relative to the nitrogen atom to which R^2 is attached (eg corresponding to positions shown for A^2 or A^3 in partial formula Ar1).

In some embodiments, R^2 is selected from any one of the following radicals:

methyl, 












In some embodiments, R^2 is selected from any one of the following radicals:



In some embodiments of the compound of formula (I)

X is selected from an optionally substituted C_{1-4}alkyl, an optionally substituted haloC_{1-4}alkyl and an optionally substituted C_{3-6}cycloalkyl;

Y and Z are independently selected from H and -OC_1alkylaryl,

R^1 and R^3 are H; and

R^2 is 6-membered heteroaryl comprising 1 or 2 nitrogen atoms, which is substituted by 0 or 1 substituents selected from methyl, trifluoromethyl and methoxy.

In some embodiments of the compound of formula (I)

X is selected from an optionally substituted haloC_{1-4}alkyl, preferably an optionally substituted haloC_{1-2}alkyl, more preferably difluoromethyl;

Y is -OR^4, preferably optionally substituted -OC_{1-4}alkylaryl, more preferably (S)-1-(4-fluorophenyl)-1-methyl-methoxy;

Z is H

R^1 and R^3 are H; and

R^2 is 5- or 6-membered heteroaryl comprising 1 or 2 heteroatoms selected from N and O substituted by 0 or 1 substituents selected from methyl, trifluoromethyl and methoxy, preferably substituted by 0 or 1 methyl substituents.

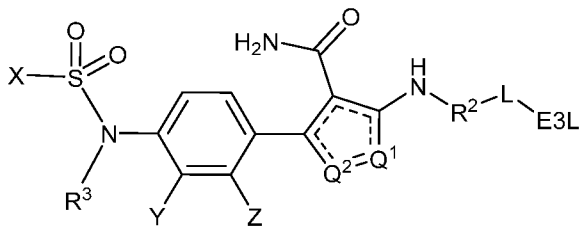
In some embodiments, the compound of the invention is selected from any of compounds 1001-1014, 1016-1037, 1039-1053 and 1055-1060 described herein.

In some embodiments, the compound of the invention is selected from any of compounds 1001-1014 and 1016-1036 described herein, preferably from any of compounds 1001-1014, 1016-1030, 1032-1033 and 1036, more preferably from any one of compounds 1001, 1005, 1007, 1013, 1016, 1019-1021 and 1023-1030.

In some embodiments, the compound comprises a radical of compounds 1-320 described herein, preferably 9, 14, 21-22, 24-25, 34, 39, 41-43, 53, 62-63, 66, 68, 71, 84, 88, 90, 92-93, 101-102, 108, 113, 115, 123-124, 127-128, 139-140, 143-144, 146, 150, 152-158, 160-166, 169-171, 175-176, 181, 188, 190-191, 194, 196, 198-199, 202, 208, 222-223, 229, 233-235, 238, 242, 245-246, 248-249, 251-253, 256, 259-260, 262, 264-266, 271, 273-279, 281-286,288-299, 301-312, 314 and 316-320.

In some embodiments, MLKLi is a compound of formula comprising a radical at R^2 so that R^2 and L are covalently bound.

In some embodiments, the compound of formula (X) may be provided as a compound of formula (XI):

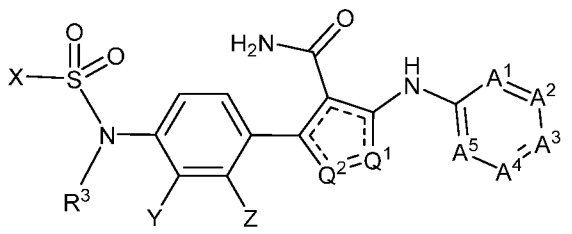


(XI)

wherein X, R^2, R^3, Y, Z, Q^1, Q^2, L and E3L are as defined herein.

In some embodiments of the compound of formula (X) or (XI), R^2 is an optionally substituted aryl or an optionally substituted heterocyclyl.

In some embodiments, the compound of formula (X) may be provided by the following formula (XII):



(XII)

wherein A^1-A^5 are independently selected from N, CR^{11} and C–L-E3L,

one of A^1-A^5 is C–L-E3L

wherein not more than 2 of A^1, A^2, A^3, A^4 and A^5 are N;

each R^{11} is independently selected from H and R^{10};

each R^{10} is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

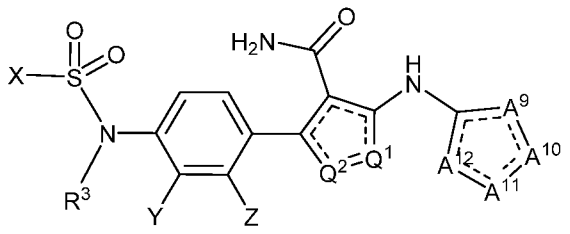
or when two adjacent groups selected from A^1, A^2, A^3, A^4, A^5, are CR^{11}, two R^{11} may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl.

A^1-A^5 may be defined as any one of embodiments 1-4:

Embodiment No.	A^1	A^2	A^3	A^4	A^5
1	CR^{11}	C-L-E3L	N	CR^{11}	CR^{11}
2	N	CR^{11}	C-L-E3L	CR^{11}	CR^{11}
3	N	CR^{11}	C-L-E3L	N	CR^{11}
4	N	C-L-E3L	N	CR^{11}	CR^{11}

Embodiments 1-3 are preferred.

In some embodiments, the compound of formula (X) may be provided by the following formula (XIII):



(XIII)

wherein:

A^9, A^{10}, A^{11} and A^{12} are independently selected from $C(R^{11})_q$, O, S, N, NR^{12}, $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

one of A^9, A^{10}, A^{11} and A^{12} is selected from $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

at least one of A^9, A^{10}, A^{11} and A^{12} is selected from $C(R^{11})_2$, O, S, NR^{12}, $C(R^{11})$–L-E3L;

each R^{11} is independently selected from H and R^{10};

each R^{10} is independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, -OC_{1-6}alkylC_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, nitrile, amido, C_{1-6}alkylamido, (C_{1-6}alkyl)$_2$amido, haloC_{1-6}alkylamido, (haloC_{1-6}alkyl)$_2$amido, acyl, C_{1-6}alkylacyl, haloC_{1-6}alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, haloC_{1-6}alkoxy, C_{3-10}cycloalkyl, C_{1-6}alkylC_{3-10}cycloalkyl, C_{1-6}alkoxyC_{3-10}cycloalkyl, haloC_{1-6}alkylC_{3-10}cycloalkyl, haloC_{1-6}alkoxyC_{3-10}cycloalkyl, C_{1-6}alkylheterocyclyl, C_{1-6}alkoxyheterocyclyl, haloC_{1-6}alkylheterocyclyl, haloC_{1-6}alkoxyheterocyclyl, C_{1-6}alkylC_{1-6}alkoxy, and -COOH;

each R^{12} is independently selected from H, C_{1-6}alkyl, haloC_{1-4}alkyl, C_{1-6}alkylacyl and haloC_{1-6}alkylacyl;

or when two adjacent groups selected from A^9, A^{10}, A^{11} and A^{12} are selected from CR^{11}, $C(R^{11})$–L-E3L and NR^{12}, two R^{11}, two R^{12} or one R^{11} and one R^{12} may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl;

q is 1 or 2.

In some embodiments, A^{12} is N, A^{11} is N-L-E3L, A^{10} is CR^{11} and A^9 is CR^{11}.

E3L

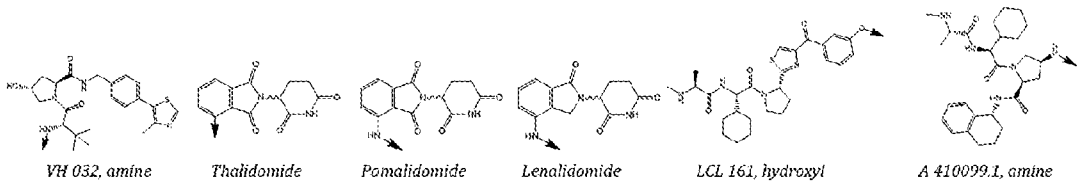
In the compounds of formula (X) E3L denotes an E3 ligase binding moiety. Any suitable E3 ligase binding moiety may be included in the compounds of the invention. Suitable E3 ligase binding moieties include different suitable linker attachment points and/or different suitable stereochemistries of E3 ligase binding moieties. E3 ligase binding moieties have been reviewed in Bricelj et al, *Front. Chem.*, **2021**, *9*, 707317, Schapira *et al*, Nat Rev Drug Discovery, **2019**, *18*, 949, Bricelj, A. *et al.*, *Front. Chem.* **2021**, *9*, 707317, Maple, H. J. *et al.*, *Med. Chem. Commun.*, **2019**, *10*, 1755, and Ishida, T. and Ciulli, A. *SLAS Discovery*, **2021**, *26(4)*, 484, the entire contents of each of which is incorporated by referenced. The skilled person would appreciate that a suitable E3 ligase binding moiety includes the E3 ligase binding structures depicted in Bricelj et al, *Front. Chem.*, **2021**, *9*, 707317, Schapira *et al*, Nat Rev Drug Discovery, **2019**, *18*, 949, Bricelj, A. *et al.*, *Front. Chem.* **2021**, *9*, 707317, Maple, H. J. *et al.*, *Med. Chem. Commun.*, **2019**, *10*, 1755, and Ishida, T. and Ciulli, A. *SLAS Discovery*, **2021**, *26(4)*, 484; as well as E3 ligase binding structures that features different suitable linker attachment points and/or different suitable stereochemistries.

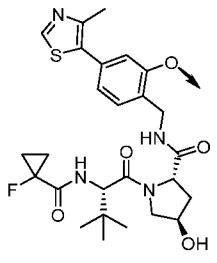
The human genome includes more than 600 E3 ligases (or E3 ubiquitin ligases). E3 ligases are involved in the protein ubiquitination cascade, whereby one or more

molecules of ubiquitin are linked to a substrate protein, marking those proteins for degradation via the ubiquitin-proteasome pathway. The E3 ligases are categorised into 3 broad classes: Really Interesting New Gene (RING), Homologous to E6AP C-terminus (HECT) and RING-between-RING (RBR). Of these, RING E3 ligases are the most common. Accordingly, the E3 ligase binding moiety may bind a RING, HECT or RBR E3 ligase, with E3L typically representing a RING E3 ligase binding moiety. Examples include, without limitation, MDM2 (mouse double minute 2 homologue) and cellular IAP (inhibitors of apoptosis).

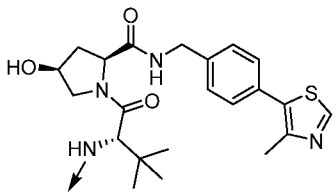
E3L may also be a moiety capable of binding any of these E3 ligases. Binders of the following E3 ligases have been described: RING-type zinc-finger protein 114 (RNF114), damage-specific DNA binding protein 1 (DDB1)-CUL4 associated factor 16 (DCAF16), Kelchlike ECH-associated protein 1 (KEAP1), cereblon (CRBL or CRBN) and von Hippel-Lindau (VHL) tumor suppressor protein. Preferably when E3L is a moiety capable of binding any of these E3 ligases, it is a moiety capable of binding CRBL and/or VHL.

In some embodiments, the E3 ligase binding moiety is selected from:




VH 101, phenol

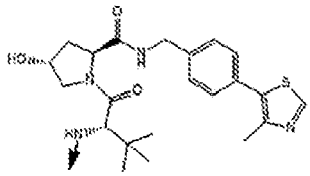
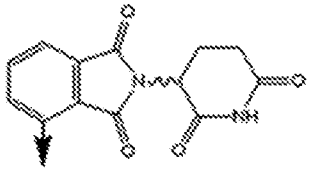
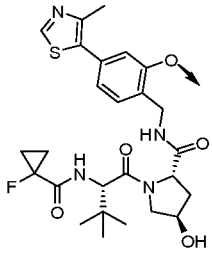
and

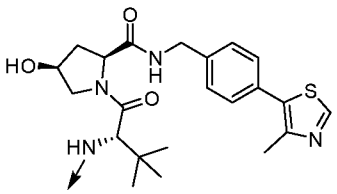


wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

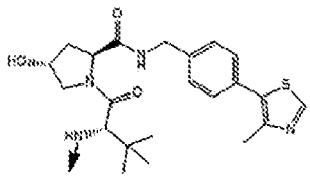
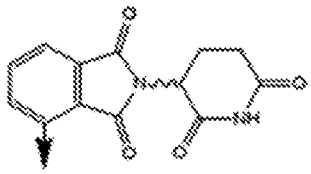

,

,

VH 101, phenol and

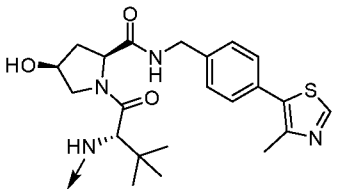


wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

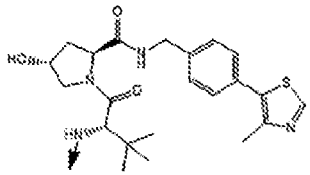

,

and



wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

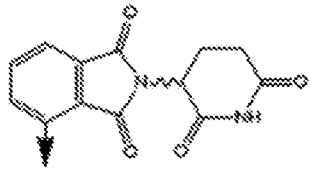
In some embodiments, the E3 ligase binding moiety is:



wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

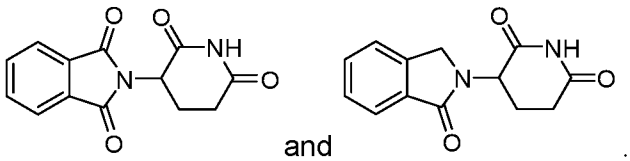
In some embodiments, the E3 ligase binding moiety is:



wherein the arrow denotes the covalent bond to L

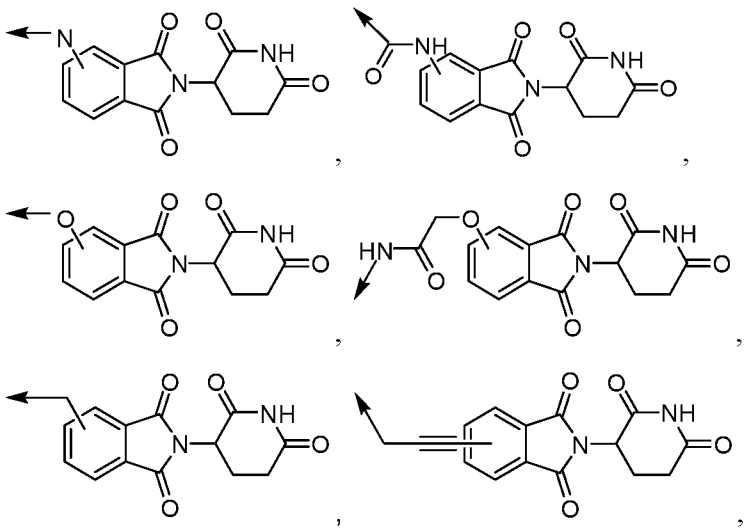
or an E3 ligase binding derivative thereof.

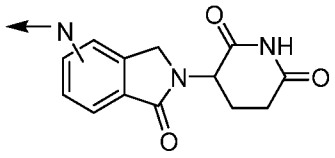
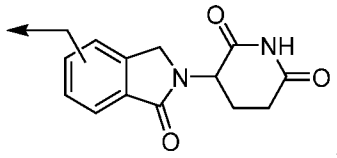
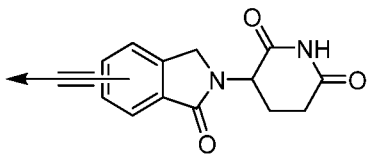
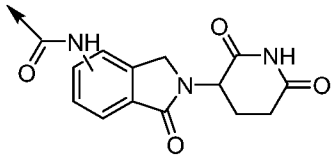
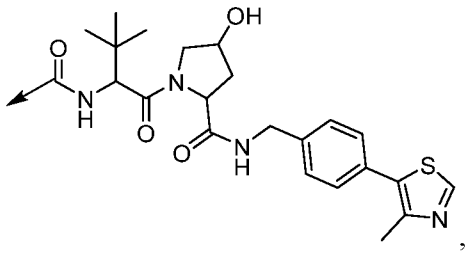
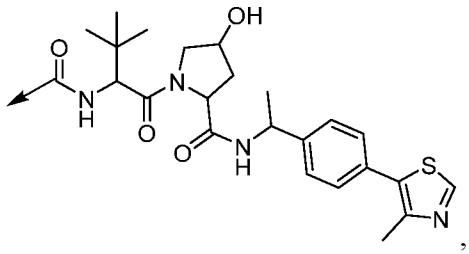
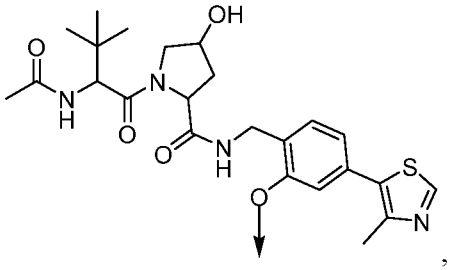
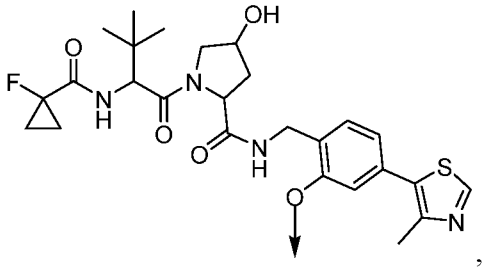
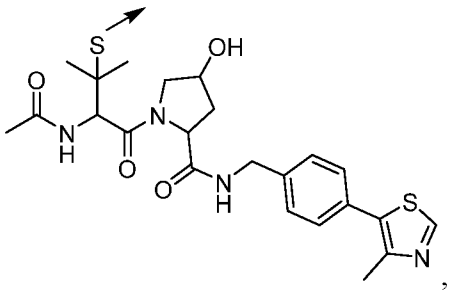
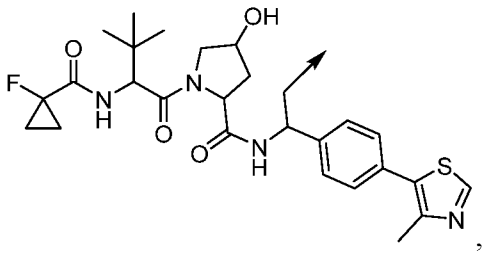
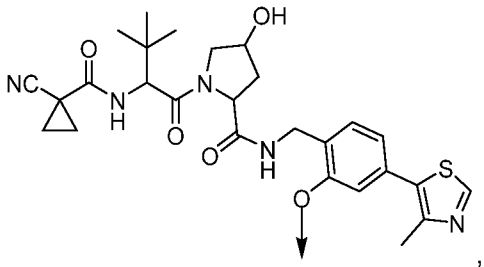
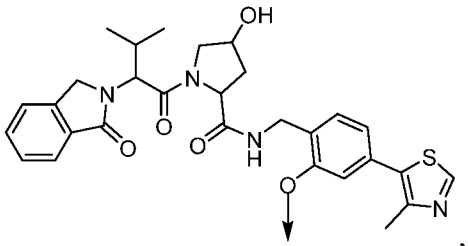
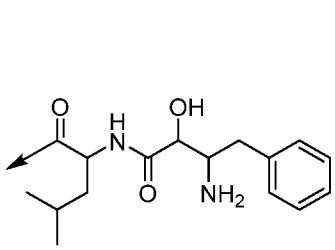
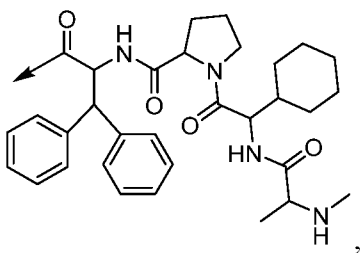
In some embodiments, the E3 ligase binding moiety is selected from a radical of:

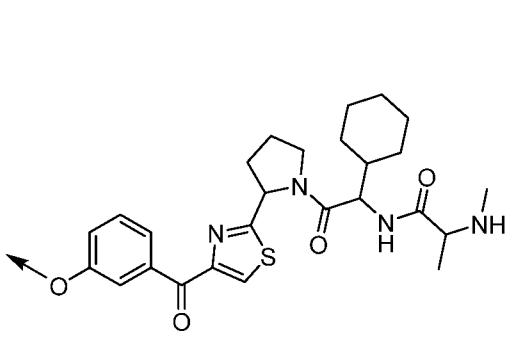
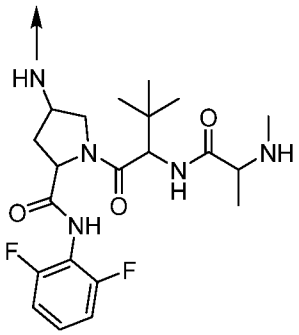
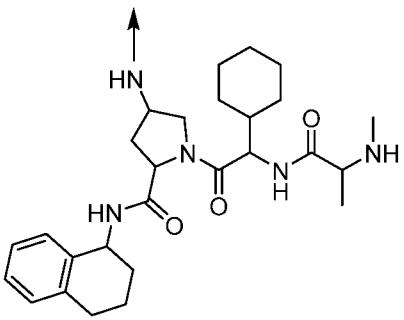
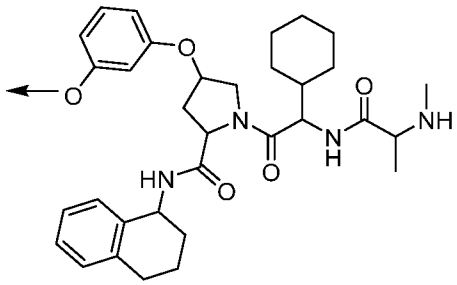
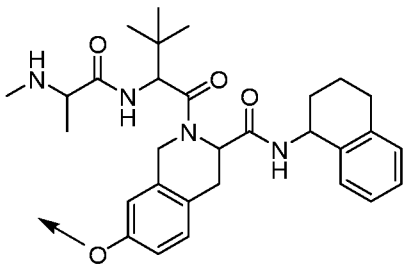
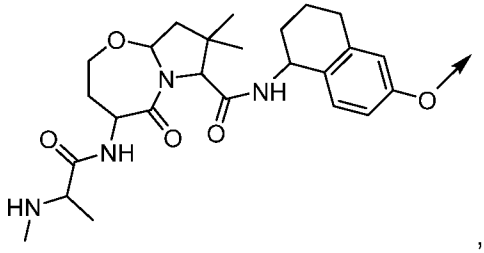
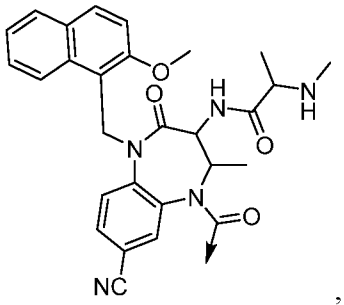
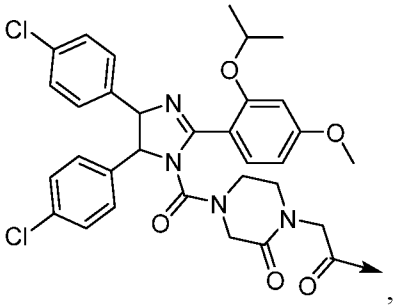
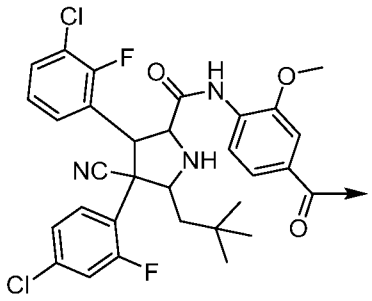
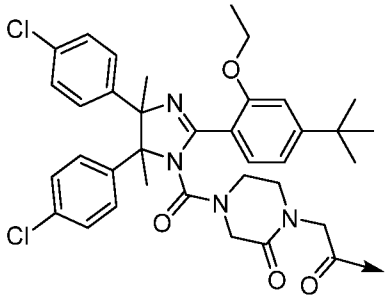


and .

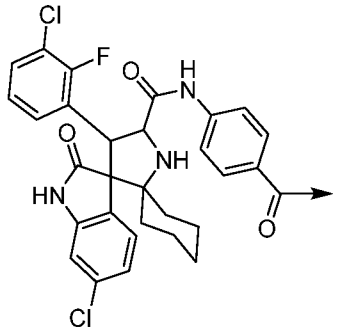
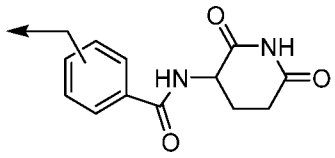
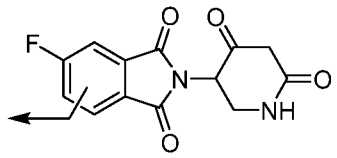
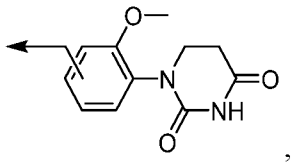
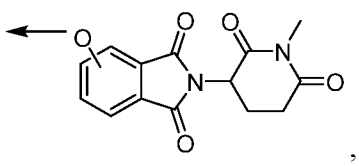
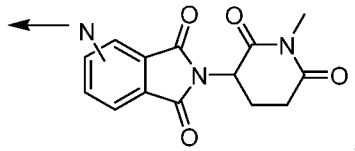
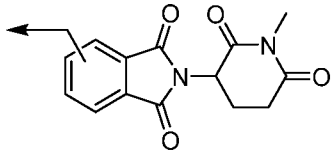
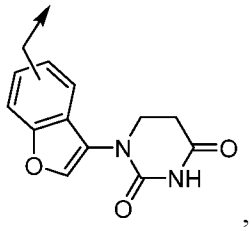
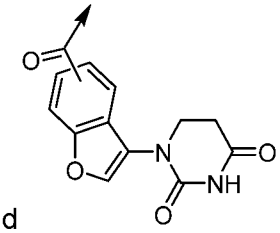
In some embodiments, the E3 ligase binding moiety is selected from:




,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

5

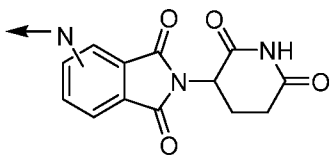
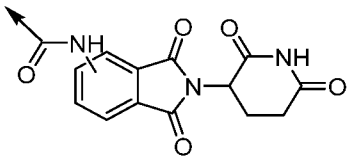
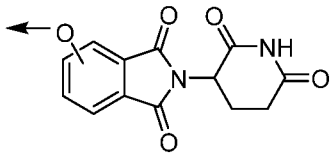
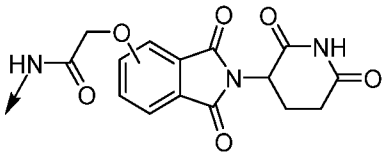
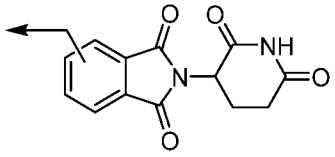
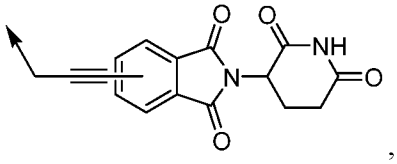
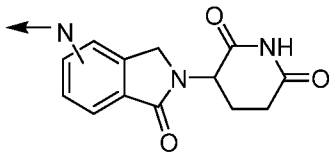
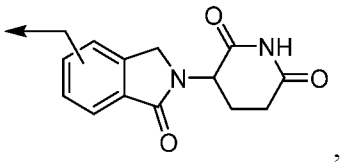
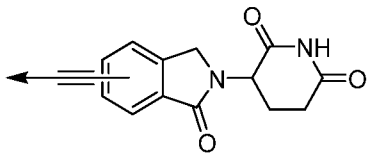
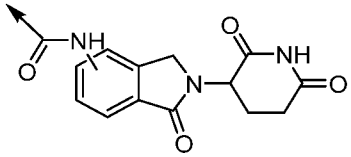
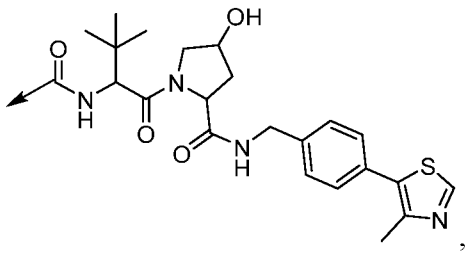
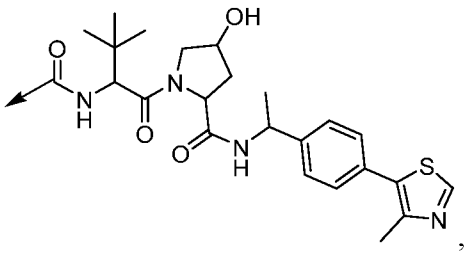
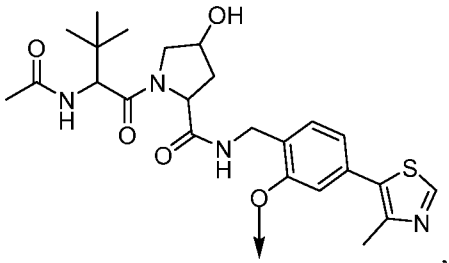
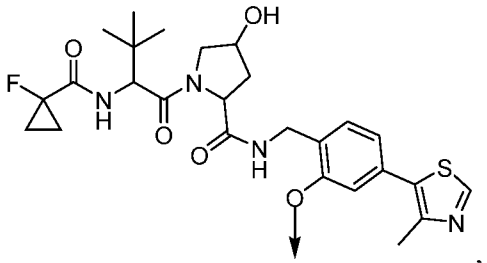
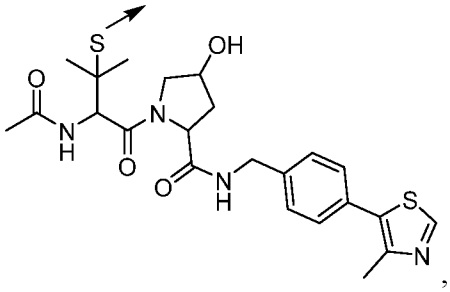
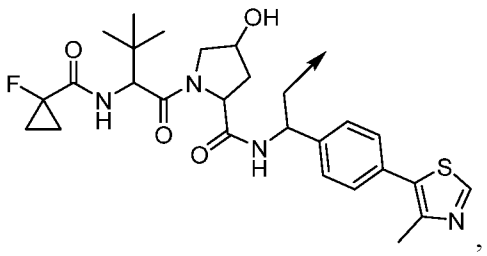









and ;

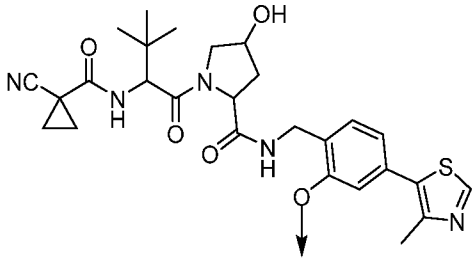
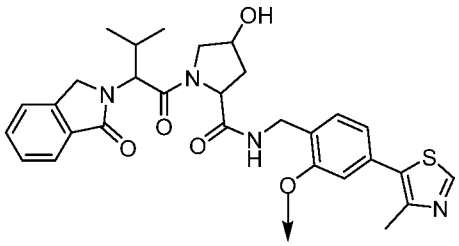
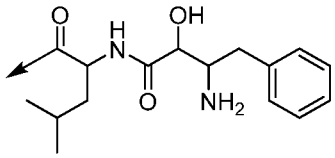
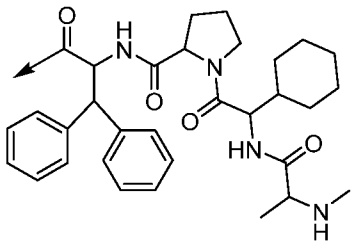
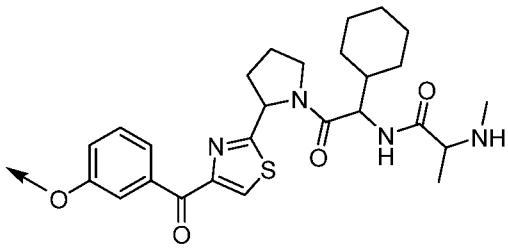
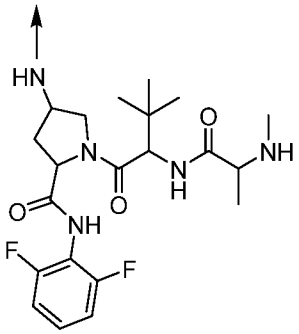
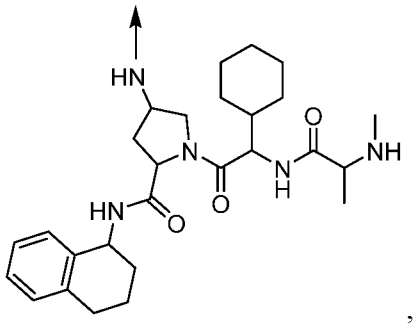
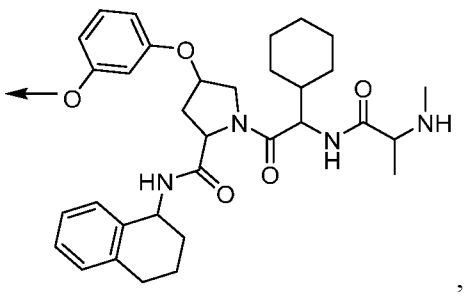
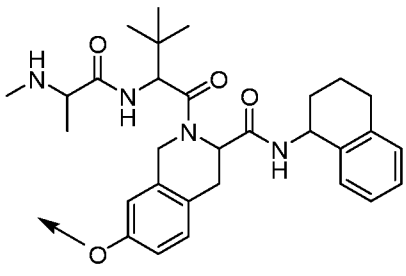
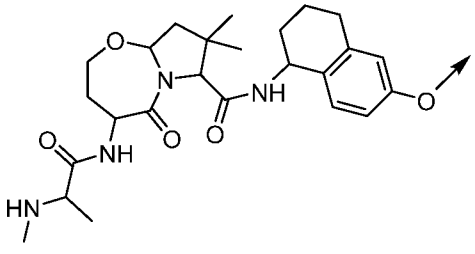
wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

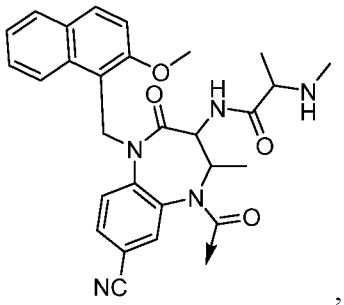
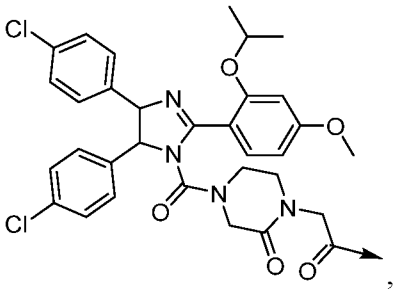
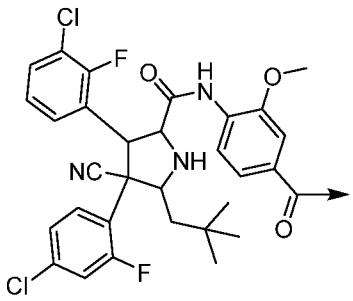
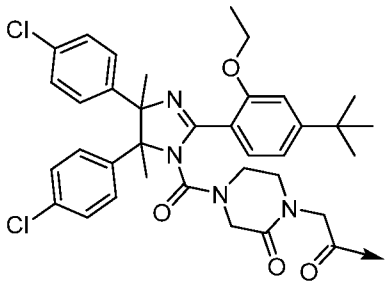
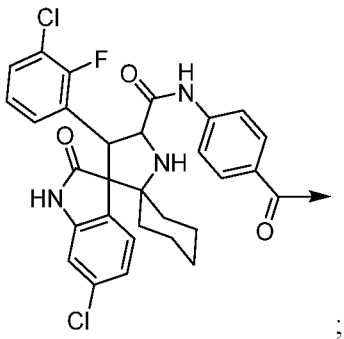
an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

5

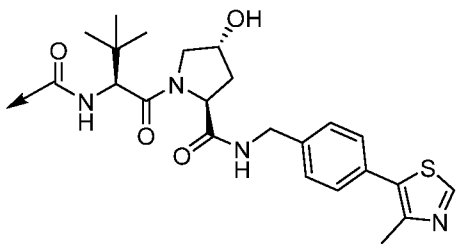
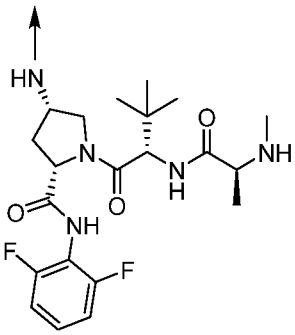
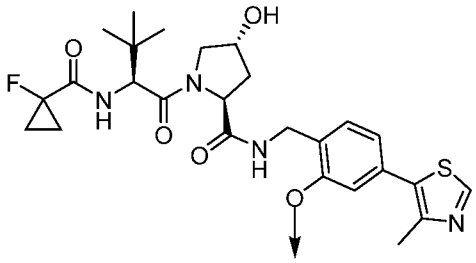
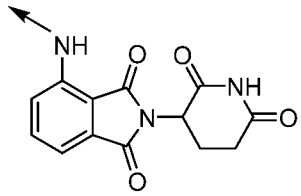
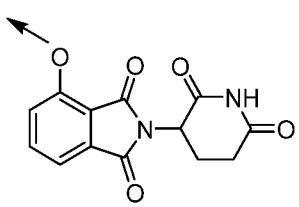
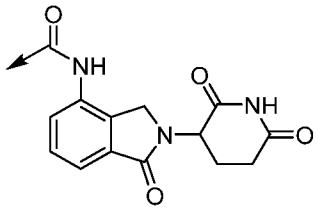
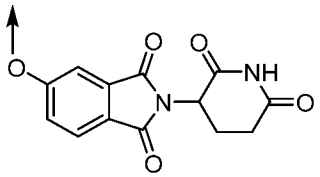
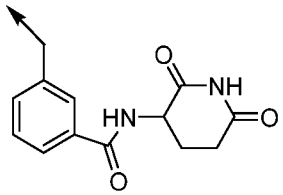
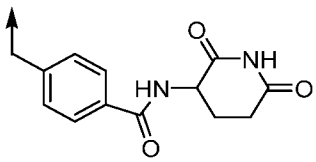
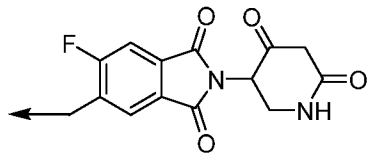
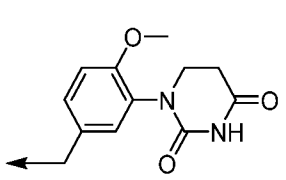
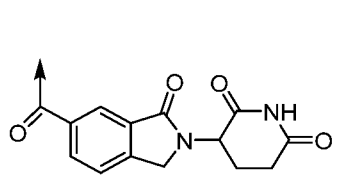
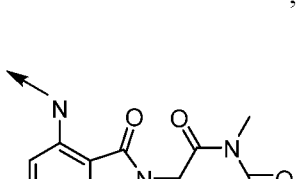
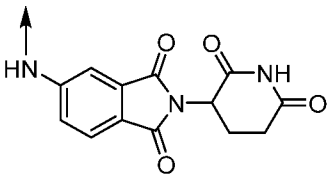

,

,

,

and

;

wherein the arrow denotes the covalent bond to L,

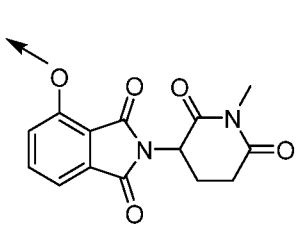
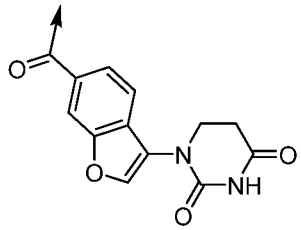
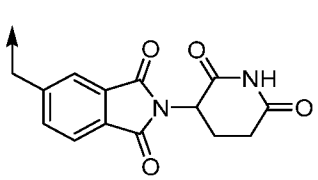
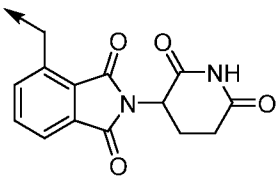
the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

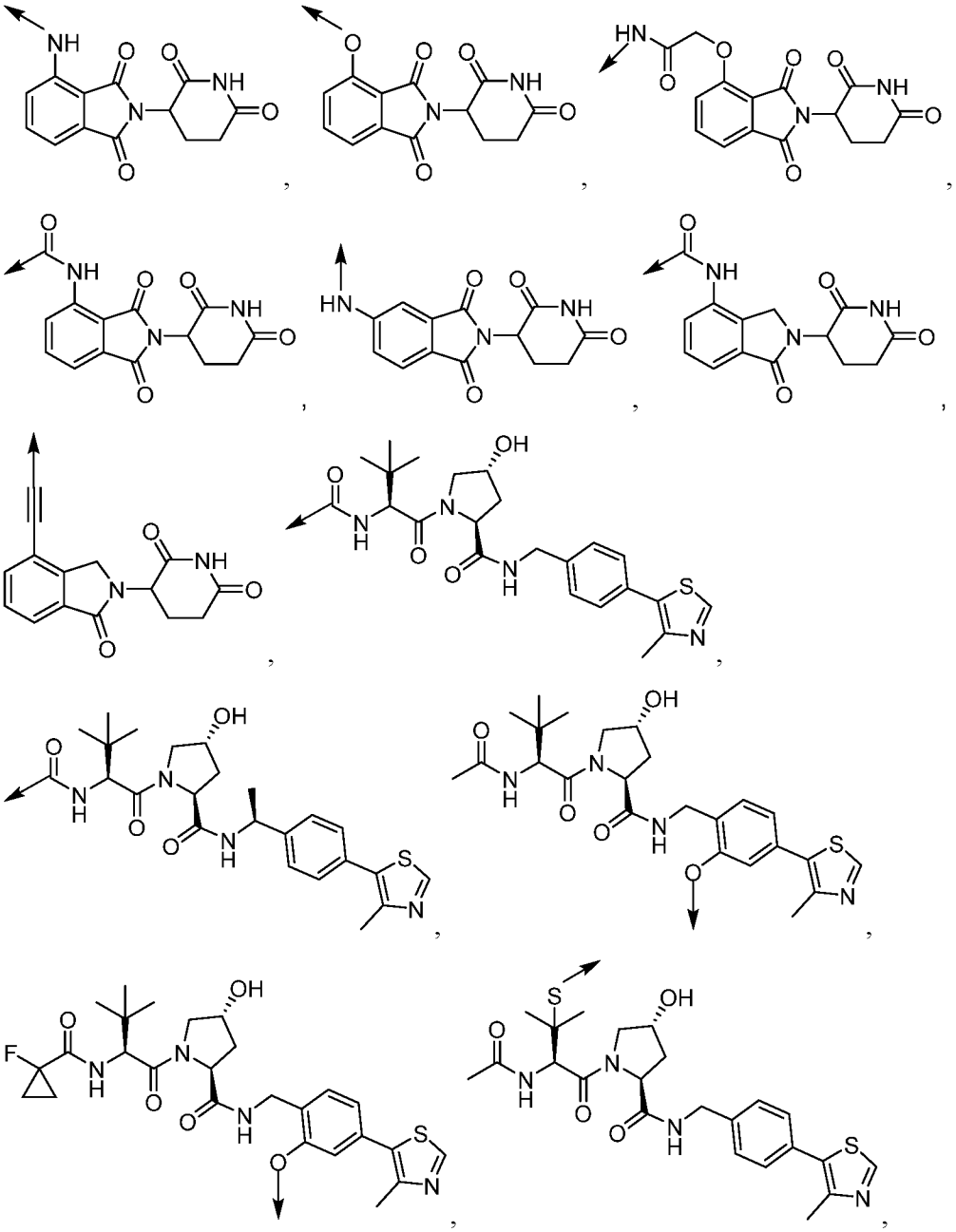
,

,

,

,

;

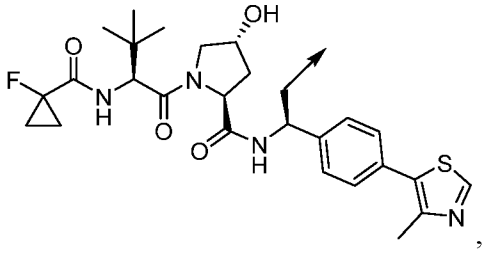
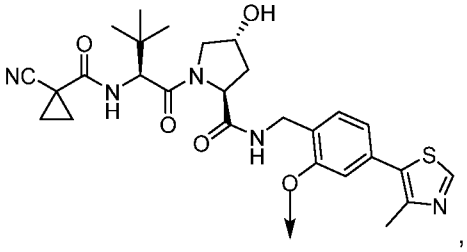
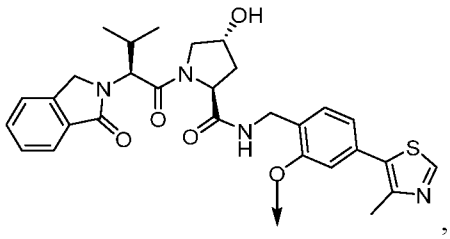
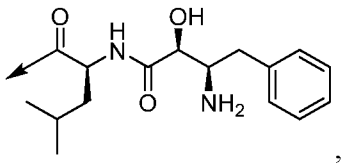
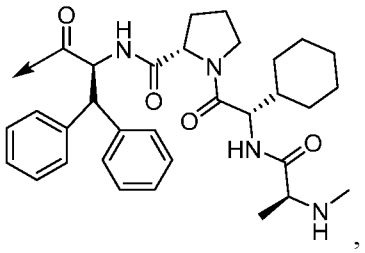
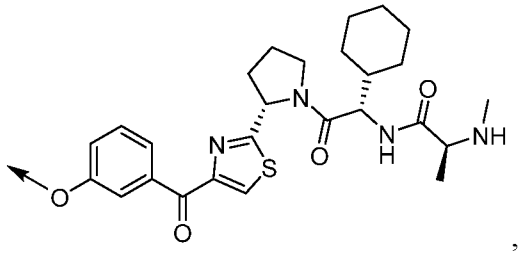
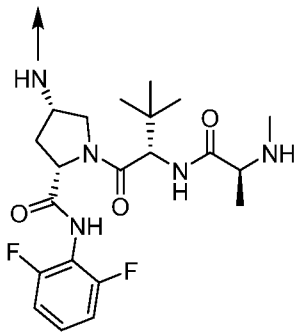
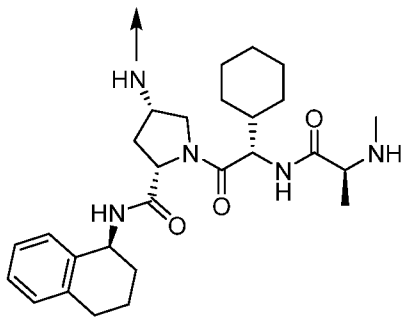
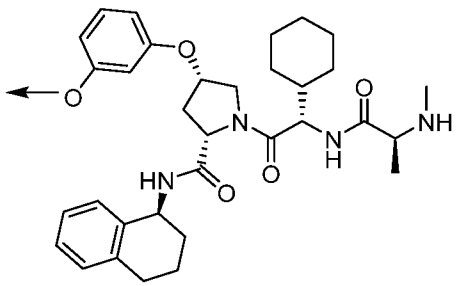
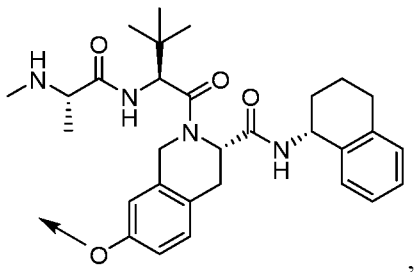
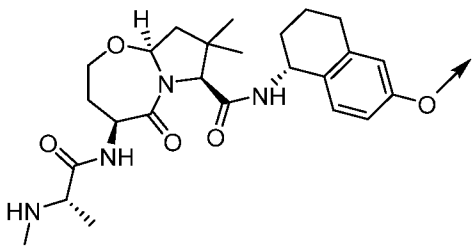
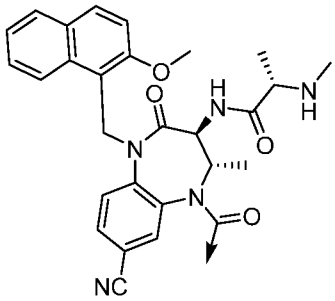
wherein the arrow denotes the covalent bond to L,

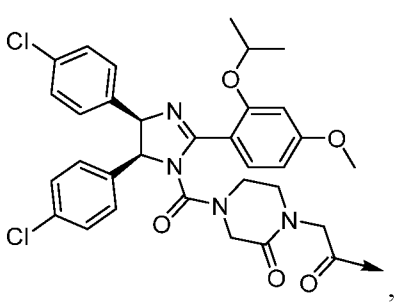
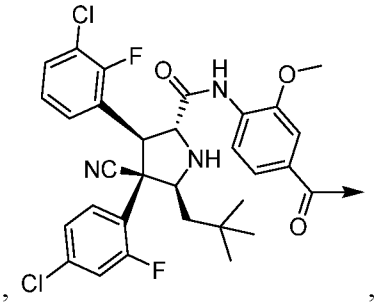
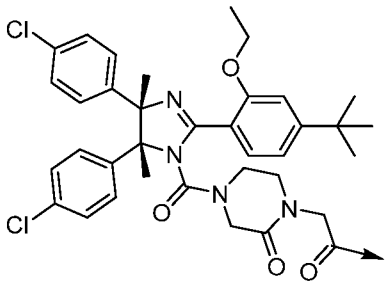
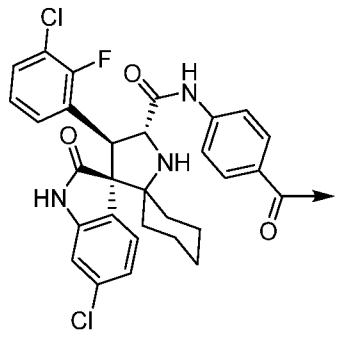
the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:




,

,

,

,

,

,

,

,

,

,

,

,

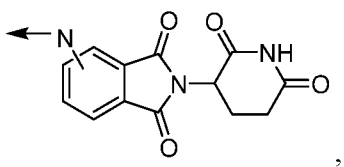
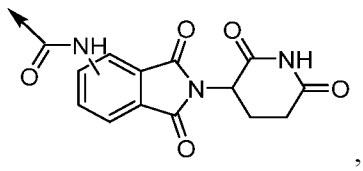
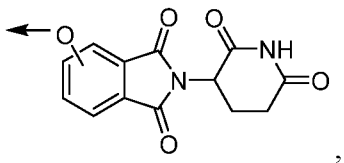
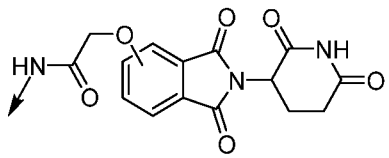
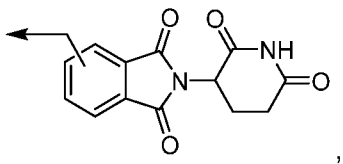
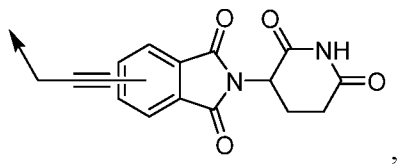



and

;

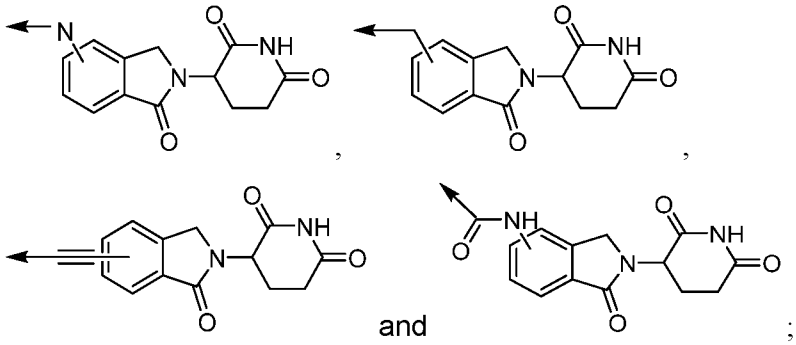
wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

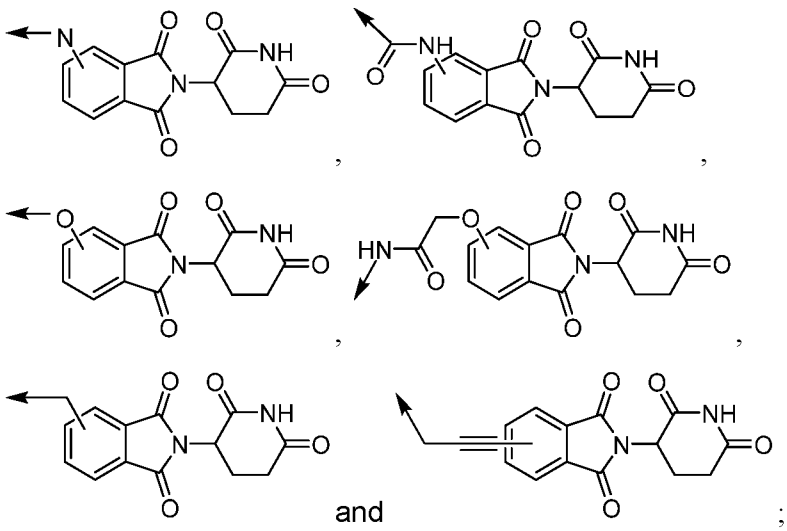


wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

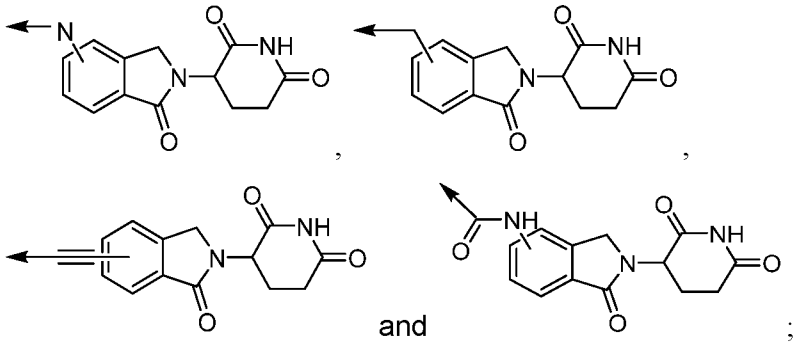


wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:



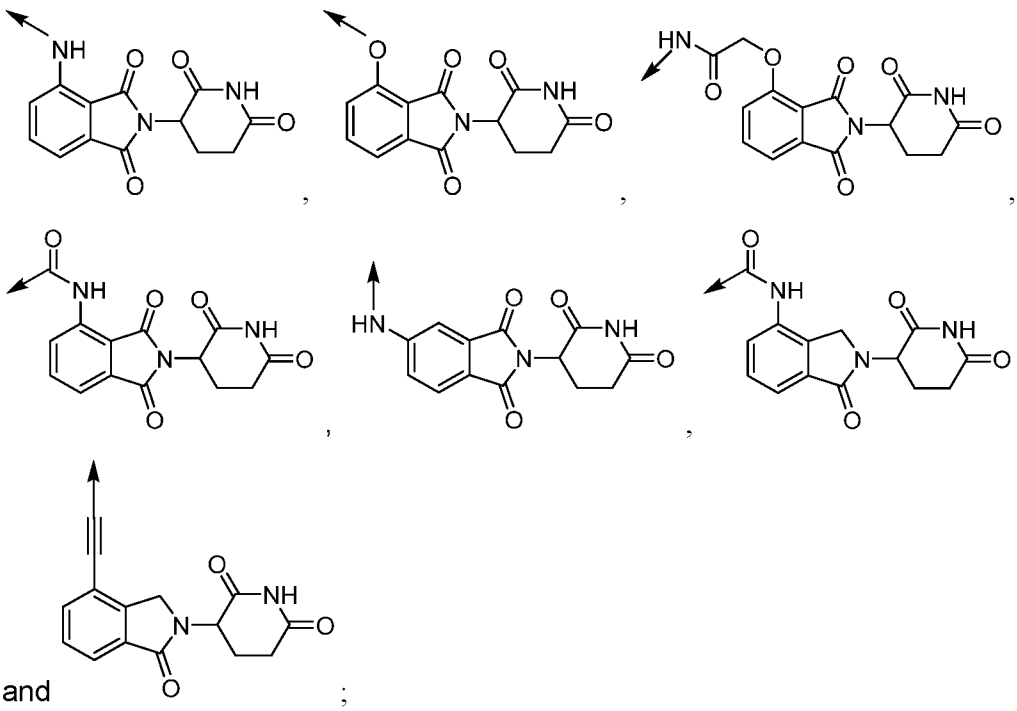
and ;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:



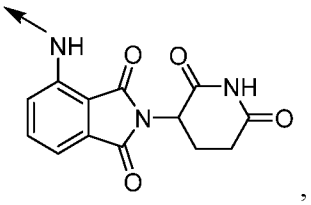
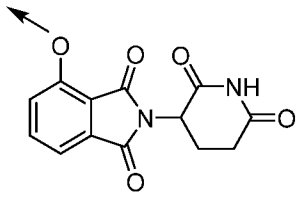
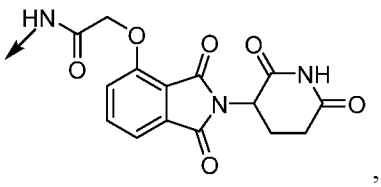
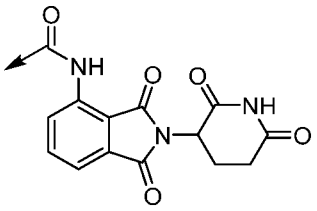
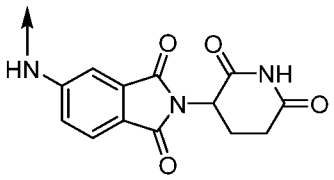
and ;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

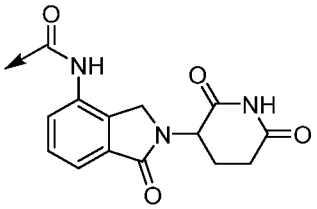
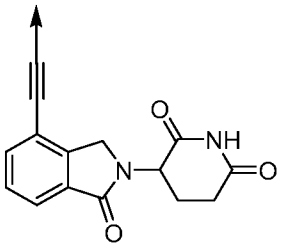




and

;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

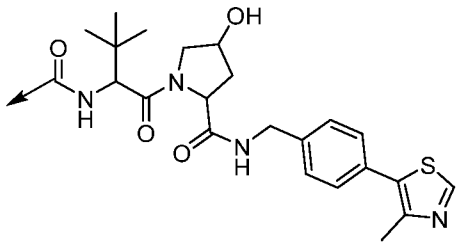
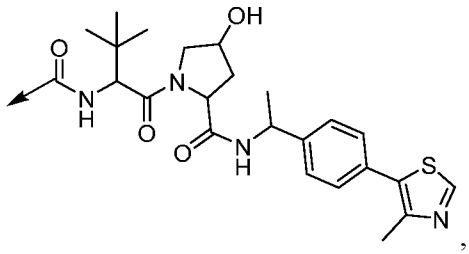
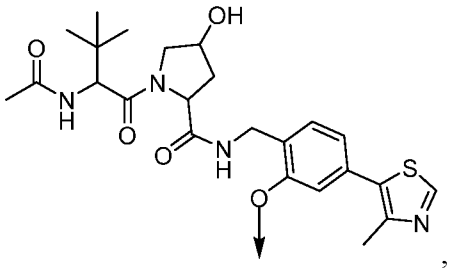
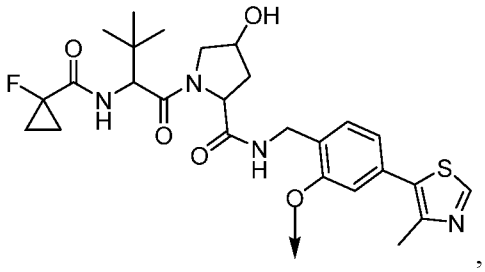
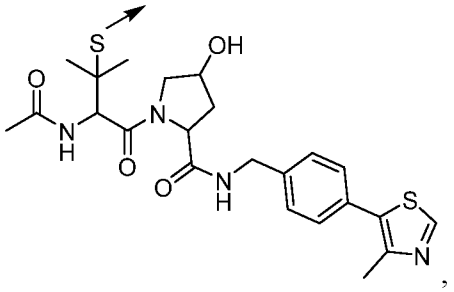
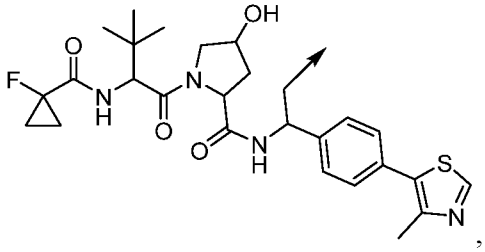
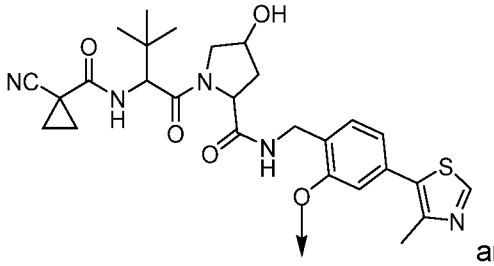
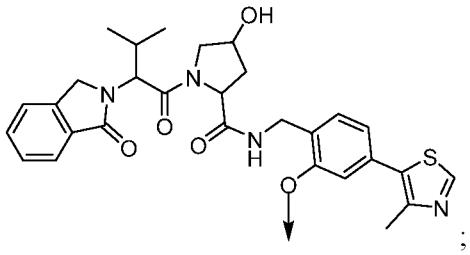

and

;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

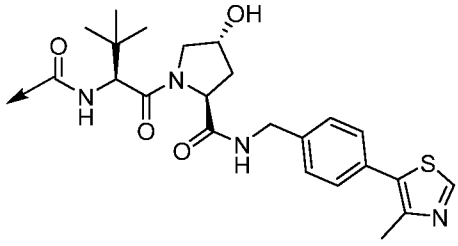
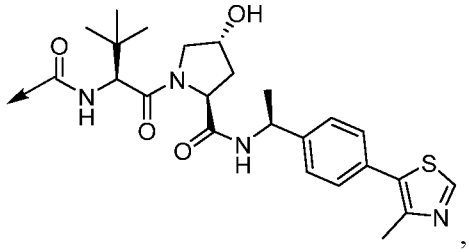
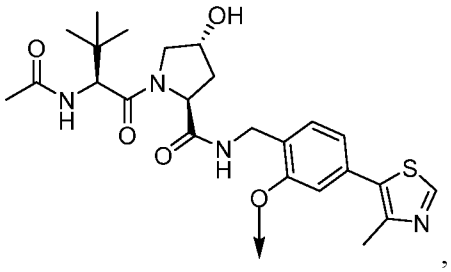
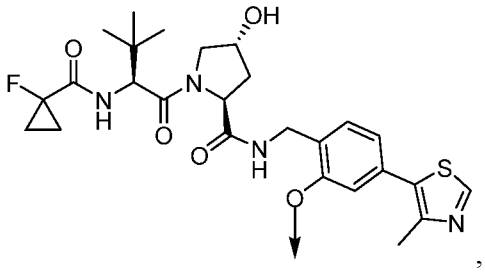
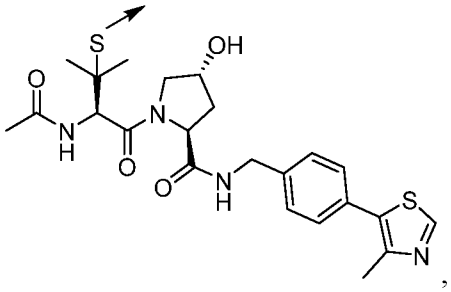
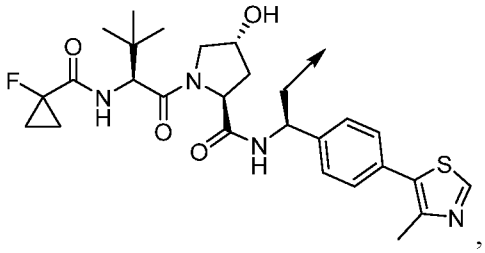
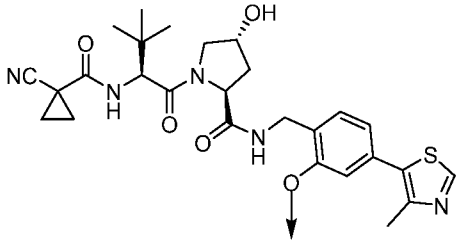
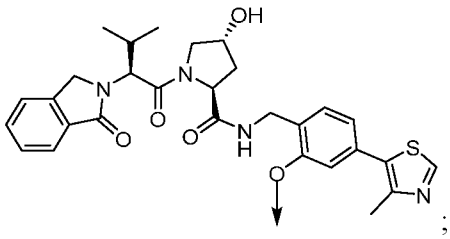
In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

and

;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

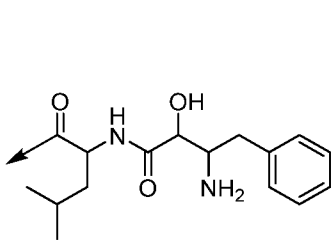
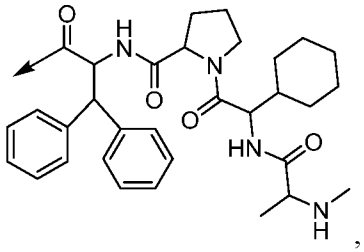
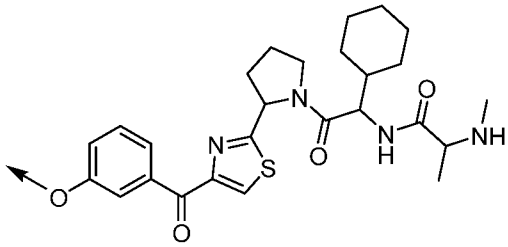
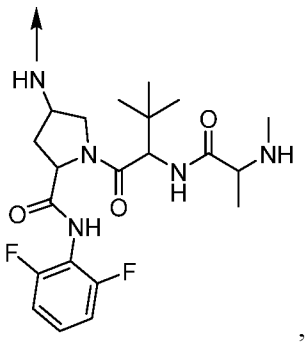
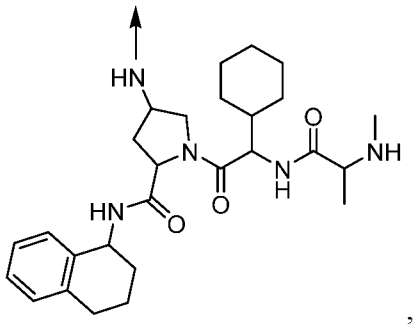
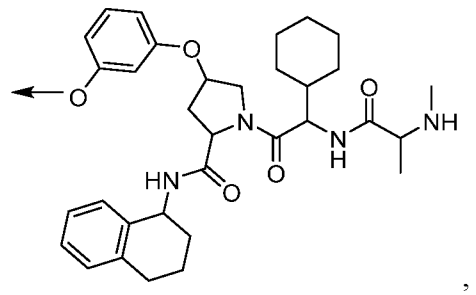
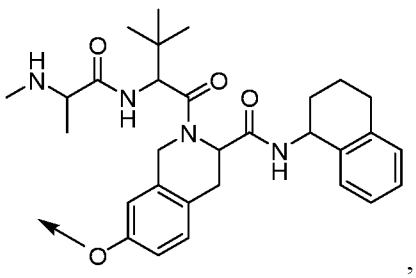
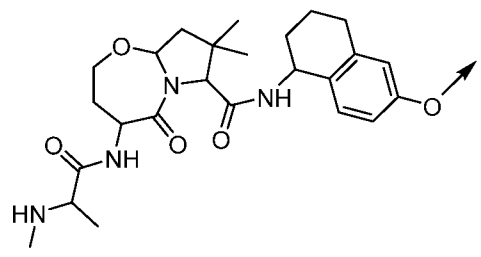
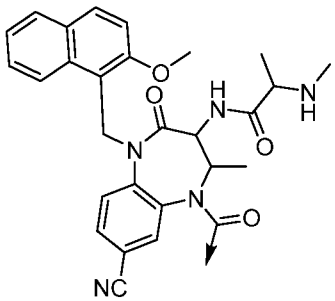
In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

and

;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

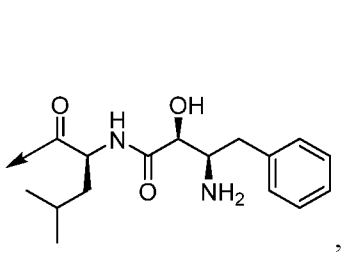
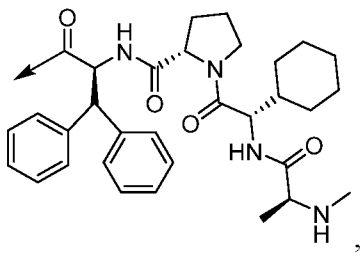
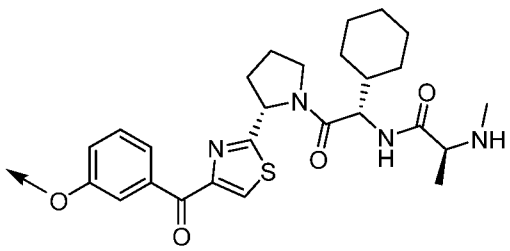
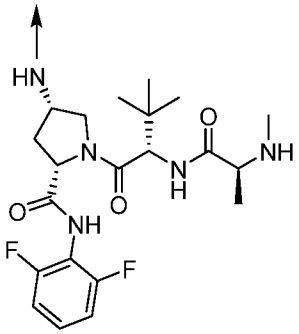
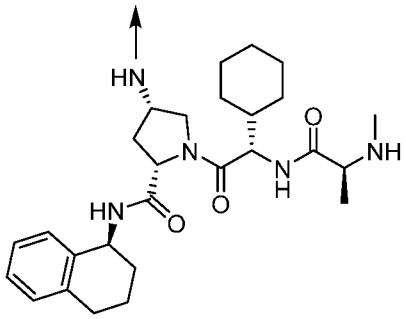
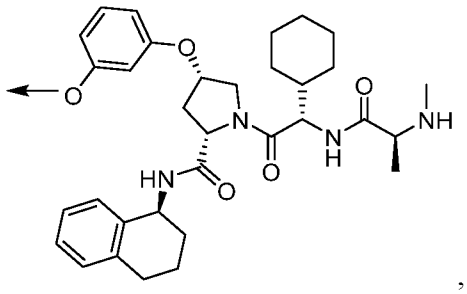
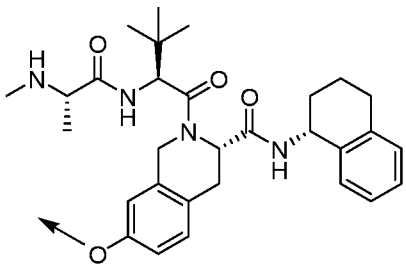
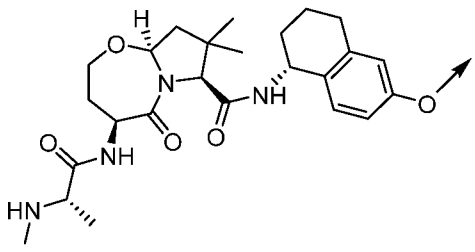
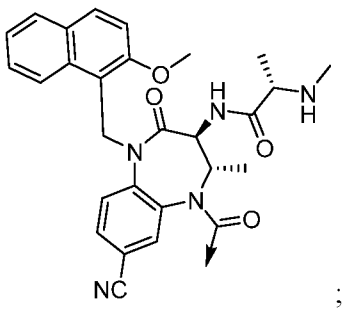
In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

,

and

;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

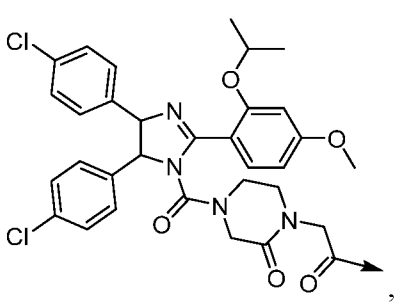
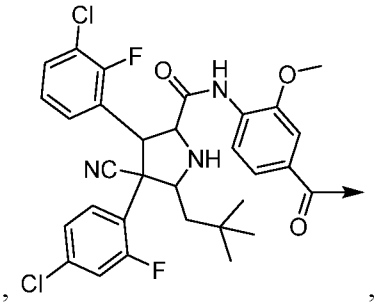
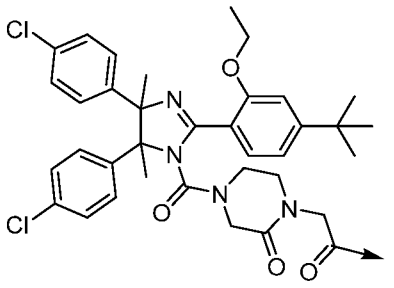
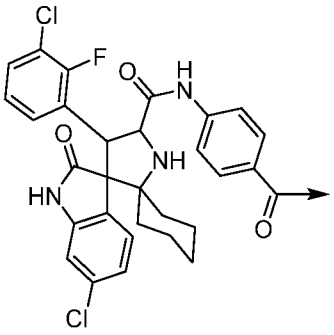
In some embodiments, the E3 ligase binding moiety is selected from:


,

,

,

,

,

,

,

and

;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

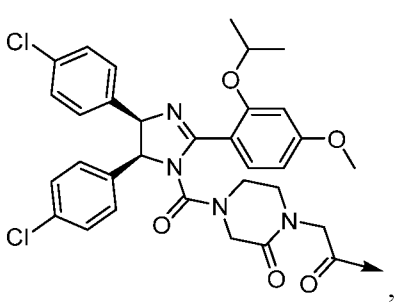
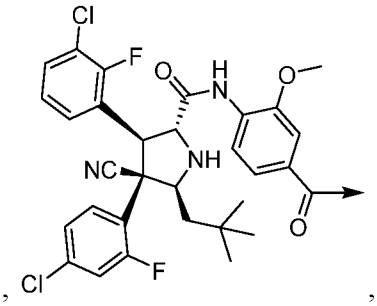
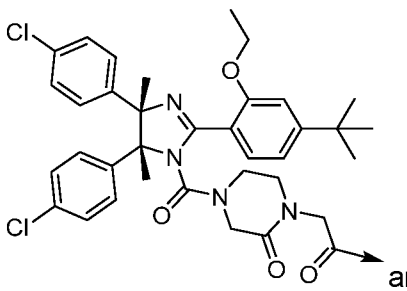
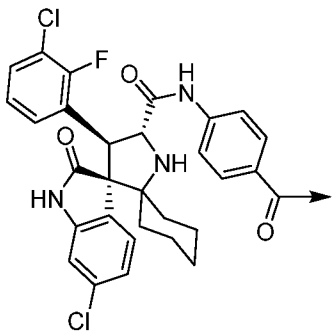





and ;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

In some embodiments, the E3 ligase binding moiety is selected from:

and ;

wherein the arrow denotes the covalent bond to L

or an E3 ligase binding derivative thereof.

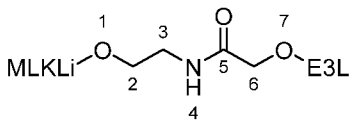
In some embodiments, the E3 ligase binding derivative is an optionally substituted derivative of any of the E3 ligase binding moieties described herein.

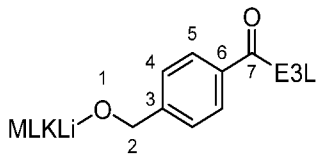
L

In the compounds of formula (X), L denotes a linker covalently linking MLKLi and E3L. Any suitable linking group may be used that it is compatible with MLKLi and E3L, does not interfere with the binding of MLKLi and E3L to their respective protein targets, and allows ubiquitin transfer from the E3 ligase to MLKL.

In some embodiments, the linker has a shortest linear chain length of 1 to 50 atoms.

As used herein "shortest linear chain length" defines the number of atoms in a chain defining the shortest path from MLKLi to E3L in a compound of the invention. For example, the shortest linear chain length in each of the following structures is 7 atoms (shortest chain length is numbered in each structure):





In some embodiments, the linker has a minimum shortest linear chain length of at least 1, 2, 3, 4, 5, 6, or 7 atoms. The linker may have a maximum shortest linear chain length of not more than 50, 45, 40, 35, 30, 25, 20, 15, 10, 9, 8 or 7 atoms. The linker may be characterised by a shortest linear chain length from any of these minimum lengths to any of these maximum lengths provided the minimum is less than the maximum. For example, the linker may be characterised by a shortest linear chain length of 1 to 35 atoms, 1-25 atoms, 1-20 atoms, 1-10 atoms, 2-10 atoms, 3-10 atoms or 5-9 atoms.

In some embodiments, the linker is a C_{1-50}alkyl optionally interrupted by one or more groups selected from:

a. -O-,

b. -NR^z-,

c. C_{3-8}cycloalkyl,

d. aryl,

e. C_{1-4}alkaryl,

f. heteroaryl,

g. $(C_{1-4}alkoxy)_{1-4}aryl$,
h. haloaryl,
i. 4-8-membered non-aromatic heterocyclyl,
j. $-C(O)NR^z-$,
k. alkenyl,
l. alkynyl,
wherein each R^z is indepedently selected from H and $C_{1-4}alkyl$,

and wherein each of the one or more groups a-l. may be further optionally substituted with a group selected from: $C_{3-6}cycloalkyl$, halo, -OH, -CN, $-NR^z_2$, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, oxo, $C_{1-4}alkylketone$, -COOH, $-C(O)N(R^z)_2$, and $-NR^zC(O)R^z$. In some embodiments, the one or more groups a-l. may be optionally substituted with one or more groups selected from oxo, $-C(O)N(R^z)_2$, and $-NR^zC(O)R^z$.

In some embodiments, each of the one or more groups a-l. may be further optionally substituted with a group selected from: halo, -OH, -CN, $-NR^z_2$, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, oxo, $C_{1-4}alkylketone$, -COOH, $-C(O)N(R^z)_2$, and $-NR^zC(O)R^z$. In some embodiments, the one or more groups a-l. may be optionally substituted with one or more groups selected from oxo, $-C(O)N(R^z)_2$, and $-NR^zC(O)R^z$.

$C_{1-50}alkyl$ may be optionally interrupted by any number of groups a-l provided the stability of the linker is sufficient to maintain the covalent connection between MLKLi and E3L under physiological conditions. Typically no more than 2 optional interrupting groups are included at consecutive positions along the $C_{1-50}alkyl$ chain. In some embodiments, the $C_{1-50}alkyl$ linker may be optionally interrupted by any number of groups a-l and optionally substituted.

In some embodiments, the $C_{1-50}alkyl$ linker may comprise 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of the one or more groups a-l. In some embodiments, the $C_{1-50}alkyl$ linker may comprise any number of groups a-l from any of these numbers to any other of these numbers, for example, from 1 to 20 or from 4-12 groups.

In some embodiments, the heteroaryl comprises at least one N heteroatom, such as triazolyl or pyrazolyl, preferably pyrazolyl.

The linker may comprise the moiety $-(OCH_2CH_2)_v-$, wherein v is an integer from 1 to 15. Inclusion of the repeating ethylene oxide moiety may assist to control the hydrophilicity (and hence solubility) of the compounds of the invention. In some

embodiments, the linker may comprise 1-6 ethylene glycol units, preferably 2-5 ethylene glycol units.

The linker may comprises at least one coupling moiety selected from: -C(O)O-, -C(O)NR^z-, -OC(O)O-, -NR^{z}C(O)NR^z-, -OC(O)NR^z-, triazolyl, aryl, α,β-unsubstituted ketone, β-hydroxy-ketone, 4-8-membered heteroaryl, unsaturated C_6-cycloalkyl and optionally substituted C_2alkenyl, wherein each R^z is independently selected from H and C_{1-4}alkyl. The coupling moiety is typically the product of the reaction used to couple MLKLi with E3L. In some embodiments the coupling moiety is selected from: -C(O)O, C(O)NR^z-, triazolyl, aryl, 4-8 membered heteroaryl (such as pyrazolyl) and aryl.

In some embodiments, the linker is a C_{1-50}alkyl optionally substituted by one or more groups selected from: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, hydroxyl, oxo, C_{1-6}alkoxy, aryloxy, C_{1-6}alkoxyaryl, halo, C_{1-6}alkylhalo, C_{1-6}alkoxyhalo, carboxyl, ester, cyano, nitro, amino, substituted amino, disubstituted amino, acyl, ketone, substituted ketone, amide, aminoacyl, substituted amide, disubstituted amide, thiol, alkylthio, thioxo, sulfate, sulfonate, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfonylamide, substituted sulfonamide, disubstituted sulfonamide, aryl, arC_{1-6}alkyl, heterocyclyl and heteroaryl wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclyl and groups containing them may be further optionally substituted.

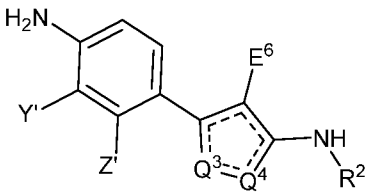
In some embodiments, the linker is a C_{1-50}alkyl optionally substituted by one or more groups selected from: C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-4}cycloalkyl, hydroxyl, oxo, C_{1-4}alkoxy, C_{1-4}alkoxyaryl, halo, C_{1-4}alkylhalo, C_{1-4}alkoxyhalo, carboxyl, ester, cyano, nitro, amino, substituted amino, disubstituted amino, acyl, ketone, substituted ketone, amide, thiol, alkylthio, thioxo, sulfate, sulfonate, sulfinyl, heterocyclyl and heteroaryl wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclyl and groups containing them may be further optionally substituted.

The C_{1-50}alkyl may be optionally substituted by any number of groups provided the stability of the linker is sufficient to maintain the covalent connection between MLKLi and E3L under physiological conditions. Typically no more than 2 optional substituting groups are included at consecutive positions along the C_{1-50}alkyl chain.Typically, the compounds of the invention may be prepared by techniques known in the art.

In another aspect, there is also provided a process for preparing a compound of formula (I) or a salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

In some embodiments, the process comprises any of the following 4 steps:

- reacting a compound of formula (III) with a compound of formula (IV)



III



IV

wherein X and R^2 are as defined for formula (I)

Q^3 and Q^4 are selected from N and N-PG^1, wherein when Q^3 is N, Q^4 is N-PG^1 and when Q^4 is N, Q^3 is N-PG^1;

Y' is selected from halo and Y, wherein Y is as defined for formula (I);

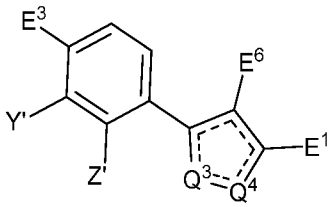
Z' is selected from halo and Z, wherein Z is as defined for formula (I);

PG^1 is R^1 or an amino protecting group, such as *tert*-butyl, benzyl, BOC and the like, wherein R^1 is as defined for formula (I); and

LG is a leaving group, such as halo. The leaving group may be any that is capable of activating the sulphonyl moiety of the compound of formula (IV) as an electrophile capable of reacting under appropriate conditions with the free aniline nitrogen of the compound of formula (III); and

E^6 is selected from -CN and $-C(O)NH_2$.

- reacting a compound of formula (V) with a compound of formula (VI)



V



VI

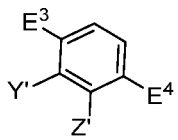
wherein Q^3, Q^4, E^6, Y' and Z' are as defined for formula (III) and R^2 is as defined for formula (I)

E^3 is selected from $-NO_2$, $-NHR^3$, $-NR^3PG^2$ and $-NHSO_2X$, wherein X an R^3 are as defined in formula (I) and PG^2 is an amino protecting group

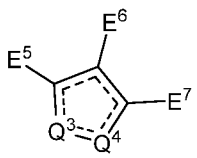
E^1 is selected from NH_2 or halo

E^2 is selected from NH_2 or halo with the proviso that one of E^1 and E^2 is NH_2 and the other is halo;

- reacting a compound of formula (VII) with a compound of formula (VIII)



VII



VIII

wherein E^3 is as defined for formula (V) and Q^3, Q^4, E^6, Y' and Z' are as defined for formula (III),
E^4 is selected from halo, a boronic acid and a boronic ester,
E^5 is selected from halo, a boronic acid and a boronic ester, with the proviso that one of E^4 and E^5 is halo and the other is a boronic acid or a boronic ester,
E^7 is selected from halo, $-NH_2$ and $-NHR^2$, wherein R^2 is as defined for formula (I);

- converting a compound of formula (I) into one of its salts.

In some embodiments, Q^3 is N and Q^4 is N-PG^1.

In some embodiments, Q^3 is N-PG^1 and Q^4 is N.

In some embodiments of the above process, wherein PG^1 is an amino protecting group, the process further comprises a deprotection step.

In some embodiments, wherein Y' is halo, the process comprises reacting the compound of formula (III), (V) or (VII) with Y-LG^2, wherein LG^2 is a leaving group and Y is as defined in formula (I). Typically, this reaction is a palladium mediated cross-coupling reaction. In some embodiments, this reaction takes place on the reaction product of the compound of formula (III) and (IV), (V) and (VI) or (VII) and (VIII).

In some embodiments, wherein Z' is halo, the process comprises reacting the compound of formula (III), (V) or (VII) with Z-LG^3, wherein LG^3 is a leaving group and Z is as defined in formula (I). Typically, this reaction is a palladium mediated cross-coupling reaction. In some embodiments, this reaction takes place on the reaction product of the compound of formula (III) and (IV), (V) and (VI) or (VII) and (VIII).

In some embodiments, wherein E^6 is -CN, the process further comprises conversion of the -CN into $-C(O)NH_2$.

Embodiments of these steps are shown in Schemes 1-7 below with reference to compounds wherein R^2 is represented by partial formula Ar1.

In another aspect, there is also provided a process for preparing a compound of formula (X) or a salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

In some embodiments, the process comprises a reaction with one or more of formula (XIII), formula (XIV) and formula (XV)

LG_V-L'-LG_A LG_V-L'-E3L' LG_V-E3L'

(XIII) (XIV) (XV)

wherein

L' is a linker moiety or a protected form of a linker moiety;

E3L' is an E3 ligase binding moiety or a protected form of an E3 ligase binding moiety;

LG_V is a group cleavable in the reaction with its coupling partner, wherein the coupling partner is selected from a compound of formula (I), formula (1A), formula (1B), formula (1A'), formula (1B'), formula (SI), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII) and formula (VIII); and

LG_A is H or a group cleavable in a subsequent step reacting moiety L' with E3L'.

In some embodiments, the process comprises reacting a compound of formula (I) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (1A) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (1B) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (1A') with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (1B') with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (SI) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (II) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (III) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (IV) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (V) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (VI) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (VII) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, the process comprises reacting a compound of formula (VIII) with a compound selected from the group consisting of formula (XIII), formula (XIV) and formula (XV).

In some embodiments, L' may be deprotected before deprotection of E3L'. In some embodiments, L' may be deprotected subsequent to deprotection of E3L'.

In some embodiments, L' may be deprotected before coupling with the coupling partner. In some embodiments, L' may be deprotected subsequent to coupling with the coupling partner.

In some embodiments, L' may be deprotected before cleavage of LG_A. In some embodiments, L' may be deprotected subsequent to cleavage of LG_A.

In some embodiments, E3L' may be deprotected before coupling with the coupling partner. In some embodiments, E3L' may be deprotected subsequent to coupling with the coupling partner.

In some embodiments, E3L' may be deprotected before cleavage of LG_A. In some embodiments, E3L' may be deprotected subsequent to cleavage of LG_A.

In some embodiments, LG_A is cleaved prior to coupling with the coupling partner. In preferred embodiments where LG_A is cleaved prior to coupling with the coupling partner, the process comprises reacting a compound of formula (XIII) with a compound of formula (XIV), thereby forming a compound of formula (XV). In some embodiments, LG_A is cleaved subsequent to coupling with the coupling partner.

In some embodiments, the process involving a reaction with one or more of formula (XIII), formula (XIV) and formula (XV) comprises a palladium mediated cross-coupling reaction.

In some embodiments, the process involving a reaction with one or more of formula (XIII), formula (XIV) and formula (XV) comprises deprotection of an amino protein group.

In some embodiments of the above process, wherein PG^1 is an amino protecting group, the process further comprises a deprotection step.

Embodiments of these steps are shown in the syntheses below.

The specific reagents and conditions for effecting each of these steps will depend on the specific substituents selected for each reaction partner. The skilled person would readily appreciate how to determine and/or optimise these reagents and conditions. Similarly, where a starting material is not commercially available, the skilled person would be able to design and implement its preparation based on techniques and reactions previously described. Embodiments of these steps are provided in the Examples with reference to specific compounds described herein.

Methods

In another aspect, there is provided a method for inhibiting necroptosis in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound according to Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

Without wishing to be bound by theory, it is believed that the compounds of the invention treat necroptosis by binding to the ATP-binding site of the pseudokinase domain of Mixed Lineage Kinase Domain-like (MLKL) protein and triggering its ubiquitination and protein degradation via the ubiquitin-proteasome pathway.

As such, in another aspect, there is a method of degrading mixed lineage kinase domain-like protein (MLKL). As used herein in the context of this invention, the terms “degrading” and “degradation” would be understood by the person skilled in the art to mean partial or complete proteolysis of the protein via the ubiquitin-proteasome pathway. The E3 ubiquitin ligase, prompts transfer of ubiquitin from an E2 ubiquitin conjugating enzyme, leading to ubiquitination of the target protein and degradation by the proteasomes.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

In one embodiment of the present disclosure, administration of a compound according to Formula (X) inhibits a conformational change of MLKL. In another embodiment, the conformational change of MLKL involves release of the four-helix bundle (4HB) domain of MLKL. In another embodiment, administration of the compound inhibits oligomerisation of MLKL. In yet another embodiment, administration of the compound inhibits translocation of MLKL to the cell membrane. In a further embodiment, administration of the compound inhibits a conformational change of MLKL, inhibits oligomerisation of MLKL and inhibits translocation of MLKL to the cell membrane.

It is envisaged that some compounds of the present disclosure can bind to MLKL in various species and inhibit necroptosis.

As used herein, the term “pseudokinase domain” as understood by a person skilled in the art, means a protein containing a catalytically-inactive or catalytically-defective kinase domain. “Pseudokinase domains” are often referred to as “protein kinase-like domains” as these domains lack conserved residues known to catalyse phosphoryl transfer. It would be understood by a person skilled in the art that although pseudokinase domains are predicted to function principally as catalysis independent protein-interaction modules, several pseudokinase domains have been attributed unexpected catalytic functions. Accordingly, in the present disclosure the term

"pseudokinase domain" includes "pseudokinase domains" which lack kinase activity and "pseudokinase domains" which possess weak kinase activity.

As used herein, the term "ATP-binding site" as understood by a person skilled in the art, means a specific sequence of protein subunits that promotes the attachment of ATP to a target protein. An ATP binding site is a protein micro-environment where ATP is captured and hydrolyzed to ADP, thereby releasing energy that is utilized by the protein to work by changing the protein shape and/or making the enzyme catalytically active. In pseudokinase domains, the "ATP-binding site" is often referred to as the "pseudoactive site". The term "ATP-binding site" may also be referred to as a "nucleotide-binding site" as binding at this site includes the binding of nucleotides other than ATP. It would be understood by a person skilled in the art that the term "nucleotide" includes any nucleotide. Exemplary nucleotides include, but are not limited to, AMP, ADP, ATP, AMPPNP, GTP, CTP and UTP.

As described herein, treatment and/or inhibition of necroptosis includes both complete and partial inhibition of necroptosis. In one embodiment, inhibition of necroptosis is complete inhibition. In another embodiment, inhibition of necroptosis is partial inhibition.

Binding of the compound to the ATP-binding site of the pseudokinase domain of MLKL may inhibit phosphorylation of MLKL by an effector kinase or binding of the compound to the ATP-binding site of the pseudokinase domain of MLKL may not inhibit phosphorylation of MLKL by an effector kinase. The present disclosure demonstrates that compounds that bind to the ATP-binding site of the pseudokinase domain of the MLKL protein, as described herein, can inhibit necroptosis without inhibiting phosphorylation of MLKL by an effector kinase. In one embodiment, binding of the compound to the ATP-binding site of the pseudokinase domain of MLKL does not inhibit phosphorylation of MLKL by an effector kinase. In another embodiment, binding of the compound to the ATP-binding site of the pseudokinase domain of MLKL inhibits phosphorylation of MLKL by an effector kinase.

RIP1, RIP3 and MLKL are three proteins implicated in the necroptotic pathway. Upon necroptotic stimulus (e.g. using the combination of TNF, SMAC mimetic and QVD-OPh on suitable cell lines), RIP1 is auto-phosphorylated leading to association with RIP3, which in turn auto-phosphorylates itself. Activated RIP3 phosphorylates MLKL leading to a putative conformational change that triggers its necroptotic activity (Murphy, *Immunity*, 39, pp 443 – 453, 2013). MLKL acts downstream of RIP1 and RIP3, and is therefore understood to be a key effector of necroptosis. Compounds of

this invention may bind to MLKL and block this conformational change or any other key event in its activation.

The compounds of the invention may be selective for MLKL. In some embodiments, the compounds of the invention are selective for MLKL over RIP1. In some embodiments, the compounds of the invention are selective for MLKL over RIP3. In some embodiments, the compounds of the invention are selective for MLKL over RIP1 and RIP3. A selective compound may have 5-fold, 10-fold, 50-fold, 100-fold, 500-fold, 1000-fold or greater selectivity for MLKL compared to RIP1 and/or RIP3. Typically, the relative selectivity may be assessed by comparing K_D values for each respective compound binding to the relevant protein (ie MLKL and either or both of RIP1 and RIP3). Suitable assay conditions are described in the Examples below. Compounds selective for MLKL may avoid undesired side-effects associated with RIP1 and/or RIP3 loss of function.

In another aspect, there is provided a compound of Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, N-oxide and/or prodrug thereof for use as a medicament.

In another aspect, there is provided use of a compound of Formula (X) a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof in the preparation of a medicament for the inhibition of necroptosis in a subject.

In another aspect, there is provided use of a composition comprising a compound of Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof for the inhibition of necroptosis in a subject.

In another aspect, there is provided use of a compound of Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof for inhibiting necroptosis.

In another aspect, there is provided use of a composition comprising a compound of Formula (X) or a salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof for inhibiting necroptosis.

In yet another aspect, there is provided a compound according to Formula (X) or a salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof for use in inhibiting necroptosis.

In yet another aspect, there is provided a composition comprising a compound according to Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof for use in inhibiting necroptosis. In some embodiments, the composition is a pharmaceutical composition.

In yet another aspect, there is provided a compound according to Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof when used for inhibiting necroptosis.

In yet another aspect, there is provided a composition comprising a compound according to Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof when used for inhibiting necroptosis.

In another aspect, there is provided a method of inhibiting MLKL, comprising contacting a cell with an effective amount of a compound of formula (X) or a salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

The salts of the compounds of Formula (X) are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present disclosure, for example, as these may be useful as intermediates in the preparation of pharmaceutically acceptable salts or in methods not requiring administration to a subject.

The term “pharmaceutically acceptable” may be used to describe any salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, or any other compound which upon administration to a subject, is capable of providing (directly or indirectly) a compound of Formula (X) or an active metabolite or residue thereof and typically that is not deleterious to the subject.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, zinc, ammonium, alkylammonium such as salts formed from triethylamine,

alkoxyammonium such as those formed with ethanolamine and salts formed from ethylenediamine, choline or amino acids such as arginine, lysine or histidine. General information on types of pharmaceutically acceptable salts and their formation is known to those skilled in the art and is as described in general texts such as "*Handbook of Pharmaceutical salts*" P.H.Stahl, C.G.Wermuth, 1st edition, 2002, Wiley-VCH.

In the case of compounds that are solids, it will be understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

The invention includes all crystalline forms of a compound of Formula (X) including anhydrous crystalline forms, hydrates, solvates and mixed solvates. If any of these crystalline forms demonstrates polymorphism, all polymorphs are within the scope of this invention.

Formula (X) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, Formula (X) includes compounds having the indicated structures, including the hydrated or solvated forms, as well as the non-hydrated and non-solvated forms.

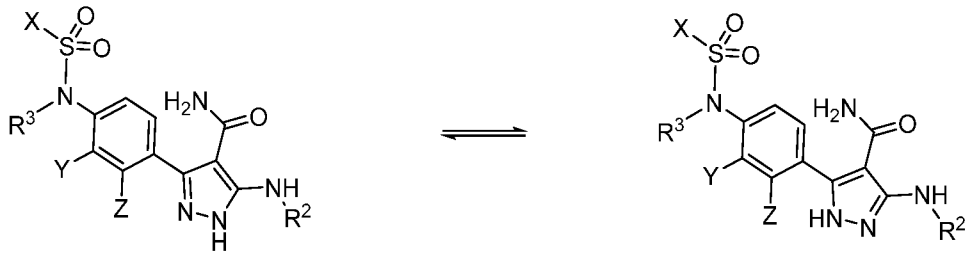
The compounds of Formula (X) or salts, tautomers, N-oxides, polymorphs or prodrugs thereof may be provided in the form of solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, alcohols such as methanol, ethanol or isopropyl alcohol, DMSO, acetonitrile, dimethyl formamide (DMF), acetic acid, and the like with the solvate forming part of the crystal lattice by either non-covalent binding or by occupying a hole in the crystal lattice. Hydrates are formed when the solvent is water, alcoholates are formed when the solvent is alcohol. Solvates of the compounds of the present invention can be conveniently prepared or formed during the processes described herein. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the invention.

Basic nitrogen-containing groups may be quarternised with such agents as C_{1-6}alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

Nitrogen containing groups may also be oxidised to form an N-oxide.

The compound of Formula (X) or salts, tautomers, N-oxides, solvates and/or prodrugs thereof that form crystalline solids may demonstrate polymorphism. All polymorphic forms of the compounds, salts, tautomers, N-oxides, solvates and/or prodrugs are within the scope of the invention.

The compound of Formula (I) (and therefore also the compound of formula (X)) may demonstrate tautomerism. Tautomers are two interchangeable forms of a molecule that typically exist within an equilibrium. Any tautomers of the compounds of Formula (I) are to be understood as being within the scope of the invention when included in a compound of the invention as moiety MLKLi. For example, when R^1 is H the compounds of formula (1A) and (1B) may exist as tautomers, eg in equilibrium with each other. The compounds of formula (1A) and (1B) wherein R^1 is H are depicted below as compounds of formulas (1A') and (1B'). The proportion of compounds of formula (1A') to (1B') in equilibrium may depend on the specific compound and conditions, such as solvent, temperature, concentration, etc. This equilibrium may be described as follows:



(1A') (1B')

Similar tautomerism may occur for any pyrazole-containing compound described herein, including compounds of formula (II), (III), (V), (VIII) and (SI), compounds 1-320 and compounds 1001-1014, 1016-1037, 1039-1053 and 1055-1060. All tautomers of these compounds are contemplated and considered within the scope of the present invention. In addition, further tautomeric forms may exist for the compounds described herein for example depending on various substituents selected.

The compound of Formula (X) may contain one or more stereocentres. All stereoisomers of the compounds of formula (X) are within the scope of the invention. Stereoisomers include enantiomers, diastereomers, geometric isomers (*E* and *Z* olephinic forms and *cis* and *trans* substitution patterns) and atropisomers. In some embodiments, the compound is a stereoisomerically enriched form of the compound

of formula (X) at any stereocentre. The compound may be enriched in one stereoisomer over another by at least about 60, 70, 80, 90, 95, 98 or 99%.

The compound of Formula (X) or its salts, tautomers, solvates, N-oxides, and/or stereoisomers, may be isotopically enriched with one or more of the isotopes of the atoms present in the compound. For example, the compound may be enriched with one or more of the following minor isotopes: ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N and/or ^{17}O. An isotope may be considered enriched when its abundance is greater than its natural abundance.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a subject or patient, to produce a compound of formula (X) provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, carboxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, carboxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to generate the parent compounds.

Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (eg, two, three or four) amino acid residues which are covalently joined to free amino, and amido groups of compounds of Formula (X). The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvlin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of Formula (X) through the carbonyl carbon prodrug sidechain.

Pharmaceutical compositions may be formulated from compounds according to Formula (X) for any appropriate route of administration including, for example, oral, rectal, nasal, vaginal, topical (including transdermal, buccal, ocular and sublingual), parenteral (including subcutaneous, intraperitoneal, intradermal, intravascular (for example, intravenous), intramuscular, spinal, intracranial, intrathecal, intraocular, periocular, intraorbital, intrasynovial and intraperitoneal injection, intracisternal

injection as well as any other similar injection or infusion techniques), inhalation, insufflation, infusion or implantation techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions).

In certain embodiments, compositions in a form suitable for oral use or parenteral use are preferred. Suitable oral forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. For intravenous, intramuscular, subcutaneous, or intraperitoneal administration, one or more compounds may be combined with a sterile aqueous solution which is preferably isotonic with the blood of the recipient. Such formulations may be prepared by dissolving solid active ingredient in water containing physiologically compatible substances such as sodium chloride or glycine, and having a buffered pH compatible with physiological conditions to produce an aqueous solution, and rendering said solution sterile. The formulations may be present in unit or multi-dose containers such as sealed ampoules or vials. Examples of components are described in Martindale – The Extra Pharmacopoeia (Pharmaceutical Press, London 1993), and Remington: *The Science and Practice of Pharmacy*, 21st Ed., 2005, Lippincott Williams & Wilkins. All methods include the step of bringing the active ingredient, for example a compound defined by Formula (X), or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, N-oxide and/or prodrug thereof, into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient, for example a compound defined by Formula (X), or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, N-oxide and/or prodrug thereof, into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect. In some embodiments, the method of the invention comprises administering a pharmaceutical comprising a compound of Formula (X) or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, N-oxide and/or prodrug thereof and a pharmaceutically acceptable carrier, diluent and/or excipient.

In the context of this specification the term “administering” and variations of that term including “administer” and “administration”, includes contacting, applying, delivering or providing a compound or composition of the invention to an organism, or a surface by any appropriate means.

For the inhibition of necroptosis, the dose of the biologically active compound according to the invention may vary within wide limits and may be adjusted to individual requirements. Active compounds according to the present invention are generally administered in a therapeutically effective amount. The daily dose may be administered as a single dose or in a plurality of doses. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the subject, time of administration, route of administration, and rate of excretion, drug combination (i.e. other drugs being used to treat the subject), and the severity of the particular disorder undergoing therapy. Such treatments may be administered as often as necessary and for the period of time judged necessary by the treating physician. A person skilled in the art will appreciate that the dosage regime or therapeutically effective amount of the compound of formula (X) to be administered may need to be optimized for each individual.

It will also be appreciated that different dosages may be required for treating different disorders. An effective amount of an agent is that amount which causes a statistically significant decrease in necroptosis.

For *in vitro* analysis, the necroptosis inhibition may be determined by assays used to measure TSQ-induced necroptosis, as described in the biological tests defined herein.

The terms “treating”, “treatment” and “therapy” are used herein to refer to curative therapy, prophylactic therapy and preventative therapy. Thus, in the context of the present disclosure the term “treating” encompasses curing, ameliorating or tempering the severity of necroptosis and/or associated diseases or their symptoms.

“Preventing” or "prevention" means preventing the occurrence of the necroptosis or tempering the severity of the necroptosis if it develops subsequent to the administration of the compounds or pharmaceutical compositions of the present invention.

“Subject” includes any human or non-human animal. Thus, in addition to being useful for human treatment, the compounds of the present invention may also be useful for

veterinary treatment of mammals, including companion animals and farm animals, such as, but not limited to dogs, cats, horses, cows, sheep, and pigs.

The term “inhibit” is used to describe any form of inhibition that results in prevention, reduction or otherwise amelioration of necroptosis and/or MLKL function, including complete and partial inhibition.

The term “degrade” is used to describe any degree of degradation of the target protein that results in diminished function of MLKL and otherwise amelioration of necroptosis. In some embodiments, a compound of the invention trigger substantially complete degradation of the target MLKL protein to which it binds. Accordingly, also described herein are methods of degrading MLKL in a subject, comprising administering to the subject a compound of the invention.

As the compounds of the invention include both an MLKL binding moiety – MLKLi – that is based on a series of MLKL inhibitors described in WO 2021/253,095 A1 (entirely incorporated herein by reference), compounds of the invention may both inhibit and degrade MLKL, which may enhance the amelioration of necroptosis in a subject.

The compounds of the present invention may be administered along with a pharmaceutical carrier, diluent and/or excipient as described above.

The methods of the present disclosure can be used to prevent or treat the following disease(s), condition(s) and/or disorder(s) in a subject:

- diseases of the bones, joints, connective tissue and of cartilage, such as osteoporosis, osteomyelitis including chronic recurrent multifocal osteomyelitis, arthritises including for example osteoarthritis, rheumatoid arthritis and psoriatic arthritis, avascular necrosis, progressive fibrodysplasia ossificans, rickets, Cushing's syndrome;
- muscular diseases such as muscular dystrophy, such as for example Duchenne's muscular dystrophy, myotonic dystrophies, myopathies and myasthenias;
- diseases of the skin, such as dermatitis, eczema, psoriasis, aging or even alterations of scarring;
- cardiovascular diseases such as cardiac and/or vascular ischemia, myocardial infarction, ischemic cardiopathy, chronic or acute congestive heart failure,

cardiac dysrythmia, atrial fibrillation, ventricular fibrillation, paroxystic tachycardia, congestive heart failure, hypertrophic cardiopathy, anoxia, hypoxia, secondary effects due to therapies with anti-cancer agents;

- circulatory diseases such as atherosclerosis, arterial scleroses and peripheral vascular diseases, strokes including cerebrovascular strokes, aneurisms;
- haematological and vascular diseases such as: anemia, aplastic anemia, vascular amyloidosis, haemorrhages, drepanocytosis, red cell fragmentation syndrome, neutropenia, leukopenia, medullar aplasia, pantocytopenia, thrombocytopenia, haemophilia;
- lung diseases including pneumonia, asthma; obstructive chronic diseases of the lungs such as for example chronic obstructive pulmonary disease (COPD), chronic bronchitis and emphysema;
- diseases of the gastro-intestinal tract, such as ulcers; inflammatory bowel diseases (IBD), including Crohn's disease, ulcerative colitis;
- diseases of the liver such as for example hepatitis particularly hepatitis of viral origin or having as causative agent other infectious agents, auto-immune hepatitis, fulminating hepatitis, inflammatory hepatitis, certain hereditary metabolic disorders, Wilson's disease, cirrhoses, non-alcoholic fatty liver disease (NAFLD) including non-alcoholic hepatic steatosis and/or non-alcoholic steatohepatitis (NASH), diseases of the liver due to toxins and to drugs such as drug-induced liver injury, ethanol (or alcohol)-induced liver disease;
- diseases of the pancreas such as for example acute or chronic pancreatitis;
- metabolic diseases such as diabetes, including diabetes mellitus, pre-diabetes and insipid diabetes; thyroiditis;
- diseases of the kidneys such as acute renal disorders (such as acute kidney injury (AKI), including ischaemic reperfusion injury (IRI)) or glomerulonephritis;
- viral and bacterial infections such as septicemia;
- severe intoxications by chemicals, toxins or drugs;

- degenerative diseases associated with the Acquired Immune Deficiency Syndrome (AIDS);
- disorders associated with aging such as the syndrome of accelerated aging;
- inflammatory diseases such as Terminal ileitis including Crohn's disease, rheumatoid polyarthritis, TNF-induced systemic inflammatory syndrome;
- auto-immune diseases such as erythematous lupus (including systemic lupus erythematosus), cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome;
- dental disorders such as those resulting in degradation of tissues such as for example periodontitis;
- ophthalmic diseases or disorders including diabetic retinopathies, glaucoma, macular degenerations, retinal degeneration, retinitis pigmentosa, retinal holes or tears, retinal detachment, retinal ischemia, acute retinopathies associated with trauma, inflammatory degenerations, post-surgical complications, medicinal retinopathies, cataract, cone cell degeneration;
- disorders of the audition tracts, such as otosclerosis and deafness induced by antibiotics;
- Ischemic reperfusion injury, including retinal ischaemic reperfusion injury;
- Neuronal loss, including Alzheimer's disease and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS; also referred to as motor neuron disease (MND) and Charcot disease);
- diseases associated with mitochondria (mitochondrial pathologies), such as Friedrich's ataxia, congenital muscular dystrophy with structural mitochondrial abnormality, certain myopathies (MELAS syndrome, MERFF syndrome, Pearson's syndrome), MIDD (mitochondrial diabetes and deafness) syndrome, Wolfram's syndrome, dystonia;
- cancer and metastasis including but not limited to cancers of the lung and bronchus, including non-small cell lung cancer (NSCLC), squamous lung cancer, brochioloalveolar carcinoma (BAC), adenocarcinoma of the lung, and small cell lung cancer (SCLC); prostate cancer, including androgen-dependent and androgen-independent prostate cancer; breast cancer,

including metastatic breast cancer; pancreatic cancer; cancers of the colon and rectum; thyroid cancer; cancers of the liver and intrahepatic bile duct; hepatocellular cancer; gastric cancer; endometrial cancer; melanoma; cancers of the kidney, renal pelvis, urinary bladder, uterine corpus and uterine cervix; ovarian cancer, including progressive epithelial or primary peritoneal cancer; multiple myeloma; oesophageal cancer, including squamous cell carcinoma and adenocarcinoma of the oesophagus; acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); lymphocytic leukemia; myeloid leukemia; acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non- Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL); T-cell lymphoma; multiple myeloma (MM); amyloidosis; Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes; cancers of the brain, including glioma/glioblastoma, anaplastic oligodendroglioma, and adult anaplastic astrocytoma; neuroendocrine cancers, including metastatic neuroendocrine tumors; cancers of the head and neck, including , e.g., squamous cell carcinoma of the head and neck, and nasopharyngeal cancer; cancers of the oral cavity, pharynx and small intestine; bone cancer; soft tissue sarcoma; and villous colon adenoma; and

- diseases of the central nervous system (CNS), such as multiple sclerosis (MS).

In some embodiments, the methods of the present disclosure may be for treating and/or preventing any one or more of the diseases, conditions and/or disorders disclosed herein. For example, in some embodiments, there is provided a method for treating and/or preventing any one or more of: retinal ischaemic reperfusion injury, chronic recurrent multifocal osteomyelitis, aplastic anaemia, CRIA, ethanol-induced liver disease, NASH, inflammatory hepatitis, acute kidney injury, IRI, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, stroke, systemic lupus erythematosus, myocardial infarction, diabetes, Crohn's disease, inflammatory bowel disease and COPD, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

The methods can also be used for protecting cells, tissues and/or transplanted organs, whether before, during (removal, transport and/or re-implantation) or after transplantation.

In some embodiments, the compound of the invention may be administered in combination with a further active pharmaceutical ingredient (API). The API may be any that is suitable for treating any of the diseases, conditions and/or disorders associated with necroptosis, such as those described herein. The compound of the invention may be co-formulated with the further API in any of the pharmaceutical compositions described herein, or the compound of the invention may be administered in a concurrent, sequential or separate manner. Concurrent administration includes administering the compound of the invention at the same time as the other API, whether coformulated or in separate dosage forms administered through the same or different route. Sequential administration includes administering, by the same or different route, the compound of the invention and the other API according to a resolved dosage regimen, such as within about 0.5, 1, 2, 3, 4, 5, or 6 hours of the other. When sequentially administered, the compound of the invention may be administered before or after administration of the other API. Separate administration includes administering the compound of the invention and the other API according to regimens that are independent of each other and by any route suitable for either active, which may be the same or different.

The methods may comprise administering the compound of Formula (X) in any pharmaceutically acceptable form. In some embodiments, the compound of Formula (X) is provided in the form of a pharmaceutically acceptable salt, solvate, N-oxide, polymorph, tautomer or prodrug thereof, or a combination of these forms in any ratio.

The methods may also comprise administering a pharmaceutical composition comprising the compound of formula (X) or a pharmaceutically acceptable salt, solvate, N-oxide, polymorph, tautomer or prodrug thereof to the subject in need thereof. The pharmaceutical composition may comprise any pharmaceutically acceptable carrier, diluent and/or excipient described herein.

The compounds of Formula (X), or a pharmaceutically acceptable salt or prodrug thereof, as defined herein, may be administered by any suitable means, for example, orally, rectally, nasally, vaginally, topically (including buccal and sub-lingual), parenterally, such as by subcutaneous, intraperitoneal, intravenous, intramuscular, or intracisternal injection, inhalation, insufflation, infusion or implantation techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions).

The compounds of the invention may be provided as pharmaceutical compositions including those for oral, rectal, nasal, topical (including buccal and sub-lingual), parenteral administration (including intramuscular, intraperitoneal, sub-cutaneous and intravenous), or in a form suitable for administration by inhalation or insufflation. The compounds of Formula (X), or a pharmaceutically acceptable salt or prodrug thereof, together with a conventional adjuvant, carrier or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids as solutions, suspensions, emulsions, elixirs or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use.

Also provided is a kit of parts, comprising in separate parts:

- a compound of Formula (X) or a pharmaceutically acceptable salt, solvate, N-oxide, polymorph, tautomer or prodrug thereof; and
- instructions for its use in any of the methods of the invention.

The compounds, compositions, kits and methods described herein are described by the following illustrative and non-limiting examples.

Examples

CHEMISTRY

Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents, which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd. Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., 1H or 13C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high-performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, “ambient temperature,” “room temperature,” “RT” and “r.t.”, as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 ºC to about 30 ºC.

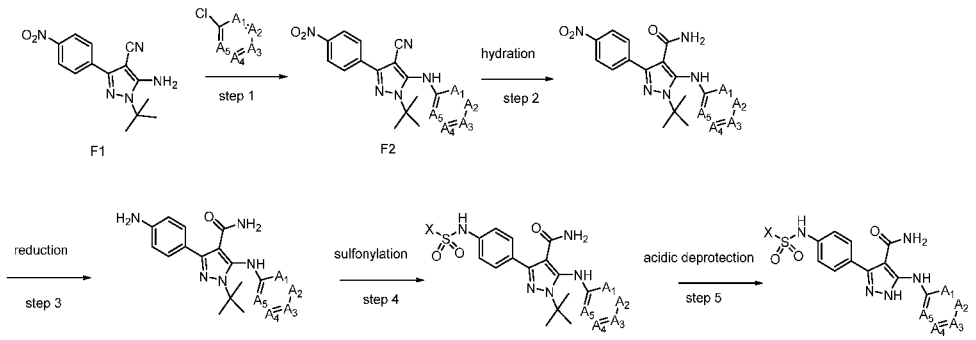
Compounds of the invention can be prepared according to numerous preparatory routes known in the literature. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

General description of chemistry

Scheme 1 shows a general synthesis of aminopyrazolocarboxamide compounds of the invention. Aminopyrazolonitrile (F1), which can be prepared *via* routes known to one skilled in the art, can be converted to N-heteroaryl aminopyrazolonitrile F2 (step 1) by treatment with a haloheteroarene in the presence of palladium such as tris(dibenzylideneacetone)dipalladium(0) or palladium(II) acetate and a ligand such as Xantphos with a base such as cesium carbonate in a solvent such as 1,4-dioxane or diglyme at elevated temperature such as 65 °C or under microwave reaction such as 150 °C. The nitrile group can be converted to a primary amide in a presence of a reagent such as Ghaffar-Parkins catalyst in a solvent such as 1,4-dioxane and water at elevated temperature such as 100 °C, or with 30% hydrogen peroxide in water with an aqueous sodium hydroxide solution in a polar solvent such as dimethyl sulfoxide and a protic solvent such as ethanol at elevated temperature such as 100 °C (step 2). The nitro substituent can be reduced to the aniline in the presence of an aqueous solution of ammonium chloride in a protic solvent such as methanol in a presence of

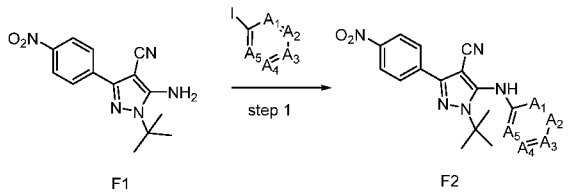
zinc dust at room temperature (step 3). The aniline can subsequently be converted to the sulfonamide with the appropriate sulfonyl chloride in the presence of an amine base such as pyridine or triethylamine in a chlorinated solvent such as dichloromethane or chloroform or neat at room temperature (step 4). The compounds of invention can be obtained *via* an acidic deprotection with an acid such as trifluoroacetic acid in a solvent such as dichloromethane at room temperature.

Scheme 1



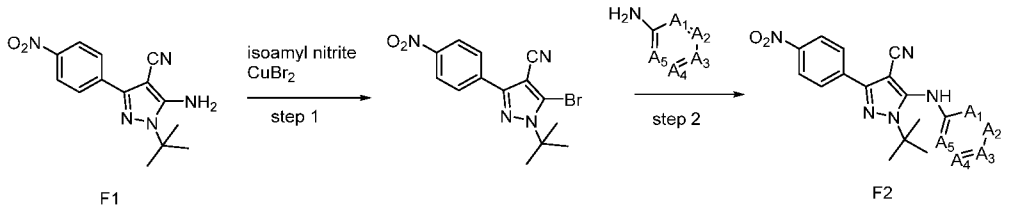
Alternatively, compound F2 can be prepared from the iodoheteroarenes (examples where A1 and A5 are CH) by treatment with palladium species such as palladium acetate in the presence of a ligand such as Xantphos with a base such as cesium carbonate in a solvent such as 1,4-dioxane at elevated temperature such as 65 °C.

Scheme 2



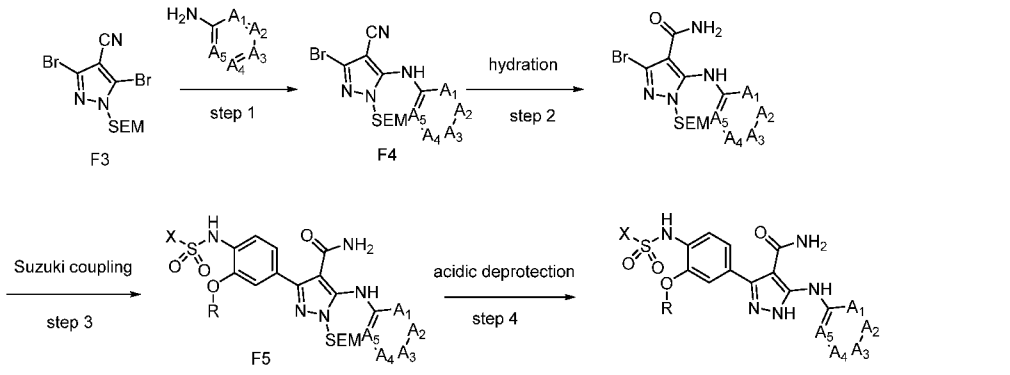
Alternatively, compound F2 can be prepared from F1 by treatment with a reagent such as isoamyl nitrite in the presence of a copper species such as copper(II) bromide in a polar solvent such as acetonitrile at room temperature (step 1). The bromopyrazole can be converted to F2 with arylamines by treatment with a palladium species such as tris(dibenzylideneacetone)dipalladium(0) in the presence of a ligand such as Xantphos with a base such as cesium carbonate in a solvent such as 1,4-dioxane at elevated temperature such as 65 °C.

Scheme 3



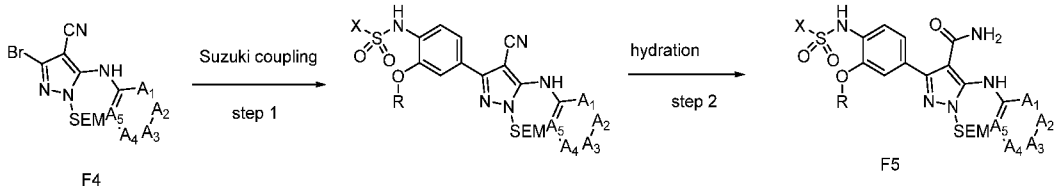
Scheme 4 shows an alternative general synthesis of aminopyrazolocarboxamide compounds of the invention. Dibromopyrazole (F3), which can be prepared *via* routes known to one skilled in the art, can be converted to N-heteroaryl bromopyrazolonitrile F4 in the presence of a palladium catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as Xantphos, a base such as cesium carbonate, in a non-polar solvent such as 1,4-dioxane at an elevated temperature such as 65 °C (Step 1). Conversion of the nitrile group to a primary amide can be performed in the presence of a reagent such as Ghaffar-Parkins catalyst in a solvent such as 1,4-dioxane and water at elevated temperature such as 100 °C, or with 30% hydrogen peroxide in water with an aqueous sodium hydroxide solution in a polar solvent such as dimethyl sulfoxide and protic solvent such as ethanol at elevated temperature such as 100 °C (step 2). The subsequent coupling reaction can be performed in the presence of a palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) or palladium(II) acetate with a ligand such as SPhos and a base such as sodium carbonate or potassium carbonate in a solvent such as a mixture 1,4-dioxane and water or acetonitrile and water at elevated temperature such as 100 °C or under microwave irradiation at elevated temperature such as 100 °C to provide F5 (step 3). The SEM protecting group can be removed to provide compounds of the invention under acidic conditions such as trifluoroacetic acid in a solvent such as dichloromethane or using an aqueous hydrogen chloride solution at room temperature.

Scheme 4



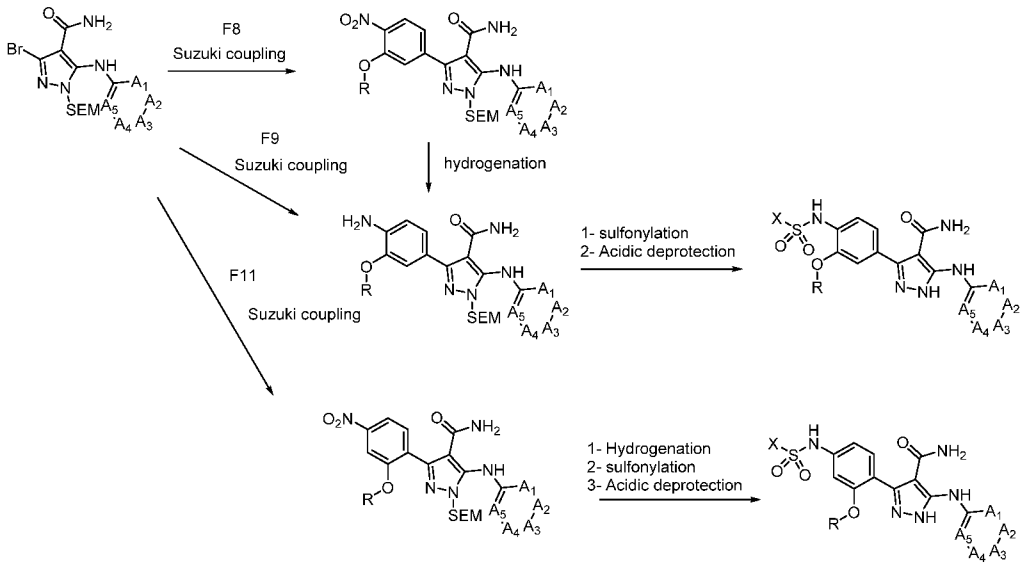
Alternatively (scheme 5), step 2 and step 3 from scheme 4 can be interconverted to provide F5 from F4 following the same description as depicted in scheme 4.

Scheme 5



Alternatively, the Suzuki cross coupling reaction can be performed with boronate ester F8, F9 or F11 following the previously described reactions (scheme 6).

Scheme 6



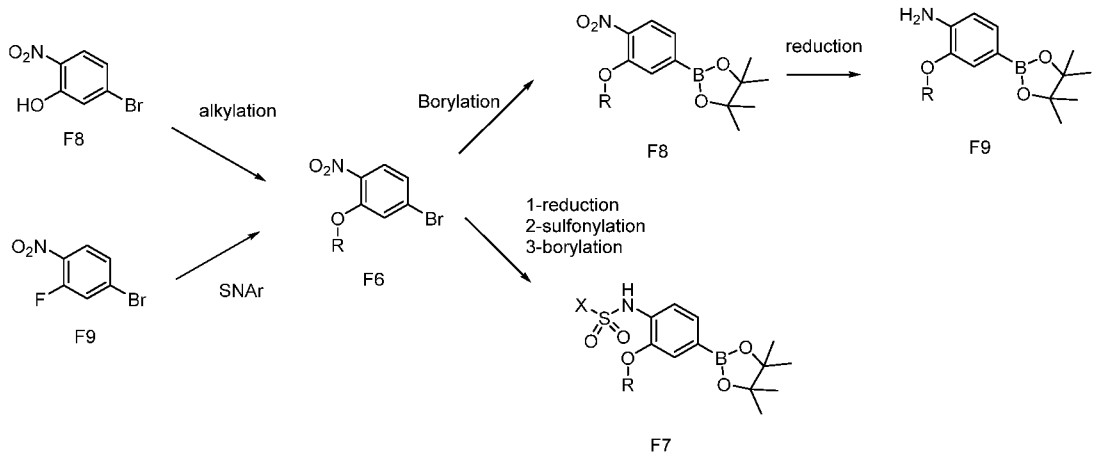
Scheme 7 summarizes the preparation of the bromoaryl F6 and the boronate esters F7, F8, F9 and F11 which can be obtained from F6 or F10.

F7 can be obtained following a nitro reduction and sulfonylation reaction previously described above and a borylation reaction in the presence of bis(pinacolato)diboron and palladium species such as [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) and a base such as potassium acetate in a solvent such as 1,4-dioxane at elevated temperature such as 100 °C. F8 can be obtained from F6 *via* a borylation reaction previously described and F9 can be prepared from F8 *via* a nitro reduction previously described.

F11 can be obtained from F10 *via* a borylation reaction previously described and F10 can be obtained from a phenol and the desired alcohol *via* a Mitsunobu reaction with PPh_3, DIAD or DEAD in a solvent such as THF or toluene at room temperature or elevated temperature such as 70 °C.

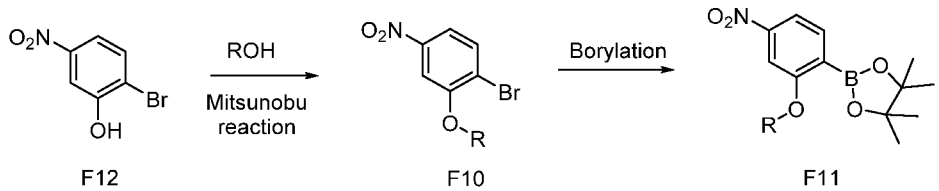
F6 can be obtained *via* either alkylation of the substituted phenol F8 with the corresponding halogenoalkyl or halogenomethyl(hetero)aryl in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, or *via* the nucleophilic substitution of the fluoronitroarene F9 with the corresponding alcohol/(hetero)arylalcohol in the presence of a strong base such as sodium hydride in a polar solvent such as N,N-dimethylformamide or tetrahydrofuran.

Scheme 7



Scheme 8 summarize the synthesis of F10 and F11. F10 can be obtained *via* alkylation of the substituted phenol F12 with the corresponding halogenoalkyl or halogenomethyl(hetero)aryl in the presence of a base such as potassium carbonate in a solvent such as acetonitrile and F11 can be obtain via a borylation reaction of F10 already described.

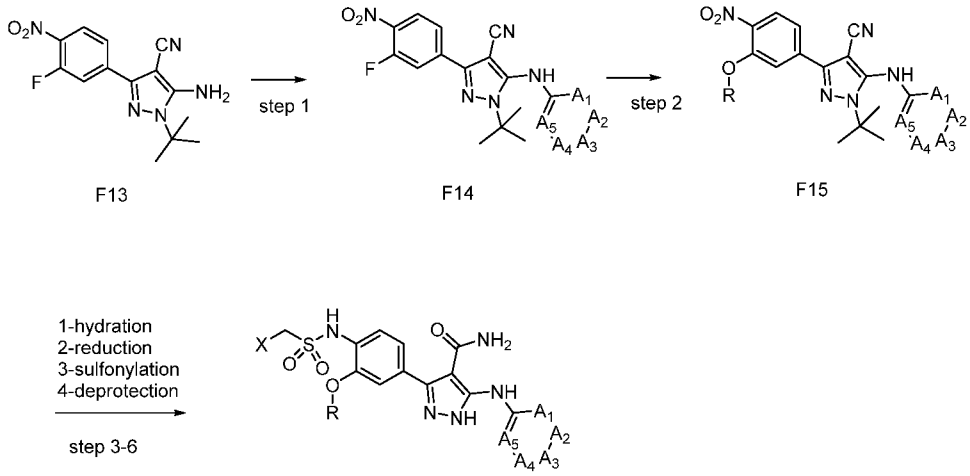
Scheme 8



Scheme 9 shows an alternative route for the trisubstituted phenyl derivatives synthesis. Compound F13, which can be prepared *via* routes known to one skilled in

the art, can be converted to N-(hetero)aryl pyrazolonitrile F14 as described above (step 1). Displacement of the fluoroaryl F14 in the presence of alcohols/ (hetero)arylalcohols with strong base such as sodium hydride in a polar solvent such as N,N-dimethylformamide or tetrahydrofuran can provide F15, which can then be substituted to the compound of the invention following route described below (steps 3-6).

Scheme 9



General chemistry methods

Definitions:

AcCl	(acetyl chloride);
Ac_2O	(acetic anhydride);
AcOH	(acetic acid);
atm	(atmosphere);
B_2pin_2	(bis(pinacolato)diboron);
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl);
BnBr	(benzyl bromide);
Boc_2O	(di-*tert*-butyl dicarbonate);
c-Hex	(cyclohexane);
$C_6H_{19}O_3P_3Pt$	(dimethylphosphinite;dimethylphosphinous acid;platinum(2+) - Ghaffar-Parkins catalyst);
$CDCl_3$	(deuterated chloroform);
CD_3OD	(deuterated methanol);
$CHCl_3$	(chloroform);
Cs_2CO_3	(cesium carbonate);

	CsF	(cesium fluoride);
	conc.	(concentrated);
	d	(day);
	DAST	(diethylaminosulphur trifluoride);
	dba	(dibenzylideneacetone);
	DCM	(dichloromethane);
	DEAD	(diethyl azodicarboxylate);
	DIAD	(diisopropyl azodicarboxylate);
	DIPEA	(*N*,*N*-diisopropylethylamine);
	DMAP	(4-dimethylaminopyridine);
	DME	(1,2-dimethoxyethane);
	DMF	(*N*,*N*-dimethylformamide);
	DMSO	(dimethyl sulfoxide);
	DMSO-d_6	(deuterated dimethyl sulfoxide);
	EDCI	(1-ethyl-3-(3-dimethylaminopropyl)carbodiimide);
	eq	(equivalent);
	ES-API	(electrospray atmospheric pressure ionization);
	Et_3N	(triethylamine);
	Et_2O	(diethyl ether);
	EtOAc	(ethyl acetate);
	EtOH	(ethanol);
	$EtSO_2Cl$	(ethanesulfonyl chloride);
	g	(gram);
	h	(hour);
	H_2	(hydrogen);
	H_2O_2	(hydrogen peroxide);
	HATU	(1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate);
	HCl	(hydrochloric acid/hydrogen chloride);
	HOBt	(hydroxybenzotriazole);
	^1H NMR	(proton nuclear magnetic resonance);
	Hz	(hertz);
	i-PrOH	(*iso*-propanol);
	KF	(potassium fluoride);
	KI	(potassium iodide);
	L	(litre);
	LCMS	(liquid chromatography-mass spectrometry);
	LiHMDS	(lithium bis(trimethylsilyl)amide);

M	(molar);
MeCN	(acetonitrile);
Me_2NH	(dimethylamine);
MeOH	(methanol);
MeOD-d_4	(deuterated methanol);
mg	(milligrams);
MHz	(megahertz);
min	(minutes);
mL	(millilitres);
mmol	(millimoles);
MsCl	(methanesulfonyl chloride);
n-BuLi	(*n*-butyllithium);
NaH	(sodium hydride);
$NaHCO_3$	(sodium bicarbonate);
NaOEt	(sodium ethoxide);
NaOH	(sodium hydroxide);
NaOMe	(sodium methoxide);
Na_2SO_4	(sodium sulphate);
NBS	(*N*-bromosuccinimide);
NIS	(*N*-iodosuccinimide);
NH_4Cl	(ammonium chloride);
NMP	(*N*-methyl-2-pyrrolidone);
Pd/C	(palladium on activated charcoal);
$Pd_2(dba)_3$	(tris(dibenzylideneacetone)dipalladium(0));
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	([1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM);
$Pd(OH)_2$	(palladium(II) hydroxide on carbon - Pearlman's catalyst);
PE	(Petroleum Ether);
prep-HPLC	(preparative high-performance liquid chromatography);
prep-TLC	(preparative thin layer chromatography);
ppm	(parts per million);
psi	(pounds per square inch);
p-TSA	(*p*-toluenesulfonic acid);
quant.	(quantitative yield)
RT	(room temperature);
SEMCl	(2-(trimethylsilyl)ethoxymethyl chloride);
SPhos	(2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl);
TBAF	(tetra-*n*-butylammonium fluoride);

t-BuNHNH$_2$.HCl	(*tert*-butylhydrazine hydrochloride);
TFA	(trifluoroacetic acid);
THF	(tetrahydrofuran);
TLC	(thin layer chromatography);
v/v	(volume/volume);
Xantphos	(9,9-Dimethyl-4,5-bis(di-tert-butylphosphino)xanthene);

LCMS methodology

Electrospray mass spectroscopy (MS) was carried out using the following method;

Method A (5 minutes): LC model: Agilent 1200 (Pump type: Binary Pump, Detector type: DAD) MS model: Agilent G6110A Quadrupole. Column: Xbridge-C18, 2.5 µm, 2.1×30 mm. Column temperature: 30 ºC. Acquisition of wavelength: 214 nm, 254 nm. Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH. Run time: 5 min. MS: Ion source: ES+ (or ES-). MS range: 50~900 m/z. Fragmentor: 60. Drying gas flow: 10 L/min. Nebulizer pressure: 35 psi. Drying gas temperature: 350 ºC. Vcap: 3.5 kV.

Method B (3.5 minutes): LC model: Agilent 1200 (Pump type: Binary Pump, Detector type: DAD) MS model: Agilent G6110A Quadrupole. Column: Xbridge-C18, 2.5 µm, 2.1×30 mm. Column temperature: 30 ºC. Acquisition of wavelength: 214 nm, 254 nm. Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH. Run time: 5 min. MS: Ion source: ES+ (or ES-). MS range: 50~900 m/z. Fragmentor: 60. Drying gas flow: 10 L/min. Nebulizer pressure: 35 psi. Drying gas temperature: 350 ºC. Vcap: 3.5 kV.

Method C (4 minutes): Agilent LCMS system composed of an Agilent G6120B Mass Detector, 1260 Infinity G1312B Binary pump, 1260 Infinity G1367E HiPALS autosampler, and 1260 Infinity G4212B Diode Array Detector. Conditions for LCMS were as follows: column, Poroshell 120 EC-C18, 2.1 × 50 mm, 2.7 µm at 30 °C; injection volume, 2 µL; gradient, 5−100% B over 3 min (solvent A: water/0.1% formic acid; solvent B: AcCN/0.1% formic acid); flow rate, 1.0 mL/min; detection, 214 and 254 nm; acquisition time, 4.1 min; ion source: single quadrupole; ion mode: API-ES; drying gas temperature: 350 ºC; capillary voltage: 4.0 kV; scan range 100-1000; step size: 0.1.

Method D: (8 minutes) LC model: Waters 2695 alliance, Pump: Quaternary Pump, Detector: 2996 Photodiode Array Detector, MS model: Micromass ZQ, LC: Column: Xbridge-C18, 3.5µm, 2.1×50 mm, Column temperature: 20 ºC. Acquisition of wavelength: 214 nm, 254 nm. Mobile phase: A: 0.05% HCOOH aqueous solution, B: CAN Run time: 8 min MS: Ion source: ES+ (or ES-) MS range: 100~1000 m/z

Capillary: 3 kv Cone: 40 V Extractor: 3 V Drying gas flow: 800 L/hr cone: 50 L/hr Desolvation temperature: 500 °C Source temperature: 120 ºC.

Method E (5 minutes): LC model: Method A 1200 (Pump type: Binary Pump, Detector type: DAD) MS model: Method A G6110A Quadrupole. Column: Xbridge-C18, 2.5 µm, 2.1×30 mm. Column temperature: 30 ºC. Acquisition of wavelength: 214 nm, 254 nm. Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH. Run time: 5 min. MS: Ion source: ES+ (or ES-). MS range: 50~900 m/z. Fragmentor: 60. Drying gas flow: 10 L/min. Nebulizer pressure: 35 psi. Drying gas temperature: 350 ºC. Vcap: 3.5 kV.

Method F: Mass detector: Agilent G6120B MSD Pump: 1260 Infinity G1312B Binary pump Autosampler: 1260 Infinity G1367E HiPALS Detector: 1260 Infinity G4212B DAD Column: Poroshell 120 EC-C18, 2.1 x 30mm 2.7 Micron Column temperature: 30 °C Injection volume: 2 µL Flowrate: 1.0 ml/min Solvent A: Water 0.1% Formic Acid Solvent B: Acetonitrile 0.1% Formic Acid Gradient: 5-100% B over 3.8 min Acquisition time: 4.1 min Detection: 254 nm and 254 nm Ion source: Single Quadrupole Ion Mode: API-ES Drying gas temperature: 350 °C Capillary voltage (V): 4000 (positive) Capillary voltage (V): 4000 (negative) Scan Range: 100-1000 Step size: 0.1 sec

Method G: Agilent, Mass detector: Agilent G6120B MSD, Pump: 1260 Infinity G1312B Binary pump, Autosampler: 1260 Infinity G1367E HiPALS, Detector: 1260 Infinity G4212B DAD. LC conditions: Column: Poroshell 120 EC-C18, 2.1 x 30mm 2.7 Micron, Column temperature: 30 ºC, Injection volume: 1 uL, Flowrate: 1.0 ml/min, Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: 5-100% B over 3.8 min, Acquisition time: 4.1 min, Detection: 214 and 254 nm. MS conditions: Ion source: Single Quadrupole, Ion Mode: API-ES, Drying gas temperature: 350 ºC, Capillary voltage (V): 4000 (positive), Capillary voltage (V): 4000 (negative), Scan Range: 100-1000, Step size: 0.1 sec.

Method H: Agilent High MW, Mass detector: Agilent G6120B MSD, Pump: 1260 Infinity G1312B Binary pump, Autosampler: 1260 Infinity G1367E HiPALS, Detector: 1260 Infinity G4212B DAD. LC conditions: Column: Poroshell 120 EC-C18, 2.1 x 30mm 2.7 Micron, Column temperature: 30 ºC, Injection volume: 1 uL, Flowrate: 1.0 ml/min, Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: 5-100% B over 3.8 min, Acquisition time: 4.1 min, Detection: 214 and 254 nm. MS conditions: Ion source: Single Quadrupole, Ion Mode: API-ES, Drying gas temperature: 350 ºC, Capillary voltage (V): 4000 (positive), Capillary voltage (V): 4000 (negative), Scan Range: 100-2000, Step size: 0.1 sec.

Method I: Waters, Waters ZQ 3100 –Mass Detector, Waters 2545-Pump, Waters SFO System Fluidics Organizer, Waters 2996 Diode Array Detector, Waters 2767 Sample

Manager. LC conditions: Reverse Phase HPLC analysis, Column: Xbridge TM C18 5µm 4.6 x 100mm, Injection Volume 10µL, Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: 10-100% B over 8min, Flow rate: 1.5 ml/min, Detection: 100-600nm. MS conditions: Ion Source: Single-quadrupole, Ion Mode: ES positive, Source Temp: 150°C, Desolvation Temp: 350 °C, Detection: Ion counting, Capillary (KV)-3.00, Cone (V): 30, Extractor (V):3, RF Lens (V): 0.1, Scan Range: 100-1000 Amu, Scan Time: 0.5 sec, Acquisition time: 10min, Gas Flow: Desolvation L/hr-650, Cone L/hr-100.

Preparative HPLC

Method A: Instrument type: VARIAN 940 LC. Pump type: Binary Pump. Detector type: PDA. LC conditions: Column: Waters SunFire prep C18 OBD, 5 µm, 19×100 mm. Acquisition wavelength: 214 nm, 254 nm. Mobile Phase: A: 0.07% TFA aqueous solution, B: MeOH.

Unless otherwise indicated, preparative HPLC was performed according to Method A.

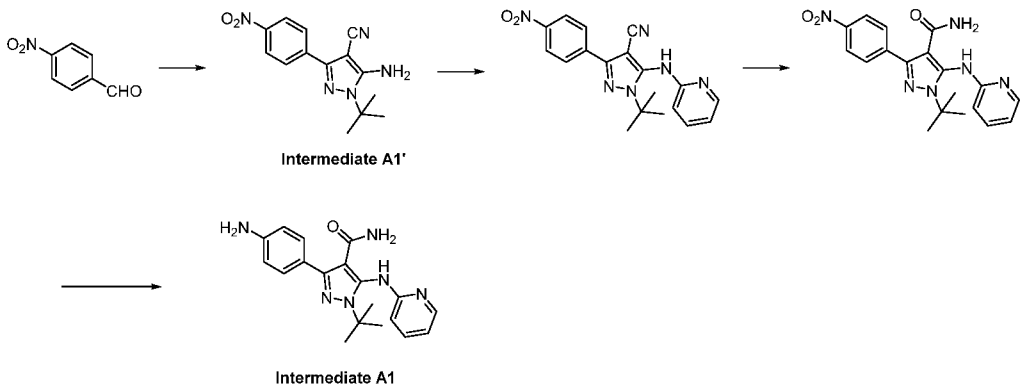
Method B: Waters ZQ 3100 –Mass Detector, Waters 2545-Pump,Waters SFO System Fluidics Organizer, Waters 2996 Diode Array Detector, Waters 2767 Sample Manager. LC conditions: Reverse Phase HPLC analysis, Column: Xbridge TM prep C18 OBD 5µm 19 x 100mm, Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: variable, Flow rate: 20 ml/min, Detection: 100-600nm. MS conditions: Ion Source: Single-quadrupole, Ion Mode: ES positive, Source Temp: 150°C, Desolvation Temp: 350 °C, Detection: Ion counting, Capillary (KV)-3.00, Cone (V): 30, Extractor (V):3, RF Lens (V): 0.1, Scan Range: 100-1000 Amu, Scan Time: 0.5 sec, Acquisition time: 20min, Gas Flow: Desolvation L/hr-650, Cone L/hr-100.

NMR

Nuclear magnetic resonance spectra were recorded on a Bruker Avance DRX 300 instrument at 300.13 MHz or Bruker 400 MHz for 1H nuclei as specified. Samples were recorded in deuterated solvent as specified, and data acquired at 25 °C. Chemical shifts are reported in ppm on the δ scale and referenced to the appropriate solvent peak. In reporting spectral data, the following abbreviations have been used: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Synthesis of common intermediates

Intermediate A1: 3-(4-aminophenyl)-1-(tert-butyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide



Step 1: Intermediate A1': 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 4-nitrobenzaldehyde (100 g, 0.66 mol) and *t*-BuNHNH$_2$.HCl (90.7 g, 0.73 mol) in DMF (500 mL) was stirred at RT overnight. The reaction mixture was cooled to 0 ºC and NBS (129.6 g, 0.73 mol) was added slowly. The resultant mixture was stirred at 0 ºC for 5 h and then a solution of malononitrile (52.5 g, 0.79 mol) and NaOEt (112.7 g, 1.66 mol) in EtOH (300 mL) was slowly added over a 30 min period at 0 °C. The mixture was stirred at RT for 16 h, then partitioned between H_2O (3 L) and EtOAc (3 L). The aqueous layer was extracted with EtOAc (2 x 3 L), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford Intermediate A1' (58 g, 31%) as a yellow solid. LCMS (Method A): 1.93 min; m/z: 286.1 $[M+H]^+$.

Step 2: 1-(tert-butyl)-3-(4-nitrophenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carbonitrile

To a solution of 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4- carbonitrile (13 g, 45.6 mmol) in diglyme (200 mL) was added 2-bromopyridine (7.6 g, 47.8 mmol), $Pd(OAc)_2$ (614 mg, 2.73 mmol), Xantphos (1.6 g, 2.73 mmol) and Cs_2CO_3 (37.1 g, 114 mmol) and the mixture was stirred at 150 °C under N_2 for 8 h. The reaction mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the title product (7.0 g, 42%) as a yellow solid. LCMS (Method A): 2.91 min; m/z: 363.2 $[M+H]^+$.

Step 3: 1-(tert-butyl)-3-(4-nitrophenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide

To a solution of 1-(tert-butyl)-3-(4-nitrophenyl)-5-(pyridin-2-ylamino)-1H- pyrazole-4-carbonitrile (11 g, 30.3 mmol) in DMSO (35 mL) and EtOH (130 mL), was added 30% aq. H_2O_2 (35 mL) and 5% aq. NaOH (0.3 mL), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water to form a yellow suspension. The solids were collected by filtration and dried under reduced pressure to afford the title product (10.5 g, 90%) as a yellow solid. LCMS (Method A): 2.65 min; m/z: 381.1 $[M+H]^+$.

Step 4: 3-(4-aminophenyl)-1-(tert-butyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide

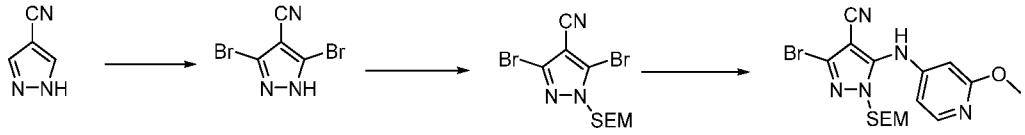
To a solution of 1-(tert-butyl)-3-(4-nitrophenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (10 g, 26.3 mmol) in MeOH (200 mL), was added sat. aq. NH_4Cl (100 mL) and Zn dust (8.6 g, 131.5 mmol) and the mixture was stirred at 40 °C for 2 h. The reaction mixture was filtered through Celite, and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and diluted with H_2O, then basified to pH 10 with sat. aq. Na_2CO_3. The mixture was extracted with DCM (3 x 100 mL) and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (8.0 g, 75%) as a yellow solid. LCMS (Method A): 0.53 min; m/z: 351.1 $[M+H]^+$.

The following intermediates (Table 1) were similarly prepared from 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile according to the escribed for the synthesis of 3-(4-aminophenyl)-1-(tert-butyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (intermediate A1)

Table 1

Compound No.	Name	Structure	LCMS data	^{1}H NMR data	Starting material
Intermediate A2	3-(4-aminophenyl)-1-(tert-butyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.44 min; m/z: 419.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 8.84 (s, 1H), 7.75 (d, J = 16.0 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.15 (br s, 2H), 6.83 (s, 1H), 6.67 (s, 1H), 6.56 (t, J = 8.4 Hz, 2H), 5.28 (s, 2H), 1.54 (s, 9H).	2-chloro-6-(trifluoromethyl)pyridine
Intermediate A3	3-(4-aminophenyl)-1-(tert-butyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.53 min; m/z: 352.4 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 8.72 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 6.73 (s, 1H), 6.55 (d, J = 8.4 Hz, 2H), 5.16 (s, 2H), 1.54 (s, 9H).	2-chloropyrazine

Intermediate B1: 3-bromo-5-((2-methoxypyridin-4-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile



Intermediate B1' **Intermediate B1**

Step 1: 3,5-dibromo-1H-pyrazole-4-carbonitrile

To a stirred solution of 1H-pyrazole-4-carbonitrile (15.0 g, 161 mmol) and NaOAc (89.3 g, 1.09 mol) in 40% aq. EtOH (550 mL), was added Br_2 (24 mL, 644 mmol) slowly at RT. The mixture was stirred at 30 °C for 3.5 h, then diluted with H_2O (600 mL) and extracted with DCM (3 x 300 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (25 g, 62%) as a yellow solid. LCMS (Method B): 0.87 min; m/z: 249.7 $[M+H]^+$.

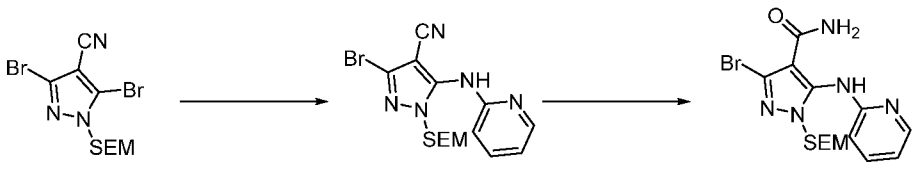
Step 2: Intermediate B1': 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile

To a solution of 3,5-dibromo-1H-pyrazole-4-carbonitrile (25 g, 99.6 mmol) in DMF (150 mL), was added NaH (60 % in oil, 2.85 g, 119 mmol) at RT and the mixture was stirred for 0.5 h. SEM-Cl (24.8 g, 149 mmol) was added and the mixture was stirred at RT for 4 h, then diluted with H_2O (200 mL) and extracted with Et_2O (3 x 150 mL). The combined organics were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 20:1) to afford Intermediate B1' (16.0 g, 42%) as a clear oil. LCMS (Method B): 0.43 min; m/z: 380.0, 382.0 $[M+H]^+$.

Step 3: 3-bromo-5-[(2-methoxypyridin-4-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (13.8 g, 36.2 mmol), 2-methoxypyridin-4-amine (4.9 g, 39.8 mmol), $Pd(OAc)_2$ (812 mg, 3.62 mmol), Xantphos (4.18 g, 7.24 mmol) and Cs_2CO_3 (17.6 g, 54.3 mmol) in degassed 1,4-dioxane (200 mL) was heated to 110 °C under N_2 for 12 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 12:1) to afford the title product (7.5 g, 49%) as a white solid. LCMS (Method B): 2.56 min; m/z: 424.1, 426.1 $[M+H]^+$.

Intermediate B2: 3-bromo-5-(pyridin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide



Intermediate B2

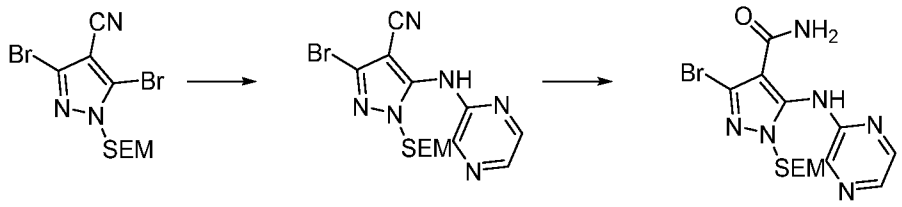
Step 1: 3-bromo-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (10 g, 26.2 mmol), pyridin-2-amine (2.46 g, 26.2 mmol), $Pd_2(dba)_3$ (2.39 g, 2.62 mmol), Xantphos (3.03 g, 5.24 mmol) and Cs_2CO_3 (25.6 g, 78.6 mmol) in degassed 1,4-dioxane (150 mL) was stirred at 100 °C under N_2 for 16 h. The reaction mixture was filtered, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the title product (5.0 g, 49%) as a yellow solid. LCMS (Method A: 3.79 min; m/z: 394.0, 396.0 $[M+H]^+$.

Step 2: 3-bromo-5-(pyridin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (Intermediate B2)

A mixture of 3-bromo-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (4.3 g, 10.9 mmol) and Ghaffar-Parkins catalyst (50.0 mg, 0.1170 mmol) in 50% aq. 1,4-dioxane (200 mL) was stirred at 100 °C for 16 h. The reaction mixture was extracted with EtOAc (2 x 200 mL), and the combined organics were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (2.5 g, 56%) as a yellow solid. LCMS (Method A): 3.77 min; m/z: 412.1, 414.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 8.84 (s, 1H), 8.24 (s, 1H), 9.01 (d, J = 4.0 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.29 (s, 1H), 6.79 (t, J = 6.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.27 (s, 2H), 3.44 (t, J = 8.4 Hz, 2H), 0.74 (t, J = 8.0 Hz, 2H), 0.11 (s, 9H).

Intermediate B3 (3-bromo-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazole-4-carbonitrile) and **Intermediate B4** (3-bromo-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazole-4-carboxamide)



Intermediate B3 Intermediate B4

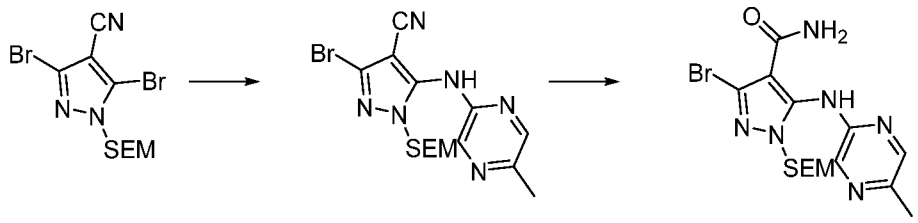
Step 1: 3-bromo-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile (Intermediate B3)

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (4 g, 10.4 mmol), pyrazin-2-amine (989 mg, 10.4 mmol), $Pd_2(dba)_3$ (952 mg, 1.04 mmol), Xantphos (1.20 g, 2.08 mmol) and Cs_2CO_3 (10.1 g, 31.2 mmol) in degassed 1,4-dioxane (50 mL) was stirred at 100 °C under N_2 for 16 h. The reaction mixture was filtered, and the filter cake was rinsed with EtOAc (3 x 20 mL). The combined filtrates were concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1 to 8:1) to afford the title compound (2.5 g, 61%) as a yellow solid. LCMS (Method A): 4.14 min; m/z: 395.0, 397.0 $[M+H]^+$.

Step 2: 3-bromo-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (Intermediate B4)

A mixture of 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazole-4-carbonitrile (6 g, 15.1 mmol), Ghaffar-Parkins catalyst (100 mg, 0.2340 mmol) and 50% aq. 1,4-dioxane (120 mL) was stirred at 100 °C under N_2 for 16 h. The mixture was concentrated and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 200:1 to 10:1) to afford the title product (2.1 g, 34%) as a brown solid. LCMS (Method A): 3.59 min; m/z: 415.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.34 (s, 1H), 8.19 (d, J = 1.2 Hz, 1H), 8.05-8.03 (m, 1H), 8.02-8.00 (m, 1H), 7.31 (s, 1H), 7.04 (s, 1H). 5.31 (s, 2H), 8.46 (t, J = 8.4 Hz, 2H), 0.75 (t, J = 7.6 Hz, 2H), -0.11 (s, 9H).

Intermediate B5 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile and **Intermediate B6** 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide



Intermediate B5 Intermediate B6

Step 1: 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (Intermediate B5)

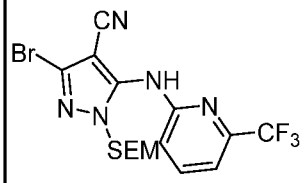
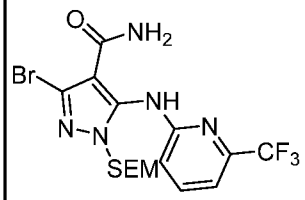
To a solution of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (2 g, 5.24 mmol) in 1,4-dioxane (100 mL), was added 5-methylpyrazin-2-amine (571 mg, 5.24 mmol), Xantphos (302 mg, 0.524 mmol), Cs_2CO_3 (3.38 g, 10.4 mmol) and $Pd_2(dba)_3$ (239 mg, 0.262 mmol). The mixture was evacuated and back-filled with N_2 three times and then stirred at 100 °C overnight. The mixture was concentrated and the residue purified by prep-TLC (PE:EtOAc, 20:1) to afford the title product (1.03 g, 48%) as a yellow solid. LCMS (Method A): 4.10 min; m/z: 409.1, 411.1 $[M+H]^+$.

Step 2: 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B6)

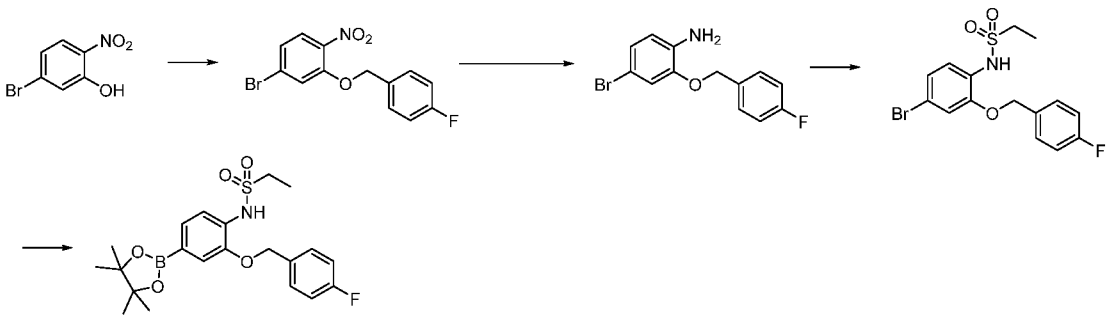
A mixture of 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (1.05 g, 2.56 mmol), Ghaffar-Parkin's catalyst (150 mg, 0.35 mmol) and 75% aq. 1,4-dioxane (55 mL) was stirred at 100 ºC under N_2. After 16 h, the reaction mixture was concentrated and the crude residue was purified by prep-TLC (DCM:MeOH, 60:1) to afford the title product (490 mg, 45%) as a yellow solid. LCMS (Method A): 3.58 min; m/z: 427.1, 429.1 $[M+H]^+$.

The following intermediates B (see Table 2, below) were similarly prepared from the appropriate amino aryl/alkyl (step 1) according to the method described for the synthesis of intermediate B5.

Table 2

Compound No	Name	Structure	LCMS data	SM
Intermediate B7	3-bromo-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile		LCMS (Method A): 4.51 min; m/z: 462.1, 464,1 $[M+H]^+$	6-(trifluoromethyl)pyridin-2-amine
Intermediate B8	3-bromo-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.11 min; m/z: 480.1, 482,1 $[M+H]^+$	n/a

Intermediate C1: N-(2-((4-fluorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)phenyl)ethanesulfonamide



intermediate C1

Step 1: 4-bromo-2-((4-fluorobenzyl)oxy)-1-nitrobenzene

A mixture of 5-bromo-2-nitrophenol (10 g, 45.8 mmol), K_2CO_3 (12.6 g, 91.6 mmol) and 1-(bromomethyl)-4-fluorobenzene (8.65 g, 45.8 mmol) in MeCN (100 mL) was stirred at 70 °C under N_2 for 16 h. The mixture was diluted with H_2O (100 mL) extracted with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to afford the title product (15.0 g, 100%) as a white solid.

Step 2: 4-bromo-2-((4-fluorobenzyl)oxy)aniline

To a solution of 4-bromo-2-((4-fluorobenzyl)oxy)-1-nitrobenzene (15 g, 45.9 mmol) in MeOH (300 mL) and sat. aq. NH_4Cl (100 mL) was added Zn dust (14.9 g, 229 mmol) and the reaction mixture was stirred at 60 °C for 4 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was partitioned between H_2O (250 mL) and EtOAc (300 mL), and the organic layer was separated, dried (Na_2SO_4) and then concentrated under reduced pressure to afford the title product (13.0 g, 96%) as a black oil. LCMS (Method A): 4.24 min; m/z: 296.0 $[M+H]^+$.

Step 3: N-(4-bromo-2-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide

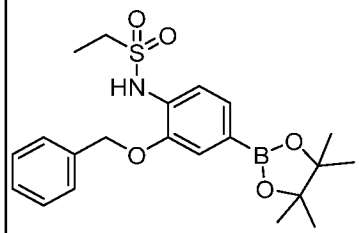
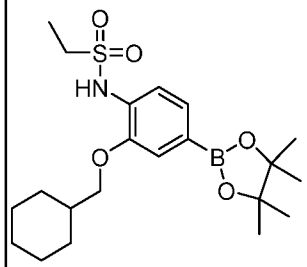
A mixture of 4-bromo-2-((4-fluorobenzyl)oxy)aniline (13 g, 43.8 mmol), $EtSO_2Cl$ (8.43 g, 65.6 mmol) and pyridine (50 mL) in $CHCl_3$ (50 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (12.5 g, 73%) as a yellow solid. LCMS (Method A): 4.24 min; m/z: 410.0 $[M+H]^+$.

Step 4: N-(2-((4-fluorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)phenyl)ethanesulfonamide

A mixture of N-(4-bromo-2-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide (12.5 g, 32.1 mmol) $Pd(dppf)Cl_2$ (1.46 g, 1.60 mmol), KOAc (6.29 g, 64.2 mmol) and B_2pin_2 (8.96 g, 35.2 mmol) in degassed 1,4-dioxane (200 mL) was stirred at 100 °C under N_2 for 16 h. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (14.8 g, >100%) as a brown solid. LCMS (Method A): 4.51 min; m/z: 453.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.99 (s, 1H), 7.63-7.60 (m, 2H), 7.38-7.32 (m, 2H), 7.28-7.21 (m, 3H), 5.15 (s, 2H), 3.03 (q, J = 14.8, 7.2 Hz, 2H), 1.29 (s, 12H), 1.11 (t, J = 7.2 Hz, 3H).

The following intermediates C (Table 3) were similarly prepared from the appropriate bromo aryl/alkyl (step 1) according to the method described for the synthesis of N-(2-((4-fluorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)phenyl)ethanesulfonamide (intermediate C1).

Table 3

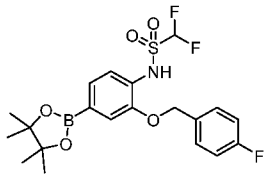
Compound No	Name	Structure	LCMS data	SM
Intermediate C2	N-(2-(benzyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.51 min; m/z: 440.1 $[M+Na]^+$.	(bromomethyl)benzene
Intermediate C3	N-(2-(cyclohexylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 3.85 min; m/z: 424.0 $[M+H]^+$.	(bromomethyl)cyclohexane

Intermediate C4	N-(2-((4-chlorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.65 min; m/z: 474.1 $[M+Na]^+$.	1-(bromomethyl)-4-chlorobenzene
Intermediate C5	N-(2-((3-chlorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.65 min; m/z: 474.1 $[M+Na]^+$.	1-(bromomethyl)-3-chlorobenzene

Intermediate C6	N-(2-(pyridin-4-ylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 3.29 min; m/z: 419.1 $[M+H]^+$.	4-(bromomethyl)pyridine
Intermediate C7	N-(2-(pyridin-3-ylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 3.55 min; m/z: 419.2 $[M+H]^+$.	3-(bromomethyl)pyridine

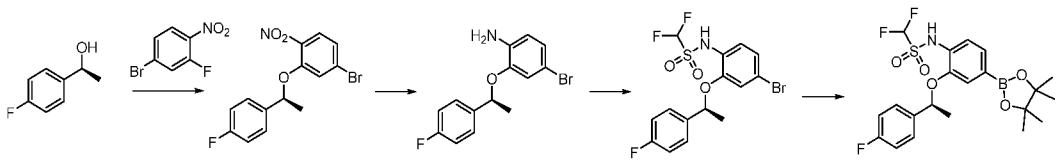
Intermediate C8	N-(2-(cyclopentylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.79 min; m/z: 410.2 $[M+H]^+$.	(bromomethyl)cyclopentane
Intermediate C9	N-(2-isobutoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.61 min; m/z: 384.2 $[M+H]^+$.	1-bromo-2-methylpropane
Intermediate C10	N-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide		LCMS (Method A): 4.02 min; m/z: 364.1 $[M+Na]^+$.	methyliodide

Intermediate C1a:



Intermediate C1a was prepared according to the procedure for **Intermediate C1**, using difluoromethanesulfonyl chloride in the appropriate step. ^{1}H NMR (300 MHz, $CDCl_3$): 7.55 (d, *J* = 7.9 Hz, 1 H), 7.45-7.37 (m, 4 H), 7.13-7.08 (m, 3 H), 6.22 (t, *J* = 53.5 Hz, 1 H), 5.11 (s, 2 H), 1.34 (s, 12 H).

Intermediate C11



Step 1: (S)-4-bromo-2-(1-(4-fluorophenyl)ethoxy)-1-nitrobenzene

To a solution of (1S)-1-(4-fluorophenyl)ethan-1-ol (40 g, 285 mmol) in THF (600 mL) was added NaH (57.1 g, 1425 mmol). The mixture was stirred at 0 °C under N_2 for 30 min. Then 4-bromo-2-fluoro-1-nitrobenzene (62.6 g, 285 mmol) was added to the mixture and stirred at RT overnight. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (70 g, 72%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 7.80 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.48 (q, *J* = 4.8 Hz, 2H), 7.26 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.20 (t, *J* = 8.8 Hz, 1H), 5.89 (q, *J* = 6.4 Hz, 1H), 1.54 (d, *J* = 6.0 Hz, 3H).

Step 2: 4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]aniline

To a solution of 4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]-1-nitrobenzene (70 g, 205 mmol) in MeOH (500 mL), was added Zn dust (67.0 g, 1025 mmol) followed by sat. aq. NH_4Cl (170 mL). The mixture was stirred at 60 °C for 6 h, then diluted with water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The

crude residue was purified by silica gel column chromatography (PE:EtOAc, 100:1) to afford the title product (40 g, 63%) as a brown oil. LCMS (Method A): 4.13 min; m/z: 311.0, 311.9 $[M+H]^+$.

Step 3: N-{4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1,1-difluoromethanesulfonamide

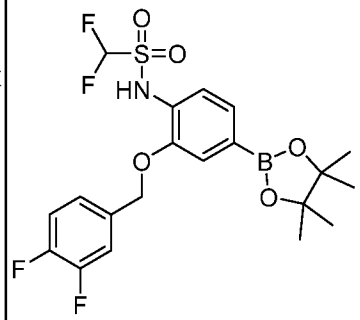
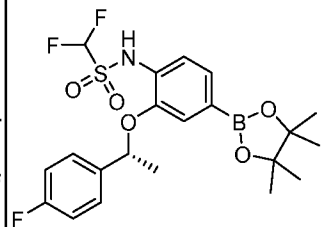
To a solution of 4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]aniline (40 g, 128 mmol) in DCM (200 mL) and pyridine (40.5 g, 512 mmol) was added difluoromethanesulfonyl chloride (24.9 g, 166 mmol). After stirring at RT overnight, the residue was diluted with water (500 mL) and extracted with DCM (3 x 500 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EtOAc, 100:1) to give the title product (39 g, 72%) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6): 10.43 (s, 1H), 7.57 (q, J = 4.8 Hz, 2H), 7.21-7.15 (m, 3H), 7.07-7.04 (m, 2H), 6.98 (t, J = 52.4 Hz, 1H), 5.65 (q, J = 6.4 Hz, 1H), 1.54 (d, J = 6.0 Hz, 3H).

Step 4: (S)-1,1-difluoro-N-(2-(1-(4-fluorophenyl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanesulfonamide

To a solution of N-{4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1,1-difluoromethanesulfonamide (39 g, 91.9 mmol) in dioxane (300 mL), was added KOAc (26.9 g, 275 mmol), B_2pin_2 (34.7 g, 137 mmol) and $Pd(dppf)Cl_2$ (2.01 g, 2.75 mmol). The mixture was stirred at 100 °C under N_2 overnight, then concentrated *in vacuo*. The residue was diluted with water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EtOAc, 50:1) to give the title product (41 g, 94%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 10.41 (s, 1H), 7.58 (q, J = 4.8 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.20-7.16 (m, 3H), 7.12 (s, 1H), 6.98 (t, J = 52.4 Hz, 1H), 5.63 (q, J = 6.4 Hz, 1H), 1.54 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 4.8 Hz, 12H).

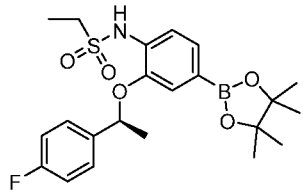
The following intermediates C12-C15 (Table 4) were similarly prepared according to the method described for the synthesis of (S)-1,1-difluoro-N-(2-(1-(4-fluorophenyl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanesulfonamide (intermediate C11).

Table 4

Compound No	Name	Structure	^{1}H NMR data	SM
Intermediate C12	N-{2-[(3,4-difluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}-1,1-difluoromethanesulfonamide		^{1}H NMR (400 MHz, DMSO-d_6): 10.48 (br s, 1H), 7.72-7.67 (m, 1H), 7.50-7.39 (m, 2H), 7.33-7.25 (m, 3H), 6.91 (t, J = 52.5 Hz, 1H), 5.18 (s, 2H), 1.29 (s, 12H).	(3,4-difluorophenyl)methanol
Intermediate C13	(R)-1,1-difluoro-N-(2-(1-(4-fluorophenyl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanesulfonamide		^{1}H NMR (400 MHz, DMSO-d_6): 10.41 (s, 1H), 7.58 (q, J = 4.8 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.20-7.16 (m, 3H), 7.12 (s, 1H), 6.98 (t, J = 52.4 Hz, 1H), 5.63 (q, J = 6.4 Hz, 1H), 1.54 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 4.8 Hz, 12H).	(1R)-1-(4-fluorophenyl)ethan-1-ol

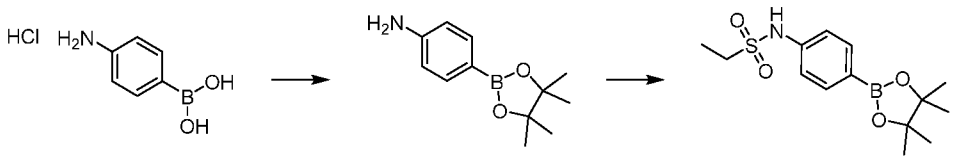
Intermediate C14	1,1-difluoro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(thiazol-2-ylmethoxy)phenyl)methanesulfonamide		LCMS (Method A): 4.1 min, $[M+H]^+$=447.2
Intermediate C15	1,1-difluoro-N-{2-[1-(1,3-oxazol-2-yl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide		LCMS (Method A): 4.00 min, $[M+H]^+$=445.2

Intermediate C11a: N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide



Intermediate C11a was prepared according to the procedure for Intermediate C11, using methanesulfonyl chloride in the appropriate step. ^{1}H NMR (400 MHz, DMSO-d_6): 9.08 (s, 1H), 7.61-7.58 (m, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.19-7.17 (m, 3H), 7.14 (s, 1H), 5.64 (q, J = 6.0 Hz, 1H), 3.09 (q, J = 7.6 Hz, 2H), 1.56 (d, J = 6.0 Hz, 3H), 1.29-1.13 (m, 15H).

Intermediate C16: N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane sulfonamide



Step 1: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

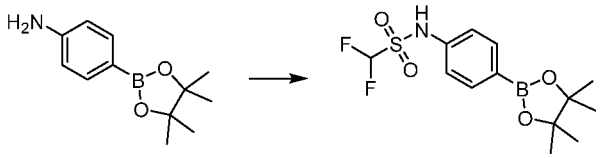
A mixture of (4-aminophenyl)boronic acid hydrochloride (2 g, 11.5 mmol), pinacol (1.48 g, 12.6 mmol), $MgSO_4$ (4.15 g, 34.5 mmol) and $NaHCO_3$ (1.93 g, 23.0 mmol) in anhydrous THF (11.5 mL) was stirred under N_2 at RT overnight. The mixture was diluted with EtOAc, filtered over Celite and concentrated to give an off-white solid. The solid was triturated with Et_2O, collected *via* filtration, washed with Et_2O and air-dried to afford the title compound (1.49 g, 59%) as a white solid. LCMS (method C): 1.44 min, m/z: 220.4 $[M+H]^+$.

Step 2: N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.49 g, 6.80 mmol) in anhydrous DCM (13.6 mL) were added pyridine (2.74 mL, 33.9 mmol) and $EtSO_2Cl$ (1.28 mL, 13.6 mmol), and the reaction was stirred at RT under N_2 for 4 h. The mixture was concentrated, and the residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (0-50% EtOAc:*c*-Hex) to afford the title compound (1.88 g, 89%) as a white solid. LCMS (method C): 1.98 min, m/z: 312.2 $[M+H]^+$. ^{1}H NMR ($CDCl_3$):

7.77 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.72 (s, 1H), 3.15 (q, *J* = 7.4 Hz, 2H), 1.33 (t, *J* = 7.4 Hz, 3H).

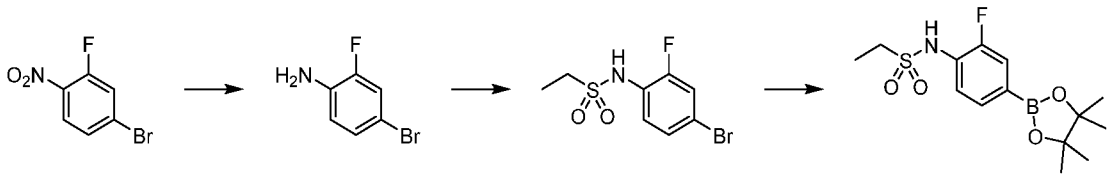
Intermediate C17: 1,1-difluoro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide



Step 1: 1,1-difluoro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (500 mg, 2.28 mmol) in DCM (8 mL) were added pyridine (921 µL, 11.4 mmol) and difluoromethanesulfonyl chloride (241 µL, 2.73 mmol), and the reaction was stirred at RT under N_2. After 1 h, the mixture was concentrated and then azeotroped with PhMe (10 mL). The residue was purified by flash chromatography (0-25% EtOAc/heptane) to afford the title compound (555 mg, 73%) as a white solid. LCMS (Method G): 2.47 min, m/z: 334.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.81-7.79 (m, 2H), 7.27-7.24 (m, 2H), 6.71 (br. s, 1H), 6.25 (t, J = 53.5 Hz, 1H), 1.33 (s, 12H).

Intermediate C18: N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide



Step 1: 4-bromo-2-fluoroaniline

To a solution of 4-bromo-2-fluoro-1-nitrobenzene (5 g, 22.7 mmol) in MeOH (12 mL) and sat. aq. NH_4Cl (4 mL) was added Zn (7.39 g, 113 mmol), And the reaction was stirred at 60 °C for 6 h. The mixture was concentrated, and the residue was diluted with water (150 mL) and extracted with EtOAc (150 mL x 3). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to afford the title product (2.5 g, 58%) as a brown oil. LCMS (method A): 3.39 min, m/z: 189.9,191.9 $[M+H]^+$.

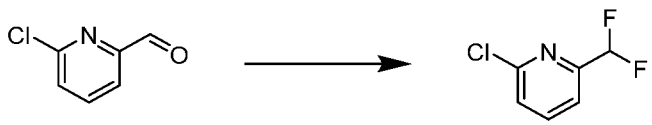
Step 2: N-(4-bromo-2-fluorophenyl)ethane-1-sulfonamide

To a solution of 4-bromo-2-fluoroaniline (5 g, 26.3 mmol) in pyridine (20 mL) and DCM (80 mL) was added $EtSO_2Cl$ (3.38 g, 26.3 mmol), and the reaction was stirred at RT overnight. The mixture was diluted with water and extracted with EtOAc (x 3). The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (DCM/MeOH = 20/1, v/v) to afford the title product (6.67 g, 90%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): 9.77 (s, 1H), 9.63 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.39-7.35 (m, 2H), 3.11 (q, *J* = 7.6 Hz, 2H), 1.24, (t, *J* = 7.6 Hz, 3H).

Step 3: N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide

A mixture of N-(4-bromo-2-fluorophenyl)ethane-1-sulfonamide (1.1 g, 3.89 mmol), bis(pinacolato)diboron (987 mg, 3.89 mmol), AcOK (763 mg, 7.78 mmol) and $Pd(dppf)Cl_2$ (317 mg, 389 µmol) in dioxane (10 mL) was stirred at 100 °C under N_2 overnight. The mixture was concentrated, and the residue was diluted with water (200 mL) and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The residue was purified by prep-TLC (DCM/MeOH = 20/1, v/v) to afford the title compound (1 g, 78%) as a black oil. ^1H NMR (400 MHz, DMSO-d_6): 9.87 (bs, 1H), 7.45-7.35 (m, 3H), 3.11 (q, J = 7.6 Hz, 2H), 1.28 (s, 12H), 1.22, (t, J = 7.6 Hz, 3H).

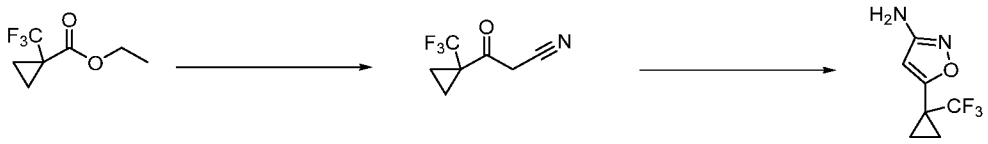
Intermediate D1: 5-((6-(difluoromethyl)pyridin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide.



Step 1: 5-((6-(difluoromethyl)pyridin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide.

A solution of 6-chloropyridine-2-carbaldehyde (5 g, 35.3 mmol) in DCM (50 mL) was stirred at -20 °C for 1 h. DAST (9.65 ml, 60.0 mmol) was then added, and the mixture was stirred at RT for 16 h. The mixture was neutralized to pH 7-8 with sat. aq. $NaHCO_3$ and extracted with DCM (3 x 20 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (1.65 g, 29%) as a black liquid. LCMS (Method A): 0.92 min; m/z: 164.0 $[M+H]^+$.

Intermediate E1: 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-amine



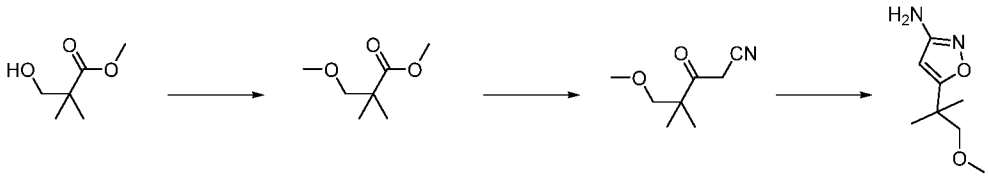
Step 1: 3-oxo-3-(1-(trifluoromethyl)cyclopropyl)propanenitrile

To a solution of NaH (60% in oil, 2.18 g, 54.8 mmol) in THF (70 mL) was added ethyl 1-(trifluoromethyl)cyclopropane-1-carboxylate (5 g, 27.4 mmol), followed by the dropwise addition of acetonitrile (1.68 g, 41.0 mmol) over 45 min. The suspension was heated at 70 °C overnight. Once cooled, the reaction mixture was poured into water (150 mL) and the organics were extracted with EtOAc (2 × 100 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound (4.60 g, 95%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 3.95 (s, 2H), 1.60 (dtd, *J* = 5.4, 3.8, 1.5 Hz, 2H), 1.49 (t, *J* = 3.6 Hz, 2H).

Step 2: 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-amine

A mixture of 3-oxo-3-[1-(trifluoromethyl)cyclopropyl]propanenitrile (460 mg, 2.59 mmol), $NH_2OH.HCl$ (0.215mg, 3.10 mmol), and $NaHCO_3$ (435 mg, 5.2 mmol) in MeOH (1mL) and water (9mL) was heated at 140 °C under microwave irradiation for 5 min. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (10 mL) and extracted with EtOAc (5 mL x 2). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (330mg, 66%) as a pale yellow solid. LCMS (Method A): 3.00 min; m/z: 193.1 $[M+H]^+$.

Intermediate E2: 5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-amine



Step 1: methyl 3-methoxy-2,2-dimethylpropanoate

A mixture of methyl 3-hydroxy-2,2-dimethylpropanoate (5 g, 37.8 mmol), KOH (8.47 g, 151 mmol) and MeI (21.4 g, 151 mmol) in DMSO (150 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (500 mL) and extracted with EtOAc (300 mL x 5). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (3

g, 54%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 3.59 (s, 3H), 3.32 (s, 2H), 3.22 (s, 3H), 1.10 (s, 6H).

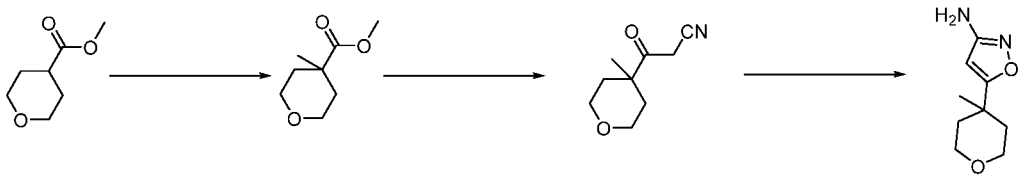
Step 2: 5-methoxy-4,4-dimethyl-3-oxopentanenitrile

Acetonitrile (1.68 g, 41.0 mmol) was added dropwise to a solution of LDA (4.39 g, 41.0 mmol) in THF (60 mL) and the solution was stirred at -78 °C for 30 minutes. Methyl 3-methoxy-2,2-dimethylpropanoate (3 g, 20.5 mmol) was then added dropwise at -78 °C and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (100 mL) and extracted with EtOAc (50 mL x 2). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (2.3 g, 72 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 4.18 (s, 2H), 3.36 (s, 3H), 3.34 (s, 2H), 1.06 (s, 6H).

Step 3: 5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-amine

A mixture of 5-methoxy-4,4-dimethyl-3-oxopentanenitrile (2.3 g, 14.8 mmol), $NH_2OH.HCl$ (1.12 g, 16.2 mmol) and NaOH (647 mg, 16.2 mmol) in water (20 mL) and EtOH (20 mL) was stirred at 80 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (100 mL) and extracted with EtOAc (50 mL x 2). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (960 mg, 38%) as a yellow oil. LCMS (Method A): 0.9 min; m/z: 171.1 $[M+H]^+$.

Intermediate E3: 5-(4-methyltetrahydro-2H-pyran-4-yl)isoxazol-3-amine



Step 1: methyl 4-methyltetrahydro-2H-pyran-4-carboxylate

To a solution of methyl oxane-4-carboxylate (5 g, 34.6 mmol) in dry THF (15 mL) was added LDA (2M in THF, 34.6 mL, 69.2 mmol) and the mixture was stirred at -78 °C for 30 min. MeI (5.89 g, 41.5 mmol) was then added dropwise and the mixture was stirred at RT overnight. The mixture was adjusted to pH = 3 with aq. HCl (0.5 M) and the organics were extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by

column chromatography on silica gel (PE/EtOAc = 100/1, V/V) to give the title product (5.40 g, 34.1 mmol, 98.7%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (dt, *J* = 11.8, 4.1 Hz, 2H), 3.70 (s, 3H), 3.50-3.42 (m, 2H), 2.10-2.01 (m, 2H), 1.53-1.43 (m, 2H), 1.21 (s, 3H).

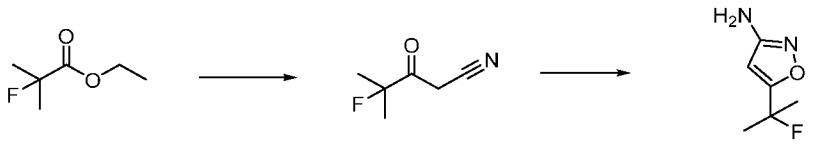
Step 2: 3-(4-methyltetrahydro-2H-pyran-4-yl)-3-oxopropanenitrile

Acetonitrile (4.31 g, 105 mmol) was slowly added to a solution of lithium diisopropylamide (2M/THF, 10.9 g, 102 mmol) in dry THF (50mL), and the mixture was stirred at -78 °C for 1h followed by the addition of methyl 4-methyloxane-4-carboxylate (5.4 g, 34.1 mmol) in dry THF (40mL) over 10min. The mixture was stirred at -78°C for 1h and at RT overnight. The mixture was diluted with water (100mL) and the pH was adjusted to pH = 3 with HCl (2M). The organics were extracted with EtOAc (3 X 50 mL) and the combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (4.20 g, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 3.74 (ddd, *J* = 12.0, 6.4, 3.7 Hz, 2H), 3.55 (ddd, *J* = 11.7, 8.1, 3.3 Hz, 2H), 2.02-1.95 (m, 2H), 1.90 (d, *J* = 0.7 Hz, 2H), 1.59-1.51 (m, 2H), 1.24 (s, 3H).

Step 3: 5-(4-methyltetrahydro-2H-pyran-4-yl)isoxazol-3-amine

A mixture of 3-(4-methyltetrahydro-2H-pyran-4-yl)-3-oxopropanenitrile (7 g, 41.8 mmol), $NH_2OH.HCl$ (3.30 g, 50.1 mmol) and $NaHCO_3$ (8.73 g, 104 mmol) in water (63 mL) and MeOH (7 mL) was stirred at 65 °C overnight under N_2. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (40 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 9:1 to 1:9) to give the title product (1.20 g, 16%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): 4.96 (s, 1H), 4.52 (br s, 2H), 3.82-3.71 (m, 2H), 3.64-3.57 (m, 2H), 2.03-1.97 (m, 2H), 1.63 (ddd, *J* = 13.6, 9.5, 4.0 Hz, 2H), 1.26 (s, 3H).

Intermediate E4: 5-(2-fluoropropan-2-yl)isoxazol-3-amine



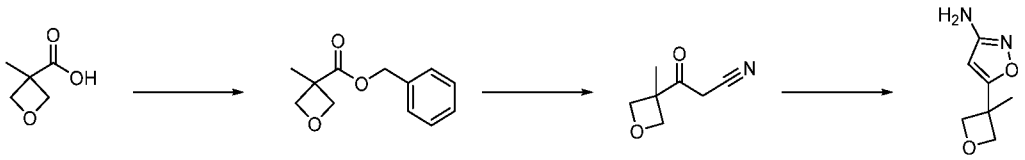
Step 1: 4-fluoro-4-methyl-3-oxopentanenitrile

To a suspension of NaH (60% in oil, 2.49 g, 104 mmol) in THF (30 mL) was added ethyl 2-fluoro-2-methylpropanoate (3.5 g, 26.0 mmol), followed by the dropwise addition of acetonitrile (1.66 g, 40.5 mmol). The resulting mixture was heated at 70 °C for 3h. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (3.10 g, 92%) as a yellow oil.

Step 2: 5-(2-fluoropropan-2-yl)isoxazol-3-amine

A mixture of 4-fluoro-4-methyl-3-oxopentanenitrile (2.3 g, 17.8 mmol), $NaHCO_3$ (3.73 g, 44.5 mmol) and $NH_2OH.HCl$ (703 mg, 21.3 mmol) in H_2O (27 mL) and MeOH (3 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA, 5:1) to afford the title product (450 mg, 18%) as a yellow oil. LCMS (Method A): 2.496min; m/z: 145.1 $[M+H]^+$.

Intermediate E5: 5-(3-methyloxetan-3-yl)isoxazol-3-amine



Step 1: benzyl 3-methyloxetane-3-carboxylate

A mixture of 3-methyloxetane-3-carboxylic acid (4 g, 34.4 mmol), K_2CO_3 (14.2 g, 103 mmol) and benzyl bromide (5.88 g, 34.4 mmol) in acetonitrile (50 mL) was stirred at 70 °C under N_2 overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (100 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 10:1) to give the title product (6.9 g, 97%) as a colorless oil. ^1H NMR (400 MHz, DMSO-d_6): 7.41-7.31 (m, 5H), 5.18 (s, 2H), 4.77 (d, J = 5.9 Hz, 2H), 4.34 (d, J = 5.9 Hz, 2H), 1.53 (s, 3H).

Step 2: 3-(3-methyloxetan-3-yl)-3-oxopropanenitrile

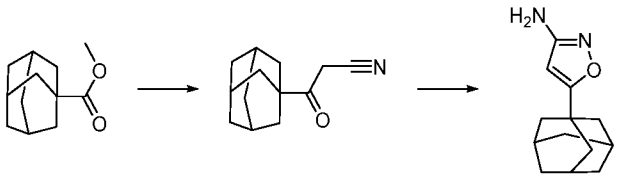
Acetonitrile (2.04 g, 49.7 mmol) was added to a solution of LDA (2 M inTHF, 25mL, 49.7 mmol) in dry THF (100 mL) and the solution was stirred at -78 °C under N_2 for 1 hour.

Benzyl 3-methyloxetane-3-carboxylate (7.9 g, 38.3 mmol) was then added at -78 °C and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (3 g, 56%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): 4.74 (d, J = 6.2 Hz, 2H), 4.28 (t, J = 3.1 Hz, 4H), 1.49 (s, 3H).

Step 3: 5-(3-methyloxetan-3-yl)isoxazol-3-amine

A mixture of 3-(3-methyloxetan-3-yl)-3-oxopropanenitrile (3 g, 21.5 mmol), $NH_2OH.HCl$ (1.63 g, 23.6 mmol) and NaOH (943 mg, 23.6 mmol) in water (40 mL) and EtOH (40 mL) was stirred at 80 °C under N_2 overnight. The reaction mixture was concentrated under reduced pressure and the residue was poured into water (100 mL). The mixture was extracted with EtOAc (50 mL x 2), and the combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (1.9 g, 57%) as a yellow solid. LCMS (Method A): 3.22 min; m/z: 155.1 $[M+H]^+$.

Intermediate E6: 5-(adamantan-1-yl)isoxazol-3-amine



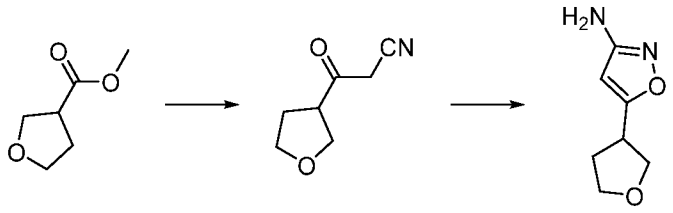
Step 1: 3-(adamantan-1-yl)-3-oxopropanenitrile

A solution of LDA (2 M in THF, 23.1mL, 46.2 mmol) was slowly added to a pre-cooled solution of acetonitrile (1.26 g, 30.8 mmol) in dry THF (25 mL) at -78 °C, and the mixture was stirred at -78 °C for 1h. A solution of methyl adamantane-1-carboxylate (3 g, 15.4 mmol) in dry THF (15 mL) was then added dropwise at -78 °C and the mixture was stirred at RT overnight. A sat. aq. Solution of NH_4Cl (50 mL) was added and the organics were extracted with EtOAc (3 x 50mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (3.5 g, 99%) as a yellow liquid.

Step 2: 5-(adamantan-1-yl)isoxazol-3-amine

A mixture of 3-(adamantan-1-yl)-3-oxopropanenitrile (3.5 g, 17.2 mmol), $NH_2OH.HCl$ (1.36 g, 20.6 mmol) and $NaHCO_3$ (3.60 g, 42.9 mmol) in water (54 mL) and MeOH (6 mL) was stirred under N_2 at 65 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA, 5:1) to give the title product (0.8 g, 21%) as a yellow solid. LCMS (Method A): 4.74 min, m/z: 292.2 $[M+H]^+$.

Intermediate E7: 5-(tetrahydrofuran-3-yl)isoxazol-3-amine



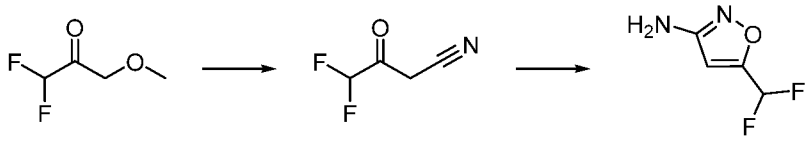
Step 1: 3-oxo-3-(tetrahydrofuran-3-yl)propanenitrile

Acetonitrile (4.14 mL) was added to a solution of LDA (2 M in THF, 12.5mL, 24.9 mmol) in dry THF (50 mL) and the mixture was stirred at -78 °C for 1 hour under N_2. Methyl tetrahydrofuran-3-carboxylate (2.5g 19.2 mmol) was then added at -78 °C and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (2g, 75%) as a yellow oil.

Step 2: 5-(tetrahydrofuran-3-yl)isoxazol-3-amine

To a solution of 3-oxo-3-(tetrahydrofuran-3-yl)propanenitrile (2 g, 14.3 mmol) in H_2O (10 mL) and EtOH (10 mL) were added $NH_2OH.HCl$ (1.09 g, 15.7 mmol) and NaOH (627 mg, 15.7 mmol), and the reaction mixture was stirred at 80 °C overnight. The mixture was diluted with water (50 mL) and the organics were extracted with EtOAc (50 mL x 3). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (1.9 g, 86 %) as a yellow solid. LCMS (Method A): 1.08 min; m/z: 155.1 $[M+H]^+$.

Intermediate E8: 5-(difluoromethyl)isoxazol-3-amine



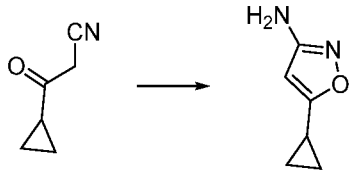
Step 1: 4,4-difluoro-3-oxobutanenitrile

To a solution of diisopropylamine (5.28 g, 52.2 mmol) in dry THF (100 ml), cooled to -78 °C under N_2, was added a solution of n-BuLi (1.6 M in hexanes, 52.2 mmol) dropwise, and the mixture was stirred at -78 °C for 1 h. A solution of MeCN (2.14 g, 52.2 mmol) in dry THF (20 ml) was then added dropwise and the resulting mixture was stirred at -78 °C for 30 min. A solution of ethyl 2,2-difluoroacetate (5 g, 40.2 mmol) in dry THF (10 ml) was then added and the reaction mixture was stirred at RT overnight. Water (100 mL) was then added, and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with EtOAc (200 mL x 3) and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (5 g, >100%) as a brown oil.

Step 2: 5-(difluoromethyl)isoxazol-3-amine

To a mixture of 4,4-difluoro-3-oxobutanenitrile (5 g, 41.9 mmol) and NaOH (1.83 g, 46.0 mmol) in EtOH (100 mL) and H_2O (100 mL) was added $NH_2OH.HCl$ (3.19 g, 46.0 mmol), and the mixture was stirred at 80 °C overnight. Water (30 mL) was added and the organics were extracted with EtOAc (300 mL x 3). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA, 10:1) to give the title product (876 mg, 16%) as a yellow oil.

Intermediate E9: 5-cyclopropyl-1,2-oxazol-3-amine

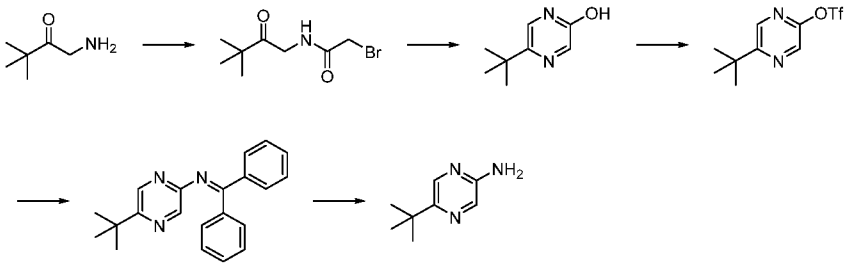


Step 1: 5-cyclopropyl-1,2-oxazol-3-amine

A mixture of 3-cyclopropyl-3-oxopropanenitrile (1 g, 9.16 mmol), $NH_2OH.HCl$ (359 mg, 10.9 mmol) and $NaHCO_3$ (1.92 g, 22.9 mmol) in MeOH (2 mL) and H_2O (18 mL) was stirred at 65 °C for 15 h under N_2. The reaction mixture was concentrated under reduced pressure,

and the residue was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA, 5:1) to afford the title product (320 mg, 28%) as a brown oil. LCMS (Method A): 0.78 min; m/z: 145.1 $[M+H]^+$.

Intermediate F1: 5-(tert-butyl)pyrazin-2-amine



Step 1: 2-bromo-N-(3,3-dimethyl-2-oxobutyl)acetamide

To a solution of 2-bromoacetyl bromide (17.5 g, 86.8 mmol) in DCM (120 mL) was added sat. aq. Na_2CO_3 (60 mL) followed by 1-amino-3,3-dimethylbutan-2-one (10 g, 86.8 mmol) at 0 °C. The solution was stirred at RT for 4 h. Water (100 mL) was then added and the organics were extracted with DCM (200 mL x 3). The combined organics were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (6.76 g, 33%) as a white solid. LCMS (Method A): 2.80 min; m/z: 236.1 $[M+H]^+$.

Step 2: 5-(tert-butyl)pyrazin-2-ol

To a solution of 2-bromo-N-(3,3-dimethyl-2-oxobutyl)acetamide (6.76 g, 28.6 mmol) in EtOH.NH_3 (20 mL) was added KI (949 mg, 5.72 mmol), and the reaction was stirred at 60 °C overnight. The mixture was poured into water (200 mL) and the organics were extracted with DCM (120 mL x 4). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM:MeOH, 30:1) to give the title product (2.6 g, 50%) as a yellow oil. LCMS (Method B): 1.90 min; m/z: 152.9 $[M+H]^+$.

Step 3: 5-(tert-butyl)pyrazin-2-yl trifluoromethanesulfonate

To a mixture of 5-tert-butylpyrazin-2-ol (2.6 g, 17.0 mmol) and Et_3N (3.44 g, 34.0 mmol) in DCM (70 mL) at 0 °C was added Tf_2O (7.19 g, 25.5 mmol), and the reaction was stirred at RT overnight. The mixture was poured into water (60 mL) and the organics were extracted with EtOAc (150 mL x 2). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column

chromatography on silica gel (PE:EtOAc, 20:1) to give the title product (2.72 g, 56%) as a yellow oil. LCMS (Method B): 5.30 min; m/z: 284.9 $[M+H]^+$.

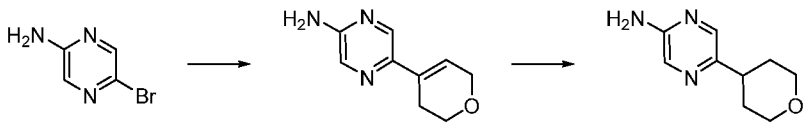
Step 4: N-(5-(tert-butyl)pyrazin-2-yl)-1,1-diphenylmethanimine

A mixture of 5-tert-butylpyrazin-2-yl trifluoromethanesulfonate (2.72 g, 9.56 mmol), Xantphos (1.10 g, 1.91 mmol), $Pd_2(dba)_3$ (875 mg, 956 µmol), Cs_2CO_3 (6.22 g, 19.1 mmol) and diphenylmethanimine (2.06 g, 11.4 mmol) in degassed 1,4-dioxane (80 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (PE:EtOAc, 10:1) to give the title product (2 g, 66%) as a white solid. LCMS (Method B): 5.42 min; m/z: 316.1 $[M+H]^+$.

Step 5: 5-(tert-butyl)pyrazin-2-amine

A mixture of N-(5-tert-butylpyrazin-2-yl)-1,1-diphenylmethanimine (150 mg, 475 µmol) in aq. HCl (2 M, 6 mL) and MeOH (6 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (PE:EtOAc, 2:1) to give the title product (47 mg, 65%) as a white solid. LCMS (Method B): 4.33 min; m/z 152.1 $[M+H]^+$.

Intermediate F2: 5-(tetrahydro-2H-pyran-4-yl)pyrazin-2-amine



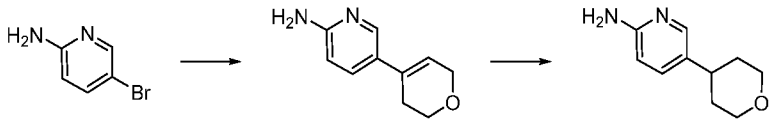
Step 1: 5-(3,6-dihydro-2H-pyran-4-yl)pyrazin-2-amine

To a mixture of 5-bromopyrazin-2-amine (828 mg, 4.76 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1g, 4.76 mmol) and Na_2CO_3 (1.50 g, 14.2 mmol) in degassed 1,4-dioxane (30 mL) and H_2O (7.5 mL) was added $Pd(dppf)Cl_2$ (217 mg, 238 µmol), and the reaction mixture was stirred at 100 °C under N_2 overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (PE:EtOAc, 1:1 to 0:1) to give the title product (700 mg, 83%) as a brown solid.

Step 2: 5-(tetrahydro-2H-pyran-4-yl)pyrazin-2-amine

A mixture of 5-(3,6-dihydro-2H-pyran-4-yl)pyrazin-2-amine (700 mg, 3.95 mmol) and 10% Pd/C (70 mg, 0.658 mmol) in MeOH (30 mL) was stirred at 50 °C under H_2 overnight. The reaction mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 4:1 to 1:4) to give the title product (520 mg, 74%) as a brown oil. LCMS (Method A): 0.85 min, m/z: 180.0 $[M+H]^+$.

Intermediate F3: 5-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine



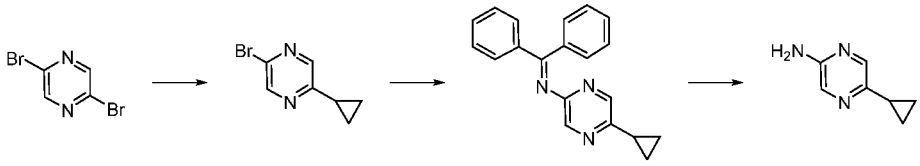
Step 1: 5-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine

A mixture of 5-bromopyridin-2-amine (2 g, 11.5 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.41 g, 11.5 mmol), Na_2CO_3 (4.87 g, 46.0 mmol) and $Pd(dppf)Cl_2$ (516 mg, 2.30 mmol) in degassed 1,4-dioxane (100 mL) and H_2O (20 mL) was heated at 100 °C for 12 h under N_2. The mixture was cooled to RT and the organics were extracted with EtOAc (2 x 10 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc, 10:1) to give the title product (800 mg, 4.53 mmol) as a yellow oil. LCMS (Method A): 3.02 min; m/z: 177.1 $[M+H]^+$.

Step 2: 5-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine

A mixture of 5-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine (3g, 17 mmol) and10% Pd/C (361 mg, 3.40 mmol) in MeOH (20 mL) was stirred at RT for 6 h under H_2. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (PE:EtOAc, 5:1 to 1:5) to give the title product (2.0 g, 11.2 mmol) as a yellow oil. LCMS (Method A): 0.72 min, m/z: 179.2 $[M+H]^+$.

Intermediate F4: 5-cyclopropylpyrazin-2-amine



Step 1: 2-bromo-5-cyclopropylpyrazine

To a solution of 2,5-dibromopyrazine (4.0 g, 16.8 mmol) in degassed 1,4-dioxane (80 mL) was added a solution of K_2CO_3 (5.80 g, 42.0 mmol) in water (20 mL), followed by cyclopropylboronic acid (1.72 g, 20.1 mmol), $Pd(OAc)_2$ (188 mg, 840 µmol) and $Pd(dppf)Cl_2$ (685 mg, 840 µmol). The reaction mixture was stirred at 120 °C for 16 h before being filtered through Celite. The filtrate was diluted with EtOAc (200 mL) and the organics were separated, washed with water (100 mL) and brine (100mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA, 100:1) to afford the title product (1.6 g, 43%) as a yellow solid. LCMS (Method A): 3.83 min, m/z: 200.9 $[M+H]^+$.

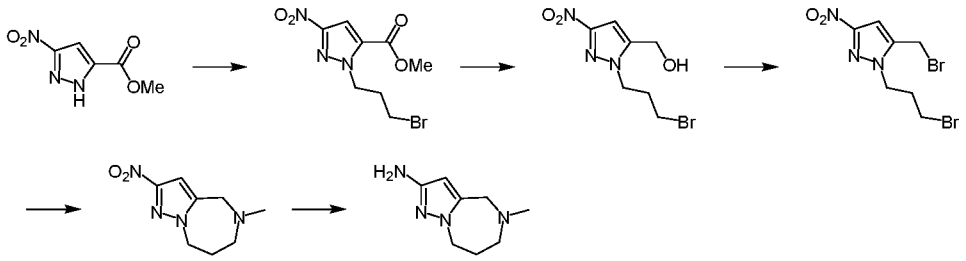
Step 2: N-(5-cyclopropylpyrazin-2-yl)-1,1-diphenylmethanimine

A mixture of 2-bromo-5-cyclopropylpyrazine (700 mg, 3.51 mmol), $Pd_2(dba)_3$ (160 mg, 175 µmol), Xantphos (203 mg, 351 µmol), Cs_2CO_3 (2.28 g, 7.02 mmol) and diphenylmethanimine (699 mg, 3.86 mmol) in degassed 1,4-dioxane (5 mL) was stirred overnight at 100 °C under N_2. The mixture was poured into water (10 mL) and the organics were extracted with EtOAc (50 mL x 2). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 5:1) to give the title product (1.3 g, 62%) as a yellow solid. LCMS (Method A): 4.27 min, m/z 300.2 $[M+H]^+$.

Step 3: 5-cyclopropylpyrazin-2-amine

To a solution of N-(5-cyclopropylpyrazin-2-yl)-1,1-diphenylmethanimine (1.3 g, 4.34 mmol) in MeOH (40 mL) was added aq. HCl (2 M, 10 mL), and the mixture was stirred at 30 °C overnight. Most of the MeOH was removed under reduced pressure and the remaining mixture was adjusted to pH = 8 with sat. aq. Na_2CO_3.The aqueous mixture was extracted with EtOAc (50 mL x 2) and the combined organics were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc; 1:1) to give the title product (100 mg, 17 %) as a brown solid. LCMS (Method A): 4.45 min, m/z: 136.0 $[M+H]^+$.

Intermediate G1: 5-methyl-2-nitro-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine



Step 1: methyl 1-(3-bromopropyl)-3-nitro-1H-pyrazole-5-carboxylate

To a solution of methyl 3-nitro-1H-pyrazole-5-carboxylate (1.0 g, 5.84 mmol) in acetone (30 mL) were added K_2CO_3 (4.02 g, 29.1 mmol) and 1,3-dibromopropane (2.10 mL, 17.5 mmol), and the reaction was then heated at reflux for 2 h. The mixture was then cooled to 0 °C, filtered and concentrated. The residue was purified by flash chromatography (EtOAc:*n*-Hep 0-50%) to give the title compound (1.22 g, 72%) as a colourless oil. LCMS (Method D): 1.90 min, m/z 291.8/293.8 $[M+H]^+$.

Step 2: [1-(3-bromopropyl)-3-nitro-1H-pyrazol-5-yl]methanol

To a 0 °C solution of methyl 1-(3-bromopropyl)-3-nitro-1H-pyrazole-5-carboxylate (1.22 g, 4.17 mmol) in THF (40 mL) was added $LiBH_4$ (2.08 mL, 4.17 mmol) in portions. The reaction was stirred at 0 °C for 4 h, then quenched with sat. NH_4Cl (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were dried ($MgSO_4$) and concentrated to give the title compound (882 mg, 80%) as a colourless oil. LCMS (Method D): 1.17 min, m/z 263.8/265.8 $[M+H]^+$.

Step 3: 5-(bromomethyl)-1-(3-bromopropyl)-3-nitro-1H-pyrazole

To a suspension of [1-(3-bromopropyl)-3-nitro-1H-pyrazol-5-yl]methanol (880 mg, 3.33 mmol) in $CHCl_3$ (30 mL) was added PBr_3 (468 µL, 4.99 mmol) and the reaction was heated at reflux for 2 h. Once cooled, the mixture was basified to pH 9 with sat. $NaHCO_3$. The mixture was extracted with $CHCl_3$ (3 x 25 mL), and the combined organics were washed with water (25 mL), dried ($MgSO_4$) and concentrated to give the title compound (1.09 g, Quant.) as a white solid. LCMS (Method D): 1.98 min, m/z 327.8 $[M+H]^+$.

Step 4: 5-methyl-2-nitro-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine

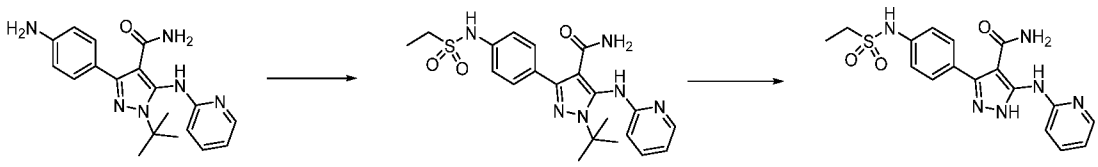
To a solution of 5-(bromomethyl)-1-(3-bromopropyl)-3-nitro-1H-pyrazole (1.09 g, 3.33 mmol) in THF (33.3 mL) was added $MeNH_2$ (2.0 M in THF, 9.95 mL, 19.9 mmol) and the reaction was stirred at RT overnight. The mixture was concentrated and the residue was diluted with sat. $NaHCO_3$ (15 mL). The aqueous mixture was extracted with DCM (2 x 20

mL), and the combined organics were washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-20% MeOH:DCM) to give the title compound (468 mg, 72%) as a yellow oil. LCMS (Method D): 0.14 min, m/z 197.0 $[M+H]^+$.

Step 5: 5-methyl-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepin-2-amine

A mixture of 5-methyl-2-nitro-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine (465 mg, 2.36 mmol) and 10% Pd/C (251 mg, 236 µmol) in MeOH (11.7 mL) was stirred under H_2 overnight. The reaction was filtered over Celite and concentrated to give the title compound (387 mg, 99%) as a yellow oil. LCMS (Method D): rt 0.10 min, m/z 167.0 $[M+H]^+$.

Compound 131



Step 1: 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-(tert-butyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (Intermediate A, 200 mg, 0.57 mmol), $EtSO_2Cl$ (88 mg, 0.69 mmol) and pyridine (90 mg, 1.14 mmol) in $CHCl_3$ (5 mL) was stirred at RT for 16 h. The mixture was diluted with H_2O (5 mL) and then extracted with DCM (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (100 mg, 40%) as a yellow solid. LCMS (Method A): 2.12 min; m/z: 443.2 $[M+H]^+$.

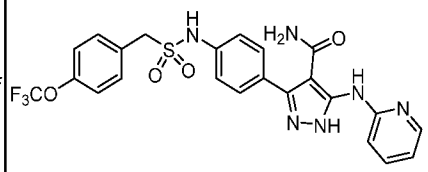
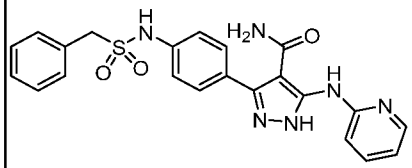
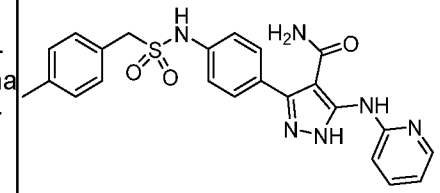
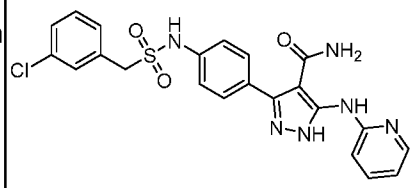
Step 2: 3-(4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (compound 131)

A solution of 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (50 mg, 0.11 mmol) in TFA (4 mL) was stirred at 60 ºC for 2 h. The mixture was concentrated under reduced pressure, basified with NH_4OH (1 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH:NH_4OH, 10:1:0.1) to afford the title product (40 mg, 94%) as a yellow solid. LCMS (Method A): 0.29 min; m/z: 387.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.83 (s,

1H), 10.26 (br s, 1H), 9.48 (s, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.80-7.60 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.13-7.12 (m, 3H), 6.85-6.84 (m, 1H), 6.05 (br s, 1H), 3.17 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

The following compounds (Table 5) were similarly prepared from the appropriate sulfonyl chloride and Intermediate A1 according to the method described for the synthesis of 3-(4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide.

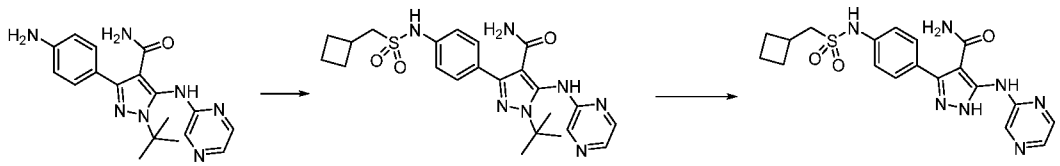
Table 5

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
135	5-(pyridin-2-ylamino)-3-(4-(((4-(trifluoromethoxy)phenyl)methyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A: 2.37 min; m/z: 533.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.31-8.30 (m, 1H), 7.76 (t, J = 6.4 Hz, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.45-7.43 (m, 3H), 7.37 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.00 (t, J = 6.8 Hz, 1H), 4.56 (s, 2H).	(4-(trifluoromethoxy)phenyl)methanesulfonyl chloride
136	3-(4-(phenylmethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.95 min; m/z: 449.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (s, 1H), 10.17 (s, 1H), 9.54 (s, 1H), 8.18 (d, J = 2.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.73-7.68 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.37-7.28 (m, 9H), 6.85 (s, 1H), 5.98 (br s, 1H), 4.57 (s, 2H).	phenylmethanesulfonyl chloride
132	5-(pyridin-2-ylamino)-3-(4-((p-tolylmethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.22 min; m/z: 463.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.7 (br s, 1H), 10.0-9.98 (m, 1H), 9.67(br s, 1H), 8.99 (d, 1H, J = 7.2 Hz), 8.36-8.21 (m, 2H), 7.85-7.71 (m, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.33-7.29 (m, 3H), 7.18-7.16 (m, 5H), 7.03-6.89 (m, 1H), 4.49 (d, J = 5.2 Hz, 2H), 2.30 (s, 3H).	p-tolylmethanesulfonyl chloride
129	3-(4-(((3-chlorophenyl)methyl)sulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.21 min; m/z: 483.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.55(br s, 1H), 9.71 (s, 1H), 8.30-8.20 (m, 1H), 8.03 (s, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.32-7.27 (m, 4H), 7.20-7.17 (m, 4H), 6.98 (d, J = 8.4 Hz, 2H), 6.83 (t, J = 6.4 Hz, 1H), 5.73 (s, 1H), 3.98 (s, 2H).	(3-chlorophenyl)methanesulfonyl chloride

134	3-(4-((cyclobutylmethyl)sulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A: 2.54 min; m/z: 426.9 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.28 (br s, 1H), 7.71-7.36 (m, 6H), 6.95 (t, J = 6.0 Hz, 1H), 3.30 (s, 2H), 2.85-2.81 (m, 1H), 2.18-2.16 (m, 2H), 1.95-1.62 (m, 4H).	cyclobutylmethanesulfonyl chloride
133	3-(4-(phenylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.98 min; m/z: 434.9 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.83 (br s, 1H), 9.53 (br s, 1H), 8.18 (d, J = 4.4 Hz, 1H), 7.85-7.80 (m, 3H),7.68 (t, J = 6.8 Hz, 1H), 7.60-7.45 (m, 4H), 7.42 (d, J = 8.4 Hz, 2H), 7.23-7.10 (m, 3H), 6.84 (t, J = 6.0 Hz, 1H), 5.87 (s, 1H).	benzenesulfonyl chloride
130	3-(4-((2-phenylethyl)sulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.61 min; m/z: 463.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.77 (br s, 1H), 10.18 (br s, 1H), 9.50 (s, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.50 (t, J = 6.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37-7.20 (m, 8H), 6.85 (br s, 1H), 6.00 (br s, 1H), 3.46 (t, J = 8.0 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H).	2-phenylethanesulfonyl chloride
48	3-(4-((difluoromethyl)sulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.70 min; m/z: 409.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.81 (s, 1H), 9.47 (s, 1H), 8.18 (s, 1H), 7.97 (s, 1H), 7.72-7.68 (m, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.21-6.95 (m, 1H), 6.85 (br s, 1H).	difluoromethanesulfonyl chloride

268	5-[(pyridin-2-yl)amino]-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide		LCMS (Method D): 3.29 min; m/z: 440.9 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (s, 1H), 10.72 (s, 1H), 9.51 (s, 1H), 8.17 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 6.85 (s, 1H), 6.02 (s, 1H), 4.61 (t, J = 9.6 Hz, 2H).	2,2,2-trifluoroethanesulfonyl chloride

Compound 81



Step 1: 1-(tert-butyl)-3-(4-((cyclobutylmethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide

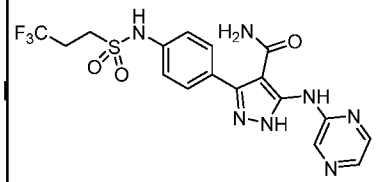
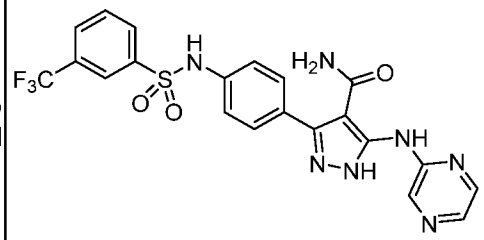
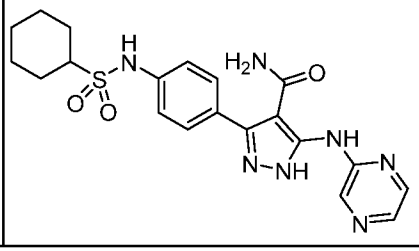
A mixture of 3-(4-aminophenyl)-1-(tert-butyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Intermediate A3, 300 mg, 853 µmol), cyclobutylmethanesulfonyl chloride (286 mg, 1.7 mmol) and pyridine (202 mg, 2.56 mmol) in $CHCl_3$ (10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 12:1) to afford the title product (120 mg, 29%) as a white solid. LCMS (Method A): 3.53 min; m/z: 484.2 $[M+H]^+$.

Step 2: 3-(4-((cyclobutylmethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (compound 81)

A mixture of 1-(tert-butyl)-3-(4-((cyclobutylmethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (60 mg, 124 µmol) in DCM (4 mL) and TFA (4 mL) was stirred at 30 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was neutralized to pH 7-8 with NH_4OH, then extracted with DCM (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 12:1) to afford the title product (20 mg, 37%) as a white solid. LCMS (Method A): 3.20 min; m/z: 428.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 12.94 (s, 1H), 10.10 (s, 1H), 9.64 (s, 1H), 9.26 (s, 1H), 8.22 (t, *J* = 4.0 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.30 (s, 2H), 2.08 (s, 1H), 1.83-1.73 (m, 4H).

The following compounds (Table 6) were similarly prepared from the appropriate sulfonyl chloride and Intermediate A3 according to the method described for the synthesis of 3-(4-((cyclobutylmethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide.

Table 6

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
72	5-(pyrazin-2-ylamino)-3-(4-((3,3,3-trifluoropropyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.21 min; m/z: 456.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 10.35 (s, 1H), 9.63 (s, 1H), 9.26 (s, 1H), 8.25-8.21 (m, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 6.15 (s, 1H), 3.45 (t, *J* = 7.6 Hz, 3H), 2.85-2.72 (m, *J* = 8.8 Hz, 3H).	3,3,3-trifluoropropane-1-sulfonyl chloride
73	5-(pyrazin-2-ylamino)-3-(4-((3-(trifluoromethyl)phenyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.56 min; m/z: 504.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (br s, 1H), 9.59 (br s, 1H), 9.21 (br s, 1H), 8.20-7.80 (m, 7H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H).	4-methyl-3-(trifluoromethyl) benzenesulfonyl chloride
74	3-(4-(cyclohexanesulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.30 min; m/z: 442.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 1H), 10.09 (br s, 1H), 9.63 (br s, 1H), 9.26 (s, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 3.10-3.05 (m, 1H), 2.07-2.04 (m, 2H), 1.79-1.76 (m, 2H), 1.61-1.27 (m, 4H), 1.33-1.11 (m, 2H).	cyclohexanesulfonyl chloride

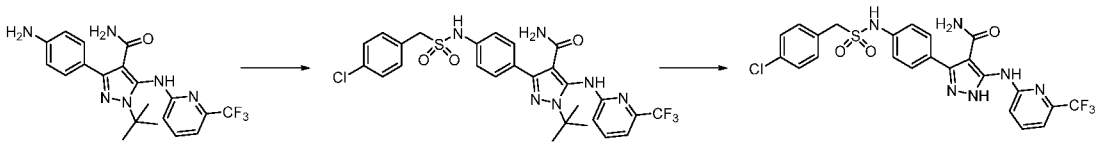
82	3-(4-((4-methoxyphenyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.24 min; m/z: 466.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.89 (s, 1H), 10.57 (s, 1H), 9.58 (s, 1H), 9.23 (s, 1H), 8.22 (s, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 5.98 (s, 1H), 3.81 (s, 3H).	4-methoxybenzenesulfonyl chloride
78	5-(pyrazin-2-ylamino)-3-(4-((4-(trifluoromethoxy)phenyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.63 min; m/z: 520.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 10.83 (s, 1H), 9.54 (s, 1H), 9.20 (s, 1H), 8.20 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.60 (s, 2H), 7.50 (s, 2H), 7.26 (s, 3H).	4-(trifluoromethoxy)benzenesulfonyl chloride
79	5-(pyrazin-2-ylamino)-3-(4-((4-(trifluoromethyl)phenyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.42 min; m/z: 503.6 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (s, 1H), 11.03 (s, 1H), 9.56 (s, 1H), 8.20 (s, 1H), 8.07 (s, J = 11.6 Hz, 4H), 7.50 (s, 2H), 7.27 (s, 2H), 8.20 (s, 1H).	4-(trifluoromethyl)benzenesulfonyl chloride
70	3-(4-(((4-chlorophenyl)methyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.48 min; m/z: 484.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 10.16 (s, 1H), 9.65 (s, 1H), 9.27 (s, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.51 (br s, 4H), 7.32 (s, 4H), 4.59 (s, 2H).	(4-chlorophenyl)methanesulfonyl chloride

83	5-[(pyrazin-2-yl)amino]-3-(4-{[3-(trifluoromethyl)phenyl]methanesulfonamido}phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.55 min; m/z: 518.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.25 (s, 1H), 9.66 (s, 1H), 9.27 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.73-7.68 (m, 2H), 7.59-7.54 (m, 5H), 7.32 (d, J = 7.2 Hz, 2H), 6.07 (s, 1H), 4.74 (s, 3H).	(3-(trifluoromethyl)phenyl)methanesulfonyl chloride
76	5-[(pyrazin-2-yl)amino]-3-(4-{[4-(trifluoromethyl)phenyl]methanesulfonamido}phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.69 min; m/z: 518.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (s, 1H), 10.24 (s, 1H), 9.65 (s, 1H), 9.27 (s, 1H), 8.23-8.22 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.58-7.52 (m, 5H), 7.35 (d, J = 8.4 Hz, 3H), 4.71 (s, 2H).	(4-(trifluoromethyl)phenyl)methanesulfonyl chloride
80	5-(pyrazin-2-ylamino)-3-(4-(((4-(trifluoromethoxy)phenyl)methyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.63 min; m/z: 534.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (s, 1H), 10.24 (s, 1H), 9.65 (s, 1H), 9.27 (s, 1H), 8.23-8.22 (m, 1H), 8.11 (d, 1H), 7.56 (d, 2H), 7.46-7.33 (m, 6H), 6.14 (br s, 1H), 4.64 (s, 2H), 2.08 (s, 1H).	(4-(trifluoromethoxy)phenyl)methanesulfonyl chloride
77	3-(4-((phenylmethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.22 min; m/z: 450.1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.98 (s, 1H), 10.17 (s, 1H), 9.67 (s, 1H), 9.28 (s, 1H), 8.23 (s, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 3.6 Hz, 3H), 7.32 (s, 2H), 7.31 (d, J = 2.8 Hz, 2H), 4.56 (s, 2H), 0.87-0.84 (m, 1H).	phenylmethanesulfonyl chloride

71	3-(4-((1-methylethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.92 min; m/z: 402.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 10.09 (s, 1H), 9.63 (s, 1H), 9.26 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.55 (t, J = 8.4 Hz, 2H), 7.33 (t, J = 8.4 Hz, 2H), 1.28 (t, J = 6.8 Hz, 6H).	propane-2-sulfonyl chloride
108	3-(4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.78 min; m/z: 388.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.94 (s, 1H), 10.13 (s, 1H), 9.64 (s, 1H), 9.26 (s, 1H), 8.22 (t, J = 4.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.30 (s, 2H), 2.08 (s, 1H), 1.83-1.73 (m, 4H).	ethanesulfonyl chloride
68	3-(4-(cyclopropanesulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.25 min; m/z: 400.1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.99 (s, 1H), 10.11 (s, 1H), 9.60 (s, 1H), 9.26 (s, 1H), 8.22 (s, 1H), 8.12 (s, 1H), 7.45 (dd, J = 7.6, 7.2 Hz, 5H), 6.04 (s, 1H), 2.72 (s, 1H), 0.99 (s, 4H).	cyclopropanesulfonyl chloride
97	3-(4-(propylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.06 min; m/z: 401.8 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (s, 1H), 10.13 (s, 1H), 9.63 (s, 1H), 9.25 (s, 1H), 8.22 (s, 1H), 8.11 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.2 Hz, 2H), 3.15 (t, J = 5.6 Hz, 2H), 1.72 (q, J = 14.8 Hz, 2H), 0.45 (t, J = 14.8 Hz, 3H).	propane-1-sulfonyl chloride

63	3-(4-((difluoromethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.05 min; m/z: 410.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (s, 1H), 11.24 (s, 1H), 9.57 (s, 1H), 9.23 (s, 1H), 8.21 (s, 1H), 8.11 (s, 1H), 7.59 (d, J = 9.4 Hz, 2H), 7.39-7.34 (m, 3H), 7.21-7.08 (m, 1H), 6.17 (s, 1H).	difluoromethanesulfonyl chloride
69	3-(4-((1,1-dimethylethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.15 min; m/z: 416.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.96 (br s, 1H), 9.93 (br s, 1H), 9.65 (br s, 1H), 9.26 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 1.33 (s, 9H). Two active protons not observed.	2-methylpropane-2-sulfonyl chloride
23	3-(4-((3,3-difluoropropyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.06 min; m/z: 438.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.62 (s, 1H), 9.25 (s, 1H), 8.23 (br s, 1H), 8.11 (t, J = 2.8 Hz, 1H), 7.59 (t, J = 8.4 Hz, 2H), 7.37 (t, J = 8.4 Hz, 2H), 6.21 (m, 1H), 2.30 (br s, 2H).	3,3-difluoropropane-1-sulfonyl chloride

Compound 60



Intermediate A2

Step 1: 1-tert-butyl-3-{4-[(4-chlorophenyl)methanesulfonamido]phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4- carboxamide

To a solution of 3-(4-aminophenyl)-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (Intermediate A2, 124 mg, 296 µmol) in pyridine (5 mL) at 0 °C was added (4-chlorophenyl)methanesulfonyl chloride (115 mg, 510 µmol) and the resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (70 mg, 39%) as a yellow solid. LCMS (Method A): 4.32 min; m/z: 607.1 $[M+H]^+$.

Step 2: 3-(4-(((4-chlorophenyl)methyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide (compound 60)

A solution of 1-tert-butyl-3-{4-[(4-chlorophenyl)methanesulfonamido]phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4- carboxamide (70 mg, 115 µmol) in DCM (4 mL) and TFA (4 mL) was stirred at 35 °C for 2 h. The reaction mixture was concentrated under reduced pressure and then neutralized to pH 7-8 with sat. aq. Na_2CO_3. The mixture was diluted with H_2O (10 mL), and the precipitate was collected *via* filtration and purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (18 mg, 28%) as a yellow solid.

The following compounds (Table 7) were similarly prepared from the appropriate sulfonyl chloride starting material (SM) and Intermediate A2 according to the method described for the synthesis of 3-(4-(((4-chlorophenyl)methyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide.

Table 7

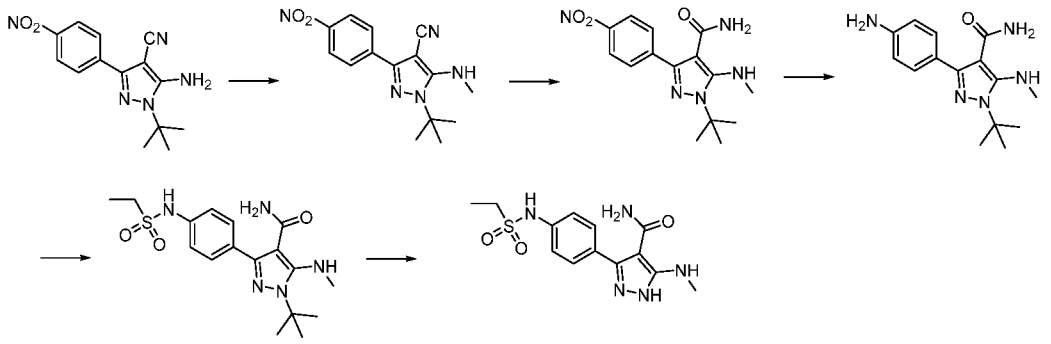
Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
56	3-(4-((3,4-dichlorophenyl)methylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.23 min; m/z: 585.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 10.22 (s, 1H), 9.79 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.99 (t, J = 8.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 2.8 Hz, 2H), 7.35-7.26 (m, 5H), 6.13 (br s, 1H), 4.65 (s, 2H).	(3,4-dichlorophenyl)methanesulfonyl chloride
55	3-(4-(((4-fluorophenyl)methyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.03 min; m/z: 535.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.16 (s, 1H), 9.79 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.33 (s, 5H), 7.21(t, J = 8.4 Hz, 2H), 7.57 (s, 2H). Three active protons not observed.	(4-fluorophenyl)methanesulfonyl chloride
59	3-(4-(((3-chlorophenyl)methyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.10 min; m/z: 551.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.23 (s, 1H), 9.80 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.45-7.25 (m, 7H), 4.63 (s, 2H). Three active protons not observed.	(3-chlorophenyl)methanesulfonyl chloride

53	3-(4-(((2-chlorophenyl)methyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.08 min; m/z: 551.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 9.92 (s, 1H), 8.29 (d, J = 7.6 Hz, 1H), 7.47 (q, J = 5.6 Hz, 1H), 7.38 (q, J = 5.6 Hz, 1H), 7.30-7.24 (m, 6H), 7.08 (d, J = 8.4 Hz, 1H), 4.28 (s, 2H). Four active protons not observed.	(2-chlorophenyl)methanesulfonyl chloride
126	3-(4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.53 min; m/z: 455.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.20-8.16 (m, 1H), 7.85-7.77 (m, 1H), 7.49-7.46 (m, 2H), 7.32-7.30 (m, 2H), 7.23-7.10 (m, 1H), 3.10 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H).	Ethylsulfonyl chloride
57	3-(4-((p-tolylmethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.12 min; m/z: 531.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.12 (br s, 1H), 9.80 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.98 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.34-7.30 (m, 3H), 7.17 (s, 4H), 4.50 (s, 2H), 2.29 (s, 3H).	p-tolylmethanesulfonyl chloride
54	3-(4-((1-methylethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.78 min; m/z: 469.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 10.09 (s, 1H), 9.76 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 9.78 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 6.11 (s, 1H), 1.28 (d, J = 6.8 Hz, 6H).	propane-2-sulfonyl chloride

53	3-(4-((difluoromethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.85 min; m/z: 477.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 11.29 (s, 1H), 9.72 (s, 1H), 8.21 (d, J = 8.8 Hz 1H), 7.98 (t, J = 8 Hz 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz 2H), 7.31-7.05 (m, 2H).	difluoromethanesulfonyl chloride
50	3-(4-((2-methoxyethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.59 min; m/z: 485.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.14 (s, 1H), 9.77 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.36-7.30 (m, 4H), 6.10 (s, 1H), 3.67 (t, J = 6.0 Hz, 2H), 3.44 (t, J = 6.0 Hz, 2H), 3.19 (s, 3H).	2-methoxyethane-1-sulfonyl chloride
51	3-(4-((2-(dimethylamino)ethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.83 min; m/z: 498.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.78 (s, 1H), 9.86 (s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.97 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.2Hz, 1H),7.13 (d, J = 8.4 Hz, 2H), 5.93 (s, 1H), 3.09-3.05 (m, 2H), 2.61-2.58 (m, 2H), 2.08 (s, 6H).	2-chloroethane-1-sulfonyl chloride
29	3-(4-((cyanomethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.59 min; m/z: 466.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (s, 1H), 11.06 (s, 1H), 9.97 (s, 1H), 8.52 (s, 1H), 8.07 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.42-7.39 (m, 4H), 4.99 (s, 2H).	cyanomethanesulfonyl chloride

52	3-(4-(cyclopropanesulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.68 min; m/z: 467.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.10 (br s, 1H), 9.75 (s, 1H), 8.21 (s, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.58-7.56 (m, 2H), 7.39-7.30 (m, 4H), 6.10 (br s, 1H), 2.76-2.70 (m, 1H), 1.00-0.98 (m, 4H).	cyclopropanesulfonyl chloride
49	3-(4-((2,2-difluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.72 min; m/z: 491.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 10.54 (s, 1H), 9.79 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.99 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.2 Hz, 1H) 6.41 (tt, J = 5.4 Hz, 4.4 Hz, 1H), 4.02 (dt, J = 14.8, 4.0 Hz, 2H).	2,2-difluoroethane-1-sulfonyl chloride
43	3-(4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.86 min; m/z: 509.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.72 (s, 1H), 9.92 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 5.84 (s, 1H), 3.66 (q, J = 10.4 Hz, 2H).	2,2,2-trifluoroethane-1-sulfonyl chloride

Compound 119



Step 1: 1-(tert-butyl)-5-(methylamino)-3-(4-nitrophenyl)-1H-pyrazole-4- carbonitrile

A mixture of 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (300 mg, 1.05 mmol), paraformaldehyde (315 mg, 10.5 mmol), NaOMe (228 mg, 4.2 mmol),and MeOH (20 mL) was stirred at RT for 16 h. $NaBH_4$ (160mg, 4.2mmol) was added and the mixture was stirred for 2h at RT. The mixture was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to afford the crude product (300 mg, 76%) as a yellow solid. LCMS (Method B): 2.45 min; m/z: 300.0 $[M+H]^+$.

Step 2: 1-tert-butyl-5-(methylamino)-3-(4-nitrophenyl)-1H-pyrazole-4- carboxamide

To a solution of 1-tert-butyl-5-(methylamino)-3-(4-nitrophenyl)-1H-pyrazole-4- carbonitrile (270 mg, 0.9 mmol) in DMSO (20 mL) and EtOH (20 mL) were added 30% aq. H_2O_2 (20 mL) and 5% aq. NaOH (1 mL). The mixture was stirred at RT for 20 min, and then heated to 80 °C for 16 h. The mixture was concentrated under reduced pressure and then diluted with H_2O (20 mL). The precipitate was collected *via* filtration, washed with H_2O and dried under reduced pressure to afford the title product (250 mg, 87%) as yellow solid. LCMS (Method B): 1.92 min; m/z: 318.0 $[M+H]^+$.

Step 3: 3-(4-aminophenyl)-1-tert-butyl-5-(methylamino)-1H-pyrazole-4- carboxamide

A mixture of 1-tert-butyl-5-(methylamino)-3-(4-nitrophenyl)-1H-pyrazole- 4-carboxamide (185mg, 0.58mmol), sat. aq. NH_4Cl (5 mL), Zn dust (190 mg, 2.91 mmol) and MeOH (10 mL) was heated to 60 °C for 16 h. The reaction mixture was filtered, concentrated under reduced pressure, and then diluted with H_2O. The precipitate was collected by filtratation and dried under reduced pressure to afford the title product (150 mg, 90%) as yellow solid. LCMS (Method B): 0.35 min; m/z: 288.1 $[M+H]^+$.

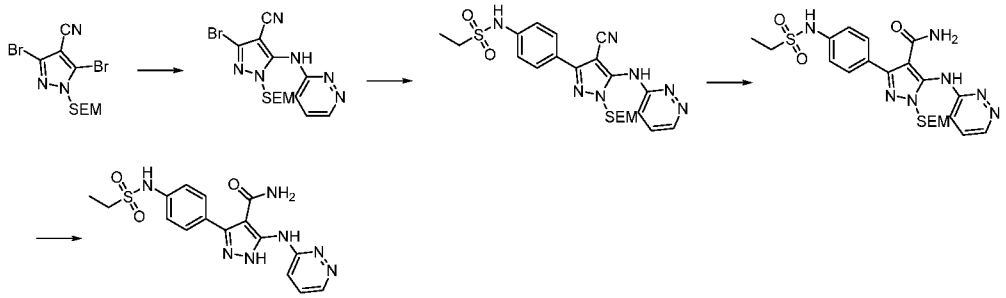
Step 4: 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-(methylamino)-1H- pyrazole-4-carboxamide

To a solution of 3-(4-aminophenyl)-1-tert-butyl-5-(methylamino)-1H-pyrazole-4-carboxamide (100 mg, 0.35 mmol) and pyridine (55.0 mg, 0.7 mmol) in $CHCl_3$ (5 mL) was added $EtSO_2Cl$ (53.6 mg, 0.42 mmol) and the mixture was stirred at RT overnight. The reaction mixture was concentrated and the crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (35 mg, 27%) as yellow solid. LCMS (Method B): 0.87 min; m/z: 380.0 $[M+H]^+$.

Step 5: 3-(4-(ethylsulfonamido)phenyl)-5-(methylamino)-1H-pyrazole-4- carboxamide (compound 119)

A solution of 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-(methylamino)-1H-pyrazole-4-carboxamide (35 mg, 0.09 mmol) in TFA (2 mL) and DCM (2 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH:NH_4OH, 10:1:0.1) to afford the title product (12 mg, 40%) as a grey solid. LCMS (Method B): 3.50 min; m/z: 324.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.51 (d, J = 8.4 Hz, 2H),7.38 (d, J = 8.4 Hz, 2H), 3.19-3.14 (q, J = 7.2 Hz, 2H), 2.94 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H).

Compound 64



Step 1: 3-bromo-5-[(pyridazin-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}- 1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (2 g, 5.24 mmol), pyridazin-3-amine (498 mg, 5.24 mmol), $Pd_2(dba)_3$ (479 mg, 524 µmol), Xantphos (599 mg, 1.04 mmol) and Cs_2CO_3 (5.11 g, 15.7 mmol) in degassed 1-4-dioxane (150 mL) was stirred at 80 °C under N_2 for 16 h. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography

(PE:EtOAc, 1:1) to afford title product (380 mg, 18%) as a yellow solid. LCMS (Method A): 3.15 min; m/z: 395.0, 397.1 $[M+H]^+$.

Step 2: N-(4-{4-cyano-5-[(pyridazin-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-3-yl}phenyl)ethane-1-sulfonamide

A mixture of 3-bromo-5-[(pyridazin-3-yl)amino]-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazole-4-carbonitrile (300 mg, 758 µmol), N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (235 mg, 758 µmol), $Pd(dppf)Cl_2$ (69.4 mg, 75.8 µmol), mmol) and Na_2CO_3 (3.79 mmol) in degassed 1,4-dioxane (10 mL) was stirred at 100 ºC under microwave irradiation for 20min. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 0:1) to afford title product (230 mg, 87%) as a yellow solid. LCMS (Method A): 3.31 min; m/z: 500.0 $[M+H]^+$.

Step 3: 3-(4-ethanesulfonamidophenyl)-5-[(pyridazin-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

To a solution of N-(4-{4-cyano-5-[(pyridazin-3-yl)amino]-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazol-3-yl}phenyl)ethane-1-sulfonamide (200 mg, 400 µmol) in 50% aq. 1,4-dioxane (20 mL), was added Ghaffar-Parkins catalyst (10 mg, 23.4 µmol) and the mixture was heated to 100 °C under N_2 for 16 h. The reaction mixture was then concentrated under reduced pressure and the crude residue was purified by prep-TLC (PE:EtOAc, 10:1) to afford the title product (80 mg, 38%) as a yellow solid. LCMS (Method A): 3.53 min; m/z: 518.2 $[M+H]^+$.

Step 4: 3-(4-ethanesulfonamidophenyl)-5-[(pyridazin-3-yl)amino]-1H-pyrazole- 4-carboxamide (compound 64)

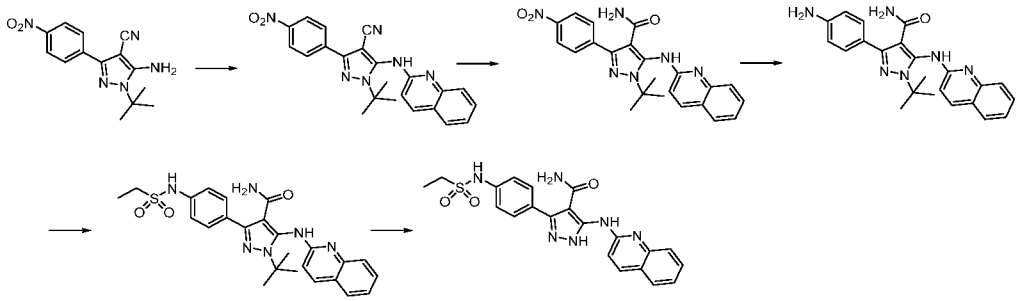
A mixture of 3-(4-ethanesulfonamidophenyl)-5-[(pyridazin-3-yl) amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (80 mg, 154 µmol), 12.0 M HCl (0.5 mL) and THF (5 mL) was stirred at 30 °C under N_2 overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH:NH_4OH, 10:1:0.1) to afford the title product (10 mg, 25%) as a yellow solid. LCMS (Method A): 2.44 min; m/z: 388.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.67 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.41- 7.37 (m, 1H), 7.30-7.26 (m, 1H), 3.35 (s, 1H), 3.20 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H).

Following the full synthesis of Compound 64, starting from 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile with the mentioned intermediates used as described in step 1, the following compounds (Table 8) were prepared:

Table 8

Compound No	Name	Structure	LCMS data	^{1}H NMR data	Intermediates
44	3-(4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.44 min; m/z: 456.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.17 (s, 1H), 9.99 (s, 1H), 9.42 (s, 1H), 8.54 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 3.18 (q, J = 6.4 Hz, 2H), 1.23 (t, J = 6.4 Hz, 3H).	6-(trifluoromethyl)pyrazin-2-amine
90	3-(4-(ethylsulfonamido)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.13 min; m/z: 418.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.81 (s, 1H), 10.13 (s, 1H), 9.40 (s, 1H), 8.85 (s, 1H), 7.99 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.87 (s, 3H), 3.19 (q, J = 6.8 Hz, 2H), 1.23 (t, J = 6.8 Hz, 3H).	5-methoxypyrazin-2-amine

Compound 89



Step 1: 1-tert-butyl-3-(4-nitrophenyl)-5-[(quinolin-2-yl)amino]-1H-pyrazole-4- carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (2 g, 7.00 mmol), 2-chloroquinoline (1.03 g, 6.30 mmol), $Pd_2(dba)_3$ (641 mg, 0.7 mmol), Xantphos (810 mg, 1.40 mmol) and Cs_2CO_3 (6.84 g, 21.0 mmol) in degassed 1,4-dioxane (5 mL) was stirred at 100 °C for 16 h. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (520 mg, 18% yield) as a yellow oil. LCMS (Method A): 3.54 min; m/z: 413.0 $[M+H]^+$.

Step 2: 1-tert-butyl-3-(4-nitrophenyl)-5-[(quinolin-2-yl)amino]-1H-pyrazole-4-carboxamide

To a mixture of 1-tert-butyl-3-(4-nitrophenyl)-5-[(quinolin-2-yl)amino]-1H-pyrazole- 4-carbonitrile (520 mg, 1.26 mmol) in EtOH (20 mL) and DMSO (10 mL) were added 30% aq. H_2O_2 (10 mL) and 5% aq. NaOH (1.5 mL), and the reaction was stirred at 80 °C overnight. The mixture was concentrated under reduced pressure, then the residue was diluted with H_2O (150 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (1 g, > 100%) as a brown solid. LCMS (Method A): 3.80 min; m/z: 431.1 $[M+H]^+$.

Step 3: 3-(4-aminophenyl)-1-tert-butyl-5-[(quinolin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-(4-nitrophenyl)-5-[(quinolin-2-yl)amino]-1H-pyrazole- 4-carboxamide (500 mg, 1.16 mmol) and 10% Pd/C (50 mg) in MeOH (10 mL) was stirred at RT overnight under H_2. The suspension was filtered over Celite and the filtrate wasconcentrated under reduced pressure to afford the title product (460 mg, 99%) as a yellow solid. LCMS (Method A): 2.60 min; m/z: 401.2 $[M+H]^+$.

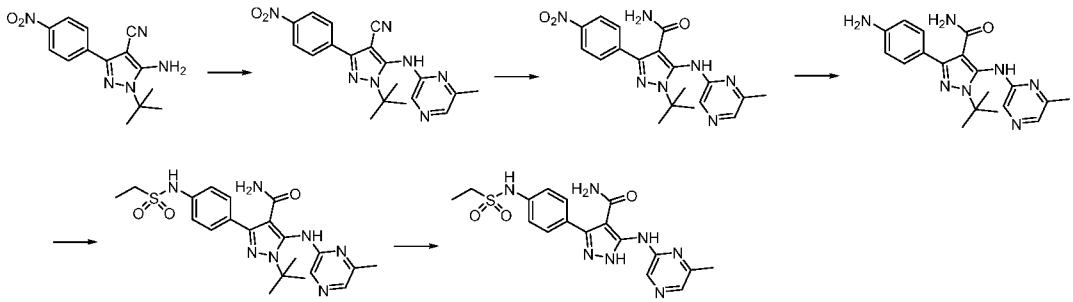
Step 4: 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(quinolin-2-yl)amino]- 1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(quinolin-2-yl)amino]- 1H-pyrazole-4-carboxamide (460 mg, 1.14 mmol), $EtSO_2Cl$ (174 mg, 1.36 mmol) and pyridine (270 mg, 3.42 mmol) in $CHCl_3$ (5 mL) was stirred at RT overnight. The mixture was concentrated and the crude residue was purified by prep-TLC (DCM:MeOH, 12:1) to afford the title product (120 mg, 21%) as a yellow solid. LCMS (Method A): 2.12 min; m/z: 493.1 $[M+H]^+$.

Step 5: 3-(4-(ethylsulfonamido)phenyl)-5-(quinolin-2-ylamino)-1H-pyrazole-4-carboxamide (compound 89)

A solution of 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(quinolin-2-yl)amino]-1H-pyrazole-4-carboxamide (120 mg, 0.2436 mmol) in TFA (5 mL) and DCM (5 mL) was stirred at RT overnight. The mixture was concentrated, and the residue was basified to pH 9-10 with 1.0 M NH_4Cl. The precipitate was triturated with PE (3 x 5 mL), collected by filtration and then dried under reduced pressure to afford the title product (80 mg, 75%) as a yellow solid. LCMS (Method A): 2.80 min; m/z: 437.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.52 (br s, 1H), 12.93 (br s, 1H), 10.31 (br s, 1H), 10.04 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.33-7.66 (m, 8H), 6.17 (br s, 1H), 3.18 (t, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).

Compound 84



Step 1: 1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-3-(4-nitrophenyl)-1H- pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (2 g, 7.00 mmol), 2-chloro-6-methylpyrazine (899 mg, 7.00 mmol), $Pd_2(dba)_3$ (641 mg, 700 µmol), Xantphos (810 mg, 1.40 mmol) and Cs_2CO_3 (6.84 g, 21.0 mmol) in degassed 1,4-

dioxane (60 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (2.22 g, 84%) as a yellow solid. LCMS (Method A): 3.20 min; m/z: 378.2 $[M+H]^+$.

Step 2: 1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-3-(4-nitrophenyl)-1H- pyrazole- 4-carboxamide

To a solution of 1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (1 g, 2.64 mmol) in DMSO (15 mL) and EtOH (30 mL), were added 30% aq. H_2O_2 (15 mL) and 5% aq. NaOH (0.8 mL). The mixture was heated to 80 ºC overnight, then concentrated under reduced pressure and diluted with H_2O (50 mL). The precipitate was collected by filtration and dried under reduced pressure to afford the title product (750 mg, 72%) as a yellow solid. LCMS (Method A): 2.65 min; m/z: 396.2 $[M+H]^+$.

Step 3: 3-(4-aminophenyl)-1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-1H- pyrazole-4-carboxamide

A mixture of 1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-3- (4-nitrophenyl)-1H-pyrazole-4-carboxamide (200 mg, 505 µmol) and 10% Pd/C (20 mg) in MeOH (10 mL) was stirred at RT overnight under H_2. The reaction mixture was filtered, concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (210 mg, >100%) as a yellow solid. LCMS (Method A): 1.02 min; m/z: 366.2 $[M+H]^+$.

Step 4: 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(6-methylpyrazin-2-yl) amino]-1H-pyrazole-4-carboxamide

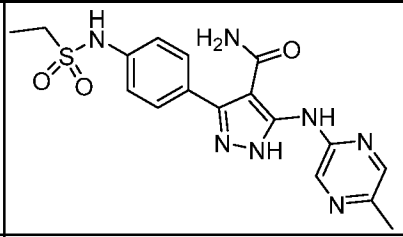
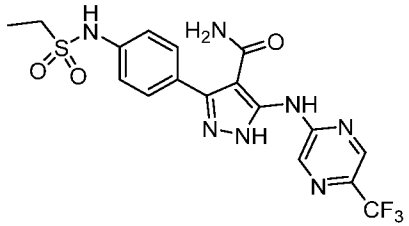
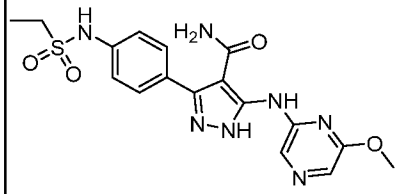
A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(6-methylpyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (200 mg, 547 µmol), $EtSO_2Cl$ (84.3 mg, 656 µmol) and pyridine (86.2 mg, 1.09 mmol) in $CHCl_3$ (7 mL) was stirred at RT overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (140 mg, 56%) as a yellow solid. LCMS (Method A): 1.49 min; m/z: 458.2 $[M+H]^+$.

Step 5: 3-(4-(ethylsulfonamido)phenyl)-5-((6-methylpyrazin-2-yl)amino)-1H- pyrazole-4-carboxamide (compound 84)

A solution of 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(6-methylpyrazin- 2-yl)amino]-1H-pyrazole-4-carboxamide (130 mg, 284 µmol) in DCM (4 mL) and TFA (4 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and then neutralized to pH=7-8 with NH_4OH. The precipitate was collected by filtration, triturated with PE (2 x 5 mL) and dried under reduced pressure to afford the title product (80 mg, 70%) as a yellow solid. LCMS (Method A): 2.97 min; m/z: 402.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.91 (s, 1H), 10.13 (s, 1H), 9.55 (s, 1H), 9.09 (s, 1H), 8.01 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 6.09 (s, 1H), 3.19 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H).

Following the full synthesis of Compound 84, starting from 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile with the mentioned starting materials used as described in step 1, the following compounds (Table 9) were prepared:

Table 9

Compound No	Name	Structure	LCMS data	^{1}H NMR data	Starting material
101	3-(4-(ethylsulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method B): 3.50 min; m/z: 402.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.54 (br s, 1H), 9.12 (br s, 1H), 8.11 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.18 (q, J = 6.0 Hz, 2H), 2.39 (s, 3H), 1.23 (t, J = 6.0 Hz, 3H). Five active protons not detected.	2-chloro-5-methylpyrazine
75	3-(4-ethanesulfonamidophenyl)-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.48 min; m/z: 456.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.16 (s, 1H), 10.13 (s, 1H), 9.19 (s, 1H), 8.66 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.36 (s, 1H), 3.18 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H).	2-chloro-5-(trifluoromethyl)pyrazine
99	3-(4-(ethylsulfonamido)phenyl)-5-((6-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.63 min; m/z: 418.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (br s, 1H), 10.15 (br s, 1H), 9.47 (br s, 1H), 8.82 (s, 1H), 7.75 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.13 (br s, 1H), 3.88 (s, 3H), 3.20 (q, J = 6.0 Hz, 2H), 1.24 (t, J = 6.8 Hz, 3H). Two active protons not observed.	2-chloro-6-methoxypyrazine

96	5-((6-ethoxypyridin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.53 min; m/z: 431.5 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.74 (s, 1H), 10.21 (s, 1H), 9.33 (s, 1H), 7.59 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 8.0 Hz, 1H), 5.99 (S, 1H), 4.25 (q, J = 6.8 Hz, 2H), 3.14 (q, J = 6.8 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (q, J = 7.2 Hz, 3H).	2-chloro-6-ethoxypyridine
92	5-((6-(difluoromethyl)pyridin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.84 min; m/z: 437.8 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.87 (s, 1H), 10.08 (s, 1H), 9.68 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.83 (s, 1H), 6.69 (s, 1H), 3.18 (q, J = 6.8 Hz, 2H), 1.23 (d, J = 7.2 Hz, 3H).	Intermediate D1
94	3-(4-(ethylsulfonamido)phenyl)-5-((6-methylpyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.95 min; m/z: 401.1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.73 (s, 1H), 10.09 (s, 1H), 9.40 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.70 (s, 1H), 5.98 (s, 1H), 3.18 (d, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.23 (t, J = 7.6 Hz, 3H).	2-chloro-6-methylpyridine

124	3-(4-(ethylsulfonamido)phenyl)-5-(phenylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.02 min; m/z: 386.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.57 (d, J = 8.8 Hz, 2H), 7.43 (m, 4H), 7.25 (t, J = 7.6 Hz, 2H), 6.87 (t, J = 7.6 Hz, 1H), 3.20 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.2 Hz, 3H).	bromophenyl
123	3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxypyrimidin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.34 min; m/z: 418.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.11(d, J = 4.8 Hz, 1H), 7.48 (m, 3H), 7.31(d, J = 6.4 Hz, 2H), 4.48 (s, 3H), 3.11 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H).	4-chloro-2-methoxypyrimidine
125	3-(4-(ethylsulfonamido)phenyl)-5-((2-methylpyrimidin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method B): 0.32 min; m/z: 402.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.41 (d, J = 5.6 Hz,1H), 8.02 (d, J = 4.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 3.20 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).	4-chloro-2-methylpyrimidine
111	3-(4-(ethylsulfonamido)phenyl)-5-((5-fluoro-2-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.39 min; m/z: 419.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.54 (d, J = 7.6 Hz,1H), 8.48 (d, J = 9.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 3.23 (q, J = 7.2 Hz, 2H), 2.63 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).	4-bromo-5-fluoro-2-methylpyridine

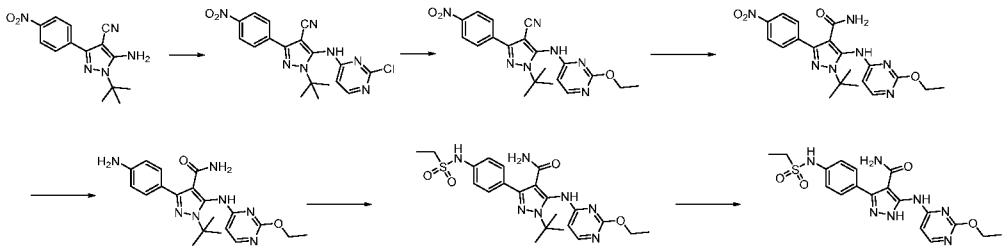
104	3-(4-(ethylsulfonamido)phenyl)-5-((2-(trifluoromethyl)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.25 min; m/z: 455.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.37 (d, J = 6.0 Hz, 1H), 8.11 (s, 1H), 7.67 (d, J = 4.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 3.21 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).	4-Chloro-(2-trifluoromethyl)pyridine
88	3-(4-(ethylsulfonamido)phenyl)-5-((5-methoxypyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.20 min; m/z: 417.4 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.83 (br s, 1H), 8.10 (s, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.65 (dd, J = 6.8, 2.0 Hz, 2H), 7.26 (dd, J = 9.2, 3.2 Hz, 1H), 7.20 (dd, J = 9.2, 2.0 Hz, 2H), 7.09 (s, 1H), 6.99 (s, 1H),6.52 (d, J =8.8 Hz, 1H), 3.71 (s, 3H), 3.13 (q, J = 7.6 Hz, 2H), 1.55 (t, J = 7.6 Hz, 3H).	2-chloro-5-methoxypyridine
85	3-(4-(ethylsulfonamido)phenyl)-5-((4-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.52 min; m/z: 455.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.96 (s, 1H), 10.14 (s, 1H), 9.90 (s, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 4.0 Hz, 1H), 6.12 (s, 1H), 3.18 (d, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).	2-chloro-4-(trifluoromethyl)pyridine

95	3-(4-(ethylsulfonamido)phenyl)-5-((4-methoxypyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.02 min; m/z: 416.8 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.87 (s, 1H), 10.10 (s, 1H), 9.52 (s, 1H), 8.02 (d, J = 5.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.50 (d, J = 4.4 Hz, 1H), 3.83 (s, 3H), 3.18 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H).	2-chloro-4-methoxypyridine
93	3-(4-(ethylsulfonamido)phenyl)-5-((5-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.45 min; m/z: 454.8 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 1H), 10.09 (br s, 1H), 9.94 (s, 1H), 8.53 (s, 1H), 8.07 (s, 2H), 7.56 (d, J=8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 6.18 (br s, 1H), 3.18 (q, J = 6.8 Hz, 2H), 1.23 (t, J = 6.8 Hz, 3H).	2-chloro-5-(trifluoromethyl)pyridine
107	3-(4-(ethylsulfonamido)phenyl)-5-((6-methoxypyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.11 min; m/z: 417.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.76 (s, 1H), 10.10 (s, 1H), 9.32 (s, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.56-7.53 (m, 3H), 7.36 (d, J = 8.8 Hz, 2H), 6.27 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 3.20 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). Two active protons not observed.	2-chloro-6-methoxypyridine
103	3-(4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethoxy)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.20 min; m/z: 471.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.98-7.82 (m, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 6.72-6.55 (m, 1H), 3.20 (q, J = 7.2 Hz, 2H) 1.33 (t, J = 7.2 Hz, 3H).	2-Chloro-6-(trifluoromethoxy)pyridine

67	3-(4-(ethylsulfonamido)phenyl)-5-(quinoxalin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.29 min; m/z: 438.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.49 (s, 1), 13.06 (s, 1H), 9.91 (s,1H), 9.44 (s, 1H), 8.88 (s, 1H), 8.21 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 7.2 Hz, 2H), 6.43 (br s, 1H), 3.18 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).	2-chloroquinoxaline
65	5-((6-chloroquinoxalin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.48 min; m/z: 472.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.51 (s, 1H), 8.30 (s, 1H), 7.70 (m, 4H), 7.46 (s, 1H), 7.15 (s, 1H), 6.54 (s, 1H), 4.13 (s, 1H), 3.16 (s, 2H), 1.21 (t, J = 7.2 Hz, 3H).	2,6-dichloroquinoxaline
87	3-(4-(ethylsulfonamido)phenyl)-5-(isoquinolin-3-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.38 min; m/z: 437.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.82 (s, 1H), 9.71 (s, 1H), 9.04 (s, 1H), 8.23 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.64-7.60 (m, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.39-7.36 (m, 3H), 3.18 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 6.8 Hz, 3H).	3-chloroisoquinoline

128	3-(4-(ethylsulfonamido)phenyl)-5-((6-(2-methoxyethoxy)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.38 min; m/z: 461.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.77 (s, 1H), 10.12 (s, 1H), 9.32 (s, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.52-7.57 (m, 4H), 7.35 (d, J = 8.6 Hz, 2H), 7.33 (br s, 1H), 6.05 (br s, 1H), 4.33 (t, J = 5.4 Hz,, 2H), 3.65 (t, J = 5.4 Hz,, 2H), 3.31 (s, 3H), 3.18 (q, J = 7.0 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H).	2-bromo-6-(2-methoxyethoxy)pyridine

Compound 98



Step 1: 1-tert-butyl-5-[(2-chloropyrimidin-4-yl)amino]-3-(4-nitrophenyl)- 1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (3 g, 10.5 mmol), 2,4-dichloropyrimidine (1.6 g, 11 mmol), $Pd_2(dba)_3$ (960 mg, 1.05 mmol), Cs_2CO_3 (10.27 g, 31.5 mmol) and Xantphos (1.2 g, 2.1 mmol) in degassed 1,4-dioxane (100 mL) was stirred at 100 °C under N_2 for 16 h. The mixture was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (1.2 g, 28%) as a yellow solid. LCMS (Method A): 2.46 min; m/z: 398.0 $[M+H]^+$.

Step 2: 1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]-3-(4-nitrophenyl)-1H- pyrazole-4-carbonitrile

A mixture of 1-tert-butyl-5-[(2-chloropyrimidin-4-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (700 mg, 1.75 mmol) and NaOEt (595 mg, 8.75 mmol) in THF (30 mL) was stirred at 65 °C under N_2 overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 15:1) to afford the title product (735 mg, 96%) as a yellow solid. LCMS (Method A): 3.38 min; m/z: 409.1 $[M+H]^+$.

Step 3: 1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]-3-(4-nitrophenyl)-1H- pyrazole-4-carboxamide

To a mixture of 1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (635 mg, 1.55 mmol) in DMSO (44.5 mL) and EtOH (200 mL) were added 30% aq. H_2O_2 (44.5 mL) and aq. NaOH solution (2M, 5 drops), and the resulting mixture was stirred at 100 °C under N_2 overnight. The mixture was concentrated under reduced pressure and the residue was diluted with H_2O and

EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (675 mg, 88%) as a yellow solid. LCMS (Method A): 2.61 min; m/z: 426.0 $[M+H]^+$.

Step 4: 3-(4-aminophenyl)-1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]-3-(4-nitrophenyl)- 1H-pyrazole-4-carboxamide (625 mg, 1.46 mmol), sat. NH_4Cl (12 mL) and Zn dust (476 mg, 7.29 mmol) in MeOH (50 mL) was stirred at 60 °C under N_2 overnight. The reaction mixture was filtered, concentrated under reduced pressure and the residue diluted with H_2O and EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (475 mg, 82%) as a white solid. LCMS (Method A): 3.14 min; m/z: 396.2 $[M+H]^+$.

Step 5: 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(2-ethoxypyrimidin-4-yl) amino]-1H-pyrazole-4-carboxamide

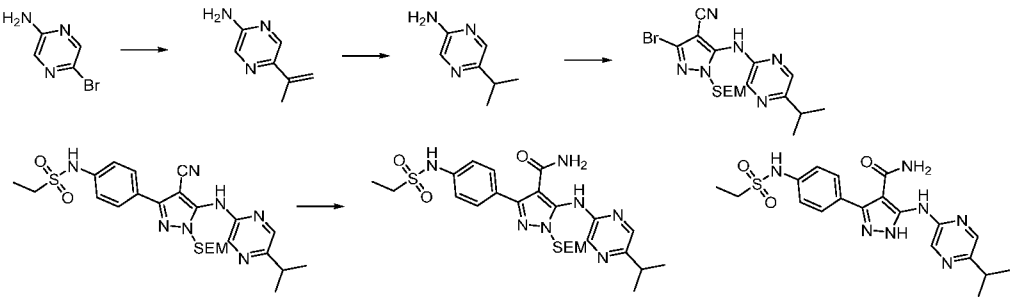
A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(2-ethoxypyrimidin-4-yl)amino]- 1H-pyrazole-4-carboxamide (271 mg, 0.685 mmol), $EtSO_2Cl$ (131 mg, 1.02 mmol) and pyridine (107 mg, 1.36 mmol) in $CHCl_3$ (25 mL) was stirred at RT overnight, then diluted with H_2O and EtOAc. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 50:1) to afford the title product (110 mg, 19%) as a yellow solid. LCMS (Method A): 3.12 min; m/z: 488.2 $[M+H]^+$.

Step 6: 5-((2-ethoxypyrimidin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide (compound 98)

A solution of 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(2-ethoxy pyrimidin-4-yl)amino]-1H-pyrazole-4-carboxamide (110 mg, 225 µmol) in TFA (2 mL) was stirred at 60 °C under N_2 for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was basified with sat. NH_4Cl (2 mL). The precipitate was filtered, and the filter cake was washed with Et_2O (2 x 2 mL) followed by *n*-hexane (2 mL) to afford the title product (71 mg, 73%) as a white solid. LCMS (Method A): 0.96 min; m/z: 433.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 10.11 (s, 1H), 9.75 (s, 1H), 8.26 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.35 (d, J = 8.4 Hz,

2H), 4.31 (q, *J* = 6.8 Hz, 2H), 3.19 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 14.0 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

Compound 66



Step 1: 5-(prop-1-en-2-yl)pyrazin-2-amine

A mixture of 5-bromopyrazin-2-amine (5 g, 28.7 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (5.78 g, 34.4 mmol), K_2CO_3 (7.93 g, 57.4 mmol) and $Pd(dppf)Cl_2$ (2.34 g, 2.87 mmol) in degassed 80% aq. 1,4-dioxane (300 mL) was heated to 100 °C under N_2 overnight. The mixture was diluted with H_2O (300 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 4:1) to afford the title product (2.9 g, 75%) as a yellow solid. LCMS (Method A): 1.38 min; m/z: 136.1 $[M+H]^+$.

Step 2: 5-(propan-2-yl)pyrazin-2-amine

A mixture of 5-(prop-1-en-2-yl)pyrazin-2-amine (1 g, 7.39 mmol), $Pd(OH)_2$ (24 mg, 167 µmol) and MeOH (8 mL) was stirred at RT under H_2 overnight. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure to afford the title product (850 mg, 84%) as a brown solid. LCMS (Method A): 0.94 min; m/z: 138.0 $[M+H]^+$.

Step 3: 3-bromo-5-{[5-(propan-2-yl)pyrazin-2-yl]amino}-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole- 4-carbonitrile (2.08 g, 5.46 mmol), 5-(propan-2-yl)pyrazin-2-amine (750 mg, 5.46 mmol), $Pd_2(dba)_3$ (499 mg, 546 µmol), Xantphos (630 mg, 1.09 mmol) and Cs_2CO_3 (5.31 g, 16.3 mmol) in degassed 1,4-dioxane (70 mL) was stirred at 100 ºC under N_2 overnight. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude

residue was purified by silica gel column chromatography (PE:EtOAc, 8:1) to afford the title product (1.48 g, 62%) as a yellow solid. LCMS (Method A): 4.64 min; m/z: 438.1 $[M+H]^+$.

Step 4: N-[4-(4-cyano-5-{[5-(propan-2-yl)pyrazin-2-yl]amino}-1-{[2-(trimethyl silyl)ethoxy]methyl}-1H-pyrazol-3-yl)phenyl]ethane-1-sulfonamide

A mixture of 3-bromo-5-{[5-(propan-2-yl)pyrazin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (1.38 g, 3.15 mmol), N[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (980 mg, 3.15 mmol), $Pd(dppf)Cl_2$ (257 mg, 315 µmol) and K_2CO_3 (870 mg, 6.30 mmol) in degassed 80% aq. 1,4-dioxane (50 mL) was stirred at 100 °C under N_2 overnight. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 4:1) to afford the title product (1.2 g, 71%) as a yellow solid. LCMS (Method A): 4.39 min; m/z: 542.2 $[M+H]^+$.

Step 5: 3-(4-ethanesulfonamidophenyl)-5-{[5-(propan-2-yl)pyrazin-2-yl]amino}- 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4- carboxamide

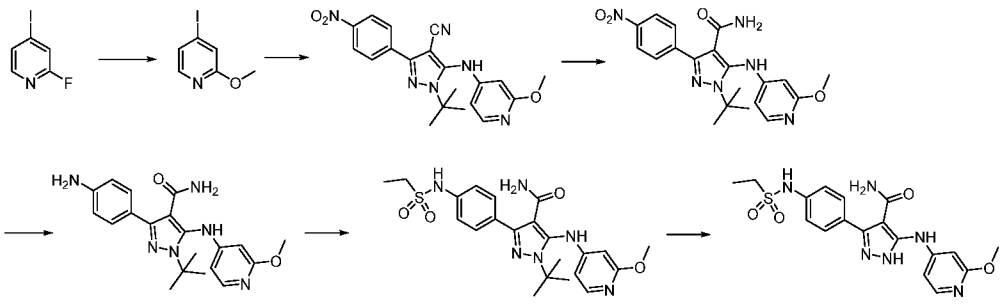
A mixture of N-[4-(4-cyano-5-{[5-(propan-2-yl)pyrazin-2-yl]amino}-1- {[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl)phenyl]ethane-1-sulfonamide (540 mg, 996 µmol), 30% aq. H_2O_2 (60 mL) and 5% aq. NaOH (60 drops) in EtOH (120 mL) and DMSO (60 mL) was stirred at 100 °C under N_2 overnight. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (90 mg, 16%) as a yellow solid. LCMS (Method A): 3.99 min; m/z: 560.2 $[M+H]^+$.

Step 6: 3-(4-(ethylsulfonamido)phenyl)-5-((5-isopropylpyrazin-2-yl)amino)-1H- pyrazole-4-carboxamide (compound 66)

A mixture of 3-(4-ethanesulfonamidophenyl)-5-{[5-(propan-2-yl)pyrazin-2-yl] amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (90 mg, 0.16 mmol) and 2.0 M HCl (0.5 mL) in THF (5 mL) was stirred at RT for 2 h. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (12 mg, 17%) as a white solid. LCMS (Method A): 3.34 min; m/z: 430.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 10.07 (s, 1H), 9.52 (s, 1H), 9.20 (s, 1H), 8.14 (s,

1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.10 (br s, 1H), 3.19 (q, *J* = 6.8 Hz, 2H), 3.08-2.99 (m, 1H), 1.24 (t, *J* = 8.0 Hz, 9H).

Compound 121



Step 1: 4-iodo-2-methoxypyridine

A mixture of 2-fluoro-4-iodo-pyridine (1.00 g, 4.48 mmol), Cs_2CO_3 (4.41 g, 13.5 mmol), DMF (20 mL) and MeOH (0.5 mL) was stirred at 90 ºC for 2 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and then concentrated under reduced pressure to afford the title compound (868 mg, 82%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.83 (dd, *J* = 5.4, 0.5 Hz, 1H), 7.20 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.17 (dd, *J* = 1.4, 0.5 Hz, 1H), 3.90 (s, 3H).

Step 2: 1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (1.05 g, 3.68 mmol), 4-iodo-2-methoxy-pyridine (804 mg, 3.42 mmol), $Pd(OAc)_2$ (83.4 mg, 0.368 mmol), Xantphos (426 mg, 0.736 mmol) and Cs_2CO_3 (1.81 g, 5.52 mmol) in 1,4-Dioxane (22 mL) was stirred at 110 ºC for 3 h. The reaction mixture was diluted with EtOAc (40 mL), filtered through Celite and concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 0:1) to afford the title compound (1.04 g, 77%) as an orange foam. LCMS (Method C): 2.31 min; m/z: 393.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 8.33-8.28 (m, 2H), 8.19-8.16 (m, 2H), 7.96 (d, *J* = 6.1 Hz, 1H), 6.46 (dd, *J* = 6.0, 2.0 Hz, 1H), 6.19 (br s, 1H), 3.92 (s, 3H), 1.70 (s, 9H).

Step 3: 1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (500 mg, 1.20 mmol) and Ghaffar-Parkins catalyst (25.7 mg, 59.9 μmol) in 90% aq. EtOH (50 mL) was stirred at 120 ºC for 16 h. The mixture was filtered through Celite and concentrated under reduced pressure to give the title compound (530 mg, quant.) as a yellow solid. LCMS (Method C): 1.98 min; m/z: 411.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 8.51 (s, 1H), 8.30-8.27 (m, 2H), 8.03-8.00 (m, 2H), 7.79 (d, *J* = 5.7 Hz, 1H), 7.41 (br s, 1H), 7.39 (br s, 1H), 6.32 (br s, 1H), 5.82 (br s, 1H), 3.74 (s, 3H), 1.59 (s, 9H).

Step 4: 3-(4-aminophenyl)-1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (280 mg, 0.68 mmol) and 5% Pd/C (14 mg) in MeOH (30 mL) was stirred at RT under H_2 for 3 d. The reaction mixture was filtered through Celite and concentrated to give the title compound (257 mg, 99%) as a yellow solid. LCMS (Method C): 1.36 min; m/z: 381.2 $[M+H]^+$. ^{1}H NMR (300 MHz, MeOD-d_4): 7.76 (d, *J* = 5.9 Hz, 1H), 7.46-7.43 (m, 2H), 6.78-6.73 (m, 2H), 6.29 (d, *J* = 4.9 Hz, 1H), 5.93 (s, 1H), 3.80 (s, 3H), 1.63 (m, 9H).

Step 5: 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-(tert-butyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (50.0 mg, 0.13 mmol) and pyridine (106 μL, 1.31 mmol) in DCM (1 mL) was cooled to 0 ºC and $EtSO_2Cl$ (25 μL, 0.26 mmol) was added dropwise. After 1 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM:MeOH (9:1, 5 x 2 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 1:0 to 9:1) to afford the title compound (28.0 mg, 45%) as a white solid. LCMS (Method C): 1.81 min; m/z: 473.2 $[M+H]^+$. ^{1}H NMR (300 MHz, MeOD-d_4): 7.77 (d, *J* = 5.9 Hz, 1H), 7.71-7.67 (m, 2H), 7.30-7.26 (m, 2H), 6.31 (d, *J* = 4.8 Hz, 1H), 5.94 (br s, 1H), 3.80 (s, 3H), 3.11 (q, *J* = 7.3 Hz, 2H), 1.65 (s, 9H), 1.30 (t, *J* = 7.3 Hz, 3H).

Step 6: 3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (compound 121)

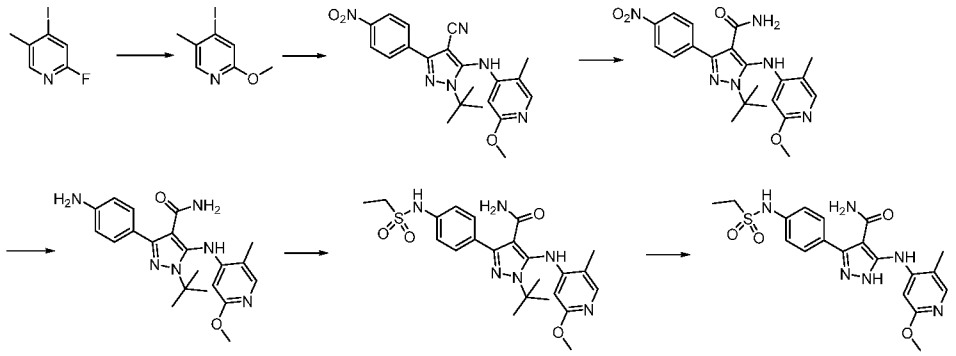
A solution of 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (28.0 mg, 0.059 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by SCX cartridge (MeOH, then 2.0 M NH_3 in MeOH) to afford the title compound (24.2 mg, 98%) as a white solid. LCMS (Method C): 1.58 min; m/z: 417.0 $[M+H]^+$. ^1H NMR (300 MHz, MeOD-d_4): 7.84 (d, J = 6.1 Hz, 1H), 7.59-7.55 (m, 2H), 7.45-7.40 (m, 2H), 7.18 (s, 1H), 6.93-6.90 (m, 1H), 3.87 (s, 3H), 3.19 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 3H).

Following the full synthesis of Compound 121 with the corresponding alcohol in step 1, the following compounds (Table 10) were prepared:

Table 10

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
105	5-((2-ethoxypyridin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.29 min; m/z: 431.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.92 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.28 (br s, 1H), 5.35 (t, J = 4.8 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.6 Hz, 3H).	ethanol
106	5-((2-(2,2-difluoroethoxy)pyridin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.47 min; m/z: 467.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 10.14 (s, 1H), 9.33 (s, 1H), 7.89 (d, J = 6.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.19 (s, 1H), 6.97 (dd, J = 7.6, 1.6 Hz, 1H), 6.36 (tt, J = 54.8, 3.6 Hz, 1H), 4.51 (q, J = 7.2 Hz, 2H), 3.18 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). Two active protons not observed.	2,2-difluoroethan-1-ol

Compound 118



Step 1: 4-iodo-2-methoxy-5-methylpyridine

A mixture of 2-fluoro-4-iodo-5-methylpyridine (1.06 g, 4.47 mmol), Cs_2CO_3 (4.36 g, 13.4 mmol), MeOH (542 µL, 13.4 mmol) and DMF (10 mL) was stirred at 90 °C for 3 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (5 x 50 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 9:1) to afford the title compound (746 mg, 67%) as a white solid. LCMS (Method C): 2.44 min; m/z: 250.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.91 (s, 1H), 7.26 (s, 1H), 3.87 (s, 3H), 2.30 (s, 3H).

Step 2: 1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbo nitrile (696 mg, 2.43 mmol), 4-iodo-2-methoxy-5-methylpyridine (724 mg, 2.91 mmol), $Pd(OAc)_2$ (54.5 mg, 0.24 mmol), Xantphos (281 mg, 0.486 mmol) and Cs_2CO_3 (1.18 g, 3.64 mmol) in 1,4-Dioxane (35 mL) was stirred at 110 °C for 21 h. The reaction mixture was diluted with EtOAc (40 mL), filtered through Celite and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 2:3) to afford the title compound (992 mg, 83%) as an orange oil. LCMS (Method C): 2.31 min; m/z: 407.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.43-8.38 (m, 2H), 8.18-8.13 (m, 3H), 7.80 (s, 1H), 5.62 (s, 2H), 3.71 (s, 3H), 2.18 (s, 3H), 1.62 (s, 9H).

Step 3: 1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-3-(4-nitro phenyl)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (443 mg, 1.08 mmol), Ghaffar-Parkins catalyst (23.1 mg, 54.0 μmol) and 90% aq. EtOH (50 mL) was stirred at 110 ºC for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by recrystallization (EtOH) to afford the title compound (346 mg, 72%) as an off-white solid. LCMS (Method C): 1.95 min; m/z: 425.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 8.30-8.25 (m, 2H), 8.06-8.01 (m, 2H), 7.73 (s, 1H), 7.56 (s, 1H), 7.34 (br s, 1H), 7.27 (br s, 1H), 5.43 (s, 1H), 3.67 (s, 3H), 2.17 (s, 3H), 1.59 (s, 9H).

Step 4: 3-(4-aminophenyl)-1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (246 mg, 0.553 mmol) and 10% Pd/C (25 mg) in MeOH (30 mL) was stirred at RT under H_2 for 16 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (215 mg, 96%) as a white solid. LCMS (Method C): 1.44 min; m/z: 395.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 7.69 (s, 1H), 7.46 (s, 1H), 7.45-7.41 (m, 2H), 7.07 (br s, 1H), 7.00 (br s, 1H), 6.58-6.51 (m, 2H), 5.41 (s, 1H), 5.16 (br s, 2H), 3.66 (s, 3H), 2.14 (s, 3H), 1.54 (s, 9H).

Step 5: 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-(tert-butyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (115 mg, 0.291 mmol), $EtSO_2Cl$ (55 μL, 0.583 mmol), pyridine (235 μL, 2.91 mmol) and DCM (5 mL) was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 1:0 to 4:1) to give a yellow residue (75.7 mg). Further purification by SCX cartridge (MeOH, then 2 M NH_3 in MeOH) afforded the title compound (32.7 mg, 22%) as a white solid. LCMS (Method C): 1.82 min; m/z: 487.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.84 (br s, 1H), 7.72-7.68 (m, 3H), 7.48 (s, 1H), 7.26-7.21 (m, 2H), 7.18 (br s, 1H), 7.10 (br s, 1H), 5.41 (s, 1H), 3.68 (s, 3H), 3.11 (q, J = 7.3 Hz, 2H), 2.16 (s, 3H), 1.56 (s, 9H), 1.21 (t, J = 7.3 Hz, 3H).

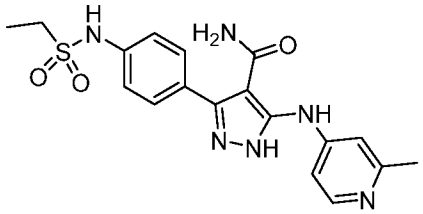
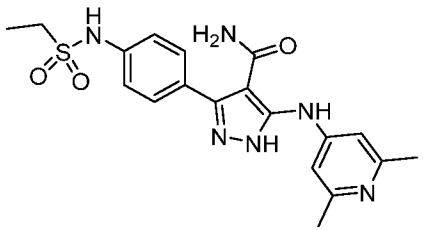
Step 6: 3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxy-5-methylpyridin-4-yl) amino)-1H-pyrazole-4-carboxamide (compound 118)

A solution of 1-(tert-butyl)-3-(4-(ethylsulfonamido)phenyl)-5-((2-methoxy-5-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (29.6 mg, 0.0569 mmol) in TFA (0.5 mL) and

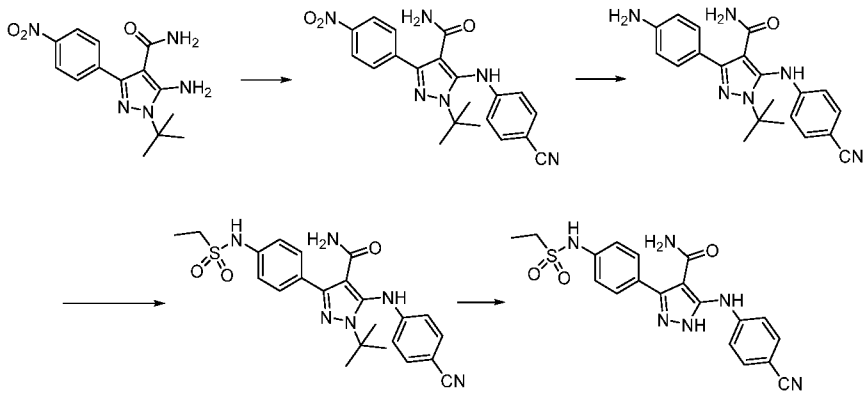
DCM (0.5 mL) was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and purified by SCX cartridge (MeOH, then 2 M NH_3 in MeOH) to afford the title compound (22.0 mg, 90%) as a white solid. LCMS (Method C): 1.66 min; m/z: 431.0 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 12.88 (br, s, 1H), 9.59 (s, 1H), 7.77 (s, 1H), 7.55-7.53 (m, 3H), 7.38-7.34 (m 2H), 3.77 (s, 3H), 3.22-3.14 (m, 2H), 2.14 (s, 3H), 1.22 (t, J = 7.3 Hz, 3H).

Following the full synthesis of Compound 118, starting from 5-amino-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile with the mentioned intermediates as described in step 2, the following compounds (Table 11) were prepared:

Table 11

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
113	3-(4-(ethylsulfonamido)phenyl)-5-((2-methylpyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method C): 1.33 min; m/z: 401.0 $[M+H]^+$.	^{1}H NMR (300 MHz, DMSO-d_6): 12.84 (br s, 1H), 9.22 (br s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.38-7.30 (m, 3H), 7.28-7.24 (m, 1H), 3.21-3.14 (m, 2H), 2.37 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H).	4-bromo-2-methylpyridine
112	5-((2,6-dimethylpyridin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method C): 1.38 min; m/z: 415.0 $[M+H]^+$.	^{1}H NMR (300 MHz, DMSO-d_6): 12.82 (br s, 1H), 9.18 (br s, 1H), 7.56-7.53 (m, 2H), 7.36-7.32 (m, 2H), 7.13 (s, 2H), 3.17 (q, J = 7.3 Hz, 2H), 2.32 (s, 6H), 1.22 (t, J = 7.3 Hz, 3H).	4-bromo-2,6-dimethylpyridine

Compound 102



Step 1: 1-(tert-butyl)-5-((4-cyanophenyl)amino)-3-(4-nitrophenyl)-1H- pyrazole-4-carboxamide

A mixture of 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4- carboxamide (455 mg, 1.50 mmol), CsF (683 mg, 4.50 mmol) and 4-fluorobenzonitrile (236 mg, 1.95 mmol) in DMSO (10 mL) was stirred at 150 °C under microwave irradiation for 3 h. The mixture was diluted with H_2O (20 mL) and then extracted with EtOAc (20 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (304 mg, 23%) as a yellow solid. LCMS (Method B): 2.40 min; m/z: 405.0 $[M+H]^+$.

Step 2: 3-(4-aminophenyl)-1-(tert-butyl)-5-((4-cyanophenyl) amino)-1H- pyrazole-4-carboxamide

A mixture of 1-tert-butyl-5-[(4-cyanophenyl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (304 mg, 0.751 mmol), sat. aq. NH_4Cl (6 mL) and Zn dust (245 mg, 3.75 mmol) in MeOH (18 mL) was stirred at 60 °C overnight. The mixture was filtered, concentrated under reduced pressure and the residue partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the title product (255 mg, 90%) as a yellow solid. LCMS (Method B): 0.82 min; m/z: 375.1 $[M+H]^+$.

Step 3: 1-(tert-butyl)-5-((4-cyanophenyl)amino)-3-(4-(ethylsulfonamido) phenyl)-1H-pyrazole-4-carboxamide

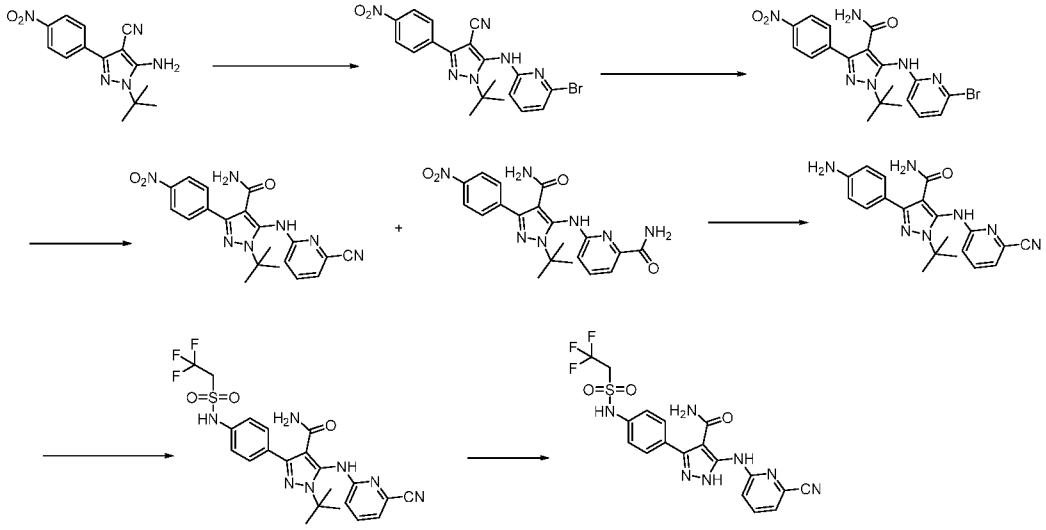
To a stirred solution of 3-(4-aminophenyl)-1-tert-butyl-5-[(4-cyanophenyl) amino]-1H-pyrazole-4-carboxamide (150 mg, 400 mmol) and pyridine (126 mg, 1.60 mmol) in $CHCl_3$

(10 mL) was added $EtSO_2Cl$ (102 mg, 800 mmol). The mixture was stirred at RT overnight then diluted with H_2O (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (27 mg, 14%) as a yellow solid. LCMS (Method A): 2.57 min; m/z: 467.3 $[M+H]^+$.

Step 4: 5-((4-cyanophenyl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H- pyrazole-4-carboxamide (compound 102)

A solution of 1-tert-butyl-5-[(4-cyanophenyl)amino]-3- (4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide (27 mg, 0.0578 mmol) in TFA (1 mL) was stirred at 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with Et_2O (3 x 3 mL) then dried under reduced pressure to afford the title product as the TFA salt (10 mg, 40%) as a yellow solid. LCMS (Method A): 1.28 min; m/z: 411.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.69 (d, J = 8.4 Hz, 2H), 7.62-7.57 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 3.21 (q, J = 7.2 Hz, 2H), 1.34(t, J = 7.2 Hz, 3H).

Compound 237



Step 1: 5-[(6-bromopyridin-2-yl)amino]-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (3.0 g, 10.5 mmol), 2,6-dibromopyridine (2.48 g, 10.5 mmol), $Pd_2(dba)_3$ (961 mg, 1.05 mmol), Xantphos (1.21 g, 2.10 mmol) and Cs_2CO_3 (6.84 g, 21.0 mmol) in 1,4-dioxane (60 mL) was stirred at 100 ºC under N_2 for 16 h. The reaction mixture was

concentrated and the residue purified by silica gel column chromatography (DCM:MeOH, 30:1) to afford the title product (3.6 g, 77%) as a yellow solid. LCMS (Method A): 4.37 min; m/z: 441.1, 443.1 $[M+H]^+$.

Step 2: 5-((6-bromopyridin-2-yl)amino)-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide

A mixture of 5-[(6-bromopyridin-2-yl)amino]-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (2.0 g, 4.53 mmol), Ghaffar-Parkin's catalyst (194 mg, 0.45 mmol) and 90% aq. 1,4-dioxane (110 mL) was stirred at 100 ºC under N_2. After 16 h, the reaction mixture was concentrated and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 40:1) to afford the title product (630 mg, 30%) as a yellow solid. LCMS (Method A): 3.92 min; m/z: 459.0, 461.0 $[M+H]^+$.

Step 3: 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide and 6-((1-(tert-butyl)-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl)amino)picolinamide

A mixture of 5-[(6-bromopyridin-2-yl)amino]-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (10 g, 21.7 mmol), CuI (4.13 g, 21.7 mmol) and CuCN (3.88 g, 43.4 mmol) in NMP (100 mL) was stirred at 150 °C under N_2 overnight. The reaction was poured into EtOAc (100 mL) and washed with water (100 mL x 3). The organic layer was collected and washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:PE, 1:4) to give 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (2.2 g, 25 %) as a yellow solid LCMS (Method A): 3.65 min, m/z: 406.1 $[M+H]^+$, and 6-((1-(tert-butyl)-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl)amino)picolinamide (390 mg) as a brown solid. LCMS (Method A): 3.25 min, m/z : 424.1 $[M+H]^+$.

Step 4: 3-(4-aminophenyl)-1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (90 mg, 0.22 mmol), Zn powder (71.9 mg, 1.10 mmol), sat. NH_4Cl (2 mL) and MeOH (10 mL) was stirred at 60 ºC for 16 h. The reaction mixture was filtered and the filtrate was concentrated, then purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (50 mg, 60%) as a yellow solid. LCMS (Method A): 2.80 min; m/z: 376.2 $[M+H]^+$.

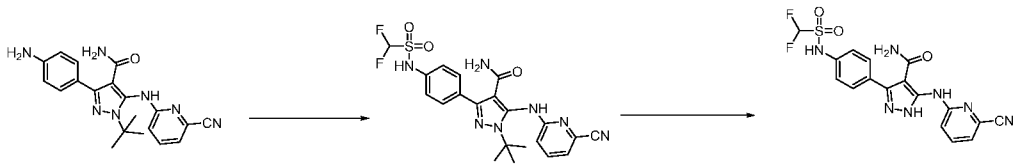
Step 5: 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (50 mg, 0.13 mmol), 2,2,2-trifluoroethane-1-sulfonyl chloride (31.5 mg, 0.17 mmol), pyridine (31.5 mg, 0.39 mmol) and DCM (4 mL) was stirred at RT for 16. The reaction mixture was concentrated and the residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (20 mg, 29%) as a yellow solid. LCMS (Method A): 3.53 min; m/z: 522.2 $[M+H]^+$.

Step 6: 5-[(6-cyanopyridin-2-yl)amino]-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (compound 237)

A solution of 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (20 mg, 0.03 mmol) in DCM (3 mL) and TFA (2 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and air dried to afford the title compound (10 mg, 56%) as a white solid. LCMS (Method A): 3.32 min; m/z: 466.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.99 (br s, 1H), 10.75 (br s, 1H), 9.88 (br s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 4.60 (q, J = 10.0 Hz, 2H).

Compound 258



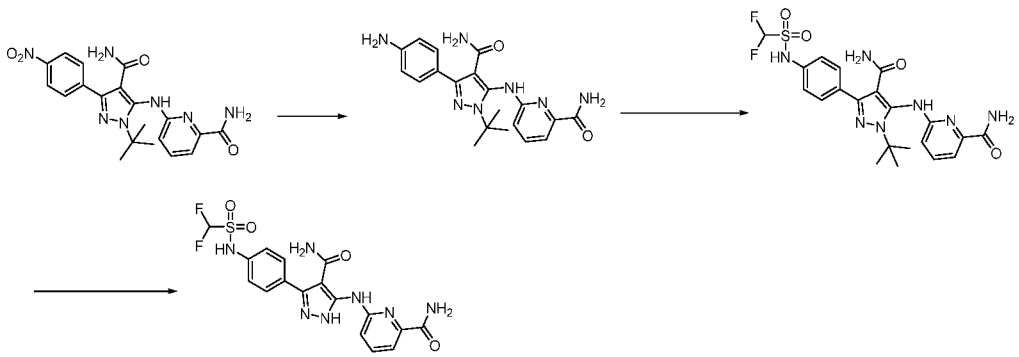
Step 1: 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (200 mg, 0.53 mmol), F_2CHSO_2Cl (120 mg, 0.79 mmol), pyridine (210 mg, 2.66 mmol) and DCM (10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (100 mg, 38%) as a yellow solid. LCMS (Method A): 3.48 min; m/z: 490.2 $[M+H]^+$.

Step 2: 5-[(6-cyanopyridin-2-yl)amino]-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (compound 258)

A mixture of 1-tert-butyl-5-[(6-cyanopyridin-2-yl)amino]-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (50 mg, 0.1021 mmol) and 1:1 DCM:TFA (8 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (20 mg, 45%) as a yellow solid. LCMS (Method A): 3.18 min; m/z: 434.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.00 (br s, 1H), 9.76 (br s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 9.25 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 12.4 Hz, 1H).

Compound 257



Step 1: 6-((3-(4-aminophenyl)-1-(tert-butyl)-4-carbamoyl-1H-pyrazol-5-yl)amino)picolinamide

A mixture of 6-{[1-tert-butyl-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridine-2-carboxamide (From Compound 237, 390 mg, 0.9210 mmol) and Zn dust (300 mg, 4.60 mmol) in MeOH (10 mL) and aq. sat. NH_4Cl (2 mL) was stirred at 45 °C overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH:DCM, 1:35) to give the title product (320 mg, 88 %) as a yellow solid. LCMS (Method A): 2.33 min, m/z: 394.2 $[M+H]^+$.

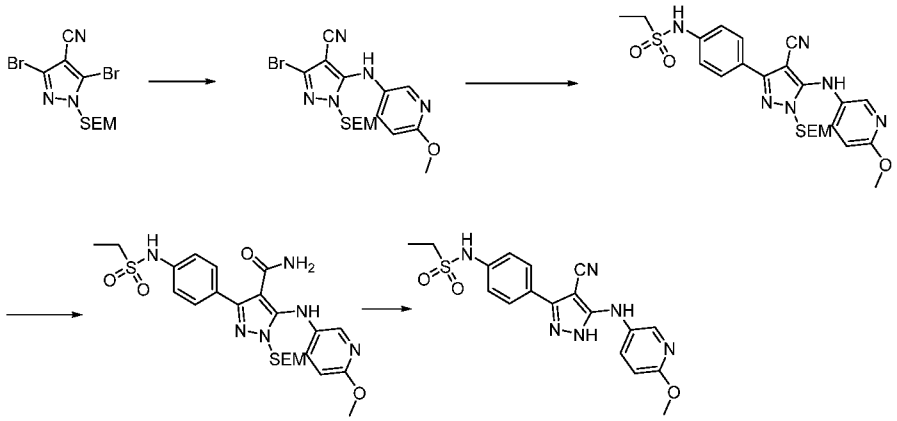
Step 2: 6-({1-tert-butyl-4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-2-carboxamide

A mixture of 6-{[3-(4-aminophenyl)-1-tert-butyl-4-carbamoyl-1H-pyrazol-5-yl]amino}pyridine-2-carboxamide (150 mg, 0.38 mmol), F_2CHSO_2Cl (86.0 mg, 0.57 mmol), pyridine (150 mg, 1.90 mmol) and DCM (10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (75 mg, 39%) as a yellow solid. LCMS (Method A): 3.12 min; m/z: 508.2 $[M+H]^+$.

Step 3: 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-2-carboxamide (compounds 257)

A solution of 6-({1-tert-butyl-4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-2-carboxamide (50 mg, 0.09 mmol) in 1:1 DCM:TFA (4 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then dried to afford the title product (30 mg, 68%) as a yellow solid. LCMS (Method A): 2.71 min; m/z: 452.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.62 (br s, 1H), 9.69 (br s, 1H), 8.16 (br s, 1H), 7.95 (br s, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.52-7.47 (m, 2H), 7.28 s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.24 (t, J = 54.8 Hz, 1H), 5.82 (br s, 1H).

Compound 115



Step 1: 3-bromo-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile (400 mg, 1.04 mmol), 5-amino-2-methoxypyridine (153 mg, 1.24 mmol), $Pd(OAc)_2$ (23.3 mg, 0.104 mmol), Xantphos (120 mg, 0.208 mmol) and Cs_2CO_3 (508 mg, 1.56 mmol) in

1,4-dioxane (20 mL) was stirred at 110 °C for 3 h. The reaction mixture was diluted with EtOAc (25 mL), filtered through Celite and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 3:2) to afford the title compound (257 mg, 58%) as a white solid. LCMS (Method A): 2.80 min; m/z: 426.0 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.23 (br s, 1H), 8.04 (dd, J = 2.8, 0.6 Hz, 1H), 7.58 (dd, J = 8.8, 2.8 Hz, 1H), 6.84 (dd, J = 8.8, 0.6 Hz, 1H), 5.38 (s, 2H), 3.84 (s, 3H), 3.64-3.58 (m, 2H), 0.89-0.84 (m, 2H), -0.04 (s, 9H).

Step 2: N-(4-(4-cyano-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl) ethoxy)methyl)-1H-pyrazol-3-yl)phenyl)ethanesulfonamide

A mixture of 3-bromo-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazole-4-carbonitrile (200 mg, 0.471 mmol), N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide (Intermediate C16, 219 mg, 0.706 mmol), $Pd(OAc)_2$ (5.28 mg, 23.5 μmol), SPhos (19.3 mg, 47.1 μmol) and K_2CO_3 (194 mg, 1.41 mmol) in 60% aq. MeCN (10 mL) was stirred at 100 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 1:1) to afford the title compound (191 mg, 76%) as a colourless glass. LCMS (Method A): 2.72 min; m/z: 529.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 10.04 (br s, 1H), 8.97 (br s, 1H), 8.02 (dd, J = 2.8, 0.6 Hz, 1H), 7.76-7.71 (m, 2H), 7.54 (dd, J = 8.8, 2.8 Hz, 1H), 7.32-7.27 (m, 2H), 6.83 (dd, J = 8.8, 0.6 Hz, 1H), 5.45 (s, 2H), 3.83 (s, 3H), 3.66-3.61 (m, 2H), 3.14 (q, J = 7.3 Hz, 2H), 1.19 (t, J = 7.4 Hz, 3H), 0.90-0.84 (m, 2H), -0.061 (s, 9H).

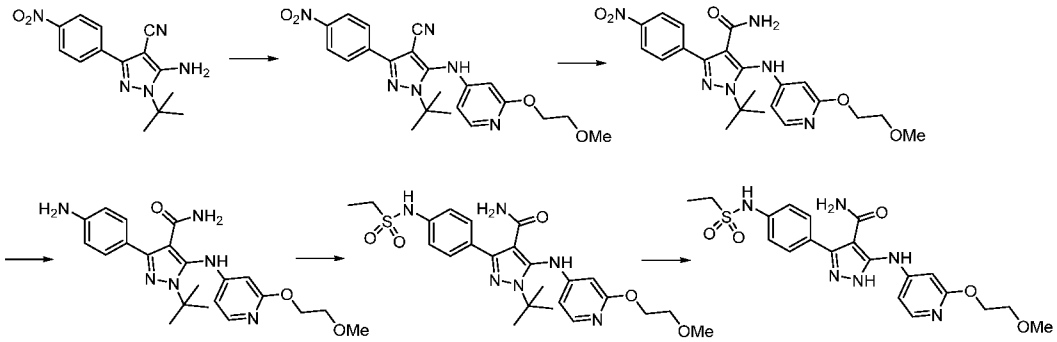
Step 3: 3-(4-(ethylsulfonamido)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of N-(4-(4-cyano-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazol-3-yl)phenyl)ethanesulfonamide (180 mg, 0.340 mmol) and Ghaffar-Parkins catalyst (7.30 mg, 17.0 μmol) in 80% aq. EtOH (10 mL) was stirred at 110 ºC for 16 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (181 mg, 97%) a colourless glass. LCMS (Method A): 2.47 min; m/z: 547.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.93 (br s, 1H), 7.84 (s, 1H), 7.69-7.64 (m, 2H), 7.63 (dd, J = 2.9, 0.5 Hz, 1H), 7.25-7.21 (m, 2H), 7.18 (br s, 1H), 7.14 (br s, 1H), 7.12 (dd, J = 8.8, 2.9 Hz, 1H), 6.66 (dd, J = 8.8, 0.5 Hz, 1H), 5.33 (s, 2H), 3.74 (s, 3H), 3.52-3.46 (m, 2H), 3.12 (q, J = 7.4 Hz, 2H), 1.21 (t, J = 7.4 Hz, 3H), 0.79-0.74 (m, 2H), -0.10 (s, 9H).

Step 4: 3-(4-(ethylsulfonamido)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1H-pyrazole-4-carboxamide (Compound 115)

A solution of 3-(4-(ethylsulfonamido)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (30 mg, 54.8 μmol) in TFA (0.5 mL) and DCM (0.5 mL) was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC to afford the title compound as a white solid (6.7 mg, 29%). LCMS (Method A): 1.83 min; m/z: 417.0 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 12.59 (s, 1H), 10.10 (br s, 1H), 8.74 (s, 1H), 8.37 (s, 1H), 7.94 (d, J = 6.7 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.6 Hz, 1H), 5.75 (s, 1H), 3.79 (s, 3H), 3.21-3.14 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H).

Compound 127



Step 1: 1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-5-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 3-amino-1-(tert-butyl)-5-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (Intermediate A, 103 mg, 0.360 mmol), 4-bromo-2-(2-methoxyethoxy)pyridine (0.1 g, 0.43 mmol), $Pd(OAc)_2$ (8.11mg, 0.0400 mmol), Xantphos (36 mg, 0.070 mmol) and Cs_2CO_3 (0.18g, 0.54 mmol) in 1,4-dioxane (3 mL) was stirred at 80 ºC under N_2 for 0.5 h. The reaction mixture was heated to 100 ºC for a further 1.5 h, then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 1:1) to afford the title compound (105 mg, 67%) as a yellow oil. LCMS (Method A): 2.37 min; m/z: 437.2 $[M+H]^+$.

Step 2: 1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-5-(4-nitrophenyl)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-5-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (105 mg, 0.240 mmol), K_2CO_3 (0.10 g, 0.72 mmol) and 30% aq. H_2O_2 (2 mL) in DMSO (5 mL) was stirred at 60 °C for 1 h. An additional charge of H_2O_2 was added and the mixture was stirred for a further 2 h. The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:0 to 1:1) to afford the title product (25 mg, 23%) as a yellow oil. LCMS (Method A): 2.00 min; m/z: 455.2 $[M+H]^+$.

Step 3: 5-(4-aminophenyl)-1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-5-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (25 mg, 0.05 mmol) 10% Pd/C (5 mg) and MeOH (5 mL) was stirred at RT under H_2 overnight. The reaction mixture was filtered over celite and concentrated under reduced pressure to afford the title product (21 mg, 90%) as a yellow oil that solidified upon standing. LCMS (Method A): 1.52 min; m/z: 425.2 $[M+H]^+$.

Step 4: 1-(tert-butyl)-5-(4-(ethylsulfonamido)phenyl)-3-((2-(2-methoxyethoxy) pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 5-(4-aminophenyl)-1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (21 mg, 0.050 mmol), $EtSO_2Cl$ (0.01 mL, 0.10 mmol) and pyridine (0.04 mL, 0.49 mmol) in DCM (2 mL) was stirred at RT for 1 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 1:0 to 9:1) to afford the title product (12 mg, 47%) as an off white solid. LCMS (Method A): 1.82 min; m/z: 517.2 $[M+H]^+$.

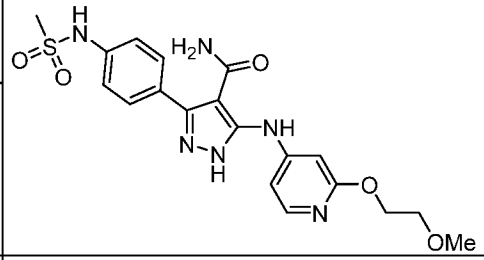
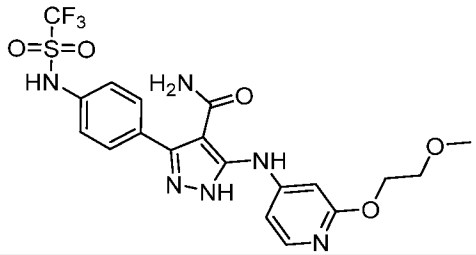
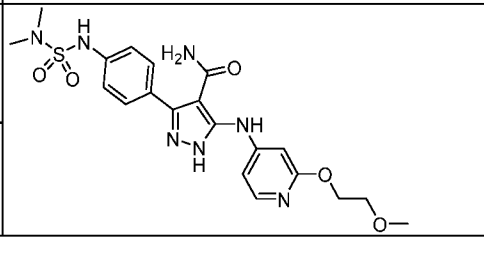
Step 5: 5-(4-(ethylsulfonamido)phenyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl) amino)-1H-pyrazole-4-carboxamide (Compound 127)

A solution of 1-(tert-butyl)-5-(4-(ethylsulfonamido)phenyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide (12 mg, 0.020 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at RT for 5 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by SCX cartridge (MeOH, then 2.0 M NH_3 in MeOH) to afford the title product (10 mg, 93%) as a cream solid. LCMS (Method A): 1.64

min; m/z: 461.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.85 (d, J = 5.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.22 (br s, 1H), 6.92 (dd, J = 5.9, 1.9 Hz, 1H), 4.35 (m, 2H), 3.76 (m, 2H), 3.43 (s, 3H), 3.21 (q, J = 7.3 Hz, 2H), 1.35 (t, J = 7.5 Hz, 2H).

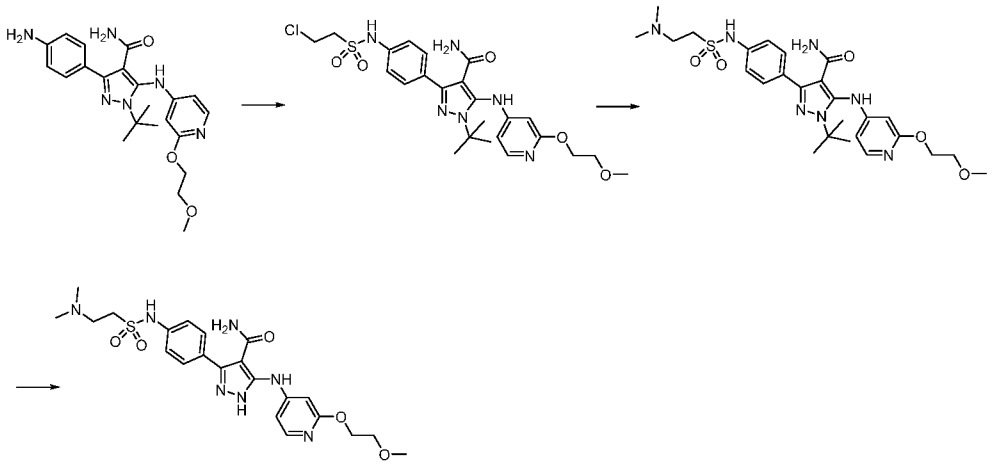
Following the full synthesis of compound 127, starting from 5-(4-aminophenyl)-1-(tert-butyl)-3-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide with the corresponding sulfonyl chloride as described in step 4, the following compounds (Table 12) were prepared:

Table 12

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
122	5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-(methylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.25 min; m/z: 447.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.85 (d, J = 5.2 Hz, 1H), 7.59-7.42 (m, 4H), 7.25 (br s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.35 (t, J = 4.4 Hz, 2H), 3.75 (t, J = 4.4 Hz, 2H), 3.44 (s, 3H), 3.06 (s, 3H).	methanesulfonyl chloride
114	5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-((trifluoromethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.62 min; m/z: 501.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.94 (d, J = 7.2 Hz, 1H), 7.68-7.62 (m, 3H), 7.49 (d, J = 8.8 Hz, 2H), 7.38 (br s, 1H), 4.5 (t, J = 4.0 Hz, 2H), 3.82 (t, J = 4.0 Hz, 2H), 3.43 (s, 3H).	trifluoro methanesulfonyl chloride
221	3-(4-((N,N-dimethylsulfamoyl)amino)phenyl)-5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.42 min; m/z: 476.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.83 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.22 (s, 1H), 6.91 (dd, J = 5.6, 0.8 Hz, 1H), 4.34 (t, J = 4.4 Hz, 2H), 3.75 (t, J = 4.4 Hz, 2H), 3.42 (s, 3H), 2.79 (s, 6H).	dimethylsulfamoyl chloride

120	5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-((2-methoxyethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.30 min; m/z: 491.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.92 (d, J = 6.8 1H), 7.67 (br s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 6.0 Hz, 1H), 4.51 (t, J = 4.4 Hz, 2H), 3.83-3.77 (m, 4H), 3.43-3.40 (m, 5H), 3.30 (m,3H).	2-methoxyethyl sulfonylchloride
110	3-(4-((cyanomethyl)sulfonamido)phenyl)-5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.73 min; m/z: 472.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.84 (d, J = 6.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4, 2H), 7.23 (s, 1H), 6.93 (dd, J = 5.6, 0.8 Hz, 1H), 4.58 (s, 1H), 4.35 (t, J = 4.4 Hz, 2H), 3.75 (t, J = 4.4, 2H), 3.64 (s, 1H), 3.42 (s, 3H).	cyanomethanesulfonyl chloride
109	5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-(prop-2-yn-1-ylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method B): 0.39 min; m/z: 471.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.94 (d, J = 7.2 Hz, 1H), 7.66 (s, 1H), 7.62-7.59 (m, 2H), 7.50-7.48 (m, 2H), 7.36 (s, 1H), 4.50 (q, J = 2.8 Hz, 2H), 4.14 (d, J = 2.4 Hz, 2H), 3.84-3.81 (m, 2H), 3.43 (s, 3H), 2.90 (t, J = 2.4 Hz, 1H).	prop-2-yne-1-sulfonyl chloride

Compound 116



Step 1: 1-(tert-butyl)-3-(4-((2-chloroethyl)sulfonamido)phenyl)-5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-{[2-(2-methoxyethoxy) pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide (400 mg, 0.9422 mmol), 2-chloroethane-1-sulfonyl chloride (306 mg, 1.88 mmol) and pyridine (297 mg, 3.76 mmol) in DMF (10 mL) was stirred at RT overnight. The mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford a mixture of the title product and the elimination product 1-(tert-butyl)-5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-(vinylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide (100 mg, 19%) as a yellow solid. LCMS (Method B): 0.43 min; m/z: 551.0 $[M+H]^+$.

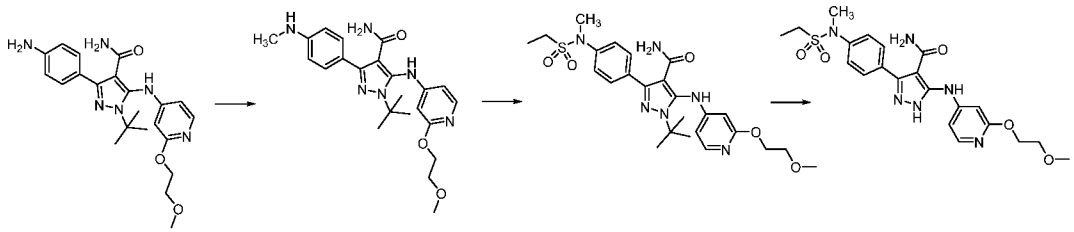
Step 2: 1-tert-butyl-3-{4-[2-(dimethylamino)ethanesulfonamido]phenyl}-5- {[2-(2-methoxyethoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide

To a solution of 1-tert-butyl-3-[4-(2-chloroethanesulfonamido)phenyl] -5-{[2-(2-methoxyethoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide (100 mg, 0.18 mmol) in THF (5 mL), was added Me_2NH (905 µL, 1.81 mmol) and the mixture was stirred at 40 °C overnight. Additional Me_2NH (136 µL, 0.27 mmol) was added and the solution was stirred at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was used directly in the next step without further purification. LCMS (Method B): 0.34 min; m/z: 560.1 $[M+H]^+$.

Step 3: 3-(4-((2-(dimethylamino)ethyl)sulfonamido)phenyl)-5-((2-(2-methoxy ethoxy) pyridin-4-yl)amino)-1H-pyrazole-4-carboxamide

A solution of 1-tert-butyl-3-{4-[2-(dimethylamino)ethanesulfonamido]phenyl} -5-{[2-(2-methoxyethoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide (80 mg, 0.036 mmol) in TFA (1.5 mL) and DCM (1.5 mL) was stirred at RT overnight. The mixture was concentrated under reduced pressure and then triturated with Et_2O (2 x 5 mL) to afford the title product as the mono TFA salt (28 mg, 38%) as a white solid. LCMS (Method B): 0.33 min; m/z: 505.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.93 (d, J = 5.6 Hz, 1H), 7.63-7.61 (d, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.32 (br s,1H), 4.49 (t, J = 3.6 Hz, 2H), 3.82 (t, J = 4.0 Hz, 2H), 3.76 (t, J = 7.6 Hz, 2H), 3.63 (t, J = 7.6 Hz, 2H), 3.43 (s, 3H), 2.95 (s, 6H). Five active protons not observed.

Compound 117



Step 1: 1-(tert-butyl)-5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3- (4-(methylamino)phenyl)-1H-pyrazole-4-carboxamide

A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-{[2-(2-methoxyethoxy) pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide (100 mg, 0.1177 mmol), NaOMe (25.4 mg, 0.4708 mmol) and paraformaldehyde (35.1 mg, 1.17 mmol) in MeOH (5 mL) was heated to 60 °C under N_2 for 3 h. $NaBH_4$ (44.2 mg, 1.17 mmol) was then added and the resulting mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 12:1) to afford the the title compound (45 mg, 44%) as a yellow solid. LCMS (Method B): 0.48 min; m/z: 439.2 $[M+H]^+$.

Step 2: 1-tert-butyl-5-{[2-(2-methoxyethoxy)pyridin-4-yl]amino}-3-[4-(N-methylethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide

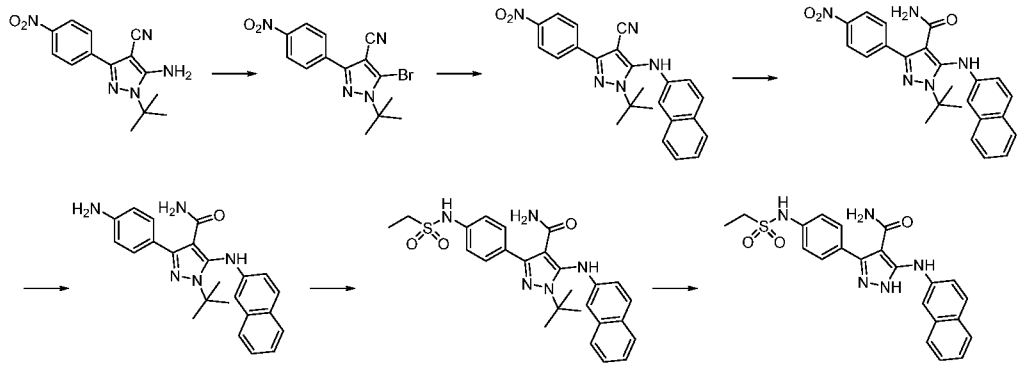
To a solution of 1-tert-butyl-5-{[2-(2-methoxyethoxy)pyridin-4-yl]amino}-3- [4-(methylamino)phenyl]-1H-pyrazole-4-carboxamide (40 mg, 0.09121 mmol) in $CHCl_3$ (5 mL),

were added $EtSO_2Cl$ (23.4 mg, 0.1824 mmol) and pyridine (28.8 mg, 0.3648 mmol). The mixture was stirred at RT overnight then diluted with H_2O (10 mL) and DCM (20 mL). The organic layer was dried (Na_2SO_4) and the crude residue was purified by prep-TLC (DCM:MeOH, 12:1) to afford the title product (13 mg, 27%) as a yellow solid. LCMS (Method B): 1.13 min; m/z: 531.2 $[M+H]^+$.

Step 3: 5-((2-(2-methoxyethoxy)pyridin-4-yl)amino)-3-(4-((2-methoxyethyl) sulfonamido)phenyl)-1H-pyrazole-4-carboxamide (Compound 117)

A solution of 1-tert-butyl-5-{[2-(2-methoxyethoxy)pyridin-4-yl]amino}- 3-[4-(N-methylethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (13 mg, 0.024 mmol) in TFA (1.5 mL) and DCM (1.5 mL) was stirred at RT overnight. The mixture was then concentrated under reduced pressure to afford the title product as the mono TFA salt (10 mg, 86%) as a brown solid. LCMS (Method B): 2.37 min; m/z: 475.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 7.94 (d, J = 5.6 Hz, 1H), 7.67-7.62 (m, 5H), 7.36 (s, 1H), 4.50 (t, J = 4.0 Hz, 2H), 3.83 (t, J = 4.0 Hz, 2H), 3.42 (s, 3H), 3.39 (s, 3H), 3.22 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H).

Compound 86



Step 1: 5-bromo-1-(tert-butyl)-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (500 mg, 1.75 mmol), $CuBr_2$ (448 mg, 2.01 mmol) and isobutyl nitrite (215 mg, 2.09 mmol) in MeCN (60 mL) was stirred at RT under N_2 overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with EtOAc (100 mL) and sat. aq. NH_4Cl (100 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 15:1) to afford the title product (310 mg, 50%) as a yellow solid. LCMS (Method B): 2.13 min;

m/z: 349.0, 351.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.41 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 1.77 (s, 1H).

Step 2: 1-tert-butyl-5-[(naphthalen-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole- 4-carbonitrile

A mixture of 5-bromo-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (2 g, 5.72 mmol), naphthalen-2-amine (819 mg, 5.72 mmol), $Pd_2(dba)_3$ (523 mg, 0.5720 mmol), Xantphos (659 mg, 1.14 mmol) and Cs_2CO_3 (5.57 g, 17.1 mmol) in degassed 1,4-dioxane (50 mL) was stirred at 100 °C overnight. The reaction mixture was diluted with DCM (150 mL), filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the the title product (970 mg, 41%) as a yellow solid. LCMS (Method A): 3.92 min; m/z: 412.1 $[M+H]^+$.

Step 3: 1-tert-butyl-5-[(naphthalen-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole- 4-carboxamide

A mixture of 1-tert-butyl-5-[(naphthalen-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (970 mg, 2.35 mmol), 30% aq. H_2O_2 (15 mL), 5% aq. NaOH (1.5 mL) and DMSO (15 mL) in EtOH (30 mL) was stirred at 80 °C overnight. The reaction mixture was concentrated under reduced pressure and diluted with H_2O. The precipitated solids were collected by filtration and dried under reduced pressure to afford the title product (1.0 g, 100%) as a yellow solid. LCMS (Method A): 2.12 min; m/z: 430.2 $[M+H]^+$.

Step 4: 3-(4-aminophenyl)-1-tert-butyl-5-[(naphthalen-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-5-[(naphthalen-2-yl)amino]-3-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (500 mg, 1.16 mmol) and 10% Pd/C (100 mg) in *i*-PrOH (15 mL) was stirred at RT under H_2 overnight. The reaction mixture was filtered, concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 15:1) to afford the title product (160 mg, 34%) as a yellow solid. LCMS (Method A): 2.97 min; m/z: 399.9 $[M+H]^+$.

Step 5: 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(naphthalen-2-yl)amino]-1H-pyrazole-4-carboxamide

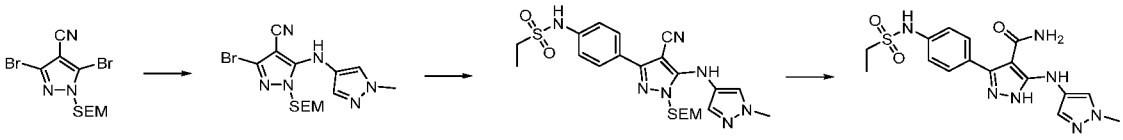
A mixture of 3-(4-aminophenyl)-1-tert-butyl-5-[(naphthalen-2-yl)amino]-1H-pyrazole-4-carboxamide (160 mg, 0.401 mmol), $EtSO_2Cl$ (61.7 mg, 0.48 mmol) and pyridine (76.0 mg, 0.9612 mmol) in $CHCl_3$ (7 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC

(DCM:MeOH, 12:1) to afford the title product (80 mg, 41%) as a yellow solid. LCMS (Method A): 4.02 min; m/z: 492.2 $[M+H]^+$.

Step 6: 3-(4-(ethylsulfonamido)phenyl)-5-(naphthalen-2-ylamino)-1H-pyrazole-4-carboxamide (compound 86)

A solution of 1-tert-butyl-3-(4-ethanesulfonamidophenyl)-5-[(naphthalen-2-yl)amino]-1H-pyrazole-4-carboxamide (75 mg, 0.1525 mmol) in TFA (3 mL) and DCM (3 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue was basified to pH 9-10 with NH_4OH. The precipitated solids were collected by filtration, washed (H_2O) and dried under reduced pressure to afford the title product (20 mg, 30%) as a yellow solid. LCMS (Method A): 3.70 min; m/z: 436.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 10.11 (br s, 1H), 9.23 (s, 1H), 8.23 (s, 1H), 7.78 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.47-7.35 (m, 4H), 7.27 (t, J = 7.2 Hz, 1H), 6.07 (br s, 1H), 3.18 (q, J = 6.8 Hz, 2H), 1.23 (t, J = 3.2 Hz, 3H).

Compound 100



Step 1: 3-bromo-5-[(1-methyl-1H-pyrazol-4-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (500 mg, 1.31 mmol), 1-methyl-1H-pyrazol-4-amine (127 mg, 1.31 mmol), $Pd_2(dba)_3$ (119 mg, 0.131 mmol), Xantphos (151 mg, 0.262 mmol) and Cs_2CO_3 (1.28 g, 3.93 mmol) in 1,4-dioxane (30 mL) was stirred at 100 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (220 mg, 42%) as a brown oil. LCMS (Method A): 3.05 min; m/z: 396.9, 398.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.81 (s, 1H), 7.78 (s, 1H), 7.38 (s, 1H), 5.33 (s, 2H), 3.80 (s, 3H), 3.60 (t, J = 8.4 Hz, 2H), 0.85 (t, J = 8.4 Hz, 2H), 0.00 (s, 9H).

Step 2: N-(4-{4-cyano-5-[(1-methyl-1H-pyrazol-4-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl}phenyl)ethane-1-sulfonamide

A mixture of 3-bromo-5-[(1-methyl-1H-pyrazol-4-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (210 mg, 0.5284 mmol) and N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (164 mg, 0.5284 mmol), $Pd(dppf)Cl_2$ (38.6 mg, 0.05 mmol) and Na_2CO_3 (111 mg, 1.05 mmol) in 80% aq. 1,4-dioxane (5 mL) was stirred at 120 °C under microwave irradiation for 1 h. The reaction mixture was diluted with EtOAc (5 mL), filtered and the filtrate concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (170 mg, 64%) as a brown solid. LCMS (Method A): 2.91 min; m/z: 502.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.00 (s, 1H), 8.55 (s, 1H), 7.76 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 5.41 (s, 2H), 3.81 (s, 3H), 3.64 (t, J = 7.6 Hz, 2H), 3.13 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.6 Hz , 2H), 0.87 (t, J = 8.0 Hz, 2H), -0.04 (s, 9H).

Step 3: 3-(4-(ethylsulfonamido)phenyl)-5-((1-methyl-1H-pyrazol-4-yl)amino)-1H-pyrazole -4-carboxamide (compound 100)

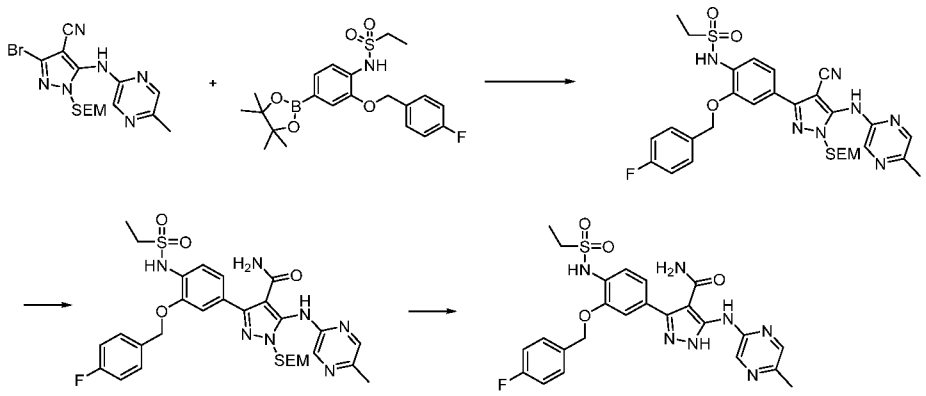
A mixture of N-(4-{4-cyano-5-[(1-methyl-1H-pyrazol-4-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl}phenyl)ethane-1-sulfonamide (20 mg, 0.039 mmol) in conc. H_2SO_4 (1 mL) and H_2O (1 mL) was stirred at 60 °C for 2 d. The reaction mixture was basified to pH 9-10 with NH_4OH and then extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by prep-TLC (DCM:MeOH:NH_4OH, 8:1:0.1) to afford the title product (4 mg, 25%) as a white solid. LCMS (Method A): 2.57 min; m/z: 390.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.39 (br s, 1H), 8.26 (s, 1H), 7.76 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.20 (br s, 1H), 6.64 (br s,1H), 3.77 (s, 3H), 3.16 (q, J = 7.2 Hz, 2H), 1.22 (m, 3H).

Following the synthesis of Compound 100, starting from 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile with the mentioned intermediate as described in step 1, the following compound (Table 13) was prepared:

Table 13

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
91	3-(4-(ethylsulfonamido)phenyl)-5-((1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.80 min; m/z: 390.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.52 (br s, 1H), 10.00 (br s, 1H), 8.89 (br s, 1H), 7.50 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.0 Hz, 2H), 6.39 (br s, 1H), 3.72 (s, 3H), 3.16 (t, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).	1-methyl-1H-pyrazol-3-amine

Compound 22



Step 1: N-(4-(4-cyano-5-((5-methylpyrazin-2-yl)amino)-1-((2-(trimethylsilyl) ethoxy)methyl)-1H-pyrazol-3-yl)-2-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide

A mixture of 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1- {[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (Intermediate B5, 200 mg, 488 µmol), N-{2-[(4-fluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (Intermediate C1, 212 mg, 488 µmol), $Pd(dppf)Cl_2$ (39.8 mg, 48.8 µmol) and Na_2CO_3 (103 mg, 976 µmol) in degassed 80% aq. 1,4-dioxane (12.5 mL) was stirred at 100 °C for 1 h under microwave irradiation. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (200 mg, 64%) as a yellow solid. LCMS (Method A): 4.49 min; m/z: 638.2 $[M+Na]^+$.

Step 2: 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5- ((5-methylpyrazin-2-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of N-(4-(4-cyano-5-((5-methylpyrazin-2-yl)amino)-1-((2-(trimethylsilyl) ethoxy)methyl)-1H-pyrazol-3-yl)-2-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide (200 mg, 313 µmol) and Ghaffar-Parkins catalyst in 50% aq. EtOH (20 mL) was stirred at 100°C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (100 mg, 48%) as a yellow solid. LCMS (Method A): 4.14 min; m/z: 656.2 $[M+H]^+$.

Step 3: 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide

A solution of 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5- ((5-methylpyrazin-2-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (100 mg, 152 µmol) in TFA (2 mL) and DCM (2 mL) was stirred at RT for 1 h. The reaction mixture was neutralized to pH 7-8 with sat. aq. Na_2CO_3 and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (40.0 mg, 50%) as a white solid. LCMS (Method A): 3.50 min; m/z: 526.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.05 (s, 1H), 9.51 (s, 1H), 9.17 (s, 1H), 8.11 (s, 1H), 7.62 (dd, *J* = 4.8 Hz, 2H), 7.44 (d, *J* = 9.6 Hz, 2H), 7.24 (t, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 1.2 Hz, 8Hz, 1H), 6.18 (s, 1H), 5.19 (s, 2H), 3.05 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H).

The following compounds (Table 14) were similarly prepared from the appropriate aryl amine starting material according to the method described for the synthesis of 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide:

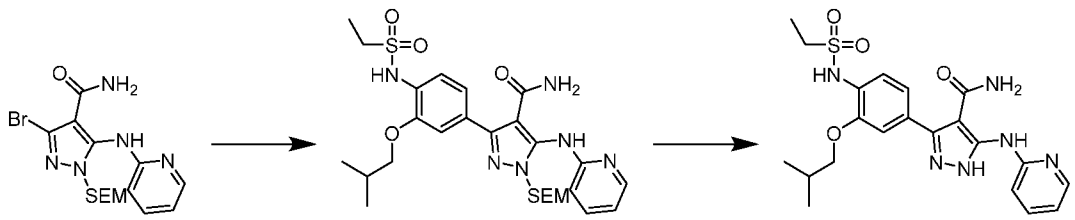
Table 14

Compound No	Name	Structure	LCMS data	^{1}H NMR data	Arylamine
34	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-isopropylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.93 min; m/z 554.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 9.53 (s, 1H), 9.20 (s, 2H), 8.15 (s, 1H), 7.65-7.62 (m, 2H), 7.48-7.41 (m, 2H), 7.28-7.22 (m, 4H), 6.20 (br s, 1H), 5.20 (s, 2H), 3.08-3.03 (m, 3H), 1.25 (d, J = 6.4 Hz, 6H), 1.17 (t, J = 6.8 Hz, 3H).	5-isopropylpyrazin-2-amine
11	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-methoxypyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.85 min; m/z 541.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.83 (s, 1H), 9.33 (s, 1H), 9.12 (s, 1H), 7.62-7.60 (m, 3H), 7.56-7.54 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.25 (t, J = 8.8 Hz, 2H), 7.18 (d, J = 8.04 Hz, 2H), 6.27 (d, J = 7.6 Hz, 1H), 5.18 (s, 2H), 3.82 (s, 3H), 3.07 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	6-methoxypyridin-2-amine
6	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyridin-3-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.89 min; m/z 511.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_{64}): 9.19 (s, 1H), 9.04 (s, 1H), 8.72 (s, 1H), 8.72 (d, J = 5.2 Hz, 2H), 7.63-7.61 (m, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.29-7.23 (m ,3H), 7.20 (dd, J = 8.4, 1.6 Hz, 1H), 5.20 (s, 2H), 3.05 (t, J = 7.2 Hz, 2H), 1.84 (t, J = 7.6 Hz, 3H).	pyridin-3-amine

13	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((2-methoxypyridin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.90 min; m/z 541.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 9.51 (s, 1H), 9.28 (s, 1H), 9.18 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.62 (q, J =4.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.27-7.09 (m, 4H), 5.18 (s, 2H), 3.80 (s, 3H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).	2-methoxypyridin-4-amine
15	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.72 min; m/z 542.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.51 (br s, 1H), 8.81 (br s, 1H), 7.75 (s, 1H), 7.62-7.59 (m, 2H), 7.44-7.36 (m, 3H), 7.24 (t, J = 8.8 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 5.17 (s, 2H), 3.89 (s, 3H), 3.01 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).	6-methoxypyrazin-2-amine
17	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.81 min; m/z 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.21 (s, 1H), 9.99 (s, 1H), 9.41 (s, 1H), 8.55 (s, 1H), 7.62 (d, J = 4.8 Hz, 2H), 7.44 (d, J = 9.6 Hz, 2H), 7.27-7.21 (m, 3H), 5.19 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H).	6-(trifluoromethyl)pyrazin-2-amine

13	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.88 min; m/z 580.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.23 (s, 1H), 10.12 (s, 1H), 9.16 (s, 1H), 8.66 (s, 1H), 7.63 (q, J = 6.0 Hz, 2H), 7.44 (d, J = 10.4 Hz, 2H), 7.25 (q, J = 8.8 Hz, 3H), 6.47 (m, 1H), 5.18 (s, 2H), 3.05 (d, J = 7.2 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).	5-(trifluoromethyl)pyrazin-2-amine
14	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.60 min; m/z 542.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.88 (s, 1H), 9.41 (s, 1H), 9.19 (s, 1H), 8.85 (s, 1H), 7.99 (s, 1H), 7.62 (t, J = 5.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.25 (t, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H), 3.87 (s, 3H), 3.05 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	5-methoxypyrazin-2-amine
62	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.41 min; m/z 512.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.27 (s, 1H), 8.08 (s, 1H), 7.66 (s, 1H), 7.60 (d, J = 7.2Hz, 1H), 7.47 (s, 2H), 7.26 (s, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 2H), 5.19 (s, 2H), 3.11 (q, J = 4.8 Hz, 2H), 1.29 (t, J = 6.8 Hz, 3H).	pyrazin-2-amine

Compound 37



Step 1: 3-[4-ethanesulfonamido-3-(2-methylpropoxy)phenyl]-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

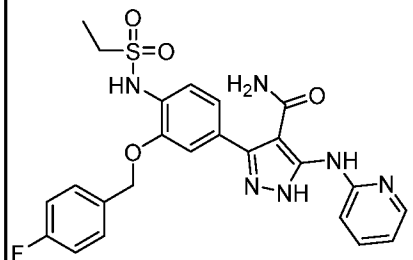
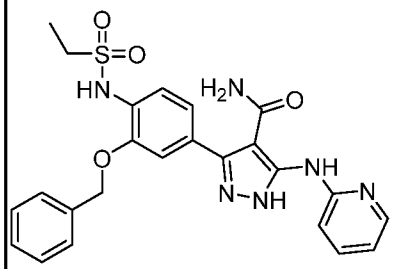
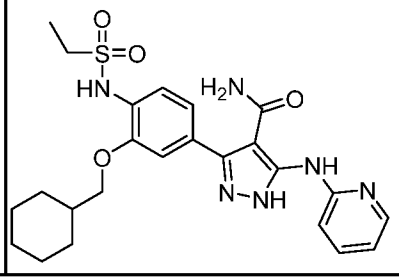
A mixture of 3-bromo-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B2, 90 mg, 0.2182 mmol), N-[2-(2-methylpropoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (Intermediate C9, 83.6 mg, 0.218 mmol), $Pd(dppf)Cl_2$ (16.0 mg, 0.022 mmol) and Na_2CO_3 (69.3 mg, 0.65 mmol) in 80% aq. 1,4-dioxane (2.5 mL) was stirred at 100 ºC for 2 h under microwave irradiation. The mixture was concentrated under reduced pressure, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 18:1) to afford the title product (110 mg, 86%) as a yellow solid. LCMS (Method A): 4.18 min; m/z: 589.2 $[M+H]^+$.

Step 2: 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide (compound 37)

A solution of 3-[4-ethanesulfonamido-3-(2-methylpropoxy)phenyl]-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4- carboxamide (100 mg, 0.1698 mmol) in TFA (2 mL) and DCM (2 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure and the residue neutralized to pH 7-8 with sat. aq. Na_2CO_3. The mixture was diluted with H_2O (30 mL) and the precipitated solids collected by filtration. The crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (20 mg, 25%) as a white solid. LCMS (Method A): 3.06 min; m/z: 459.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 12.84 (s, 1H), 9.57 (s, 1H), 9.01 (s, 1H), 8.20 (s, 1H), 7.72 (t, J =8.4 Hz, 1H), 7.43 (d, J =8.0 Hz, 1H), 7.24 (s, 1H), 7.14 (d, J =8.0 Hz, 1H), 6.87 (s, 1H), 6.14 (s, 1H), 3.83 (d, J =6.4 Hz, 2H), 3.11 (q, J =7.2 Hz, 2H), 2.18-2.08 (m, 1H), 1.27 (t, J =7.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 6H).

The following compounds (Table 15) were similarly prepared from Intermediate B1 and the appropriate Intermediate C according to the method described for the synthesis of 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide:

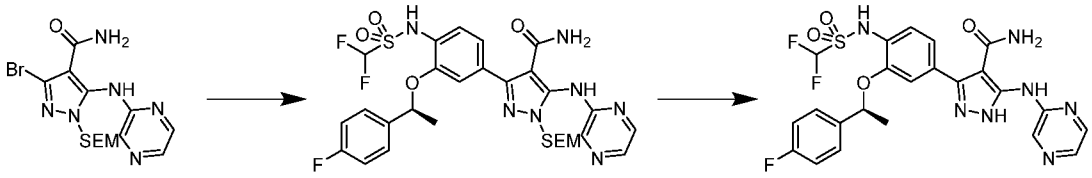
Table 15

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
30	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.16 min; m/z: 511.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 9.50 (s, 1H), 9.15 (br s, 1H), 8.27-8.18 (m, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.64-7.61 (m, 2H), 7.46-7.40 (m, 2H), 7.25 (t, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.86-6.85 (m, 1H), 5.19 (s, 2H), 3.05 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).	Intermediate C1
20	3-(3-(benzyloxy)-4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.96 min; m/z: 493.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.87 (s, 1H), 9.44 (s, 1H), 9.11 (s, 1H), 8.17 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 3H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 6.12 (s, 1H), 5.19 (s, 2H), 3.04 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).	Intermediate C2
35	3-(3-(cyclohexylmethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.47 min; m/z: 499.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.82 (s, 1H), 9.50 (s, 1H), 9.23 (s, 1H), 8.18 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.50-7.37 (m, 1H), 7.26- 7.13 (m, 2H), 6.85 (d, *J* = 5.2 Hz, 1H), 3.86 (d, *J* = 5.6 Hz, 2H), 3.12 (q, *J* = 7.2 Hz, 2H), 1.91-1.88 (m, 3H), 1.74-1.65 (m, 3H), 1.28-1.25 (m, 6H), 1.09-1.01 (m, 2H).	Intermediate C3

39	3-(3-((4-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.33 min; m/z: 527.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 9.49 (s, 1H), 9.20 (s, 1H), 8.18 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 5.20 (s, 2H), 3.05 (q, J = 7.6 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	Intermediate C4
38	3-(3-((3-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.31 min; m/z: 527.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.85 (s, 1H), 9.50 (s, 1H), 9.24 (s, 1H), 8.22 (m, 1H), 7.98 (s, 1H), 7.72 (s, 2H), 7.51-7.39 (m, 6H), 7.16 (m, 2H), 6.88 (m, 1H), 5.22 (s, 2H), 3.07 (s, 2H), 1.18 (s, 3H).	Intermediate C5
27	3-(4-(ethylsulfonamido)-3-(pyridin-4-ylmethoxy)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.35 min; m/z: 494.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.48 (s, 1H), 9.34 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 8.18 (s, 1H) , 7.96 (s, 1H), 7.72-7.68 (m, 1H), 7.61 (d, J = 4.8 Hz, 2H), 7.54 (s, 3H), 7.41 (s, 3H), 7.29 (s, 3H), 7.20 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 5.30 (s, 2H), 3.09 (q, J = 6.8 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).	Intermediate C6

31	3-(4-(ethylsulfonamido)-3-(pyridin-3-ylmethoxy)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.38 min; m/z: 494.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.56 (s, 1H), 8.80 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 4.8, 1.2 Hz, 1H), 8.20 (s, 1H), 8.02-7.99 (m, 1H), 7.73-7.69 (m, 1H), 7.47-7.43 (m, 3H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 6.87 (t, J = 4.2 Hz, 1H), 6.10 (s, 1H), 5.25 (s, 2H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).	Intermediate C7
36	3-(3-(cyclopentylmethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.31 min; m/z: 485.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 9.79 (s, 1H), 8.98 (s, 1H), 8.22 (d, J = 4.8 Hz, 1H), 7.79 (s, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.21 (s, 1H), 3.93 (d, J = 7.2 Hz, 2H), 3.11 (m, 2H), 1.80 (m, 2H), 1.59 (m, 4H), 1.34 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H).	Intermediate C8

Compound 223



Step 1: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (Intermediate C11, 23.5 g, 50 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]- 1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B4, 18.2 g, 44 mmol), Na_2CO_3 (10.6 g, 100 mmol) and $Pd(dppf)Cl_2$ (2.5 g, 3 mmol) in degassed 80% aq. 1,4-dioxane (250 mL) was stirred at 100 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title compound (23 g, 77%) as a yellow solid. LCMS (Method A): 3.99 min; m/z: 678.2 $[M+H]^+$.

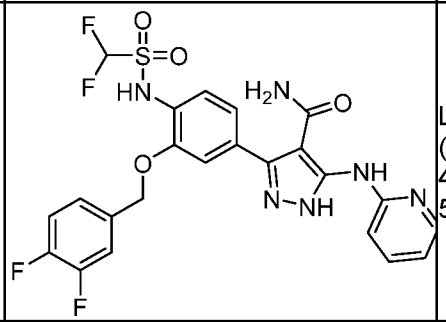
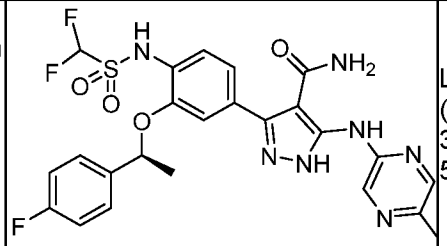
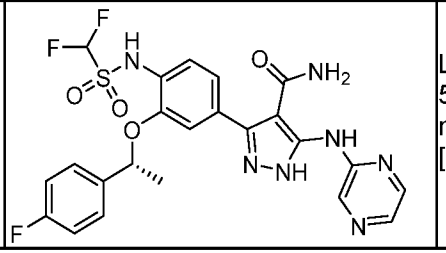
Step 2: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1- (4-fluorophenyl)ethoxy] phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 223)

A mixture of 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (23 g, 33.9 mmol), DCM (400 mL) and TFA (20 mL) was stirred at RT for 16 h. The mixture was neutralized to pH 7-8 with an sat. Na_2CO_3 and the organic phase was washed with water (3 x 50 mL) and dried (Na_2SO_4). The organic layer was concentrated under reduced pressure and the residue purified by silica gel column chromatography (DCM:MeOH, 1:0 to 20:1) to afford the titled product (5.8 g, 31%) as a white solid. LCMS (Method A): 3.45 min; m/z: 548.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.40 (s, 1H), 10.28 (s, 1H), 8.35 (s, 1H), 8.20-8.15 (m, 2H), 7.61 (d, *J* = 8.0Hz, 1H), 7.31 (q, *J* = 4.8 Hz, 2H), 7.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 1.6 Hz, 1H), 6.35 (t, *J* = 53.6 Hz, 1H), 5.40 (q, *J* = 6.4 Hz, 1H), 5.21 (s, 2H), 1.67 (d, *J* = 6.4 Hz, 3H).

The following compounds (Table 16) were similarly prepared from the appropriate Intermediate C and Intermediate B according to the method described for the synthesis of

3-[4-(difluoromethanesulfonamido)-3-[(1S)-1- (4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide:

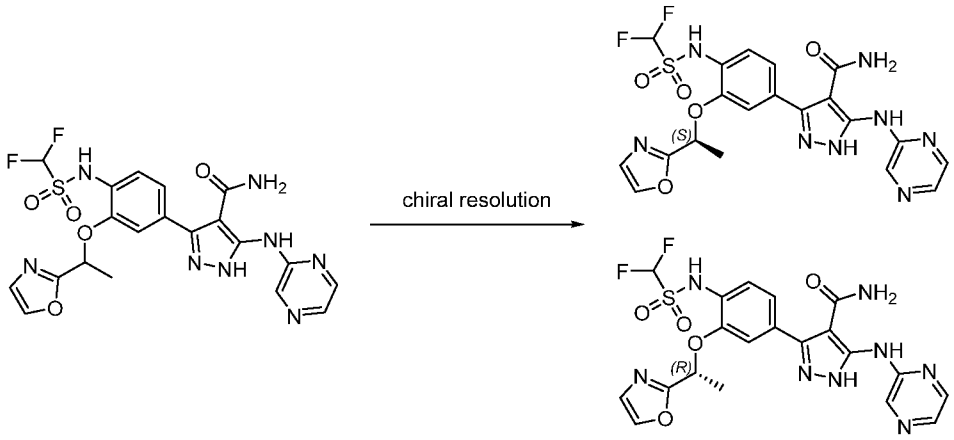
Table 16

Compound No	Name	Structure	LCMS data	^{1}H NMR data	Intermediates	
226	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyridin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method D): 4.44 min; m/z: 551.0 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.80 (s, 1H), 10.57 (s, 1H), 9.51 (s, 1H), 8.17 (s, 1H), 7.98 (s, 1H), 7.69 (m, 2H), 7.45 (m, 4H), 7.18 (m, 5H), 5.17 (s, 2H).	B2	C12
245	3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(5-methylpyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.52 min; m/z: 562.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.91 (s, 1H), 10.52 (s, 1H), 9.44 (s, 1H), 9.13 (s, 1H), 8.10 (s, 1H), 7.57 (s, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.20-7.10 (m, 5H), 5.64 (s, 1H), 2.39 (s, 3H), 1.57 (d, J = 5.6 Hz, 3H).	B6	C11
271	(R)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (acidic 5 min): 3.67 min; $[M+H]^+$=548.2	^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (s, 1H), 10.53 (s, 1H), 9.54 (s, 1H), 9.20 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.63-7.54 (m, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.24-6.85 (m, 6H), 5.64 (q, J = 6.1 Hz, 1H), 1.58 (d, J = 6.3 Hz, 3H).	B4	C13

291	3-(3-((3,4-difluorobenzyl)oxy)-4-((difluoromethyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.56 min; m/z 566.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6):12.95 (br s, 1H), 9.51 (br s, 1H), 9.16 (br s, 1H), 8.11 (s, 1H), 7.65 (m, 2H), 7.40 (m, 5H), 7.17 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 51.0 Hz, 1H), 6.11 (br s, 1H), 5.18 (s, 2H), 2.40 (s, 3H).	B6	C12
275	3-(4-((difluoromethyl)sulfonamido)-3-(thiazol-2-ylmethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.25 min, m/z 523.5 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.08 (s, 1H), 10.64 (s, 1H), 9.60 (s, 1H), 9.23 (s, 1H), 8.22 (dd, J = 2.6, 1.5 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.88 (d, J = 3.2 Hz, 1H), 7.83 (d, J = 3.2 Hz, 1H), 7.55 (s, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.26 (dd, J = 8.1, 1.8 Hz, 1H), 7.04 (s, 1H), 5.55 (s, 2H).	B4	C14
293	3-(4-((difluoromethyl)sulfonamido)-3-(1-(oxazol-2-yl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.00 min, m/z 521.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.84 (s, 1H), 9.89 (s, 1H), 9.35 (s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.23 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.93-6.84 (m, 1H), 6.34 (t, J = 54.8 Hz, 1H), 5.88 (s, 1H), 5.82 (q, J = 6.5 Hz, 1H), 1.68 (d, J = 6.6 Hz, 3H).	B4	C15

260	3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.21 min; m/z: 547.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.77 (s, 1H), 9.46 (s, 1H), 8.17 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.68 (t, J = 8.4 Hz, 1H), 7.56 (t, J = 6.8 Hz, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 8.4 Hz, 2H), 7.09 (s, 2H), 6.84 (t, J = 52.8 Hz, 1H), 5.64 (q, J = 7.6 Hz, 1H), 1.56 (d, J = 5.6 Hz, 3H).	B2	C11

Compounds 279 and 280



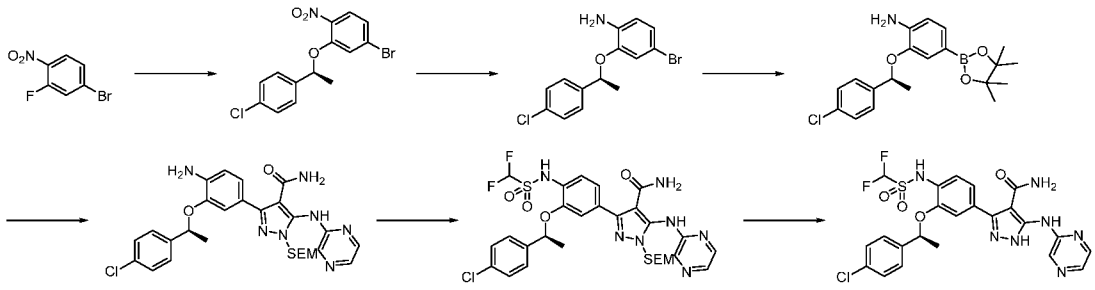
The racemate Compound 293 (500 mg) was subjected to purification by chiral HPLC on a UniChiral CND-5H column, (Column size 50 mm I.D x 250 mm L. Mobile phase 60% n-Hexane/40% Ethanol /0.1% TFA (v/v/v), flow rate 90 mL/min, temperature 25°C). The fractions corresponding to the appropriate peaks were combined and concentrated under reduced pressure. The residue was dissolved in DCM (50 mL), and the mixture was neutralized to pH 7-8 with sat. aq. Na_2CO_3. The organic phase was washed with water (3 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue purified by silica gel column chromatography (DCM:MeOH, 1:0 to 20:1) to afford the titled products. The enantiomeric excess was calculated on UniChiral CND-5H, (4.6 x 250 mm, 50% n-hexanes/50% Ethanol. Flow rate 1 mL/min, injection 5µL, temperature 30 °C).

Peak 1: (S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(oxazol-2-yl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (143 mg, retention time 7.49 min, ee > 99%). LCMS (Method A): 3.00 min; m/z: 521.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.41 (s, 1H), 10.32 (s, 1H), 8.39 (s, 1H), 8.21 (dd, *J* = 2.9, 1.4 Hz, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 7.66 (dd, *J* = 4.5, 3.7 Hz, 2H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.12 (d, *J* = 0.8 Hz, 1H), 6.33 (t, *J* = 53.6 Hz, 1H), 5.50 (q, *J* = 6.7 Hz, 1H), 5.44 (s, 2H), 1.84 (d, J = 6.7 Hz, 3H).

Peak 2: (R)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(oxazol-2-yl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (147 mg, retention time 9.06 min, ee > 99%). LCMS (Method A): 3.00 min; m/z: 521.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.41 (s, 1H), 10.32 (s, 1H), 8.39 (s, 1H), 8.21 (dd, *J* = 2.9, 1.4 Hz, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 7.66 (dd, *J* = 4.5, 3.7 Hz, 2H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.30 (dd,

J = 8.2, 1.9 Hz, 1H), 7.12 (d, *J* = 0.8 Hz, 1H), 6.33 (t, *J* = 53.6 Hz, 1H), 5.50 (q, *J* = 6.7 Hz, 1H), 5.44 (s, 2H), 1.84 (d, *J* = 6.7 Hz, 3H).

Compound 252



Step 1: 4-bromo-2-[(1S)-1-(4-chlorophenyl)ethoxy]-1-nitrobenzene

To a solution of (1S)-1-(4-chlorophenyl)ethan-1-ol (1.00 g, 6.38 mmol) in THF (20 mL) at 0 ºC was added NaH (60% in oil,763 mg, 19.1 mmol). After 1 h, 4-bromo-2-fluoro-1-nitrobenzene (1.40 g, 6.38 mmol) was added, and the mixture was stirred at RT for 16 h. The reaction mixture was concentrated, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (1.78 g, 78%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): 7.82 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.46 (s, 4H), 7.29 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.91 (q, *J* = 6.4 Hz, 1H), 1.54 (d, *J* = 6.4 Hz, 3H).

Step 2: 4-bromo-2-[(1S)-1-(4-chlorophenyl)ethoxy]aniline

A mixture of 4-bromo-2-[(1S)-1-(4-chlorophenyl)ethoxy]-1-nitrobenzene (1.78 g, 4.99 mmol), Zn powder (1.62 g, 24.9 mmol), sat. NH_4Cl (3 mL) and MeOH (12 mL) was stirred at 60 ºC for 30 min. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the title product (1.40 g, 86%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): 7.48-7.39 (m, 4H), 6.81 (d, *J* = 2Hz, 1H), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.52 (q, *J* = 6.4 Hz, 1H), 4.99 (s, 2H), 1.52 (d, *J* = 6.4 Hz, 3H).

Step 3: 2-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

A mixture of 4-bromo-2-[(1S)-1-(4-chlorophenyl)ethoxy]aniline (1.4 g, 4.28 mmol), B_2pin_2 (1.19 g, 4.70 mmol), $Pd(dppf)Cl_2$ (174 mg, 214 µmol), KOAc (840 mg, 8.56 mmol) and 1,4-dioxane (20 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated, and the residue was diluted with H_2O (200 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silca gel column chromatography (PE:EtOAc, 1:1) to afford the title product (1.08 g, 68%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 7.49-7.38 (m, 4H), 7.00 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.94 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.47 (q, *J* = 6.4 Hz, 1H), 5.24 (s, 2H), 1.50 (d, *J* = 6.4 Hz, 3H), 1.21 (s, 12H).

Step 4: 3-{4-amino-3-[(1S)-1-(4-chlorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (945 mg, 2.52 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B4, 987 mg, 2.39 mmol), $Pd(dppf)Cl_2$.DCM (102 mg, 126 µmol), Na_2CO_3 (534 mg, 5.04 mmol) and 80% aq. 1,4-dioxane (2.5 mL) was irradiated at 100 ºC in a microwave reactor. After 1 h, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 30:1) to afford the title product (561 mg, 38%) as a gray solid. LCMS (Method A): 4.07 min; m/z: 580.2 $[M+H]^+$.

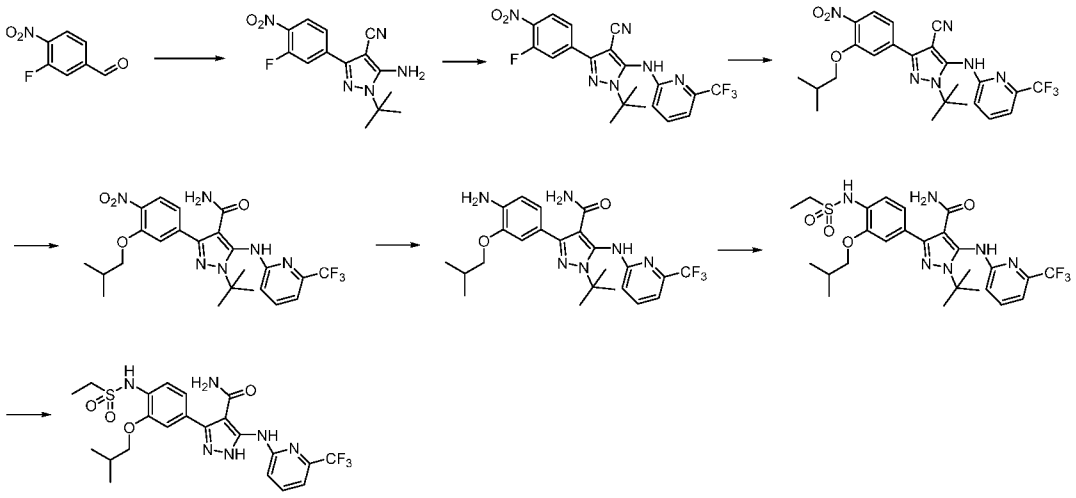
Step 5: 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{4-amino-3-[(1S)-1-(4-chlorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (70 mg, 120 µmol) and F_2CHSO_2Cl (27.0 mg, 180 µmol) in 1:1 DCM:pyridine (4 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (30 mg, 36%) as a white solid. LCMS (Method D): 5.06 min; m/z: 715.9 $[M+Na]^+$.

Step 6: 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 252)

A solution of 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (40 mg, 57.6 µmol) in 10:1 DCM:TFA (5 mL) was stirred at RT for 16 h. The reaction mixture was neutralized with sat. Na_2CO_3 and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title compound (10.6 mg, 33%) as a white solid. LCMS (Method A): 1.80 min; m/z: 564.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.54 (s, 1H), 9.64 (s, 1H), 9.04 (s, 1H), 8.21-8.20 (m, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.15 (dd, J = 8.0, 1.6 Hz, 1H), 7.04 (t, J = 52.8 Hz, 1H), 6.20 (br s, 1H), 5.63 (q, J = 6.0 Hz, 1H), 1.59 (d, J = 6.4 Hz, 3H).

Compound 12



Step 1: 5-amino-1-(tert-butyl)-3-(3-fluoro-4-nitrophenyl)-1H-pyrazole-4- carbonitrile

A mixture of 3-fluoro-4-nitrobenzaldehyde (10 g, 59.1 mmol) and *t*-BuNHNH$_2$.HCl (8.09 g, 65.0 mmol) in DMF (50 mL) was stirred at RT overnight to give a solution of the hydrazone intermediate. LCMS (Method A): 4.38 min; m/z: 240.2 $[M+H]^+$. To this mixture was added NBS (11.4 g, 64.3 mmol) slowly at 0 °C over 5 h, and the mixture was stirred at RT for a further 5 h. The reaction mixture was then cooled to 0 ºC, and a pre-mixed solution of malonitrile (8.39 g, 127 mmol) and NaOEt (14.4 g, 212 mmol) in EtOH (20 mL) was added. After 2 h at 0 ºC, the reaction mixture was concentrated under reduced pressure and diluted with H_2O (20 mL). The precipitated solids were collected by filtration, washed with H_2O (2 x 10 mL) and dried under reduced pressure to afford the title product (15 g, 60%) as a yellow solid. LCMS (Method A): 4.18 min; m/z: 304.1 $[M+H]^+$.

Step 2: 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-1H-pyrazole-4-carbonitrile (5 g, 16.4 mmol), 2-chloro-6-(trifluoromethyl)pyridine (3.55 g, 19.6 mmol), $Pd_2(dba)_3$ (1.50 g, 1.64 mmol), Xantphos (1.89 g, 3.28 mmol) and Cs_2CO_3 (15.9 g, 49.1 mmol) in degassed 1,4-dioxane (30 mL) was heated at 110 °C overnight. The reaction mixture was concentrated under reduced pressure, diluted with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (PE:EtOAc, 30:1) to afford the title product (2.5 g, 34%) as a yellow solid. LCMS (Method A): 4.60 min; m/z: 449.1 $[M+H]^+$.

Step 3: 1-tert-butyl-3-[3-(2-methylpropoxy)-4-nitrophenyl]-5-{[6-(trifluoromethyl) pyridin-2-yl]amino}-1H-pyrazole-4-carbonitrile

A mixture of 2-methylpropan-1-ol (131 mg, 1.78 mmol), 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carbonitrile (800 mg, 1.78 mmol) and NaH (876 mg, 7.12 mmol) in THF (12 mL) was stirred at 0 °C overnight. The mixture was concentrated under reduced pressure, diluted with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (740 mg, 82%) as a yellow solid. LCMS (Method A): 3.55 min; m/z: 503.2 $[M+H]^+$.

Step 4: 1-tert-butyl-3-[3-(2-methylpropoxy)-4-nitrophenyl]-5-{[6-(trifluoromethyl) pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-[3-(2-methylpropoxy)-4-nitrophenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carbonitrile (680 mg, 1.35 mmol) and Ghaffar-Parkins catalyst (106 mg, 270 µmol) in 50% aq. 1,4-dioxane (22 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure, diluted with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (610 mg, 87%) as a yellow solid. LCMS (Method A): 2.67 min; m/z: 521.2 $[M+H]^+$.

Step 5: 3-[4-amino-3-(2-methylpropoxy)phenyl]-1-tert-butyl-5-{[6- (trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-[3-(2-methylpropoxy)-4-nitrophenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (460 mg, 883 µmol), sat. NH_4Cl (3 mL) and Zn dust (288 mg, 4.41 mmol) in MeOH (12 mL) was stirred at 60 °C overnight. The reaction mixture was concentrated, diluted with sat. $NaHCO_3$ (10 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (270 mg, 61%) as a yellow solid. LCMS (Method A): 4.08 min; m/z: 491.2 $[M+H]^+$.

Step 6: 1-tert-butyl-3-[4-ethanesulfonamido-3-(2-methylpropoxy)phenyl]-5- {[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4- carboxamide

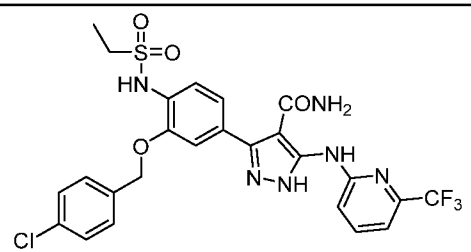
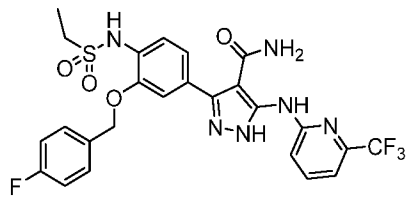
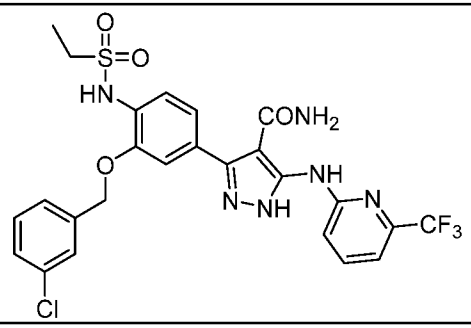
A mixture of 3-[4-amino-3-(2-methylpropoxy)phenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (136 mg, 277 µmol), $EtSO_2Cl$ (42.6 mg, 332 µmol) and pyridine:$CHCl_3$ (1:1, 6 mL) was stirred at RT overnight. The reaction mixture was concentrated, diluted with sat. $NaHCO_3$ (10 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (79 mg, 49%) as a yellow solid. LCMS (Method A): 4.27 min; m/z: 583.2 $[M+H]^+$.

Step 7: 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-((6-(trifluoromethyl) pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide (compound 12)

A solution of 1-tert-butyl-3-[4-ethanesulfonamido-3-(2-methylpropoxy)phenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4- carboxamide (100 mg, 171 µmol) in DCM (4 mL) and TFA (4 mL) was stirred at RT overnight. The reaction mixture was concentrated, neutralized to pH 7-8 with NH_4OH, diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated to afford the title product (30 mg 33%) as a yellow solid. LCMS (Method A): 4.21 min; m/z: 527.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H) 12.97 (s, 1H), 9.77 (s, 1H), 9.02 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.98 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.6 Hz, 2H), 7.16 (q, J = 1.2 Hz, 1H), 3.85 (d, J = 6.8 Hz, 2H), 3.14 (q, J = 7.5 Hz, 2H), 2.17-2.10 (m, 1H), 1.26 (q, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).

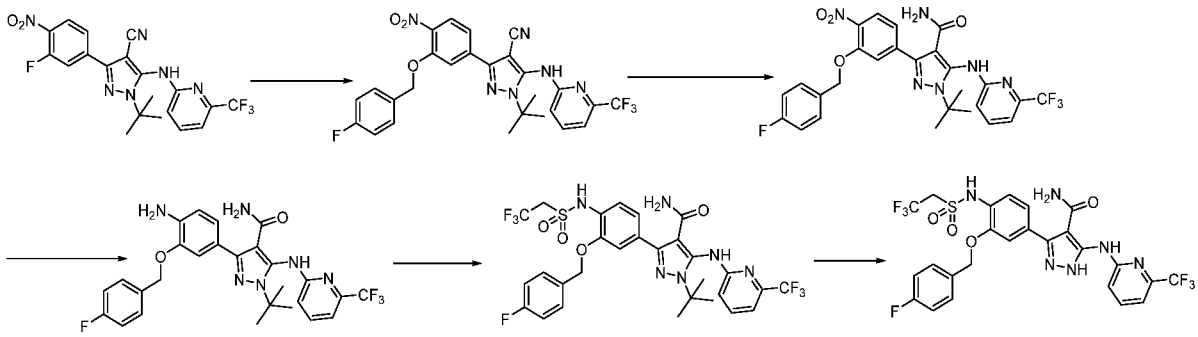
The following compounds (Table 17) were similarly prepared using the appropriate aryl/alkyl methanol in step 3 according to the method described for the synthesis of 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide:

Table 17

Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
4	3-(3-((4-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.32 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.77 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.49 (q, J = 8.4 Hz, 4H), 7.31 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.21 (s, 2H), 3.07 (q, J = 8.0 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H).	(4-chlorophenyl) methanol
8	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.05 min; m/z: 579.4 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.77 (s, 1H), 9.19 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 6.8 Hz, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.31 (d, J = 7.2 Hz, 1H), 7.27-7.19 (m, 3H), 6.21 (s, 1H), 5.19 (s, 2H), 3.05 (q, J = 6.4 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	(4-fluorophenyl)methanol
3	3-(3-((3-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.31 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 9.76 (s, 1H), 9.30 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.47 (q, J = 7.6 Hz, 4H), 7.30 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 5.22 (s, 2H), 3.06 (q, J = 8.0 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).	(3-chlorophenyl) methanol

16	3-(4-(ethylsulfonamido)-3-(pyridin-4-ylmethoxy)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.20 min; m/z: 562.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.07 (s, 1H), 9.82 (s, 1H), 9.40 (s, 1H), 8.67 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.8 Hz, 1H), 8.04 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 5.2 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 1.2 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.29-7.27 (m, 2H) 6.30 (br s, 1H) 5.34 (s, 2H), 3.16 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H).	pyridin-4-ylmethanol
33	3-(4-(ethylsulfonamido)-3-(pyridin-3-ylmethoxy)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.17 min; m/z: 562,1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 13.02 (s, 1H), 9.78 (s, 1H), 9.26 (s, 1H), 8.79 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 4.8, 1.6 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.01-7.96 (m, 2H), 7.48-7.44 (m, 3H), 7.31 (d, J = 7.2 Hz, 1H), 7.21 (dd, J = 8.0, 1.2 Hz, 1H), 5.25 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).	pyridin-3-ylmethanol
10	3-(3-(cyclopentylmethoxy)-4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.24 min; m/z: 553.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.30 (d, J = 8.0 Hz, 1H), 7.95 (m, 1H), 7.63-7.56 (m, 1H), 7.40 (m, 1H), 7.26 (d, J = 1.6 Hz, 1H), 7.22-7.19 (m, 1H), 4.02 (d, J = 7.2 Hz, 2H), 3.19-3.13 (m, 2H),2.53-2.46 (m, 1H), 1.94-1.89 (m, 2H),1.71-1.63 (m, 4H), 1.46-1.39 (m, 2H),1.35 (t, J = 8.0 Hz, 3H).	cyclopentylmethanol

Compound 5



Step 1: 1-(tert-butyl)-3-(3-((4-fluorobenzyl)oxy)-4-nitrophenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carbonitrile

To a solution of (4-fluorophenyl)methanol (209 mg, 1.66 mmol) in THF (20 mL) at 0 °C, was added NaH (133 mg, 3.33 mmol). After 10 min, 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carbonitrile (500 mg, 1.11 mmol) was added and the mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 50:1) to afford the title product (500 mg, 81%) as a yellow solid. LCMS (Method A): 4.87 min; m/z: 555.2 $[M+H]^+$.

Step 2: 1-(tert-butyl)-3-(3-((4-fluorobenzyl)oxy)-4-nitrophenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide

A mixture of 1-(tert-butyl)-3-(3-((4-fluorobenzyl)oxy)-4-nitrophenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carbonitrile (500 mg, 0.90 mmol) and Ghaffar-Parkins catalyst (100 mg) in 70% aq. 1,4-dioxane (7 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM) to afford the title product (400 mg, 78%) as yellow solid. LCMS (Method A): 2.66 min; m/z: 573.1 $[M+H]^+$.

Step 3: 3-(4-amino-3-((4-fluorobenzyl)oxy)phenyl)-1-(tert-butyl)-5- ((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide (compound 5)

A mixture of 1-(tert-butyl)-3-(3-((4-fluorobenzyl)oxy)-4-nitrophenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide (500 mg, 0.87 mmol), sat. aq. NH_4Cl (2 mL) and Zn dust (285mg, 4.36 mmol) in MeOH (10 mL) was stirred at 60 °C for 5 h. The reaction mixture was filtered, concentrated under reduced pressure and diluted with H_2O. The precipitated solids were collected by filtration and then purified by

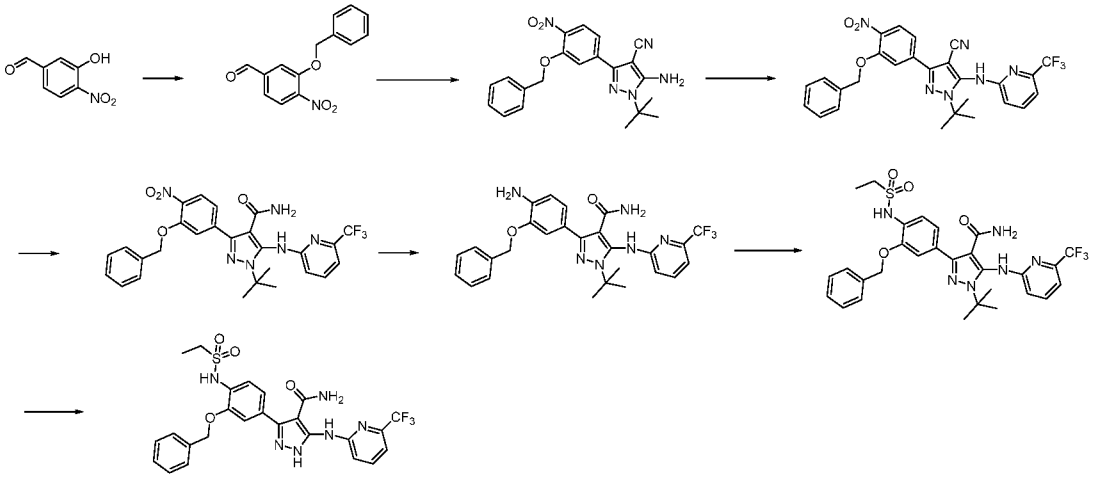
silica gel column chromatography (DCM:MeOH, 50:1) to afford the title product (230 mg, 49%) as a yellow solid. LCMS (Method A): 4.17 min; m/z: 543.2 $[M+H]^+$.

The compound shown in Table 18 was prepared by a similar synthetic route described for compound 46 (steps 6 and 7).

Table 18

Compound No	name	structure	LCMS data	^{1}H NMR data	SM
5	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.32 min; m/z: 633.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.11 (s, 1H), 9.96 (s, 1H), 9.76 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.61 (q, J = 4.8 Hz, 2H), 7.45 (q, J = 5.6 Hz, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.26 (s, 1H), 5.21 (s, 2H), 4.35 (q, J = 9.6 Hz, 2H).	2,2,2-trifluoroethane-1-sulfonyl chloride

Compound 46



Step 1: 3-(benzyloxy)-4-nitrobenzaldehyde

A mixture of 3-hydroxy-4-nitrobenzaldehyde (10 g, 59.8 mmol), benzyl bromide (10.2 g, 59.8 mmol) and K_2CO_3 (16.4 g, 119 mmol) in MeCN (200 mL) was stirred at 70 °C under N_2 overnight. The mixture was diluted with H_2O (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (PE:EtOAc, 15:1) to afford the title product (3 g, 20%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.69 (dd, J = 8.0, 1.2 Hz, 1H), 7.48-7.34 (m, 5H), 5.42 (s, 2H).

Step 2: 5-amino-3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-1H-pyrazole-4-carbonitrile

A solution of 3-(benzyloxy)-4-nitrobenzaldehyde (3 g, 11.6 mmol) and *t*-BuNHNH$_2$.HCl (1.44 g, 11.6 mmol) in DMF (60 mL) was stirred at RT overnight. The mixture was neutralized to pH 7-8 with sat. aq. Na_2CO_3 and diluted with H_2O (100 mL). The precipitated solids were collected by filtration and dried under reduced pressure to provide the hydrazone intermediate (3.5 g, 92%). LCMS (Method A): 4.61 min; m/z: 328.1 $[M+H]^+$. The crude material was dissolved in DMF (60 mL) and NBS (2.06 g, 11.6 mmol) was added at RT. After 2 h, a pre-mixed solution of malononitrile (1.04 g, 15.7 mmol) and NaOEt (1.06 g, 15.7 mmol) in EtOH (40 mL) was added and the mixture stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (70 mL) and extracted with DCM (3 x 60 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by silica

gel column chromatography (PE:EtOAc, 4:1) to afford the title product (1.6 g, 39%) as a yellow solid. LCMS (Method A): 4.49 min; m/z: 392.2 $[M+H]^+$.

Step 3: 3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-1H-pyrazole-4-carbonitrile (1.5 g, 3.83 mmol), 2-chloro-6-(trifluoromethyl)pyridine (764 mg, 4.21 mmol), $Pd_2(dba)_3$ (350 mg, 383 µmol), Xantphos (221 mg, 383 µmol) and Cs_2CO_3 (2.49 g, 7.66 mmol) in degassed 1,4-dioxane (75 mL) was stirred at 100 °C under N_2 for 16 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (PE:EtOAc, 4:1) to afford the title product (2 g, 98%) as a yellow solid. LCMS (Method A): 4.78 min; m/z: 537.3 $[M+H]^+$.

Step 4: 3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carboxamide

A mixture of 3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carbonitrile (1.9 g, 3.54 mmol), 30% aq. H_2O_2 (100 mL) 5% aq. NaOH (10 mL) and DMSO (100 mL) in EtOH (200 mL) was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure, diluted with water (60 mL) to form a precipitate. The precipitated solids were collected by filtration and dried under reduced pressure to afford the title product (1.8 g, 92%) as a white solid. LCMS (Method A): 4.45 min; m/z: 555.2 $[M+H]^+$.

Step 5: 3-[4-amino-3-(benzyloxy)phenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carboxamide

A mixture of 3-[3-(benzyloxy)-4-nitrophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carboxamide (500 mg, 901 µmol), sat. aq. NH_4Cl (2 mL) and Zn dust (294 mg, 4.50 mmol) in MeOH (8 mL) was stirred at 60 °C overnight. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (300 mg, 63%) as a yellow solid. LCMS (Method A): 3.27 min; m/z: 525.3 $[M+H]^+$.

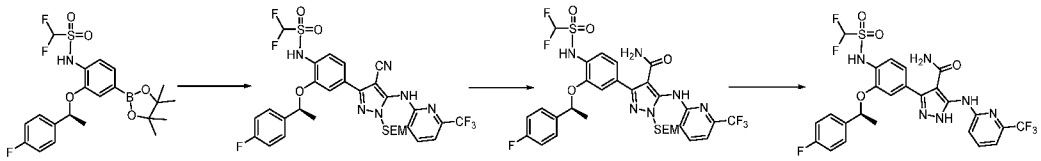
Step 6: 3-[3-(benzyloxy)-4-ethanesulfonamidophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl) pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 3-[4-amino-3-(benzyloxy)phenyl]-1-tert-butyl-5-{[6-(trifluoromethyl)pyridin-2-yl] amino}-1H-pyrazole-4-carboxamide (200 mg, 0.38 mmol) and $EtSO_2Cl$ (73.4 mg, 0.57 mmol) in pyridine (5 mL) was stirred at 35 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (140 mg, 60%) as a yellow solid. LCMS (Method A): 4.28 min; m/z: 617.2 $[M+H]^+$.

Step 7: 3-(3-(benzyloxy)-4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl) amino)- 1H-pyrazole-4-carboxamide (compound 46)

A solution of 3-[3-(benzyloxy)-4-ethanesulfonamidophenyl]-1-tert-butyl-5-{[6-(trifluoromethyl) pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (120 mg, 194 µmol) in TFA (2 mL) and DCM (2 mL) was stirred at 30 °C for 1 h. The reaction mixture was concentrated under reduced pressure, neutralized to pH 7-8 with sat. aq. Na_2CO_3 and diluted with H_2O (10 mL). The precipitated solids were collected by filtration and dried under reduced pressure to afford the title product (50 mg, 46%) as a white solid. LCMS (Method A): 4.13 min; m/z: 561.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.78 (s, 1H), 9.19 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.63-7.15 (m, 10H), 6.21 (br s, 1H), 5.21 (s, 2H), 3.06 (q, J = 6.8 Hz, 2H), 1.17 (t, J = 6.8 Hz, 3H).

Compound 229



Step 1: N-[4-(4-cyano-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl)-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1,1-difluoromethanesulfonamide

A mixture of 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (Intermediate C11, 200 mg, 424 µmol), 3-bromo-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (196 mg, 424 µmol), $Pd(dppf)Cl_2$.DCM (34.6 mg, 42.4 µmol), Na_2CO_3 (89.8 mg, 848 µmol) and 80% aq.

1,4-dioxane (15 mL) was stirred at 100 ºC under N_2. After 1 h, the reaction mixture was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 30:1) to afford the title product (190 mg, 61%) as a yellow solid. LCMS (Method A): 4.35 min; m/z: 725.2 $[M+H]^+$.

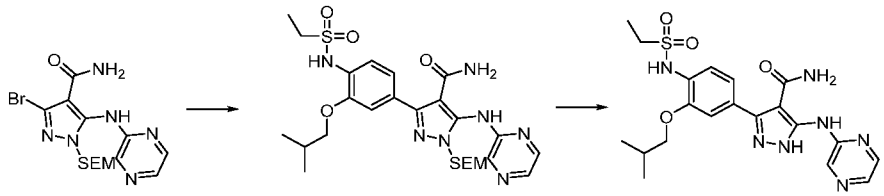
Step 2: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A solution of N-[4-(4-cyano-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl)-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1,1-difluoromethanesulfonamide (160 mg, 220 µmol) and Ghaffar-Parkins catalyst (16 mg, 37.4 µmol) in 50% aq. 1,4-dioxane (4 mL) was stirred at 100 ºC under N_2. After 16 h, the reaction mixture was diluted with H_2O (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 30:1) to afford the title product (70.0 mg, 43%) as a yellow solid. LCMS (Method D): 6.41 min; m/z: 745.0 $[M+H]^+$.

Step 3: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (compound 229)

A solution of 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (45 mg, 60.4 µmol) in DCM:TFA (4:1, 2.5 mL) was stirred at RT for 5 min. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified sequentially four times by prep-TLC (DCM:MeOH, 60:1) to afford the title compound (19.2 mg, 52%) as a white solid. LCMS (Method A): 4.03 min; m/z: 615.1 $[M+H]^+$. ^1H NMR: (400 MHz, DMSO-d_6): 13.01 (s, 1H), 10.55 (s, 1H), 9.67 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.99-7.95 (m, 1H), 7.60-7.57 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.21-7.14 (m, 5H), 7.02 (t, J = 52.8 Hz, 1H), 6.12 (br s 1H), 5.65 (m, 1H), 1.58 (d, J = 6.0 Hz, 3H).

Compound 45



Step 1: 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyrazin-2-ylamino)-1- ((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

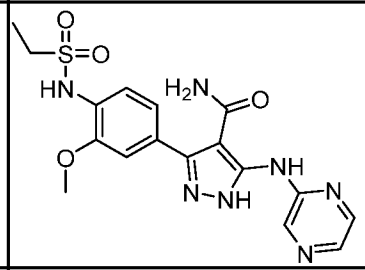
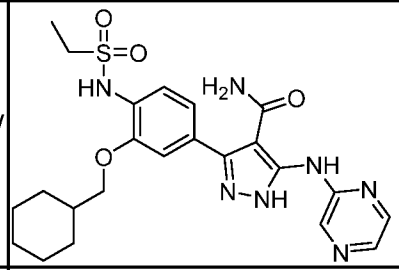
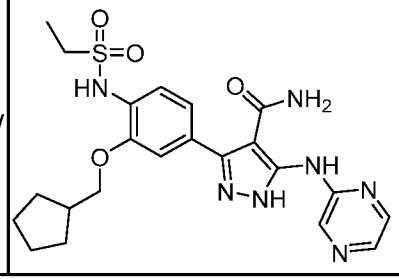
A mixture of 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B4, 100 mg, 0.2419 mmol), N-(2-isobutoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide (Intermediate C9, 120 mg, 0.3130 mmol), $Pd(dppf)Cl_2$ (17.7 mg, 24.1 µmol) and Na_2CO_3 (76.9 mg, 0.7257 mmol) in degassed 70% aq. 1,4-dioxane (6.5 mL) was stirred at 100 ºC for 2 h under microwave irradiation. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by prep-TLC (DCM:MeOH, 18:1) to afford the title product (90 mg, 63%) as a yellow solid. LCMS (Method A): 4.16 min; m/z: 590.2 $[M+H]^+$.

Step 2: 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyrazin-2-ylamino)-1H- pyrazole-4-carboxamide (compound 45)

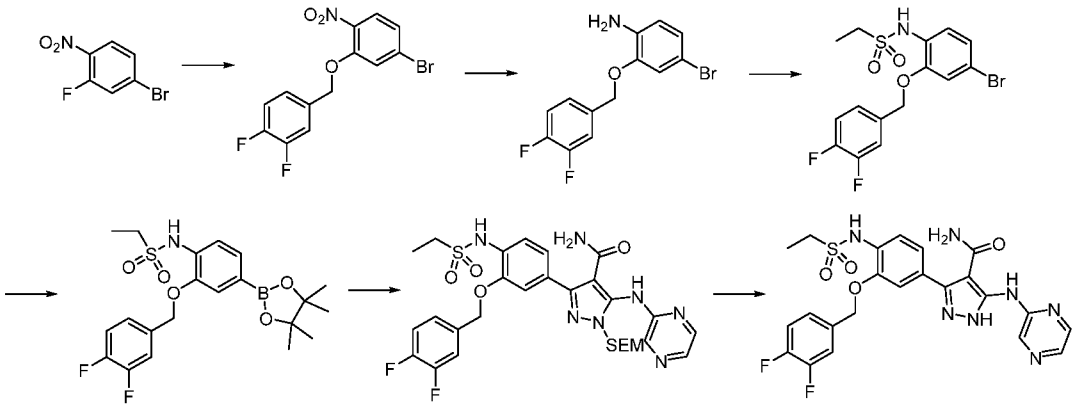
A solution of 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (90 mg, 0.1525 mmol) in DCM (3 mL) and TFA (3 mL) was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure, neutralized to pH 7-8 with sat. aq. Na_2CO_3 and then diluted with H_2O (30 mL). The precipitated solids were collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (25 mg, 36%) as a white solid. LCMS (Method A): 3.45 min; m/z: 460.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 8.27 (s, 1H), 13.00 (s, 1H), 9.63 (s, 1H), 9.26 (s, 1H), 9.05 (s, 1H), 8.22 (s, 1H), 8.12 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.29 (s, 1H), 3.84 (d, J = 6.4 Hz, 2H), 3.13 (q, J = 7.2 Hz, 2H), 2.14 (s, 1H), 1.27 (t, J = 7.6 Hz, 3H), 1.03 (d, J = 6.4 Hz, 6H).

According to the method described for the synthesis of 3-(4-(ethylsulfonamido)-3-isobutoxyphenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide, the following compounds (Table 19) were similarly prepared using the appropriate intermediate C in step 1:

Table 19

Compound no	Name	Structure	LCMS data	^{1}H NMR data	SM
61	3-(4-(ethylsulfonamido)-3-methoxyphenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.86 min; m/z: 418.1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (s, 1H), 8.40 (s, 1H), 8.24-8.21 (m, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 1.2 Hz, 1H), 6.96 (s, 1H), 5.53 (s, 2H), 3.94 (s, 3H), 3.14 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).	Intermediate C10
47	3-(3-(cyclohexylmethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.82 min; m/z: 500.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (s, 1H), 9.64 (s, 1H), 9.26 (s, 1H), 9.03 (br s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.62 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 5.6 Hz, 2H), 3.11 (q, *J* = 7.2 Hz, 2H), 1.91-1.68 (m, 7H), 1.28-1.25 (m, 5H), 1.07-1.04 (m, 2H).	Intermediate C3
40	3-(3-(cyclopentylmethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.63 min; m/z: 486.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.98 (s, 1H), 9.64 (s, 1H), 9.26 (s, 1H), 9.00 (s, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.24 (s, 1H), 3.94 (d, *J* = 6.8 Hz, 2H), 3.12 (q, *J* = 6.8 Hz, 2H), 2.41 (m, 1H), 1.83 (m, 2H), 1.58 (m, 4H), 1.37 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).	Intermediate C8

Compound 1



Step 1: 4-bromo-2-[(3,4-difluorophenyl)methoxy]-1-nitrobenzene

To a solution of (3,4-difluorophenyl)methanol (981 mg, 6.81 mmol) in THF (15 mL) at 0 ºC, was added NaH (489 mg, 20.4 mmol). After 10 min, 4-bromo-2-fluoro-1-nitrobenzene (1.5 g, 6.81 mmol) was added, and the resulting mixture was stirred at RT for 2 h. The reaction mixture was diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 30:1) to afford the title product (1.8 g, 77%) as a white solid.

Step 2: 4-bromo-2-[(3,4-difluorophenyl)methoxy]aniline

A mixture of 4-bromo-2-[(3,4-difluorophenyl)methoxy]-1-nitrobenzene (1 g, 2.90 mmol), sat. aq. NH_4Cl (5 mL) and Zn dust (941 mg, 14.4 mmol) in MeOH (10 mL) was stirred at 60 °C for 3 h. The reaction mixture was diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (810 mg, 89%) as a white solid. LCMS (Method A): 4.18 min; m/z: 314.0, 316.0 $[M+H]^+$.

Step 3: N-{4-bromo-2-[(3,4-difluorophenyl)methoxy]phenyl}ethane-1-sulfonamide

A mixture of 4-bromo-2-[(3,4-difluorophenyl)methoxy]aniline (800 mg, 2.54 mmol), $EtSO_2Cl$ (489 mg, 3.81 mmol) and pyridine (8 mL) in $CHCl_3$ (8 mL) was stirred at RT for 16 h. The reaction mixture was diluted with H_2O (200 mL) and then extracted with DCM (3 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column

chromatography (PE:EtOAc, 3:1) to afford the title product (720 mg, 70%) as a white solid. LCMS (Method A): 4.26 min; m/z: 427.9, 429.9 $[M+H]^+$.

Step 4: N-{2-[(3,4-difluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide

A mixture of N-{4-bromo-2-[(3,4-difluorophenyl)methoxy]phenyl}ethane-1-sulfonamide (600 mg, 1.47 mmol), $Pd(dppf)Cl_2$ (1.07 g, 1.47 mmol), KOAc (432 mg, 4.41 mmol) and B_2pin_2 (558 mg, 2.20 mmol) in 1,4-dioxane (20 mL) was stirred at 110 °C for 16 h. The reaction mixture was diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (480 mg, 72%) as a white solid. LCMS (Method A): 4.46 min; m/z: 476.4 $[M+H]^+$.

Step 5: 3-{3-[(3,4-difluorophenyl)methoxy]-4-ethanesulfonamidophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

To a mixture of N-{2-[(3,4-difluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (200 mg, 441µmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B4, 182 mg, 441 µmol), $Pd(dppf)Cl_2$ (32.2 mg, 44.1 µmol) and Na_2CO_3 (139 mg, 1.32 mmol) in 70% aq. 1,4-dioxane (15 mL) was stirred at 110 °C for 16 h. The reaction mixture was diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 30:1) to afford the title product (180 mg, 62%) as a yellow oil. LCMS (Method A): 4.15 min; m/z: 660.2 $[M+H]^+$.

Step 6: 3-(3-((3,4-difluorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (compound 1)

A solution of 3-{3-[(3,4-difluorophenyl)methoxy]-4-ethanesulfonamidophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (150 mg, 227 µmol) in DCM (5 mL) and TFA (5 mL) was stirred at 25 °C for 3 h. The reaction mixture was neutralized to pH 7-8 with sat. aq. $NaHCO_3$ and then extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 30:1) to afford the title product (50 mg, 41%) as a white solid. LCMS (Method A): 3.59 min; m/z:

530.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.64 (s, 1H), 9.26 (s, 2H), 8.23 (s, 1H), 8.12 (s, 1H), 7.78-7.74 (m, 1H), 7.52-7.41 (m, 3H), 7.20 (d, J = 8.4 Hz, 1H), 6.22 (s, 1H), 5.21 (s, 2H), 3.11-3.05 (m, 2H), 1.19 (t, J =7.2 Hz, 3H).

According to the method described for the synthesis of 3-(3-((3,4-difluorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-yl amino)-1H-pyrazole-4-carboxamide, the following compounds (Table 20) were similarly prepared using the appropriate alcohol in step 1:

Table 20

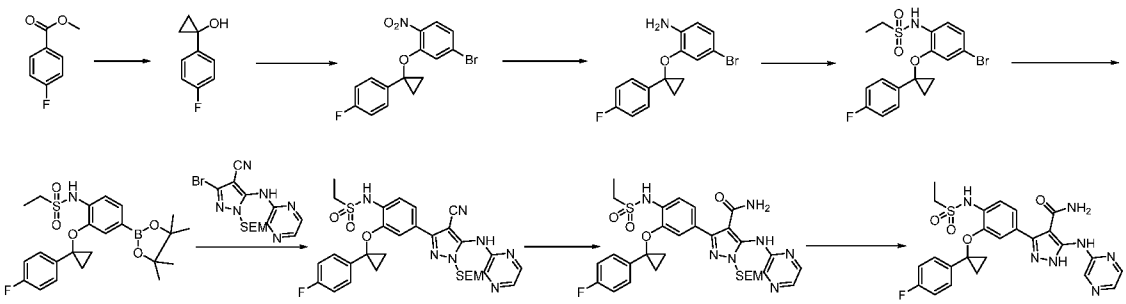
Compound No	Name	Structure	LCMS data	^{1}H NMR data	SM
25	3-(3-(benzyloxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.32 min; m/z: 494.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.05 (s, 1H), 9.61 (s, 1H), 9.24 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.40 (m, 5H), 7.19 (d, J = 7.6 Hz, 1H), 6.23 (s, 1H), 5.20 (s, 2H), 3.05 (q, J = 6.8 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	phenylmethanol
42	3-(3-((4-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.65 min; m/z: 528.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 9.63 (s, 1H), 9.23 (d, J = 9.2 Hz, 2H), 8.22 (q, J = 1.6 Hz, 1H), 8.11 (d, J = 2.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.45 (q, J = 8.4 Hz, 4H),7.20 (q, J = 1.6 Hz, 1H), 5.75 (s, 1H), 5.20 (s, 1H), 3.05 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).	(4-chlorophenyl)methanol
41	3-(3-((3-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.65 min; m/z: 528.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.87 (s, 1H), 8.27 (s, 1H), 8.08 (d, J = 2.4 Hz, 2H), 7.60 (t, J = 8.0 Hz, 2H), 7.46-7.32 (m, 4H), 7.21 (d, J = 7.6 Hz, 2H), 5.26 (s, 2H), 3.12 (q, J = 7.6 Hz, 4H), 1.29 (s, 1H).	(3-chlorophenyl)methanol

28	3-(4-(ethylsulfonamido)-3-(226yridine-4-ylmethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.44 min; m/z: 495.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.65 (s, 1H), 9.25 (s, 1H), 8.66 (s, 2H), 8.22 (s, 1H), 8.12 (s, 1H), 7.61 (d, J = 3.6 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.26 (s, 1H), 5.28 (s, 2H), 3.10 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H).	pyridin-4-ylmethanol
32	3-(4-(ethylsulfonamido)-3-(226yridine-3-ylmethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.41 min; m/z: 495.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (s, 1H), 9.64 (s, 1H), 9.27 (s, 1H), 8.83 (s, 1H), 8.60 (s, 1H), 8.22 (s, 1H), 8.12 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.47 (s, 3H), 7.21 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 5.26 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).	pyridin-3-ylmethanol
2	3-(4-(ethylsulfonamido)-3-((2-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.34 min; m/z: 512.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.74 (s, 1H), 9.30 (s, 1H), 8.22 (t, J = 2.4 Hz, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.22-7.14 (m, 3H), 7.09 (s, 1H), 6.96 (q, J = 1.6 Hz, 1H), 5.17 (s, 2H), 4.09 (d, J = 4.4 Hz, 2H), 1.23 (s, 3H).	(2-fluorophenyl)methanol

24	3-(4-(ethylsulfonamido)-3-(4-fluorophenethoxy)phenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.58 min; m/z: 526.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 9.62 (s, 1H), 9.24 (s, 1H), 8.95 (s, 1H), 8.21 (q, J = 1.6 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.44-7.40 (m, 3H), 7.32 (s, 1H), 7.17-7.11 (m, 3H), 4.28 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 6.8 Hz, 2H), 2.96 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H).	2-(4-fluorophenyl)ethan-1-ol
224	3-{4-ethanesulfonamido-3-[(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)oxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide		LCMS (Method A): 5.40 min; m/z: 456.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.65 (s, 1H), 9.27 (s, 1H), 8.93 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.54 (s, 1H), 7.44-7.38 (m, 3H), 7.18 (dd, J = 8.4, 1.6 Hz, 1H), 7.05-7.02 (m, 2H), 8.23 (t, J = 1.2 Hz, 1H), 2.96 (t, J = 5.2 Hz, 2H), 2.85-2.75 (m, 2H), 2.13-1.95 (m, 3H), 1.75-1.72 (m, 1H), 1.04 (d, J = 8.4 Hz, 3H).	6-fluoro-1,2,3,4-tetrahydronaphthalen-1-ol
228	3-(4-ethanesulfonamido-3-{[2-(4-fluorophenyl)propan-2-yl]oxy}phenyl)-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.44 min m/z:540.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.85 (s, 1H), 9.40 (s, 1H), 9.13 (s, 2H), 8.19 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.49 (q, J = 4.8 Hz, 3H), 7.17-7.06 (m, 3H), 6.44 (s, 1H), 3.17 (q, J = 7.2 Hz, 2H), 1.77 (s, 6H), 1.36 (t, J = 8.4 Hz, 3H).	2-(4-Fluorophenyl)-2-propanol

232	3-[4-ethanesulfonamido-3-(1,2,3,4-tetrahydronaphthalen-1-yloxy)phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.51 min; m/z: 534.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 9.65 (s, 1H), 9.27 (s, 1H), 8.22-8.19 (m, 1H), 8.02-8.00 (m, 1H), 7.54 (s, 1H), 7.44-7.42 (m, 1H), 7.35 (d, J = 7.2 Hz, 2H), 7.28-7.25 (m, 1H), 7.21-7.26 (m, 3H), 5.67 (s, 1H), 2.97-2.93 (m, 2H), 2.89-2.84 (m, 1H), 2.78-2.71 (m, 1H), 2.16-2.10 (m, 1H), 2.05-1.98 (m, 2H), 1.76-1.72 (m, 1H), 1.03 (t, J = 7.2 Hz, 3H).	1,2,3,4-tetrahydronaphthalen-1-ol
7	3-(3-((1-acetylpiperidin-4-yl)methoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.02 min; m/z: 543.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.63 (s, 1H), 9.26 (s, 1H), 9.08 (s, 1H), 8.24 (s, 1H), 8.11 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.28 (s, 1H), 7.16 (m, J = 8.4 Hz, 1H), 3.93 (d, J = 6.4 Hz, 2H), 3.10 (m, 4H), 2.58 (m, 2H), 2.10 (br s, 1H), 2.00 (s, 3H), 1.99 (s, 1H), 1.87 (t, J = 17.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).	1-[4-(hydroxymethyl)piperidin-1-yl]ethan-1-one

Compound 248



Step 1: 1-(4-fluorophenyl)cyclopropan-1-ol

To a solution of methyl 4-fluorobenzoate (9.0 g, 58.3 mmol) and Ti(O*i*-Pr)$_4$ (29.5 g, 104 mmol) in THF (180 mL) at 0 ºC, was added EtMgBr (23.1 g, 174 mmol), and the mixture was stirred at RT for 16 h. The reaction mixture was quenched with sat. NH_4Cl (100 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (PE:EtOAc, 20:1) to afford the title product (7.5 g, 85%) as a yellow oil.

Step 2: 4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]-1-nitrobenzene

To a solution of 1-(4-fluorophenyl)cyclopropan-1-ol (4.5 g, 29.5 mmol) in THF (90 mL) at 0 ºC, was added NaH (3.20 g, 80.4 mmol). After 15 min, 4-bromo-2-fluoro-1-nitrobenzene (5.89 g, 26.8 mmol) was added, and the mixture was stirred at RT for 16 h. The mixture was quenched with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product (10.0 g, >100%) as a brown oil.

Step 3: 4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]aniline

A mixture of 4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]-1-nitrobenzene (13.0 g, 36.9 mmol), Zn powder (12.0 g, 184 mmol), sat. NH_4Cl (35 mL) and MeOH (105 mL) was stirred at 60 ºC for 2 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the crude product (10.0 g, 42%) as a brown oil. LCMS (Method D): 5.20 min; m/z: 322.0, 324.0 $[M+H]^+$.

Step 4: N-{4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]phenyl}ethane-1-sulfonamide

A mixture of 4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]aniline (2.0 g, 6.20 mmol) and $EtSO_2Cl$ (956 mg, 7.44 mmol) in $CHCl_3$:pyridine (4:1, 25 mL) was stirred at RT for 16 h. The reaction

mixture was concentrated and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 30:1) to afford the title product (1.0 g, 39%) as a yellow solid. LCMS (Method D): 4.05 min; m/z: 322.0, 324.0 $[M+H]^+$.

Step 5: N-{2-[1-(4-fluorophenyl)cyclopropoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide

A mixture of N-{4-bromo-2-[1-(4-fluorophenyl)cyclopropoxy]phenyl}ethane-1-sulfonamide (500 mg, 1.20 mmol), B_2pin_2 (454 mg, 1.79 mmol), $Pd(dppf)Cl_2$ (87.7 mg, 0.12 mmol), KOAc (235 mg, 2.40 mmol) and 1,4-dioxane (10 mL) was stirred at 100 ºC under N_2 for 16 h. The mixture was concentrated, and the residue was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (PE:EtOAc, 20:1) to afford the title product (240 mg, 43%) as a yellow solid. LCMS (Method D): 5.48 min; 462.2 $[M+H]^+$.

Step 6: N-(4-{4-cyano-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl}-2-[1-(4-fluorophenyl)cyclopropoxy]phenyl)ethane-1-sulfonamide

A mixture of N-{2-[1-(4-fluorophenyl)cyclopropoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (250 mg, 0.54 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (Intermediate B3, 214 mg, 0.54 mmol), $Pd(dppf)Cl_2$.DCM (44.2 mg, 0.05 mmol), Na_2CO_3 (114 mg, 1.08 mmol) and 80% aq. 1,4-dioxane (10 mL) was heated at 100 ºC with microwave irradiation for 2 h. The reaction mixture was concentrated, diluted with H_2O (100 mL) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (50 mg, 14%) as a yellow solid. LCMS (Method D): 5.48 min; 650.2 $[M+H]^+$.

Step 7: 3-{4-ethanesulfonamido-3-[1-(4-fluorophenyl)cyclopropoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1Hpyrazole-4-carboxamide

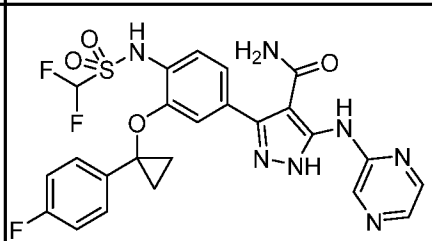
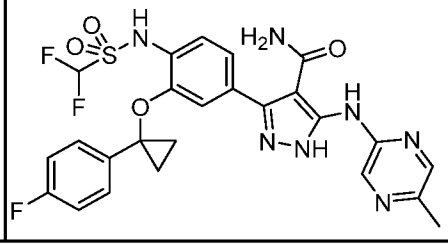
A mixture of N-(4-{4-cyano-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl}-2-[1-(4-fluorophenyl)cyclopropoxy]phenyl)ethane-1-sulfonamide (50 mg, 76.9 µmol), Ghaffar-Parkins catalyst (20 mg, 46.8 µmol) and 65% aq. 1,4-dioxane (4.5 mL) was stirred at 100 ºC for 16 h. The mixture was concentrated, and the residue diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (30 mg, 59%) as a yellow solid. LCMS (Method D): 4.82 min; m/z: 668.2 $[M+H]^+$.

Step 8: 3-{4-ethanesulfonamido-3-[1-(4-fluorophenyl)cyclopropoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 248)

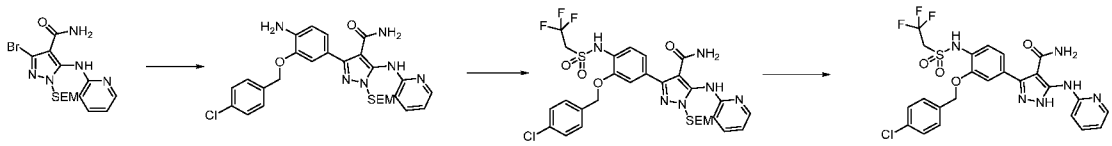
A mixture of 3-{4-ethanesulfonamido-3-[1-(4-fluorophenyl)cyclopropoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1Hpyrazole-4-carboxamide (30 mg, 44.9 µmol) in DCM:TFA (1:1, 3 mL) was stirred at RT for 2 h. The mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then washed with MeOH to afford the title compound (10 mg, 41%) as a yellow solid. LCMS (Method A): 3.87 min; m/z: 538.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 12.93 (s, 1H), 9.59 (s, 1H), 9.22 (s, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.8 Hz, 2H), 7.13 (t, J = 8.8 Hz, 3H), 7.05 (s, 1H), 6.21 (s, 1H), 3.16 (q, J = 6.8 Hz, 2H), 1.47 (s, 2H), 1.41 (s, 2H), 1.31 (t, J = 7.2 Hz, 3H).

The compounds below (Table 21) were similarly prepared following the synthesis of Compound 248, using the appropriate sulfonyl chloride in step 4 and appropriate Intermediate B in step 6:

Table 21

Compound No	Name	Structure	LCMS data	^{1}H NMR data	Sulfonyl chloride	Intermediate B
307	3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)cyclopropoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.48 min; m/z: 560.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (s, 1H), 9.50 (s, 1H), 8.19 (s, 1H), 8.08 (s, 1H), 7.40-6.99 (m, 9H), 6.19 (s, 1H), 1.41 (s, 4H).	difluoromethanesulfonyl chloride	Intermediate B3
290	3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)cyclopropoxy)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.59 min; m/z 574.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 9.42 (s, 1H), 9.11 (s, 1H), 8.09 (s, 1H), 7.40-7.00 (m, 9H), 2.38 (s, 3H), 1.42 (d, J =6.8 Hz, 4H).	difluoromethanesulfonyl chloride	Intermediate B5

Compound 269



Step 1: 3-{4-amino-3-[(4-chlorophenyl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B2, 500 mg, 1.21 mmol), 2-[(4-chlorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (435 mg, 1.21 mmol), $Pd(dppf)Cl_2$ (98.8 mg, 121 µmol) and Na_2CO_3 (256 mg, 2.42 mmol) in 80% aq. 1,4-dioxane (12.5 mL) was irradiated at 100 ºC in a microwave reactor. After 1 h, the reaction mixture was concentrated and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 20:1) to afford the title product (680 mg, 95%) as a yellow solid. LCMS (Method A): 4.43 min; m/z: 595.1 $[M+H]^+$.

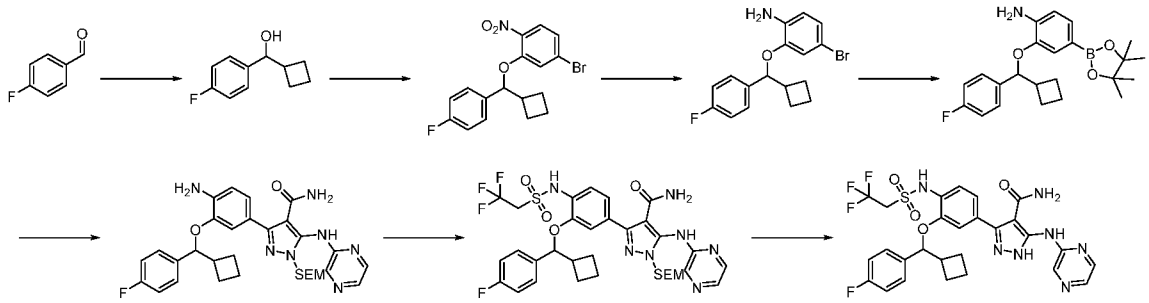
Step 2: 3-{3-[(4-chlorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

To a solution of 3-{4-amino-3-[(4-chlorophenyl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (300 mg, 530 µmol) in $CHCl_3$:pyridine (1:1, 6 mL), was added 2,2,2-trifluoroethane-1-sulfonyl chloride (145 mg, 795 µmol). The mixture was stirred at RT for 16 h and then concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated. The residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (100 mg, 33%) as a yellow solid. LCMS (Method A): 3.56 min; m/z: 710.5 $[M+H]^+$.

Step 3: 3-{3-[(4-chlorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 269)

A solution of 3-{3-[(4-chlorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (100 mg, 28.1 μmol) in DCM:TFA (1:1, 6 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (30 mg, 26%) as a yellow solid. LCMS (Method A): 3.41 min; m/z: 580.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.56 (s, 1H), 9.67 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.69 (t, J = 6.8 Hz, 1H), 7.52-7.32 (m, 8H), 6.96 (d, J = 11.2 Hz, 2H), 6.84 (d, J = 6.4 Hz, 1H), 5.07 (s, 1H), 3.67-3.58 (m, 2H).

Compound 266



Step 1: cyclobutyl(4-fluorophenyl)methanol

To a solution of 4-fluorobenzaldehyde (3.10 g, 25.0 mmol) in THF (10 mL) at 0 °C, was added c-BuMgBr (21.40 g, 161 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was quenched with sat. NH_4Cl (100 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 20:1 to 5:1) to afford the title product (4.30 g, 95%) as a colorless oil. ^1H NMR (400 MHz, DMSO-d_6): 7.38-7.29 (m, 2H), 7.15-7.05 (m, 2H), 5.17 (d, J = 4.4 Hz, 2H), 4.48 (d, J = 5.6 Hz, 1H), 2.46-2.38 (m, 1H), 1.94-1.61 (m, 5H).

Step 2: 4-bromo-2-[cyclobutyl(4-fluorophenyl)methoxy]-1-nitrobenzene

To a mixture of cyclobutyl(4-fluorophenyl)methanol (4.30 g, 23.8 mmol) in THF (100 mL) at 0 ºC, was added NaH (2.85 g, 71.4 mmol). After 30 min, 4-bromo-2-fluoro-1-nitrobenzene (5.23 g, 23.8 mmol) was added, and the mixture was stirred at RT for 16 h. The reaction mixture was concentrated, and the residue diluted with H_2O (200 mL) and extracted with EtOAc (2 x 80 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title product (6.50 g, 72%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.80 (d, J = 8.8 Hz, 1H), 7.43-7.42 (m, 3H), 7.26-7.24 (m, 1H), 7.22-7.17 (m, 2H), 5.70 (d, J = 7.2 Hz, 1H), 2.73-2.68 (m, 1H), 2.05-1.74 (m, 6H).

Step 3: 4-bromo-2-[cyclobutyl(4-fluorophenyl)methoxy]aniline

A mixture of 4-bromo-2-[cyclobutyl(4-fluorophenyl)methoxy]-1-nitrobenzene (6.50 g, 17.0 mmol), Zn powder (5.55 g, 85.0 mmol), sat. NH_4Cl (30 mL) and MeOH (100 mL) was stirred at 60 ºC for 3 h. The reaction mixture was filtered, and the filtrate concentrated, diluted with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title product (6.00 g, 17.1 mmol) as a brown oil.

Step 4: 2-[cyclobutyl(4-fluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

A mixture of 4-bromo-2-[cyclobutyl(4-fluorophenyl)methoxy]aniline (1.0 g, 2.85 mmol), B_2pin_2 (723 mg, 2.85 mmol), $Pd(dppf)Cl_2$ (260 mg, 285 µmol), KOAc (559 mg, 5.70 mmol) and 1,4-dioxane (150 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated, and the residue diluted with H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (660 mg, 58%) as a black oil. LCMS (Method A): 4.67 min; m/z: 398.2 $[M+H]^+$.

Step 5: 3-{4-amino-3-[cyclobutyl(4-fluorophenyl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-[cyclobutyl(4-fluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (600 mg, 1.51 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (624 mg, 1.51 mmol), $Pd(dppf)Cl_2$.DCM (123 mg, 151 µmol), Na_2CO_3 (320 mg, 3.02 mmol) and 80% aq. 1,4-dioxane (100 mL) was stirred at 100 ºC under N_2. After 16 h the reaction mixture was concentrated, and the residue diluted with H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 60:1) to afford the title product (400 mg, 43%) as a brown solid. LCMS (Method A): 4.18 min; m/z: 604.3 $[M+H]^+$.

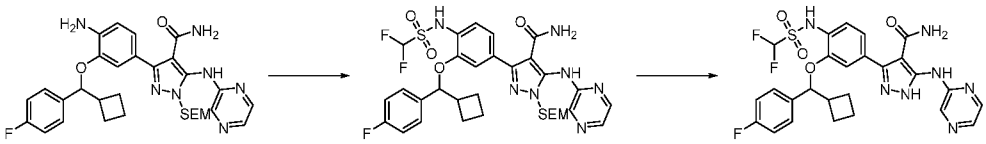
Step 6: 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{4-amino-3-[cyclobutyl(4-fluorophenyl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (400 mg, 662 µmol), 2,2,2-trifluoroethanesulfonyl chloride (181 mg, 993 µmol) and DCM:pyridine (1:1, 30 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, and the residue diluted with H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 50:1) to afford the title product (350 mg, 70%) as a brown solid. LCMS (Method A): 4.32 min; m/z: 750.3 $[M+H]^+$.

Step 7: 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 266)

A solution of 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (200 mg, 266 μmol) in DCM:TFA (10:1, 11 mL) was stirred at RT for 5 min. The reaction mixture was concentrated, and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 20:1) to afford the title compound (20.0 mg, 12%) as a white solid. LCMS (Method A): 3.85 min; m/z: 620.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.94 (s, 1H), 9.58 (s, 1H), 9.21 (s, 1H), 8.21-8.20 (m, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.59-7.56 (m, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.15-7.09 (m, 3H), 5.46-5.44 (m, 1H), 4.55-4.42 (m, 2H), 2.85-2.78 (m, 1H), 2.07-1.99 (m, 2H), 1.83 (s, 3H), 1.73-1.68 (m, 1H).

Compound 236



Step 1: 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[cyclobutyl(4-fluorophenyl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (700 mg, 1.15 mmol) and F_2CHSO_2Cl (258 mg, 1.72 mmol) in DCM:pyridine (1:1, 10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, and the residue was diluted with H_2O (80 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 55:1) to afford the title product (400 mg, 48%) as a yellow solid. LCMS (Method A): 4.37 min; 718.3 $[M+H]^+$.

Step 2: 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 236)

A solution of 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(difluoromethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (180 mg, 250 μmol) in DCM:TFA (8:1, 9 mL) was stirred at RT for 5 min. The reaction mixture was concentrated, and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-HPLC to afford the title compound (20 mg, 13%) as a white solid. LCMS (Method A): 3.74 min; m/z: 588.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.92 (s, 1H), 10.51 (s, 1H), 9.56 (s, 1H), 9.20 (s, 1H), 8.20 (s, 1H), 8.10-8.09 (m, 1H), 7.54-7.51 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.15-7.07 (m, 5H), 6.05 (s, 1H), 5.39 (d, J = 6.4 Hz, 1H), 2.80-2.74 (m, 1H), 2.17-2.09 (m, 1H), 2.03-1.90 (m, 2H), 1.84-1.72 (m, 3H).

The following compounds (Table 22) were similarly prepared from the appropriate benzyl alcohol 1-(4-fluorophenyl)-2-methoxyethan-1-ol following step 2 of Compound 266 synthesis according to the method described for the synthesis of compound 23.

Table 22

Compound no	Name	Structure	LCMS data	^{1}H NMR data
319	3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)-2-methoxyethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.34 min, m/z: 578.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.31 (s, 1H), 10.26 (s, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.19 (dd, J = 2.9, 1.4 Hz, 1H), 8.15 (d, J = 2.9 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.44-7.36 (m, 2H), 7.31 (s, 1H), 7.10 (t, J = 8.6 Hz, 2H), 6.92 (d, J = 1.9 Hz, 1H), 6.37 (t, J = 53.6 Hz, 1H), 4.98 (dd, J = 9.4, 2.8 Hz, 1H), 3.81 (dd, J = 10.4, 9.4 Hz, 1H), 3.57 (dd, J = 10.5, 2.9 Hz, 1H), 3.54 (s, 3H).
298	3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)-2-methoxyethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.54 min, m/z: 581.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.77 (s, 1H), 10.61 (s, 1H), 9.08 (s, 1H), 7.58 (dd, J = 8.6, 5.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 8.8 Hz, 2H), 7.16-6.89 (m, 3H), 6.55 (s, 1H), 6.03 (br s, 1H), 5.67 (dd, J = 7.2, 4.0 Hz, 1H), 3.81 (dd, J = 10.8, 7.1 Hz, 1H), 3.60 (dd, J = 10.8, 3.9 Hz, 1H), 3.32 (s, 3H), 2.35 (s, 3H).

The following compounds were similarly prepared from the appropriate benzyl alcohol following step 1 according to the method described for the synthesis of 3-{3-[cyclobutyl(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide:

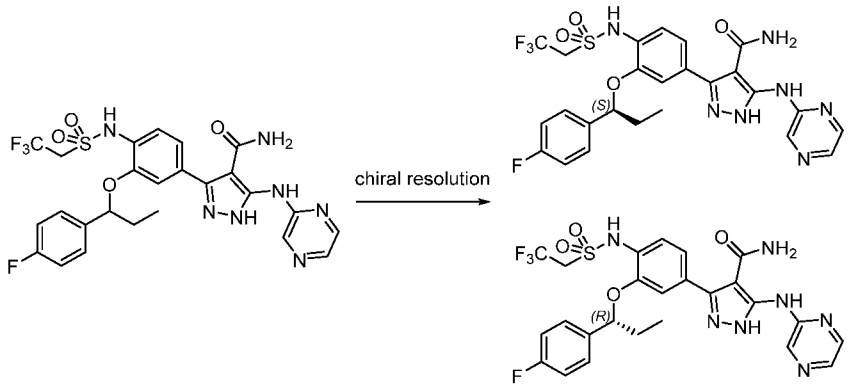
Compound 263



3-(3-(1-(4-fluorophenyl)propoxy)-4-(2,2,2-trifluoroethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide

A solution of 3-{3-[1-(4-fluorophenyl)propoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (90 mg, 124 µmol) in $CHCl_3$:TFA (1:1, 5 mL) was stirred at RT for 2 min. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then concentrated under reduced pressure. The crude residue was purified by prep-HPLC to afford the title compound (22.0 mg, 29%) as a white solid. LCMS (Method A): 3.67 min; m/z: 594.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 9.77 (s, 1H), 9.31 (br s, 1H), 8.36-8.29 (m, 1H), 8.21 (d, J = 2.8 Hz, 1H), 7.68-7.62 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.30-7.24 (m, 3H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 6.17 (br s, 1H), 5.54-5.44 (m, 1H), 4.50 (t, J = 7.2 Hz, 2H), 2.21-2.09 (m, 1H), 2.08-1.86 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H).

Compounds 250 and 251

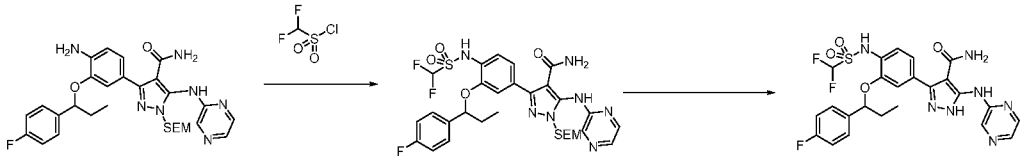


The racemic 3-(3-(1-(4-fluorophenyl)propoxy)-4-(2,2,2-trifluoroethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide was subjected to purification by chiral HPLC on a AD-H column using heptane:EtOH, 60:40 with 0.1% Et_2NH as the mobile phase.

Peak 1: (S)-3-(3-(1-(4-fluorophenyl)propoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide. Product retention time = 2.72 min. LCMS (Method A): 2.13 min; m/z: 594.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.95 (s, 1H), 9.93 (s, 1H), 9.60 (s, 1H), 9.22 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.56 (q, J = 4.8 Hz, 3H), 7.43 (d, J = 7.2 Hz, 1H), 7.18-7.10 (m, 5H), 5.40 (s, 1H), 4.48 (q, J = 6.4 Hz, 2H), 2.08-2.02 (m, 1H), 1.88-1.81 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H).

Peak 2: (R)-3-(3-(1-(4-fluorophenyl)propoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide. Product retention time = 7.29 min. LCMS (Method A): 2.13 min; m/z: 594.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 9.91 (s, 1H), 9.60 (s, 1H), 9.22 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.57 (q, J = 4.8 Hz, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.18-7.09 (m, 5H), 5.38 (s, 1H), 4.46 (q, J = 5.6 Hz, 2H), 2.07-2.02 (m, 1H), 1.87-1.80 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H).

Compound 233



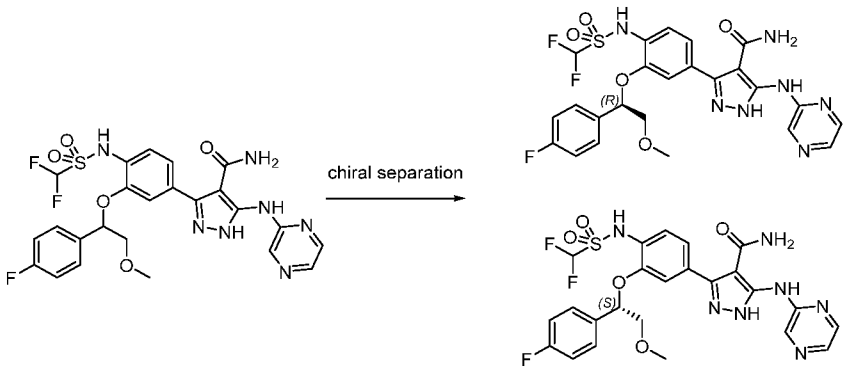
Step 1: 3-[4-(difluoromethanesulfonamido)-3-[1-(4-fluorophenyl)propoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[1-(4-fluorophenyl)propoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (420 mg, 726 μmol) and F_2CHSO_2Cl (141 mg, 943 μmol) in $CHCl_3$:pyridine (2:1, 15 mL) was stirred at RT for 5 min. The reaction mixture was concentrated and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 5:1 to 0:1) to afford the title product (190 mg, 37%) as a brown solid. LCMS (Method A): 4.10 min; m/z: 692.2 $[M+H]^+$.

Step 2:3-[4-(difluoromethanesulfonamido)-3-[1-(4-fluorophenyl)propoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A solution of 3-[4-(difluoromethanesulfonamido)-3-[1-(4-fluorophenyl)propoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (190 mg, 274 μmol) in DCM:TFA (1:1, 6 mL) was stirred at RT for 5 min. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then concentrated under reduced pressure. The crude residue was purified by prep-HPLC to afford the title compound (7.9 mg, 5%) as a white solid. LCMS (Method A): 3.57 min; m/z: 562.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.52 (br s, 1H), 9.53 (s, 1H), 9.19 (s, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.58-7.46 (m, 2H), 7.38 (d, J = 7.2 Hz, 1H), 7.22-7.06 (m, 4H), 6.10 (br s, 1H), 5.39 (s, 1H), 2.10-1.94 (m, 1H), 1.93-1.76 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H).

Compounds 272 and 273

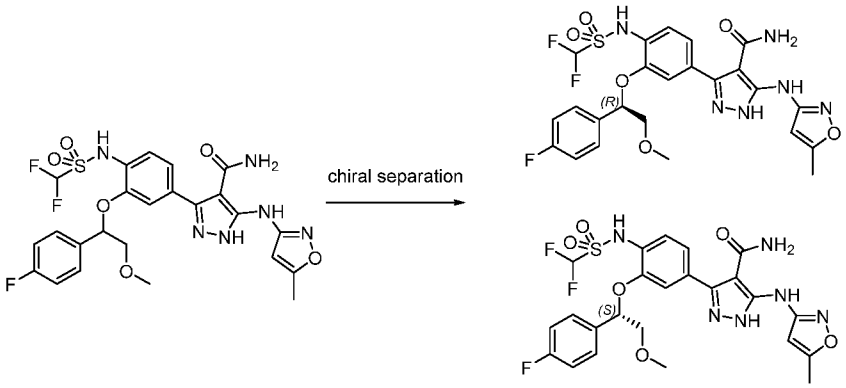


The racemic Compound 233 (232 mg) was subjected to purification by chiral HPLC. The separation was performed on a UniChiral CMD-5H column, (Column size 21.2mm I.D x 250 mm L. Mobile phase 100% Ethanol, flow rate 12 mL/min, temperature 25 °C). The enantiomeric excess was calculated on UniChiral CMD-5H, 4.6*250mm (100% MeOH, flow rate 1 mL/min, injection 10 µL, temperature 25 °C).

Peak 1: (R)-3-(4-((difluoromethyl)sulfonamido)-3-(2-(4-fluorophenyl)-3-methoxypropyl)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (91 mg, retention time 5.89 min, ee >99%).

Peak 2: (S)-3-(4-((difluoromethyl)sulfonamido)-3-(2-(4-fluorophenyl)-3-methoxypropyl)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (114mg, retention time 11.92 min, ee >99%).

Compounds 299 and 300

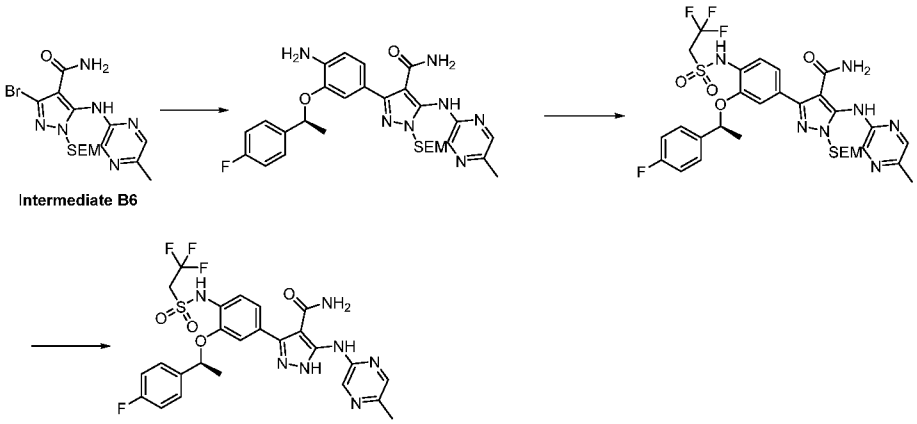


The racemic Compound 298 was subjected to purification by chiral SFC separation (CHIRALPAK IG 4.6*100 mm 3µm, CO_2:Methanol 55:45, 130 bars, flow rate 2.5 mL/min).

Peak 1: (R)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)-2-methoxyethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide.

Peak 2: (S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)-2-methoxyethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide.

Compound 264



Intermediate B6

Step 1: 3-{4-amino-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (Intermediate B6, 300 mg, 0.70 mmol), 2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (250 mg, 0.70 mmol), $Pd(dppf)Cl_2$ (57.3 mg, 0.07 mmol), Na_2CO_3 (222 mg, 2.10 mmol) and 80% aq. 1,4-dioxane (25 mL) was stirred at 100 ºC under N_2 for 16 h. The reaction mixture was concentrated, and the residue was

diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (220 mg, 54%) as a yellow solid. LCMS (Method A): 2.86 min; m/z: 578.3 $[M+H]^+$.

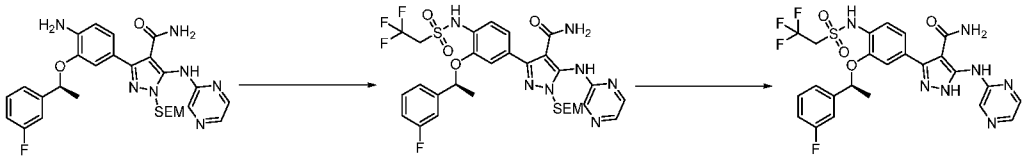
Step 2: 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole4-carboxamide (210 mg, 0.36 mmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (99 mg, 0.54 mmol) in DCM:pyridine (3:1, 20 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the crude residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (150 mg, 57%) as a yellow solid. LCMS (Method A): 3.37 min; m/z: 724.2 $[M+H]^+$.

Step 3: 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(5-methylpyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 264)

A solution of 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(5-methylpyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (190 mg, 0.26 mmol) in DCM:TFA (10:1, 21 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and then neutralized to pH 7-8 with sat. Na_2CO_3. The mixture was concentrated, and the residue was triturated with MeOH to afford the title compound (40 mg, 26%) as a white solid. LCMS (Method A): 1.95 min; m/z: 594.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 12.91 (s, 1H), 9.96 (s, 1H), 9.48 (s, 1H), 9.14 (s, 1H), 8.11 (s, 1H), 7.59 (t, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.20-7.11 (m, 5H), 5.65 (d, J = 6.0 Hz, 1H), 4.49-4.43 (m, 2H), 2.40 (s, 3H), 1.60 (t, J = 6.4 Hz, 3H).

Compound 265



Step 1: 3-{3-[(1S)-1-(3-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

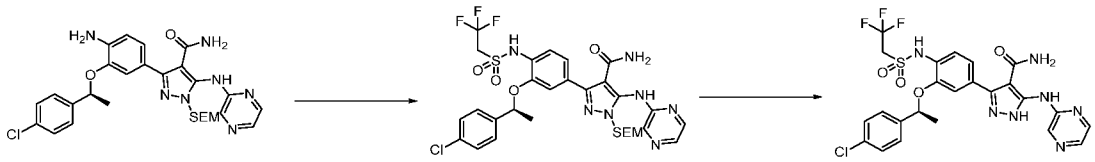
A solution of 3-{4-amino-3-[(1S)-1-(3-fluorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (200 mg, 0.35 mmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (77.6 mg, 0.42 mmol) in DCM:pyridine (3:1, 4 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (130 mg, 51%) as a white solid. LCMS (Method A): 3.30 min; m/z: 710.2 $[M+H]^+$.

Step 2: 3-{3-[(1S)-1-(3-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 265)

A solution of 3-{3-[(1S)-1-(3-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (130 mg, 0.18 mmol) in DCM:TFA (10:1, 13 mL) was stirred at RT for 16 h. The reaction mixture was neutralized with sat. Na_2CO_3 and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title compound (54 mg, 47%) as a white solid. LCMS (Method A): 3.52 min; m/z: 580.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.01 (s, 1H), 9.58 (s, 1H), 9.21 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.46-7.35 (m, 4H),

7.21-7.07 (m, 4H), 6.15 (s, 1H), 5.66 (q, *J* = 6.4 Hz, 1H), 4.48 (q, *J* = 4.4 Hz, 2H), 1.60 (d, *J* = 6.0 Hz, 3H).

Compound 259



Step 1: 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

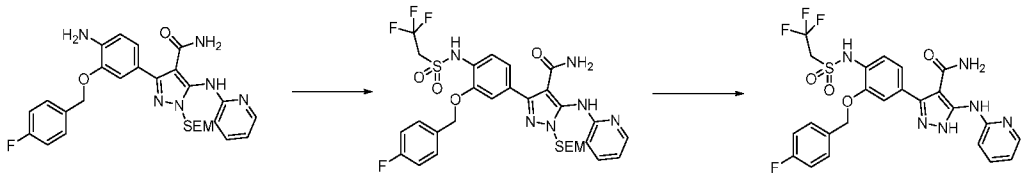
A solution of 3-{4-amino-3-[(1S)-1-(4-chlorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (240 mg, 413 µmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (112 mg, 619 µmol) in DCM:pyridine (3:1, 4 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (210 mg, 70%) as a white solid. LCMS (Method D): 5.27 min; m/z: 747.8 $[M+Na]^+$.

Step 2: 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 259)

A solution of 3-{3-[(1S)-1-(4-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (210 mg, 289 µmol) in DCM:TFA (10:1, 11 mL) was stirred at RT for 16 h. The reaction mixture was neutralized with sat. Na_2CO_3 and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 15:1) and then by prep-HPLC to afford the title compound (9.0 mg, 22%) as a white solid. LCMS (Method A): 2.17 min; m/z: 596.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.95 (s, 1H), 9.96 (s, 1H),

9.60 (s, 1H), 9.21 (s, 1H), 8.21 (s, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.42-7.40 (m, 3H), 7.20 (s, 1H), 7.14-7.12 (m, 1H), 6.16 (br s, 1H), 5.65-5.64 (m, 1H), 4.44-4.42 (m, 2H), 1.59 (d, *J* = 6.4 Hz, 3H).

Compound 239



Step 1: 3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

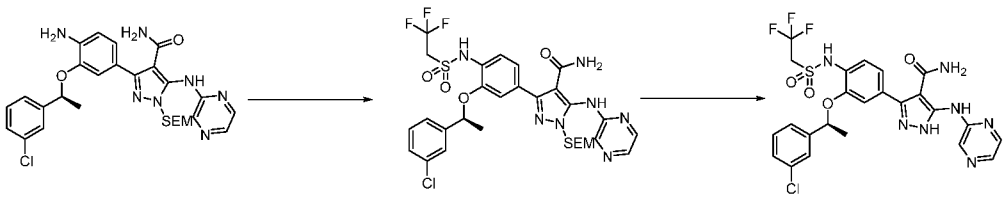
A solution of 3-{4-amino-3-[(4-fluorophenyl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (400 mg, 729 µmol), 2,2,2-trifluoroethane-1-sulfonyl chloride (145 mg, 795 µmol) and pyridine (209 mg, 2.65 mmol) in $CHCl_3$ (3 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, and the residue diluted with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (100 mg, 24%) as a yellow solid. LCMS (Method A): 4.13 min; m/z: 694.6 $[M+H]^+$.

Step 2: 3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 239)

A solution of 3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (200 mg, 287 µmol) in DCM:TFA (1:1, 6 mL) was stirred at RT for 1 h. The reaction mixture was concentrated, and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title

compound (100 mg, 62%) as a yellow solid. LCMS (Method A): 3.27 min; m/z: 565.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.90 (s, 1H), 9.95 (s, 1H), 9.52 (s, 1H), 8.19 (s, 1H), 7.98 (s, 1H), 7.72-7.58 (m, 3H), 7.39-7.16 (m, 6H), 6.85 (s, 1H), 6.09 (s, 1H), 5.18 (s, 2H), 4.24 (s, 2H).

Compound 256



Step 1: 3-{3-[(1S)-1-(3-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

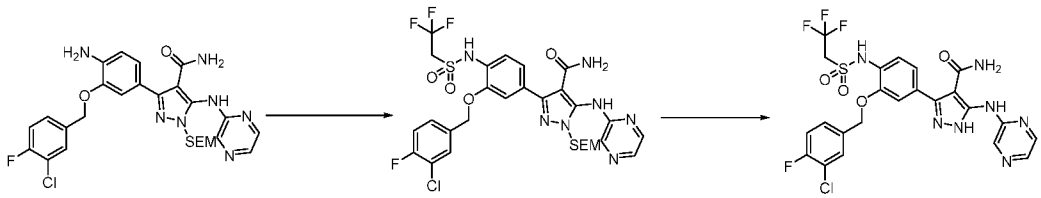
A solution of 3-{4-amino-3-[(1S)-1-(3-chlorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (180 mg, 310 µmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (84.5 mg, 465 µmol) in DCM:pyridine (1:1, 6 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, and the residue was diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (150 mg, 66%) as a yellow solid. LCMS (Method A): 4.19 min; m/z: 726.2 $[M+H]^+$.

Step 2: 3-{3-[(1S)-1-(3-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compounds 256)

A solution of 3-{3-[(1S)-1-(3-chlorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-

(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (150 mg, 206 µmol) in DCM:TFA (10:1, 16 mL) was stirred at RT for 16 h. The reaction mixture was neutralized to pH 7-8 with NH_4OH, diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried over (Na_2SO_4) and concentrated to afford the title compound (60 mg, 50%) as a yellow solid. LCMS (Method A): 1.99 min; m/z: 596.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.02 (s, 1H), 9.60 (s, 1H), 9.22 (s, 1H), 8.21 (s, 1H), 8.10 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.40-7.32 (m, 3H), 7.21 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.15 (br s, 3H), 5.65 (d, *J* = 6.0 Hz, 1H), 4.49-4.45 (m, 3H), 1.60 (d, *J* = 6.0 Hz, 3H).

Compound 225



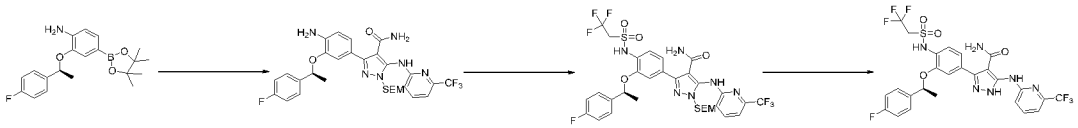
Step 1: 3-{3-[(3-chloro-4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{4-amino-3-[(3-chloro-4-fluorophenyl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-4-carboxamide (320 mg, 0.54 mmol), 2,2,2-trifluoroethane-1-sulfonyl chloride (149 mg, 0.82 mmol), pyridine (131 uL, 1.64 mmol) and $CHCl_3$ (10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 50:1) to afford the title product (100 mg, 25%) as a yellow solid. LCMS (Method A): 4.10 min; m/z: 730.2, 732.2 $[M+H]^+$.

Step 2: 3-{3-[(3-chloro-4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 225)

A solution of 3-{3-[(3-chloro-4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (100 mg, 136 µmol) in DCM:TFA (1:1, 8 mL) was stirred at RT for 10 min. The reaction mixture was concentrated, and the residue neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then triturated with Et_2O to afford the title compound (33.0 mg, 40%). LCMS (Method A): 3.60 min; m/z: 600.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.81 (br s, 1H), 9.28 (br s, 1H), 8.21 (s, 1H), 8.10 (s, 1H), 7.35 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51-7.32 (m, 4H), 7.01-6.98 (m, 2H), 5.07 (s, 2H), 3.65 (q, *J* = 10.8 Hz, 2H).

Compound 249



Step 1: 3-{4-amino-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-{[6-(trifluoromethyl) pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (360 mg, 1.00 mmol), 3-bromo-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (480 mg, 1 mmol), $Pd(dppf)Cl_2$ (81.6 mg, 100 µmol), Na_2CO_3 (211 mg, 2.00 mmol) and 80% aq. 1,4-dioxane (5 mL) was irradiated at 100 ºC in a microwave reactor. After 1 h, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 80:1) to afford the title

product (330 mg, 56%) as a brown solid. LCMS (Method A): 3.71 min; m/z: 631.3 $[M+H]^+$.

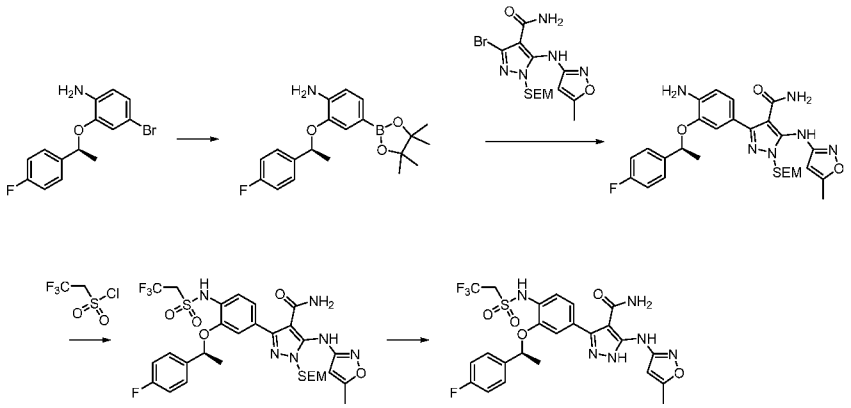
Step 2: 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (330 mg, 523 µmol) and 2,2,2-trifluoroethanesulfonyl chloride (143 mg, 784 µmol) in $CHCl_3$:pyridine (1:1, 20 mL) was stirred at RT. After 16 h, the mixture was concentrated and the residue diluted with H_2O (80 mL) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 70:1) to afford the title product (400 mg, 98%). LCMS (Method A): 3.84 min; m/z: 777.2 $[M+H]^+$.

Step 3: 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide (compound 249)

A solution of 3-{3-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-{[6-(trifluoromethyl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (150 mg, 193 µmol) in DCM:TFA (5:1, 12 mL) was stirred at RT for 5 min. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 20:1) afford the title compound (84 mg, 67%) as a yellow solid. LCMS (Method A): 4.08 min; m/z: 647.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 9.96 (s, 1H), 9.74 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.97 (t, J = 7.6 Hz, 1H), 7.62-7.59 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.23 (s, 1H), 7.20-7.13 (m, 3H), 5.66 (q, J = 6.0 Hz, 1H), 4.52-4.43 (m, 2H), 1.60 (d, J = 6.0 Hz, 3H).

Compound 311



Step 1: (S)-2-(1-(4-fluorophenyl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

Amixture of 4-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]aniline (3 g, 9.67 mmol), $Pd(dppf)Cl_2$ (789 mg, 967 µmol), AcOK (2.84 g, 29.0 mmol) and B_2pin_2 (2.94 g, 11.6 mmol) in 1,4-dioxane (20 mL) was stirred at 100 °C overnight. The mixture was filtered and the filtrste was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to give the title product (1.55 g, 45%) as a yellow oil. LCMS (Method A): 4.25 min; m/z: 358.2 $[M+H]^+$.

Step 2: (S)-3-(4-amino-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of (S)-2-(1-(4-fluorophenyl)ethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (1.5 g, 4.19 mmol), Na_2CO_3 (1.32 g, 12.5 mmol), $Pd(dppf)Cl_2$ (343 mg, 419 µmol) and 3-bromo-5-[(5-methyl-1,2-oxazol-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (1.91 g, 4.60 mmol) in degassed 1,4-dioxane (80 mL) and H_2O (20 mL) was stirred at 100 °C overnight. The mixture was filtered and the organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EtOAc,

1:1) to give the title product (900 mg, 38%) as a brown solid. LCMS (Method A): 3.10 min; m/z: 567.3 $[M+H]^+$.

Step 3: (S)-3-(3-(1-(4-fluorophenyl)ethoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

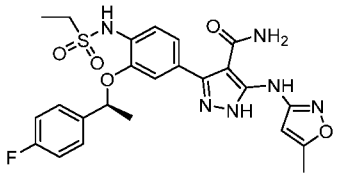
A mixture of (S)-3-(4-amino-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (400 mg, 705 µmol), 2,2,2-trifluoroethanesulfonyl chloride (154 mg, 846 µmol) and pyridine (278 mg, 3.52 mmol) in DCM (20 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 7:3 to 2:8) to give the title product (340 mg, 68%) as a brown solid. LCMS (Method B): 5.43 min; m/z: 713.1 $[M+H]^+$.

Step 4: (S)-3-(3-(1-(4-fluorophenyl)ethoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide (compound 311)

A mixture of (S)-3-(3-(1-(4-fluorophenyl)ethoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (300 mg, 420 µmol) in HCOOH (2 mL) was stirred at RT for 3 h. The mixture was basified to pH = 8 with sat. aq. $NaHCO_3$ and the organics were extracted with DCM (3 x 20mL). The combined organics were washed with water, dried (Na_2SO_4) and concentrated under reduced poressure. The residue was purified by silica gel column chromatography (PE:EtOAc, 95:5 to 5:95) to give the title product (103.3 mg, 42%) as a white solid. LCMS (Method A): 3.68 min; m/z: 583.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.76 (s, 1H), 9.96 (s, 1H), 9.16 (s, 1H), 7.58 (dd, J = 8.6, 5.6 Hz, 2H), 7.40 (d, J = 7.7 Hz, 1H), 7.21-7.13 (m, 3H), 7.09 (dd, J = 8.2, 1.6 Hz, 1H), 6.58 (s, 1H), 5.63 (q, J = 5.5 Hz, 1H), 4.51-4.34 (m, 2H), 2.35 (s, 3H), 1.58 (d, J = 6.3 Hz, 3H).

The following compound was prepared similarly, employing $EtSO_2Cl$ in the place of 2,2,2-trifluoroethanesulfonyl chloride in step 1:

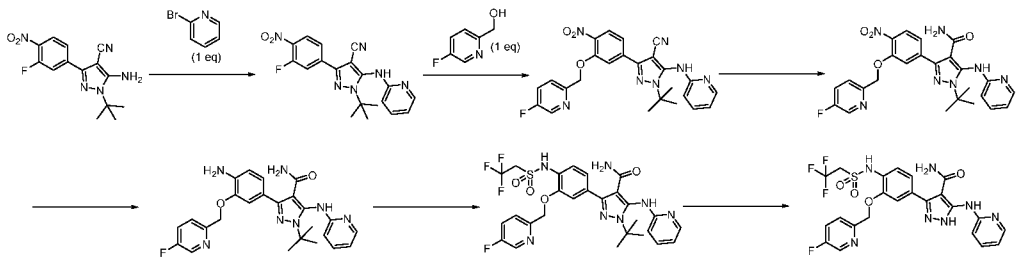
Compound 317



(S)-3-(4-(ethylsulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide

LCMS (Method A): 3.50 min; [M+H]+529.2. ^{1}H NMR (400 MHz, DMSO-d_6): 12.71 (s, 1H), 9.16 (d, *J* = 19.4 Hz, 2H), 7.70-7.54 (m, 2H), 7.49-7.33 (m, 1H), 7.21-7.12 (m, 3H), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.58 (s, 1H), 5.75 (s, 1H), 5.63 (d, *J* = 6.5 Hz, 1H), 3.11 (q, *J* = 7.3 Hz, 2H), 2.35 (d, *J*= 0.9 Hz, 3H), 1.60 (d, *J* = 6.2 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H).

Compound 240



Step 1: 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-1H-pyrazole-4-carbonitrile (5.0 g, 16.4 mmol), 2-bromopyridine (2.59 g, 16.4 mmol), $Pd_2(dba)_3$ (1.50 g, 1.64 mmol), Xantphos (1.89 g, 3.28 mmol), Cs_2CO_3 (15.9 g, 49.1 mmol) and 1,4-dioxane (40 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated and

the residue diluted with H_2O (60 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (760 mg, 12%) as a yellow solid. LCMS (Method D): 3.70 min; m/z: 381.0 $[M+H]^+$.

Step 2: 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carbonitrile

To a mixture of (5-fluoropyridin-2-yl)methanol (183 mg, 1.44 mmol) and THF (20 mL) at 0 ºC, was added NaH (172 mg, 7.19 mmol). After 15 min, 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carbonitrile (550 mg, 1.44 mmol) was added and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (600 mg, 85%) as a yellow solid. LCMS (Method D): 3.90 min; m/z: 488.2 $[M+H]^+$.

Step 3: 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carbonitrile (600 mg, 1.23 mmol), Ghaffar-Parkins catalyst (52.5 mg, 123 µmol) and 80% aq. 1,4-dioxane (16 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated and the residue diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (550 mg, 72%) as a yellow solid. LCMS (Method D): 3.90 min; m/z: 506.3 $[M+H]^+$.

Step 4: 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (280 mg, 553 µmol), Zn powder (180 mg, 2.76 mmol), sat. NH_4Cl (2 mL) and MeOH (10 mL) was stirred at 60 ºC for 1 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (178 mg, 67%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): 8.56 (d, J = 2.2 Hz, 1H), 8.21 (s, 1H), 8.05-8.03 (m, 1H), 7.78-7.75 (m, 2H), 7.53 (m, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.14 (dd, J = 8.1, 2.7 Hz, 1H), 7.09 (br s, 1H), 6.82 (br s, 1H), 6.72-6.69 (m, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 5.12 (s, 2H), 4.96 (br s, 2H), 1.52 (s, 9H).

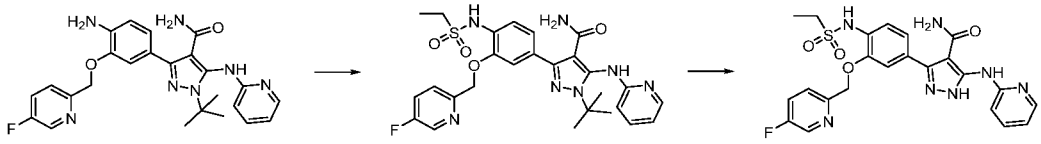
Step 5: 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (200 mg, 420 µmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (115 mg, 630 µmol) in DCM:pyridine (1:1, 8 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (39 mg, 14%) as a yellow solid. LCMS (Method D): 4.77 min; m/z: 622.1 $[M+H]^+$.

Step 6: 3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 240)

A solution of 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (100 mg, 160 µmol) in DCM:TFA (1:1 4 mL) was stirred at RT for 16 h and then concentrated under reduced pressure. The residue was neutralized to pH 7-8 with NH_4OH then diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated to afford the title compound (45 mg, 49%) as a yellow solid. LCMS (Method A): 3.00 min; m/z: 566.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.84 (s, 1H), 10.10 (s, 1H), 9.77 (s, 1H), 9.52 (s, 1H), 8.56 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 6.4 Hz, 1H), 7.84-7.78 (m, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.45-7.37 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 6.10 (s, 1H), 5.28 (s, 1H), 4.42 (s, 1H).

Compound 241



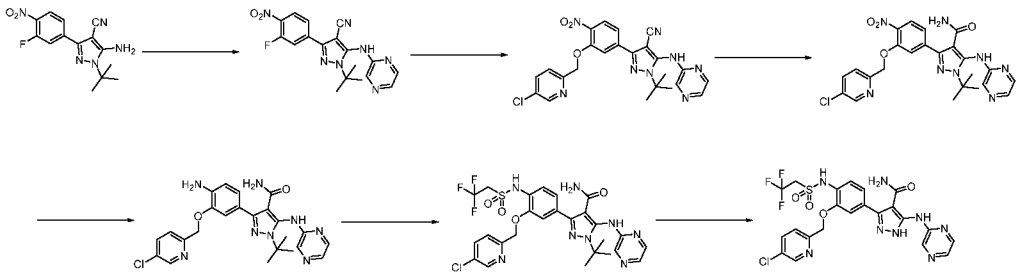
Step 1: 1-tert-butyl-3-{4-ethanesulfonamido-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (170 mg, 357 µmol) and $EtSO_2Cl$ (68.7 mg, 535 µmol) in DCM:pyridine (1:1 10 mL) was stirred at RT for 16 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (70 mg, 34%) as a yellow solid. LCMS (Method D): 4.05 min; m/z: 568.1 $[M+H]^+$.

Step 2: 3-{4-ethanesulfonamido-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 241)

A solution of 1-tert-butyl-3-{4-ethanesulfonamido-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-5-[(pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide (70 mg, 123 µmol) in DCM:TFA (1:1, 10 mL) was stirred at RT for 16 h. The reaction mixture was neutralized to pH 7-8 with sat. Na_2CO_3 and then extracted with DCM (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title compound (17.9 mg, 28%) as a white solid. LCMS (Method A): 2.71 min; m/z: 512.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.83 (s, 1H), 9.49 (s, 1H), 9.23 (s, 1H), 8.57 (s, 1H), 8.07 (m, 2H), 7.83 (d, J = 6.8 Hz, 2H), 7.72 (t, J = 16.0 Hz, 1H), 7.40 (m, 2H), 7.18 (m, 2H), 6.83 (m, 1H), 6.13 (s, 1H), 5.30 (s, 2H), 3.08 (q, J = 22.0 Hz, 2H), 1.18 (t, J = 14.8 Hz, 3H).

Compound 262



Step 1: 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-(tert-butyl)-3-(3-fluoro-4-nitrophenyl)-1H-pyrazole-4-carbonitrile (10.0 g, 23.4 mmol), 2-bromopyrazine (3.72 g, 23.4 mmol), $Pd_2(dba)_3$ (1.07 g, 1.17 mmol), Xantphos (1.35 g, 2.34 mmol), Cs_2CO_3 (22.8 g, 70.2 mmol) and 1,4-dioxane (500 mL) was stirred at 100 ºC. After 16 h, the reaction mixture was concentrated and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (5.10 g, 43%) as a yellow solid. LCMS (Method D): 5.60 min; m/z: 382.0 $[M+H]^+$.

Step 2: 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile

To a solution of (5-chloropyridin-2-yl)methanol (383 mg, 2.67 mmol) in THF (20 mL) at 0 ºC, was added NaH (313 mg, 7.86 mmol). After 1 h, 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (1.0 g, 2.62 mmol) was added and the mixture was stirred at RT for 16 h. The reaction mixture was concentrated and the residue diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 4:1) to afford the title product (720 mg, 54%) as a yellow solid. LCMS (Method D): 5.79 min; m/z: 505.0 $[M+H]^+$.

Step 3: 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A solution of 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (720 mg, 1.42 mmol) and Ghaffar-Parkins catalyst (72 mg, 168 µmol) in 50% aq. 1,4-dioxane (10 mL) was stirred at 100 ºC under N_2 for 16 h. The reaction mixture was concentrated, diluted with H_2O (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title product (680 mg, 91%) as a red solid. LCMS (Method D): 4.75 min; m/z: 523.0 $[M+H]^+$.

Step 4: 3-(4-amino-3-((5-chloropyridin-2-yl)methoxy)phenyl)-1-(tert-butyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (680 mg, 1.30 mmol), Zn powder (424 mg, 6.50 mmol), sat. NH_4Cl (3 mL) and MeOH (12 mL) was stirred at 60 ºC for 30 min. The reaction mixture was filtered and the filtrate concentrated and then purified by prep-TLC (PE:EtOAc, 3:1) to afford the title product (70.0 mg, 11%) as a yellow solid. LCMS (Method D): 3.77 min; m/z: 493.7 $[M+H]^+$.

Step 5: 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

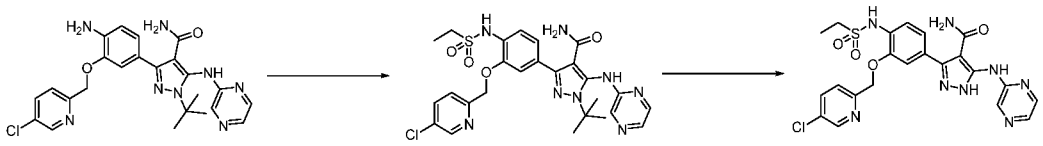
A mixture of 3-(4-amino-3-((5-chloropyridin-2-yl)methoxy)phenyl)-1-(tert-butyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (70 mg, 141 µmol), 2,2,2-

trifluoroethane-1-sulfonyl chloride (51.4 mg, 282 µmol) and DCM:pyridine (1:1, 2 mL) was stirred at RT. After 16 h, the mixture was concentrated and the crude residue purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (53.0 mg, 59%) as a white solid. LCMS (Method D): 4.64 min; m/z: 639.0 $[M+H]^+$.

Step 6: 3-{3-[(5-chloropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 262)

A solution of 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (50 mg, 78.2 µmol) in DCM:TFA (1:1, 2 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the residue neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 10:1) to afford the title compound (11.2 mg, 24%) as a white solid. LCMS (Method A): 3.37 min; m/z: 583.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 10.07 (br s, 1H), 9.65 (s, 1H), 9.25 (s, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.23-8.22 (m, 1H), 8.11 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 8.4, 2.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.47-7.42 (m, 2H), 7.23 (dd, J = 8.0, 1.6 Hz, 1H), 6.28 (br s, 1H), 5.30 (s, 2H), 4.46 (q, J = 9.6 Hz, 2H).

Compound 242



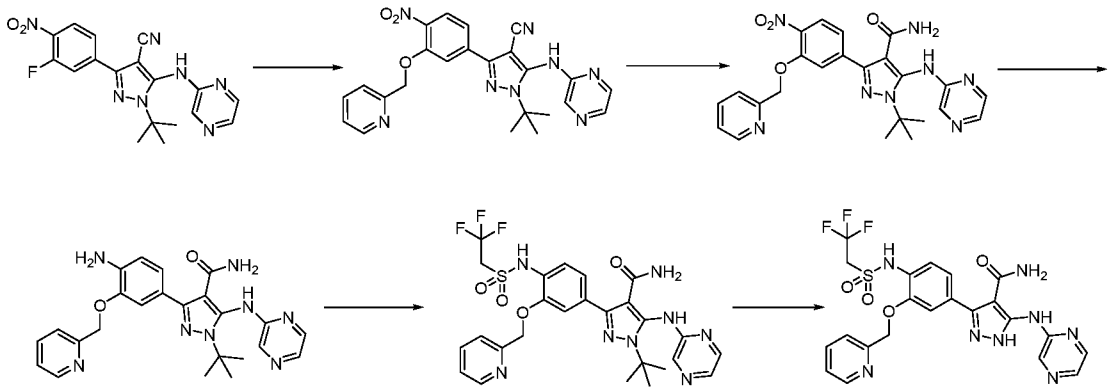
Step 1: 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-ethanesulfonamidophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 3-(4-amino-3-((5-chloropyridin-2-yl)methoxy)phenyl)-1-(tert-butyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (42.9 mg, 87 µmol) and $EtSO_2Cl$ (14.3 mg, 112 µmol) in DCM:pyridine (2:1, 3 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the crude residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (30.0 mg, 59%) as a white solid. LCMS (Method D): 4.18 min; m/z: 585.0 $[M+H]^+$.

Step 2: 3-{3-[(5-chloropyridin-2-yl)methoxy]-4-ethanesulfonamidophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (compound 242)

A solution of 1-tert-butyl-3-{3-[(5-chloropyridin-2-yl)methoxy]-4-ethanesulfonamidophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (30 mg, 51.2 µmol) in DCM:TFA (1:1, 2 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title compound (6.90 mg, 25%) as a white solid. LCMS (Method A): 3.14 min; m/z: 529.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.64 (s, 1H), 9.36 (s, 1H), 9.25 (s, 1H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.22-8.21 (m, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 8.04 (dd, J = 8.4, 2.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 0.8 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.27 (br. s, 1H), 5.30 (s, 2H), 3.10 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H).

Compound 227



Step 1: 1-tert-butyl-3-{4-nitro-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile

To a solution of (pyridin-2-yl)methanol (285 mg, 2.62 mmol) in THF (30 mL) at 0 °C, was added NaH (314 mg, 13.1 mmol). After 15 min, 1- tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (1.0 g, 2.62 mmol)

was added and the mixture was stirred at RT for 16 h. The reaction mixture was concentrated and the residue diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (1.0 g, 81%) as a brown solid. LCMS (Method D): 4.53 min; m/z: 471.1 $[M+H]^+$.

Step 2: 1-tert-butyl-3-{4-nitro-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{4-nitro-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (1.5 g, 3.18 mmol), Ghaffar-Parkins catalyst (400 mg, 0.93 mmol) and 80% aq. 1,4-dioxane (50 mL) was stirred at 100 ºC under N_2 for 16 h. The reaction mixture was concentrated and the residue diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (1.0 g, 65%) as a brown solid. LCMS (Method A): 3.28 min; m/z: 489.2 $[M+H]^+$.

Step 3: 3-{4-amino-3-[(pyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{4-nitro-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (1.3 g, 2.66 mmol), Zn powder (863 mg, 13.2 mmol), sat. NH_4Cl (5 mL) and MeOH (15 mL) was stirred at 60 ºC. After 2 h, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and then purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (480 mg, 40%) as a brown solid. LCMS (Method A): 2.49 min; m/z: 459.2 $[M+H]^+$.

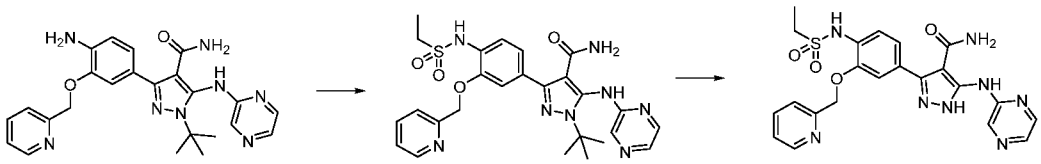
Step 4: 1-tert-butyl-5-[(pyrazin-2-yl)amino]-3-{3-[(pyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-1H-pyrazole-4-carboxamide

To a solution of 3-{4-amino-3-[(pyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (150 mg, 327 µmol) in DCM:pyridine (3:1, 8 mL) was added 2,2,2-trifluoroethane-1-sulfonyl chloride (89.5 mg, 0.49 mmol). After stirring at RT for 16 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (40 mg, 20%) as a yellow solid. LCMS (Method A): 3.26 min; m/z: 605.2 $[M+H]^+$.

Step 5: 5-[(pyrazin-2-yl)amino]-3-{3-[(pyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-1H-pyrazole-4-carboxamide (compound 227)

A solution of 1-tert-butyl-5-[(pyrazin-2-yl)amino]-3-{3-[(pyridin-2-yl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-1H-pyrazole-4-carboxamide (28 mg, 46.3 µmol) in DCM:TFA (1:1, 2 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3 and then concentrated under reduced pressure. The residue was slurried in MeOH (20 mL), filtered and the filtrate concentrated then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (20 mg, 78%) as a yellow solid. LCMS (Method A): 3.03 min; m/z: 549.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 13.06 (s, 1H), 9.64 (s, 1H), 9.24 (s, 1H), 8.56 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.87 (t, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.41-7.21 (m, 7H), 5.30 (s, 2H), 4.47 (q, J = 9.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).

Compound 261



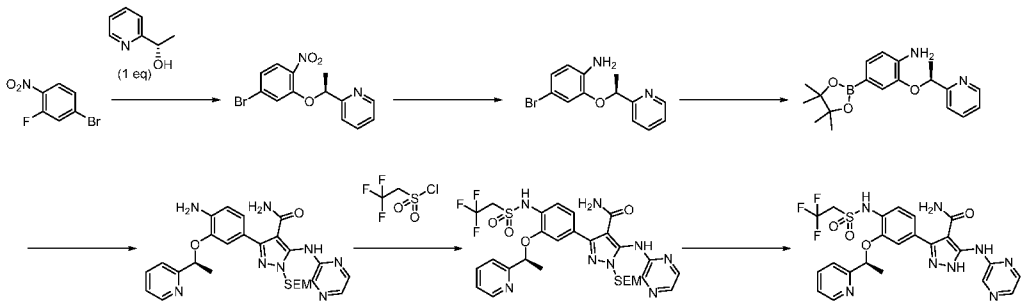
Step 1: 1-tert-butyl-3-{4-ethanesulfonamido-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

To a solution of 3-{4-amino-3-[(pyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (100 mg, 0.21 mmol) in DCM:pyridine (1:1, 2 mL), was added $EtSO_2Cl$ (33.6 mg, 0.26 mmol). The reaction mixture was stirred at RT for 16 h then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (30 mg, 25%) as a yellow solid. LCMS (Method A): 2.97 min; m/z: 551.2 $[M+H]^+$.

Step 2: 3-{4-ethanesulfonamido-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 261)

A solution of 1-tert-butyl-3-{4-ethanesulfonamido-3-[(pyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (30 mg, 54.4 µmol) in DCM:TFA (1:1, 2 mL) was stirred at RT. After 16 h, the mixture was concentrated and the residue neutralized to pH 7-8 with aq. Na_2CO_3. The mixture was diluted with H_2O (30 mL), and the resulting precipitate was collected by filtration and purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (10 mg, 37%) as a yellow solid. LCMS (Method A): 2.66 min; m/z: 495.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 13.06 (s, 1H), 9.64 (s, 1H), 9.25 (s, 1H), 8.59 (d, J = 4.0 Hz, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.88 (t, J = 6.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.48-7.37 (m, 3H), 7.22 (d, J = 8.0 Hz, 1H), 6.28 (s, 1H), 5.29 (s, 2H), 3.10 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H).

Compound 267



Step 1: 2-[(1S)-1-(5-bromo-2-nitrophenoxy)ethyl]pyridine

To mixture of (1S)-1-(pyridin-2-yl)ethan-1-ol (1.0 g, 8.18 mmol) in THF (20 mL) at 0 ºC, was added NaH (981 mg, 40.9 mmol). After 15 min, 4-bromo-2-fluoro-1-nitrobenzene (1.8 g, 8.18 mmol) was added and the mixture was stirred at RT. After 16 h, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 20:1) to afford the title product (1.25 g, 50%) as a yellow liquid. LCMS (Method D): 5.01 min; m/z: 322.8 $[M+H]^+$.

Step 2: 4-bromo-2-[(1S)-1-(pyridin-2-yl)ethoxy]aniline

A mixture of 2-[(1S)-1-(5-bromo-2-nitrophenoxy)ethyl]pyridine (2.20 g, 6.80 mmol), Zn powder (2.21 g, 33.9 mmol), sat. NH_4Cl (10 mL) and MeOH (30 mL) was stirred at 60 ºC for 1 h. The reaction mixture was filtered and the filtrate was concentrated, diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (880 mg, 75%) as a yellow solid. LCMS (Method D): 3.90 min; m/z: 294.9 $[M+H]^+$.

Step 3: 2-[(1S)-1-(pyridin-2-yl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

A mixture of 4-bromo-2-[(1S)-1-(pyridin-2-yl)ethoxy]aniline (1.17 g, 3.99 mmol), B_2pin_2 (1.21 g, 4.78 mmol), $Pd(dppf)Cl_2$ (325 mg, 399 µmol), KOAc (1.16 g, 11.9 mmol) and 1,4-dioxane (16 mL) was stirred at 100 ºC. After 16 h, the mixture was concentrated and the residue diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product (600 mg, 74%) as a yellow liquid. LCMS (Method A): 3.50 min; m/z: 341.2 $[M+H]^+$.

Step 4: 3-{4-amino-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-[(1S)-1-(pyridin-2-yl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (680 mg, 1.99 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (822 mg, 1.99 mmol), $Pd(dppf)Cl_2$ (162 mg, 199 µmol), Na_2CO_3 (740 mg, 5.97 mmol) and 80% aq. 1,4-dioxane (10 mL) was stirred at 100 ºC. After 16 h, the reaction mixture was concentrated, diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (330 mg, 30%) as a yellow solid. LCMS (Method A): 3.18 min; m/z: 547.3 $[M+H]^+$.

Step 5: 5-[(pyrazin-2-yl)amino]-3-{3-[(1S)-1-(pyridin-2-yl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

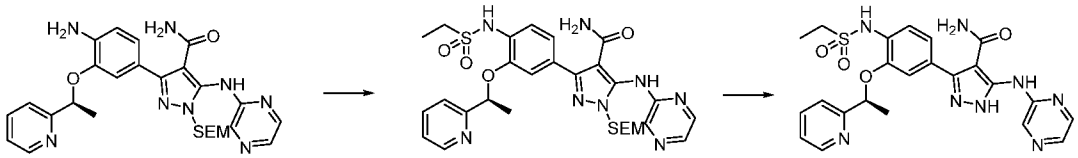
A solution of 3-{4-amino-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (330 mg, 603 µmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (165 mg, 904 µmol) in DCM:pyridine (1:1, 8 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The

combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (180 mg, 43%) as a yellow solid. LCMS (Method A): 3.79 min; m/z: $[M+H]^+$.

Step 6: 5-[(pyrazin-2-yl)amino]-3-{3-[(1S)-1-(pyridin-2-yl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide (Compound 267)

A solution of 5-[(pyrazin-2-yl)amino]-3-{3-[(1S)-1-(pyridin-2-yl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (180 mg, 259 µmol) in DCM:TFA (4:1, 20 mL) was stirred for 5 min. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title compound (50 mg 34%) as a yellow solid. LCMS (Method A): 3.20 min; m/z: 563.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.16 (br s, 1H), 9.60 (s, 1H), 9.34 (s, 1H), 9.22 (s, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.36-7.31 (m, 1H), 7.20-7.13 (m, 2H), 6.12 (br s, 1H), 5.62 (q, J = 6.4 Hz, 1H), 4.63 (q, J = 10.0 Hz, 2H), 4.63 (d, J = 6.4 Hz, 3H).

Compound 230



Step 1: 3-{4-ethanesulfonamido-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

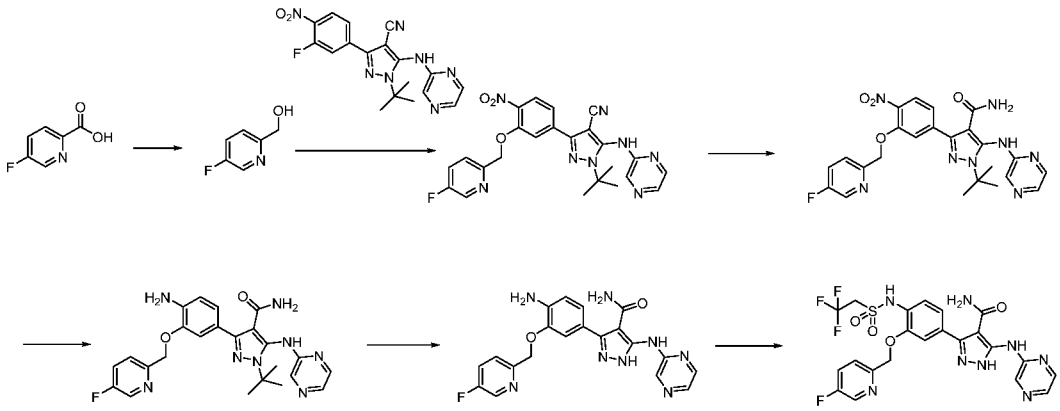
A solution of 3-{4-amino-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (100 mg, 182 µmol) and $EtSO_2Cl$ (35.0 mg, 273 µmol) in DCM:pyridine (1:1, 10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, diluted with H_2O (30

mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (65 mg, 56%) as a yellow solid. LCMS (Method A): 3.57 min; m/z: 639.3 $[M+H]^+$.

Step 2: 3-{4-ethanesulfonamido-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 230)

A solution of 3-{4-ethanesulfonamido-3-[(1S)-1-(pyridin-2-yl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (100 mg, 156 µmol) in DCM:TFA (10:1, 10 mL) was stirred at RT. After 16 h, the reaction mixture was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 12:1) to afford the title compound (50 mg, 63%) as a yellow solid. LCMS (Method A): 2.85 min; m/z: 509.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 9.59 (s, 1H), 9.22 (s, 1H), 8.53 (d, J = 4.4 Hz, 1H), 8.21 (s, 1H), 8.10 (s, 2H), 7.81 (t, J = 8.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 4.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.11 (s, 1H), 5.56 (s, 1H), 3.18-3.12 (m, 2H), 1.66 (d, J = 6.4 Hz, 3H).

Compound 231



Step 1: (5-fluoropyridin-2-yl)methanol

To a solution of 5-fluoropyridine-2-carboxylic acid (5.0 g, 35.4 mmol) in THF (200 mL) at 0 ºC, was added BH_3.DMS (10.7 g, 141 mmol) and the resulting solution was stirred at 60 ºC. After 3 h, the solution was cooled to 0 ºC, quenched with MeOH (10 mL) and then heated to reflux for 1 h. The reaction mixture was concentrated and the residue diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (2.6 g, 58%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): 8.46 (d, J = 2.9 Hz, 1H), 7.71 (td, J = 8.8, 2.9 Hz, 1H), 7.52 (ddd, J = 8.7, 4.6, 0.5 Hz, 1H), 4.54 (s, 2H).

Step 2: 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile

To a mixture of (5-fluoropyridin-2-yl)methanol (200 mg, 1.57 mmol) in THF (15 mL) at 0 ºC, was added NaH (37.6 mg, 1.57 mmol). After 15 min, 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (598 mg, 1.57 mmol) was added and the mixture stirred at RT for 16 h. The reaction mixture was quenched with H_2O (100 mL) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue

purified by silica gel column chromatography (PE/EtOAc, 3:1) to afford the title product (300 mg, 39%) as a yellow solid. LCMS (Method D): 4.31 min; m/z: 489.1 $[M+H]^+$.

Step 3: 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carbonitrile (800 mg, 1.63 mmol), Ghaffar-Parkins catalyst (696 mg, 1.63 mmol) and 80% aq. 1,4-dioxane (25 mL) was stirred at 100 ºC. After 16 h, the reaction mixture was diluted with H_2O (100 mL) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residue purified by silica gel column chromatography (DCM:MeOH, 60:1) to afford the title product (630 mg, 76%) as a yellow solid. LCMS (Method D): 4.06 min; m/z: 507.3 $[M+H]^+$.

Step 4: 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(5-fluoropyridin-2-yl)methoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (620 mg, 1.22 mmol), Zn powder (398 mg, 6.10 mmol), sat. NH_4Cl (1 mL) and MeOH (10 mL) was stirred at 60 ºC for 16 h. The mixture was filtered and the filtrate diluted with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (200 mg, 34%) as a red solid. LCMS (Method D): 3.01 min; m/z: 477.2 $[M+H]^+$.

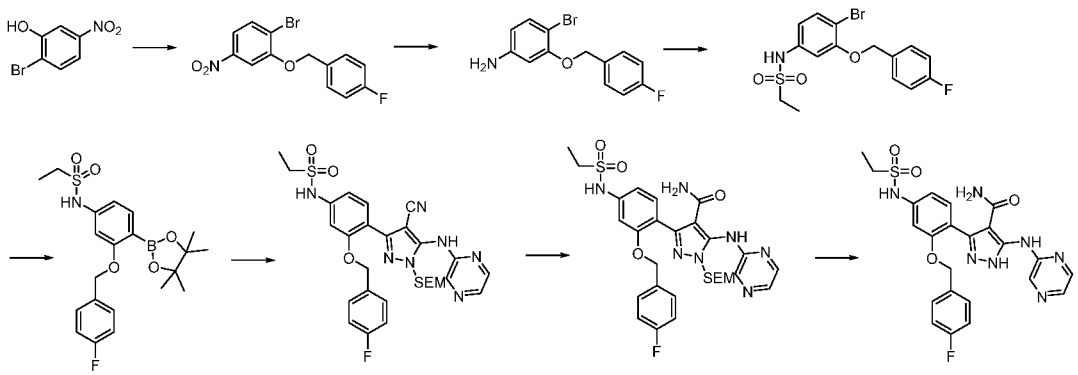
Step 5: 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-1-tert-butyl-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (100 mg, 209 µmol) in DCM:TFA (1:1, 6 mL) was stirred at RT. After 16 h, the reaction mixture was neutralized to pH 7-8 and then extracted with DCM (2 x 50 mL). The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (30 mg, 34%) as a white solid. LCMS (Method A): 2.68 min; m/z: 421.2 $[M+H]^+$.

Step 6: 3-(3-((5-fluoropyridin-2-yl)methoxy)-4-((2,2,2-trifluoroethyl)sulfonamido) phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Compound 231)

A mixture of 3-{4-amino-3-[(5-fluoropyridin-2-yl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (30 mg, 71.3 µmol), 2,2,2-trifluoroethane-1-sulfonyl chloride (19.3 mg, 106 µmol) and DCM:pyridine (1:1, 10 mL) was stirred at RT. After 16 h, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude residue purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title compound (10 mg, 25%) as a white solid. LCMS (Method A): 3.23 min; m/z: 567.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 10.05 (s, 1H), 9.64 (s, 1H), 9.24 (s, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.21 (t, J = 4.0 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.81 (m, 2H), 7.21 (m, 1 H), 7.45 (d, J = 8.0 Hz, 2H), 7.23 (m, 2H), 6.26 (s, 1H), 5.29 (s, 2H), 4.45 (q, J = 29.6 Hz, 2H).

Compound 21



Step 1: 1-bromo-2-((4-fluorobenzyl)oxy)-4-nitrobenzene

A mixture of 2-bromo-5-nitrophenol (10 g, 45.8 mmol), 1-(bromomethyl)-4-fluorobenzene (8.65 g, 45.8 mmol) and K_2CO_3 (12.6 g, 91.6 mmol) in MeCN (100 mL) was stirred at 70 °C under N_2 overnight. The mixture was diluted with H_2O (100 mL) and then extracted with EtOAc (3 x 200 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound (15.0 g, 100%) as a white solid.

Step 2: 4-bromo-3-((4-fluorobenzyl)oxy)aniline

A mixture of 1-bromo-2-((4-fluorobenzyl)oxy)-4-nitrobenzene (15 g, 45.9 mmol), sat. aq. NH_4Cl (100 mL) and Zn dust (14.9 g, 229 mmol) in MeOH (300 mL) was stirred at 60 °C for 4 h. The reaction mixture was filtered, diluted with H_2O (250 mL) and then extracted with EtOAc (3 x 300 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (13.0 g, 96%) as a black oil. LCMS (Method A): 4.24 min; m/z: 296.0 $[M+H]^+$.

Step 3: N-(4-bromo-3-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide

A mixture of 4-bromo-3-((4-fluorobenzyl)oxy)aniline (13 g, 43.8 mmol), $EtSO_2Cl$ (8.43 g, 65.6 mmol) and pyridine (50 mL) in $CHCl_3$ (50 mL) was stirred at RT under N_2 for 3 h. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (12.5 g, 73%) as a yellow solid. LCMS (Method A): 4.24 min; m/z: 410.0 $[M+H]^+$.

Step 4: N-(3-((4-fluorobenzyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide

A mixture of N-(4-bromo-3-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide (12.5 g, 32.1 mmol), $Pd(dppf)Cl_2$ (1.46 g, 1.60 mmol), KOAc (6.29 g, 64.2 mmol) and B_2pin_2 (8.96 g, 35.2 mmol) in degassed 1,4-dioxane (200 mL) was stirred at 100°C under N_2overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford the title product

(14.8 g, >100%) as a brown solid. LCMS (Method A): 4.51 min; m/z: 453.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.99 (s, 1H), 7.63-7.60 (m, 2H), 7.38-7.32 (m, 2H), 7.28-7.21 (m, 3H), 5.15 (s, 2H), 3.03 (q, *J* =14.8, 7.2 Hz, 2H), 1.29 (s, 12H), 1.11 (t, *J* = 7.2 Hz, 3H).

Step 5: N-(4-(4-cyano-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-3-((4-fluorobenzyl)oxy)phenyl)ethanesulfonamide

A mixture of N-{3-[(4-fluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (500 mg, 1.14 mmol), 3-bromo-5-[(pyrazin-2-yl)amino] -1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (450 mg, 1.14 mmol), $Pd(dppf)Cl_2$ (104 mg, 0.114 mmol) and Na_2CO_3 (241 mg, 2.28 mmol) in degassed 80% aq. 1,4-dioxane (15 mL) was stirred at 100 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (420 mg, 59%) as a yellow solid. LCMS (Method A): 4.09 min; m/z: 624.2 $[M+H]^+$.

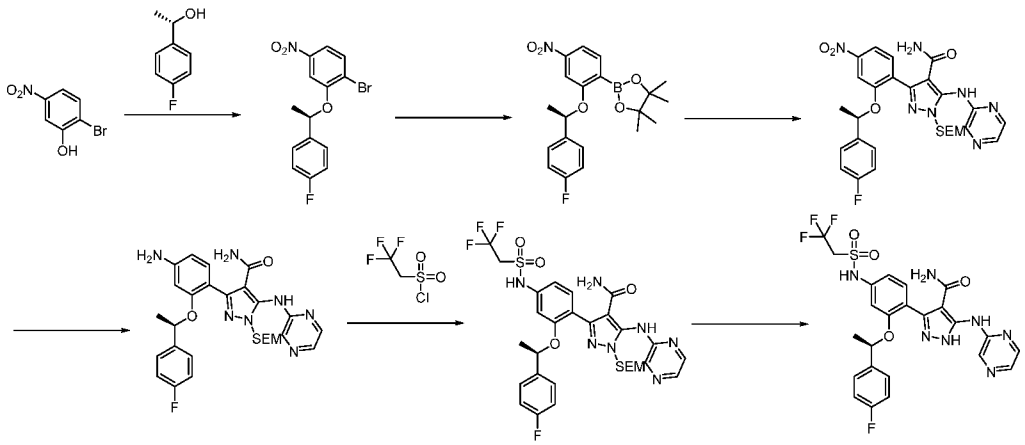
Step 6: 3-(4-(ethylsulfonamido)-2-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of N-(4-{4-cyano-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-3-yl}-3-[(4-fluorophenyl)methoxy]phenyl)ethane-1-sulfonamide (420 mg, 0.673 mmol) and Ghaffar-Parkins catalyst (4 mg, 9.30 µmol) in 60% aq. 1,4-dioxane (14 mL) was stirred at 110 ºC under N_2 overnight. The reaction mixture was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 50:1) to afford the title product (108 mg, 25%) as a brown solid. LCMS (Method A): 3.76 min; m/z: 642.2 $[M+H]^+$.

Step 7: 3-(4-(ethylsulfonamido)-2-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Compound 21)

A solution of 3-{4-ethanesulfonamido-2-[(4-fluorophenyl)methoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (108 mg, 0.1682 mmol) in DCM (2 mL) and TFA (2 mL) was stirred at 30 °C for 1 h then concentrated under reduced pressure. The residue was neutralized to pH 7-8 with NH_4OH, diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 1:0 to 9:1) to afford the title product (60.6 mg, 68%) as a yellow solid. LCMS (Method A): 3.19 min; m/z: 512.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.84 (s, 1H), 10.15 (br s, 1H), 9.74 (s, 1H), 9.30 (s, 1H), 8.24-8.22 (m, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.45-7.41 (m. 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.17(t, J = 8.8 Hz, 2H), 7.07 (s, 1H), 6.94 (dd, J = 8.8, 1.6 Hz, 1H), 5.68 (br s, 1H), 5.10 (s, 2H), 3.15 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).

Compound 254



Step 1: 1-bromo-2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrobenzene

A mixture of 2-bromo-5-nitrophenol (2.40 g, 11.0 mmol), (1S)-1-(4-fluorophenyl)ethan-1-ol (1.54 g, 11.0 mmol), PPh_3 (4.32 g, 16.5 mmol), DIAD (3.33 g, 16.5 mmol) and THF (20 mL) was stirred at 70 ºC for 16 h. The reaction mixture was concentrated and then diluted with H_2O (60 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 50:1) to

afford the title product (2.5 g, 73%) as a yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.86 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 7.68 (dd, J = 8.7, 2.5 Hz, 1H), 7.53-7.48 (m, 2H), 7.23-7.17 (m, 2H), 5.89 (q, J = 6.3 Hz, 1H), 1.59 (d, J = 6.3 Hz, 3H).

Step 2: 2-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A mixture of 1-bromo-2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrobenzene (2.50 g, 7.34 mmol), B_2pin_2 (2.14 g, 8.44 mmol), Pd(dppf)Cl_2 (599 mg, 734 µmol), KOAc (2.15 g, 22.0 mmol) and 1,4-dioxane (10 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated and then diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (2.20 g, 77%) as a yellow solid.

Step 3: 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 g, 2.58 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (1.06 g, 2.58 mmol), Pd(dppf)Cl_2 (210 mg, 258 µmol), Na_2CO_3 (820 mg, 7.74 mmol) and 80% aq. 1,4-dioxane (15 mL) was stirred at 100 ºC for 1 h. The reaction mixture was concentrated, diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc) to afford the title product (1.20 g, 66%) as a yellow solid. LCMS (Method A): 4.15 min; m/z: 594.2 $[M+H]^+$.

Step 4: 3-{4-amino-2-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (1.1 g, 1.85 mmol), Zn powder (604 mg, 9.25 mmol), sat. NH_4Cl (5 mL) and MeOH (15 mL) was stirred at 60 ºC for 1 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and then purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford product (540 mg, 48%) as a yellow solid. LCMS (Method A): 3.69 min; m/z: 564.3 $[M+H]^+$.

Step 5: 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

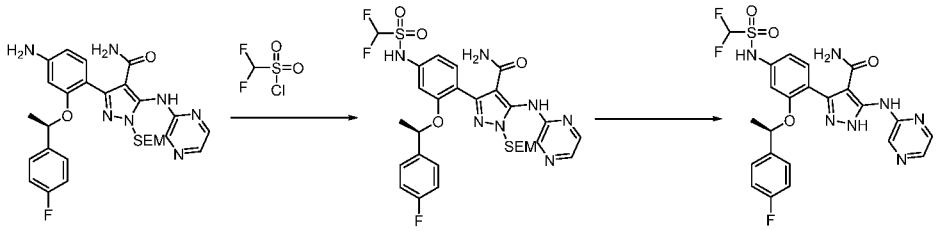
A mixture of 3-{4-amino-2-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (250 mg, 421 µmol), 2,2,2-trifluoroethanesulfonyl chloride (115 mg, 631 µmol) and DCM:pyridine (1:1, 12 mL) was stirred at RT for 16 h. The reaction mixture was concentrated then diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (120 mg, 40%) as a yellow solid. LCMS (Method A): 3.96 min; m/z: 710.3 $[M+H]^+$.

Step 6: 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 254)

A mixture of 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (120 mg, 169 µmol) and DCM:TFA (10:1, 12 mL) was stirred at RT for 16 h. The reaction mixture was neutralized to pH 7-8 with NH_4OH and then diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and

concentrated to afford the title compound (50 mg 51%) as a yellow solid. LCMS (Method A): 3.44 min; m/z: 580.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.85 (s, 1H), 10.74 (s, 1H), 9.77 (s, 1H), 9.34 (s, 1H), 8.24 (s, 1H), 8.13 (s, 1H), 7.36 (s，3H), 7.14 (t, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.69 (s, 1H), 5.42 (d, J = 6.0 Hz, 1H), 4.48 (t, J = 10.4 Hz, 2H), 1.45 (d, J = 5.6 Hz, 3H).

Compound 255



Step 1: 3-[4-(difluoromethanesulfonamido)-2-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

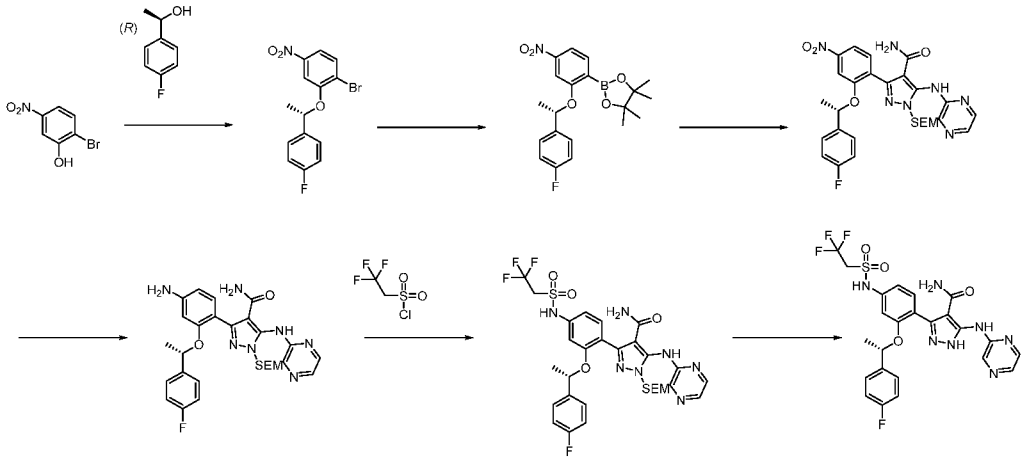
A solution of 3-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4- carboxamide (280 mg, 471 µmol) and F_2CHSO_2Cl (106 mg, 706 µmol) in DCM:pyridine (1:1, 4 mL) was stirred at RT for 16 h. The reaction mixture was concentrated, diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (180 mg, 56%) as a yellow solid. LCMS (Method A): 3.89 min; m/z: 678.2 $[M+H]^+$.

Step 2: 3-[4-(difluoromethanesulfonamido)-2-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 255)

A solution of 3-[4-(difluoromethanesulfonamido)-2-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (180 mg, 265 µmol) in DCM:TFA (10:1, 20 mL) was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was neutralized to pH

7-8 with NH_4OH, then diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title compound (60 mg, 41%) as a yellow solid. LCMS (Method A): 3.35 min; m/z: 548.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 11.22 (s, 1H), 9.71 (s, 1H), 9.32 (s, 1H), 8.23 (s, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.34 (t, J = 5.6 Hz, 3H), 7.24-6.98 (m, 4H), 6.90 (t, J = 8.4 Hz, 2H), 5.66 (s, 1H), 5.38 (d, J = 6.4 Hz, 2H), 1.44 (d, J = 6.0 Hz, 3H).

Compound 244



Step 1: 1-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrobenzene

A mixture of 2-bromo-5-nitrophenol (3.00 g, 13.7 mmol), (1R)-1-(4-fluorophenyl)ethan-1-ol (1.92 g, 13.7 mmol), DIAD (4.14 g, 20.5 mmol), PPh_3 (5.37 g, 20.5 mmol) and THF (12 mL) was stirred at 70 ºC. After 16 h, the reaction mixture was concentrated then diluted with H_2O (60 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (3.50 g, 75%) as a yellow liquid.

Step 2: 2-2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A mixture of 1-bromo-2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrobenzene (3.63 g, 10.6 mmol), B_2pin_2 (2.94 g, 11.6 mmol), $Pd(dppf)Cl_2$ (857 mg, 1.05 mmol), KOAc (3.12 g, 31.8 mmol) and 1,4-dioxane (100 mL) was stirred at 100 ºC. After 16 h, the reaction mixture was concentrated and the residue diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (2.60 g, 59%) as a yellow liquid.

Step 3: 3-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 2-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.25 g, 3.22 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (1.33 g, 3.22 mmol), $Pd(dppf)Cl_2$ (262 mg, 0.32 mmol), Na_2CO_3 (1.02 g, 9.66 mmol) and 80% aq. 1,4-dioxane (15 mL) was stirred at 100 ºC for 16 h. The reaction mixture was concentrated and then diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc) to afford the title product (1.20 g, 66%) as a yellow solid. LCMS (Method A): 4.11 min; m/z: 594.3 $[M+H]^+$.

Step 4: 3-4-amino-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (1.25 g, 2.10 mmol), Zn powder (686 mg, 10.5 mmol), NH_4Cl (5 mL) and MeOH (15 mL) was stirred at 60 ºC. After 1 h, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine),

dried (Na_2SO_4), concentrated and the residue purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (1.10 g, 93%) as a yellow solid. LCMS (Method A): 3.71 min; m/z: 564.1 $[M+H]^+$.

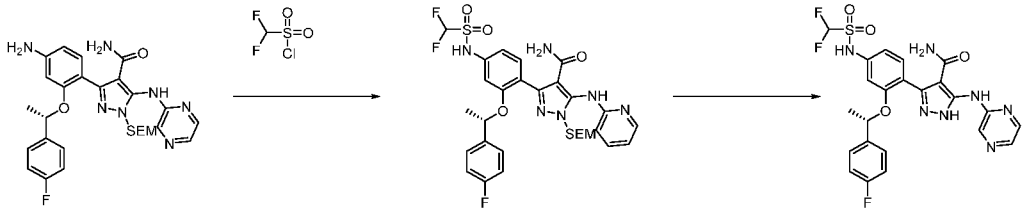
Step 5: 3-2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-{4-amino-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (450 mg, 0.79 mmol), 2,2,2-trifluoroethanesulfonyl chloride (206 mg, 1.13 mmol) and DCM:pyridine (1:1, 12 mL) was stirred at RT for 16 h. The reaction mixture was concentrated and then diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (260 mg, 46%) as a yellow solid. LCMS (Method A): 3.96 min; m/z: 710.3 $[M+H]^+$.

Step 6: 3-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethanesulfonamido) phenyl}-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 244)

A mixture of 3-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(2,2,2-trifluoroethane-sulfonamido)phenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (100 mg, 140 µmol) in DCM:TFA (10:1, 11 mL) was stirred at RT for 16 h. The reaction mixture was neutralized with NH_4OH and then diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to afford the title compound (45 mg, 55%) as a yellow solid. LCMS (Method A): 3.44 min; m/z: 580.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.84 (s, 1H), 10.72 (s, 1H), 9.77 (s, 1H), 9.34 (s, 1H), 8.24 (t, J = 0.8 Hz, 1H), 8.13 (d, J = 2.8 Hz, 1H), 7.36 (m, 4H), 7.14 (t, J = 8.8 Hz, 2H), 6.87 (d, J = 10.4 Hz, 2H), 5.69 (s, 1H), 5.41 (s, 1H), 4.47 (s, 2H), 1.45 (s, 3H).

Compound 243



Step 1: 3-[4-(difluoromethanesulfonamido)-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

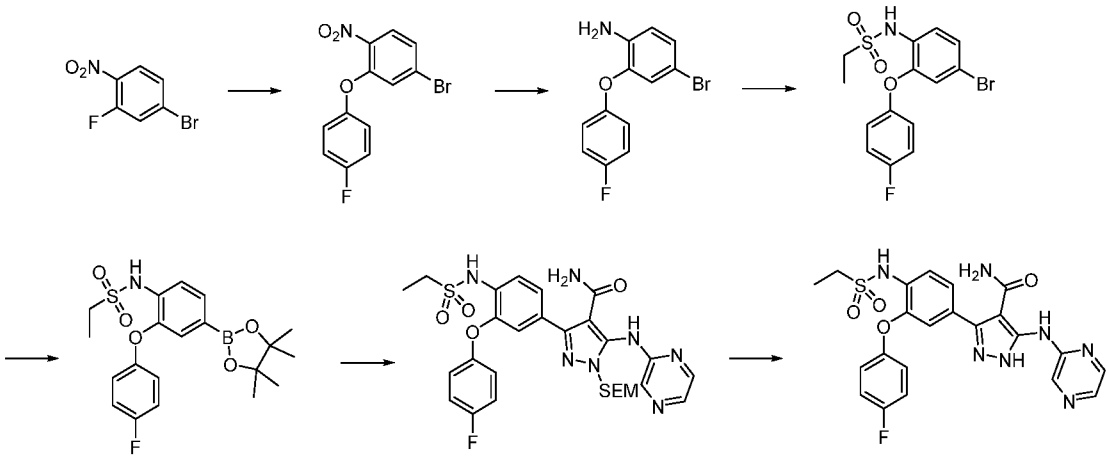
A mixture of 3-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-nitrophenyl}-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (530 mg, 892 µmol), F_2CHSO_2Cl (200 mg, 1.33 mmol) and DCM:pyridine (1:1, 8 mL) was stirred at RT. After 16 h, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 20:1) to afford the title product (150 mg, 25%) as a yellow solid. LCMS (Method A): 3.91 min; m/z: 678.2 $[M+H]^+$.

Step 2: 3-[4-(difluoromethanesulfonamido)-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 243)

A mixture of 3-[4-(difluoromethanesulfonamido)-2-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(pyridin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (90 mg, 132 µmol) in DCM:TFA (9:1, 10 mL) was stirred at RT for 16 h. The reaction mixture was neutralized to pH 7-8 with NH_4OH then diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), and then concentrated to afford the title product (30 mg, 42%) as a yellow solid. LCMS (Method A): 3.39 min; m/z: 548.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 11.21 (s, 1H), 9.72 (s, 1H), 9.32 (s, 1H), 8.23 (s, 1H), 8.12 (d, J = 2.8

Hz, 1H), 7.35 (t, *J* = 6.0 Hz, 3H), 7.14 (t, *J* = 9.2 Hz, 3H), 6.91 (t, *J* = 8.0 Hz, 2H), 5.66 (br s, 1H), 5.38 (q, *J* = 6.0 Hz, 1H), 1.44 (s, 3H).

Compound 19



Step 1: 4-bromo-2-(4-fluorophenoxy)-1-nitrobenzene

A mixture of 4-bromo-2-fluoro-1-nitrobenzene (10 g, 45.4 mmol), 4-fluorophenol (6.09 g, 54.4 mmol), and K_2CO_3 (18.7 g, 136 mmol) in acetone (100 mL) was stirred at 80 °C overnight. The mixture was filtered, concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (12 g, 99%) as a yellow oil.

Step 2: 4-bromo-2-(4-fluorophenoxy)aniline

A mixture of 4-bromo-2-(4-fluorophenoxy)-1-nitrobenzene (14 g, 44.8 mmol), sat. aq. NH_4Cl (50 mL) and Zn dust (14.6 g, 224 mmol) in MeOH (50 mL) was stirred at 60 °C overnight. The mixture was filtered, and the filtrate concentrated under reduced pressure to afford the title product (13 g, >100%) as a yellow oil. LCMS (Method A): 4.13 min; m/z: 282.0 $[M+H]^+$.

Step 3: N-(4-bromo-2-(4-fluorophenoxy)phenyl)ethanesulfonamide

A mixture of 4-bromo-2-(4-fluorophenoxy)aniline (13 g, 46.0 mmol), $EtSO_2Cl$ (8.87 g, 69.0 mmol) and pyridine (10.9 g, 138 mmol) in $CHCl_3$ (20 mL) was stirred at RT overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (8 g, 46%) as a yellow solid.

Step 4: N-(2-(4-fluorophenoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) ethanesulfonamide

A mixture of N-(4-bromo-2-(4-fluorophenoxy)phenyl)ethanesulfonamide (1 g, 2.67 mmol), B_2pin_2 (744 mg, 2.93 mmol), $Pd(dppf)Cl_2$ (217 mg, 267 µmol) and KOAc (524 mg, 5.34 mmol) in degassed 1,4-dioxane (10 mL) was stirred at 100 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (500 mg, 44%) as a white solid. LCMS (Method A): 4.50 min; m/z: 422.1 $[M+H]^+$.

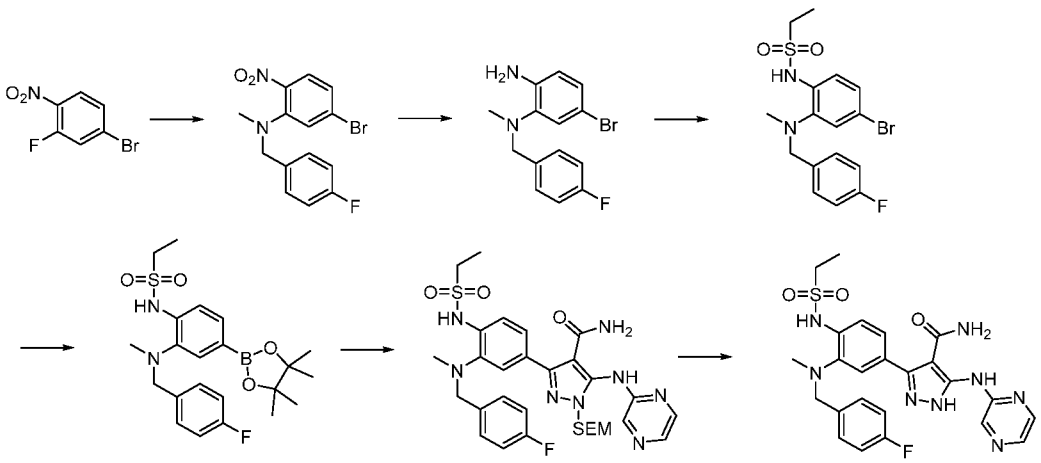
Step 5: 3-(4-(ethylsulfonamido)-3-(4-fluorophenoxy)phenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (150 mg, 362 µmol), N-(2-(4-fluorophenoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) ethanesulfonamide (228 mg, 543 µmol), $Pd(dppf)Cl_2$ (29.5 mg, 36.2 µmol) and Na_2CO_3 (114 mg, 1.08 mmol) in degassed 80% aq. 1,4-dioxane (5 mL) was stirred at 100 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by prep-TLC (DCM:MeOH, 10:1) to afford the title product (500 mg, 44%) as a white solid. LCMS (Method A): 3.95 min; m/z: 628.2 $[M+H]^+$.

Step 6: 3-(4-(ethylsulfonamido)-3-(4-fluorophenoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Compound 19)

A solution of 3-(4-(ethylsulfonamido)-3-(4-fluorophenoxy)phenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide (30 mg, 47.7 µmol) in TFA (3 mL) and DCM (3 mL) was stirred at 30 °C for 2 h. The mixture was neutralized to pH 7-8 with sat. aq. Na_2CO_3 solution and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 1:1) to afford the title product (8.4 mg, 35%) as a yellow solid. LCMS (Method A): 3.25 min; m/z: 498.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.64 (s, 1H), 9.25 (s, 1H), 8.30 (s, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.68 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 2.4 Hz, 2H), 7.26 (br s, 2H), 7.17 (d, J = 2.0 1H), 3.25 (br s, 2H), 1.31 (br s, 3H).

Compound 13



Step 1: 5-bromo-N-[(4-fluorophenyl)methyl]-N-methyl-2-nitroaniline

A mixture of 4-bromo-2-fluoro-1-nitrobenzene (100 mg, 0.4545 mmol), [(4-fluorophenyl)methyl](methyl)amine (69.5 mg, 0.499 mmol) and K_2CO_3 (125 mg, 0.909 mmol) in 60% aq. EtOAc (2.5 mL) was stirred at 85 °C for 16 hours. The mixture was acidified to pH 5-6 with 1.2 M aq. HCl and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (100 mg, 65%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): 7.73 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.29 (m, 2H), 7.18 (m, 2H), 7.11 (m, 1H), 4.41 (s, 2H), 2.71 (s, 3H).

Step 2: 5-bromo-N1-(4-fluorobenzyl)-N1-methylbenzene-1,2-diamine

A mixture of 5-bromo-N-[(4-fluorophenyl)methyl]-N-methyl-2-nitroaniline (4.3 g, 12.6 mmol), sat. aq. NH_4Cl (2 mL) and Zn dust (4.09 g, 63.0 mmol) in MeOH (20 mL) was stirred at 60 °C overnight. The mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with H_2O (2 x 20 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the title product (3.67 g, 94%) as a black oil. ^{1}H NMR (400 MHz, DMSO-d_6): 7.34 (m, 2H), 7.12 (m, 2H), 6.97 (d, J = 2.4 Hz, 1H), 6.92 (m, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.02 (s, 2H), 3.96 (s, 2H), 2.45 (s, 3H).

Step 3: N-(4-bromo-2-{[(4-fluorophenyl)methyl](methyl)amino}phenyl)ethane-1-sulfonamide

A mixture of 5-bromo-N1-[(4-fluorophenyl)methyl]-N1-methylbenzene-1,2-diamine (3.67 g, 11.8 mmol), $EtSO_2Cl$ (2.27 g, 17.7 mmol) and pyridine (10 mL) in $CHCl_3$ (10 mL) was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (4 g, 85%) as a black oil. LCMS (Method A): 3.35 min; m/z: 402.8 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (s, 1H), 7.36 (m, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.25 (m, 2H), 7.12 (t, J = 17.6 Hz, 2H), 4.08 (s, 2H), 3.22 (m, 2H), 2.55 (s, 3H), 1.22 (t, J = 14.8 Hz, 3H).

Step 4: N-(2-((4-fluorobenzyl)(methyl)amino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide

A mixture of N-(4-bromo-2-{[(4-fluorophenyl)methyl](methyl)amino}phenyl)ethane-1-sulfonamide (800mg, 1.99mmol), B_2pin_2 (756 mg, 2.98 mmol), $Pd(dppf)Cl_2$ (145 mg, 199 µmol) and KOAc (585 mg, 5.97 mmol) in degassed 1,4-dioxane (10 mL) was heated at 100 °C overnight. The mixture was filtered concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (PE:EtOAc, 10:1) to afford the title product (800 mg, 89%) as a yellow liquid. LCMS (Method A): 4.69 min; m/z:

449.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.50 (s, 1H), 7.39 (m, 4H), 7.13 (t, J = 18.0 Hz, 2H), 3.99 (s, 2H), 3.24 (m, 2H), 3.16 (s, 3H), 1.28 (s, 12H), 1.19 (m, 3H).

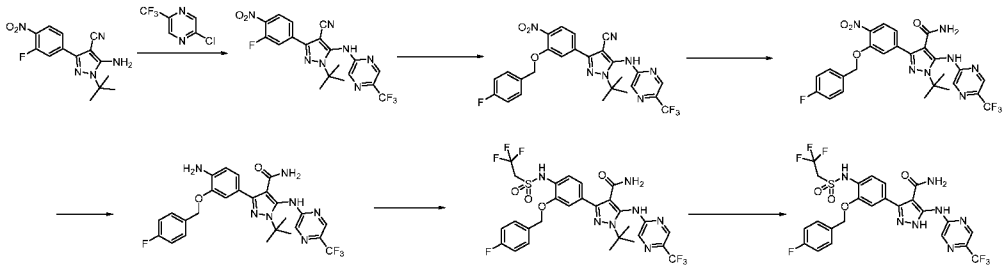
Step 5: 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)(methyl)amino)phenyl)-5-(pyrazin-2-ylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of N-(2-{[(4-fluorophenyl)methyl](methyl)amino}-4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)phenyl)ethane-1-sulfonamide (300 mg, 0.67 mmol), 3-bromo-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (276 mg, 669 µmol), $Pd(dppf)Cl_2$ (48.9 mg, 66.9 µmol) and Na_2CO_3 (211 mg, 2.00 mmol) in degassed 80% aq. 1,4-dioxane (12.5 mL) was stirred at 100 °C overnight. The reaction mixture was diluted with H_2O (20 mL) and then extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford the title product (450 mg, >100%) as a brown liquid. LCMS (Method A): 4.16 min; m/z: 655.2 $[M+H]^+$.

Step 6: 3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)(methyl)amino)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Compound 13)

A solution of 3-(4-ethanesulfonamido-3-{[(4-fluorophenyl)methyl](methyl)amino}phenyl)-5-[(pyrazin-2-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (200 mg, 305 µmol) in TFA (3 mL) and DCM (3 mL) was stirred at RT for 2 h. The reaction mixture was neutralized to pH 7-8 with sat. aq. Na_2CO_3 solution and then extracted with DCM (3 x 50 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (40 mg, 25%) as a yellow solid. LCMS (Method A): 3.62 min; m/z: 525.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.68 (s, 1H), 9.20 (s, 1H), 8.67 (s, 1H), 8.22-8.21 (m, 1H), 8.13 (d, J = 4.0 Hz, 1H), 7.50-7.46 (m, 2H), 7.42-7.38 (m, 2H), 7.33-7.31 (m, 1H), 7.13 (t, J = 17.6 Hz, 2H), 4.09 (s, 2H), 3.3-3.28 (m, 1H), 2.58 (s, 3H), 1.26-1.24 (m, 3H).

Compound 238



Step 1: 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carbonitrile

A mixture of 5-amino-1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-1H-pyrazole-4-carbonitrile (2.20 g, 7.25 mmol), 2-chloro-5-(trifluoromethyl)pyrazine (1.10 g, 6.02 mmol), $Pd_2(dba)_3$ (551 mg, 602 µmol), Xantphos (692 mg, 1.20 mmol) and Cs_2CO_3 (5.86 g, 18.0 mmol) in 1,4-dioxane (120 mL) was stirred at 100 ºC under N_2. After 16 h, the solvent was concentrated and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the title product (1.70 g, 63%) as a yellow solid. LCMS (Method A): 4.32 min; m/z: 450.1 $[M+H]^+$.

Step 2: 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carbonitrile

To a solution of (4-fluorophenyl)methanol (238 mg, 1.89 mmol) in THF (30 mL) at 0 ºC, was added NaH (136 mg, 5.67 mmol). After 10 min, 1-tert-butyl-3-(3-fluoro-4-nitrophenyl)-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carbonitrile (850 mg, 1.89 mmol) was added and the resulting mixture was stirred at RT for 16 h. The solvent was removed by concentration and the residue was diluted with EtOAc (100 mL). The organic layer was washed with H_2O (3 x 100 mL), dried (Na_2SO_4) and then concentrated under reduced pressure to afford the title product (1.30 g, >100%) as a yellow solid. LCMS (Method A): 4.52 min; m/z: 556.2 $[M+H]^+$.

Step 3: 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carbonitrile (1.2 g, 2.16 mmol) and Ghaffar-Parkins catalyst (92.2 mg, 216 µmol) in 50% aq. 1,4-dioxane (40 mL) was stirred at 100 ºC. After 16 h, the reaction mixture was diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layer was washed (brine), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (450 mg, 36%) as a yellow solid. LCMS (Method A): 4.15 min; m/z: 574.1 $[M+H]^+$.

Step 4: 3-{4-amino-3-[(4-fluorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (380 mg, 662 µmol), Zn powder (215 mg, 3.30 mmol), sat. NH_4Cl (6 mL) and MeOH (30 mL) was stirred at 60 ºC. After 16 h, the mixture was filtered and the filtrate concentrated. The residue was diluted with H_2O (100 mL) and then extracted with EtOAc (200 mL). The organic layer was washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 1:1) to afford the title product (200 mg, 55%) as a yellow solid. LCMS (Method A): 3.83 min; m/z: 544.2 $[M+H]^+$.

Step 5: 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

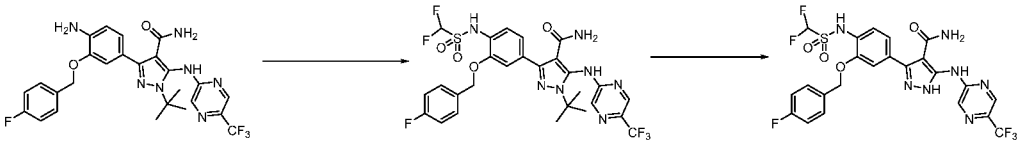
To a solution of 3-{4-amino-3-[(4-fluorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (100 mg, 183 µmol) and pyridine (43.4 mg, 549 µmol) in $CHCl_3$ (20 mL) was added 2,2,2-trifluoroethane-1-sulfonyl chloride (50.0 mg, 274 µmol). The mixture was stired at RT for 16 h and then concentrated under reduced pressure. The crude residue was purified by prep-

TLC (DCM:MeOH, 20:1) to afford the title product (40 mg, 31%) as a yellow solid. LCMS (Method A): 4.02 min; 690.1 $[M+H]^+$.

Step 6: 3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (Compound 238)

A mixture of 1-tert-butyl-3-{3-[(4-fluorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido)phenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (60 mg, 87.0 µmol) in DCM:TFA (1:1, 4 mL) was stirred at RT. After 16 h, the mixture was concentrated and the residue neutralized to pH 7-8 with sat. Na_2CO_3. The residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title compound (10 mg, 18%) as a white solid. LCMS (Method A): 3.85 min; 634.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.24 (s, 1H), 10.13 (s, 1H), 9.93 (s, 1H), 9.18 (s, 1H), 8.65 (s, 1H), 7.60 (s, 2H), 7.49-7.42 (m, 2H), 7.25-7.21 (m, 3H), 5.19 (s, 2H), 4.33 (t, J = 8.8 Hz, 2H).

Compound 246



Step 1: 1-tert-butyl-3-[4-(difluoromethanesulfonamido)-3-[(4-fluorophenyl)methoxy]phenyl]-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

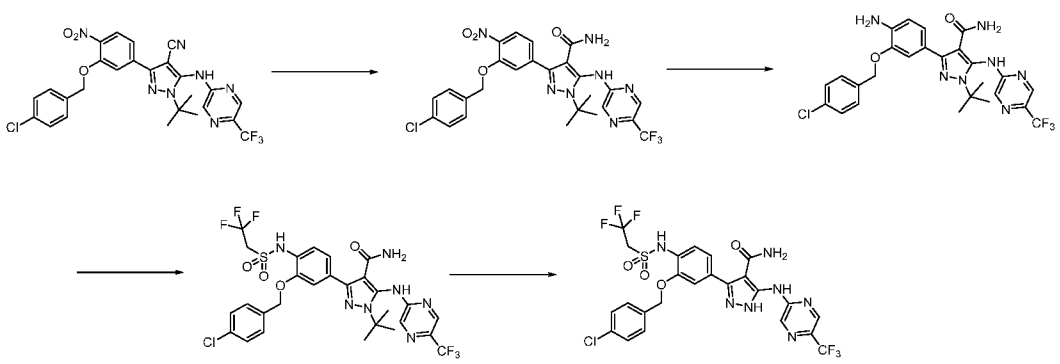
To a solution of 3-{4-amino-3-[(4-fluorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (100 mg, 183 µmol) and pyridine (43.4 mg, 549 µmol) in $CHCl_3$ (20 mL) was added CF_2HSO_2Cl (41.2 mg, 274 µmol). The mixture was stirred at RT for 16 h, and then concentrated reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford

the title product (30 mg, 25%) as a yellow solid. LCMS (Method A): 3.97 min; 658.1 $[M+H]^+$.

Step 2: 3-[4-(difluoromethanesulfonamido)-3-[(4-fluorophenyl)methoxy]phenyl]-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (Compound 246)

A mixture of 1-tert-butyl-3-[4-(difluoromethanesulfonamido)-3-[(4-fluorophenyl)methoxy]phenyl]-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (40 mg, 60.8 µmol) in DCM:TFA (1:1, 4 mL) was stirred at RT. After 16 h, the mixture was concentrated and the residue neutralized to pH 7-8 with sat. Na_2CO_3. The crude residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title compound (6.0 mg, 16%) as a white solid. LCMS (Method A): 3.79 min; 602.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) 13.45 (s, 1H), 10.56 (s, 1H), 10.12 (s, 1H), 9.06 (s, 1H), 8.63 (s, 1H), 7.61 (q, J = 4.8 Hz, 2H), 7.53 (s, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.26-7.22 (m, 3H), 6.94 (t, J = 52.8 Hz, 1H), 5.22 (s, 2H).

Compound 234



Step 1: 1-tert-butyl-3-{3-[(4-chlorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(4-chlorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carbonitrile (400 mg, 21.9 mmol) and Ghaffar-Parkins catalyst (150 mg, 351 µmol) in 50% aq. 1,4-dioxane (100 mL) was stirred at 100 ºC. After 16 h, the mixture was concentrated and the residue

diluted with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to afford the title product (400 mg, 100%). LCMS (Method A): 4.28 min; m/z: 590.2 $[M+H]^+$.

Step 2: 3-{4-amino-3-[(4-chlorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 1-tert-butyl-3-{3-[(4-chlorophenyl)methoxy]-4-nitrophenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (300 mg, 508 µmol), Zn powder (165 mg, 2.53 mmol), sat. NH_4Cl (5 mL) and MeOH (15 mL) was stirred at 60 ºC under N_2. After 16 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM:MeOH, 30:1) to afford to the title product (200 mg, 70%) as a yellow solid. LCMS (Method A): 3.99 min; m/z: 560.1 $[M+H]^+$.

Step 3: 1-(tert-butyl)-3-(3-((4-chlorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide

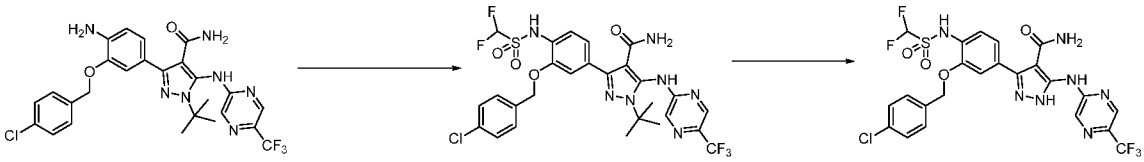
A solution of 3-{4-amino-3-[(4-chlorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (50 mg, 89.2 µmol) and 2,2,2-trifluoroethane-1-sulfonyl chloride (16.2 mg, 89.2 µmol) in $CHCl_3$:pyridine (1:1, 6 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the residue diluted with H_2O (30 mL) and then extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (25 mg, 50%) as a yellow solid. LCMS (Method A): 4.14 min; m/z: 706.1 $[M+H]^+$.

Step 4: 3-{3-[(4-chlorophenyl)methoxy]-4-(2,2,2-trifluoroethanesulfonamido) phenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (Compound

234)

A solution of 1-(tert-butyl)-3-(3-((4-chlorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide (124 mg, 190 µmol) in DCM:TFA (1:1, 10 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the residue was neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (10 mg, 20%) as a yellow solid. LCMS (Method A): 3.07 min; m/z: 650.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.20 (s, 1H), 10.17 (s, 1H), 9.18 (s, 1H), 8.65 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 5.18 (s, 1H), 4.22 (t, J = 9.2 Hz, 2H).

Compound 235



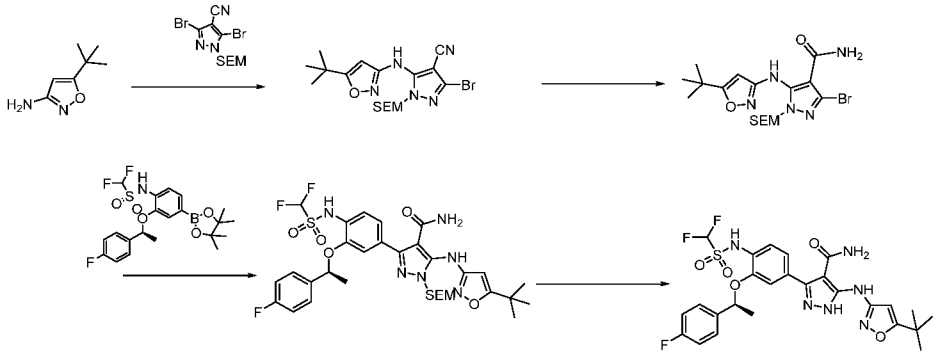
Step 1: 1-(tert-butyl)-3-(3-((4-chlorobenzyl)oxy)-4-((difluoromethyl) sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide

A solution of 3-{4-amino-3-[(4-chlorophenyl)methoxy]phenyl}-1-tert-butyl-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (50 mg, 89.2 µmol) and F_2CHSO_2Cl (20.0 mg, 133 µmol) in $CHCl_3$:pyridine (1:1, 6 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated and the residue diluted with H_2O (30 mL) and then extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-TLC (DCM;MeOH, 15:1) to afford the title product (20 mg, 33%) as a yellow solid. LCMS (Method A): 4.05 min; m/z: 674.2 $[M+H]^+$.

Step 2: 3-(3-((4-chlorobenzyl)oxy)-4-((difluoromethyl)sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide (Compound 235)

A solution of 1-tert-butyl-3-{3-[(4-chlorophenyl)methoxy]-4-(difluoromethanesulfonamido)phenyl}-5-{[5-(trifluoromethyl)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide (20.0 mg, 29.6 μmol) in DCM:TFA (1:1, 10 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure and the residue neutralized to pH 7-8 with sat. Na_2CO_3. The resulting precipitate was collected by filtration and then purified by prep-TLC (DCM:MeOH, 15:1) to afford the title product (6.0 mg, 33%) as a yellow solid. LCMS (Method A): 3.99 min; m/z: 618.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 13.38 (s, 1H), 10.60 (s, 1H), 10.11 (s, 1H), 9.09 (s, 1H), 8.65 (s, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 7.4 Hz, 3H), 7.40 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.65 (s, 1H), 5.23 (s, 2H).

Compound 282



Step 1: 3-bromo-5-[(5-tert-butyl-1,2-oxazol-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile

A mixture of 5-tert-butyl-1,2-oxazol-3-amine (500 mg, 3.56 mmol), 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (1.35 g, 3.56 mmol), $Pd_2(dba)_3$ (325 mg, 356 μmol), Xantphos (411 mg, 712 μmol) and Cs_2CO_3 (3.45 g, 10.6 mmol) in degassed 1,4-dioxane (30 mL) was heated at 100 °C under N_2 for 14h. The reaction was filtered through a pad of celite and the filtrate was concentrated

under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 3:1) to give the title compound (600 mg, 39%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H), 6.04 (d, J = 2.3 Hz, 1H), 5.42 (d, J = 2.4 Hz, 2H), 3.51 (t, J = 7.7 Hz, 2H), 1.28 (d, J = 2.3 Hz, 9H), 0.81 (t, J = 7.6 Hz, 2H), -0.09 (d, J = 2.3 Hz, 10H).

Step 2: 3-bromo-5-((5-(tert-butyl)isoxazol-3-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-5-[(5-tert-butyl-1,2-oxazol-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (1274 mg, 2.88 mmol) and Ghaffar-Parkins catalyst (121 mg, 0.288 mmol) in in 50% aq. 1,4-dioxane (80 mL) was stirred at 100 °C under N_2 overnight. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (PE:EtOAc, 4:1 to 1:4) to give the title product (700 mg, 1.52 mmol, 53%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 8.93 (s, 1H), 7.41 (s, 1H), 7.07 (s, 1H), 5.80 (d, J = 1.5 Hz, 1H), 5.32 (d, J = 1.5 Hz, 2H), 3.46 (t, J = 8.2 Hz, 2H), 1.23 (d, J = 1.6 Hz, 9H), 0.78 (t, J = 8.2 Hz, 2H), -0.09 (d, J = 1.5 Hz, 9H).

Step 3: 5-[(5-tert-butyl-1,2-oxazol-3-yl)amino]-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-5-[(5-tert-butyl-1,2-oxazol-3-yl)amino]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (500 mg, 1090 µmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (537 mg, 1140 µmol), Pd(dppf) Cl_2 (89 mg, 109 µmol) and Na_2CO_3 (231 mg, 2180 µmol) in water (5 mL) and degassed 1,4-dioxane (20 mL) was stirred at 100 °C under microwave for 1h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (PE:EtOAc, 4:1 to 1:4) to give the title product (300 mg, 38%) as a yellow solid. LCMS (Method A): 4.47 min; m/z: 723.4 $[M+H]^+$.

Step 4: (S)-5-((5-(tert-butyl)isoxazol-3-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide (Compound 282)

A mixture of 5-[(5-tert-butyl-1,2-oxazol-3-yl)amino]-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (300 mg, 415 µmol) in TFA (0.5 mL) and dichloromethane (20 mL) was stirred at RT under N_2 for 1h. The reaction mixture was adjusted to pH = 8 with sat. aq. Na_2CO_3. The mixture was poured into water (5 mL) and the organics were extracted with EtOAc (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH, 15:1) to give the title product (58.8 mg, 24%) as a white solid. LCMS (Method A): 4.88 min, m/z 593.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.72 (s, 1H), 10.53 (s, 1H), 9.14 (s, 1H), 7.58-7.52 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20-7.13 (m, 2H), 7.06 (d, *J* = 12.5 Hz, 2H), 6.54 (s, 1H), 5.62 (d, *J* = 6.5 Hz, 1H), 1.55 (d, *J* = 6.3 Hz, 3H), 1.29 (s, 9H).

The examples below (Table 23) were synthesized according to procedures described in the previous examples. These compounds and their tautomers, enantiomers, stereoisomers and salts are further preferred embodiments of the present invention.

Further exemplary compounds prepared by the methods similar to those described herein are detailed in Table 24 below.

Table 23

Compound No	Name	Structure	LCMS data	NMR data	SM
270	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1,3-dimethyl-1H-pyrazol-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.36 min; m/z 564.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.44 (s, 1H), 10.52 (s, 1H), 8.09 (s, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.57 (dd, J = 8.6, 5.6 Hz, 2H), 7.38 (d, J = 7.4 Hz, 1H), 7.18 (t, J = 8.9 Hz, 2H), 7.13-6.86 (m, 3H), 5.67-5.59 (m, 1H), 3.71 (s, 3H), 2.09 (s, 3H), 1.57 (d, J = 6.3 Hz, 3H).	1,3-dimethyl-1H-pyrazol-4-amine
285	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.31 min; m/z 564.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.50-7.47 (m, 3H), 7.06 (dd, J = 8.0, 4.0 Hz, 4H), 6.80-6.53 (t, J = 5.2 Hz,1H), 5.53 (d, J = 8 Hz, 1H), 3.75 (s, 2H), 2.27 (s, 3H), 1.67 (d, J = 4.0 Hz, 3H).	1,5-dimethyl-1H-pyrazol-3-amine
286	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1,4-dimethyl-1H-pyrazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.36 min, m/z 564.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.24 (s, 1H), 10.49 (s, 1H), 9.21 (s, 1H), 7.59-7.50 (m, 2H), 7.40 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.9 Hz, 2H), 7.09-7.01 (m, 2H), 7.00-6.82 (m, 1H), 5.58 (q, J = 6.3 Hz, 1H), 3.72 (s, 3H), 1.92 (s, 3H), 1.56 (d, J = 6.3 Hz, 3H).	1,4-dimethyl-1H-pyrazol-3-amine
283	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1-methyl-1H-1,2,4-triazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.32 min, m/z: 551.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.18 (s, 1H), 7.51 (m, 3H), 7.09 (m, 4H), 6.77 (t, J = 53.4 Hz, 1H), 5.56 (q, J = 18.8 Hz, 1H), 3.88 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).	1-methyl-1H-1,2,4-triazol-3-amine

308	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.55 min, m/z: 592.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.54 (s, 1H), 10.50 (s, 1H), 8.82 (s, 1H), 7.55 (dd, J = 8.8, 5.6 Hz, 2H), 7.36 (d, J = 4.2 Hz, 1H), 7.16 (t, J = 8.8 Hz, 2H), 7.11-7.06 (m, 2H), 6.98 (t, J = 52.4 Hz, 1H), 6.24 (s, 1H), 5.60 (q, J = 5.6 Hz, 1H), 4.73 (s, 2H), 4.04-3.93 (m, 4H), 1.56 (d, J = 6.6 Hz, 3H).
277	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.79 min, m/z 618.2 $[M+H]^+$.	^{1}HNMR (400 MHz, DMSO-d_6): 12.67(s, 1H), 10.54 (s, 1H), 9.04 (s, 1H), 7.58 (dd, J = 8.8, 5.6 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.20-7.15 (m, 3H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.02 (t, J = 52.4 Hz, 1H), 6.92 (s, 1H), 5.64 (q, J = 6.0 Hz, 1H), 3.83 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
274	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-ethylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.68 min; m/z 565.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 9.82 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.30 (dd, J = 8.7, 5.2 Hz, 2H), 7.07 (q, J = 8.3 Hz, 3H), 6.92 (s, 1H), 6.38 (t, J = 53.5 Hz, 2H), 5.80 (s, 1H), 5.42 (q, J = 6.3 Hz, 1H), 5.17 (s, 2H), 2.64 (q, J = 7.6 Hz, 2H), 1.70 (d, J = 6.4 Hz, 3H), 1.26 (s, 3H).
284	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((4,5-dimethylthiazol-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.41 min; m/z: 581.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.56 (d, J = 8.3 Hz, 1H), 7.53-7.48 (m, 2H), 7.15 (d, J = 6.2 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 6.68 (t, J = 53.2 Hz, 1H), 5.56 (q, J = 6.3 Hz, 1H), 2.28 (s, 6H), 1.69 (d, J = 6.4 Hz, 3H).

294	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-methoxy-1-methyl-1H-pyrazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.09 min; m/z: 580.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.08 (s, 1H), 10.58 (s, 1H), 9.53 (s, 1H), 7.58 (t, J = 5.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.20-7.03 (m, 5H), 7.02 (t, J = 52.4 Hz, 1H), 6.37 (s, 0.5H), 6.63 (s, 1H), 5.27 (s, 1H), 3.07 (s, 3H), 3.00 (s, 3H), 1.58 (d, J = 5.6 Hz, 3H).	5-methoxy-1-methyl-1H-pyrazol-3-amine
295	(S)-5-((3-(tert-butyl)isoxazol-5-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.80 min; m/z: 593.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 10.59 (s, 1H), 9.72 (s, 1H), 7.57 (t, J = 5.6 Hz, 2H), 7.37 (d, J =8.0 Hz, 1H), 7.17 (t, J =8.8 Hz, 3H), 7.08 (d, J = 8.4 Hz, 1H), 6.93-6.68 (m, 1H), 6.25 (s, 0.5H), 5.91 (s, 1H), 5.63 (q, J = 6.4 Hz, 1H), 1.56 (d, J = 6.4 Hz, 3H), 1.25 (s, 9H).	3-(tert-butyl)isoxazol-5-amine
302	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((3-methylisoxazol-5-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.49 min, m/z: 551.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.94 (s, 1H), 10.55 (s, 1H), 9.73 (s, 1H), 7.58 (dd, J = 8.7, 5.5 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.21-7.17 (m, 2H), 7.17-6.88 (m, 3H), 5.85 (s, 1H), 5.62 (q, J = 6.2 Hz, 1H), 2.15 (s, 3H), 1.58 (d, J = 6.3 Hz, 3H).	3-methylisoxazol-5-amine
303	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(tetrahydro-2H-pyran-4-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.52 min, m/z: 621.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.55 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 8.7, 5.3 Hz, 2H), 7.13-7.05 (m, 4H), 6.05 (s, 1H), 5.56 (q, J = 6.4 Hz, 1H), 4.01 (ddd, J = 11.6, 4.3, 2.2 Hz, 2H), 3.56 (td, J = 11.6, 2.5 Hz, 2H), 2.95 (tt, J = 11.4, 4.1 Hz, 1H), 1.92-1.78 (m, 4H), 1.69 (d, J = 6.4 Hz, 3H).	5-(tetrahydropyran-4-yl)isoxazol-3-amine

306	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.39 min; m/z: 620.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.45 (s, 1H), 10.51 (s, 1H), 8.24 (s, 1H), 7.84 (s, 1H), 7.56 (t, J = 8.4 Hz, 2H), 7.51 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.8 Hz, 2H), 7.11 (d, J = 12 Hz, 2H), 7.07 (s, 0.3H), 7.02 (s, 0.4H), 6.89 (s, 0.2H), 5.62 (q, J = 5.6 Hz, 1H), 4.35-4.27 (m, 1H), 3.95 (d, J =10.4 Hz, 2H), 3.46 (t, J =9.6 Hz, 3H), 1.97-1.84 (m, 4H), 1.59 (d, J = 6.4 Hz, 3H).	1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-amine
281	(S)-5-((5-cyclobutylisoxazol-3-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.80 min; m/z: 591.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.58-7.44 (m, 3H), 7.14-7.05 (m, 3H), 6.65 (t, J = 53.3 Hz, 1H), 6.06 (s, 1H), 5.63-5.30 (m, 2H), 3.53 (p, J = 8.8 Hz, 1H), 2.42-2.31 (m, 2H), 2.29-2.22 (m, 1H), 2.10 (q, J = 9.3, 8.8 Hz, 1H), 1.99 (ddd, J = 24.3, 16.0, 8.5 Hz, 2H), 1.68 (d, J = 6.4 Hz, 3H), 1.31 (d, J = 10.9 Hz, 6H).	5-cyclobutylisoxazol-3-amine
289	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.86 min, m/z: 645.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.79 (s, 1H), 10.08 (s, 1H), 9.27 (s, 1H), 7.55 (dd, J = 8.5, 5.7 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.9 Hz, 3H), 7.10-7.01 (m, 2H), 6.90 (s, 1H), 6.62 (d, J = 48.0 Hz, 1H), 6.06 (s, 1H), 5.60 (q, J = 6.1 Hz, 1H), 1.55 (d, J = 6.3 Hz, 3H), 1.54-1.46 (m, 4H).	5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-amine

276	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(1-methylcyclopropyl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.80 min; m/z: 591.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.52 (s, 1H), 9.23 (s, 1H), 7.48 (t, J = 5.6 Hz, 2H), 7.35 (d, J =8.0 Hz, 1H), 7.12 (t, J = 8.8 Hz, 2H), 6.83 (t, J = 8.4 Hz, 2H), 6.57 (s, 1H), 6.41-6.14 (m, 1H), 5.63-5.58 (m, 1H), 1.48 (d, J =6.4 Hz, 3H), 1.41 (s, 3H), 1.08 (q, J = 4.4 Hz, 2H), 0.88 (q, J = 4.0 Hz, 2H), 6.21 (s, 1H), 5.30 (s, 2H), 3.05 (q, J =7.2 Hz, 2H), 1.15 (t, J =7.6 Hz, 3H).	5-(1-methylcyclopropyl)isoxazol-3-amine
288	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.83 min; m/z: 623.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.79 (s, 1H), 10.57 (s, 1H), 9.10 (s, 1H), 7.57 (dd, J = 8.6, 5.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.21-7.09 (m, 4H), 7.08-6.86 (m, 1H), 6.56 (s, 1H), 5.62 (q, J = 6.3 Hz, 1H), 3.39 (s, 2H), 3.24 (s, 3H), 1.57 (d, J = 6.3 Hz, 3H), 1.25 (s, 6H).	5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-amine
301	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((4-methyltetrahydro-2H-pyran-4-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.31 min; m/z: 634.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 10.58 (s, 1H), 9.78 (s, 1H), 7.64-7.51 (m, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.24-7.15 (m, 3H), 7.10 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 52.6 Hz, 1H), 6.28 (s, 1H), 5.89 (s, 1H), 5.61 (q, J = 6.3 Hz, 1H), 3.69 (dt, J = 11.6, 4.6 Hz, 2H), 3.46 (ddd, J = 11.8, 9.1, 2.8 Hz, 3H), 2.01-1.92 (m, 2H), 1.63-1.53 (m, 4H), 1.25 (s, 3H).	5-(4-methyltetrahydro-2H-pyran-4-yl)isoxazol-3-amine

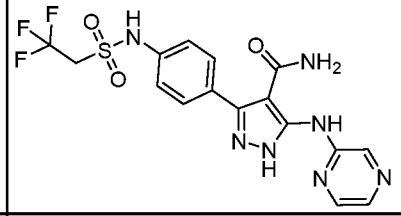
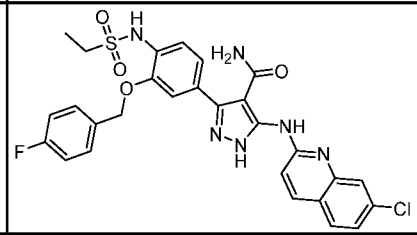
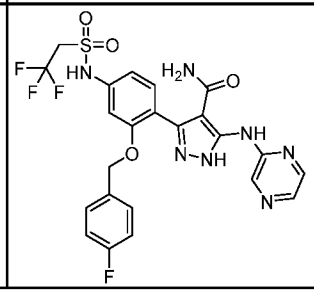
297	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(2-fluoropropan-2-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.71 min; m/z: 597.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 10.59 (s, 1H), 9.90 (s, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.38 (d, J = 7.9 Hz, 1H), 7.25-6.64 (m, 6H), 6.36 (s, 1H), 6.02 (s, 1H), 5.63 (t, J = 6.6 Hz, 1H), 1.67 (d, J = 21.9 Hz, 6H), 1.57 (d, J = 5.8 Hz, 3H).	5-(2-fluoropropan-2-yl)isoxazol-3-amine
292	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(3-methyloxetan-3-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.57 min; m/z: 607.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.94 (s, 1H), 10.57 (s, 1H), 9.85 (s, 1H), 7.57 (dd, J = 8.6, 5.6 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 8.9 Hz, 3H), 7.13-6.86 (m, 2H), 6.04 (s, 1H), 5.61 (q, J = 6.2 Hz, 1H), 4.76 (d, J = 5.7 Hz, 2H), 4.51 (d, J = 5.8 Hz, 2H), 1.62 (s, 3H), 1.57 (d, J = 6.3 Hz, 3H).	5-(3-methyloxetan-3-yl)isoxazol-3-amine
304	(S)-5-((5-(adamantan-1-yl)isoxazol-3-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A):4.27 min, m/z: 671.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 7.54 (d, J = 8.1 Hz, 1H), 7.53-7.48 (m, 2H), 7.13-7.04 (m, 4H), 6.67 (s, 1H), 6.04 (s, 1H), 5.56 (q, J = 6.4 Hz, 1H), 2.06 (d, J = 5.6 Hz, 3H), 1.98 (d, J = 2.8 Hz, 5H), 1.85-1.81 (m, 4H), 1.69 (d, J = 6.4 Hz, 3H).	5-(adamantan-1-yl)isoxazol-3-amine
305	3-(4-((difluoromethyl)sulfonamido)-3-((S)-1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(tetrahydrofuran-3-yl)isoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.46 min; m/z: 607.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 10.56 (s, 1H), 9.78 (s, 1H), 7.58 (t, J = 5.6 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.4 Hz, 3H), 7.12 (d, J = 8.0 Hz, 2H), 7.03 (s, 0.4H), 6.89 (s, 0.2H), 6.30 (s, 0.6H), 5.62 (q, J = 5.6 Hz, 1H), 3.97 (t, J =8.0 Hz, 1H), 3.88-3.83 (m, 1H), 3.76 (q, J = 7.2 Hz, 1H), 3.67 (t, J = 6.4 Hz, 1H), 3.44 (s, 1H), 2.31-2.22 (m, 1H), 2.02-1.93 (m, 1H), 1.58 (d, J =6.0 Hz, 3H).	5-(tetrahydrofuran-3-yl)isoxazol-3-amine

314	(S)-5-((5-(difluoromethyl)isoxazol-3-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.73 min; m/z: 587.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (s, 1H), 10.56 (s, 1H), 10.16 (s, 1H), 7.58 (dd, J = 8.5, 5.4 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.29-6.87 (m, 7H), 6.14 (s, 1H), 5.61 (q, J = 5.9 Hz, 1H), 1.58 (d, J = 6.1 Hz, 3H).	5-(difluoromethyl)isoxazol-3-amine
310	(S)-5-((5-cyclopropylisoxazol-3-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.73 min; m/z: 587.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.88 (s, 1H), 10.56 (s, 1H), 9.73 (s, 1H), 7.63-7.52 (m, 2H), 7.38 (dd, J = 8.1, 1.5 Hz, 1H), 7.18 (td, J = 8.9, 1.7 Hz, 3H), 7.08 (d, J = 8.1 Hz, 1H), 5.62 (d, J = 6.4 Hz, 1H), 1.90 (tt, J = 8.8, 5.1 Hz, 1H), 1.57 (d, J = 6.2 Hz, 2H), 1.01-0.94 (m, 2H), 0.75-0.69 (m, 2H).	5-cyclopropyl-1,2-oxazol-3-amine
312	(S)-5-((5-(tert-butyl)pyrazin-2-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.03 min; m/z: 604.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.94 (s, 1H), 10.52 (s, 1H), 9.41 (s, 1H), 9.13 (s, 1H), 8.26 (s, 1H), 7.58 (dd, J = 8.0, 5.8 Hz, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.23-7.11 (m, 4H), 5.75-5.56 (m, 1H), 1.58 (d, J = 6.3 Hz, 3H), 1.32 (s, 9H).	5-(tert-butyl)pyrazin-2-amine
296	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(tetrahydro-2H-pyran-4-yl)pyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.54 min; m/z: 632.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 9.23 (s, 1H), 8.35 (s, 1H), 8.16 (s, 1H), 7.49 (dd, J = 8.6, 5.5 Hz, 3H), 7.13-7.03 (m, 4H), 6.66 (t, J = 53.3 Hz, 1H), 5.54 (q, J = 6.3 Hz, 1H), 4.08-4.01 (m, 2H), 3.57 (td, J = 11.7, 9.5, 11.6, 2.5 Hz, 2H), 2.96 (td, J = 11.7, 9.5, 5.7 Hz, 1H), 1.95-1.78 (m, 4H), 1.68 (d, J = 6.3 Hz, 3H).	5-(tetrahydro-2H-pyran-4-yl)pyrazin-2-amine

278	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.31 min; m/z: 631.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.78 (s, 1H), 9.86 (s, 1H), 8.14 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.56-7.44 (m, 2H), 7.38-7.29 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 16.0, 7.4 Hz, 3H), 6.82 (d, J = 8.5 Hz, 1H), 6.34 (t, J = 53.6 Hz, 1H), 5.42 (d, J = 5.8 Hz, 1H), 5.12 (s, 2H), 4.11 (t, J = 7.2 Hz, 2H), 3.60-3.50 (m, 2H), 2.86-2.67 (m, 1H), 1.83-1.72 (m, 4H), 1.67 (d, J = 6.4 Hz, 3H).	5-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine
287	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((4-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.19 min; m/z: 631.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.83 (s, 1H), 10.56 (s, 1H), 9.81 (s, 1H), 9.41 (s, 1H), 8.19-8.04 (m, 1H), 7.91 (s, 1H), 7.57 (dd, J = 8.3, 5.7 Hz, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.18 (t, J = 8.8 Hz, 3H), 7.14-7.05 (m, 2H), 7.04-6.71 (m, 3H), 5.68-5.55 (m, 1H), 3.99-3.91 (m, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.76 (s, 1H), 1.77-1.61 (m, 4H), 1.57 (d, J = 6.2 Hz, 3H).	4-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine
316	(S)-5-((5-cyclopropylpyrazin-2-yl)amino)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.88 min; m/z: 588.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$): 12.39 (s, 1H), 10.07 (s, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.10 (d, J = 1.4 Hz, 1H), 7.78 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.34-7.28 (m, 2H), 7.12 (dd, J = 8.2, 1.7 Hz, 1H), 7.04 (t, J = 8.6 Hz, 2H), 6.97 (d, J = 1.7 Hz, 1H), 6.36 (t, J = 53.6 Hz, 1H), 5.39 (q, J = 7.3, 6.5 Hz, 1H), 5.21 (s, 2H), 2.03 (tt, J = 7.7, 5.1 Hz, 1H), 1.66 (d, J = 6.4 Hz, 3H), 1.00 (dd, J = 7.6, 5.3 Hz, 3H).	5-cyclopropylpyrazin-2-amine

318	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method D): 1.42 min; m/z: 619.8 $[M+H]^+$.	^{1}H NMR (300 MHz, DMSO-d_6): 12.46 (s, 1H), 8.85 (s, 1H), 7.54 (dd, J = 8.4, 5.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 8.7 Hz, 2H), 7.01 (d, J = 6.5 Hz, 2H), 6.79 (dd, J = 55.4 Hz, 1H), 6.38 (s, 1H), 5.61 (q, J = 5.8 Hz, 1H), 4.18 (s, 2H), 3.86 (s, 2H), 3.03 (s, 2H), 2.34 (s, 3H), 1.80 (s, 2H), 1.55 (d, J = 6.2 Hz, 3H).	

Table 24

Compound No.	Name	Structure	LCMS data	NMR data
137	5-(pyrazin-2-ylamino)-3-(4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.08 min; m/z: 442.0 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.99 (s, 1H), 9.71 (s, 1H), 9.23 (s, 1H), 8.22 (s, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.10 (s, 1H), 4.50 (q, J = 9.6 Hz, 2H).
138	5-((7-chloroquinolin-2-yl)amino)-3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.83 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.56 (s, 1H), 10.40 (s, 1H), 9.10 (s, 1H), 8.48 (s, 1H), 8.25 (q, J = 8.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.63 (q, J = 5.6 Hz, 2H), 7.46-7.37 (m, 4H), 7.27-7.21 (m, 3H), 6.35 (s, 1H), 5.20 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).
139	3-(2-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.92 min; m/z: 566.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.83 (s, 1H), 9.79 (s, 1H), 9.32 (s, 1H), 8.22 (m, 1H), 8.10 (d, J = 3.2 Hz, 1H), 7.41 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.8 Hz, 2H), 6.97 (s, 1H), 6.84 (d, J = 14.4 Hz, 1H), 5.07 (s, 2H), 4.20 (s, 2H).

140	3-(2-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.92 min; m/z: 633.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.85 (s, 1H), 10.83 (s, 1H), 9.89 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 7.6 Hz, 1H), 7.44-7.39 (m, 3H), 7.30 (d, J = 7.2 Hz, 1H), 7.17 (t, J = 8.8 Hz, 2H), 7.10-7.09 (m, 1H), 6.97-6.95 (m, 1H), 5.11 (s, 2H), 4.64 (q, J = 10.4 Hz, 2H).
141	3-(4-(ethylsulfonamido)-2-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.58 min; m/z: 579.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.82 (s, 1H), 10.16 (s, 1H), 9.87 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.44-7.41 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.19-7.15 (m, 2H), 7.09-7.08 (m, 1H), 6.96-6.93 (m, 1H), 5.69 (s, 1H), 5.09 (s, 1H), 3.17-3.15 (m, 2H), 1.20 (t, J = 7.2 Hz, 1H).
142	3-(4-(ethylsulfonamido)-3-((4-fluoro-2,6-dimethylbenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.13 min; m/z: 540.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (s, 1H), 9.66 (s, 1H), 9.27 (s, 1H), 8.23-8.22 (m, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.55 (br s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 8.0, 1.6Hz, 1H), 6.98 (d, J = 9.6 Hz, 2H), 5.11 (s, 2H), 2.96 (q, J = 14.0, 6.8 Hz, 2H), 2.37 (s, 6H), 1.07 (t, J = 7.2 Hz, 3H).
143	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.55 min; m/z: 596.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (s, 1H), 9.94 (s, 1H), 9.41 (s, 1H), 8.84 (s, 1H), 7.98 (s, 1H), 7.59 (q, J = 5.6 Hz, 2H), 7.43-7.40 (m, 1H), 7.26 -7.17 (m, 4H), 5.18 (s, 2H), 4.30 (d, J = 10.8 Hz, 2H), 3.86 (s, 3H).

144	3-(3-(1-(4-fluorophenyl)cyclopropoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.27 min; m/z: 592.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.97 (s, 1H), 10.06 (s, 1H), 9.62 (s, 1H), 9.21 (s, 1H), 8.20 (s, 1H), 8.09 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.8 Hz, 3H), 7.17-7.04 (m, 4H), 6.21 (s, 1H), 4.47 (d, J = 8.8 Hz, 2H), 1.47 (s, 2H), 1.40 (s, 2H).
145	3-(4-((difluoromethyl)sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method B): 1.63 min; m/z: 477.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 11.27 (s, 1H), 9.89 (s, 1H), 8.53 (s, 1H), 8.06 (t, J = 9.2 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4Hz, 2H), 7.22 (s, 1H), 6.17 (s, 1H).
146	3-(3-((4-chloro-3-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.46 min; m/z: 613.9 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.00 (s, 1H), 9.52 (s, 1H), 9.16 (s, 1H), 8.11 (s, 1H), 7.70-7.61 (m, 2H), 7.46-7.40 (m, 4H), 7.22-7.19 (m, 1H), 6.22 (s, 1H), 5.21 (s, 2H), 3.11-3.05 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H).
147	3-(4-((difluoromethyl)sulfonamido)-3-(4-fluorophenoxy)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.90 min; m/z: 587.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 10.91 (s, 1H), 9.61 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.37 (m, 1H), 7.27 (m, 3H), 7.18 (m, 2H), 7.07 (m, 2H).

148	3-(3-(4-fluorophenoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.01 min; m/z: 619.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (s, 1H), 10.38 (s, 1H), 9.68 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.97 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.38 (m, 1H), 7.29 (m, 3H), 7.19 (m, 2H), 7.07 (s, 1H), 4.52 (m, 2H),
149	3-(4-(ethylsulfonamido)-3-(4-fluorophenoxy)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.82 min; m/z: 565.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 9.70 (s, 1H), 8.17 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.36 (m, 1H), 7.27 (m, 3H), 7.15 (m, 2H), 7.07 (d, J = 2.0 Hz, 1H), 3.13 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 2H).
150	3-(3-((3-chloro-4-fluorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.38 min; m/z: 560.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (br s, 1H), 9.35 (br s, 1H), 9.16 (br s, 1H), 8.11 (s, 1H), 7.88 (dd, J = 7.2, 2.0 Hz, 1H), 7.59-7.37 (m, 5H), 7.18 (dd, J = 8.4, 2.0 Hz, 1H), 5.19 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H).
151	3-(3-((3,4-difluorobenzyl)oxy)-4-((difluoromethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.23 min; m/z: 619.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 10.61 (s, 1H), 9.72 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.97 (t, J = 8.0 Hz, 1H), 7.71-7.66 (m, 1H), 7.51-7.39 (m, 4H), 7.30 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 52.8 Hz, 1H), 6.22 (s, 1H), 5.21 (s, 1H).

152	3-(4-(ethylsulfonamido)-3-(1-phenylcyclopropoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method B): 1.29 min; m/z: 520.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (br s, 1H), 9.60 (s, 1H), 9.31 (br s, 1H), 9.21 (s, 1H), 8.19 (s, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.44 (br s, 1H), 7.38-7.22 (m, 5H), 7.21-7.12 (m, 2H), 7.03 (br s, 1H), 6.18 (br s, 1H) 3.17 (q, J = 7.2 Hz, 2H), 1.49 (m, 2H), 1.42 (m, 2H) 1.32 (t, J = 7.6 Hz, 3H).
153	3-(4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.60 min; m/z: 509.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 10.08 (s, 1H), 8.53 (s, 1H), 8.08 (s, 2H), 7.37 (d, J = 8.4Hz, 3H), 7.14 (d, J = 8.4 Hz, 2H), 5.96 (s, 1H), 4.01 (t, J = 4.8 Hz, 2H).
154	(S)-3-(3-(1-(4-fluorophenyl)ethoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyridine-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.00 min; m/z: 578.9 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 8.28 (s, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.54-7.48 (m, 3H), 7.14-7.05 (m, 5H), 6.93 (t, J = 4.8 Hz, 1H), 5.58 (q, J = 6.0 Hz, 1H), 4.24 (q, J = 9.2 Hz, 2H), 1.69 (d, J = 6.4 Hz, 2H).
155	3-(3-((3-chloro-4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.58 min; m/z: 614.1, 616.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (br s, 1H), 12.02 (br s, 1H), 9.51 (br s, 1H), 9.16 (br s, 1H), 8.11 (s, 1H), 7.83 (dd, J = 7.2, 2.0 Hz, 1H), 7.58-7.38 (m, 5H), 7.20 (dd, J = 7.6, 2.0 Hz, 1H), 5.19 (s, 2H), 4.34 (q, J = 10.0, Hz, 2H), 2.40 (s, 3H).
156	3-(4-(ethylsulfonamido)-3-((5-fluoropyridin-2-yl)methoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.03 min; m/z: 513.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.63 (s, 1H), 9.24 (s, 1H), 8.58 (s, 1H), 8.22 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.84 (t, J = 6.8 Hz, 2H), 7.48 (m, 4H), 7.21 (m, 1H), 6.25 (s, 1H), 5.28 (s, 2H), 3.09 (m, 2H), 1.18 (t, J = 14.8 Hz, 3 H).

157	3-(3-((4-chlorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.85 min; m/z: 612.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.83 (s, 1H), 9.45 (s, 1H), 8.84 (s, 1H), 7.97 (s, 1H), 7.54 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 7.06 (s, 1H), 5.14 (s, 2H), 3.86 (m, 3H), 3.35 (m, 2H).
158	5-((5-cyclopropylpyrazin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.14 min; m/z: 428.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.88 (s, 1H), 9.55 (s, 1H), 9.05 (s, 1H), 8.30 (s, 1H), 8.18 (S, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.17 (q, J = 14.8 Hz, 2H), 2.11 (m, 1H), 1.22 (m, 3H), 0.93 (m, 2H), 0.85 (m, 2H).
159	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.63 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.71 (s, 1H), 9.96 (s, 1H), 8.75 (s, 1H), 8.39 (s, 1H), 9.96 (d, J = 11.2 Hz, 1H), 7.62-7.58 (m, 2H), 7.43-7.40 (m, 2H), 7.26-7.22 (m, 2H), 7.19-7.17 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.18 (s, 2H), 4.31 (q, J = 10.0 Hz, 2H), 3.80 (s, 3H).
160	3-(3-((3,4-difluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyridine-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.35 min; m/z: 583.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.89 (s, 1H), 9.94 (s, 1H), 9.50 (s, 1H), 8.18 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.72-7.69 (m, 2H), 7.51-7.40 (m, 4H), 7.21 (d, J = 7.6 Hz, 1H), 6.92-6.86 (m, 1H), 6.13 (s, 1H), 5.20 (s, 2H), 4.38 (q, J = 9.2 Hz, 2H).

161	3-(3-(1-phenylcyclopropoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.62 min; m/z: 574.3 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (s, 1H), 10.05 (br s, 1H), 9.63 (s, 1H), 9.22 (s, 1H), 8.19 (s, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.50-7.38 (m. 1H), 7.32-7.22 (m, 5H), 7.21-7.10 (m, 2H), 7.03 (s, 1H), 6.20 (br s, 1H), 4.44 (d, J = 6.8 Hz, 2H), 1.52-1.45 (m, 2H), 1.51-1.38 (m, 2H).
162	3-(3-((4-chlorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.68 min; m/z: 596.1, 598.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (br s, 1H), 9.98 (br s, 1H), 9.51 (br s, 1H), 9.16 (br s, 1H), 8.11 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.44-7.34 (m, 3H), 7.20 (dd, J = 8.0, 2.0 Hz, 1H), 5.21 (s, 2H), 4.33 (q, J = 9.6 Hz, 2H), 2.40 (s, 3H).
163	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.55 min; m/z: 560.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.06 (br s, 1H), 10.02 (br s, 1H), 9.49 (br s, 1H), 9.15 (br s, 1H), 8.12 (s, 1H), 7.61-7.57 (m, 2H), 7.47-7.38 (m, 3H), 7.26-7.18 (m, 3H), 5.19 (s, 2H), 4.31 (q, J = 9.6 Hz, 2H), 2.39 (s, 3H).
164	(S)-3-(3-(1-(4-fluorophenyl)ethoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.55 min; m/z: 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.96 (s, 1H), 9.60 (s, 1H), 9.21 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 5.6 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.20-7.13 (m, 3H), 6.15 (s, 1H), 5.66 (q, J = 5.6 Hz, 1H), 4.52-4.41(m, 2H), 1.59 (d, J = 6.4 Hz, 3H).

165	3-(3-((4-chloro-3-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.62 min; m/z: 600.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 10.01 (s, 1H), 9.66 (s, 1H), 9.26 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.69-7.61 (m, 2H), 7.45-7.36 (m, 4H), 7.20 (d, J = 8.4 Hz, 1H), 6.22 (s, 1H), 5.21 (s, 2H),4.29 (s, 2H).
166	3-(3-((4-chloro-3-fluorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.46 min; m/z: 546.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.64 (s, 1H), 9.31 (s, 1H), 9.25 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.76-7.73 (m, 1H),7.73-7.76 (m, 1H), 7.48- 7.38 (m, 4H), 7.22-7.19 (m, 1H), 6.22 (s, 1H), 5.21 (s, 2H), 3.11-3.05 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H).
167	3-(3-(3-fluorophenoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.53 min; m/z: 552.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 10.36 (s, 1H), 9.55 (s, 1H), 9.20 (s, 1H), 8.20 (s, 1H), 8.09 (d, J = 2.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.46-7.41 (m, 2H), 7.21-7.19 (m, 1H), 6.99-6.94 (m, 2H), 4.50-4.48 (m, 2H).
168	3-(3-(4-chlorophenoxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.53 min; m/z: 568.1, 570.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.11 (br s, 1H), 9.55 (br s, 1H), 9.19 (br s, 1H), 8.19 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.59-7.56 (m, 1H), 7.44-7.35 (m, 4H), 7.14-7.06 (m, 3H), 4.42 (q, J = 9.6 Hz, 2H).

169	3-(4-(cyclopropanesulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.36 min; m/z: 524.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.31 (s, 1H), 8.44 (s, 1H), 8.32-8.23 (m, 1H), 8.08 (s, 1H), 7.61-7.54 (m, 3H), 7.34 (m, 1H), 7.20 (d, J = 9.2 Hz, 1H), 7.13 (t, J = 8.4 Hz, 2H), 5.24 (s, 1H), 2.60-2.54 (m, 1H), 1.12-0.98 (m, 2H), 0.90-0.85 (m, 2H).
170	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.49 min; m/z: 566.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.07 (s, 1H), 9.95 (s, 1H), 9.64 (s, 1H), 9.25 (s, 1H), 8.23-8.22 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.62-7.59 (m, 2H), 7.45-7.43 (m, 1H), 7.27-7.21 (m, 3H), 5.19 (s, 2H), 4.34 (q, J = 9.6 Hz, 2H).
171	3-(4-(ethylsulfonamido)-3-((4-fluoro-2-methylbenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A: 3.42 min; m/z: 526.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.63 (s, 1H), 9.25 (s, 1H), 9.13 (s, 1H), 8.22 (q, J = 1.6 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.55 (q, J = 6.4 Hz, 1H), 7.45 (t, J = 5.2 Hz, 2H), 7.20 (q, J = 1.6 Hz, 1H), 7.12 (q, J = 2.4 Hz, 1H), 7.08-7.03 (m, 1H), 5.14 (s, 2H), 3.03 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H).
172	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethoxy)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.99 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.60 (s, 1H), 9.19 (s, 1H), 7.95-7.88 (m, 2H), 7.61 (q, J = 6.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.27-7.17 (m, 3H), 6.68 (q, J = 1.6 Hz, 1H), 5.18 (s, 2H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).

173	5-((6-(difluoromethyl)pyridine-2-yl)amino)-3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.89 min; m/z: 615.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.96 (s, 1H), 9.68 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 7.60 (q, J = 3.2 Hz, 2H), 8.13 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.35 (m, 2H), 7.22 (m, 1H), 7.13 (d, J = 7.2 Hz, 1H), 6.82 (t, J =5.2 Hz, 1H), 6.17 (s, 1H), 5.19 (s, 2H), 4.35 (q, J = 9.6 Hz, 2H).
174	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(2-methoxyethoxy)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.78 min; m/z: 585.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.79 (s, 1H), 9.38 (s, 1H), 7.63 (m, 4H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.26 (t, J = 2.4 Hz, 3H), 7.12 (d, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.16 (s, 2H), 4.35 (s, 2H), 3.67 (t, J = 4.8Hz, 2H), 3.31 (s, 3H), 3.02-2.66 (m, 2H), 1.17 (t, J = 7.2, 3H).
175	3-(3-((3,4-difluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.69 min; m/z: 584.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 9.99 (s, 1H), 9.63 (s, 1H), 9.24 (s, 1H), 8.23-8.22 (m, 1H), 8.11-8.09 (m, 1H), 7.72-7.67 (m, 1H), 7.55-7.39 (m, 5H), 7.24-7.21 (m, 1H), 6.25 (s, 1H), 5.19 (s, 2H), 4.42-4.35 (m, 2H).
176	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridine-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.91 min; m/z: 633.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.96 (s, 1H), 9.43 (s, 1H), 8.82 (d, J = 2.4Hz, 1H), 8.27 (dd, J = 8.4, 2.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.62-7.59 (m, 2H), 7.46 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.27-7.22 (m, 3H), 5.19 (s, 2H), 4.35 (q, J = 9.6 Hz, 2H).

177	3-(4-((difluoromethyl)sulfonamido)-3-(4-fluorophenoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.30 min; m/z: 520.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.0 (br s, 1H), 9.53 (br s, 1H), 9.19 (br s, 1H), 8.19 (s, 1H), 8.08 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.40-7.14 (m, 5H), 7.10-7.02 (m, 3H).
178	3-(4-((2,2-difluoroethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.07 min; m/z: 615.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.78 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 7.6 Hz, 1H), 7.61 (q, J = 5.6 Hz, 2H), 7.44 (t, J = 3.6 Hz, 2H), 7.31-7.20 (m, 5H), 7.47-6.17 (m, 1H), 5.19 (s, 2H), 3.85-3.77 (m, 2H).
179	5-((6-(difluoromethyl)pyridine-2-yl)amino)-3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.47 min; m/z: 561.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.94 (s, 1H), 9.68 (s, 1H), 9.19 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 8.0 Hz, 1H), 7.62 (q, J = 5.6 Hz, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.26-7.12 (m, 4H), 6.82 (t, J = 5.2 Hz, 1H), 5.18 (s, 2H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 1H).
180	3-(4-((2,2-difluoroethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.37 min; m/z: 548.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 9.79 (s, 1H), 9.65 (s, 1H), 9.25 (s, 1H), 8.23-8.22 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.45-7.43 (m, 2H), 7.27-7.21 (m, 3H), 6.37-6.17 (m, 2H), 5.19 (s, 2H), 3.81 (td, J =14.1, 4.0 Hz, 2H).

181	5-((5-(tert-butyl)pyrazin-2-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.38 min; m/z: 444.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.89 (s, 1H), 10.08 (s, 1H), 9.49 (s, 1H), 9.18 (s, 1H), 8.26 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 3H), 6.11 (s, 1H), 3.20-3.15 (m, 2H), 1.32 (s, 9H),1.22 (t, J = 7.2 Hz, 3H).
182	3-(3-((4-fluorobenzyl)oxy)-4-((3,3,3-trifluoropropyl)sulfonamido)phenyl)-5-((6-(trifluoromethyl)pyridine-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.08 min; m/z: 647.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.17 (s, 1H), 9.77 (s, 1H), 8.22 (s, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.64 (m, 2H), 7.43 (t, J = 8.4 Hz, 2H), 7.31 (d, J = 7.2 Hz, 1H), 7.23 (m, 3H), 6.30 (s, 1H), 5.19 (m, 2H), 3.20 (m, 2H), 2.67 (m, 2H).
183	3-(3-((4-fluorobenzyl)oxy)-4-((3,3,3-trifluoropropyl)sulfonamido)phenyl)-5-((5-methylpyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.59 min; m/z: 594.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.54 (s, 1H), 9.17 (s, 1H), 8.11 (s, 1H), 7.61 (m, 2H), 7.39 (m, 2H), 7.22 (t, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 5.16 (s, 2H), 3.15 (m, 2H), 2.65 (m, 2H), 2.40 (s, 3H).
184	3-(3-((4-fluorobenzyl)oxy)-4-((3,3,3-trifluoropropyl)sulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.52 min; m/z: 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (s, 1H), 9.72 (s, 1H), 9.63 (s, 1H), 9.24 (s, 1H), 8.20 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.63 (m, 2H), 7.43 (m, 2H), 7.23 (t, J = 8.8 Hz, 3H), 5.19 (s, 2H), 3.22 (m, 2 H), 2.66 (m, 2H).

185	3-(3-(4-chlorophenoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.33 min; m/z: 514.1, 516.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (br s, 1H), 9.55 (br s, 1H), 9.20 (br s, 1H), 9.19 (d, J = 0.8 Hz, 1H), 8.09 (d, J = 0.8 Hz, 1H), 7.62-7.60 (m, 1H), 7.47-7.40 (m, 4H), 7.16-7.14 (m, 3H), 3.15 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).
186	3-(3-((4-fluorobenzyl)oxy)-4-((2,2,2-trifluoroethyl)sulfonamido)phenyl)-5-((2-(trifluoromethyl)pyrimidin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.83 min; m/z: 634.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.32 (s, 1H), 10.21 (s, 1H), 9.96 (s, 1H), 8.66 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 6.0 Hz, 1H), 7.61 (t, J = 5.6 Hz, 2H), 7.49 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.8 Hz, 3H), 6.54 (s, 1H), 5.19 (s, 2H), 4.35 (q, J = 10.0 Hz, 2H).
187	3-(4-(ethylsulfonamido)-3-((1-methylpiperidin-3-yl)methoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.35 min; m/z: 515.2 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.05 (s, 1H), 10.54 (s, 1H), 9.64 (s, 1H), 9.25 (s, 1H), 9.16 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.48 (s, 1H), 7.31 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 4.03 (s, 1H), 3.92 (s, 1H), 3.69 (s, 1H), 3.41 (s, 1H), 3.12 (q, J = 6.8 Hz, 2H), 2.82 (m, 4H), 1.89 (s, 3H).
188	3-(4-((difluoromethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyridine-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.84 min; m/z: 601.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (s, 1H), 10.56 (br s, 1H), 9.38 (s, 1H), 8.81 (d, J = 2.4 Hz, 1H), 8.26 (dd, J = 8.8, 2.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.61-7.58 (m, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.27-7.18 (m, 3H), 6.87 (t, J = 49.6 Hz, 1H), 5.18 (s, 2H).

189	5-((6-(trifluoromethyl)pyridine-2-yl)amino)-3-(4-((3,3,3-trifluoropropyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.71 min; m/z: 523.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (s, 1H), 10.40 (s, 1H), 9.77 (s, 1H), 8.21 (s, 1H), 7.98 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 3.44 (m, 2H), 2.77 (m, 2H).
190	3-(3-((4-chlorobenzyl)oxy)-4-((difluoromethyl)sulfonamido)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.36 min; m/z: 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.53 (s, 1H), 8.84 (s, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 8.4Hz, 2H), 7.42 (d, J = 8.4Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 1.2 Hz, 1H), 6.93 (dd, J = 8.0, 2.0Hz, 1H), 6.22 (t, J = 55.2 Hz, 1H), 5.07 (s, 2H), 3.86 (s, 3H).
191	3-(4-((difluoromethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-methoxypyrazin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.75 min; m/z: 564.3 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.70 (s, 1H), 9.53 (s, 1H), 8.84 (s, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.54-7.51 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.19 (t, J = 6.8 Hz, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 8.0, 2.0Hz, 1H), 6.21 (t, J = 55.2 Hz, 1H), 5.05 (s, 2H), 3.86 (s, 3H).
192	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((2-(trifluoromethyl)pyridine-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.77 min; m/z: 579.3 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 10.09 (s, 1H), 9.00 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 4.4 Hz, 1H), 7.67-7.60 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.27-7.23 (m, 2H), 7.18 (dd, J = 8.0, 1.6Hz, 1H), 5.19 (s, 2H), 3.06 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).

193	(R)-3-(4-(ethylsulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.93 min; m/z: 526.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 9.59 (s, 1H), 9.22 (s, 2H), 8.21-8.20 (m, 1H), 8.11-8.09 (m, 1H), 7.63-7.59 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.29-7.15 (m, 4H), 7.12-7.09 (m, 1H), 6.09 (s, 1H), 5.63 (s, 1H), 3.14-3.08 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).
194	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethpyridinedin-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.93 min; m/z: 579.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.41 (s,1H), 9.17 (br s, 1H), 8.81 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.45-7.41 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.19 (dd, J = 8.0, 1.6 Hz, 1H), 5.18 (s, 1H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).
195	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((2-(trifluoromethyl)pyrimidin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.82 min; m/z: 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.26 (s, 1H), 10.21 (s, 1H), 9.19 (s, 1H), 8.65 (s, 1H), 7.93 (s, 1H), 7.62 (t, J = 5.6 Hz, 2H), 7.45 (s, 2H), 7.25 (t, J =8.8 Hz, 3H), 6.45 (s, 1H), 5.75 (s, 1H), 5.18 (s, 2H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J =7.6 Hz, 3H).
196	3-(4-((difluoromethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.63 min; m/z: 563.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.73 (s, 1H), 10.56 (s, 1H), 8.69 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.8, 2.8 Hz, 1H), 7.62-7.59 (m, 2H), 7.42-7.39 (m, 2H), 7.27-7.18 (m, 3H), 7.06-6.80 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.20 (s, 2H), 3.80 (s, 3H).

197	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-methoxypyridin-3-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.48 min; m/z: 541.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.66 (s, 1H), 9.18 (s, 1H), 8.75 (s, 1H), 8.40-8.39 (m, 1H), 7.97-7.94 (m, 1H), 7.64-7.60 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.39-7.38 (m, 1H), 7.27-7.22 (m, 1H), 7.17 (dd, J = 8.0, 1.6 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.18 (s, 2H), 3.80 (s, 3H), 3.04 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).
198	3-(2-((4-chlorobenzyl)oxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.33 min; m/z: 528.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.84 (s, 1H), 10.11 (br s, 1H), 9.73 (s, 1H), 9.30 (s, 1H), 8.23-8.22 (m, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.40 (s, 4H), 7.37 (t, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.94 (dd, J = 8.4, 1.6 Hz, 1H), 5.11 (s, 2H), 3.14 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H).
199	(S)-3-(4-(ethylsulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.93 min; m/z: 526.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.93 (s, 1H), 9.59 (s, 1H), 9.22 (s, 2H), 8.21-8.20 (m, 1H), 8.11-8.09 (m, 1H), 7.63-7.59 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.29-7.15 (m, 4H), 7.12-7.09 (m, 1H), 6.09 (s, 1H), 5.63 (s, 1H), 3.14-3.08 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).
200	3-(3-(cyclohexylmethoxy)-4-(ethylsulfonamido)phenyl)-5-((6-(trifluoromethpyridinedin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.64 min; m/z: 567.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 9.77 (s, 1H), 9.03 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 16.0 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.38-7.26 (m, 3H), 7.16-7.13 (m, 1H), 6.23 (s, 1H), 3.86 (d, J = 6.0 Hz, 2H), 3.11 (q, J = 22.0 Hz, 2H), 1.9 (s, 1H), 1.74-1.64 (m, 3H), 1.32-1.16 (m, 10H).

201	3-(4-(ethylsulfonamido)-2-((4-fluorobenzyl)oxy)phenyl)-322yridinedin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.86 min; m/z: 511.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.66 (s, 1H), 10.14 (s, 1H), 9.61 (s, 1H), 8.18 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 6.8 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.8 Hz, 3H), 7.08 (s, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.84 (t, J = 5.6 Hz, 1H), 5.09 (s, 2H), 3.15 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).
202	3-(4-((difluoromethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.21 min; m/z: 534.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.14 (br s, 1H), 10.57 (br s, 1H), 9.60 (br s, 1H), 9.22 (br s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.61-7.58 (m, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.26-7.13 (m, 4H), 6.99-6.54 (m, 1H), 5.19 (s, 2H).
203	3-(4-(ethylsulfonamido)-3-((1-methylpiperidin-4-yl)methoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.40 min; m/z: 515.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (s, 1H), 9.66 (s, 1H), 9.24 (s, 1H), 9.08 (s, 1H), 8.22 (q, J = 1.6 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.17 (d, J = 1.6 Hz, 1H), 3.94 (m, 2H), 3.12 (q, J = 7.6 Hz, 2H), 2.46 (br s, 4H), 1.97 (m, 3H), 1.50 (br s, 2H), 1.24 (m, 3H).
204	3-(4-(ethylsulfonamido)-3-(3-fluorophenoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.26 min; m/z: 498.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (s, 1H), 9.64 (s, 1H), 9.66 (s, 1H), 9.55 (s, 1H), 9.21 (s, 1H), 8.20 (s, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.46-7.40 (m, 2H), 7.21 (s, 1H), 7.01-6.93 (m, 3H), 3.13 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).

205	5-((6-(trifluoromethpyridinedin-2-yl)amino)-3-(4-((trifluoromethyl)sulfonamido)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.94 min; m/z: 495.0 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 9.90 (s, 1H), 8.52 (s, 1H), 8.04-7.94 (m, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.21- 6.95 (m, 2H).
206	3-(3-(2-chlorophenethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.67 min; m/z: 542.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 12.97 (s, 1H), 9.63 (s, 1H), 9.25 (s, 1H), 8.94 (s, 1H), 8.22 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 2.6, 2.0 Hz, 1H), 7.46 (m, 2H), 7.34 (m, 3H), 7.18 (dd, J = 2.0, 1.6 Hz, 1H), 4.32 (t, J = 6.8 Hz, 2H), 3.28 (d, J = 6.8 Hz, 2H), 3.01 (q, J = 7.6 Hz, 2H), 1.16 (d, J = 7.2 Hz, 3H).
207	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((5-(trifluoromethpyridinedin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.01 min; m/z: 579.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 9.95 (s, 1H), 9.26 (s, 1H), 9.19 (s, 1H), 8.53 (s, 1H), 8.07 (s, 1H), 7.64-7.60 (m, 2H), 7.46-7.42 (m, 2H), 7.27-7.19 (m, 3H), 5.18 (s, 2H), 3.05 (q, J = 7.6 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).
208	3-(4-(ethylsulfonamido)-2-((3-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.60 min; m/z: 512.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 10.16 (s, 1H), 9.76 (s, 1H), 9.32 (s, 1H), 8.23 (s, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.42-7.30 (m, 3H), 7.22-7.18(m, 2H), 7.12 (t, J = 8.8 Hz, 1H), 7.05 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H) 5.71 (br s, 1H), 5.14 (s, 2H), 3.15 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H).

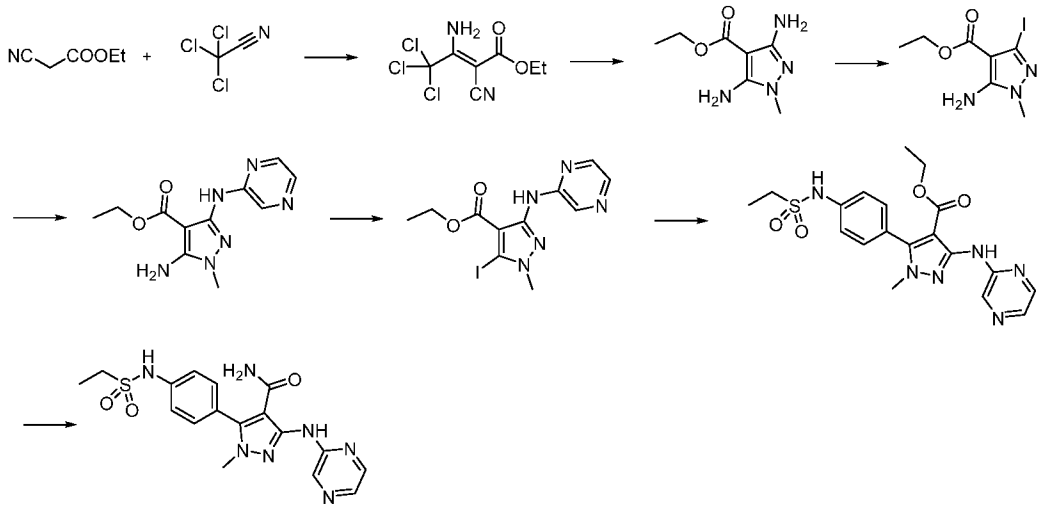
209	3-(4-(ethylsulfonamido)-2-methoxyphenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.70 min; m/z: 418.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.79 (s, 1H), 10.14 (br s, 1H), 9.74 (s, 1H), 9.33 (s, 1H), 8.23 (s, 1H), 8.13 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (br s, 1H), 7.02 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.65 (br s, 1H), 3.76 (s, 3H), 3.2 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).
210	3-(4-(ethylsulfonamido)-3-phenethoxyphenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.49 min; m/z: 508.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.63 (s, 1H), 9.25 (s, 1H), 8.95 (s, 1H), 8.22-8.21 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.40-7.38 (m, 2H), 7.34-7.30 (m, 3H), 7.25-7.21 (m, 1H), 7.18-7.15 (m, 1H), 4.31 (t, J = 6.8 Hz, 2H), 3.15 (t, J = 6.8 Hz, 2H), 2.95 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H).
211	3-(4-(ethylsulfonamido)-3-(2-fluorophenethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.61 min; m/z: 526.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.62 (s, 1H), 9.24 (s, 1H), 8.88 (br s, 1H), 8.22-8.21 (m, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.52-7.50 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.31-7.28 (m, 1H), 7.20-7.14 (m, 3H), 4.30 (t, J = 6.8 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H), 2.99 (q, J =14.8, 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).
212	3-(3-(3-chlorophenethoxy)-4-(ethylsulfonamido)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.61 min; m/z: 526.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.64 (s, 1H), 9.25 (s, 1H), 9.03 (s, 1H), 8.22-8.21 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.51 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.33 (s, 4H), 7.16 (d, J = 1.6 Hz, 1H), 4.31 (t, J = 6.4 Hz, 2H), 3.14 (br s, 2H), 2.95 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H).

213	3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((4-(trifluoromethpyridinedin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.79 min; m/z: 580.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 9.90 (s, 1H), 9.14 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.33 (s, 1H), 7.64-7.60 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.19 (d, J = 6.4 Hz, 2H), 6.25 (s, 1H), 5.18 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2Hz, 3H).
214	3-(4-(ethylsulfonamido)-3-((3-(trifluoromethoxy)benzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.67 min; m/z: 578.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (s, 1H), 9.62 (s, 1H), 9.25 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.66-7.33 (m, 8H), 6.23 (br s, 1H), 5.26 (s, 1H), 3.04 (s, 2H), 1.18-1.84 (m, 3H).
215	3-(4-(ethylsulfonamido)-3-((4-(trifluoromethoxy)benzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.88 min; m/z: 578.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.62 (s, 1H), 9.23 (d, J = 14.4 Hz, 2H), 8.21 (s, 1H), 8.11 (s, 1H), 7.71 (d, J = 8.0 Hz, 3H), 7.47-7.41 (m, 5H), 7.21 (d, J = 8.4 Hz, 1H), 5.23 (s, 2H), 3.10-3.03 (m, 2H), 1.16 (t, J = 14.4 Hz, 3H).
216	3-(4-(ethylsulfonamido)-3-((4-(trifluoromethyl)benzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.67 min; m/z: 562.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (s, 1H), 10.12 (s, 1H), 9.61 (s, 1H), 9.23 (s, 1H), 8.21 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.81-7.77 (m, 5H), 7.48-7.42 (m, 3H), 7.21 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 3.07 (d, J = 7.2 Hz, 2H), 1.17 (t, J = 14.8 Hz, 3H).

217	3-(4-((difluoromethyl)sulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-5-((6-(trifluoromethyl)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 1.82 min; m/z: 601.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (br s, 1H), 10.64 (br s, 1H), 9.72 (br s, 1H) 8.20 (br s, 1H), 7.98 (s, 1H), 7.62-7.57 (m, 2H), 7.39-7.14 (m, 7H), 6.72-6.58 (m, 1H), 5.18 (s, 2H).
218	3-(4-(ethylsulfonamido)-3-((3-(trifluoromethyl)benzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.72 min; m/z: 562.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.02 (s, 1H), 9.61 (s, 1H), 9.24 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.98 (s, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.67 (m, 2H), 7.46 (d, J = 7.2 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 5.30 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).
219	3-(4-(ethylsulfonamido)-3-(3-fluorophenethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 0.54 min; m/z: 526.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (s, 1H), 9.62 (s, 1H), 9.25 (s, 1H), 9.00 (br s, 1H), 8.22-8.21 (m, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38-7.33 (m, 2H), 7.29-7.25 (m, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.16 (dd, J = 8.0, 1.6 Hz, 1H), 7.08-7.03 (m, 1H), 4.31 (t, J = 6.8 Hz, 2H), 3.18-3.15 (m, 2H), 2.95 (q, J = 14.8, 7.6 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H).
220	5-((6-chloroquinolin-2-yl)amino)-3-(4-(ethylsulfonamido)-3-((4-fluorobenzyl)oxy)phenyl)-1H-pyrazole-4-carboxamide		LCMS (Method A): 4.10 min; m/z: 595.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.53 (s, 1H), 10.36 (s, 1H), 9.06 (s, 1H), 8.32-8.18 (m, 2H), 7.94 (s, 1H), 7.68-7.61 (m, 3H), 7.46-7.39 (m, 3H), 7.27-7.20 (m, 3H), 5.19 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).

26	3-(4-(ethylsulfonamido)-3-((3-fluorobenzyl)oxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.52 min; m/z: 512.1 $[M+H]^+$.	^{1}H NMR (400 MHz, MeOD-d_4): 13.02 (s, 1H), 9.62 (s, 1H), 9.25 (s, 1H), 8.22 (s, 1H), 8.11 (d, J = 2.8 Hz, 1H), 7.48 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 7.19 (m, 2H), 5.74 (s, 1H), 5.23 (s, 2H), 3.07 (q, J = 7.2 Hz, 2H), 1.78 (t, J = 7.2 Hz, 3H).
309	(S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-5-((2-methylpyrimidin-4-yl)amino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 3.30 min; m/z: 563.8 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (s, 1H), 9.78 (s, 1H), 8.41 (d, J = 5.9 Hz, 1H), 7.78-7.67 (m, 1H), 7.61 (dd, J = 8.5, 5.5 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.20 (t, J = 8.7 Hz, 2H), 7.16-6.98 (m, 2H), 6.70 (t, J = 53.9 Hz, 1H), 6.06 (d, J = 20.9 Hz, 1H), 5.71 (d, J = 6.5 Hz, 1H), 2.56 (s, 3H), 1.59 (d, J = 6.3 Hz, 3H).
313	3-(4-((difluoromethyl)sulfonamido)-3-(oxazol-2-ylmethoxy)phenyl)-5-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide		LCMS (Method A): 2.93 min; m/z: 507.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (s, 1H), 10.63 (s, 1H), 9.63 (s, 1H), 9.24 (s, 1H), 8.22 (t, J = 1.8 Hz, 2H), 8.11 (d, J = 2.7 Hz, 1H), 7.56 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 7.25 (dd, J = 8.1, 1.8 Hz, 1H), 7.02 (t, J = 52.7 Hz, 1H), 5.36 (s,2H).
315	(S)-6-((4-carbamoyl-3-(4-(ethylsulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1H-pyrazol-5-yl)amino)nicotinic acid		LCMS (Method A): 3.22 min; m/z: 569.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6): 13.01 (s, 1H), 9.83 (s, 1H), 8.71 (s, 1H), 8.14 (s, 1H), 7.84 (d, J = 19.7 Hz, 1H), 7.70 (s, 1H), 7.62 (d, J = 13.7 Hz, 2H), 7.42 (s, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 18.0 Hz, 3H), 7.09 (s, 1H), 5.65 (s, 1H), 3.11 (d, J = 7.3 Hz, 2H), 1.60 (d, J = 6.1 Hz, 3H), 1.26 (s, 3H).

Compound 222



Step 1: ethyl (2Z)-3-amino-4,4,4-trichloro-2-cyanobut-2-enoate

To a solution of ethyl 2-cyanoacetate (20 mL, 196 mmol) and trichloroacetonitrile (54 g, 374 mmol) in EtOH (70 mL) at 0 ºC, was added Et_3N (1.97 g, 19.6 mmol) and the reaction mixture was stirred for 2 h under N_2. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1) to afford the title product (37 g, 79%) as a white solid. LCMS (Method A): 2.04 min; m/z: 257.1, 259.2 $[M+H]^+$.

Step 2: ethyl 3,5-diamino-1-methyl-1H-pyrazole-4-carboxylate

A solution of ethyl (2Z)-3-amino-4,4,4-trichloro-2-cyanobut-2-enoate (1 g, 3.88 mmol) and $MeNHNH_2$ (450 mg, 9.76 mmol) in DMF (10 mL) was stirred at 100 ºC for 3 h and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EtOAc, 5:1 then DCM:MeOH, 20:1) to afford the title product (660 mg, 92%) as a brown solid. LCMS (Method A): 1.01 min; m/z: 185.1 $[M+H]^+$.

Step 3: 5-amino-3-iodo-1-methyl-1H-pyrazole-4-carboxylate

A solution of ethyl 3,5-diamino-1-methyl-1H-pyrazole-4-carboxylate (100 mg, 0.54 mmol), CH_2I_2 (145 mg, 0.542 mmol) and isoamyl nitrite (160 mg, 0.542 mmol) in MeCN (3 mL) was stirred at 60 °C for 3 h under N_2. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (PE:EtOAc, 3:1) to afford the title product (30 mg, 19%) as a yellow solid. The structure was confirmed by HMBC experiment. LCMS (Method A): 3.04 min; m/z: 295.9 $[M+H]^+$.

Step 4: ethyl 5-amino-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate

A mixture of ethyl 5-amino-3-iodo-1-methyl-1H-pyrazole-4-carboxylate (1.4 g, 4.74 mmol), pyrazin-2-amine (450 mg, 4.74 mmol), $Pd_2(dba)_3$ (434 mg, 0.47 mmol), Xantphos (411 mg, 0.7110 mmol) and Cs_2CO_3 (4.62 g, 14.2 mmol) in degassed 1,4-dioxane (30 mL) was stirred at 100 ºC overnight under N_2. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1 to 1:1) to afford the title product (600 mg, 48%) as a yellow solid. LCMS (Method A): 2.78 min; m/z: 263.0 $[M+H]^+$.

Step 5: ethyl 5-iodo-1-methyl-3-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxylate

A mixture of ethyl 5-amino-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate (1 g, 3.81 mmol), isoamyl nitrite (891 mg, 7.62 mmol) and CH_2I_2 (2.03 g, 7.62 mmol) in MeCN (20 mL) was stirred at 100 °C for 3 h under N_2. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 10:1 to 3:1) to afford the title product (700 mg, 49%) as a yellow solid. LCMS (Method A): 1.28 min; m/z: 373.9 $[M+H]^+$.

Step 6: ethyl 5-(4-(ethylsulfonamido)phenyl)-1-methyl-3-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxylate

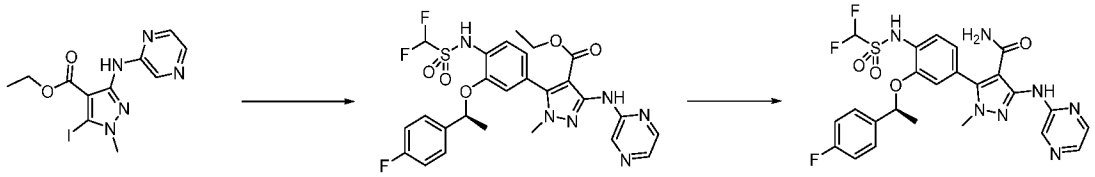
A mixture of ethyl 5-iodo-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate (150 mg, 0.401 mmol), N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (125 mg, 0.402 mmol), $Pd(dppf)Cl_2$ (32.8 mg, 0.04 mmol), K_2CO_3 (165 mg, 1.20 mmol) and 70% aq. 1,4-dioxane (7 mL) was stirred at 100 °C overnight under N_2. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1 to 1:5) to afford the title product (95 mg, 49%) as a yellow solid. LCMS (Method A): 3.87 min; m/z: 431.1 $[M+H]^+$.

Step 7: 5-(4-(ethylsulfonamido)phenyl)-1-methyl-3-(pyrazin-2-ylamino)-1H-pyrazole-4-carboxamide (Compound 222)

A solution of ethyl 5-(4-ethanesulfonamidophenyl)-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate (140 mg, 0.32 mmol) in MeOH:NH_4OH (1:1, 28 mL) was divided equally between 7 sealed tubes. The seal tubes were successively heated at 115 °C for 2 h under MW irradiation. The reaction mixtures were combined, concentrated under reduced pressure and the residue was purified by prep-TLC (DCM:MeOH, 20:1) to provide the title product (11.4 mg, 8%) as a grey solid. LCMS (Method A): 3.37 min; m/z: 402.1 $[M+H]^+$. ^1H

NMR (400 MHz, $CDCl_3$): 9.74 (s, 1H), 9.43 (s, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 3.64 (s, 3H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H).

Compound 253



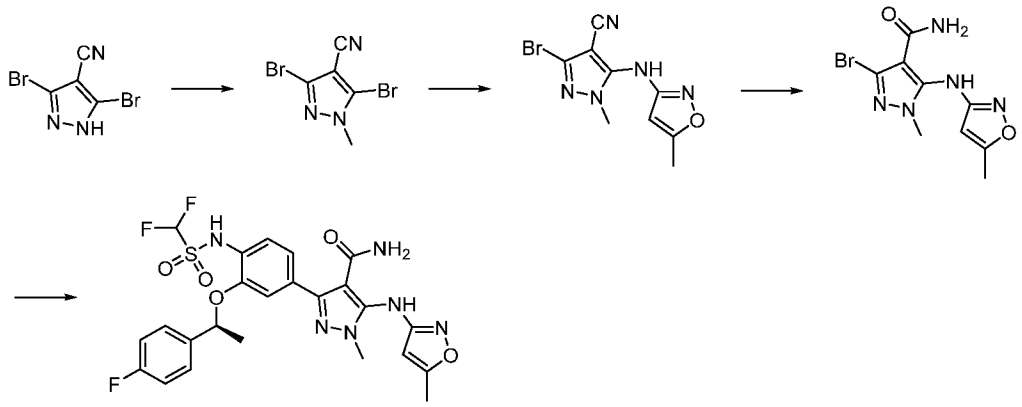
Step 1: ethyl 5-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate

A mixture of ethyl 5-iodo-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate (134 mg, 360 µmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (170 mg, 360 µmol), $Pd(dppf)Cl_2$ (29.3 mg, 36.0 µmol), K_2CO_3 (295 mg, 900 µmol) and 90% aq. 1,4-dioxane (5 mL) was stirred at 100 ºC under N_2. After 16 h, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (PE:EtOAc, 5:1 to 1:1) to afford the title product (150 mg, 70%) as a yellow solid. LCMS (Method A): 4.13 min; m/z: 591.2 $[M+H]^+$.

Step 2: 5-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxamide (Compound 253)

A solution of ethyl 5-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-methyl-3-[(pyrazin-2-yl)amino]-1H-pyrazole-4-carboxylate (40 mg, 67.7 µmol) in NH_4OH (2 mL) was stirred at 50 ºC for 2 h. The reaction mixture was concentrated and the residue was diluted with H_2O (20 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by prep-HPLC to afford the title compound (6.0 mg, 15%) as a white solid. LCMS (Method D): 4.23 min; m/z: 561.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.89 (s, 1H), 9.35 (s, 1H), 8.27 (br s, 3H), 7.48 (q, *J* = 8.4, 6.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 2H), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.30 (t, *J* = 54.4 Hz, 1H), 5.65-5.61 (m, 1H), 3.36 (s, 3H), 1.51 (d, *J* = 6.4 Hz, 3H).

Compound 320



Step 1: 3,5-dibromo-1-methyl-1H-pyrazole-4-carbonitrile

To a solution of 3,5-dibromo-1H-pyrazole-4-carbonitrile (1.0 g, 3.98 mmol) in dry DMF (20 mL) was added NaH (475 mg, 11.9 mmol) at 0 °C, and the solution was stirred for 30min at 0 °C. MeI (1.68 g, 11.9 mmol) was slowly added and the reaction mixture was stirred at RT for 1h. Water (200 mL) was added and the organics were extracted with EtOAc (3 x 200 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EtOAc, 10:1 to 5:1) to give the title product (750 mg, 71%) as a white solid. LCMS (Method A): 3.51 min, m/z 263.9/265.9/267.9 [M+H]+.

Step 2: 3-bromo-1-methyl-5-[(5-methyl-1,2-oxazol-3-yl)amino]-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-methyl-1H-pyrazole-4-carbonitrile (200 mg, 0.7549 mmol), 5-methyl-1,2-oxazol-3-amine (59.1 mg, 603 µmol), Cs_2CO_3 (736 mg, 2.26 mmol), Xantphos (86.7 mg, 150 µmol), $Pd_2(dba)_3$ (69.0 mg, 75.4 µmol) in degassed 1,4-dioxane (5 mL) was stirred under N_2 at 100 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (PE:EA, 2:1) to give the title product (70 mg, 28%) as a yellow solid. LCMS (Method A): 3.17 min, m/z 282.0/284.0 $[M+H]^+$.

Step 4: 3-bromo-1-methyl-5-[(5-methyl-1,2-oxazol-3-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-1-methyl-5-[(5-methyl-1,2-oxazol-3-yl)amino]-1H-pyrazole-4-carbonitrile (40 mg, 0.1417 mmol) and Ghaffar-Parkins catalyst (30 mg, 0.07022 mmol) in dioxane (10 mL) and H_2O (2 mL) was stirred overnight at 100 °C under N_2. The reaction mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC

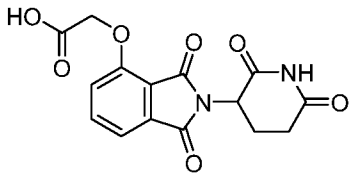
(PE:EtOAc, 1:1) to give the title product (20 mg, 47%) as a yellow solid. LCMS (Method A): 2.36 min; 300.0/302.0 [M+H]+

Step 5: (S)-3-(4-((difluoromethyl)sulfonamido)-3-(1-(4-fluorophenyl)ethoxy)phenyl)-1-methyl-5-((5-methylisoxazol-3-yl)amino)-1H-pyrazole-4-carboxamide (Compound 320)

A mixture of 3-bromo-1-methyl-5-[(5-methyl-1,2-oxazol-3-yl)amino]-1H-pyrazole-4-carboxamide (15 mg, 0.050 mmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (35.3 mg, 0.749 mmol), Na_2CO_3 (10.5 mg, 99.9 µmol) and $Pd(PPh_3)_4$ (5.76 mg, 4.99 µmol) in degassed 1,4-dioxane (4 mL) and H_2O (1 mL) was stirred at 100 °C under microwave for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (DCM:MeOH, 20:1) to give the title product (30 mg, 32%) as a white solid. LCMS (Method A): 3.56 min; 565.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.36 (s, 1H), 8.53 (s, 1H), 7.58 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.37-7.28 (m, 2H), 7.25-7.13 (m, 4H), 7.13-6.84 (m, 2H), 5.86 (d, *J* = 1.1 Hz, 1H), 5.50 (q, *J* = 6.3 Hz, 1H), 3.62 (s, 3H), 2.28 (s, 3H), 1.57 (d, *J* = 6.3 Hz, 3H).

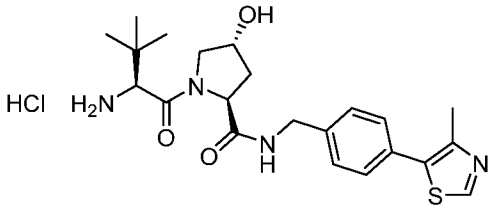
Synthesis of further intermediates

Intermediate 1: 2-[[2-(2,6-Dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]oxy] acetic acid



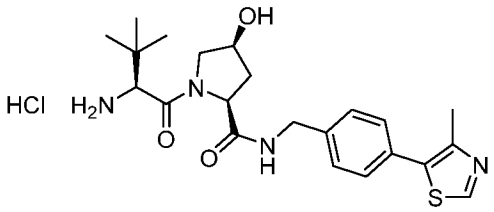
Intermediate 1 was prepared according to known methods exemplified in US20160176916A1. LCMS (method G): 0.80 min, m/z: 333.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 11.10 (s, 1H), 7.79 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.47 (dd, *J* = 7.3, 0.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 0.5 Hz, 1H), 5.10 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.99 (s, 2H), 2.96-2.83 (m, 1H), 2.63-2.54 (m, 2H), 2.09-1.99 (m, 1H).

Intermediate 2: (2S,4R)-1-[(2S)-2-Amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride



Intermediate 2 was prepared according to known methods exemplified in Carles Galdeano, Morgan S. Gadd, Pedro Soares, Salvatore Scaffidi, Inge Van Molle, Ipek Birced, Sarah Hewitt, David M. Dias, and Alessio Ciulli, *Journal of Medicinal Chemistry*, 2014, 57 (20), 8657-8663. LCMS (method E): 2.54 min, m/z: 431.2 $[M+H]^+$.

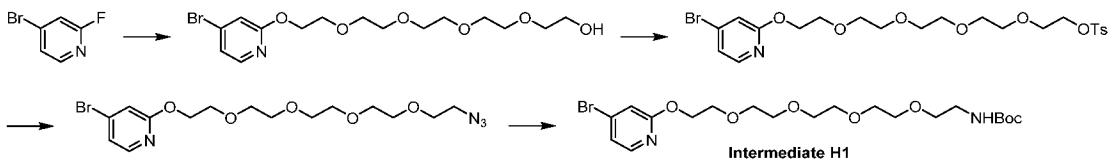
Intermediate 3: (2S,4S)-1-[(2S)-2-Amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride



Intermediate 3 was prepared according to the known procedure for **Intermediate 2**, using N-Boc-(2S,4S)-4-hydroxyproline in the appropriate step. LCMS (method G): 0.95 min, m/z: 431.0 $[M+H]^+$.

Synthesis of Intermediates H:

Intermediate H1: tert-butyl (14-((4-bromopyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl) carbamate



Step 1: 14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-ol

To a mixture of 4-Bromo-2-fluoropyridine (2.0 g, 11.3 mmol) and 3,6,9,12-tetraoxatetradecane-1,14-diol (8.07 g, 33.9 mmol) in THF (28.2 mL) was added *t*-BuOK (2.53 g, 22.6 mmol). The reaction was stirred at RT under N_2 for 2 h and then concentrated under reduced pressure. The crude residue was diluted with H_2O (50 mL) and then extracted with

EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (4.58 g, >100%) as a colourless oil. LCMS (method G): 1.29 min; m/z: 396.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.96-7.94 (m, 1H), 7.04-6.99 (m, 2H), 4.48-4.45 (m, 2H), 3.84-3.81 (m, 2H), 3.74-3.65 (m, 14H), 3.62-3.58 (m, 2H).

Step 2: 14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl 4-methylbenzene-1-sulfonate

To a mixture of 14-[(4-Bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-ol (1.98 g, 5.02 mmol) and Et_3N (838 µL, 6.02 mmol) in DCM (25 mL) was added *p*-TsOH.H_2O (1.14 g, 6.02 mmol), and the reaction was stirred at RT for 16 h. The mixture was diluted with H_2O (50 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by flash chromatography (0-100% EtOAc:*c*-Hex) to afford the title compound (1.98 g, 72%) as a colourless oil. LCMS (method G): 2.30 min; m/z: 550.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 5.5, 0.5 Hz, 1H), 7.81-7.77 (m, 2H), 7.35-7.31(m, 2H), 7.02-6.97 (m, 2H), 4.47-4.43 (m, 2H), 4.17-4.12 (m, 2H), 3.84-3.80 (m, 2H), 3.71-3.58 (m, 14H), 2.43 (s, 3H).

Step 3: 2-[(14-azido-3,6,9,12-tetraoxatetradecan-1-yl)oxy]-4-bromopyridine

To a solution of 14-[(4-Bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl 4-methylbenzene-1-sulfonate (900 mg, 1.64 mmol) in DMF (4.10 mL) was added NaN_3 (213 mg, 3.28 mmol), and the reaction was stirred at RT. After 3 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (694 mg, >100%) as a colourless oil. LCMS (method G): 1.91 min; m/z: 419.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.94 (d, *J* = 5.4 Hz, 1H), 7.01 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.98-6.97 (m, 1H), 4.47-4.44 (m, 2H), 3.84-3.81 (m, 2H), 3.71-3.64 (m, 14H), 3.38 (t, *J* = 5.1 Hz, 2H).

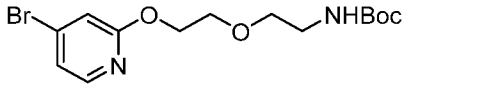
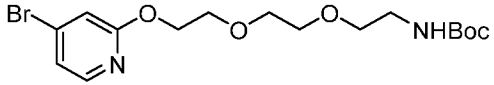
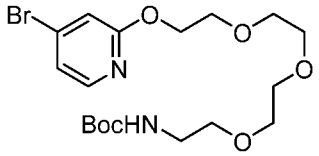
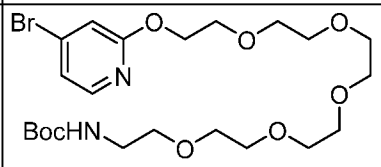
Step 4: tert-butyl N-{14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate

To a solution of 2-[(14-Azido-3,6,9,12-tetraoxatetradecan-1-yl)oxy]-4-bromopyridine (880 mg, 1.55 mmol) in 80% aq. EtOH (10 mL) were added NH_4Cl (829 mg, 15.5 mmol) and Fe dust (865 mg, 15.5 mmol), and the reaction was heated to 80 °C. After 16 h, the reaction mixture was filtered through Celite and then concentrated to give a colourless oil. The residue was taken up in 75% aq. THF, and $NaHCO_3$ (1.56 g, 18.6 mmol) and Boc_2O (405 mg, 1.86 mmol) were added. The reaction was stirred at RT for 1 h, then concentrated, diluted with H_2O (50

mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (891 mg, >100%) as a colourless oil. LCMS (method G): 2.05 min; m/z: 495.2 $[M+H]^+$. ^1H NMR (300 MHz, CDCl3): 7.97 (dd, *J* = 5.4, 0.5 Hz, 1H), 7.04 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.01 (dd, *J* = 1.6, 0.5 Hz, 1H), 4.51-4.48 (m, 2H), 3.87-3.85 (m, 2H), 3.74-3.66 (m, 14H), 3.55 (t, *J* = 5.1 Hz, 2H), 1.45 (s, 9H).

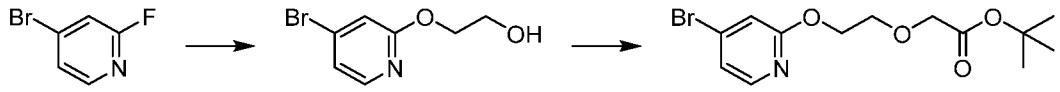
The following intermediates were similarly prepared from 4-Bromo-2-fluoropyridine and the appropriate diol according to the procedures for the synthesis of **Intermediate H1**.

Table 25: Intermediates H

Intermediate	Name	Structure	LCMS data	SM
H2	*tert*-butyl (2-(2-((4-bromopyridin-2-yl)oxy)ethoxy)ethyl)carbamate		(method E): 0.32 min; m/z: 260.9 $[M\text{-}Boc+H]^+$.	Diethylene glycol
H3	*tert*-butyl (2-(2-(2-((4-bromopyridin-2-yl)oxy)ethoxy)ethoxy)ethyl)carbamate		(method G): 2.19 min; m/z: 404.9 $[M+H]^+$.	Triethylene glycol
H4	*tert*-butyl (2-(2-(2-(2-((4-bromopyridin-2-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate		(method G): 0.34 min; m/z: 348.9 $[M\text{-}Boc+H]^+$.	Tetraethylene glycol
H5	*tert*-butyl (17-((4-bromopyridin-2-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl)carbamate		(method G): 2.04 min; m/z: 537.2 $[M+H]^+$.	Hexaethylene glycol

Synthesis of Intermediates I:

Intermediate I1: tert-butyl 2-{2-[(4-bromopyridin-2-yl)oxy]ethoxy}acetate



Intermediate I1

Step 1: 2-[(4-bromopyridin-2-yl)oxy]ethan-1-ol

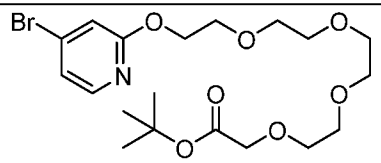
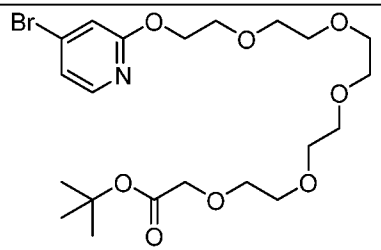
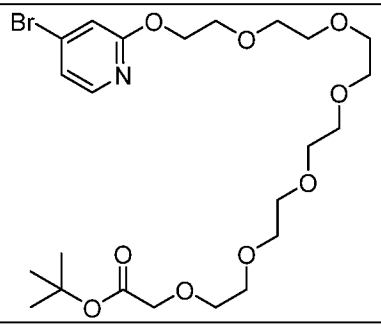
To a mixture of 4-Bromo-2-fluoropyridine (2.0 g, 11.3 mmol) and ethane-1,2-diol (934 µL, 16.9 mmol) in DMF (10.2 mL) was added NaH (903 mg, 22.6 mmol), and the reaction was stirred at RT under N_2 for 1 h. The mixture was diluted with sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed (brine), dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography (0-60% EtOAc:*c*-Hex) afforded the title compound (1.30 g, 52%) as a white solid. LCMS (method G): 1.10 min; m/z: 218.2, 220.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.95 (dd, *J* = 5.5, 0.4 Hz, 1H), 7.07 (dd, *J* = 5.5, 1.6 Hz, 1H), 7.02 (dd, *J* = 1.6, 0.4 Hz, 1H), 4.47 (m, 2H), 3.94 (m, 2H).

Step 2: tert-butyl 2-{2-[(4-bromopyridin-2-yl)oxy]ethoxy}acetate

To a mixture of 2-[(4-Bromopyridin-2-yl)oxy]ethan-1-ol (1.0 g, 4.58 mmol), $Bu_4N.HSO_4$ (385 mg, 1.14 mmol) and *tert*-butyl 2-bromoacetate (2.02 mL, 13.7 mmol) in toluene (10 mL) was added 50% aq. NaOH (10 mL), and the biphasic mixture was stirred rapidly at RT. After 1 h the mixture was diluted with sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed (brine), dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography (0-25% EtOAc:*c*-Hex) afforded the title compound (1.40 g, 92%) as a colourless oil. LCMS (method G): 2.32 min; m/z: 332.2, 334.2 $[M+H]^+$. ^1H NMR (300 MHz, CDC_3): 7.95 (dd, *J* = 5.3, 0.7 Hz, 1H), 7.03-7.00 (m, 2H), 4.52-4.48 (m, 2H), 4.06 (s, 3H), 3.91-3.88 (m, 2H), 1.47 (s, 9H).

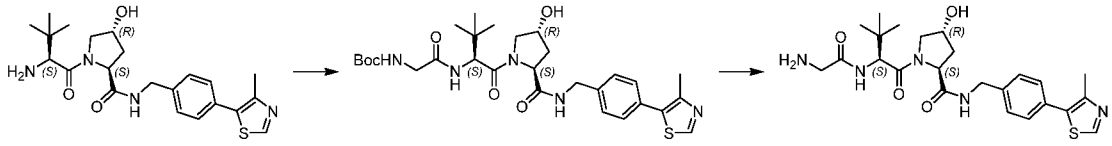
The following intermediates were similarly prepared from 4-Bromo-2-fluoropyridine and the appropriate diol according to the procedures for the synthesis of **Intermediate I1**.

Table 26: Intermediates I

Intermediate	Name	Structure	LCMS data	NMR data	SM
I2	*tert*-butyl 14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate		LCMS (method G): 2.16 min; m/z: 466.0 $[M+H]^+$.	LCMS (method G): 2.16 min; m/z: 466.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.95 (dd, *J* = 5.4, 0.3 Hz, 1H), 7.01 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.98-6.97 (m, 1H), 4.47-4.44 (m, 2H), 4.01 (s, 2H), 3.84-3.81 (m, 2H), 3.71-3.67 (m, 12H), 1.46 (s, 9H).	Tetraethylene glycol
I3	*tert*-butyl 17-[(4-bromopyridin-2-yl)oxy]-3,6,9,12,15-pentaoxaheptadecanoate		LCMS (method G): 2.15 min; m/z: 508.0 $[M+H]^+$.	LCMS (method G): 2.15 min; m/z: 508.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 5.4, 0.5 Hz, 1H), 7.01 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.98 (dd, *J* = 1.6, 0.5 Hz, 1H), 4.47-4.44 (m, 2H), 4.01 (s, 2H), 3.84-3.81 (m, 2H), 3.71-3.65 (m, 16H), 1,46 (s, 9H).	Pentaethylene glycol
I4	*tert*-butyl 20-[(4-bromopyridin-2-yl)oxy]-3,6,9,12,15,18-hexaoxaicosanoate		LCMS (method G): 2.14 min; m/z: 554.0 $[M+H]^+$.	LCMS (method G): 2.14 min; m/z: 554.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.94 (dd, *J* = 5.4, 0.5 Hz, 1H), 7.00 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.97 (dd, *J* = 1.6, 0.5 Hz, 1H), 4.47-4.43 (m, 2H), 4.00 (s, 2H), 3.84-3.80 (m, 2H), 3.69-3.64 (m, 20H), 1.46 (s, 9H).	Hexaethylene glycol

Synthesis of Intermediates J

Intermediate J1: (2S,4R)-1-[(2S)-2-(2-aminoacetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide



Step 1: tert-butyl N-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamate

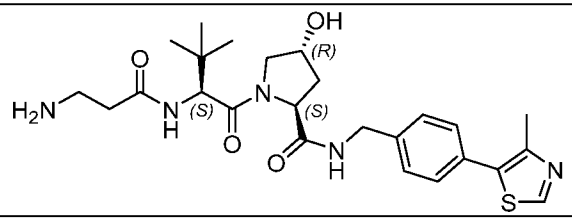
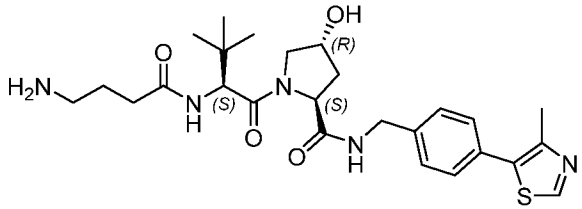
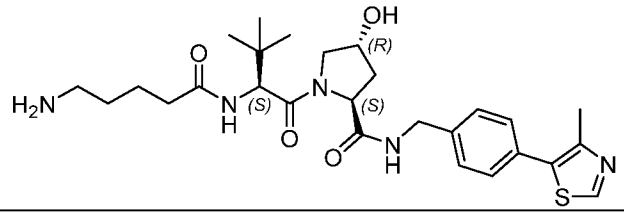
A mixture of N-(tert-Butoxycarbonyl)glycine (203 mg, 1.16 mmol), HATU (882 mg, 2.32 mmol) and Et_3N (469 mg, 4.64 mmol) in DMF (50 mL) was stirred at RT for 10 mins before (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (500 mg, 1.16 mmol) was added. The reaction mixture was stirred at rt overnight, then poured into H_2O (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were dried (Na_2SO_4) and concentrated to give the title product (680 mg, 99%) as a yellow oil. LCMS (method E): 3.12 min, m/z: 611.3 $[M+Na]^+$.

Step 2: (2S,4R)-1-[(2S)-2-(2-aminoacetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

A solution of tert-butyl N-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamate (670 mg, 1.13 mmol) in HCl/1,4-dioxane (5 M, 8.36 mL, 41.8 mmol) was stirred at RT for 1h. The reaction mixture was adjust to pH = 8 with sat. aq. $NaHCO_3$, poured into H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (2% meOH:DCM) to afford the title compound (390 mg, 70%) as a white solid. LCMS (method E): 2.48 min, m/z: 510.2 $[M+Na]^+$.

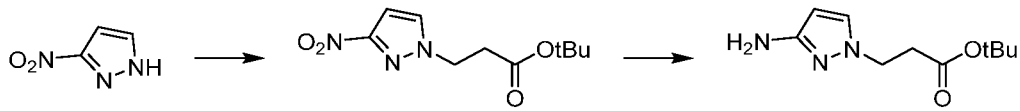
The following intermediates were similarly prepared from (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide and the appropriate amino acid according to the procedures for the synthesis of **Intermediate J1**.

Table 27: Intermediates J

Intermediate	Name	Structure	LCMS data	SM
J2	(2S,4R)-1-[(2S)-2-(3-aminopropanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide		LCMS (method E): 3.14 min, m/z: 502.3 $[M+Na]^+$.	3-{[(tert-butoxy)carbonyl]amino}propanoic acid
J3	(2S,4R)-1-[(2S)-2-(4-aminobutanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide		LCMS (method E): 3.44 min, m/z: 500.2 $[M+H]^+$.	4-{[(tert-butoxy)carbonyl]amino}butanoic acid
J4	(2S,4R)-1-[(2S)-2-(4-aminobutanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide		LCMS (method E): 2.57min, m/z: 530.2 $[M+H]^+$.	5-{[(tert-butoxy)carbonyl]amino}pentanoic acid

Synthesis of Intermediates K

Intermediate K1: tert-butyl 3-(3-amino-1H-pyrazol-1-yl)propanoate



Step 1: tert-butyl 3-(3-nitro-1H-pyrazol-1-yl)propanoate

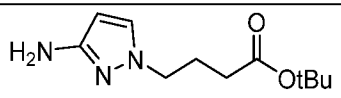
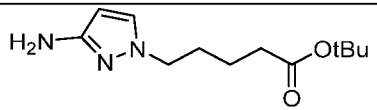
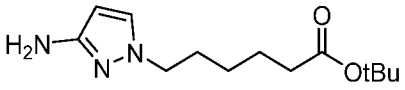
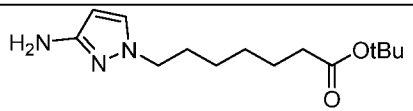
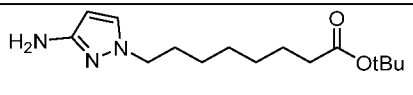
To a solution of 3-nitro-1H-pyrazole (1.0 g, 8.84 mmol) in MeCN (30 mL) were added K_2CO_3 (2.43 g, 17.6 mmol) and tert-butyl 3-bromopropanoate (2.92 mL, 17.6 mmol), and the reaction was stirred at 55 °C overnight. Once cooled, water (100 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound (2.10 g, 99%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.55 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 4.45 (t, *J* = 6.2 Hz, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 1.41 (s, 9H).

Step 2: tert-butyl 3-(3-amino-1H-pyrazol-1-yl)propanoate

A mixture of tert-butyl 3-(3-nitro-1H-pyrazol-1-yl)propanoate (2.10 g, 8.70 mmol) and 10% Pd/C (924 mg) in MeOH (43.4 mL) was stirred under H_2 overnight. The reaction was filtered over Celite and concentrated to afford the title compound (1.88 g, > 100%) as a yellow oil. LCMS (Method G): 0.89 min, m/z: 212.0 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.17 (d, *J* = 2.3 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.36 (bs, 2H), 2.73 (t, *J* = 6.6 Hz, 2H), 1.41 (s, 9H).

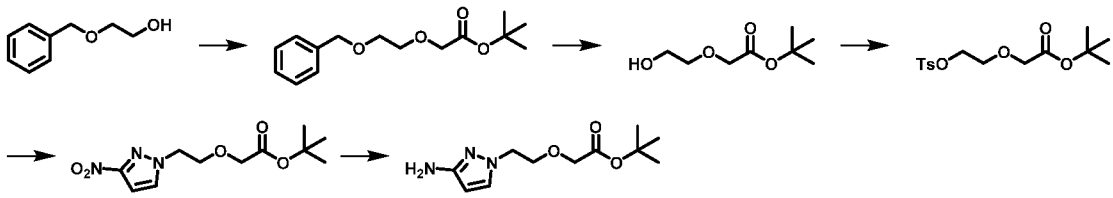
The following intermediates were similarly prepared from 3-nitro-1H-pyrazole and the appropriate alkyl bromide according to the procedures for the synthesis of **Intermediate K1**.

Table 28: Intermediates K

Intermediate	Name	Structure	Analytical data	SM
K2	tert-butyl 4-(3-amino-1H-pyrazol-1-yl)butanoate		LCMS (Method G): 1.02 min, m/z: 226.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.16 (d, *J* = 2.5 Hz, 1H), 5.59 (d, *J* = 2.5 Hz, 1H), 4.04 (t, *J* = 6.7 Hz, 2H), 3.36 (bs, 2H), 2.20 (t, *J* = 6.7 Hz, 2H), 2.10 (p, *J* = 6.7 Hz, 2H), 1.43 (s, 9H).	tert-butyl 4-bromobutanoate
K3	tert-butyl 5-(3-amino-1H-pyrazol-1-yl)pentanoate		LCMS (Method G): 1.14 min, m/z: 240.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.11 (d, *J* = 2.3 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 3.91 (t, *J* = 6.9 Hz, 2H), 3.17 (bs, 2H), 2.22 (t, *J* = 7.4 Hz, 2H), 1.86-1.77 (m, 2H), 1.60-1.50 (m, 2H), 1.43 (s, 9H).	tert-butyl 5-bromopentanoate
K4	tert-butyl 6-(3-amino-1H-pyrazol-1-yl)hexanoate		LCMS (Method G): 1.29 min, m/z: 254.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.09 (d, J = 2.3 Hz, 1H), 5.54 (d, J = 2.3 Hz, 1H), 3.89 (t, J = 7.0 Hz, 2H), 3.21 (bs, 2H), 2.19 (t, J = 7.4 Hz, 2H), 1.85-1.75 (m, 2H), 1.64-1.54 (m, 2H), 1.42 (s, 9H), 1.34-1.28 (m, 2H).	tert-butyl 6-bromohexanoate
K5	tert-butyl 7-(3-amino-1H-pyrazol-1-yl)heptanoate		LCMS (Method G): 1.46 min, m/z: 268.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.10 (d, *J* = 2.3 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 3.90 (t, *J* = 7.1 Hz, 2H), 3.46 (bs, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.84-1.75 (m, 2H), 1.59-1.51 (m, 2H), 1.43 (s, 9H), 1.33-1.27 (m, 4H).	tert-butyl 7-bromoheptanoate
K6	tert-butyl 8-(3-amino-1H-pyrazol-1-yl)octanoate		LCMS (Method G): 1.64 min, m/z: 282.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.10 (d, *J* = 2.3 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 3.90 (t, *J* = 7.1 Hz, 2H), 3.46 (bs, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.84-1.74 (m, 2H), 1.60-1.50 (m, 2H), 1.43 (s, 9H), 1.31-1.28 (m, 6H).	tert-butyl 8-bromooctanoate

Synthesis of Intermediates L

Intermediate L1: tert-butyl 2-[2-(3-amino-1H-pyrazol-1-yl)ethoxy]acetate



Step 1: tert-butyl 2-[2-(benzyloxy)ethoxy]acetate

To a solution of 2-(benzyloxy)ethan-1-ol (1.0 g, 6.57 mmol) in DCM (13 mL) was added 37% aq. NaOH (13 mL), followed by tert-butyl 2-bromoacetate (3.86 mL, 26.2 mmol) and Bu_4NCl (1.82 g, 6.57 mmol). The reaction was stirred at RT overnight, and then the mixture was extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-20% EtOAc:heptane) to afford the title product (1.85 g, >100%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): 7.35-7.33 (m, 4H), 7.28-7.30 (m, 1H), 4.58 (s, 2H), 4.04 (s, 2H), 3.76-3.73 (m 2H), 3.68-3.65 (m, 2H), 1.47 (s, 9H).

Step 2: tert-butyl 2-(2-hydroxyethoxy)acetate

To a solution of tert-butyl 2-[2-(benzyloxy)ethoxy]acetate (1.86 g, 6.98 mmol) in EtOH (20 mL) was added 10% Pd/C (742 mg), and the reaction was stirred under H_2 overnight. The reaction was filtered over Celite and concentrated to afford the title product (1.34 g, >100%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): 4.09 (s, 1H), 4.02 (s, 2H), 3.75-3.71 (m, 2H), 3.69-3.66 (m, 2H), 1.48 (s, 9H).

Step 3: tert-butyl 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}acetate

To a solution of tert-butyl 2-(2-hydroxyethoxy)acetate (1.35 g, 7.66 mmol) in DCM (10 mL) were added TsCl (1.60 g, 8.42 mmol) and Et_3N (1.58 mL, 11.4 mmol), and the reaction was stirred at RT overnight. The mixture was concentrated and the residue was purified by flash chromatography (0-100% EtOAc:heptane) to afford the title product (1.66 g, 66%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): 7.80 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 0.7, 8.2 Hz, 2H), 4.21-4.17 (m, 2H), 3.94 (s, 2H), 3.78-3.75 (m, 2H), 2.44 (s, 3H), 1.46 (s, 9H).

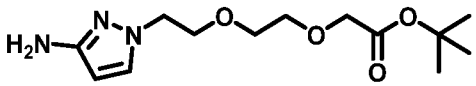
Step 4: tert-butyl 2-[2-(3-nitro-1H-pyrazol-1-yl)ethoxy]acetate

To a mixture of 3-nitro-1H-pyrazole (500 mg, 4.42 mmol) and tert-butyl 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}acetate (1.46 g, 4.42 mmol) in NMP (10 mL) was added Cs_2CO_3 (1.44 g, 4.42 mmol) and the reaction was heated at 60 °C overnight. Once cooled, water (30 mL) was added, and the mixture was extracted with EtOAc (2 x 40 mL). The combined organics were washed with brine (2 x 40 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title product (720 mg, 61%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 4.43 (t, *J* = 4.6 Hz, 2H), 3.96-3.92 (m, 4H), 1.46 (s, 9H).

Step 5: tert-butyl 2-[2-(3-amino-1H-pyrazol-1-yl)ethoxy]acetate

To a solution of tert-butyl 2-[2-(3-nitro-1H-pyrazol-1-yl)ethoxy]acetate (720 mg, 2.65 mmol) in EtOH (10 mL) was added 10% Pd/C (281 mg), and the reaction was stirred under H_2 overnight. The reaction was filtered over Celite and concentrated to afford the title product (646 mg, >100%) as a green oil. LCMS (method G): 0.91 min, m/z: 242.0 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.28 (d, *J* = 0.2 Hz, 1H), 5.59 (d, *J* = 0.2 Hz, 1H), 4.15 (t, *J* = 5.1 Hz, 2H), 3.91 (s, 2H), 3.84 (t, *J* = 5.1 Hz, 2H), 1.49 (s, 9H).

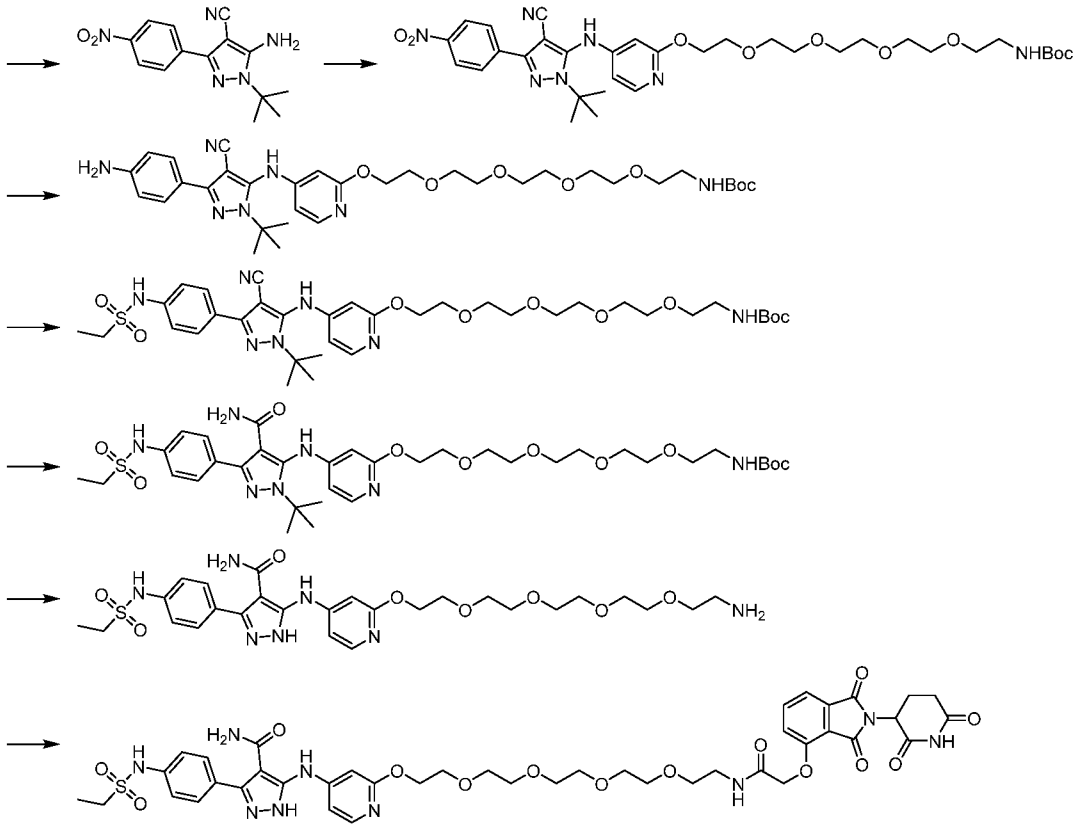
Intermediate L2: tert-butyl 2-{2-[2-(3-amino-1H-pyrazol-1-yl)ethoxy]ethoxy}acetate



The title compound was prepared according to the procedures for the synthesis of **Intermediate L1** using 2-[2-(benzyloxy)ethoxy]ethan-1-ol in Step 1. LCMS (method G): 0.98 min, m/z: 286.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.27 (d, *J* = 2.4 Hz, 1H), 5.58 (d, *J* = 2.4 Hz, 1H), 4.12 (t, *J* = 5.3 Hz, 2H), 3.98 (s, 2H), 3.79 (t, *J* = 5.5 Hz, 2H), 3.67-3.64 (m, 2H), 3.61-3.58 (m, 2H), 1.47 (s, 9H).

Synthesis of Further Examples:

Compound 1001: 5-[(2-{[14-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)-3,6,9,12-tetraoxatetradecan-1-yl]oxy}pyridin-4-yl)amino]-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide



Step 1: tert-butyl N-{14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate

A mixture of 4-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate A1'**, 250 mg, 0.88 mmol), tert-butyl N-{14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate (**Intermediate H1**, 657 mg, 1.00 mmol), $Pd(OAc)_2$ (19.6 mg, 0.09 mmol), Xantphos (101 mg, 0.18 mmol) and Cs_2CO_3 (426 mg, 1.31 mmol) in degassed 1,4-dioxane (8.76 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with EtOAc (50 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (0-5% MeOH:DCM) to afford the title compound (220 mg, 36%) as an orange gum. LCMS (method G): 2.24 min; m/z: 698.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.93 (br s, 1H), 8.42-8.38 (m, 2H), 8.17-8.13 (m, 2H), 7.88 (d, J = 5.7 Hz, 2H), 6.74-6.70 (m, 1H), 6.44 (dd, J = 5.8, 1.9 Hz, 1H), 5.97 (d, J = 1.8 Hz, 1H), 4.32-4.29 (m, 2H), 3.70-3.67 (m, 2H), 3.54-3.45 (m, 12H), 3.38-3.34 (m, 2H), 3.04 (q, J = 5.8 Hz, 2H), 1.63 (s, 9H), 1.35 (s, 9H).

Step 2: tert-butyl N-{14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12,tetraoxatetradecan-1-yl}carbamate

A mixture of tert-butyl N-{14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate (220 mg, 0.31 mmol) and 10% Pd/C (22 mg) in MeOH (10 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (197 mg, 94%) as a yellow glass. LCMS (method G): 1.71 min; m/z: 666.4 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 8.76 (br s, 1H), 7.85 (d, J = 5.7 Hz, 1H), 7.58-7.55 (m, 2H), 6.72 (br s, 1H), 6.65-6.61 (m, 2H), 6.36 (dd, J = 5.7, 1.9 Hz, 1H), 5.86 (d, J = 1.7 Hz, 1H), 5.45 (s, 2H), 4.31-4.27 (m, 2H), 3.70-3.67 (m, 2H), 3.55-3.47 (m, 12H), 3.37-3.33 (m, 2H), 3.04 (q, J = 6.0 Hz, 2H), 1.57 (s, 9H), 1.36 (s, 9H).

Step 3: tert-butyl N-{14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]3,6,9,12-tetraoxatetradecan-1-yl}carbamate

A mixture of tert-butyl N-{14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12,tetraoxatetradecan-1-yl}carbamate (190 mg, 0.28 mmol), $EtSO_2Cl$ (53.8 µL, 0.56 mmol) and pyridine (229 µL, 2.84 mmol) in DCM (4 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel chromatography (0-10% MeOH:DCM) to afford the title compound (190 mg, 88%) as a yellow foam. LCMS (method G): 1.91 min; m/z: 760.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 8.84 (br s, 1H), 7.87 (d, J = 5.8 Hz, 1H), 7.84-7.80 (m, 2H), 7.35-7.32 (m, 2H), 6.72 (br s, 1H), 6.39 (dd, J = 5.8, 1.9 Hz, 1H), 5.90 (d, J = 1.7 Hz, 1H), 4.31-4.28 (m, 2H), 3.70-3.67 (m, 2H), 3.53-3.47 (m, 12H), 3.39-3.35 (m, 2H), 3.15 (q, J = 7.4 Hz, 2H), 3.04 (q, J = 6.0 Hz, 2H), 1.59 (s, 9H), 1.35 (s, 9H), 1.20 (t, J = 7.4 Hz, 3H).

Step 4: tert-butyl N-{14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate

A mixture of Tert-butyl N-{14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]3,6,9,12-tetraoxatetradecan-1-yl}carbamate (185 mg, 0.24 mmol) and Ghaffar-Parkins' catalyst (10.4 mg, 0.02 mmol) in 80% aq. EtOH (8 mL) was heated to 130 °C under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (187 mg, 99%) as a yellow foam. LCMS (method G): 1.62 min; m/z: 778.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.82 (br s, 1H), 8.25 (s, 1H), 7.77-7.75 (m, 1H), 7.71-7.64 (m, 2H), 7.25-7.20 (m, 2H), 7.19 (br s, 1H), 7.08 (br s, 1H), 6.73 (br s, 1H), 6.30 (br s, 1H), 5.78 (br s, 1H), 4.26-4.23 (m, 2H), 3.67-3.64 (m, 2H), 3.54-3.46 (m, 12H), 3.38-3.36 (m, 2H), 3.14-3.02 (m, 4H), 1.55 (s, 9H), 1.36 (s, 9H), 1.20 (t, J = 7.3 Hz, 3H).

Step 5: 5-({2-[(14-amino-3,6,9,12-tetraoxatetradecan-1-yl)oxy]pyridin-4-yl}amino)-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide

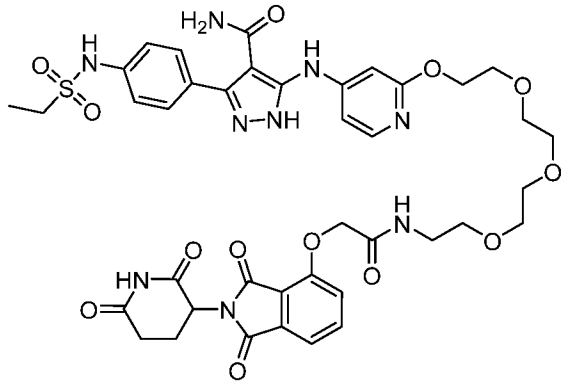
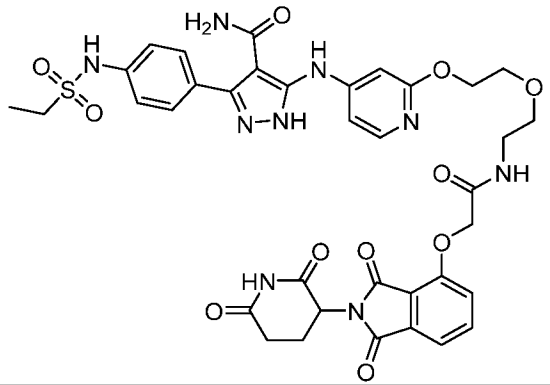
A solution of tert-butyl N-{14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecan-1-yl}carbamate (180 mg, 0.23 mmol) in 3:1 TFA/DCM (5.5 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure. Purification by SCX cartridge (MeOH, then 2.0 M NH_3 in MeOH) afforded the title compound (124 mg, 87%) as a brown foam. LCMS (method G): 0.88 min; m/z: 622.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 9.28 (br s, 1H), 7.84 (d, J = 5.8 Hz, 1H), 7.52-7.48 (m, 2H), 7.32-7.28 (m, 2H), 7.11 (d, J = 1.8 Hz, 1H), 6.86 (dd, J = 5.8, 1.9 Hz, 1H), 4.33-4.30 (m, 2H), 3.73-3.70 (m, 2H), 3.59-3.49 (m, 12H), 3.38 (t, J = 5.7 Hz, 2H), 3.11 (q, J = 7.3 Hz, 2H), 2.72-2.68 (m, 2H), 1.21 (t, J = 7.3 Hz, 3H).

Step 6: 5-[(2-{[14-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)-3,6,9,12-tetraoxatetradecan-1-yl]oxy}pyridin-4-yl)amino]-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide

A mixture of 5-({2-[(14-Amino-3,6,9,12-tetraoxatetradecan-1-yl)oxy]pyridin-4-yl}amino)-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide (60.0 mg, 96.5 µmol), 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetic acid (**Intermediate 1**, 33.6 mg, 101.3 µmol), HATU (40.3 mg, 0.11 mmol) and DIPEA (50.4 µL, 0.29 mmol) in DMF (1 mL) was stirred at RT under N_2. After 6 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (49 mg, 54%) as a white foam. LCMS (method G): 1.24 min; m/z: 936.0 $[M+H]^+$, 468.6 $[M+2H]^{2+}$. ^1H NMR (300 MHz, DMSO-d_6): 12.89 (s, 1H), 11.11 (s, 1H), 9.25 (s, 1H), 8.17 (s, 1H), 8.00 (t, J = 5.5 Hz, 1H), 7.81 (dd, J = 16.4, 7.0 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.37 (dd, J = 12.3, 8.5 Hz, 4H), 7.09 (s, 1H), 6.87 (d, J = 5.1 Hz, 1H), 5.17-5.05 (m, 1H), 4.78 (s, 2H), 4.31 (t, J = 4.8 Hz, 2H), 3.75-3.62 (m, 2H), 3.48 (dq, J = 10.9, 6.9, 5.4 Hz, 12H), 3.31 (d, J = 5.9 Hz, 2H), 3.18 (q, J = 7.3 Hz, 2H), 2.97-2.80 (m, 2H), 2.62 (s, 1H), 2.56 (s, 1H), 2.03 (dd, J = 11.9, 5.8 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H).

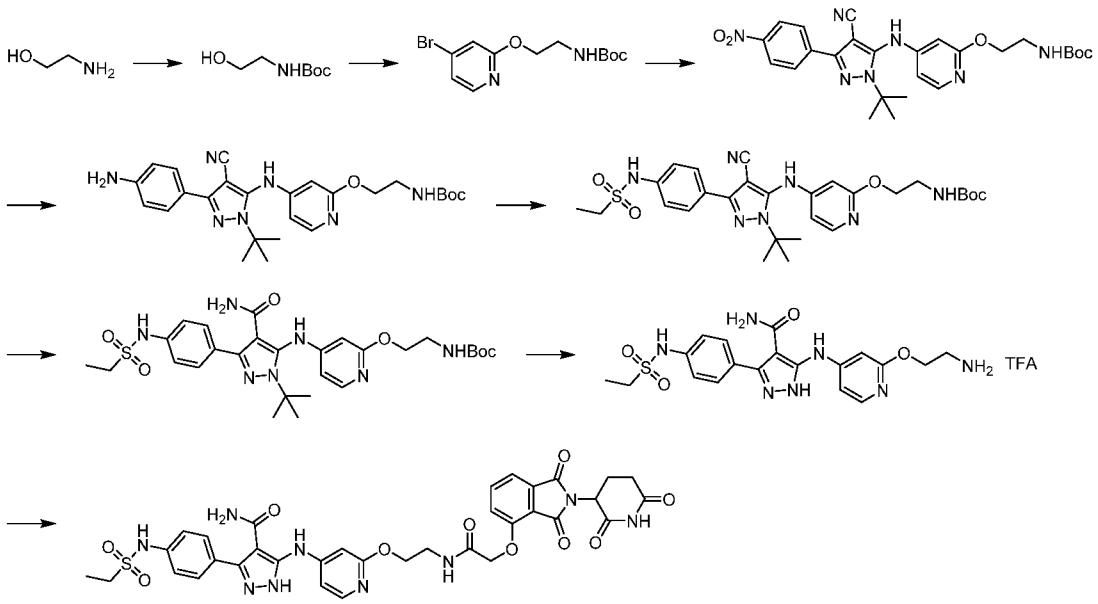
Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of **Compound 1001**, utilizing the indicated **Intermediate H** in Step 1.

Table 29: Compounds 1002-1005

Example No.	Structure	Compound Name and Analytical Data
Compound 1002		5-({2-[2-(2-{2-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)ethoxy]ethoxy}ethoxy)ethoxy]pyridin-4-yl}amino)-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide From **Intermediate H4**. LCMS (method G): 1.78 min; m/z: 892.2 $[M+H]^+$, 446.8 $[M+2H]^{2+}$. ^1H NMR (300 MHz, DMSO-d_6): 12.84 (s, 1H), 11.12 (s, 1H), 9.25 (s, 1H), 8.15 (s, 1H), 8.01 (t, J = 5.5 Hz, 1H), 7.84 (d, J = 5.9 Hz, 1H), 7.80 (dd, J = 8.5, 7.3 Hz, 1H), 7.59-7.51 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.43-7.29 (m, 3H), 7.09 (s, 1H), 6.86 (dd, J = 5.8, 2.0 Hz, 1H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 4.78 (s, 2H), 4.31 (dd, J = 5.8, 3.7 Hz, 2H), 3.70 (dd, J = 5.8, 3.9 Hz, 2H), 3.55 (dq, J = 5.6, 3.0, 2.1 Hz, 8H), 3.46 (t, J = 5.6 Hz, 4H), 3.31 (q, J = 5.6 Hz, 4H), 3.16 (q, J = 7.3 Hz, 2H), 2.98-2.80 (m, 1H), 2.60 (m, 1H), 2.55 (d, J = 6.1 Hz, 1H), 2.09-1.99 (m, 1H), 1.22 (t, J = 7.3 Hz, 3H).
Compound 1003		5-((2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)ethoxy)ethoxy)pyridin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide From **Intermediate H2**. LCMS (method G): 1.74 min; m/z: 804.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 12.84 (s, 1H), 11.12 (s, 1H), 9.23 (s, 1H), 8.06 (t, J = 5.6 Hz, 1H), 7.83 (d, J = 5.8 Hz, 1H), 7.78 (dd, J = 8.5, 7.3 Hz, 1H), 7.59-7.53 (m, 2H), 7.47 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 8.1 Hz, 3H), 7.09 (s, 1H), 6.84 (dd, J = 5.9, 1.9 Hz, 1H), 5.10 (dd, J = 12.6, 5.3 Hz, 1H), 4.78 (s, 2H), 4.39-4.28 (m, 2H), 3.72 (t, J = 4.8 Hz, 2H), 3.53 (t, J = 5.6 Hz, 2H),

		3.16 (q, *J* = 7.3 Hz, 2H), 2.97-2.79 (m, 1H), 2.61 (d, *J* = 3.4 Hz, 1H), 2.55 (d, *J* = 4.7 Hz, 1H), 2.08-1.98 (m, 1H), 1.22 (t, *J* = 7.3 Hz, 3H).
Compound 1004		5-((2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)ethoxy)ethoxy)ethoxy)pyridin-4-yl)amino)-3-(4-(ethylsulfonamido)phenyl)-1H-pyrazole-4-carboxamide From **Intermediate H3**. LCMS (method E): 1.77 min; m/z: 848.2 $[M+H]^+$, 424.5 $[M+2H]^{2+}$. ^1H NMR (300 MHz, DMSO-d_6): 12.85 (s, 1H), 11.12 (s, 1H), 9.24 (s, 1H), 8.18 (s, 1H), 8.02 (t, *J* = 5.6 Hz, 1H), 7.87-7.74 (m, 2H), 7.60-7.50 (m, 2H), 7.48 (dd, *J* = 7.3, 0.6 Hz, 1H), 7.38 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.36-7.29 (m, 2H), 7.08 (s, 1H), 6.86 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.11 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.78 (s, 2H), 4.30 (dd, *J* = 5.9, 3.7 Hz, 2H), 3.75-3.66 (m, 2H), 3.63-3.52 (m, 4H), 3.48 (t, *J* = 5.6 Hz, 2H), 3.32 (q, *J* = 5.6 Hz, 2H), 3.16 (q, *J* = 7.3 Hz, 2H), 2.89 (ddd, J = 17.2, 13.9, 5.3 Hz, 2H), 2.65-2.51 (m, 1H), 2.11-1.99 (m, 1H), 1.22 (t, *J* = 7.3 Hz, 3H).
Compound 1005		5-[(2-{[17-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)-3,6,9,12,15-pentaoxaheptadecan-1-yl]oxy}pyridin-4-yl)amino]-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide From **Intermediate H5**. LCMS (method G): 1.23 min; m/z: 980.0 $[M+H]^+$, 490.9 $[M+2H]^{2+}$.

Compound 1006: 5-({2-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)ethoxy]pyridin-4-yl}amino)-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide



Step 1: tert-butyl N-(2-hydroxyethyl)carbamate

To a 0 °C solution of 2-aminoethan-1-ol (1.38 g, 22.9 mmol) in THF (50 mL) was added Boc_2O (4.99 g, 22.9 mmol) and the mixture was allowed to warm to RT. After 16 h, the reaction mixture was concentrated, and the residue diluted with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (1.92 g, 52%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): 3.68 (t, *J* = 5.1 Hz, 2H), 3.27 (t, *J* = 5.1 Hz, 2H), 1.43 (s, 9H).

Step 2: tert-butyl N-{2-[(4-bromopyridin-2-yl)oxy]ethyl}carbamate

To a solution of tert-butyl N-(2-hydroxyethyl)carbamate (959 mg, 5.95 mmol) in THF (13 mL) was added NaH (316 mg, 7.94 mmol) in portions. The mixture was stirred at RT under N_2 for 10 min before 4-bromo-2-fluoropyridine (408 µL, 3.97 mmol) was added. The mixture was stirred at RT under N_2 for 2 h before being quenched with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica gel column chromatography (0-20% EtOAc:*c*-Hex) afforded the title compound (1.19 g, 95%) as a white solid. LCMS (method G): 2.11 min; m/z: 317.0, 319.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.95 (d, *J* = 5.5

Hz, 1H), 7.03 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H), 4.95 (br s, 1H), 4.35 (t, *J* = 5.2 Hz, 2H), 3.50 (br s, 2H), 1.43 (s, 9H).

Step 3: tert-butyl N-{2-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]ethyl}carbamate

A mixture of 4-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate A1'**, 700 mg, 2.45 mmol), tert-butyl N-{2-[(4-bromopyridin-2-yl)oxy]ethyl}carbamate (1.00 g, 2.94 mmol), $Pd(OAc)_2$ (55.0 mg, 0.25 mmol), Xantphos (283 mg, 0.49 mmol) and Cs_2CO_3 (1.19 g, 3.67 mmol) in degassed 1,4-dioxane (25 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-100% EtOAc:*c*-Hex) to afford the title compound (1.23 g, 96%) as a yellow solid. LCMS (method G): 2.22 min; m/z: 522.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 8.32-8.28 (m, 2H), 8.21-8.16 (m, 2H), 7.90 (d, J = 5.9 Hz, 1H), 6.46-6.42 (m, 1H), 6.11 (br s, 1H), 5.09 (br s, 1H), 4.31 (t, *J* = 5.1 Hz, 2H), 3.51-3.45 (m, 2H), 1.70 (s, 9H).

Step 4: tert-butyl N-{2-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]ethyl}carbamate

A mixture of tert-butyl N-{2-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate (800 mg, 1.53 mmol) and 10% Pd/C (80 mg) in MeOH (15 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (702 mg, 93%) as a red solid. LCMS (method G): 1.62 min; m/z: 490.2 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6): 8.77 (br s, 1H), 7.85 (d, *J* = 5.7 Hz, 1H), 7.59-7.54 (m, 2H), 6.66-6.61 (m, 2H), 6.36 (dd, *J* = 5.7, 1.9 Hz, 1H), 5.84 (s, 1H), 5.46 (br s, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.23 (q, *J* = 5.7 Hz, 2H), 1.57 (s, 9H), 1.35 (s, 9H).

Step 5: tert-butyl N-{2-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate

A mixture of tert-butyl N-{2-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate (500 mg, 1.01 mmol), $EtSO_2Cl$ (190 µL, 2.02 mmol) and pyridine (815 µL, 10.1 mmol) in DCM (5.0 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash chromatography (0-10% MeOH:DCM) to afford the title compound (458 mg, 77%) as a yellow foam. LCMS (method G): 1.84 min; m/z: 584.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6):

10.05 (br s, 1H), 7.88 (d, *J* = 5.9 Hz, 1H), 7.84-7.79 (m, 2H), 7.38-7.32 (m, 2H), 6.93 (d, *J* = 5.8 Hz, 1H), 6.44 (d, *J* = 5.1 Hz, 1H), 5.96 (s, 1H), 4.17 (t, *J* = 5.7 Hz, 2H), 3.24 (q, *J* = 5.7 Hz, 2H), 3.20-3.11 (m, 2H), 1.59 (s, 9H), 1.34 (s, 9H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 6: tert-butyl N-{2-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate

A mixture of tert-butyl N-{2-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate (185 mg, 0.31 mmol), EtOH (4.5 mL), DMSO (1 mL) and 5% aq. NaOH (0.15 mL) was heated to 80 °C. A solution of 30% H_2O_2 (1 mL) was added and the mixture stirred at 80 °C. Additional charges of H_2O_2 (0.5 mL) were added at 24 h intervals until full conversion of the SM was observed by LCMS. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and then concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-10% MeOH:DCM) to afford the title compound (144 mg, 75%) as a yellow gum. LCMS (method G): 1.49 min; m/z: 602.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.84 (br s, 1H), 8.27 (s, 1H), 7.75 (d, *J* = 5.7 Hz, 1H), 7.68-7.64 (m, 2H), 7.25-7.21 (m, 2H), 7.18 (br s, 1H), 7.07 (br s, 1H), 6.91 (5.7 Hz, 1H), 6.29 (br s, 1H), 5.76 (br s, 1H), 4.11 (t, *J* = 5.8 Hz, 2H), 3.21 (q, *J* = 5.7 Hz, 2H), 3.10 (q, *J* = 7.3 Hz, 2H), 1.55 (s, 9H), 1.35 (s, 9H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 7: 5-{[2-(2-aminoethoxy)pyridin-4-yl]amino}-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide

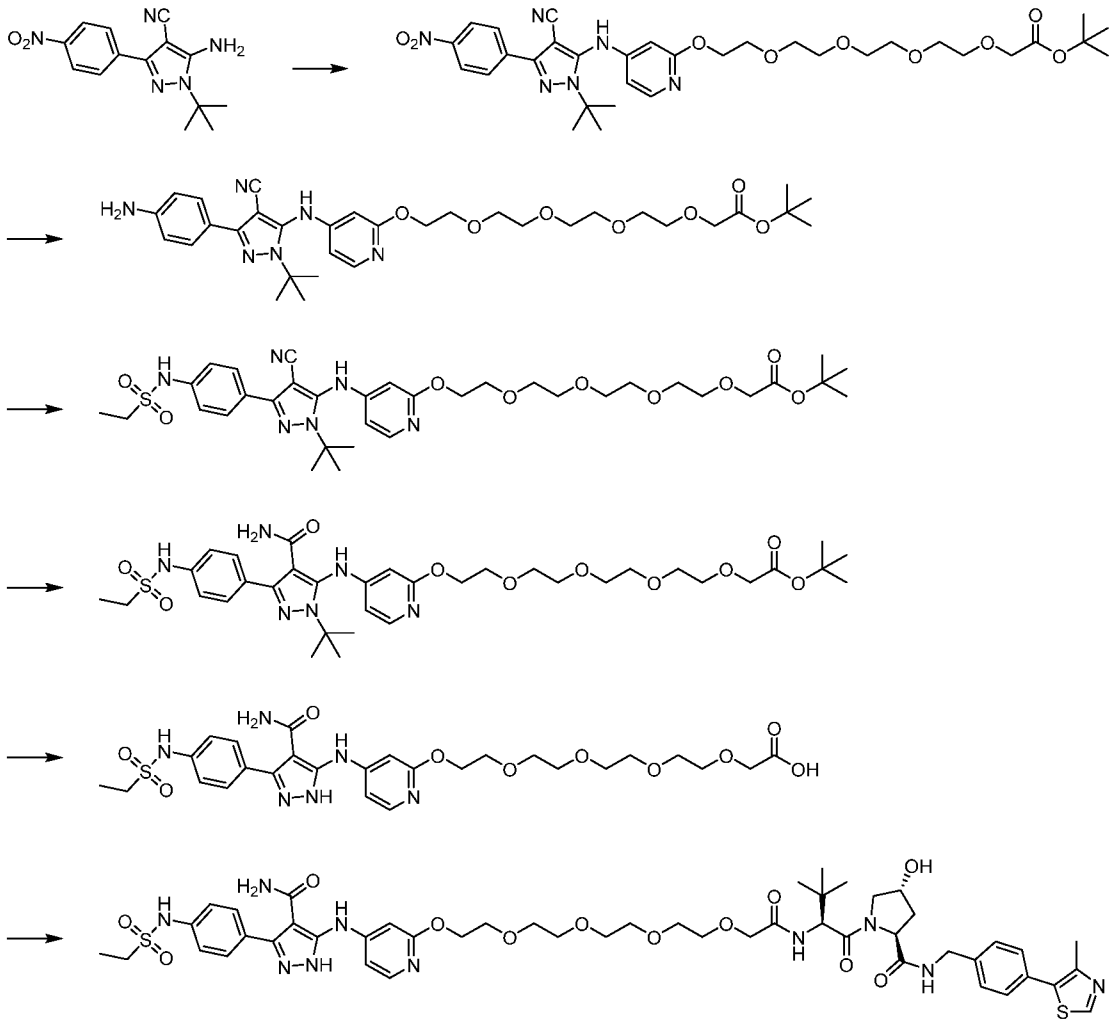
A solution of tert-butyl N-{2-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]ethyl}carbamate (190 mg, 0.31 mmol) in 1:5 TFA:DCM (12 mL) was stirred at RT. After 6 h, the reaction mixture was concentrated under reduced pressure to afford the title compound as the TFA salt (120 mg, 85%) as an off white gum. LCMS (method G): 0.66 min; m/z: 446.2 $[M+H]^+$.

Step 8: 5-({2-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetamido)ethoxy]pyridin-4-yl}amino)-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide

A mixture of 5-{[2-(2-Aminoethoxy)pyridin-4-yl]amino}-3-(4-ethanesulfonamidophenyl)-1H-pyrazole-4-carboxamide (60.0 mg, 88.8 µmol), 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy}acetic acid (**Intermediate 1**, 32.4 mg, 97.7 µmol), HATU (40.5 mg, 0.11 mmol) and DIPEA (46.3 µL, 0.27 mmol) in DMF (1 mL) was stirred at RT under N_2. After 3 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (19.0 mg, 28%)

as a white solid. LCMS (method G): 1.11 min; m/z: 760.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 12.85 (br s, 1H), 11.10 (s, 1H), 11.13 (s, 1H), 9.25 (s, 1H), 8.25 (s, 1H), 8.12 (s, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 7.55-7.53 (m, 2H), 7.45 (s, 1H), 7.36 (s, 2H), 7.11 (s, 1H), 6.86 (s, 1H), 5.11-5.07 (m, 1H), 4.80 (s, 2H), 4.29 (s, 2H), 3.18 (s, 2H), 2.90-2.81 (m, 1H), 2.59 (s, 2H), 2.05-2.03 (m, 1H), 1.23 (s, 3H).

Compound 1007: 3-(4-ethanesulfonamidophenyl)-5-({2-[(1-{[(2S)-1-[(2R,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}-2,5,8,11-tetraoxatridecan-13-yl)oyl]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate

A mixture of **Intermediate A1'** (450 mg, 1.57 mmol), tert-butyl 14-[(4-bromopyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate (**Intermediate I2**, 872 mg, 1.88 mmol), $Pd(OAc)_2$ (35.2 mg, 0.16 mmol), Xantphos (181 mg, 0.31 mmol) and Cs_2CO_3 (765 mg, 2.35 mmol) in 1,4-dioxane (15.6 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by flash column chromatography (0-5% MeOH:DCM) to afford the title compound (810 mg, 77%) as a brown oil. LCMS (method G): 2.28 min; m/z: 669.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.93 (br s, 1H), 8.42-8.38 (m, 2H), 8.17-8.12 (m, 2H), 7.87 (d, *J* = 5.7 Hz, 1H), 6.44 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.97 (d, *J* = 1.8 Hz, 1H), 4.31-4.28 (m, 2H), 3.96 (s, 2H), 3.70-3.67 (m, 2H), 3.56-3.48 (m, 12H), 1.62 (s, 9H), 1.40 (s, 9H).

Step 2: *tert*-butyl 14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate

A mixture of tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate (800 mg, 1.19 mmol) and 10% Pd/C (80 mg) in MeOH (20 mL) was evacuated and back-filled with H_2 (three times), and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (770 mg, >100%) as a yellow foam. LCMS (method G): 1.71 min; m/z: 637.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.77 (br s, 1H), 7.85 (d, *J* = 5.8 Hz, 1H), 7.59-7.55 (m, 2H), 6.66-6.62 (m, 2H), 6.36 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.86 (d, *J* = 1.9 Hz, 1H), 5.46 (br s, 2H), 4.31-4.27 (m, 2H), 3.96 (s, 2H), 3.70-3.67 (m, 2H), 3.57-3.48 (m, 12H), 1.57 (s, 9H), 1.40 (s, 9H).

Step 3: *tert*-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate

A mixture of tert-butyl 14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate (400 mg, 0.62 mmol), $EtSO_2Cl$ (117 µL, 1.25 mmol) and pyridine (506 µL, 6.26 mmol) in DCM (4 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography (0-10% MeOH:DCM) to afford the title compound (383 mg, 84%) as a yellow foam. LCMS (method G): 1.91 min; m/z: 731.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 10.0 (br s, 1H), 8.84 (s, 1H), 7.86 (d, *J* = 5.7 Hz, 1H), 7.84-7.79 (m, 2H), 7.36-7.31 (m, 2H), 6.39 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.90 (d, *J* = 1.9 Hz, 1H), 4.31-4.28 (m, 2H), 3.96 (s, 2H), 3.70-3.67 (m, 2H), 3.56-3.48 (m, 12H), 3.15 (q, *J* = 7.3 Hz, 2H), 1.59 (s, 9H), 1.40 (s, 9H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 4: *tert*-butyl 14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tertaoxatetradecanoate

A mixture of tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoate (365 mg, 0.49 mmol) and Ghaffar-Parkins' catalyst (17.1 mg, 0.04 mmol) in 80% aq. EtOH (5.0 mL) was heated to 130 ºC under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (382 mg, >100%) as a white foam. LCMS (method G): 1.64 min; m/z: 750.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 9.86 (br s, 1H), 8.28 (s, 1H), 7.76 (d, *J* = 5.7 Hz, 1H), 7.69-7.65 (m, 2H), 7.23-7.21 (m, 2H), 7.19 (br s, 1H), 7.10 (br s, 1H), 6.29 (br s, 1H), 5.78 (br s, 1H), 4.26-4.23 (m, 2H), 3.97 (s, 2H), 3.67-3.64 (m, 2H), 3.57-3.49 (m, 12H), 3.10 (q, *J* = 7.3 Hz, 2H), 1.55 (s, 9H), 1.41 (s, 9H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 5: 14-[(4-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoic acid

A solution of tert-butyl 14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]-3,6,9,12-tertaoxatetradecanoate (200 mg, 0.26 mmol) in 1:1 TFA/DCM (2 mL) was stirred at RT. After 5 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (215 mg, >100%) as a yellow oil. LCMS (method G): 0.98 min; m/z: 637.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 10.29 (s, 1H), 10.12 (s, 1H), 8.03 (d, J = 7.0 Hz, 1H), 7.58 (d, *J* =8.6 Hz, 1H), 7.41-7.32 (m, 4H), 6.73 (br s, 1H), 4.43-4.41 (m, 2H), 4.00 (s, 2H), 3.83-3.80 (m, 2H), 3.62-3.50 (m, 12H), 3.17 (q, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

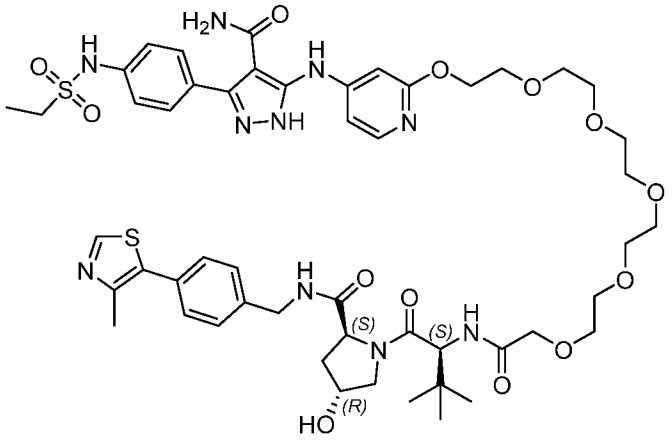
Step 6: 3-(4-ethanesulfonamidophenyl)-5-({2-[(1-{[(2S)-1-[(2R,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}-2,5,8,11-tetraoxatridecan-13-yl)oyl]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide

A mixture of 14-[(4-{[4-Carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]-3,6,9,12-tetraoxatetradecanoic acid (30 mg, 47.1 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} pyrrolidine-2-carboxamide (**Intermediate 2**, 20.6 mg, 48.0 µmol), HATU (19.7 mg, 0.05 mmol) and DIPEA (24.5 µL, 0.14 mmol) in DMF (471 µL) was stirred at RT under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B). Further purification by SCX cartridge (MeOH, then 2.0 M NH_3 in MeOH) afforded the title compound (20 mg, 40%) as a white solid. LCMS (method G): 1.29

min; m/z: 1052.2 $[M+H]^+$, 525.7 $[M+2H]^{2+}$. ^1H NMR (300 MHz, MeOD-d_4): 8.51 (s, 1H), 7.81 (d, *J* = 5.9 Hz, 1H), 7.57-7.53 (m, 2H), 7.45-7.37 (m, 6H), 7.23 (br s, 1H), 6.89-6.86 (m, 1H), 4.69-4.66 (m, 1H), 4.60-4.48 (m, 3H), 4.35-4.30 (m, 3H), 4.07-3.96 (m, 2H), 3.88-3.76 (m, 4H), 3.68-3.61 (m, 12H), 3.18 (q, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 2.26-2.18 (m, 1H), 2.12-2.03 (m, 1H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.02 (s, 9H).

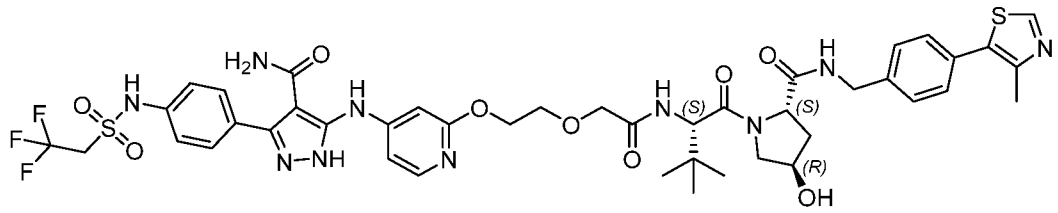
Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of **Compound 1007**, utilizing the indicated **Intermediate I** in Step 1.

Table 30: Compounds 1008 to 110

Compound No.	Structure	Compound Name and Analytical Data
Compound 1008		3-(4-ethanesulfonamidophenyl)-5-({2-[(1-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}-2,5,8,11,14-pentaoxahexadecan-16-yl)oxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate I3**. LCMS (method G): 1.44 min; m/z: 1093.4 $[M+H]^+$, 547.2 $[M+2H]^{2+}$. ^{1}H NMR (300 MHz, MeOD-d_4): 8.87 (s, 1H), 7.82 (d, J = 5.9 Hz, 1H), 7.58-7.53 (m, 2H), 7.46-7.37 (m, 6H), 7.23 (br s, 1H), 6.87 (dd, J = 5.8, 1.9 Hz, 1H), 4.68 (s, 1H), 4.60-4.48 (m, 3H), 4.36-4.31 (m, 3H), 4.07-3.96 (m, 2H), 3.89-3.78 (m, 4H), 3.69-3.58 (m, 16H), 3.18 (q, J = 7.3 Hz, 2H), 2.45 (s, 3H), 2.27-2.18 (m, 1H), 2.12-2.03 (m, 1H), 1.33 (t, J = 7.3 Hz, 3H), 1.02 (s, 9H).

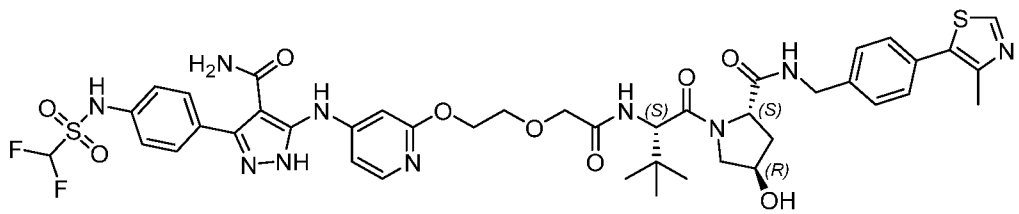
Compound 1009		3-(4-ethanesulfonamidophenyl)-5-({2-[(1-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}-2,5,8,11,14,17-hexaoxanonadecan-19-yl)oxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate I4**. LCMS (method G): 1.45 min; m/z: 1137.0 $[M+H]^+$, 569.4 $[M+2H]^{2+}$. ^1H NMR (300 MHz, MeOD-d_4): 8.86 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.60-7.54 (m, 2H), 7.46-7.38 (m, 6H), 7.24 (br s, 1H), 6.89-6.87 (m, 1H), 4.71-4.67 (m, 1H), 4.60-4.48 (m, 3H), 4.38-4.31 (m, 3H), 4.08-3.97 (m, 2H), 3.85-3.80 (m, 4H), 3.70-3.55 (m, 20H), 3.19 (q, J = 7.3 Hz, 2H), 2.45 (s, 3H), 2.27-2.18 (m, 1H), 2.14-2.06 (m, 1H), 1.33 (t, J = 7.3 Hz, 3H), 1.03 (s, 9H).
Compound 1010		3-(4-ethanesulfonamidophenyl)-5-({2-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate I1**. LCMS (method C): 1.45 min; m/z: 917.2 $[M+H]^+$, 459.2 $[M+2H]^{2+}$.

Compound 1011: 5-({2-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]pyridin-4-yl}amino)-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1010** utilizing 2,2,2-trifluoroethanesulfonyl chloride in Step 3. The title compound (17.0 mg, 44%) was obtained as a white solid. LCMS (method G): 1.66 min; m/z: 972.2 $[M+H]^+$, 486.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.87 (s, 1H), 10.75 (br s, 1H), 9.29 (s, 1H), 8.96 (s, 1H), 8.59 (t, J = 5.8 Hz, 1H), 7.84 (d, J = 5.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.48-7.33 (m, 8H), 7.12 (s, 1H), 6.90 (d, J = 5.7 Hz, 1H), 6.14 (br s, 1H), 5.16 (d, J = 3.5 Hz, 1H), 4.64-4.55 (m, 3H), 4.44 (t, J = 8.0 Hz, 1H), 4.40-4.35 (m, 4H), 4.24 (dd, J = 15.7, 5.4 Hz, 1H), 4.03 (s, 2H), 3.81 (s, 2H), 3.69-3.60 (m, 2H), 2.41 (s, 3H), 2.08-2.03 (m, 1H), 1.93-1.86 (m, 1H), 0.94 (s, 9H).

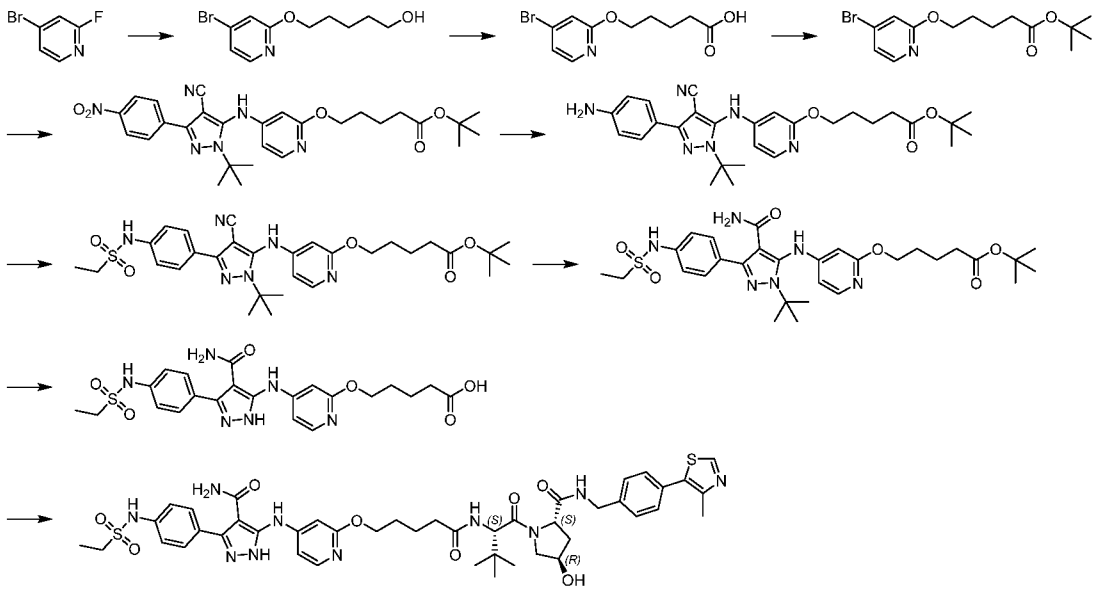
Compound 1012: 3-[4-(difluoromethanesulfonamido)phenyl]-5-({2-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1010** utilizing difluoromethanesulfonyl chloride in Step 3. The title compound (8.1 mg, 37%) was obtained as a white solid. LCMS (method G): 1.63 min; m/z: 939.2 $[M+H]^+$, 470.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.87 (br s, 1H), 11.25 (br s, 1H), 9.22 (s, 1H), 8.95 (s, 1H), 8.58 (t, J = 5.7 Hz, 1H), 7.84 (d, J = 5.7 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.47-7.29 (m, 8H), 7.16-7.02 (m, 2H), 6.90 (d, J = 5.7 Hz, 1H), 6.17 (br s, 1H), 5.15 (d, J = 2.7 Hz, 1H), 4.55 (d, J = 9.3 Hz, 1H), 4.45 (t, J = 8.2 Hz, 1H), 4.40-4.35 (m, 4H), 4.25 (dd, J = 15.7, 5.4 Hz, 1H), 4.03 (s, 2H),

3.81 (s, 2H), 3.69-3.60 (m, 2H), 2.42 (s, 3H), 2.07-2.02 (m, 1H), 1.93-1.89 (m, 1H), 0.94 (s, 9H).

Compound 1013: 3-(4-ethanesulfonamidophenyl)-5-{[2-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: 5-[(4-bromopyridin-2-yl)oxy]pentan-1-ol

To a solution of 1,5-pentanediol (892 µL, 8.52 mmol) in THF (11.3 mL) were added *t*-BuOK (637 mg, 5.68 mmol) and 4-Bromo-2-fluoropyridine (500 mg, 2.84 mmol), sequentially. The reaction was stirred at RT for 16 h before being quenched with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (0-80% EtOAc/*c*-Hex) to afford the title compound (471 mg, 64%) as a colourless oil. LCMS (method G): 1.65 min; m/z: 260.0, 262.0 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 7.96 (dd, *J* = 5.5, 0.4 Hz, 1H), 7.01 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.93 (dd, *J* = 1.6, 0.4 Hz, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 1.84-1.49 (m, 7H).

Step 2: 5-[(4-bromopyridin-2-yl)oxy]pentanoic acid

To a solution of 5-[(4-Bromopyridin-2-yl)oxy]pentan-1-ol (500 mg, 1.92 mmol) in 80% aq. MeCN (9.60 mL) was added H_5IO_6 (2.18 g, 9.60 mmol) and the mixture was cooled to 0 °C. CrO_3 was then added and the mixture was stirred at RT for 1 h. The reaction mixture was diluted with H_2O (75 mL) and extracted with EtOAc (4 x 25 mL). The combined organic layers

were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (548 mg, >100%) as a colourless, crystalline solid. LCMS (method G): 1.65 min; m/z: 274.0, 276.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 9.86 (br s, 1H), 7.97 (dd, *J* = 5.5, 0.4 Hz, 1H), 7.01 (d, *J* = 5.5, 1.6 Hz, 1H), 6.94 (d, *J* = 1.6, 0.4 Hz, 1H), 4.31-4.27 (m, 2H), 2.45-2.41 (m, 2H), 1.81 (m, 4H).

Step 3: tert-butyl 4-[(4-bromopyridin-2-yl)oxy]pentanoate

To a mixture of 5-[(4-Bromopyridin-2-yl)oxy]pentanoic acid (450 mg, 1.64 mmol), t-BuOH (390 µL, 4.10 mmol) and DMAP (100 mg, 0.82 mmol) in DCM (16.4 mL) was added DIC (380 µL, 2.46 mmol), and the reaction was stirred at RT for 16 h. The mixture was filtered through Celite and then concentrated. The crude material was purified by flash chromatography (0-20% EtOAc:*c*-Hex) to afford the title compound (330 mg, 61%) as a colourless oil. LCMS (method G): 2.86 min; m/z: 330.2, 332.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 7.95 (d, *J* = 5.5 Hz, 1H), 6.99 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.92 (d, *J* = 1.4 Hz, 1H), 4.28 (t, *J* = 6.2 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.83-1.67 (m, 4H), 1.43 (s, 9H).

Step 4: tert-butyl 5-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-5-yl)oxy]pentanoate

A mixture of 4-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate A1'**, 265 mg, 0.93 mmol, 1 equiv.), tert-butyl 4-[(4-bromopyridin-2-yl)oxy]pentanoate (322 mg, 0.97 mmol), $Pd(OAc)_2$ (20.8 mg, 0.09 mmol), Xantphos (107 mg, 0.19 mmol) and Cs_2CO_3 (452 mg, 1.39 mmol) in degassed 1,4-dioxane (10 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-60% EtOAc:*c*-Hex) to afford the title compound (430 mg, 86%) as a yellow foam. LCMS (method G): 2.57 min; m/z: 535.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 8.91 (br s, 1H), 8.42-8.38 (m, 2H), 8.18-8.12 (m, 2H), 7.87 (d, *J* = 5.8 Hz, 1H), 6.42 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.95 (d, *J* = 1.8 Hz, 1H), 4.17 (t, *J* = 6.0 Hz, 2H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.69-1.55 (m, 13H), 1.36 (s, 9H).

Step 5: tert-butyl 5-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-5-yl)oxy]pentanoate (420 mg, 0.78 mmol) and 10% Pd/C (45 mg) in MeOH (16 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (387 mg, 97%) as an orange foam. LCMS (method G): 1.98 min; m/z: 503.2

$[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6): 8.75 (br s, 1H), 7.84 (d, J = 5.8 Hz, 1H), 7.59-7.54 (m, 2H), 6.66-6.61 (m, 2H), 6.33 (dd, J = 5.8, 2.0 Hz, 1H), 5.85 (d, J = 1.8 Hz, 1H), 5.45 (br s, 2H), 4.16 (t, J = 6.1 Hz, 2H), 2.22 (t, J = 7.0 Hz, 2H), 1.68-1.57 (m, 13 H), 1.36 (s, 9H).

Step 6: tert-butyl 5-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]pentanoate (200 mg, 0.40 mmol), $EtSO_2Cl$ (74 µL, 0.79 mmol) and pyridine (320 µL, 3.96 mmol) in DCM (4 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash chromatography (0-10% MeOH:DCM) to afford the title compound (206 mg, 87%) as a yellow glass. LCMS (method G): 2.11 min; m/z: 597.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 10.05 (br s, 1H), 8.82 (s, 1H), 7.86 (d, J = 5.8 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 5.8 Hz, 1H), 5.88 (s, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.15 (q, J = 7.3 Hz, 2H), 2.22 (t, J = 6.8 Hz, 2H), 1.67-1.54 (m, 13H), 1.36 (s, 9H), 1.20 (t, J = 7.3 Hz, 3H).

Step 7: tert-butyl 5-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate (190 mg, 0.31 mmol) and Ghaffar-Parkins' catalyst (13.6 mg, 0.03 mmol) in 80% aq. EtOH (15 mL) was heated to 130 °C under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure. Purification by silica gel column chromatography (0-10% MeOH/DCM) afforded the title compound (180 mg, 92%) as a colourless glass. LCMS (method G): 1.86 min; m/z: 615.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 9.84 (br s, 1H), 8.22 (s, 1H), 7.75 (d, J = 5.8 Hz, 1H), 7.68-7.64 (m, 2H), 7.24-7.21 (m, 2H), 7.18 (s, 1H), 7.07 (s, 1H), 6.26 (br s, 1H), 5.75 (br s, 1H), 4.12 (t, J = 5.9 Hz, 2H), 3.10 (q, J = 7.3 Hz, 2H), 2.21 (t, J = 7.0 Hz, 2H), 1.66-1.55 (m, 13H), 1.20 (t, J =7.3 Hz, 3H).

Step 8: 5-[(4-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoic acid

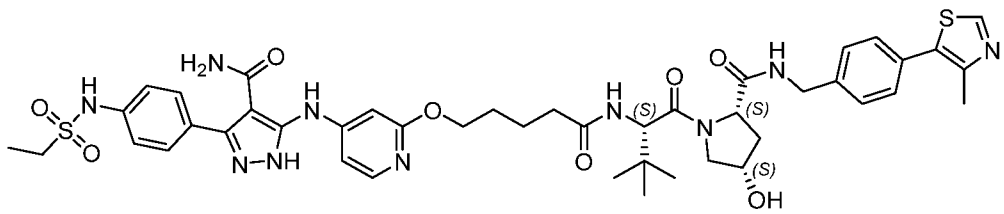
A solution of tert-butyl 5-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate (185 mg, 0.30 mmol) in 1:4 TFA:DCM (5 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (129 mg, 85%) as a white foam. LCMS (method G): 1.00 min; m/z: 503.0 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 13.26 (br s, 1H), 10.21 (s, 1H), 10.12 (s, 1H), 8.02 (d, J = 7.1 Hz, 1H), 7.60-7.56 (m, 2H), 7.37-7.32 (m, 5H), 6.70 (br s, 1H), 4.29 (t, J = 5.9

Hz, 2H), 3.18 (q, *J* = 7.3 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.86-1.76 (m, 2H), 1.73-1.61 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

Step 9: 3-(4-ethanesulfonamidophenyl)-5-{[2-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide

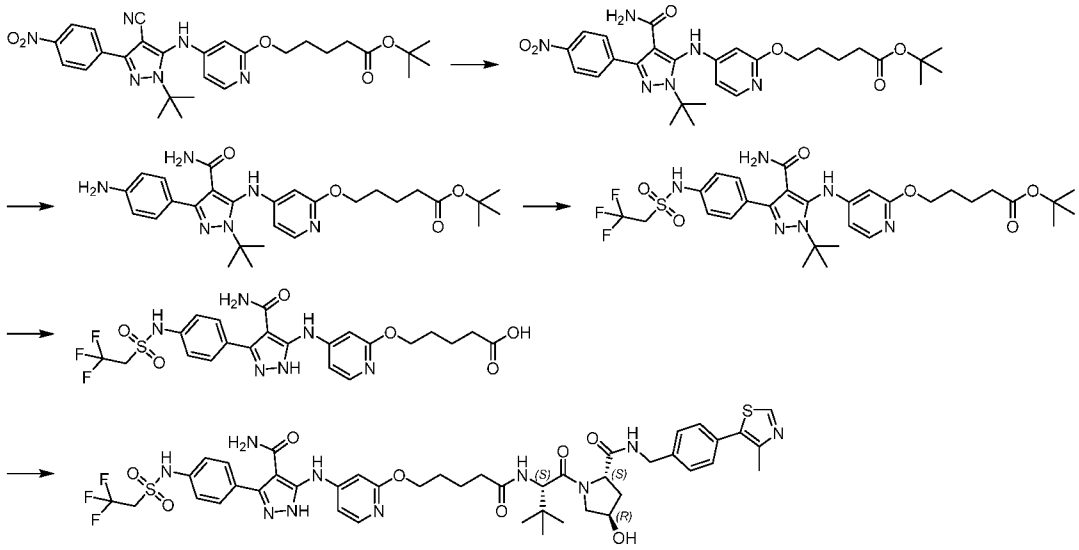
A mixture of 5-[(4-{[4-Carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]pentanoic acid (35 mg, 44.3 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 20.0 mg, 46.5 µmol), HATU (20.2 mg, 0.05 mmol) and DIPEA (23.1 µL, 0.13 mmol) in DMF (0.5 mL) was stirred at RT under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound as the formate salt (22.5 mg, 55%) as a white solid. LCMS (method G): 1.58 min; m/z: 915.3 $[M+H]^+$, 458.4 $[M+2H]^{2+}$.

Compound 1014: 3-(4-ethanesulfonamidophenyl)-5-{[2-(4-{[(2S)-1-[(2S,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1013** from 5-[(4-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoic acid (10.8 mg, 21.4 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 3**, 9.25 mg, 21.4 µmol). The title compound was obtained as a white solid (6.5 mg, 33%). LCMS (method G): 1.42 min; m/z: 916.2 $[M+H]^+$, 458.3 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (br s, 1H), 12.75 (br s, 1H), 10.12 (s, 1H), 8.98 (s, 1H), 8.65 (t, *J* = 5.6 Hz, 1H), 8.12 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.87 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.42-7.33 (m, 7H), 7.15 (br s, 1H), 6.92 (br s, 1H), 5.44 (br s, 1H), 4.47-4.41 (m, 2H), 4.35 (t, *J* = 7.2 Hz, 1H), 4.28-4.21 (m, 4H), 3.96-3.92 (m, 1H), 3.45-3.42 (m, 1H), 3.17 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.36-2.27 (m, 2H), 2.23-2.17 (m, 1H), 1.76-1.57 (m, 5H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 9H).

Compound 1016: 5-{[2-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 5-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-5-yl)oxy]pentanoate (410 mg, 0.76 mmol) and Ghaffar-Parkins' catalyst (32.9 mg, 76.7 µmol) in 80% aq. EtOH (38 mL) was heated to 130 °C under N_2. After 1 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (430 mg, >100%) as a white solid. LCMS (method G): 1.84 min; m/z: 553.4 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 8.33 (br s, 1H), 8.31-8.26 (m, 2H), 8.03-7.99 (m, 2H), 7.77 (d, J = 5.8 Hz, 1H), 7.35 (br s, 1H), 7.30 (br s, 1H), 6.28 (br s, 1H), 5.79 (br s, 1H), 4.12 (t, J = 6.2 Hz, 2H), 2.21 (t, J = 7.0 Hz, 2H), 1.67-1.54 (m, 13H), 1.37 (s, 9H).

Step 2: tert-butyl 5-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-carbamoyl-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate (420 mg, 0.75 mmol) and 10% Pd/C (40 mg) in MeOH (15 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (341 mg, 85%) as a yellow solid. LCMS (method G): 1.27 min; m/z: 523.4

$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.16 (s, 1H), 7.73 (d, J = 6.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.11 (s, 1H), 6.97 (s, 1H), 6.54 (d, J = 8.4 Hz, 2H), 6.25 (br s, 1H), 5.75 (br s, 1H), 5.16 (s, 2H), 4.11 (t, J = 5.9 Hz, 2H), 2.21 (t, J = 6.9 Hz, 2H), 1.65-1.53 (m, 13H), 1.37 (s, 9H).

Step 3: tert-butyl 5-{[4-({1-tert-butyl-4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido) phenyl]-1H-pyrazol-5-yl}amino)pyridin-2-yl]oxy}pentanoate

A mixture of tert-butyl 5-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-carbamoyl-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]pentanoate (50 mg, 95.6 µmol), 2,2,2-trifluoroethanesulfonyl chloride (12.6 µL, 114 µmol) and pyridine (38.6 µL, 478 µmol) in DCM (1 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash chromatography (0-10% MeOH:DCM) to afford the title compound (42 mg, 65%) as a white solid. LCMS (method G): 1.88 min; m/z: 669.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.50 (br s, 1H), 8.21 (s, 1H), 7.75 (d, J = 6.2 Hz, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.25-7.20 (m, 3H), 7.07 (s, 1H), 6.28 (br s, 1H), 5.75 (br s, 1H), 4.56-4.46 (m, 2H), 4.15-4.09 (m, 2H), 2.24-2.19 (m, 2H), 1.66-1.56 (m, 13H), 1.37 (s, 9H).

Step 4: 5-{[4-({4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridin-2-yl]oxy}pentanoic acid

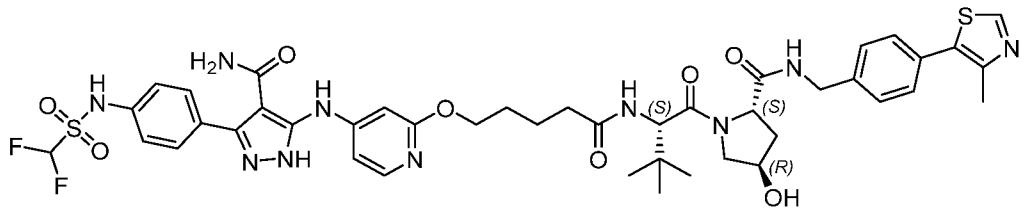
A solution of tert-butyl 5-{[4-({1-tert-butyl-4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido) phenyl]-1H-pyrazol-5-yl}amino)pyridin-2-yl]oxy}pentanoate (40 mg, 59.8 µmol) in 2:3 TFA:DCM (5 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (43 mg, >100%) as an orange oil. LCMS (method G): 1.28 min; m/z: 557.2 $[M+H]^+$.

Step 5: 5-{[2-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide

A mixture of 5-{[4-({4-Carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridin-2-yl]oxy}pentanoic acid (17 mg, 30.5 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 14.4 mg, 33.9 µmol), HATU (15.0 mg, 39.7 µmol) and DIPEA (15.9 µL, 91.6 µmol) in DMF (300 µL) was stirred at RT under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (method B) to afford the title compound (10.1 mg, 34%) as a white solid. LCMS (method G): 1.66 min; m/z: 970.3 $[M+H]^+$, 485.3 $[M+2H]^{2+}$. ^1H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 10.75 (br s, 1H), 9.27 (s, 1H), 8.97 (s, 1H), 8.57 (t, J = 6.0 Hz, 1H), 7.91 (d, J = 9.3 Hz,

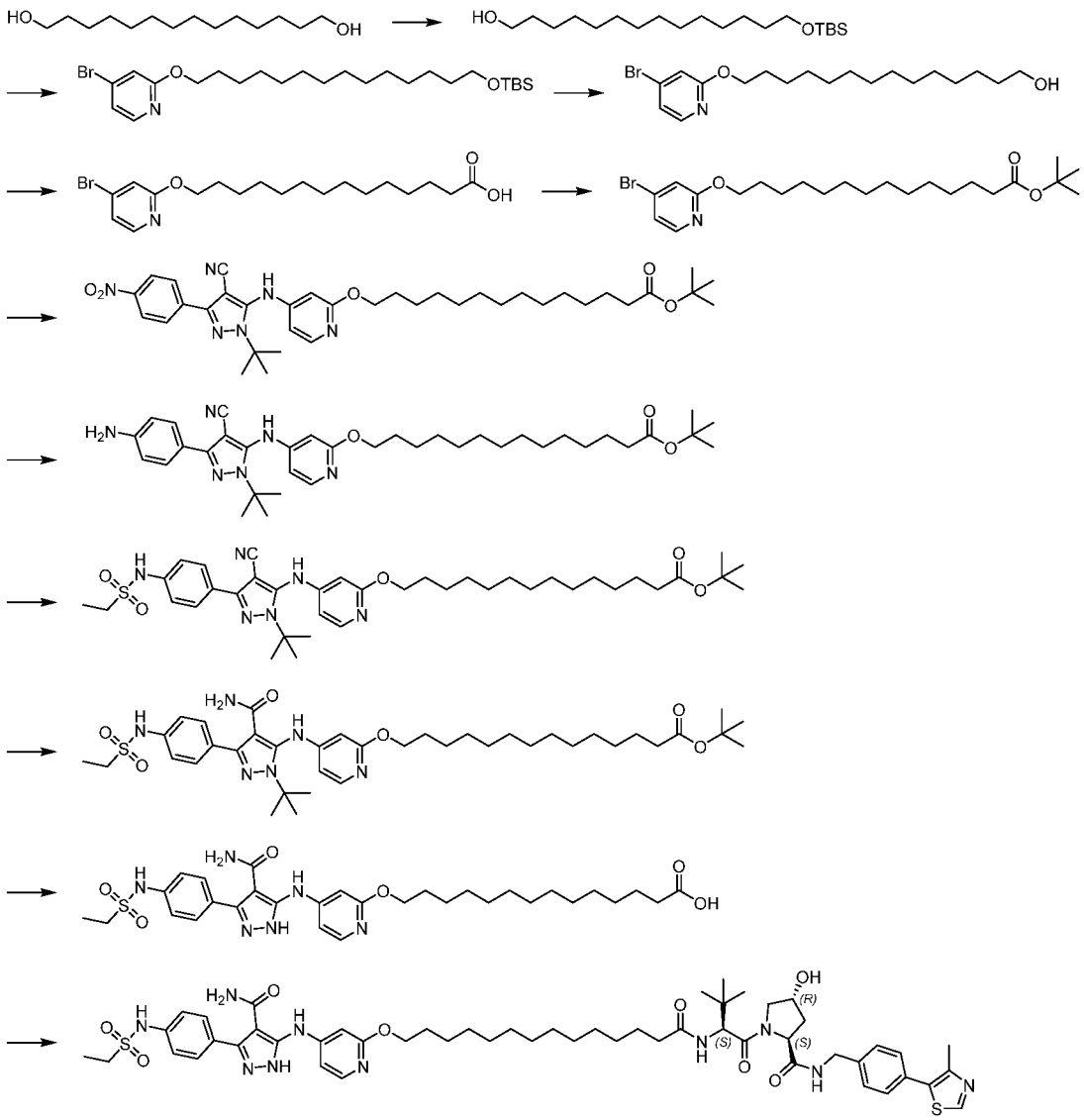
1H), 7.84 (d, *J* = 5.7 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.42-7.21 (m, 7H), 7.10 (s, 1H), 6.85 (d, *J* = 5.2 Hz, 1H), 6.15 (br s, 1H), 5.13 (d, *J* = 3.5 Hz, 1H), 4.62-4.53 (m, 3H), 4.44-4.34 (m, 2H), 4.34 (s, 1H), 4.24-4.17 (m, 3H), 3.69-3.63 (m, 2H), 2.43 (s, 3H), 2.36-2.28 (m, 1H), 2.23-2.16 (m, 1H), 2.05-2.00 (m, 1H), 1.93-1.86 (m, 1H), 1.67-1.58 (m, 4H), 0.93 (s, 9H).

Compound 1017: 3-[4-(difluoromethanesulfonamido)phenyl]-5-{[2-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-4-yl]amino}-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1016** utilizing difluoromethanesulfonyl chloride in Step 3. The title compound (11.6 mg, 40%) was obtained as a white solid. LCMS (method G): 1.63 min; m/z: 937.2 $[M+H]^+$, 469.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (br s, 1H), 11.14 (s, 1H), 10.08 (br s, 1H), 9.27 (br s, 1H), 8.97 (s, 1H), 8.55 (t, *J* = 6.0 Hz, 1H), 7.90 (d, *J* = 9.3 Hz, 1H), 7.84 (d, *J* = 5.7 Hz, 1H), 7.45-7.23 (m, 9H), 7.10 (br s, 1H), 6.85 (d, *J* = 4.5 Hz, 1H), 6.03 (br s, 1H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 9.3 Hz, 1H), 4.42 (dd, *J* = 14.6, 7.0 Hz, 2H), 4.35 (s, 1H), 4.24-4.17 (m, 3H), 3.70-3.63 (m, 2H), 2.43 (s, 3H), 2.35-2.28 (m, 1H), 2.23-2.17 (m, 1H), 2.07-2.00 (m, 1H), 1.93-1.86 (m, 1H), 1.67-1.63 (m, 4H), 0.93 (s, 9H).

Compound 1018: 3-(4-ethanesulfonamidophenyl)-5-({2-[(13-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}tridecyl)oxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: 14-[(tert-butyldimethylsilyl)oxy]tetradecan-1-ol

A mixture of tetradecane-1,14-diol (400 mg, 1.73 mmol), *n*-hexane (15 mL), MeCN (2 mL), Et_3N (293 µL, 2.11 mmol) and TBS-Cl (275 mg, 1.83 mmol) was heated to 55 °C. After 8 h, the reaction mixture was diluted with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica gel column chromatography (0-20% EtOAc:*c*-Hex) afforded the title compound (295 mg, 49%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): 3.66-3.57 (m, 4H), 1.59-1.47 (m, 4H), 1.37-1.23 (m, 20H), 0.89 (s, 9H), 0.045 (s, 6H).

Step 2: 4-bromo-2-({14-[(tert-butyldimethylsilyl)oxy]tetradecyl}oxy)pyridine

To a solution of 14-[(tert-butyldimethylsilyl)oxy]tetradecan-1-ol (290 mg, 0.84 mmol) in 2-MeTHF (15 mL) was added NaH (61.1 mg, 1.53 mmol) in portions and the mixture was heated to reflux. After 1 h, 4-bromo-2-fluoropyridine (135 mg, 0.76 mmol) was added and the reaction was heated to reflux. After 16 h, the reaction mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (487 mg, >100%) as a yellow residue. ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 (d, *J* = 5.6 Hz, 1H), 7.03 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 1.79-1.71 (m, 2H), 1.49-1.26 (m, 22H), 0.89 (s, 9H), 0.045 (s, 6H).

Step 3: 14-[(4-bromopyridin-2-yl)oxy]tetradecan-1-ol

A mixture of 4-bromo-2-({14-[(tert-butyldimethylsilyl)oxy]tetradecyl}oxy)pyridine (383 mg, 0.76 mmol) and TBAF (1.0 M in THF, 1.53 mL, 1.53 mmol) in THF (5 mL) was stirred at RT. After 4 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica gel column chromatography (0-50% EtOAc:*c*-Hex) afforded the title compound (247 mg, 83%) as a white solid. LCMS (method G): 3.56 min; m/z: 386.2, 388.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.97 (dd, *J* = 5.5, 0.4 Hz, 1H), 7.00 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.94 (dd, *J* = 1.6, 0.4 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 1.80-1.70 (m, 2H), 1.61-1.52 (m, 2H), 1.45-1.23 (m, 20H).

Step 4: 14-[(4-bromopyridin-2-yl)oxy]tetradecanoic acid

A mixture of 14-[(4-bromopyridin-2-yl)oxy]tetradecan-1-ol (240 mg, 0.62 mmol) and H_5IO_6 (706 mg, 3.10 mmol) in 80% aq. MeCN (6 mL) was stirred at 0 °C. After 10 min, CrO_3 (6.58 mg, 0.06 mmol) was added and the mixture stirred at RT for 1 h. The reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (262 mg, >100%) as a white solid. LCMS (method G): 3.39 min; m/z: 400.2, 402.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.97 (d, *J* = 5.5 Hz, 1H), 7.00 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.77-1.70 (m, 2H), 1.68-1.58 (m, 2H), 1.45-1.22 (m, 18H).

Step 5: tert-butyl 14-[(4-bromopyridin-2-yl)oxy]tetradecanoate

A mixture of 14-[(4-bromopyridin-2-yl)oxy]tetradecanoic acid (200 mg, 0.49 mmol), DMAP (30.5 mg, 0.25 mmol), *t*-BuOH (118 µL, 1.24 mmol) and DIC (115 µL, 0.75 mmol) in DCM (5 mL) was stirred at RT. After 16 h, the reaction mixture was filtered through Celite and then

concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-25% EtOAc:*c*-Hex) to afford the title compound (78 mg, 34%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.95 (dd, *J* = 5.5, 0.4 Hz, 1H), 6.98 (dd, *J* = 5.5, 1.6 Hz, 1H), 6.91 (dd, *J* = 1.6, 0.4 Hz, 1H), 4.24 (t, *J* = 6.7 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.78-1.68 (m, 2H), 1.58-1.53 (m, 2H), 1.43 (s, 9H), 1.25 (s, 18 H).

Step 6: tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]tetradecanoate

A mixture of 4-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate A1'**, 52.4 mg, 0.18 mmol), tert-butyl 14-[(4-bromopyridin-2-yl)oxy]tetradecanoate (80 mg, 0.18 mmol), $Pd(OAc)_2$ (3.93 mg, 0.02 mmol), Xantphos (20.2 mg, 0.04 mmol) and Cs_2CO_3 (85.6 mg, 0.26 mmol) in degassed 1,4-dioxane (3.5 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with EtOAc (30 mL), filtered through Celite and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-40% EtOAc:*c*-Hex) to afford the title compound (68 mg, 59%) as a yellow glass. ^{1}H NMR (300 MHz, $CDCl_3$): 8.30-8.25 (m, 2H), 8.18-8.13 (m, 2H), 7.91 (d, *J* = 5.9 Hz, 1H), 6.36 (dd, *J* = 5.9, 2.0 Hz, 1H), 6.02 (d, *J* = 1.8 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.73-1.63 (m, 11H), 1.57-1.52 (m, 2H), 1.42 (s, 9H), 1.21 (s, 18H).

Step 7: tert-butyl 14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]tetradecanoate

A mixture of tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]tetradecanoate (68 mg, 0.10 mmol) and 10% Pd/C (6 mg) in MeOH (2 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (62 mg, 95%) as a yellow residue. LCMS (method G): 3.33 min; m/z: 629.4 $[M-H]^-$. ^{1}H NMR (300 MHz, $CDCl_3$): 7.88-7.76 (m, 3H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.28 (br s, 1H), 5.93 (s, 1H), 4.17 (t, *J* = 6.6 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.73-1.65 (m, 2H), 1.62-1.52 (m, 11H), 1.42 (s, 9H), 1.22 (s, 18H).

Step 8: tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoate

A mixture of tert-butyl 14-[(4-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-2-yl)oxy]tetradecanoate (62 mg, 98.2 µmol), $EtSO_2Cl$ (10 µL, 103.3 µmol) and pyridine (39.6 µL, 0.49 mmol) in DCM (3 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash

chromatography (0-10% MeOH:DCM) to afford the title compound (56 mg, 78%) as a white glass. LCMS (method G): 3.49 min; m/z: 723.4 $[M+H]^+$.

Step 9: tert-butyl 14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoate

A mixture of tert-butyl 14-[(4-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoate (56 mg, 77.4 µmol) and Ghaffar-Parkins' catalyst (4.98 mg, 11.6 µmol) in 80% aq. EtOH (10 mL) was heated to 130 ºC under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (54 mg, 94%) as a yellow solid. LCMS (method G): 2.81 min; m/z: 741.5 $[M+H]^+$.

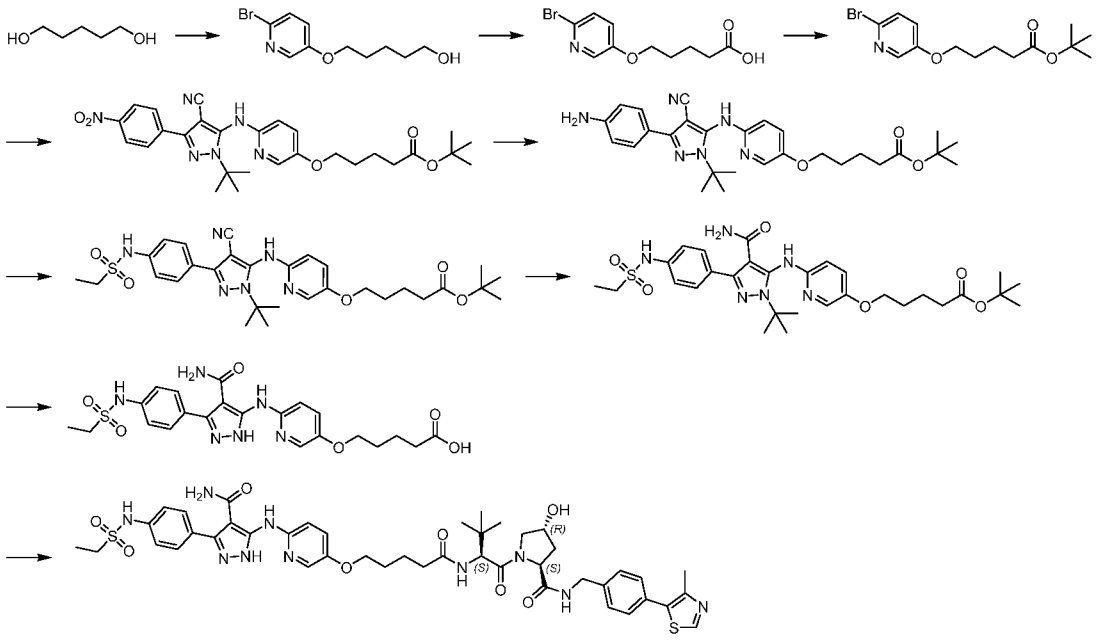
Step 10: 14-[(4-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoic acid

A solution of tert-butyl 14-[(4-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoate (54 mg, 72.8 µmol) in 1:4 TFA:DCM (3 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (50 mg, >100%) as an orange residue. LCMS (method G): 2.05 min; m/z: 629.4 $[M+H]^+$.

Step 11: 3-(4-ethanesulfonamidophenyl)-5-({2-[(13-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}tridecyl)oxy]pyridin-4-yl}amino)-1H-pyrazole-4-carboxamide

A mixture of 14-[(4-{[4-Carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-2-yl)oxy]tetradecanoic acid (20 mg, 31.8 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 14.3 mg, 33.3 µmol), HATU (14.5 mg, 38.2 µmol) and DIPEA (17 µL, 95.4 µmol) in DMF (0.4 mL) was stirred at RT under N_2. After 6 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (13.0 mg, 39%) as a white solid. LCMS (method G): 2.05 min; m/z: 1042.4 $[M+H]^+$, 521.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.90 (br s, 1H), 10.11 (s, 1H), 9.43 (br s, 1H), 8.97 (s, 1H), 8.55 (t, J = 5.7 Hz, 1H), 7.88-7.81 (m, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.42-7.33 (m, 7H), 7.13 (s, 1H), 6.94 (br s, 1H), 5.11 (br s, 1H), 4.53 (d, J = 9.3 Hz, 1H), 4.46-4.40 (m, 2H), 4.34 (s, 1H), 4.32-4.18 (m, 3H), 3.69-3.62 (m, 2H), 3.17 (q, J = 7.3 Hz, 2H), 2.44 (s, 3H), 2.27-2.22 (m, 1H), 2.16-1.99 (m, 2H), 1.93-1.86 (m, 1H), 1.70-1.65 (m, 2H), 1.50-1.21 (m, 23H), 0.93 (s, 9H).

Compound 1019: 3-(4-ethanesulfonamidophenyl)-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: 5-[(6-bromopyridin-3-yl)oxy]pentan-1-ol

To a solution of 1,5-pentanediol (709 µL, 6.81 mmol) in DMF was added NaH (361 mg, 9.08 mmol) in portions. The reaction was stirred at RT for 10 min before 2-Bromo-5-fluoropyridine (800 mg, 4.54 mmol) was added, then at RT for 16 h. The reaction mixture was diluted with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc:*c*-Hex) to afford the title compound (460 mg, 39%) as a colourless oil. LCMS (method G): 1.38 min; m/z: 260.2, 262.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.05 (d, *J* = 2.7 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.03 (br s, 1H), 1.87-1.80 (m, 2H), 1.67-1.61 (m, 2H), 1.58-1.51 (m, 2H).

Step 2: 5-[(6-bromopyridin-3-yl)oxy]pentanoic acid

To a solution of 5-[(6-Bromopyridin-3-yl)oxy]pentan-1-ol (466 mg, 1.79 mmol) in 80% aq. MeCN (17.9 mL) was added H_5IO_6 (2.04 g, 8.95 mmol) and the mixture was cooled to 0 °C. CrO_3 (18.9 mg, 0.18 mmol) was then added and the mixture was stirred at RT for 1 h. The reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 10 mL). The

combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (510 mg, >100%) as a white solid. LCMS (method G): 1.40 min; m/z: 274.2, 276.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.05 (d, *J* = 3.0 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.01 (t, *J* = 5.6 Hz, 2H), 2.24 (t, *J* = 6.7 Hz, 2H), 1.89-1.82 (m, 4H).

Step 3: tert-butyl 5-[(6-bromopyridin-3-yl)oxy]pentanoate

To a mixture of 5-[(6-Bromopyridin-3-yl)oxy]pentanoic acid (460 mg, 1.67 mmol), t-BuOH (398 µL, 4.17 mmol) and DMAP (102 mg, 0.84 mmol) in DCM (16.7 mL) was added DIC (386 µL, 2.50 mmol), and the reaction was stirred at RT for 16 h. The mixture was filtered through Celite and then concentrated. The crude material was purified by flash chromatography (0-20% EtOAc:*c*-Hex) to afford the title compound (353 mg, 64%) as a colourless oil. LCMS (method G): 2.51 min; m/z: 330.2, 332.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 8.04 (d, *J* = 3.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.98 (t, *J* = 5.9 Hz, 2H), 2.29 (t, *J* = 7.0 Hz, 2H), 1.84-1.74 (m, 4H), 1.44 (s, 9H).

Step 4: tert-butyl 5-[(6-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate

A mixture of 4-amino-1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate A1'**, 290 mg, 1.01 mmol), tert-butyl 5-[(6-bromopyridin-3-yl)oxy]pentanoate (350 mg, 1.06 mmol), $Pd(OAc)_2$ (22.6 mg, 0.10 mmol), Xantphos (116 mg, 0.20 mmol) and Cs_2CO_3 (491 mg, 1.51 mmol) in degassed 1,4-dioxane (10 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-30% EtOAc:*c*-Hex) to afford the title compound (253 mg, 47%) as a yellow solid. LCMS (method G): 2.45 min; m/z: 535.4 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 9.08 (s, 1H), 8.47 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 9.9 Hz, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 4.54 (t, *J* = 5.4 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.82-1.75 (m, 4H), 1.44 (s, 9H), 1.42 (s, 9H).

Step 5: tert-butyl 5-[(6-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate (250 mg, 0.46 mmol) and 10% Pd/C (5 mg) in MeOH (10 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 16 h, the reaction

mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (203 mg, 86%) as a yellow solid. LCMS (method G): 2.24 min; m/z: 505.4 $[M+H]^+$.

Step 6: tert-butyl 5-[(6-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[3-(4-aminophenyl)-1-tert-butyl-4-cyano-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate (230 mg, 0.45 mmol), $EtSO_2Cl$ (86 µL, 0.91 mmol) and pyridine (183 µL, 2.27 mmol) in DCM (4.5 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash chromatography (0-8% MeOH:DCM) to afford the title compound (180 mg, 66%) as a yellow foam. LCMS (method G): 2.36 min; m/z: 597.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.04 (br s, 1H), 8.65 (s, 1H), 7.59-7.55 (m, 3H), 7.39-7.29 (m, 4H), 3.99 (t, J = 6.0 Hz, 2H), 3.18 (q, J = 7.3 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 1.80-1.64 (m, 13H), 1.39 (s, 9H), 1.23 (t, J = 7.3 Hz, 3H).

Step 7: tert-butyl 5-[(6-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[1-tert-butyl-4-cyano-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate (90 mg, 0.15 mmol), K_2CO_3 (10.4 mg, 75.4 µmol), EtOH (0.8 mL), DMSO (0.8 mL) and 30% H_2O_2 (0.8 mL) was heated to 60 °C. After 30 min, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and then concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-5% MeOH:DCM) to afford the title compound (12 mg, 13%) as a white solid. LCMS (method G): 2.23 min; m/z: 615.4 $[M+H]^+$.

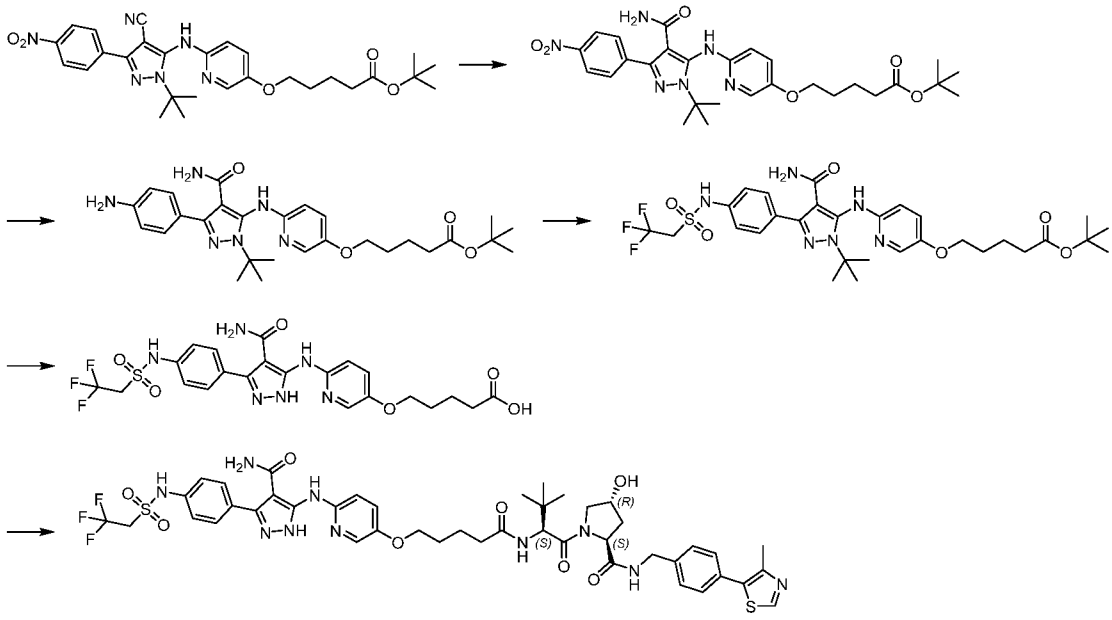
Step 8: 5-[(6-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoic acid

A solution of tert-butyl -[(6-{[1-tert-butyl-4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate (10 mg, 16.2 µmol) in 1:1 TFA/DCM (3 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (15 mg, >100%) as an orange oil. LCMS (method G): 1.11 min; m/z: 503.0 $[M+H]^+$.

Step 9: 3-(4-ethanesulfonamidophenyl)-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

A mixture of 5-[(6-{[4-Carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoic acid (100 mg, 0.17 mmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 80.9 mg, 0.18 µmol), HATU (81.6 mg, 0.21 mmol) and DIPEA (93.3 µL, 0.54 mmol) in DMF (1.8 mL) was stirred at RT under N_2. After 6 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (49 mg, 30%) as a white solid. LCMS (method G): 1.77 min; m/z: 915.3 $[M+H]^+$, 458.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.66 (br s, 1H), 10.06 (br s, 1H), 9.80 (s, 1H), 9.31 (s, 1H), 8.97 (s, 1H), 8.56 (t, *J* = 5.9 Hz, 1H), 7.96-7.90 (m, 3H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.43-7.11 (m, 8H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.46-4.40 (m, 2H), 4.34 (br s, 1H), 4.21 (dd, *J* = 15.9, 5.3 Hz, 1H), 3.97 (br s, 2H), 3.70-3.63 (m, 2H), 3.21-3.15 (m, 2H), 2.44 (s, 3H), 2.37-2.31 (m, 1H), 2.24-2.17 (m, 1H), 2.06-2.01 (m, 1H), 1.93-1.87 (m, 1H), 1.67-1.61 (m, 4H), 1.22 (t, *J* = 7.3 Hz, 3H), 0.94 (s, 9H).

Compound 1020: 5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 5-[(6-{[1-tert-butyl-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[1-tert-butyl-4-cyano-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate (14.1 g, 26.3 mmol), 5% aq. NaOH (5 mL), EtOH (200 mL), DMSO (50 mL) and 30% H_2O_2 (50 mL) was heated to 80 °C. After 16 h, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ and then concentrated under reduced pressure. The crude residue was diluted with H_2O (150 mL) and extracted with EtOAc (5 x 80 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (14.5 g, 100%) as a yellow solid. LCMS (method E): 4.25 min; m/z: 553.3 $[M+H]^+$.

Step 2: tert-butyl 5-[(6-{[3-(4-aminophenyl)-1-tert-butyl-4-carbamoyl-1H-pyrazol-5-yl]amino} pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[1-tert-butyl-4-carbamoyl-3-(4-nitrophenyl)-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate (14.4 g, 26.0 mmol) and Zn dust (8.49 g, 130 mmol) in sat. aq. NH4Cl (70 mL) and MeOH (210 mL) was heated to 60 °C. After 3 h the mixture was filtered, and the filtrate was diluted with EtOAc and H_2O. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (2% MeOH:DCM) to afford the title compound (8.0 g, 59%) as a yellow solid. LCMS (method E): 5.56 min; m/z: 523.2 $[M+H]^+$.

Step 3: tert-butyl 5-{[6-({1-tert-butyl-4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido) phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}pentanoate

A mixture of tert-butyl 5-[(6-{[3-(4-aminophenyl)-1-tert-butyl-4-carbamoyl-1H-pyrazol-5-yl]amino}pyridin-3-yl)oxy]pentanoate (113 mg, 0.19 mmol), 2,2,2-trifluoroethanesulfonyl chloride (42 µL, 0.38 mmol) and pyridine (77 µL, 0.95 mmol) in DCM (2 mL) was stirred at RT. After 2 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by silica gel flash chromatography (0-10% MeOH:DCM) to afford the title compound (180 mg, 66%) as a white solid. LCMS (method G): 2.25 min; m/z: 669.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 10.48 (br s, 1H), 7.97 (s, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.26 (dd, J = 8.8, 2.8 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.11 (br s, 1H), 6.91 (br s, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.51 (q, J = 9.7 Hz, 2H), 3.90 (t, J = 5.7 Hz, 2H), 2.24 (t, J = 6.9 Hz, 2H), 1.69-1.59 (m, 4H), 1.55 (s, 9H), 1.38 (s, 9H).

Step 4: 5-{[6-({4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazol-5-yl} amino)pyridin-3-yl]oxy}pentanoic acid

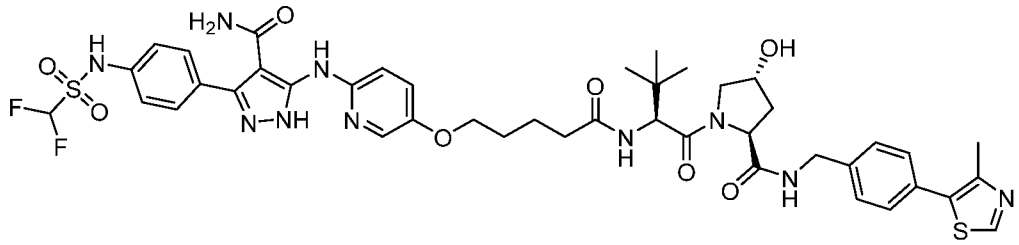
A solution of tert- butyl 5-{[6-({1-tert-butyl-4-carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido) phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}pentanoate (45 mg, 67.2 µmol) in 1:2

TFA:DCM (6 mL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (41 mg, >100%) as a yellow solid. LCMS (method G): 1.22 min; m/z: 557.2 $[M+H]^+$.

Step 5: 5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazole-4-carboxamide

A mixture of 5-{[6-({4-Carbamoyl-3-[4-(2,2,2-trifluoroethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}pentanoic acid (19 mg, 34.1 µmol) (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 16.1 mg, 37.5 µmol), HATU (16.8 mg, 44.3 µmol) and DIPEA (17.7 µL, 0.10 mmol) in DMF (340 µL) was stirred at RT under N_2. After 6 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (8.0 mg, 24%) as a white solid. LCMS (method G): 1.94 min; m/z: 969.2 $[M+H]^+$, 485.2 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.67 (br s, 1H), 10.71 (br s, 1H), 9.82 (br s, 1H), 9.35 (s, 1H), 8.97 (s, 1H), 8.56 (t, J = 5.9 Hz, 1H), 7.97-7.90 (m, 3H), 7.52 (br s, 2H), 7.43-7.10 (m, 8H), 5.12 (d, J = 3.5 Hz, 1H), 4.57-4.51 (m, 3H), 4.46-4.41 (m, 2H), 4.35 (s, 1H), 4.21 (dd, J = 15.8, 5.6 Hz, 1H), 3.97 (br s, 2H), 3.70-3.63 (m, 2H), 2.44 (s, 3H), 2.37-2.30 (m, 1H), 2.24-2.17 (m, 1H), 2.06-2.01 (m, 1H), 1.93-1.87 (m, 1H), 1.73-1.61 (m, 4H), 0.94 (s, 9H).

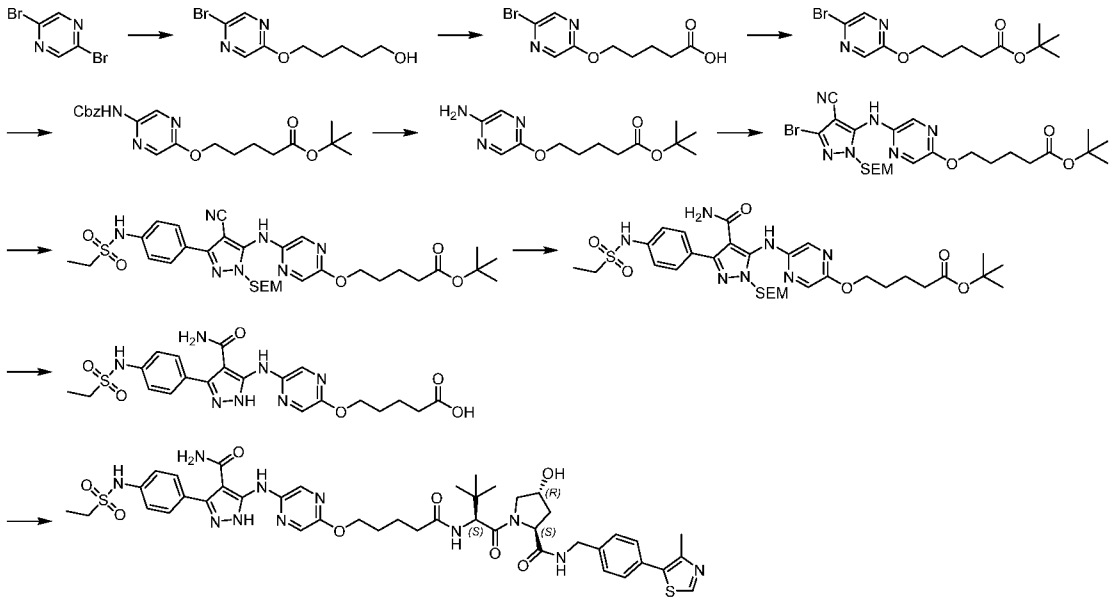
Compound 1021: 3-[4-(difluoromethanesulfonamido)phenyl]-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1020** utilizing difluoromethanesulfonyl chloride in Step 3. The title compound (7.4 mg, 5%) was obtained as a white solid. LCMS (method G): 1.92 min; m/z: 937.2 $[M+H]^+$, 469.3 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.67 (br s, 1H), 11.21 (br s, 1H), 9.29 (s, 1H), 8.97 (s, 1H), 8.56 (t, J = 6.0 Hz, 1H), 7.96-7.90 (m, 3H), 7.55-7.49 (m, 2H), 7.43-7.30 (m, 8H), 7.12 (br s, 2H), 5.12 (d, J = 3.4 Hz, 1H), 4.55 (d, J = 9.3 Hz, 1H), 4.46-4.41 (m, 2H), 4.35 (s, 1H), 4.21 (dd, J = 15.8, 5.3

Hz, 1H), 3.97 (s, 2H), 3.70-3.63 (m, 2H), 2.44 (s, 3H), 2.36-2.30 (m, 1H), 2.24-2.19 (m, 1H), 2.06-2.01 (m, 1H), 1.93-1.85 (m, 1H), 1.68-1.63 (m, 4H), 0.94 (s, 9H).

Compound 1022: 3-(4-ethanesulfonamidophenyl)-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: 5-[(5-bromopyrazin-2-yl)oxy]pentan-1-ol

To a cooled mixture of 2,5-dibromopyrazine (2.0 g, 8.40 mmol) and 1,5-pentanediol (2.62 g, 25.2 mmol) in DMF (42 mL) was added NaH (671 mg, 16.8 mmol) in portions, and the reaction was stirred at RT. After 16 h, the mixture was diluted with H_2O (200 mL) and extracted with EtOAc (4 x 50 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (2.43 g, >100%) as a yellow oil. LCMS (method E): 1.51 min; m/z: 261.2, 263.2 $[M+H]^+$.

Step 2: 5-[(5-bromopyrazin-2-yl)oxy]pentanoic acid

A mixture of 5-[(5-bromopyrazin-2-yl)oxy]pentan-1-ol (2.19 g, 8.38 mmol) and H_5IO_6 (5.72 g, 25.1 mmol) in 80% aq. MeCN (42 mL) was stirred at 0 °C. After 5 min CrO_3 (88.8 mg, 0.838 mmol) was added and the mixture stirred at RT for 1 h. The reaction mixture was concentrated, then diluted with H_2O (150 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (2.53 g, >100%) as a brown solid. LCMS (method G): 1.50 min; m/z: 275.0,

277.0 $[M+H]^+$. ^1H NMR (300 MHz,DMSO-d_6): 12.04 (br s, 1H), 8.40 (d, J = 1.3 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 4.27 (t, J = 6.3 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 1.77-1.62 (m, 4H).

Step 3: tert-butyl 5-[(5-bromopyrazin-2-yl)oxy]pentanoate

To a mixture of 5-[(5-bromopyrazin-2-yl)oxy]pentanoic acid (2.53 g, 8.43 mmol), DMAP (514 mg, 4.21 mmol) and t-BuOH (2.0 mL, 21.0 mmol) in DCM (42 mL) was added DCC (2.59 g, 12.6 mmol) and the reaction was stirred at RT. After 16 h, the reaction mixture was filtered through Celite and then concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-20% EtOAc/*n*-heptane) to afford the title compound (1.61 g, 57%) as a colourless oil. LCMS (method G): 2.70 min; m/z: 275.2 and 277.2 [(M–tBu)+H]$^+$. ^1H NMR (300 MHz, $CDCl_3$): 8.15 (d, J = 1.3 Hz, 1H), 7.99 (d, J = 1.3 Hz, 1H), 4.29 (t, J = 6.2 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 1.87-1.72 (m, 4H), 1.44 (s, 9H).

Step 4: tert-butyl 5-[(5-{[(benzyloxy)carbonyl]amino}pyrazin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(5-bromopyrazin-2-yl)oxy]pentanoate (1.0 g, 3.01 mmol), benzyl carbamate (727 mg, 4.81 mmol), $Pd(OAc)_2$ (40.5 mg, 0.18 mmol), XPhos (258 mg, 0.54 mmol) and Cs_2CO_3 (1.46 g, 4.51 mmol) in 1,4-dioxane (12.0 mL) was heated to 110 °C under N_2. After 16 h the reaction mixture was concentrated under reduced pressure, and the residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (0-20% EtOAc:*c*-Hex) to afford the title compound (538 mg, 44%) as a white solid. LCMS (Method G): 3.01 min; m/z: 402.3 $[M+H]^+$.

Step 5: tert-butyl 5-[(5-aminopyrazin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(5-{[(benzyloxy)carbonyl]amino}pyrazin-2-yl)oxy]pentanoate (535 mg, 1.33 mmol) and 10% Pd/C (50 mg) in MeOH (53 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 2 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound (401 mg, >100%) as a brown oil. LCMS (Method G): 2.14 min; m/z: 268.4 $[M+H]^+$.

Step 6: tert-butyl 5-({5-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyrazin-2-yl}oxy)pentanoate

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 518 mg, 1.36 mmol), tert-butyl 5-[(5-aminopyrazin-2-yl)oxy]pentanoate (350 mg, 1.30 mmol), $Pd(OAc)_2$ (29.1 mg, 0.13 mmol), Xantphos (150 mg, 0.26 mmol) and

Cs_2CO_3 (635 mg, 1.95 mmol) in 1,4-dioxane (13 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0-2% MeOH:DCM) to afford the title compound 433 mg, 58%) as a brown oil. LCMS (method G): 3.32 min; m/z: 567.2, 569.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.94 (br. s, 1H), 7.97 (s, 2H), 5.42 (s, 2H), 4.23 (t, J = 6.2 Hz, 2H), 3.50 (t, J = 8.2 Hz, 2H), 2.24 (t, J = 7.1 Hz, 2H), 1.73-1.59 (m, 4H), 1.38 (s, 9H), 0.80 (t, J = 8.1 Hz, 2H), –0.11 (s, 9H).

Step 7: tert-butyl 5-[(5-{[4-cyano-3-(4-ethanesulfonamidophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl]amino}pyrazin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-({5-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyrazin-2-yl}oxy)pentanoate (50 mg, 88.1 µmol), N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane-1-sulfonamide (**Intermediate C16**, 28.7 mg, 92.5 µmol), $Pd(dppf)Cl_2$ (6.44 mg, 8.8 µmol) and Na_2CO_3 (18.6 mg, 0.1761 mmol) in 80% aq. EtOH (1.76 mL) was heated at 100 °C with microwave irradiation for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (0-2.5% MeOH:DCM) to afford the title compound (30.4 mg, 51%) as a yellow gum. LCMS (method G): 3.17 min; m/z: 672.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.93 (s, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 5.44 (s, 2H), 4.21 (t, J = 6.2 Hz, 2H), 3.16 (q, J = 7.9 Hz, 2H), 2.23 (t, J = 7.3 Hz, 2H), 1.72-1.58 (m, 4H), 1.36 (s, 9H), 1.19 (t, J = 7.3 Hz, 3H), 0.78 (t, = 8.2 Hz, 2H), –0.15 (s, 9H).

Step 8: tert-butyl 5-[(5-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl]amino}pyrazin-2-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(5-{[4-cyano-3-(4-ethanesulfonamidophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl]amino}pyrazin-2-yl)oxy]pentanoate (30 mg, 44.7 µmol) and Ghaffar-Parkins' catalyst (1.91 mg, 4.5 µmol) in 80% aq. EtOH (4.5 mL) was heated to 130 °C under N_2. After 2 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (30 mg, 97%) as an orange glass. LCMS (method G): 2.91 min; m/z: 690.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.61 (br. s, 1H), 7.78 (d, J = 1.1 Hz, 1H), 7.67 (d, J = 1.1 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.18 (br. s, 1H), 7.07 (br. s, 1H), 5.32 (s, 2H), 4.15 (t, J = 6.1 Hz, 2H), 3.11 (dd, J = 14.6, 7.4 Hz, 2H), 2.23 (t, J = 7.2 Hz, 2H), 1.70-1.57 (m, 4H), 1.37 (s, 9H), 1.20 (t, J = 7.3 Hz, 2H), 0.73 (t, J = 8.2 Hz, 2H), –0.13 (s, 9H).

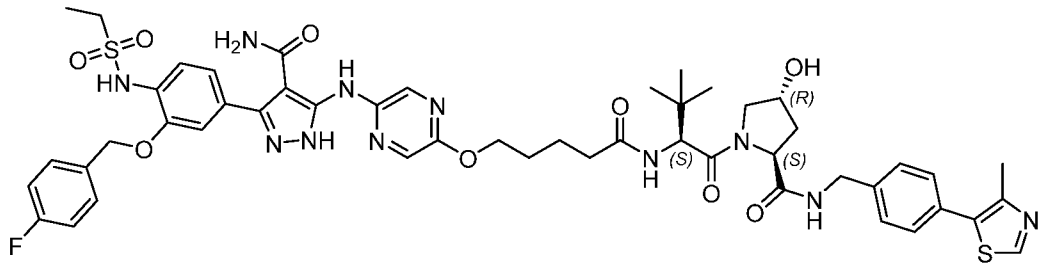
Step 9: 5-[(5-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyrazin-2-yl)oxy]pentanoic acid

A solution of tert-butyl 5-[(5-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl]amino}pyrazin-2-yl)oxy]pentanoate (28 mg, 40.6 µmol) in 1:3 TFA:DCM was stirred at RT. After 3 h the reaction mixture was concentrated under reduced pressure to afford the title compound (25 mg, >100%) as a yellow oil. LCMS (method G): 1.78 min; m/z: 504.2 $[M+H]^+$.

Step 10: 3-(4-ethanesulfonamidophenyl)-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide

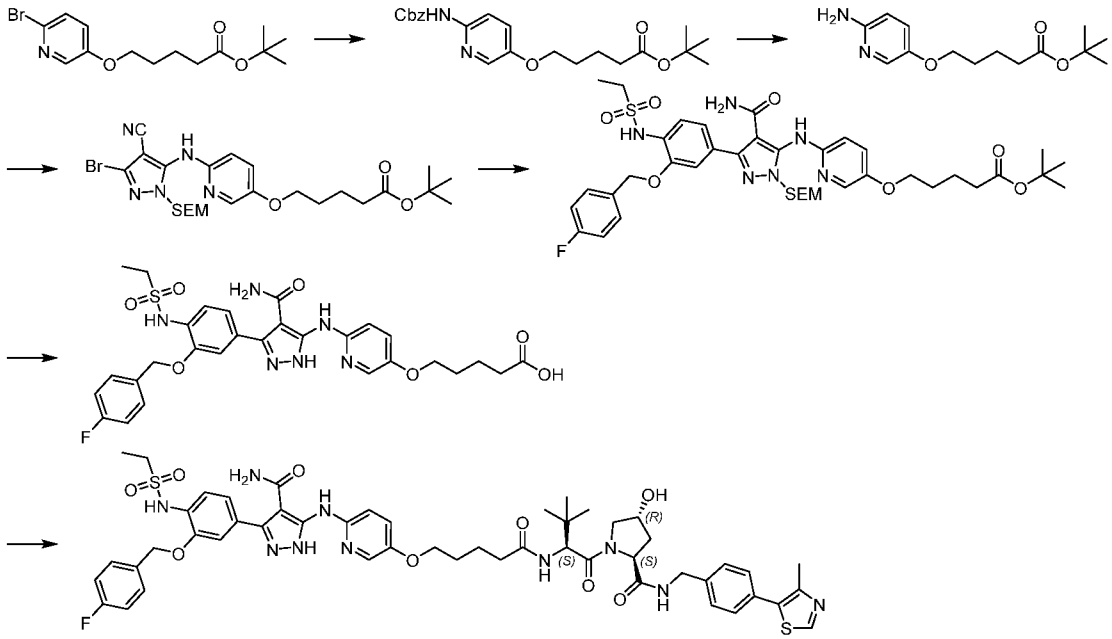
A mixture of 5-[(5-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino} pyrazin-2-yl)oxy]pentanoic acid (20 mg, 39.7 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 18.8 mg, 43.7 µmol), HATU (19.6 mg, 51.6 µmol) and DIPEA (20.6 µL, 0.12 mmol) in DMF (400 µL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (3.4 mg, 9%) as a yellow solid. LCMS (method G): 2.12 min; m/z: 916.3 $[M+H]^+$; 458.8 $[M+2H]^{2+}$.

Compound 1023: 3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyrazin-2-yl]amino}-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1022** utilizing **Intermediate C1** in Step 7. The title compound (5.3 mg, 13%) was obtained as a yellow solid. LCMS (method G): 2.46 min; m/z: 1041.4 $[M+H]^+$; 520.8 $[M+2H]^{2+}$.

Compound 1024: 3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 5-[(6-{[(benzyloxy)carbonyl]amino}pyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-bromopyridin-3-yl)oxy]pentanoate (650 mg, 1.96 mmol), *t*-BuONa (263 mg, 2.74 mmol), benzyl carbamate (444 mg, 2.94 mmol), $Pd_2(dba)_3$ (89.7 mg, 0.098 mmol) and *t*-BuXPhos (83.2 mg, 0.196 mmol) in 1,4-dioxane (7.8 mL) was heated to 45 °C under N_2. After 4 h, the reaction mixture was diluted with H_2O (70 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (0-40% EtOAc:*n*-heptane) to afford the title compound (470 mg, 60%) as a white solid. LCMS (method G): 2.92 min; m/z: 401.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.64 (br. s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 2.7 Hz, 1H), 7.41-7.32 (m, 5H), 5.22 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 2.28 (t, *J* = 6.8 Hz, 2H), 1.80-1.72 (m, 4H), 1.45 (s, 9H).

Step 2: tert-butyl 5-[(6-aminopyridin-3-yl)oxy]pentanoate

A mixture of tert-butyl 5-[(6-{[(benzyloxy)carbonyl]amino}pyridin-3-yl)oxy]pentanoate (784 mg, 1.95 mmol) and 10% Pd/C (50 mg) in MeOH (78 mL) was evacuated and back-filled with H_2 (three times) and then stirred at RT. After 2 h, the reaction mixture was filtered through Celite

and concentrated under reduced pressure to afford the title compound (477 mg, >100%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.36 (d, *J* = 4.6 Hz, 3H), 4.70 (s, 2H), 3.88 (t, *J* = 5.8 Hz, 2H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.83-1.72 (m, 4H), 1.44 (s, 9H).

Step 3: tert-butyl 5-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)pentanoate

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (499 mg, 1.31 mmol), tert-butyl 5-[(6-aminopyridin-3-yl)oxy]pentanoate (477 mg, 1.25 mmol), Cs_2CO_3 (609 mg, 1.87 mmol), $Pd(OAc)_2$ (28.0 mg, 0.13 mmol) and Xantphos (144 mg, 0.25 mmol) in 1,4-dioxane (12 mL) was heated to 110 °C under N_2. After 16 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (0-30% EtOAc:*n*-heptane) to afford the title compound (314 mg, 44%) as a yellow oil. LCMS (method G): 2.72 min; m/z: 566.2, 568.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 7.89 (d, *J* = 2.8 Hz,1H), 7.38 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.32-7.30 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.41 (s, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 8.2 Hz, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 1.71-1.60 (m, 4H), 1.38 (s, 9H), 0.79 (t, *J* = 8.2 Hz, 2H), –0.12 (s, 9H).

Step 4: tert-butyl 5-({6-[(4-cyano-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)pentanoate

A mixture of tert-butyl 5-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)pentanoate (105 mg, 0.19 mmol), N-{2-[(4-fluorophenyl)methoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (**Intermediate C1**, 84.6 mg, 0.19 mmol), $Pd(dppf)Cl_2$ (13.5 mg, 18.5 µmol) and Na_2CO_3 (39.2 mg, 0.37 mmol) in 80% aq. 1,4-dixaone (2 mL) was heated to 100 °C with microwave irradiation for 30 min. The reaction mixture was diluted with EtOAc (3 mL), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (0-50% EtOAc:*n*-heptane) to afford the title compound (52 mg, 35%) as a yellow gum. LCMS (Method G): 2.60 min; m/z: 795.4 $[M+H]^+$.

Step 5: tert-butyl 5-({6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)pentanoate

A mixture of tert-butyl 5-({6-[(4-cyano-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy] phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy) pentanoate (45 mg, 56.6 µmol) and Ghaffar-Parkins' catalyst (4.85 mg, 11.3 µmol) in 80% aq. EtOH was heated to 120 °C. After 2 h, the reaction mixture was concentrated to afford the title compound (48 mg, >100%) as a yellow gum. LCMS (method G): 3.07 min; m/z: 813.4 $[M+H]^+$.

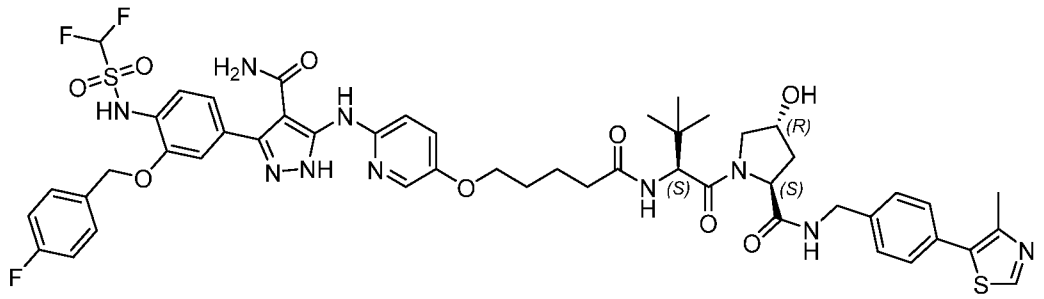
Step 6: 5-({6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)pentanoic acid

A solution of tert-butyl 5-({6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(4-fluorophenyl) methoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy) pentanoate (43 mg, 52.9 µmol) in 1:3 TFA:DCM (4 mL) was stirred at RT. After 2 h, the reaction mixture was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$. The mixture was extracted with DCM (5 x 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to afford the title compound (38 mg, >100%) as an orange oil. LCMS (method G): 1.85 min; m/z: 627.2 $[M+H]^+$.

Step 7: 3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

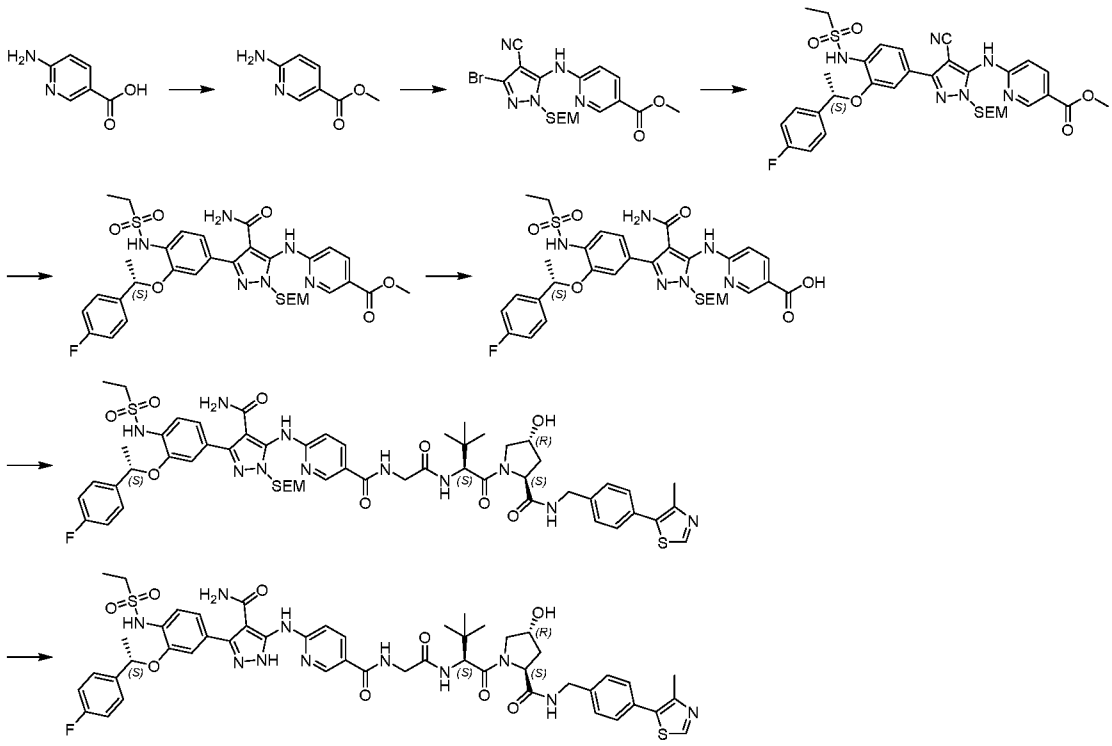
A mixture of 5-({5-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl} -1H-pyrazol-5-yl)amino]pyrazin-2-yl}oxy)pentanoic acid (33.1 mg, 52.7 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl] methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 24.9 mg, 58.0 µmol), HATU (26.0 mg, 68.5 µmol) and DIPEA (27.4 µL, 0.16 mmol) in DMF (530 µL) was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Method B) to afford the title compound (5.3 mg, 13%) as a yellow solid. LCMS (method G): 2.46 min; m/z: 1041.4 $[M+H]^+$; 520.8 $[M+2H]^{2+}$. ^1H NMR (400 MHz, MeOD-d_4): 8.88 (s, 1H), 8.06 (s, 1H), 7.64 – 7.51 (m, 3H), 7.51 – 7.43 (m, 3H), 7.42 (d, J = 6.7 Hz, 2H), 7.34 (s, 1H), 7.25-7.09 (m, 3H), 6.97 (d, J = 9.0 Hz, 1H), 5.25 (s, 2H), 4.69 – 4.51 (m, 6H), 4.40 (d, J = 8.7 Hz, 1H), 4.34 (d, J = 9.1 Hz, 1H), 4.07 (s, 2H), 3.94 (d, J = 11.3 Hz, 1H), 3.83 (dd, J = 10.9, 3.9 Hz, 1H), 3.18-3.04 (m, 3H), 2.98 (s, 1H), 2.48 (s, 3H), 2.39 (d, J = 4.2 Hz, 2H), 2.22 (d, J = 8.1 Hz, 1H), 2.18-2.03 (m, 1H), 1.29 (t, J = 7.4 Hz, 3H), 1.18 (s, 2H), 1.06 (s, 9H).

Compound 1025: 3-[4-(difluoromethanesulfonamido)-3-[(4-fluorophenyl)methoxy]phenyl]-5-{[5-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butoxy)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1024** utilizing **Intermediate C1a** in Step 4. The title compound (9.3 mg, 6%) was obtained as a white solid. LCMS (method G): 2.46 min, 1041.4 $[M+H]^+$.

Compound 1026: 3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[({[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamoyl]pyridin-2-yl}amino) -1H-pyrazole-4-carboxamide



Step 1: methyl 6-aminopyridine-3-carboxylate

A mixture of 6-aminopyridine-3-carboxylic acid (1.0 g, 7.23 mmol) and conc. H_2SO_4 (1 mL) in MeOH (100 mL) was heated to reflux. After 16 h, the reaction mixture was concentrated, diluted with 10% aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (1.01 g, 91%) as a white solid. LCMS (method G): 0.45 min; m/z: 153.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 8.50 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.8, 2.4 Hz, 1H), 6.83 (s, 1H), 6.44 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H).

Step 2: methyl 6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl) amino]pyridine-3-carboxylate

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (15 g, 39.3 mmol), methyl 6-aminopyridine-3-carboxylate (5.97 g, 39.3 mmol), $Pd_2(dba)_3$ (1.79 g, 1.96 mmol), Xantphos (2.26 g, 3.92 mmol) and Cs_2CO_3 (25.6 g, 78.6 mmol) in 1,4-dioxane (200 mL) was heated at 100 °C under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure, and the residue was poured into water (500 mL). The aqueous fraction was extracted with EtOAc (500 mL x 2) and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (10% EtOAc:PE) to afford the title product (8.6 g, 48%) as a yellow solid. LCMS (method E): 3.35 min, m/z: 452.1 $[M+H]^+$.

Step 3: methyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A mixture of methyl 6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (8.5 g, 18.7 mmol), N-{2-[(1R)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}ethane-1-sulfonamide (**Intermediate C11a**, 8.40 g, 18.7 mmol), Na_2CO_3 (3.96 g, 37.4 mmol) and $Pd(dppf)Cl_2$ (1.52 g, 1.87 mmol) in 80% aq. 1,4-dioxane (125 mL) was heated to 100 °C under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure, and the residue was poured into water (500 mL) and extracted with EtOAc(500 mL x 2).The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (1% MeOH:DCM) to afford the title product (9.5 g, 73 %) as a yellow solid. LCMS (method E): 3.76 min, m/z: 695.0 $[M+H]^+$.

Step 4: methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A mixture of methyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (9.5 g, 13.6 mmol) and Ghaffar-Parkins' catalyst (200 mg, 468 µmol) in 50% aq. 1,4-dioxane (200 mL) was heated to 100 °C under N_2. After 16 h, the reaction mixture was concentrated under reduced pressure, and the residue was poured into water (200 mL) and extracted with EtOAc (200 mL x 2). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (10% MeOH:DCM) to afford the title product (6.9 g, 71 %) as a yellow solid. LCMS (method E): 4.08 min, m/z: 713.3 $[M+H]^+$.

Step 5: 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid

A mixture of methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (6.8 g, 9.53 mmol) and KOH (1.59 g, 28.5 mmol) in 85% aq. MeOH (90 mL) was heated to 60 °C. After 16 h, the reaction mixture was concentrated under reduced pressure and the residue was poured into water (100 mL). The pH was adjusted to pH = 6 with 1 M aq. HCl and the mixture was extracted with EtOAc (100 mL x 2). The combined organic phases were dried (over Na_2SO_4) and concentrated to afford the title product (5 g, 75%) as a yellow solid. LCMS (method E): 3.73 min, m/z 699.3 $[M+H]^+$.

Step 6: 3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[({[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamoyl]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (286 mg, 410 µmol), HATU (311 mg, 820 µmol) and Et_3N (165 mg, 1.64 mmol) in DMF (15 mL) was stirred at RT. After 10 min, (2S,4R)-1-[(2S)-2-(2-aminoacetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate J1**, 200 mg, 410 µmol) was added and the reaction mixture was stirred at RT. After 16 h, the mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated. The

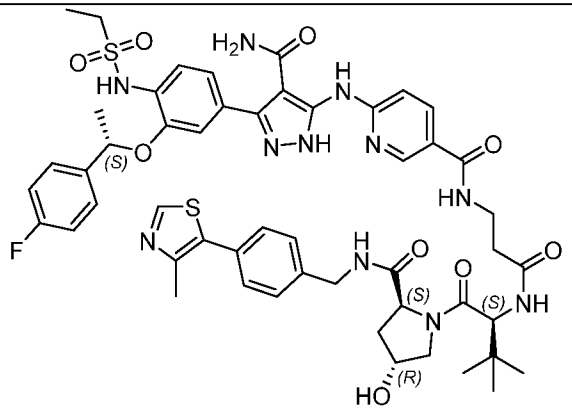
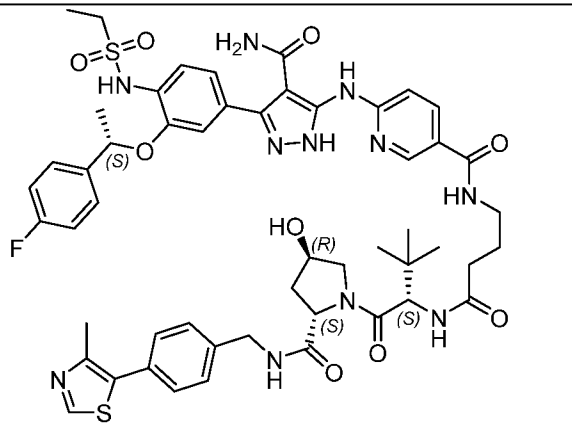
residue was purified by prep-TLC (5% MeOH:DCM) to afford the title product (80 mg, 16 %) as a yellow solid. LCMS (method E): 3.78 min, m/z: 585.9 $[M+2H]^{2+}$.

Step 7: 3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[({[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamoyl]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide

A solution of 3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[({[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)carbamoyl]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (70 mg, 59.9 μmol) in 1:10 TFA:DCM (5.5 mL) was stirred at RT for 4 mins. The reaction mixture was adjusted to pH = 8 with sat. aq. Na_2CO_3 solution and diluted with water (50 mL). The mixture was extracted with EtOAc (50 mL x 2), and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by prep-TLC (5% MeOH:DCM) to afford the title product (30 mg, 48%) as a white solid. LCMS (method E): 3.30 min, m/z: 1039.3 $[M+H]^+$, 519.8 $[M+2H]^{2+}$. ^1H NMR (400 MHz, DMSO-d_6): 12.91 (s, 1H), 9.83 (d, *J* = 15.9 Hz, 1H), 9.27 (s, 1H), 8.97 (s, 1H), 8.71 (s, 2H), 8.58 (s, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 7.99 (s, 1H), 7.90 (d, *J* = 9.4 Hz, 1H), 7.64-7.57 (m, 2H), 7.40 (q, *J* = 8.4 Hz, 5H), 7.17 (t, *J* = 8.9 Hz, 3H), 7.07 (d, *J* = 8.3 Hz, 1H), 5.65 (d, *J* = 5.7 Hz, 1H), 5.16 (d, *J* = 3.3 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.44 (q, *J* = 8.3 Hz, 2H), 4.35 (s, 1H), 4.23 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.97 (d, *J* = 5.8 Hz, 2H), 3.66 (q, *J* = 10.5 Hz, 2H), 3.06 (d, *J* = 4.8 Hz, 2H), 2.44 (s, 3H), 2.08-1.99 (m, 1H), 1.95-1.87 (m, 1H), 1.58 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 7.5 Hz, 3H), 0.94 (s, 9H).

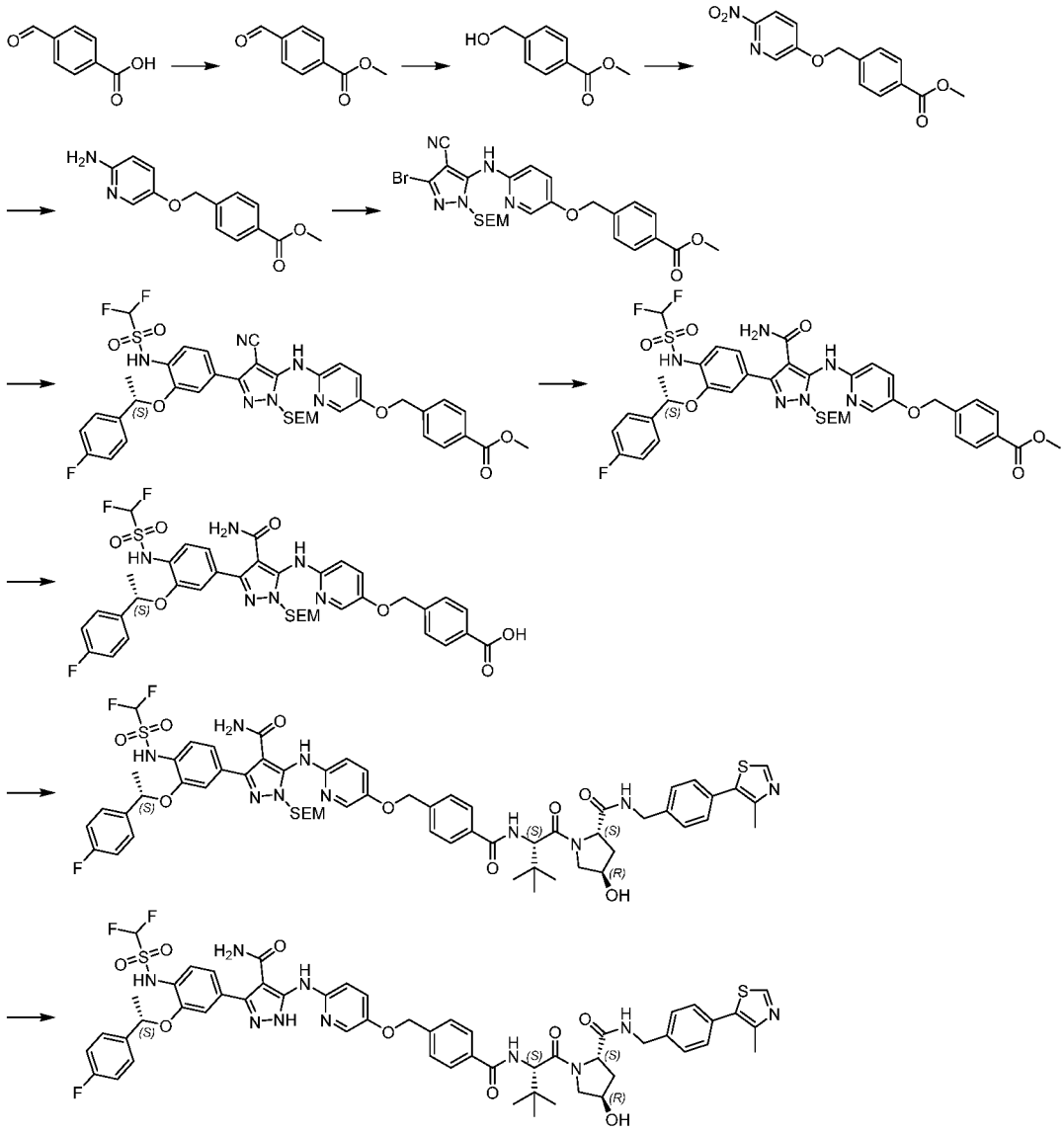
Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of **Compound 1026**, utilizing the indicated **Intermediate J** in Step 6.

Table 31: Compounds 1027 to 1029

Compound No.	Structure	Compound Name and Analytical Data
Compound 1027		3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[(2-{[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}ethyl)carbamoyl]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate J2**. LCMS (method E): 3.27 min, m/z 1053.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (s, 1H), 9.76 (s, 1H), 9.26 (s, 1H), 8.97 (s, 1H), 8.72-8.55 (m, 2H), 8.41 (s, 1H), 8.17-7.92 (m, 3H), 7.62 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.40 (q, *J* = 8.3 Hz, 5H), 7.22-7.14 (m, 3H), 7.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 5.65 (d, *J* = 7.4 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 1H), 4.56 (d, *J* = 9.2 Hz, 1H), 4.48-4.33 (m, 3H), 4.22 (dd, *J* = 15.9, 5.6 Hz, 1H), 3.68 (d, *J* = 3.9 Hz, 2H), 3.46 (dt, *J* = 13.3, 7.0 Hz, 2H), 3.11 (q, *J* = 7.3 Hz, 2H), 2.44 (s, 4H), 1.60 (d, *J* = 6.2 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 4H), 0.93 (s, 9H).
Compound 1028		3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[(3-{[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}propyl)carbamoyl]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate J3**. LCMS (method E): 3.28 min, m/z: 533.8 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, $CDCl_3$): 10.08 (s, 1H), 8.64 (s, 1H), 8.59 (s, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.45 (s, 1H), 7.25 (dd, *J* = 9.0, 3.3 Hz, 6H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.02-6.88 (m, 5H), 6.73 (dd, *J* = 29.6, 8.4 Hz, 2H), 5.38 (d, *J* = 6.5 Hz, 2H), 4.67 (t, *J* = 7.7 Hz, 1H), 4.51 (d, *J* = 10.3 Hz, 1H), 4.45 (t, *J* = 6.7 Hz, 2H), 4.26 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.00 (d, *J* = 11.1 Hz, 1H), 3.64 (td, *J* = 10.9, 3.7 Hz, 2H), 3.42 (s, 3H), 3.33 (d, *J* = 5.9 Hz, 2H), 3.12 (q, *J* = 7.3 Hz, 3H), 2.42 (s, 4H), 2.28 (m,2.31-2.24 2H), 2.07 (d, *J* = 11.1 Hz, 1H), 1.94 (dd, *J* = 13.2, 7.2 Hz, 2H), 1.83 (d, *J* = 7.2 Hz, 2H), 0.88 (s, 9H), 0.81-0.75 (m, 7H).

Compound 1029		3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[(4-{[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl)carbamoyl]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide From **Intermediate J4**. LCMS (method E): 3.36 min, m/z 1080.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.88 (s, 1H), 9.75 (s, 1H), 9.23 (s, 1H), 8.98 (s, 1H), 8.66 (s, 1H), 8.58 (t, J = 6.2 Hz, 1H), 8.40 (s, 1H), 8.13 (d, J = 8.9 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 9.3 Hz, 1H), 7.61 (dd, J = 8.4, 5.5 Hz, 2H), 7.40 (q, J = 8.4 Hz, 5H), 7.22-7.13 (m, 3H), 7.09 (dd, J = 8.2, 1.8 Hz, 1H), 6.01 (s, 1H), 5.64 (d, J = 5.4 Hz, 1H), 5.14 (d, J = 3.4 Hz, 1H), 4.54 (d, J = 9.4 Hz, 1H), 4.47-4.40 (m, 2H), 4.35 (s, 1H), 4.21 (dd, J = 15.9, 5.4 Hz, 1H), 3.66 (d, J = 4.1 Hz, 2H), 3.28-3.20 (m, 2H), 3.10 (q, J = 7.3 Hz, 2H), 2.44 (s, 3H), 2.30 (dt, J = 14.2, 6.0 Hz, 1H), 2.16 (dd, J = 14.2, 7.4 Hz, 1H), 2.03 (t, J = 10.9 Hz, 1H), 1.94-1.82 (m, 1H), 1.60 (d, J = 6.2 Hz, 3H), 1.51 (s, 4H), 1.25 (q, J = 6.1, 5.0 Hz, 4H), 0.94 (s, 9H).

Compound 1030: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methoxy]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: methyl 4-formylbenzoate

A mixture of 4-formylbenzoic acid (10 g, 66.6 mmol), DMAP (4.06 g, 33.3 mmol), DIC (15.3 mL, 99.8 mmol) and MeOH (5.31 g, 166 mmol) in DMF (150 mL) was stirred at RT overnight. The mixture was poured into EtOAc, washed with brine, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the title product (7.80 g,

72%) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6): 10.11 (s, 1H), 8.15 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H).

Step 2: methyl 4-(hydroxymethyl)benzoate

A mixture of methyl 4-formylbenzoate (7.8 g, 47.5 mmol) and $NaBH_4$ (3.59 g, 95.0 mmol) in MeOH (200 mL) was stirred at RT for 40 min. The mixture was concentrated and the residue was purified by flash chromatography to afford the title product (4.77 g, 60.6%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.95-7.88 (m, 2H), 7.46 (dd, J = 7.9, 0.8 Hz, 2H), 5.38 (t, J = 5.7 Hz, 1H), 4.58 (d, J = 5.7 Hz, 2H), 3.84 (s, 3H).

Step 3: methyl 4-{[(6-nitropyridin-3-yl)oxy]methyl}benzoate

To a 0 °C solution of methyl 4-(hydroxymethyl)benzoate (5.1 g, 30.6 mmol) in THF (5 mL) was added NaH (2.43 g, 61.2 mmol) in portions. After stirring for 15 min, 5-fluoro-2-nitropyridine (4.34 g, 30.6 mmol) was added and the mixture was stirred at RT for 2h. The mixture was poured into water (100 mL) and the precipitate collected *via* filtration to afford the title compound (3.70 g, 42%) as a yellow solid. LCMS (method E): 4.05 min, m/z: 288.9 $[M+H]^+$.

Step 4: methyl 4-{[(6-aminopyridin-3-yl)oxy]methyl}benzoate

A mixture of methyl 4-{[(6-nitropyridin-3-yl)oxy]methyl}benzoate (3.7 g, 12.8 mmol) and Zn dust (4.18 g, 64.0 mmol) in MeOH (3 mL) and sat. aq. NH_4Cl (1 mL) was heated at 60 °C for 2h. The mixture was filtered and the filtrate was concentrated to afford the title compound (3.80 g, 100%) as a yellow solid. LCMS (method E): 2.40 min, m/z: 259.0 $[M+H]^+$.

Step 5: methyl 4-[({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)methyl]benzoate

A mixture of methyl 4-{[(6-aminopyridin-3-yl)oxy]methyl}benzoate (2.7 g, 10.4 mmol), 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 4.72 g, 12.4 mmol), *t*-BuOK (2.33 g, 20.8 mmol), $Pd_2(dba)_3$ (952 mg, 1.04 mmol) and Xantphos (1.20 g, 2.08 mmol) in 1,4-dioxane (40 mL) was heated at 100 °C N_2. After 16 h, the mixture was concentrated and the residue was purified by column chromatography to afford the title product (910 mg, 1.62 mmol, 15.6%) as a yellow solid. LCMS (method E): 5.38 min, m/z: 557.9, 559.9 $[M+H]^+$.

Step 6: methyl 4-({[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} methyl)benzoate

A mixture of methyl 4-[({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)methyl]benzoate (320 mg, 572 µmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C11**, 269 mg, 572 µmol), $Pd(dppf)Cl_2$ (46.7 mg, 57.2 µmol) and Na_2CO_3 (120 mg, 1.14 mmol) in 80% aq. 1,4-dioxane (5 mL) was heated to 100 °C with microwave irradiation for 1 h. The mixture was concentrated and the reside was purified by reverse-phase column chromatography to afford the title product (130 mg, 20%) as a yellow solid. LCMS (method E): 4.35 min, m/z: 823.2 $[M+H]^+$.

Step 7: methyl 4-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}methyl)benzoate

A mixture of methyl 4-({[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}methyl)benzoate (120 mg, 145 µmol) and Ghaffar-Parkins' catalyst (12 mg, 28.0 µmol) in 50% aq. 1,4-dioxane (4 mL) was heated at 100 °C under N_2. After 16 h, the mixture was poured into water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford the title compound (110 mg, 91%) as a yellow solid. LCMS (method E): 6.25 min, m/z: 840.9 $[M+H]^+$.

Step 8: 4-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} methyl)benzoic acid

A mixture of methyl 4-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}methyl)benzoate (130 mg, 154 µmol) and KOH (25.9 mg, 462 µmol) in 33% aq. MeOH (6 mL) was heated at 60 °C under N_2. After 16 h, the mixture was poured into water (20 mL) and washed with EtOAc (2 x 20 mL). The aqueous phase was adjust to pH = 1 and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by reverse-phase column chromatography to afford the title compound (40.0 mg, 31%) as a yellow solid. LCMS (method E): 5.49 min, m/z: 827.0 $[M+H]^+$.

Step 9: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)

pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methoxy]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

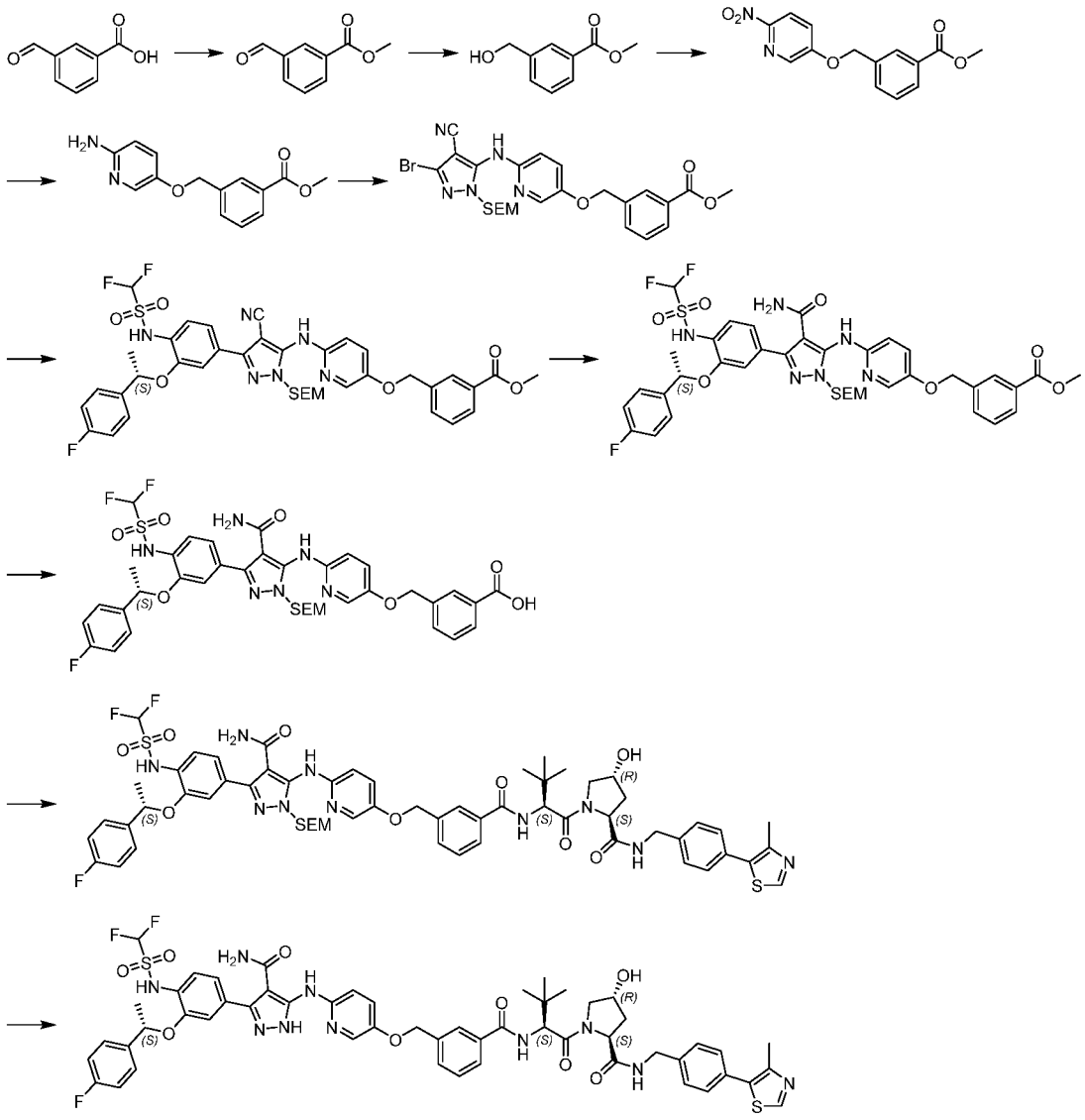
A mixture of 4-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}methyl)benzoic acid (50 mg, 60.4 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 28.5 mg, 66.4 µmol), HATU (45.5 mg, 120 µmol) and Et_3N (24.3 mg, 241 µmol) in DMF (5 mL) was stirred at RT. After 16 h, the mixture was poured into water (100 mL) and extracted with EtOAc (2 x 30 mL). The combined organics were washed with brine (2 x 50 mL) and concentrated. The residue was purified by reverse-phase column chromatography to afford the title compound (27.0 mg, 29%) as a yellow solid. LCMS (method E): 5.66 min, 620.3 $[M+2H]^{2+}$.

Step 10: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methoxy]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide

A solution of 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methoxy]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (27 mg, 21.7 µmol) in 1:40 TFA:DCM (4.1 mL) was stirred at RT for 1h. The reaction mixture was adjust to pH = 8, poured into water and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by reverse-phase column chromatography to afford the title compound (4.75 mg, 20%) as a yellow solid. LCMS (method E): 2.21 min, m/z 1109.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.49 (s, 1H), 9.45 (s, 1H), 8.98 (s, 1H), 8.60 (t, *J* = 6.1 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.98 (d, *J* = 3.1 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.49 (dt, *J* = 9.9, 5.1 Hz, 3H), 7.44-7.33 (m, 5H), 7.12 (t, *J* = 8.7 Hz, 2H), 6.85 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.81 (s, 1H), 6.29 (t, *J* = 54.8 Hz, 1H), 5.62 (q, *J* = 6.5 Hz, 1H), 5.18 (s, 2H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.42 (ddd, *J* = 25.2, 12.8, 5.9 Hz, 3H), 4.24 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.73 (s, 2H), 2.44 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H).

Compound 1031: 3-(4-(difluoromethylsulfonamido)-3-((S)-1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-((3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-

1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamoyl)benzyl)oxy)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide



Step 1: methyl 4-formylbenzoate

A mixture of 4-formylbenzoic acid (5 g, 33.3 mmol), DMAP (2.02 g, 16.6 mmol) DIC (7.71 mL, 49.9 mmol) and MeOH (2.66 g, 83.2 mmol) in DCM (33.3 mL) was stirred at RT overnight. The mixture was diluted with EtOAc, washed with brine, and concentrated under reduced pressure. The residue was purified by column chromatography to afford the title product (4.80 g, 88%) as a colourless solid. LCMS (Method A): 2.89, m/z: 165.1 $[M+H]^+$.

Step 2: methyl 3-(hydroxymethyl)benzoate

To a solution of methyl 3-formylbenzoate (4.3 g, 26.1 mmol) in meOH (20 mL) at 0 °C was added $NaBH_4$ (1.97 g, 52.2 mmol) in portions. The reaction was stirred at 0 °C for 3 h, then water (50 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by Prep-TLC (PE/EA = 2/1, v/v) to afford the title product (4.20 g, 97%) as a yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 0.4 Hz, 1H), 7.82 (d, J = 0.8 Hz, 1H), 7.58 (d, J = 0.8 Hz, 1H), 7.47 (dd, J = 0.8 Hz, 1H), 5.36 (t, J = 5.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 3.86 (s, 3H).

Step 3: methyl 4-{[(6-nitropyridin-3-yl)oxy]methyl}benzoate

To a solution of methyl 4-(hydroxymethyl)benzoate (6.6 g, 39.7 mmol) in THF (5 mL) at 0 °C was added NaH (3.16 g, 79.4 mmol) in portions. After stirring for 15 min, 5-fluoro-2-nitropyridine (5.64 g, 39.7 mmol) was added and the reaction was stirred at RT overnight. The mixture was poured into water (100 mL), concentrated and extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with brine (100 mL) and concentrated. The residue was purified by column chromatography (PE/EA = 100/1, v/v) to afford the title product (5.00 g, 33%) as a yellow solid. LCMS (method E): 3.64 min, m/z: 289.1 $[M+H]^+$.

Step 4: methyl 4-{[(6-aminopyridin-3-yl)oxy]methyl}benzoate

A mixture of methyl 4-{[(6-nitropyridin-3-yl)oxy]methyl}benzoate (1.95 g, 6.76 mmol) and Zn dust (2.20 g, 33.8 mmol) in MeOH (21 mL) and sat. aq. NH_4Cl (7 mL) was stirred at 60 °C for 1 h. The mixture was poured into water (100 mL), concentrated and extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with brine (100 mL) and concentrated. The residue was purified by column chromatography (PE/EA = 5/1, v/v) to afford the title product (2.30 g, > 100%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 8.00 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.70 (dd, J = 1.1 Hz, 2H), 7.54 (dd, J = 7.8 Hz, 2H), 7.19-7.17 (m, 1H), 6.41 (d, J = 0.9 Hz, 1H), 5.49 (bs, 2H), 5.08 (s, 2H), 3.86 (s, 3H).

Step 5: methyl 4-[({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)methyl]benzoate

A mixture of methyl 4-{[(6-aminopyridin-3-yl)oxy]methyl}benzoate (630 mg, 2.43 mmol), 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 1.38 g, 3.64 mmol), xantphos (281 mg, 486 µmol), t-BuOK (545 mg, 4.86 mmol) and $Pd_2(dba)_3$ (222 mg, 243 µmol) in 1,4-dioxane (30 mL) was stirred overnight at 100 °C under N_2. The mixture was poured into water (100 mL), concentrated and extracted with EtOAc (3 x 70 mL). The combined organics were washed with brine (100 mL) and concentrated. The residue was

purified by column chromatography (PE/EA = 5/1, v/v) to afford the title product (250 mg, 18%) as a yellow solid. LCMS (method A): 3.71 min, m/z: 558.1 & 560.1 $[M+H]^+$.

Step 6: methyl 3-({[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} methyl)benzoate

A mixture of methyl 3-[({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)methyl]benzoate (369 mg, 660 µmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C11**, 311 mg, 660 µmol), $Pd(dppf)Cl_2$ (53.8 mg, 66.0 µmol) and Na_2CO_3 (209 mg, 1.98 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was stirred at 100 °C for 10 h under N_2. The mixture was concentrated and poured into water (20 mL), then washed with EtOAc (20 mL). The aqueous phase was adjust to pH = 1 and extracted with EtOAc (3 x 20 mL). The combined organics were concentrated to afford the title product (220 mg, 40%) as a brown solid. LCMS (method E): 3,67 min, m/z: 824.2 $[M+H]^+$.

Step 7: methyl 3-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}methyl)benzoate

To a solution of methyl 3-({[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}methyl)benzoate (170 mg, 206 µmol), in 1,4-dioxane (12 mL) and H_2O (4 mL) was added Ghaffar-Parkins' catalyst (88.0 mg, 206 µmol), and the reaction was stirred under N_2 at 100 °C overnight. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (DCM/MeOH = 20/1, v/v) to afford the title product (100 mg, 57%) as a yellow solid. LCMS (method E): 4.18 min, m/z: 841.3 $[M+H]^+$.

Step 8: 3-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} methyl)benzoic acid

A mixture of methyl 3-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}methyl)benzoate (20 mg, 23.7 µmol) and KOH (3.98 mg, 71.1 µmol) in H_2O (10 mL) and MeOH (20 mL) was stirred at 60 °C under N_2 overnight. The mixture was poured into water (20 mL) and washed with EtOAc (2 x 20 mL). The aqueous phase was adjusted to pH

= 1 and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford the title product (5.00 mg, 26%) as a yellow solid. LCMS (method E): 4.08 min, m/z: 827.2 $[M+H]^+$.

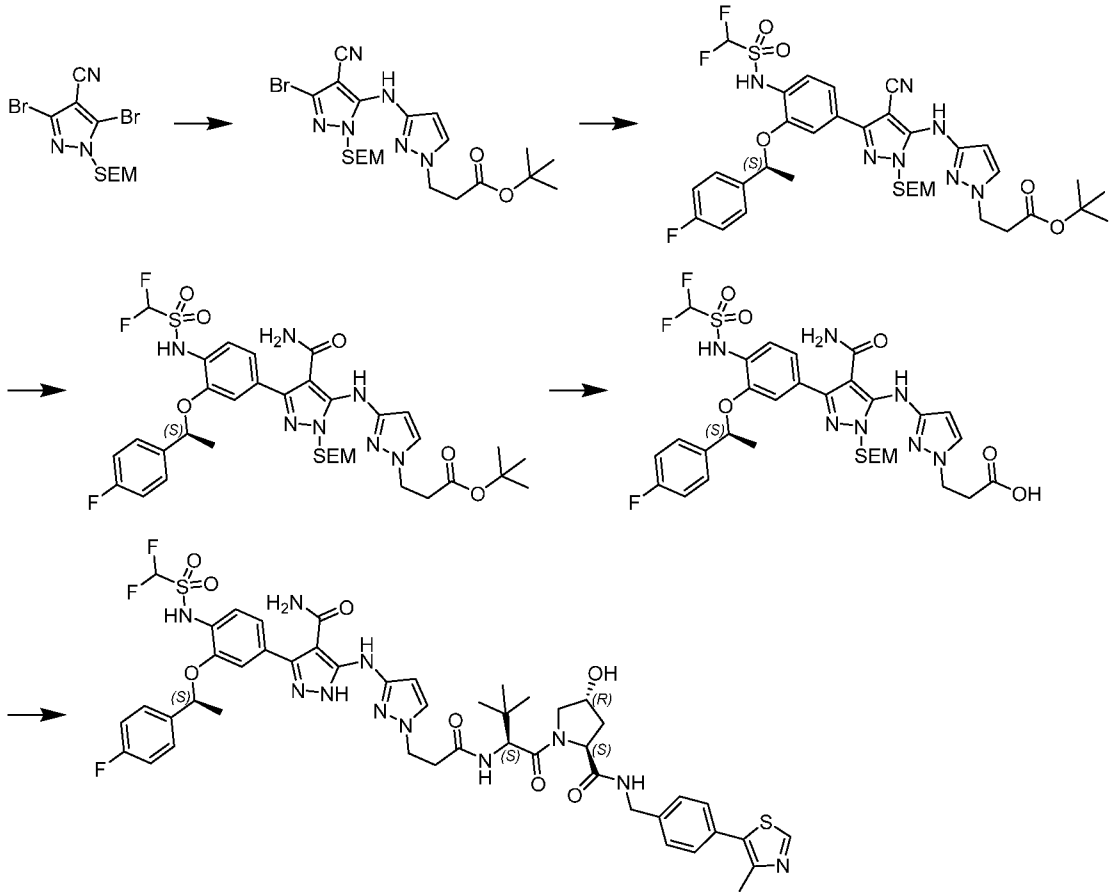
Step 9: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(3-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methoxy]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 3-({[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}methyl)benzoic acid (330 mg, 399 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 171 mg, 399 µmol), HATU (303 mg, 798 µmol) and Et_3N (160 mg, 1.59 mmol) in DMF (5 mL) was stirred at RT overnight. The mixture was poured into water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL) and concentrated. The residue was purified by RP-column to afford the title compound (220 mg, 29%) as a yellow solid. LCMS: 3.46 min, m/z: 620.4 $[M+2H]^{2+}$.

Step 10: 3-(4-(difluoromethylsulfonamido)-3-((S)-1-(4-fluorophenyl)ethoxy)phenyl)-5-((5-((3-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamoyl)benzyl)oxy)pyridin-2-yl)amino)-1H-pyrazole-4-carboxamide

A solution of 3-{4-ethanesulfonamido-3-[(1R)-1-(4-fluorophenyl)ethoxy]phenyl}-5-({5-[(2-{[(2R)-1-[(2R,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}ethyl)carbamoyl]pyridin-2-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (30 mg, 25.3 µmol) in DCM (10 mL) and TFA (1 mL) was stirred at RT for 10 min. The reaction mixture was adjusted to pH = 8 with sat. aq. Na_2CO_3 solution, then mixture was poured into water (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1, v/v) to afford the title compound (4.00 mg, 15%) as a yellow solid. LCMS (method E): 2.35 min, m/z: 555.3 $[M+2H]^{2+}$. ^1H NMR (400 MHz, $CDCl_3$): 9.78 (s, 1H), 8.66 (s, 1H), 8.12-7.78 (m, 4H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.52 (s, 3H), 7.46-7.40 (m, 2H), 7.34 (s, 5H), 7.09-6.91 (m, 5H), 6.78 (d, *J* = 6.9 Hz, 1H), 6.32 (s, 1H), 5.48-5.26 (m, 4H), 5.05 (s, 2H), 4.81-4.67 (m, 3H), 4.55 (s, 3H), 4.32 (d, *J* = 17.6 Hz, 2H), 4.12 (d, *J* = 10.6 Hz, 1H), 3.69 (d, *J* = 11.3 Hz, 2H), 3.41 (s, 3H), 2.96 (d, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.01 (s, 3H), 1.65-1.60 (m, 3H), 1.03 (s, 9H).

Compound 1032: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(2-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}ethyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 3-{3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}propanoate

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 500 mg, 1.31 mmol), tert-butyl 3-(3-amino-1H-pyrazol-1-yl)propanoate (**Intermediate K1**, 331 mg, 1.57 mmol), $Pd(OAc)_2$ (29.4 mg, 131 µmol), Cs_2CO_3 (957 mg, 2.94 mmol) and xantphos (151 mg, 262 µmol) in 1,4-dioxane was heated at 110 °C under N_2 overnight. Once cooled, the mixture was diluted with EtOAc (50 mL) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title product (493 mg, 74%) as a yellow oil. LCMS (method G): 2.83 min, m/z: 510.8 & 512.8 $[M+H]^+$.

Step 2: tert-butyl 3-[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoate

To a solution of tert-butyl 3-{3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}propanoate (490 mg, 0.9579 mmol) in 1,4-Dioxane:H_2O (4:1) (10 mL) were added 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (**Intermediate C11**, 494 mg, 1.05 mmol), Na_2CO_3 (202 mg, 1.91 mmol) and $Pd(dppf)Cl_2$ (78.1 mg, 95.7 µmol), and the reaction was heated at 100 °C under an atmosphere of N_2 for 18 h. Once cooled, the mixture was concentrated and the residue was partitioned between EtOAc (25 mL) and water (25 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title product (546 mg, 49%) as a brown oil. LCMS (method G): 3.14 min, m/z: 774.2 $[M-H]^-$.

Step 3: tert-butyl 3-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoate

A mixture of tert-butyl 3-[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoate (360 mg, 464 µmol) and Ghaffar-Parkins' catalyst (19.8 mg, 46.3 µmol) in EtOH:H_2O (4:1, 20 mL) was heated at 80 °C overnight. The mixture was concentrated *in vacuo* and partitioned between EtOAc and H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (0-5% MeOH:DCM) to afford the title product (256 mg, 70%) as a yellow glass. LCMS (method G): 2.97 min, m/z: 794.8 $[M+H]^+$.

Step 4: 3-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoic acid

A solution of tert-butyl 3-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoate (255 mg, 321 µmol) in HCO_2H (6.4 mL) was stirred at RT for 1 h. The reaction was concentrated, and the residue was purified by HPLC, followed by de-salting using

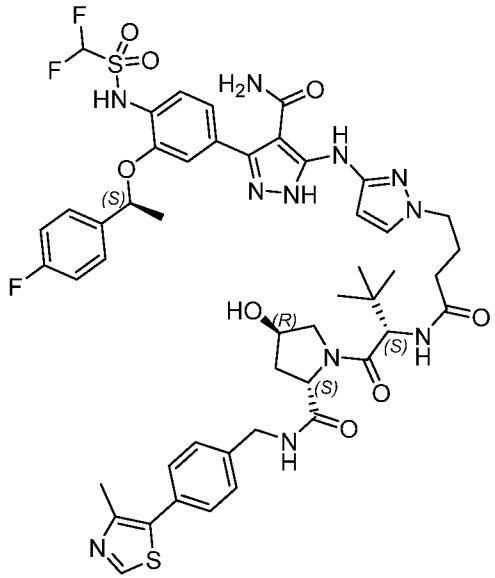
an SCX cartridge to afford the title product (140 mg, 72%) as an off-white solid. LCMS: rt 1.86 min, m/z 606.0 $[M-H]^-$.

Step 5: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(2-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}ethyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide

To a solution of 3-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]propanoic acid (130 mg, 0.2139 mmol) in dry DMF (1.0 mL) were added DIPEA (111 µL, 641 µmol), HATU (105 mg, 278 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, 109 mg, 235 µmol), sequentially. The reaction was stirred at RT under N_2 overnight, then the solvent was evaporated. The residue was purified by prep-HPLC to afford (53.3 mg, 25%) as an off-white solid. LCMS (method G): 2.05 min, m/z: 1019.6 [M-H]-. ^{1}H NMR (300 MHz, DMSO-d_6): 12.53 (s, 1H), 12.34 (s, 1H), 10.50 (s, 1H), 8.96 (s, 1H), 8.56 (t, *J* = 6.0 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 7.65-7.46 (m, 3H), 7.45-7.33 (m, 6H), 7.23-7.06 (m, 5H), 7.02 (t, *J* = 52.5 Hz, 1H), 5.61 (s, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.41 (dt, *J* = 16.1, 8.7 Hz, 3H), 4.22 (dd, *J* = 16.0, 5.6 Hz, 3H), 3.66 (s, 2H), 2.64 (s, 1H), 2.42 (s, 3H), 2.11-1.98 (m, 1H), 1.97-1.83 (m, 1H), 1.57 (d, *J* = 6.2 Hz, 3H), 0.87 (d, *J* = 19.4 Hz, 9H). [2 active protons not observed].

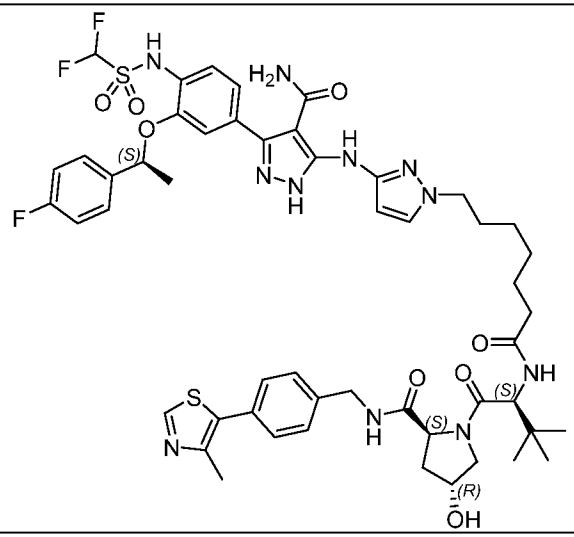
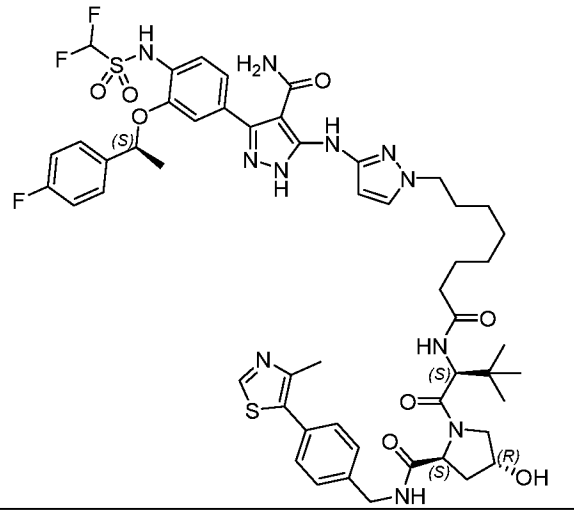
Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of **Compound 1032**, utilizing the indicated **Intermediate K** in Step 1.

Table 32: Compound 1033 to 1035, 1040, 1042

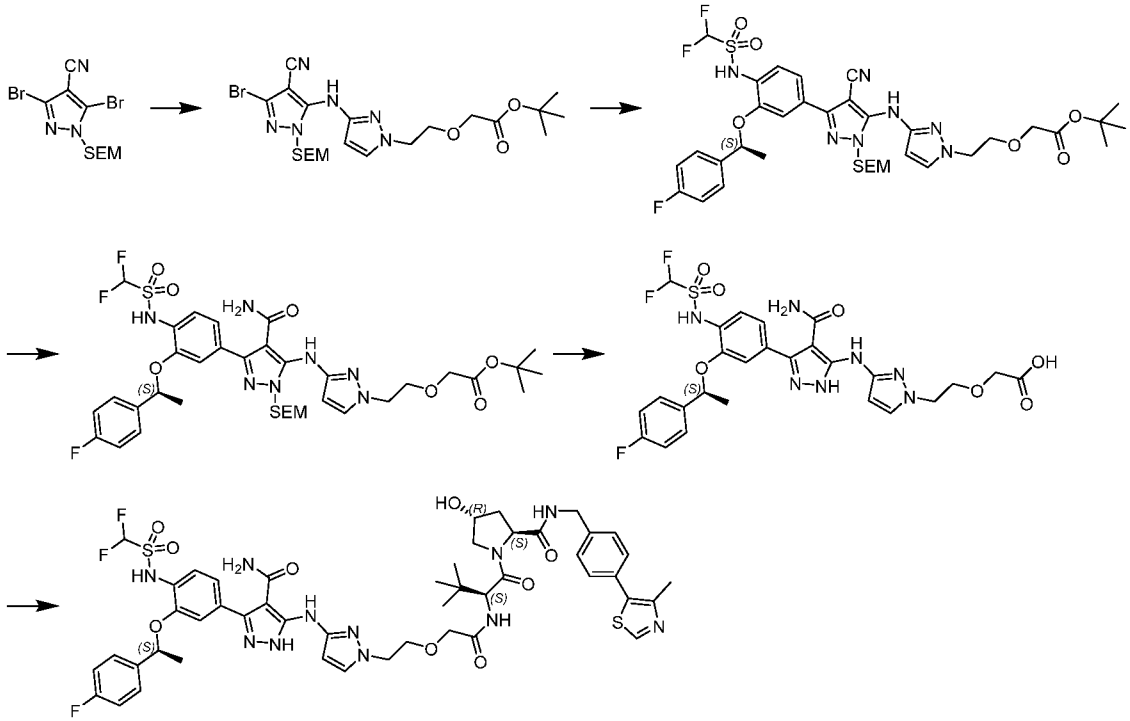
Compound No.	Structure	Compound Name and Analytical Data
Compound 1033		3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(3-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}propyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide From **Intermediate K2**. LCMS (method H): 2.12 min, m/z: 1033.1 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6): 12.53 (s, 1H), 10.51 (s, 1H), 8.98 (s, 1H), 8.83 (s, 1H), 8.57 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.57 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.52 (s, 1H), 7.46-7.33 (m, 5H), 7.23-7.13 (m, 2H), 7.13-7.05 (m, 2H), 6.93 (t, *J* = 52.6 Hz, 1H), 5.62 (d, *J* = 6.9 Hz, 1H), 5.14 (d, *J* = 3.6 Hz, 1H), 4.54 (d, *J* = 9.2 Hz, 1H), 4.49-4.37 (m, 2H), 4.35 (s, 1H), 4.21 (dd, *J* = 15.8, 5.4 Hz, 1H), 3.96 (s, 2H), 3.67 (d, *J* = 3.0 Hz, 2H), 2.44 (s, 3H), 2.31-2.09 (m, 2H), 2.09-1.83 (m, 4H), 1.57 (d, *J* = 6.2 Hz, 3H), 0.95 (s, 9H). [3 protons not observed].

Compound 1034		3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide From **Intermediate K3**. LCMS (method H): 2.15 min, m/z: 1047.1 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6): 10.49 (s, 1H), 8.97 (d, J = 0.4 Hz, 1H), 8.55 (t, J = 6.0 Hz, 1H), 7.89 (d, J = 9.4 Hz, 1H), 7.57 (dd, J = 8.7, 5.5 Hz, 3H), 7.46-7.32 (m, 5H), 7.17 (t, J = 8.9 Hz, 2H), 7.11 (s, 1H), 7.08 (dd, J = 8.1, 1.7 Hz, 1H), 6.92 (t, J = 52.6 Hz, 1H), 5.62 (q, J = 7.3, 6.5 Hz, 1H), 5.12 (d, J = 3.5 Hz, 1H), 4.54 (d, J = 9.3 Hz, 1H), 4.50-4.37 (m, 2H), 4.35 (s, 1H), 4.21 (dd, J = 15.8, 5.4 Hz, 1H), 3.97 (s, 2H), 3.66 (s, 2H), 2.44 (s, 3H), 2.31 (dt, J = 14.6, 7.6 Hz, 1H), 2.16 (dt, J = 14.1, 7.1 Hz, 1H), 2.03 (t, J = 10.5 Hz, 1H), 1.90 (ddd, J = 12.9, 8.7, 4.6 Hz, 1H), 1.81-1.66 (m, 2H), 1.57 (d, J = 6.2 Hz, 3H), 1.44 (p, J = 6.7 Hz, 2H), 0.94 (s, 9H). [5 protons not observed].

Compound 1035		3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(5-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}pentyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide From **Intermediate K4**. LCMS (method H): rt 2.19 min, m/z: 1061.1 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6): 10.49 (s, 1H), 8.97 (d, J = 0.4 Hz, 1H), 8.56 (t, J = 6.0 Hz, 1H), 7.85 (d, J = 9.3 Hz, 1H), 7.62-7.49 (m, 4H), 7.46-7.32 (m, 5H), 7.17 (t, J = 8.9 Hz, 3H), 7.13-7.04 (m, 2H), 6.92 (t, J = 52.7 Hz, 1H), 5.68-5.56 (m, 1H), 5.12 (d, J = 3.5 Hz, 1H), 4.54 (d, J = 9.4 Hz, 1H), 4.50-4.37 (m, 2H), 4.35 (s, 1H), 4.21 (dd, J = 15.8, 5.4 Hz, 1H), 3.95 (s, 2H), 3.66 (s, 2H), 3.17 (d, J = 4.7 Hz, 1H), 2.44 (s, 3H), 2.31-1.97 (m, 4H), 1.90 (ddd, J = 12.8, 8.7, 4.5 Hz, 1H), 1.82-1.67 (m, 2H), 1.57 (d, J = 6.3 Hz, 3H), 1.55-1.45 (m, 2H), 1.37 (d, J = 0.6 Hz, 1H), 1.27-1.14 (m, 2H), 0.93 (s, 9H).

Compound 1040		3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hexyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide From **Intermediate K5**. LCMS (method H): 2.22 min, m/z 1076.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 10.50 (s, 1H), 8.98 (d, *J* = 0.4 Hz, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.85 (d, *J* = 9.4 Hz, 1H), 7.57 (dd, *J* = 8.7, 5.5 Hz, 3H), 7.46-7.32 (m, 5H), 7.17 (t, *J* = 8.9 Hz, 2H), 7.13-7.04 (m, 2H), 7.01 (t, *J* = 52.6 Hz, 1H), 5.62 (q, *J* = 6.4 Hz, 1H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 9.3 Hz, 1H), 4.50-4.37 (m, 2H), 4.34 (s, 1H), 4.21 (dd, *J* = 15.9, 5.4 Hz, 1H), 3.94 (s, 2H), 3.66 (s, 2H), 2.44 (s, 3H), 2.30-2.18 (m, 1H), 2.11 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.01 (d, *J* = 9.1 Hz, 1H), 1.95-1.83 (m, 1H), 1.73 (s, 2H), 1.57 (d, *J* = 6.3 Hz, 3H), 1.48 (d, *J* = 6.7 Hz, 2H), 1.24 (s, 4H), 0.93 (s, 9H).
Compound 1042		3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[1-(7-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}heptyl)-1H-pyrazol-3-yl]amino}-1H-pyrazole-4-carboxamide From **Intermediate K6**. LCMS (method H): 2.28 min, m/z 1091.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 10.50 (s, 1H), 8.97 (d, *J* = 0.3 Hz, 1H), 8.97 (d, *J* = 0.4 Hz, 1H), 8.56 (t, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 8.97 (d, *J* = 0.4 Hz, 1H), 8.56 (t, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 7.59-7.54 (m, 3H), 7.43-7.36 (m, 5H), 7.17 (t, *J* = 8.9 Hz, 2H), 7.14-7.05 (m, 2 H), 6.99 (t, *J* = 50.8 Hz, 1H), 5.62 (q, *J* = 5.4 Hz, 1H), 5.11 (d, *J* = 3.4 Hz, 1H), 4.53 (d, *J* = 9.1 Hz, 1H), 4.47-4.39 (m, 2 H), 4.34 (s, 1H), 4.22 (dd, *J* = 5.0, 15.8 Hz, 1H), 3.95 (s, 2H), 3.65 (s, 2H), 2.44 (s, 3H), 2.27-2.20 (m, 1H), 2.16-1.99 (m, 2H), 1.99-1.85 (m, 1H), 1.73 (s, 2H), 1.56 (d, *J* = 6.3 Hz, 3H), 1.50-1.39 (m, 2H), 1.26-1.14 (m, 6H), 0.93 (s, 9H).

Compound 1036: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]
-5-({1-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl]-1H-pyrazol-3-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 2-(2-{3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}ethoxy)acetate

To a mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 500 mg, 1.31 mmol), tert-butyl 2-[2-(3-amino-1H-pyrazol-1-yl) ethoxy]acetate (**Intermediate L1**, 347 mg, 1.44 mmol), Cs_2CO_3 (957 mg, 2.94 mmol) and xantphos (151 mg, 262 µmol) in 1,4-dioxane (10 mL) was added $Pd(OAc)_2$ (29.4 mg, 131 µmol), and the reaction was heated at 110 °C under N_2 overnight. Once cooled, the mixture was diluted with EtOAc (50 mL) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title product (385 mg, 54%) as a yellow oil. LCMS (method G): 2.79 min, m/z: 540.8 & 542.8 $[M+H]^+$.

Step 2: tert-butyl 2-{2-[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetate

A mixture of tert-butyl 2-(2-{3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}ethoxy)acetate (385 mg, 0.71 mmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C11**, 368 mg, 781 µmol), Na_2CO_3 (150 mg, 1.42 mmol) and Pd(dppf)Cl_2 (57.9 mg, 71.0 µmol) in 1,4-Dioxane:H2O (4:1, 10 mL) was heated at 100 °C overnight. Once cooled, the mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The layers were separated, and the aqueous fraction was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title compound (133 mg, 23%) as a yellow oil. LCMS (method G): 3.08 min, m/z: 806.8 $[M+H]^+$.

Step 3: tert-butyl 2-{2-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetate

A mixture of tert-butyl 2-{2-[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetate (130 mg, 0.16 mmol) and Ghaffar-Parkins' catalyst (6.91 mg, 16.1 µmol) in EtOH:H_2O (4:1, 10 mL) was heated at reflux overnight. The mixture was concentrated, and the residue was partitioned between EtOAc and H_2O. The layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-5% MeOH:DCM) to afford the title product (82.9 mg, 63%) as a yellow oil. LCMS (method G): 2.92 min, m/z: 824.8 $[M+H]^+$.

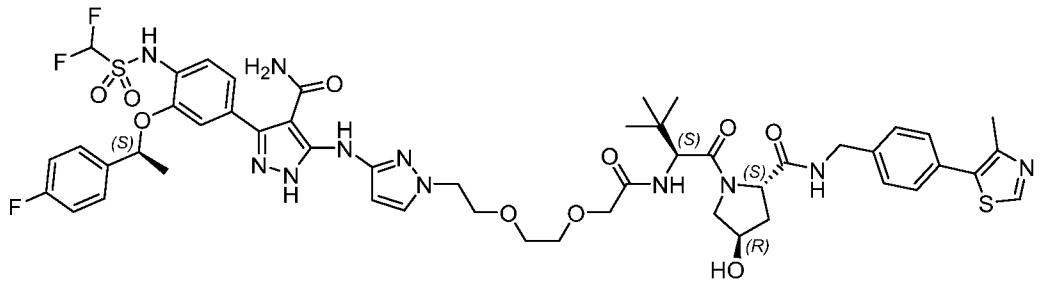
Step 4: 2-{2-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetic acid

A solution of tert-butyl 2-{2-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetate (80 mg, 97.1 µmol) in HCO_2H (485 µL) was stirred at RT for 14 h. The mixture was concentrated, and the residual formic acid removed by lyophilisation to afford the title product (48.5 mg, 78%) as an orange glass. LCMS (method G): 1.82 min, m/z: 636.0 $[M-H]^-$.

Step 5: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({1-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl]-1H-pyrazol-3-yl} amino)-1H-pyrazole-4-carboxamide

A mixture of 2-{2-[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]ethoxy}acetic acid (45 mg, 70.6 µmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, 36.2 mg, 77.6 µmol), HATU (34.8 mg, 91.7 µmol) and DIPEA (36.6 µL, 211 µmol) in DMF (1 mL) was stirred at RT overnight. The mixture was concentrated and the residue was purified by prep-HPLC to afford the title product (17.5 mg, 24%) as an off-white solid. LCMS (method H): rt 2.09 min, m/z 1051.2 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) 10.50 (s, 1H), 8.96 (s, 1H), 8.60 (t, *J* = 6.1 Hz, 1H), 7.57 (dd, *J* = 8.7, 5.5 Hz, 3H), 7.40 (s, 4H), 7.17 (t, *J* = 8.9 Hz, 3H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.93 (t, *J* = 52.2 Hz, 1H), 5.62 (q, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 9.5 Hz, 1H), 4.42 (dt, *J* = 16.1, 7.8 Hz, 3H), 4.25 (dd, *J* = 15.9, 5.5 Hz, 2H), 4.21-4.09 (m, 2H), 3.94 (s, 2H), 3.84 (s, 2H), 3.68-3.59 (m, 2H), 2.43 (s, 3H), 2.03 (d, *J* = 8.5 Hz, 1H), 1.97-1.84 (m, 1H), 1.57 (d, *J* = 6.3 Hz, 3H), 0.92 (s, 9H). [5 protons not observed]

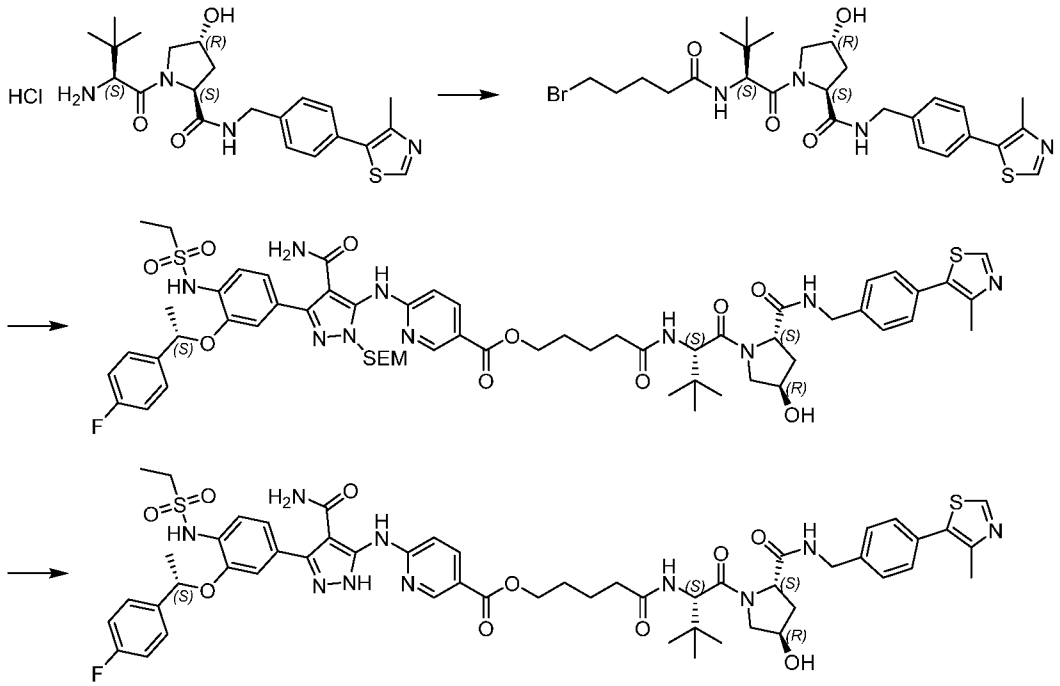
Compound 1037: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(1-{2-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]ethyl}-1H-pyrazol-3-yl)amino]-1H-pyrazole-4-carboxamide



The title compound was prepared in an analogous manner to **Compound 1036** utilizing **Intermediate L2** in Step 1. The title compound (17.5 mg, 11%) was obtained as an off-white solid. LCMS (method H): 2.11 min, m/z 547.8 $[M+2H]^{2+}$. ^{1}H NMR (300 MHz, DMSO-d_6): 10.50 (s, 1H), 8.95 (s, 1H), 8.60 (t, *J* = 5.9 Hz, 1H), 7.59-7.54 (m, 3H), 7.43-7.34 (m, 5H), 7.17 (t, *J* = 8.9 H, 2H), 7.11-7.07 (m, 2H), 7.02 (t, *J* = 52.6 Hz, 1H), 5.62 (q, *J* = 6.2 Hz, 1H), 5.16 (d, *J* = 3.5 Hz, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 4.48-4.21 (m, 4H), 4.15 (s, 2H), 3.95 (s, 2H), 3.78 (s,

2H), 3.70-3.50 (m, 6H), 2.42 (s, 3H), 2.10-2.02 (m, 1H), 1.94-1.86 (m, 1H), 1.57 (d, *J* = 6.2 Hz, 3H), 0.95 (s, 9H).

Compound 1039: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate



Step 1: (2S,4R)-1-[(2S)-2-(5-bromopentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

Amixture of (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 100 mg, 232 µmol), 5-bromopentanoic acid (46.1 mg, 255 µmol), Et_3N (70.4 mg, 696 µmol), HATU (105 mg, 278 µmol) was stirred at 25 °C under N_2 for 16 h. The mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the crude residue was purified by column chromatography (PE:EtOAc, 3:1) to afford the title compound (140 mg, 102%) as a yellow solid. LCMS (method A): 3.81 min; m/z: 593.58 $[M+H]^+$.

Step 2: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-

{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A mixture of (2S,4R)-1-[(2S)-2-(5-bromopentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (50 mg, 84.2 μmol) and 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (58.8 mg, 84.2 μmol), Cs_2CO_3 (82.7 mg, 252 μmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the crude residue was purified by Prep-TLC (DCM:MEOH, 20:1) to afford the title compound (120 mg,117%) as a yellow solid. LCMS (method A2): 3.88 min; m/z: 606.2 $[M+H]^+$.

Step 3: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

To a solution of 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (100 mg, 82.5 μmol) in dioxane (3 mL) was added a solution of HCl in dioxane (4M, 0.5 mL), and the mixture was stirred at 25 °C for 20min. The reaction mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (DCM:MeOH, 10:1) to afford the title product (4mg, 5%) as a yellow solid. LCMS (method A): 3.49 min; m/z: 541.2 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 9.97 (s, 1H), 8.97 (s, 1H), 8.73 (s, 1H), 8.56 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 9.4 Hz, 1H), 7.65-7.55 (m, 2H), 7.40 (q, *J* = 8.7, 8.0 Hz, 4H), 7.21-7.06 (m, 4H), 5.63 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 2H), 4.35 (s, 1H), 4.22 (d, *J* = 20.0 Hz, 3H), 3.66 (s, 2H), 3.09 (d, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 2.34 (d, *J* = 8.4 Hz, 1H), 2.22 (s, 1H), 2.02 (d, *J* = 9.1 Hz, 2H), 1.95-1.84 (m, 1H), 1.67 (s, 2H), 1.59 (d, *J* = 6.3 Hz, 3H), 1.25-1.22 (m, 3H), 0.94 (s, 9H).

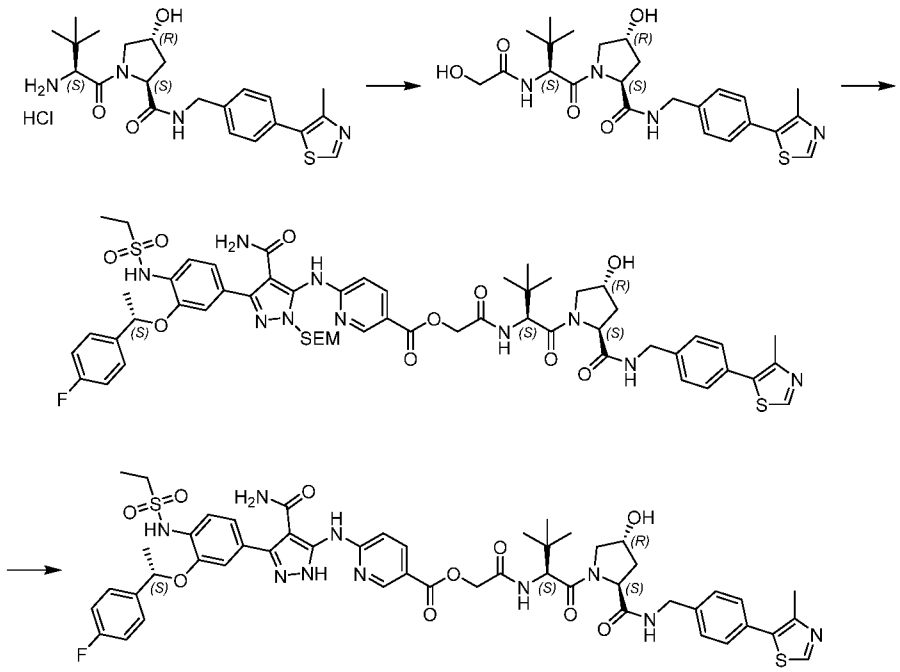
Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of **Compound 1039**, utilizing the indicated acid in **Step 1**.

Table 33: Compound 1057 and 1058

Compound No.	Structure	Compound Name and Analytical Data	Acid SM
Compound 1057		5-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}pentyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate LCMS (Method A2): 2.12 min, m/z: 548.3 $[M+2H]^{2+}$. ^1H NMR (400 MHz, DMSO-d_6): 13.98 (s, 1H), 9.50 (s, 1H), 9.14 (s, 1H), 8.98 (s, 1H), 8.55 (d, J = 6.1 Hz, 1H), 8.09-7.95 (m, 2H), 7.92-7.80 (m, 3H), 7.63 (t, J = 6.9 Hz, 2H), 7.54 (s, 2H), 7.40 (d, J = 8.6 Hz, 4H), 7.38 (s, 2H), 7.26 (s, 1H), 7.16 (s, 1H), 7.14 (s, 2H), 5.68 (d, J = 6.7 Hz, 1H), 4.53 (d, J = 9.1 Hz, 1H), 4.42 (d, J = 8.4 Hz, 2H), 4.34 (t, J = 6.0 Hz, 3H), 4.27-4.18 (m, 2H), 3.64 (s, 2H), 3.11 (q, J = 8.0, 7.6 Hz, 5H), 2.43 (s, 4H), 2.35-2.24 (m, 2H), 2.16 (d, J = 12.1 Hz, 2H), 2.02 (s, 2H), 1.89 (s, 2H), 1.76 (t, J = 8.4 Hz, 2H), 1.65 (d, J = 6.1 Hz, 4H), 1.62-1.50 (m, 3H), 1.40 (d, J = 11.2 Hz, 3H), 1.28 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H).	6-Bromohexanoic acid

Compound 1058		6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-{[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hexyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate LCMS (Method A2): 2.19 min, m/z: 555.3 $[M+2H]^{2+}$. 1H NMR (400 MHz, DMSO-d_6): 9.94 (s, 1H), 8.97 (s, 1H), 8.75 (d, J = 10.1 Hz, 1H), 8.54 (s, 1H), 8.18 (s, 1H), 8.04-7.79 (m, 2H), 7.61 (s, 3H), 7.49-7.40 (m, 4H), 7.39 (s, 2H), 7.20 (s, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.10 (s, 1H), 5.64 (s, 1H), 5.11 (s, 1H), 4.56 (s, 1H), 4.42 (s, 2H), 4.35 (s, 1H), 4.24 (s, 3H), 3.66 (s, 2H), 3.17-3.06 (m, 3H), 2.44 (s, 3H), 2.31-2.23 (m, 1H), 2.14 (s, 1H), 2.02 (s, 1H), 1.91 (s, 1H), 1.69 (s, 2H), 1.60 (d, J = 6.4 Hz, 3H), 1.52 (s, 2H), 1.39 (s, 1H), 1.25 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H).	7-Bromoheptanoic acid

Compound 1041: {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino] pyridine-3-carboxylate



Step 1: (2S,4R)-4-hydroxy-1-[(2S)-2-(2-hydroxyacetamido)-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

A mixture of 2-hydroxyacetic acid (35.3 mg, 0.46 mmol), Et_3N (186 mg, 1.85 mmol), HATU (211 mg, 0.56 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 200 mg, 0.46 mmol) in MeCN (4 mL) was stirred at RT for 4 h. The reaction was concentrated and the residue was purified by prep-TLC (DCM/MeOH) to afford the title compound (120 mg, 53%) as a yellow solid. LCMS (method A): 2.94 min; m/z: 490.5 $[M+H]^+$.

Step 2: {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

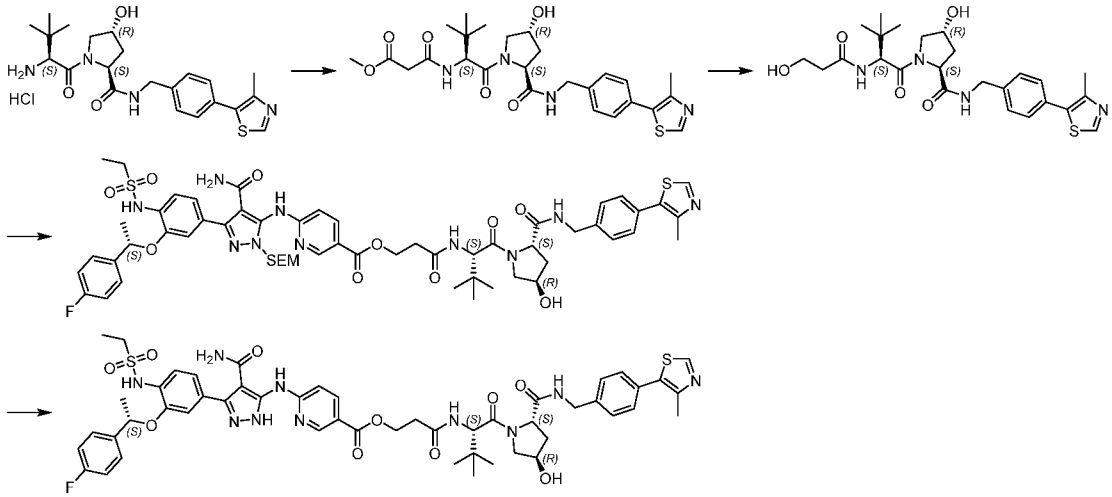
A mixture of (2S,4R)-4-hydroxy-1-[(2S)-2-(2-hydroxyacetamido)-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (120 mg, 0.25 mmol), Et_3N (99.1 mg, 0.982 mmol) and HATU (111 mg, 0.29 mmol) in MeCN (4 mL) was stirred at

RT for 5 min before 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (171 mg, 0.25 mmol) was added. The mixture was stirred at RT for 3 h, then concentrated. The residue was purified by prep-TLC to afford the title compound (180 mg 62%) as a yellow solid. LCMS (method A): 3.66 min; m/z: 585.4 $[M+H]^+$.

Step 3: {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino] pyridine-3-carboxylate

A mixture of {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (100 mg, 0.09 mmol) in formic acid (2 mL) was stirred at RT for 2 h. The mixture was concentrated, and the residue neutralized to pH 7-8 with sat. aq. Na_2CO_3. The precipitate was collected *via* filtration and purified by RP-column to afford the title compound (30 mg, 20%) as a yellow solid. LCMS (method A): 3.21 min; m/z: 520.3 $[M+2H]^{2+}$. ^1H NMR (400 MHz, MeOD-d_4): 9.08 (s, 1H), 8.90 (s, 1H), 8.32 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.58-7.50 (m, 4H), 7.48-7.40 (m, 2H), 7.21-7.17 (m, 2H), 7.14 (s, 3H), 5.65 (q, *J* = 6.4 Hz, 1H), 4.77 (d, *J* = 4.4 Hz, 1H), 4.70-4.63 (m, 2H), 4.60-4.56 (m, 1H), 4.41 (d, *J* = 15.5 Hz, 1H), 3.96 (d, *J* = 10.7 Hz, 1H), 3.91-3.85 (m, 1H), 3.24 (d, *J* = 7.3 Hz, 3H), 2.51 (s, 3H), 2.30 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.17 (dt, *J* = 8.2, 4.2 Hz, 1H), 1.77 (d, *J* = 6.4 Hz, 3H), 1.44 (t, *J* = 7.4 Hz, 3H), 1.13 (s, 9H).

Compound 1044: {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino] pyridine-3-carboxylate



Step 1: methyl 2-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl] methyl}carbamoyl)pyrrolidin-1-

A solution of 3-methoxy-3-oxopropanoic acid (98.7 mg, 0.84 mmol), Et_3N (280 mg, 2.78 mmol), HATU (344 mg, 0.91 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Intermediate 2**, 300 mg, 0.70 mmol) in MeCN (10 mL) was stirred at RT for 4 h. The mixture was concentrated and the residue was purified by prep-TLC to afford the title compound (140 mg 36%) as a yellow solid. LCMS (method A): 2.53 min, m/z 531.1 $[M+H]^+$.

Step 2: (2S,4R)-4-hydroxy-1-[(2S)-2-(3-hydroxypropanamido)-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

To a solution of methyl 2-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl] methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}acetate (100 mg, 0.19 mmol) in THF (10 mL) was added $LiAlH_4$ (21.4 mg, 0.57 mmol), and the mixture was stirred at RT for 3 h. The reaction was quenched with water and 10% aq. NaOH, then filtered and concentrated. The residue was purified by prep-TLC (DCM/MeOH = 20/1) to afford the title compound (33 mg, 35%) as a yellow solid. LCMS (method A): 2.45 min; m/z: 501.2 $[M+H]^+$.

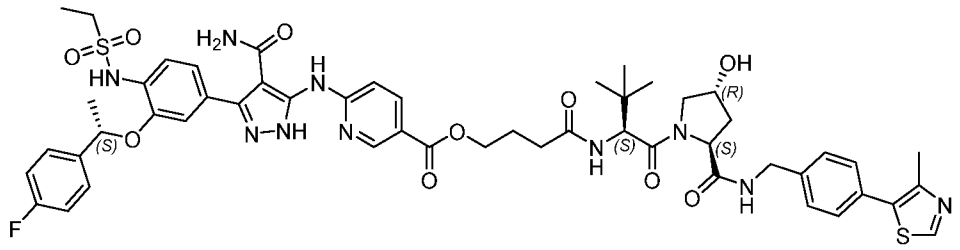
Step 3: 2-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}ethyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

To a mixture of 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (45.8 mg, 0.07 mmol), Et_3N (26.5 mg, 0.26 mmol) and HATU (29.9 mg, 0.07877 mmol) in MeCN (4 mL) was added (2S,4R)-4-hydroxy-1-[(2S)-2-(3-hydroxypropanamido)-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (33 mg, 0.06565 mmol), and the mixture was stirred at RT for 3 h. The mixture was concentrated and the residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title compound (15 mg, 19%) as a brown solid. LCMS (method A): 3.66 min; m/z: 583.8 $[M+H]^+$.

Step 4: {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino] pyridine-3-carboxylate

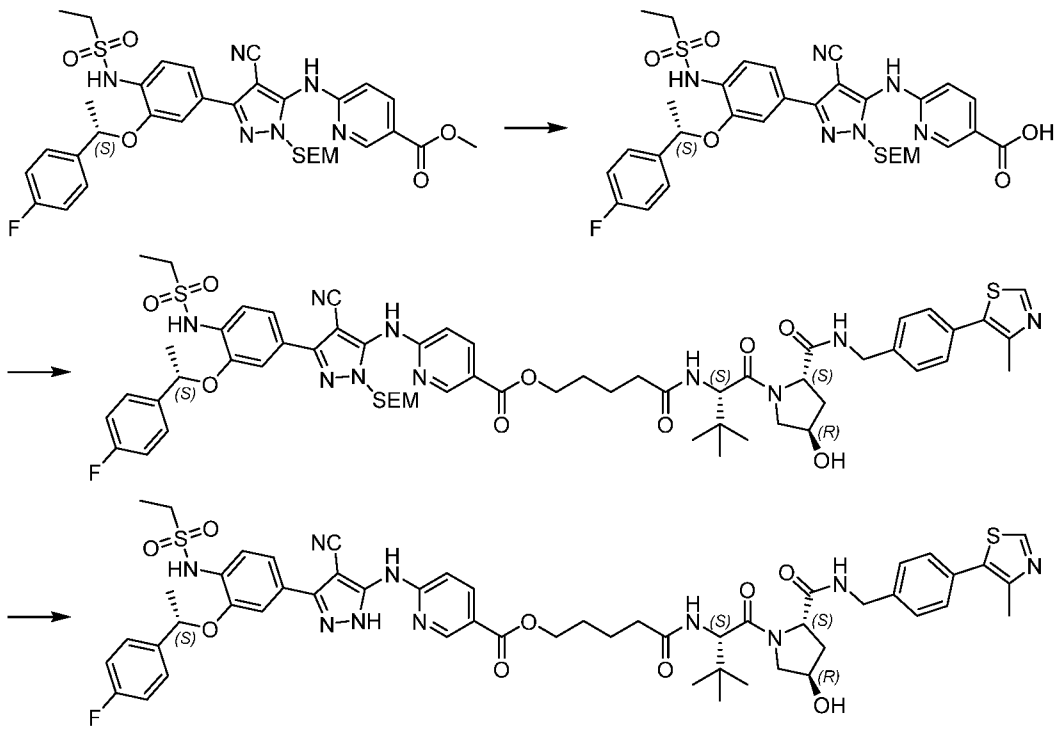
A mixture of {[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (15 mg, 0.01282 mmol) in formic acid (2 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure and the residue neutralized to pH 7-8 with sat. aq. Na_2CO_3. The precipitate was collected via filtration and purified by prep-TLC (DCM:MeOH, 25:1) to afford the title compound (2 mg, 13%) as a yellow solid. LCMS (method A): 3.17 min; m/z: 527.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4): 8.90 (s, 1H), 8.84 (s, 1H), 8.76 (d, J = 9.1 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.61-7.54 (m, 1H), 7.47 (s, 3H), 7.34 (d, J = 7.8 Hz, 3H), 7.13-7.01 (m, 4H), 5.55 (dd, J = 12.0, 5.5 Hz, 1H), 5.34 (dd, J = 5.4, 4.2 Hz, 1H), 4.70 (d, J = 13.3 Hz, 1H), 4.57 (s, 3H), 4.47 (d, J = 15.3 Hz, 3H), 4.35-4.28 (m, 2H), 3.91 (d, J = 11.2 Hz, 1H), 3.80 (dd, J = 10.9, 3.9 Hz, 1H), 3.19-3.14 (m, 2H), 2.78-2.71 (m, 2H), 2.44 (s, 3H), 2.19 (t, J = 7.6 Hz, 2H), 2.03 (t, J = 5.9 Hz, 3H), 1.69 (d, J = 6.4 Hz, 3H), 1.63-1.57 (m, 2H), 1.04 (s, 7H), 0.89 (d, J = 7.1 Hz, 3H).

Compound 1043: 3-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl] methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}propyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate



The title compound was prepared in an analogous manner to **Compound 1044** utilizing 4-methoxy-4-oxobutanoic acid in **Step 1**. The title compound (4.0 mg, 30%) was obtained as a yellow solid. LCMS (method A): 4.30 min; m/z: 534.2 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, MeOD-d_4): 8.98 (s, 1H), 8.84 (s, 1H), 8.23 (dd, *J* = 8.8, 2.3 Hz, 1H), 8.07 (s, 1H), 7.58 (s, 1H), 7.51-7.43 (m, 4H), 7.42-7.36 (m, 2H), 7.09 (ddd, *J* = 16.9, 8.3, 5.0 Hz, 5H), 5.57 (q, *J* = 6.4 Hz, 1H), 5.34 (dd, *J* = 5.3, 4.1 Hz, 1H), 4.66-4.55 (m, 3H), 4.51 (d, *J* = 6.8 Hz, 2H), 4.38-4.29 (m, 3H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.18 (s, 3H), 2.46 (s, 4H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.14-1.98 (m, 5H), 1.70 (d, *J* = 6.3 Hz, 3H), 1.60 (t, *J* = 7.3 Hz, 1H), 1.40-1.36 (m, 4H), 1.03 (s, 7H).

Compound 1061: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate



Step 1: 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid

A mixture of methyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (230 mg, 0.33 mmol) and NaOH (13.2 mg, 0.33 mmol) in MeOH (10 mL) was stirred at 50 °C for 4h. The mixture was concentrated, and the residue was diluted with water and neutralised with 1M HCl. The aqueous mixture was extracted with EtOAc, and the organics were dried over Na_2SO_4 and concentrated to afford the title compound (180 mg, 80%) as a white solid. LCMS (method A): 4.25 min, m/z: 681.9 $[M+H]^+$.

Step 2: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A mixture of (2S,4R)-1-[(2S)-2-(5-bromopentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (156 mg, 262 µmol) and 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (180 mg, 262 µmol) and Cs_2CO_3 (85.5 mg, 262 µmol) in MeCN (3 mL) was stirred at 25 °C for 16 h. The mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the crude residue was purified by Prep-TLC (DCM:MEOH, 20:1) to afford the title compound (210 mg, 67%). LCMS (method A): 4.25 min, m/z: 1096.0 $[M+H]^+$.

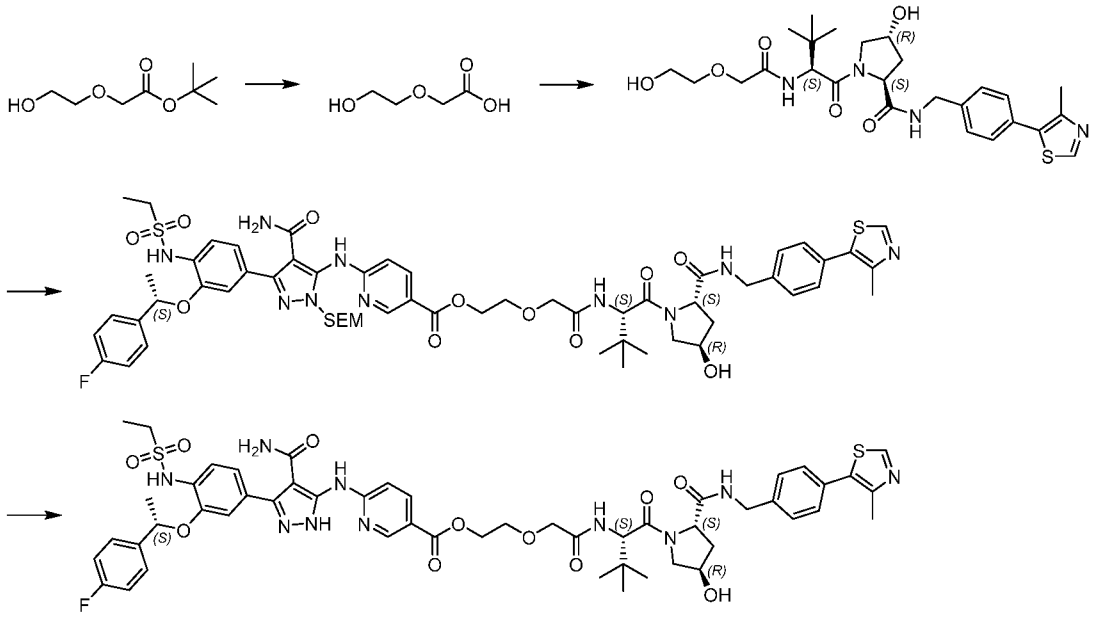
Step 3: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A solution of 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-cyano-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy] methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (210 mg, 175 µmol) in 4M HCl/Dioxane (20 mL) was stirred at RT for 20 min. The reaction was concentrated to afford the title compound (10 mg, 5%) as a yellow solid. LCMS (method A): 4.25 min, m/z:1064.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.97 (s, 1H), 8.72 (s, 1H), 8.57 (t, J = 6.0 Hz, 1H), 8.08 (d, J = 9.0

Hz, 1H), 7.92 (d, *J* = 9.3 Hz, 1H), 7.61 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.40 (dd, *J* = 9.9, 6.2 Hz, 6H), 7.24-7.14 (m, 3H), 5.60 (d, *J* = 6.6 Hz, 1H), 5.14 (s, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.47-4.39 (m, 2H), 4.35 (d, *J* = 7.8 Hz, 1H), 4.29-4.17 (m, 3H), 3.65 (s, 2H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 2.32 (d, *J* = 2.0 Hz, 1H), 2.21 (q, *J* = 7.5 Hz, 1H), 2.06-1.97 (m, 2H), 1.90 (d, *J* = 4.7 Hz, 1H), 1.67 (s, 2H), 1.62 (d, *J* = 6.2 Hz, 3H), 1.27 (s, 2H), 1.23 (s, 3H), 0.93 (s, 9H).

Compound 1061 did not exhibit any substantial binding to MLKL (K_D ~2μM) in the *in vitro* assays described herein.

Compound 1046: 2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate



Step 1: 2-(2-hydroxyethoxy)acetic acid

To a stirred solution of tert-butyl 2-(2-hydroxyethoxy)acetate (400 mg, 2.26 mmol) in MeOH (5 mL) was added 1M NaOH (4 mL), and the reaction was stirred at 60 °C for 2 h under the N_2. The mixture was concentrated and neutralised with 1M HCl. The mixture was concentrated to afford the title compound (270 mg, 99%) as a colourless oil. LCMS (method A): 0.25 min, m/z: 143.2 $[M+Na]^+$.

Step 2: (2S,4R)-4-hydroxy-1-[(2S)-2-[2-(2-hydroxyethoxy)acetamido]-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

To a stirred solution of 2-(2-hydroxyethoxy)acetic acid (50 mg, 416 µmol) in DMF (3 mL) were added (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, 194 mg, 416 µmol), HATU (205 mg, 540 µmol) and DIPEA (160 mg, 1.24 mmol), and the mixture was stirred at RT for 2 h under N_2. The mixture was diluted with water and extracted with MeOH:DCM (1:15). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (MeOH:DCM, 1:15) to afford the title compound as a white solid (750 mg, 74%). LCMS (method A): 2.97 min, m/z: 533.3 $[M+H]^+$.

Step 3: 2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

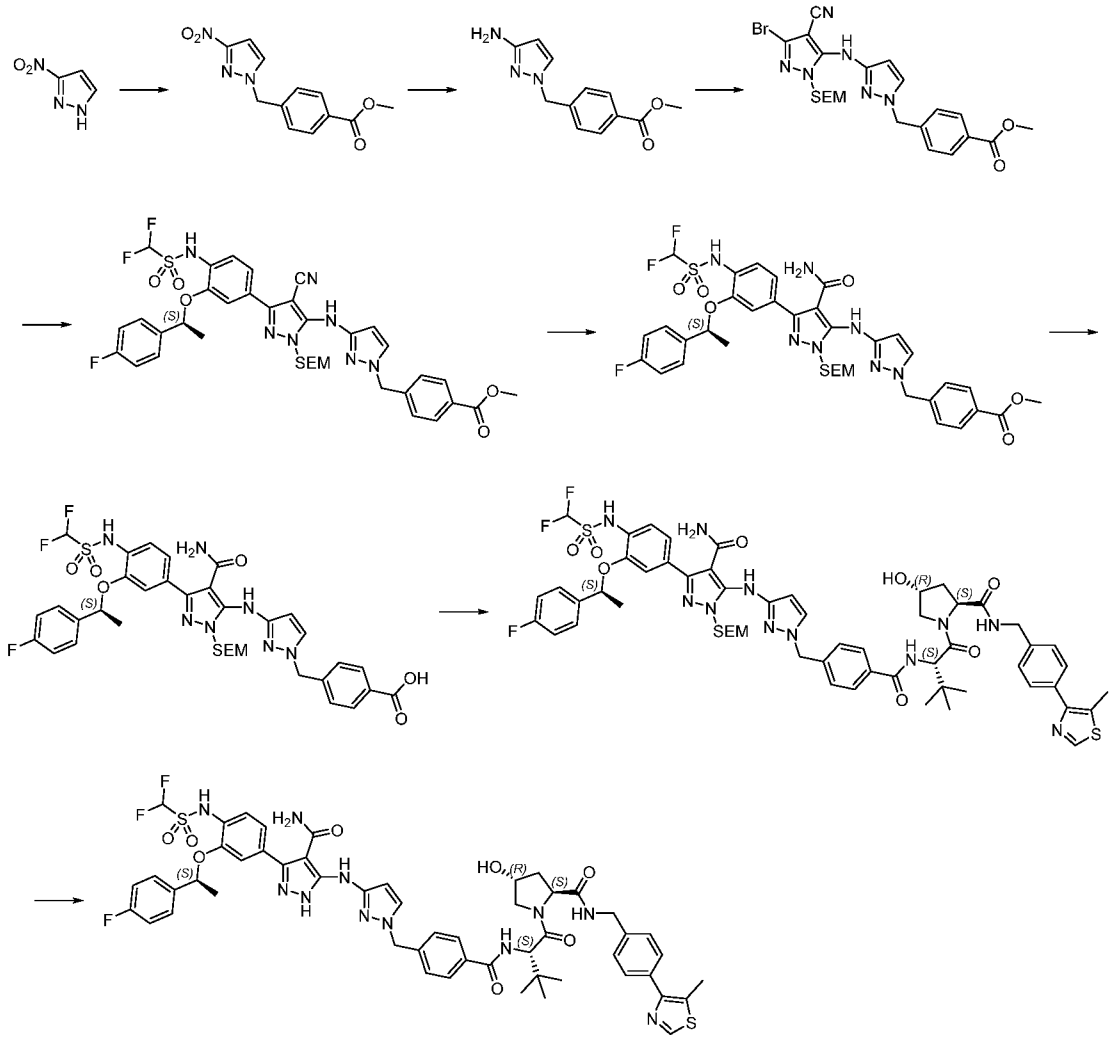
To a stirred solution of (2S,4R)-4-hydroxy-1-[(2S)-2-[2-(2-hydroxyethoxy)acetamido]-3,3-dimethylbutanoyl]-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (150 mg, 281 µmol) in DCM (3 mL) were added 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylic acid (196 mg, 281 µmol), DCC (86.7 mg, 421 µmol) and DMAP (51.4 mg, 421 µmol), and the mixture was stirred at RT for 2 h under N_2. The mixture was diluted with water and extracted with MeOH:DCM (1:10). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (MeOH:DCM, 1:15) to afford the title compound (150 mg, 44%) as a yellow solid. LCMS (method A): 4.95 min, m/z: 608.2 $[M+2H]^{2+}$.

Step 4: 2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate

A solution of 2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (100 mg, 82.4 µmol) in HCOOH (3 mL) was stirred at RT for 2 h under N_2. The mixture was concentrated and the residue was purified by Prep-TLC (8% MeOH:DCM) to afford the title compound (20 mg, 22%) as a yellow solid. LCMS (method D): 4.22 min, m/z: 1084.6 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6): 12.96 (s, 1H), 9.93 (s, 1H), 9.25 (s, 1H), 8.95 (s, 1H), 8.76 (s, 1H), 8.58 (s,

1H), 8.22 (d, *J* = 9.1 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 6.1 Hz, 2H), 7.47 (d, *J* = 9.7 Hz, 2H), 7.37 (s, 2H), 7.20-7.08 (m, 6H), 5.63 (d, *J* = 5.8 Hz, 1H), 5.15 (d, *J* = 3.5 Hz, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 4.44 (s, 1H), 4.36 (d, *J* = 6.2 Hz, 2H), 4.27 (d, *J* = 5.4 Hz, 1H), 4.05 (s, 1H), 3.84 (s, 1H), 3.67-3.59 (m, 2H), 3.19-3.12 (m, 2H), 3.09 (d, *J* = 7.3 Hz, 2H), 2.41 (s, 2H), 2.14-1.98 (m, 2H), 1.91 (td, *J* = 13.1, 11.0, 5.3 Hz, 2H), 1.60 (d, *J* = 6.2 Hz, 3H), 1.41-1.29 (m, 3H), 1.27 (d, *J* = 7.3 Hz, 3H), 0.92 (s, 9H).

Compound 1045: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]
-5-({1-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methyl]-1H-pyrazol-3-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: methyl 4-[(3-nitro-1H-pyrazol-1-yl)methyl]benzoate

To a solution of 3-nitro-1H-pyrazole (1.18 g, 10.4 mmol) in DMF (15 mL) was added NaH (495 mg, 12.4 mmol) in portions. The reaction was stirred at RT for 30 min under N_2, then cooled to 0 °C. Then, methyl 4-(bromomethyl)benzoate (2.61 g, 11.4 mmol) was added and the reaction was stirred at 0 °C for 1 h. The mixture was poured into ice-water and the precipitate was collected via filtration and dried under vacuum to afford the title compound (1.91 g, 70%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): 8.20 (d, *J* = 2.5 Hz, 1H), 7.96 (dd, *J* = 6.6, 1.9 Hz, 2H), 7.42 (dd, *J* = 8.1, 0.5 Hz, 2 H), 7.10 (d, *J* = 2.5 Hz, 1H), 5.58 (s, 2H), 3.85 (s, 3H).

Step 2: methyl 4-[(3-amino-1H-pyrazol-1-yl)methyl]benzoate

To a suspension of methyl 4-[(3-nitro-1H-pyrazol-1-yl)methyl]benzoate (1.90 g, 7.27 mmol) in EtOAc (35 mL) was added $SnCl_2 \cdot 2H_2O$ (8.19 g, 36.3 mmol), and the reaction was heated at reflux for 1 h. Once cooled, the pH was adjusted to 8-9 by the addition of sat. aq. Na_2CO_3. The aqueous mixture was extracted with EtOAc (3 x 50 mL), and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound (1.62 g, 96%) as a yellow oil. LCMS (method G): 0.89 min, m/z 232.0 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): 7.90 (dd, *J* = 6.5, 1.8 Hz, 2H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.44 (d, *J* = 2.3 Hz, 1H), 5.12 (s, 2H), 4.62 (bs, 2H), 3.83 (s, 3H).

Step 3: methyl 4-({3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}methyl)benzoate

A mixture of 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 2.66 g, 7.00 mmol), methyl 4-[(3-amino-1H-pyrazol-1-yl)methyl]benzoate (1.62 g, 7.00 mmol), Cs_2CO_3 (3.42 g, 10.5 mmol), xantphos (810 mg, 1.40 mmol) and $Pd(OAc)_2$ (157 mg, 0.70 mmol) in 1,4-dioxane (35 mL) was heated at 110 °C under a N_2 atmosphere overnight. Once cooled, the mixture was diluted with EtOAc (50 mL) and filtered over Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (0-50% EtOAc:heptane) to afford the title compound (1.47 g, 40%) as a yellow oil. LCMS (method G): 2.67 min, m/z 531.0 and 533.0 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 8.02 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.30 (dd, *J* = 8.1, 0.6 Hz, 2H), 6.13 (d, *J* = 2.3 Hz, 1H), 5.37 (s, 2H), 5.29 (s, 2H), 3.91 (s, 3H), 3.63-3.58 (m, 2H), 0.96-0.93 (m, 2H), 0.01 (s, 9H).

Step 4: methyl 4-{[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl] methyl}benzoate

A mixture of methyl 4-({3-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]-1H-pyrazol-1-yl}methyl)benzoate (1.71 g, 3.21 mmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C5**, 1.66 g, 3.53 mmol), Na_2CO_3 (680 mg, 6.42 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (262 mg, 0.32 mmol) in 80% aq. Dioxane (32.0 mL) was heated at 100 °C overnight. Once cooled, the mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The layers were separated, and the aqueous fraction was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (0-50% EtOAc:heptane) to give the title compound (1.36 g, 53%) as a yellow oil. LCMS (method G): 2.99 min, 796.0 $[M+H]^+$.

Step 5: methyl 4-{[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]methyl}benzoate

A mixture of methyl 4-{[3-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]methyl}benzoate (1.76 g, 1.69 mmol) and Ghaffar-Parkins' catalyst (72.4 mg, 0.17 mmol) in 80% aq. EtOH (20 mL) was heated at 80 °C overnight. The mixture was concentrated and partitioned between EtOAc and H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-5% MeOH:DCM) to give the title compound (1.21 g, 88%) as a yellow foam. LCMS (method G): 2.81 min, m/z 815.0 $[M+H]^+$.

Step 6: 4-{[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl] methyl}benzoic acid

A mixture of methyl 4-{[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]methyl}benzoate (1.21 g, 1.48 mmol) and KOH (248 mg, 4.43 mmol) in 66% aq. MeOH (60 mL) was stirred at 50 °C overnight. The mixture was diluted with water (50 mL) and washed with EtOAc (2 x 50 mL). The aqueous phase was acidified to pH = 1 and extracted with EtOAc (2 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to afford the title compound (1.12 g, 95%) as a beige solid. LCMS (method G): 2.51 min, m/z 801.0 $[M+H]^+$.

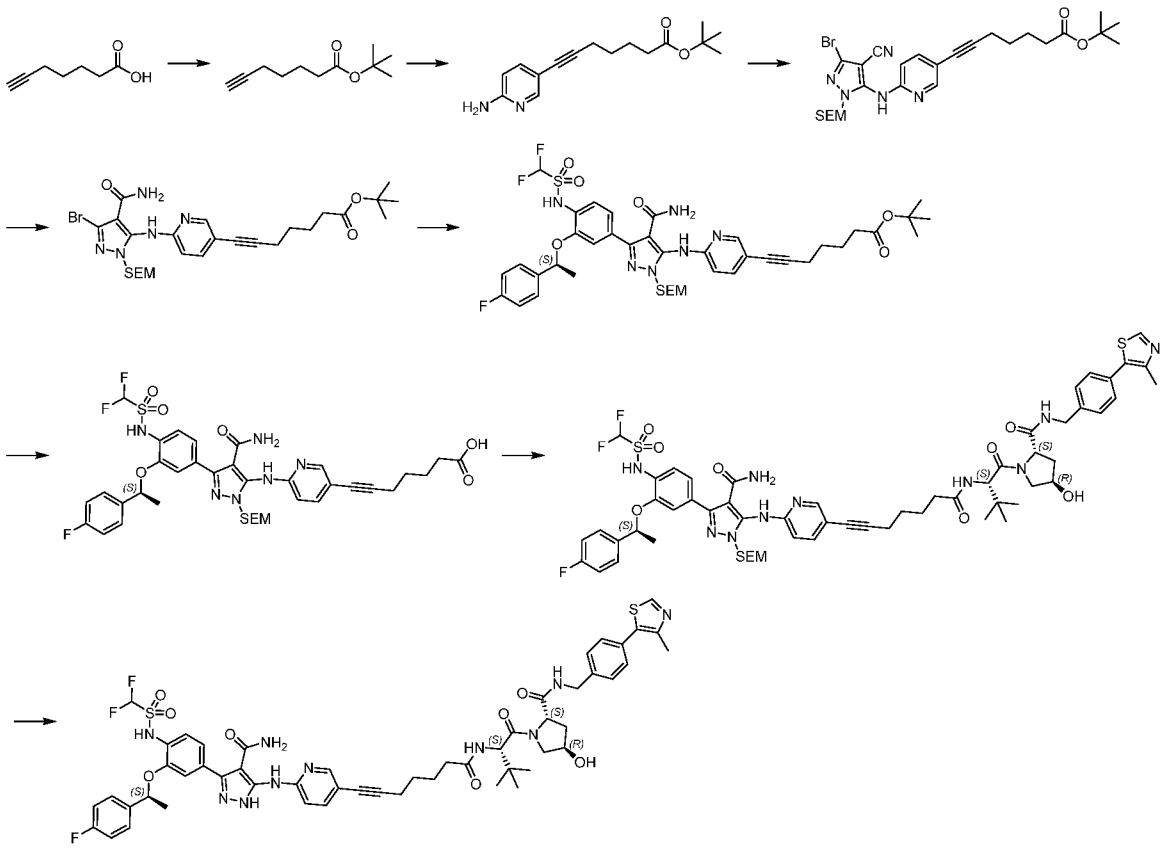
Step 7: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({1-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methyl]-1H-pyrazol-3-yl} amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide

A mixture of 4-{[3-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)-1H-pyrazol-1-yl]methyl}benzoic acid (200 mg, 0.25 mmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, 128 mg, 0.28 mmol), HATU (123 mg, 0.33 mmol) and Et_3N (104 µL, 0.75 mmol) in DMF (2.5 mL) was stirred at RT overnight. The mixture was poured into water (60 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (30 mL) and concentrated. The residue was purified by flash chromatography (0-10% MeOH:DCM) to afford the title compound (223 mg, 74%) as a white solid. LCMS (Method H): 2.63 min, m/z 1214.2 $[M+H]^+$.

Step 8: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({1-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methyl]-1H-pyrazol-3-yl} amino)-1H-pyrazole-4-carboxamide

A solution of 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({1-[(4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}phenyl)methyl]-1H-pyrazol-3-yl}amino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (220 mg, 0.18 mmol) in TFA:DCM (1:40, 4.1 mL) was stirred at RT for 1 h. The pH was adjusted to ~8 with sat. aq. $NaHCO_3$, then the mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC (method A) to afford the title compound (50.6 mg, 26%) as a white solid. LCMS (method H): 2.20 min, m/z 1084.0 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): 10.51 (s, 1H), 8.98 (s, 1H), 8.60 (t, J = 6.2 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.71 (s, 1H), 7.59-7.54 (m, 2H), 7.40-7.37 (m, 5H), 7.31 (s, 2H), 7.19-7.06 (m, 4H), 7.01 (t, J = 53.7 Hz, 1H), 6.46 (s, 1H), 5.62 (q, J = 6.1 Hz, 1H), 5.25 (s, 1H), 5.14 (d, J = 3.6 Hz, 1H), 4.74 (d, J = 9.2 Hz, 1H), 4.47-4.37 (m, 3H), 4.23 (dd, J = 15.9, 5.5 Hz, 1H), 3.73 (s, 2H), 2.44 (s, 3H), 2.08-2.00 (m, 1H), 1.95-1.87 (m, 1H), 1.57 (d, J = 6.1 Hz, 3H), 1.02 (s, 9H).

Compound 1047: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl]-5-{[5-(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hex-1-yn-1-yl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide



Step 1: tert-butyl hept-6-ynoate

A mixture of hept-6-ynoic acid (4.0 g, 31.7 mmol), t-BuOH (5.86 g, 79.2 mmol) and DCC (9.78 g, 47.5 mmol) in DCM (20 mL) was stirred at RT overnight. The mixture was concentrated and the residue was purified by flash chromatography (10:1 PE:EtOAc) to afford the title compound (5.7 g, 98%) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6): 2.74 (t, J = 2.7 Hz, 1H), 2.18-2.13 (m, 4H), 1.62-1.52 (m, 2H), 1.45 (dtd, J = 8.4, 7.0, 1.1 Hz, 2H), 1.40 (s, 9H).

Step 2: tert-butyl 7-(6-aminopyridin-3-yl)hept-6-ynoate

A mixture of tert-butyl hept-6-ynoate (500 mg, 2.74 mmol), CuI (156 mg, 0.82 mmol) and $Pd(PPh_3)_2Cl_2$ (192 mg, 0.27 mmol) in DMF (3 mL) and Et_3N (3 mL) was stirred overnight at 100 °C under N_2. The reaction mixture was concentrated under, and the residue was purified

by flash chromatography (DCM:MeOH, 20:1) to afford the title product (150 mg, 20%) as a brown oil. LCMS (method A): 2.62 min, m/z: 275.2 $[M+H]^+$.

Step 3: tert-butyl 7-{6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}hept-6-ynoate

A mixture of tert-butyl 7-(6-aminopyridin-3-yl)hept-6-ynoate (650 mg, 2.36 mmol), 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 1.07 g, 2.83 mmol), $Pd_2(dba)_3$ (215 mg, 0.24 mmol), Xantphos (204 mg, 0.35 mmol) and Cs_2CO_3 (2.30 g, 7.08 mmol) in DME (10 mL) was stirred overnight at 100 °C under N_2. Once cooled, the mixture was diluted with water and extracted with EtOAc (2 x 3 L). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (PE:EtOAc, 5:1) to afford the title product (600 mg, 38%) as a yellow solid. LCMS (Method A): 6.88 min; m/z: 576.8 $[M+H]^+$.

Step 4: tert-butyl 7-{6-[(3-bromo-4-carbamoyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}hept-6-ynoate

A mixture of tert-butyl 7-{6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}hept-6-ynoate (600 mg, 1.04 mmol) and Parkins' catalyst (60 mg, 0.26 mmol) in dioxane (4 mL) and H_2O (3 mL) was stirred overnight at 100 °C overnight under N_2. The mixture was concentrated, diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title product (200 mg, 32%) as a yellow solid. LCMS (Method A): 5.72 min, m/z: 594.8 $[M+H]^+$.

Step 5: tert-butyl 7-[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]hept-6-ynoate

A mixture of tert-butyl 7-{6-[(3-bromo-4-carbamoyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}hept-6-ynoate (200 mg, 0.34 mmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C5**, 159 mg, 0.34 mmol), K_2CO_3 (139 mg, 1.01 mmol) and $Pd(dppf)Cl_2$ (27.8 mg, 0.03 mmol) in 80% aq. 1,4-dioxane (8 mL) was stirred at 100 °C. After 16 h, the mixture was concentrated, diluted with H_2O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by prep-TLC (DCM:MeOH, 20:1) to afford the title product (200 mg, 69%) as a yellow solid. LCMS (Method A): 6.23 min, m/z: 858.0 $[M+H]^+$.

Step 6: 7-[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]hept-6-ynoic acid

A solution of tert-butyl 7-[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]hept-6-ynoate (180 mg, 0.21 mmol) in MeOH (2 mL) and 2 N NaOH (2 mL) was stirred at 60 °C for 6 h. The mixture was acidification to pH 5 with 1M HCl, then extracted with DCM (3 x 50 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (DCM:MeOH, 20:1) to afford the title product (160 mg, 95%) as a yellow solid. LCMS (method A): 4.93 min; 801.9 $[M+H]^+$.

Step 7: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[5-(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hex-1-yn-1-yl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

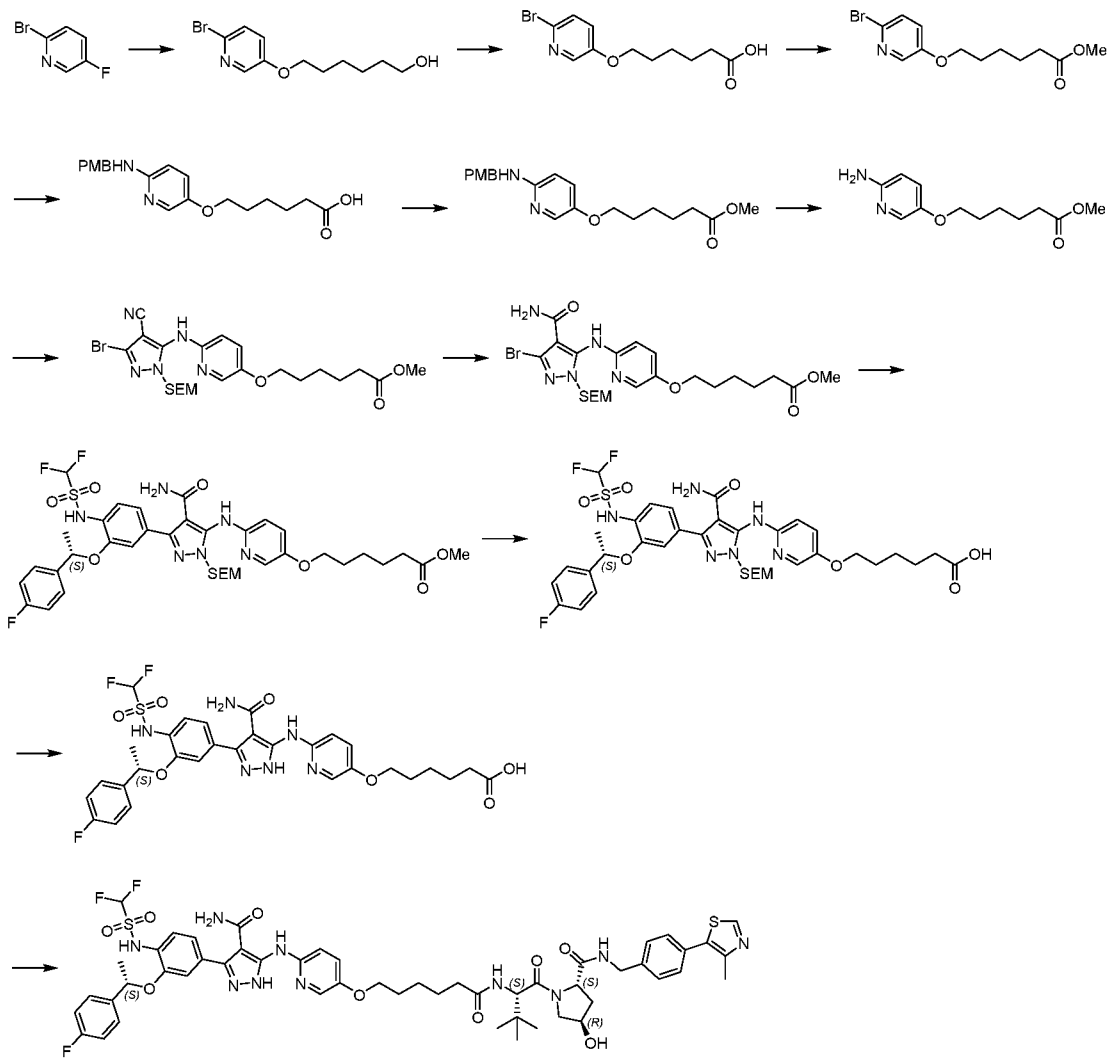
A mixture of (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (94.5 mg, 0.22 mmol), Et_3N (80.6 mg, 0. 80 mmol) and HATU (113 mg, 0.2995 mmol) in MeCN (4 mL) was stirred at RT for 5 min before 7-[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]hept-6-ynoic acid (160 mg, 0.20 mmol) was added. The mixture was stirred at RT for 3 h, then diluted with water and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by reverse-phase chromatography to afford the title product (30 mg, 14%) as a yellow solid. LCMS (method A): 5.27 min; m/z: 608.2 $[M+2H]^{2+}$.

Step 8: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[5-(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hex-1-yn-1-yl)pyridin-2-yl]amino}-1H-pyrazole-4-carboxamide

A solution of 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-{[5-(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hex-1-yn-1-yl)pyridin-2-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carboxamide (30 mg, 0.02 mmol) in HCOOH

(2 mL) was stirred at RT for 0.5 h. The mixture was concentrated under reduced pressure and the residue neutralized to pH 7-8 with sat. aq. Na_2CO_3. The mixture was purified by reverse-phase chromatography to afford the title product (6.8 mg, 25%) as a yellow solid. LCMS (method A): 3.44 min; m/z: 542.4 $[M+2H]^{2+}$. ^1H NMR (400 MHz, MeOD-d_4): 8.84 (s, 1H), 8.26 (s, 1H), 7.62 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.53-7.44 (m, 4H), 7.41 (d, *J* = 15.7 Hz, 4H), 7.12-7.03 (m, 4H), 6.67 (t, *J* = 53.2 Hz, 1H), 5.54 (q, *J* = 6.4 Hz, 1H), 4.64 (s, 1H), 4.60-4.47 (m, 4H), 4.33 (d, *J* = 15.3 Hz, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 11.0, 3.9 Hz, 1H), 2.45 (s, 5H), 2.33 (q, *J* = 7.0 Hz, 2H), 2.24-2.16 (m, 2H), 2.08 (ddd, *J* = 13.3, 9.0, 4.5 Hz, 1H), 1.78 (dd, *J* = 9.1, 6.2 Hz, 2H), 1.67 (d, *J* = 6.4 Hz, 3H), 1.64-1.59 (m, 2H), 1.46-1.36 (m, 3H), 1.04 (s, 9H), 0.89 (s, 4H).

Compound 1048: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]
-5-({5-[(5-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}pentyl)oxy]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide



Step 1: 6-[(6-bromopyridin-3-yl)oxy]hexan-1-ol

To a 0 °C solution of hexane-1,6-diol (20.0 g, 170 mmol) in DMF (100 mL) was added NaH (4.51 g, 113 mmol) under N_2. The reaction was stirred for 30 min before 2-bromo-5-fluoropyridine (10 g, 56.8 mmol) was added. The reaction was stirred at RT for 8 h, then quenched with sat. aq. NH_4Cl and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (10-30% EtOAc/PE) to afford the title compound (8.00 g, 52%). LCMS (Method A): 3.04 min, m/z: 274.0 & 276.0 $[M+H]^+$.

Step 2: 6-[(6-bromopyridin-3-yl)oxy]hexanoic acid

To a solution of 6-[(6-bromopyridin-3-yl)oxy]hexan-1-ol (8 g, 29.1 mmol) in MeCN (80 mL) were added $NaIO_4$ (18.5 g, 87.3 mmol), CrO_3 (290 mg, 2.91 mmol) and H_2O (20 mL), and the

reaction was stirred at RT for 2 h. Once complete, the mixture was diluted with water and extracted with EtOAc. The organic phase as dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (10-30% EtOAc:PE) to afford the title compound (7.00 g, 84%). LCMS (Method A): 2.99 min, m/z: 288.0 & 290.0 $[M+H]^+$.

Step 3: methyl 6-[(6-bromopyridin-3-yl)oxy]hexanoate

To a stirred solution of 6-[(6-bromopyridin-3-yl)oxy]hexanoic acid (7 g, 24.2 mmol) in MeOH (70 mL) was added conc. H_2SO_4 (3.55 g, 36.3 mmol), and the reaction was stirred at 60 °C for 2 h under N_2. The mixture was concentrated and basified to pH 8 with sat. aq. Na_2CO_3. The residue was purified by flash chromatography (10-30% EtOAc/PE) to afford the title compound (6.10 g, 83%). LCMS (Method A): 3.55 min, m/z: 302.0 & 304.0 $[M+H]^+$.

Step 4: 6-[(6-{[(4-methoxyphenyl)methyl]amino}pyridin-3-yl)oxy]hexanoic acid

To a solution of methyl 6-[(6-bromopyridin-3-yl)oxy]hexanoate (3 g, 9.92 mmol) in 1,4-Dioxane (30 mL) were added 1-(4-methoxyphenyl)methanamine (2.03 g, 14.8 mmol), $Pd_2(dba)_3$ (908 mg, 992 µmol), X-Phos (943 mg, 1.98 mmol) and t-BuOK (1.65 g, 14.8 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. Once completed, the mixture was diluted with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated to afford the title compound (5.7 g, 167%). LCMS (Method C): 5.53 min, m/z: 821.9 $[M+H]^+$.

Step 5: methyl 6-[(6-{[(4-methoxyphenyl)methyl]amino}pyridin-3-yl)oxy]hexanoate

To a solution of 6-[(6-{[(4-methoxyphenyl)methyl]amino}pyridin-3-yl)oxy]hexanoic acid (5 g, 14.5 mmol) in MeOH (10 mL) was added H_2SO_4 (2.84 g, 29.0 mmol), and the reaction was stirred at 60 °C for 2 h. The mixture was concentrated, then the residue was diluted with water and neutralised with sat. aq. $NaHCO_3$. The residue was purified by flash chromatography (30% EtOAc/PE) to afford the title compound (1.4 g, 27%). LCMS (Method A): 2.59 min, m/z: 359.2 $[M+H]^+$.

Step 6: methyl 6-[(6-aminopyridin-3-yl)oxy]hexanoate

To a solution of methyl 6-[(6-{[(4-methoxyphenyl)methyl]amino}pyridin-3-yl)oxy]hexanoate (1.4 g, 3.90 mmol) in DCM (10 mL) was added TFA (8 mL), and the reaction was stirred at RT for 2 h. The mixture was concentrated, and the residue was purified by flash chromatography (5% MeOH/DCM) to afford the title compound (410 mg, 44%). LCMS (Method A): 1.20 min, m/z: 239.1 $[M+H]^+$.

Step 7: methyl 6-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl) amino]pyridin-3-yl}oxy)hexanoate

To a solution of methyl 6-[(6-aminopyridin-3-yl)oxy]hexanoate (350 mg, 1.46 mmol) in 1,4-Dioxane (10 mL) were added $Pd_2(dba)_3$ (133 mg, 146 µmol), 3,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 667 mg, 1.75 mmol), Xantphos (168 mg, 292 µmol) and Cs_2CO_3 (951 mg, 2.92 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. The mixture was concentrated, and the residue was purified by flash chromatography (5-15% EtOAc/PE) to afford the title compound (480 mg, 61%) LCMS (Method A): 4.14 min, 538.0 & 540.0 $[M+H]^+$.

Step 8: methyl 6-({6-[(3-bromo-4-carbamoyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)hexanoate

To a solution of methyl 6-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)hexanoate (420 mg, 779 µmol) in 60% aq. 1,4-Dioxane (6.5 mL) was added Parkins' catalyst (42 mg, 779 µmol), and the reaction was stirred at 100 ° C for 2 h under N_2. The mixture was concentrated, and the residue was purified by flash chromatography (25-50% EtOAc/PE) to afford the title compound (350 mg, 81%). LCMS (Method A): 3.81 min, m/z: 542.0 & 544.0 $[M+H]^+$.

Step 9: methyl 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}hexanoate

To a solution of methyl 6-({6-[(3-bromo-4-carbamoyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)hexanoate (300 mg, 539 µmol) in 75% aq. 1,4-Dioxane (8 mL) were added 1-fluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl}methanesulfonamide (**Intermediate C11**, 366 mg, 808 µmol), $Pd(dppf)Cl_2$ (39.1 mg, 53.9 µmol) and K_2CO_3 (222 mg, 1.61 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. Once cooled, the mixture was diluted with water and extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated, and purified by flash chromatography (50% EtOAc/PE) to afford the title compound (406 mg, 92%).

Step 10: 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} hexanoic acid

To a stirred solution of methyl 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}hexanoate (400 mg, 487 µmol) in MeOH (4 mL) was added 1M NaOH (3 mL) and the reaction was stirred at 60 °C for 2 h. The mixture was concentrated and acidified to pH = 5 with 1M HCl. The aqueous mixture was then extracted with MeOH/DCM = 1/9, and the organic phase was concentrated and purified by flash chromatography (5% MeOH/DCM) to afford the title compound (250 mg, 64%). LCMS (Method A): 4.92 min, m/z: 808.7, m/z $[M+H]^+$.

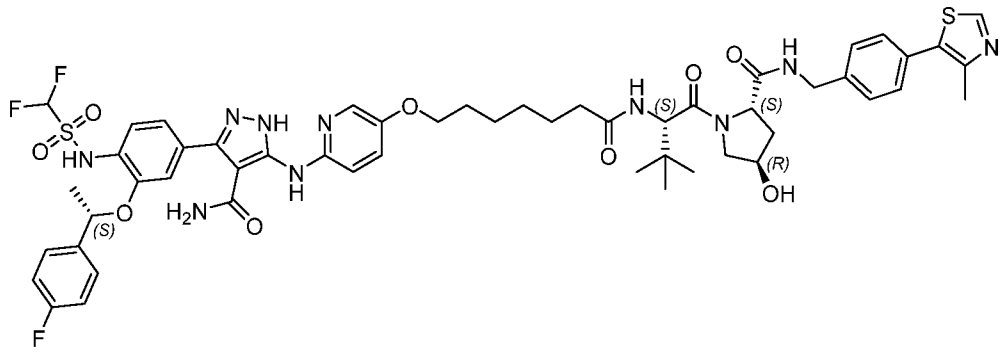
Step 11: 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}hexanoic acid

A solution of 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}hexanoic acid (40 mg, 49.5 µmol) in HCOOH (3 mL) was stirred at rt for 2 h. The mixture was then adjusted to pH = 6 with sat. aq. $NaHCO_3$ and extracted with DCM/MeOH = 9:1. The organic phase was concentrated, and the residue was purified by Prep-TLC to afford the title compound (15 mg, 45%). LCMS (Method A): 3.93 min, m/z: 677.9 $[M+H]^+$.

Step 12: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(5-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}pentyl)oxy]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide

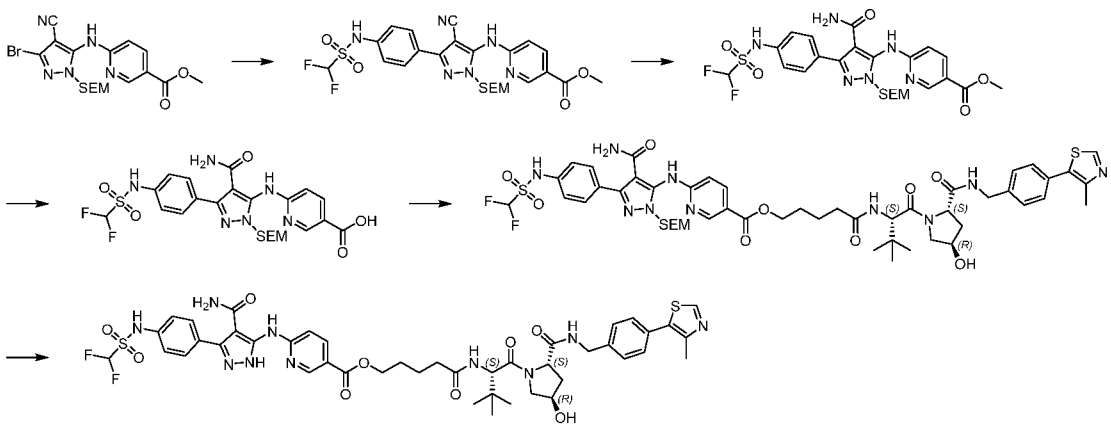
To a solution of 6-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}hexanoic acid (15 mg, 22.1 µmol) in DMF (2 mL) were added (2S,4R)-1-[(2S)-2-amino-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, 10.0 mg, 22.1 µmol), HATU (10.9 mg, 28.7 µmol) and DIPEA (8.56 mg, 66.3 µmol), and the reaction was stirred at RT for 2 h. The miture was diluted with water and extracted with DCM/MeOH = 9:1. The organic phase was concentrated, and the residue was purified by Prep-TLC (MeOH/DCM = 5%) to afford the title compound (6 mg, 25%). LCMS (Method A): 3.13 min, m/z: 1089.3 $[M+H]^+$. ^1H HNMR (400 MHz, DMSO-d_6): 13.07 (s, 1H), 12.71 (s, 1H), 10.54 (s, 1H), 9.71 (s, 1H), 9.23 (s, 1H), 8.98 (s, 1H), 8.56 (d, J = 6.3 Hz, 2H), 7.88 (d, J = 10.3 Hz, 3H), 7.57 (s, 2H), 7.40 (q, J = 8.2 Hz, 6H), 7.18 (s, 2H), 6.90 (s, 1H), 6.70 (d, J = 12.2 Hz, 1H), 5.32 (s, 1H), 5.14 (d, J = 3.6 Hz, 1H), 4.55 (d, J = 9.4 Hz, 1H), 4.45-4.40 (m, 2H), 4.35 (s, 1H), 4.26-4.20 (m, 1H), 3.96 (s, 2H), 2.73 (s, 2H), 2.44 (s, 3H), 2.30 (s, 2H), 2.18 (t, J = 7.3 Hz, 2H), 2.03-1.99 (m, 2H), 1.70 (s, 2H), 1.57 (s, 2H), 1.35 (s, 3H), 1.27 (s, 2H), 0.94 (s, 9H).

Compound 1059: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-({5-[(6-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}hexyl)oxy]pyridin-2-yl}amino)-1H-pyrazole-4-carboxamide



The title compound (8.0 mg, 25%) was prepared in an analogous manner to **Compound 1048** utilizing heptane-1,7-diol in **Step 1**. LCMS (Method A): 2.11 min, m/z: 552.3 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 12.67 (s, 1H), 10.51 (s, 1H), 9.71 (s, 1H), 9.26 (s, 1H), 8.98 (s, 1H), 8.56 (s, 1H), 7.88 (d, J = 11.7 Hz, 2H), 7.56 (s, 3H), 7.39 (t, J = 8.4 Hz, 8H), 7.17 (s, 2H), 7.08 (s, 2H), 5.63 (s, 1H), 5.12 (s, 1H), 4.55 (d, J = 9.2 Hz, 1H), 4.41 (d, J = 9.3 Hz, 2H), 4.35 (s, 1H), 4.23 (s, 1H), 3.96 (s, 2H), 3.66 (s, 2H), 2.44 (s, 2H), 2.22-2.00 (m, 5H), 1.68 (s, 2H), 1.58-1.54 (m, 3H), 1.40 (s, 6H), 0.93 (s, 9H).

Compound 1049: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate



Step 1: methyl 6-({4-cyano-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate

A mixture of 1,1-difluoro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide (**Intermediate C17**, 1.0 g, 3.00 mmol), methyl 6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate (1.35 g, 3.00 mmol), Na_2CO_3 (953 mg, 9.00 mmol) and $Pd(dppf)Cl_2$ (219 mg, 300 µmol) in 80% aq. dioxane (3.0 mL) was stirred overnight at 100 °C under N_2. The mixture was concentrated, and the residue was purified by Prep-TLC (DCM/MeOH = 20/1) to afford the title compound (1.1 g, 64%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 579.0, $[M+H]^+$.

Step 2: methyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate

A Mixture of methyl 6-({4-cyano-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate (1.1 g, 1.90 mmol) and Parkins'catalyst (81.6 mg, 0.19 mmol) in 80% aq. Dioxane (5 mL) was heated at reflux overnight. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to afford the title compound (350 mg, 31%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 597.0 $[M+H]^+$.

Step 3: 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylic acid

A mixture of methyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate (400 mg, 0.67 mmol) and NaOH (26.7 mg, 0.67 mmol) in MeOH (10 mL) was heated at 50 °C for 4 h. Once cooled, the mixture was concentrated and the residue was taken up in water. The aqueous mixture was acidified with 1M HCl and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated to afford the title compound (310 mg, 80%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 583.0 $[M+H]^+$.

Step 4: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl} amino)pyridine-3-carboxylate

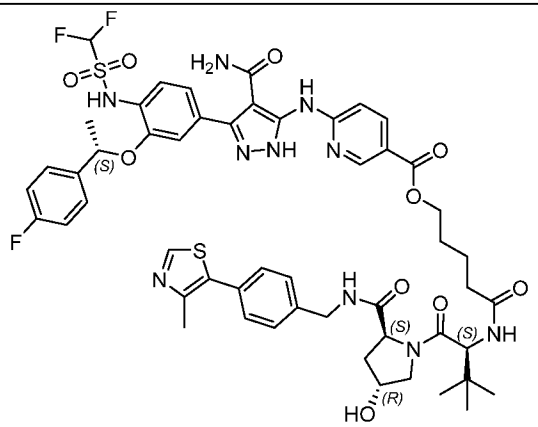
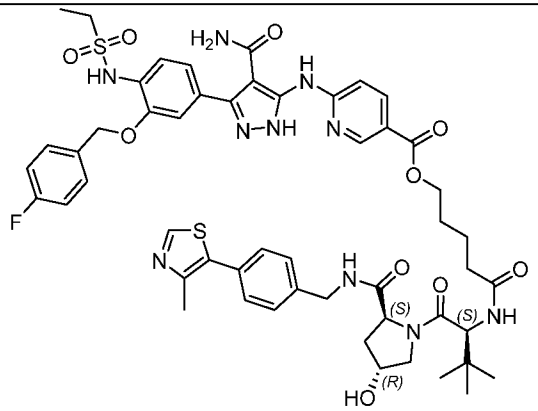
A mixture of 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl) ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylic acid (300 mg, 514 µmol), Cs_2CO_3 (167 mg, 514 µmol) and (2S,4R)-1-[(2S)-2-(5-bromopentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (305 mg, 514 µmol) in MeCN (5 mL) was stirred overnight at 50 °C under N_2. The mixture was concentrated, and the residue was poured into water. The aqueous mixture was extracted with EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to afford the title compound (150 mg, 27%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 1096.0 $[M+H]^+$.

Step 5: 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate

A solution of 4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate (50 mg, 45.6 µmol) in 4M HCl/Dioxane (5 mL) was stirred at RT for 20 min. The mixture was concentrated and the residue was poured into water. The aqueous mixture was extracted with EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by HPLC (method?) to afford the title compound (8 mg, 18%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 966.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.81 (s, 1H), 10.09 (s, 1H), 8.97 (s, 1H), 8.72 (d, *J* = 2.3 Hz, 1H), 8.60 (t, *J* = 6.1 Hz, 1H), 8.22-8.16 (m, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.93 (d, *J* = 9.4 Hz, 1H), 7.38 (dd, *J* = 9.4, 7.2 Hz, 4H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.09 (s, 1H), 6.89 (d, *J* = 3.1 Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 5.17 (d, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.46-4.40 (m, 2H), 4.34 (s, 2H), 4.23 (dd, *J* = 8.3, 4.3 Hz, 3H), 3.97 (t, *J* = 6.6 Hz, 1H), 3.66 (d, *J* = 5.1 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H), 2.33 (d, *J* = 1.9 Hz, 1H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.89 (td, *J* = 8.5, 4.2 Hz, 1H), 1.66 (d, *J* = 9.8 Hz, 2H), 1.50 (d, *J* = 6.6 Hz, 1H), 0.93 (s, 9H).

Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for the synthesis of **Compound 1049**, utilizing the indicated **Intermediate C** in **Step 1**.

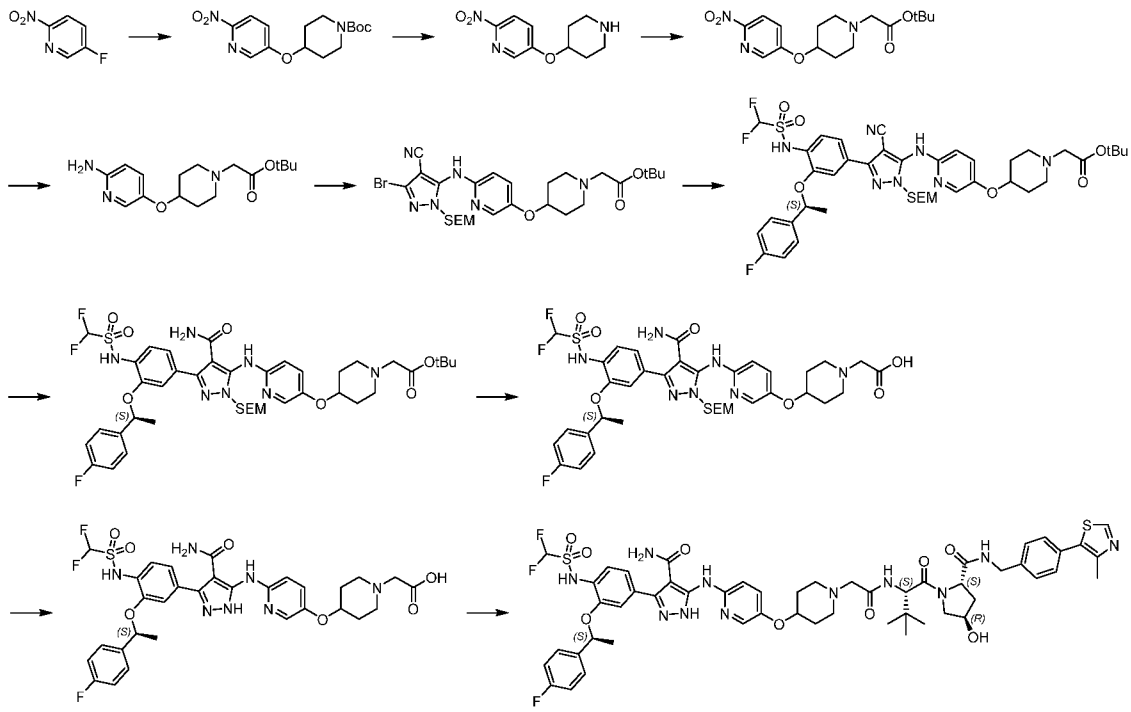
Table 34: Compounds 1051-1053, 1055, 1056 and 1060

Compound No.	Structure	Compound Name and Analytical Data
Compound 1051		4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl]-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate From **Intermediate C11**. LCMS (method A): 3.25 min, m/z: 552.3 $[M+2H]^{2+}$. ^1H NMR (400 MHz, $CDCl_3$): 10.39 (s, 1H), 8.96 (s, 1H), 8.69 (s, 1H), 8.27-8.17 (m, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.34 (d, *J* = 3.8 Hz, 8H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 3H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.51-6.17 (m, 2H), 5.49 (d, *J* = 6.5 Hz, 1H), 5.35 (s, 1H), 4.74 (t, *J* = 7.8 Hz, 1H), 4.56 (d, *J* = 6.0 Hz, 3H), 4.34-4.28 (m, 3H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.66-3.60 (m, 1H), 2.51 (s, 3H), 2.34-2.28 (m, 3H), 2.26-2.15 (m, 3H), 1.99 (dd, *J* = 13.2, 6.7 Hz, 3H), 1.70 (d, *J* = 6.2 Hz, 6H), 1.33 (s, 2H), 0.94 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 4H).
Compound 1052		4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(4-fluorophenyl)methoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate From **Intermediate C1**. LCMS (Method A): 3.13 min, m/z: 534.2 $[M+2H]^{2+}$. ^1H NMR (400 MHz, DMSO-d_6): 13.06 (s, 1H), 10.05 (s, 1H), 9.24 (s, 1H), 9.05 (s, 1H), 8.81 (s, 1H), 8.63 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.11-7.96 (m, 2H), 7.71 (ddd, *J* = 8.6, 5.7, 2.9 Hz, 2H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 5H), 7.32 (s, 3H), 6.24 (s, 1H), 5.31 (s, 2H), 5.20 (d, *J* = 3.6 Hz, 1H), 4.62 (d, *J* = 9.3 Hz, 1H), 4.50 (ddd, *J* = 10.7, 6.6, 3.2 Hz, 2H), 4.41 (d, *J* = 4.8 Hz, 1H), 4.32 (s, 3H), 3.74 (d, *J* = 4.5 Hz, 2H), 3.14 (q, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 2.46-2.36 (m, 2H), 2.33-2.23 (m, 2H), 2.11 (dd, *J* = 12.7, 7.7 Hz, 1H), 1.96 (td, *J* = 8.4, 4.4 Hz, 1H), 1.74 (dq, *J* = 13.0, 7.0 Hz, 4H), 1.23 (s, 3H), 1.01 (s, 9H).

Compound 1053		4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)phenyl]-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate From **Intermediate C18**. LCMS (Method A): 2.91 min, m/z: 492.2 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (s, 1H), 9.81 (s, 1H), 8.98 (s, 1H), 8.74 (s, 1H), 8.56 (t, J = 6.1 Hz, 1H), 8.17 (d, J = 9.5 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 10.9 Hz, 1H), 7.48 (q, J = 8.9, 8.3 Hz, 2H), 7.40 (q, J = 8.4 Hz, 5H), 7.15 (s, 1H), 5.13 (s, 1H), 4.55 (d, J = 9.4 Hz, 1H), 4.43 (td, J = 8.1, 7.4, 4.0 Hz, 2H), 4.35 (dq, J = 6.5, 3.1 Hz, 1H), 4.28-4.23 (m, 2H), 3.66 (t, J = 3.4 Hz, 2H), 3.17 (s, 1H), 2.44 (s, 3H), 2.34 (dt, J = 14.2, 6.7 Hz, 1H), 2.21 (dt, J = 11.4, 5.7 Hz, 1H), 2.06-1.99 (m, 1H), 1.90 (td, J = 8.5, 4.3 Hz, 1H), 1.73-1.60 (m, 4H), 1.27-1.21 (m, 2H), 0.94 (s, 9H).
Compound 1055		4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(4-fluorophenyl)methoxy]phenyl]-1H-pyrazol-5-yl}amino)pyridine-3-carboxylate From **Intermediate C1a**. LCMS (Method A): 3.29 min, m/z: 545.3 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (s, 1H), 10.55 (s, 1H), 8.97 (s, 1H), 8.74 (s, 1H), 8.55 (t, J = 6.3 Hz, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.60 (dd, J = 8.4, 5.6 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.40 (d, J = 7.1 Hz, 4H), 7.37 (s, 1H), 7.24 (q, J = 8.0, 7.3 Hz, 3H), 6.94 (t, J = 52.7 Hz, 1H), 5.20 (s, 2H), 5.11 (s, 1H), 4.55 (d, J = 9.4 Hz, 1H), 4.46-4.39 (m, 2H), 4.35 (s, 1H), 4.29-4.21 (m, 3H), 3.66 (s, 3H), 2.67 (s, 1H), 2.54 (s, 3H), 2.44 (s, 3H), 2.34 (d, J = 14.3 Hz, 2H), 2.21 (q, J = 8.2, 7.7 Hz, 1H), 2.03 (t, J = 10.5 Hz, 2H), 1.90 (s, 1H), 1.67 (s, 5H), 0.94 (s, 9H), 0.92 (s, 1H).

Compound 1056		4-{[(2S)-1-[(2S,4S)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-[(4-carbamoyl-3-{4-ethanesulfonamido-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl}-1H-pyrazol-5-yl)amino]pyridine-3-carboxylate From **Intermediate C11a**. LCMS (Method A): 3.441 min; m/z: 542.4 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, MeOD-d_4): 8.84 (s, 1H), 8.26 (s, 1H), 7.62 (dd, J = 8.6, 2.1 Hz, 1H), 7.53-7.44 (m, 4H), 7.41 (d, J = 15.7 Hz, 4H), 7.12-7.03 (m, 4H), 6.67 (t, J = 53.2 Hz, 1H), 5.54 (q, J = 6.4 Hz, 1H), 4.64 (s, 1H), 4.60-4.47 (m, 4H), 4.33 (d, J = 15.3 Hz, 1H), 3.91 (d, J = 11.0 Hz, 1H), 3.80 (dd, J = 11.0, 3.9 Hz, 1H), 2.45 (s, 5H), 2.33 (q, J = 7.0 Hz, 2H), 2.24-2.16 (m, 2H), 2.08 (ddd, J = 13.3, 9.0, 4.5 Hz, 1H), 1.78 (dd, J = 9.1, 6.2 Hz, 2H), 1.67 (d, J = 6.4 Hz, 3H), 1.64-1.59 (m, 2H), 1.46-1.36 (m, 3H), 1.04 (s, 9H), 0.89 (s, 4H).
Compound 1060		4-{[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}butyl 6-{[4-carbamoyl-3-(4-ethanesulfonamidophenyl)-1H-pyrazol-5-yl]amino}pyridine-3-carboxylate From **Intermediate C16**. LCMS (Method A): 1.67 min, m/z: 472.2 $[M+2H]^{2+}$. ^{1}H NMR (400 MHz, MeOD): 8.88 (s, 1H), 7.76 (s, 1H), 7.56-7.44 (m, 5H), 7.41 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.12-7.04 (m, 3H), 5.57 (d, J = 6.4 Hz, 1H), 4.35 (d, J = 15.5 Hz, 2H), 4.29 (s, 3H), 3.96 (d, J = 11.1 Hz, 1H), 3.84 (dd, J = 11.0, 3.9 Hz, 1H), 2.55 (t, J = 6.9 Hz, 2H), 2.48 (s, 3H), 2.39 (dd, J = 8.5, 4.5 Hz, 2H), 2.25 (dd, J = 12.8, 7.6 Hz, 1H), 2.12 (td, J = 9.0, 4.6 Hz, 1H), 1.83 (p, J = 7.5 Hz, 2H), 1.71 (d, J = 6.4 Hz, 5H), 1.42 (d, J = 11.3 Hz, 1H), 1.06 (s, 9H).

Compound 1050: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy] phenyl]-5-[(5-{[1-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)piperidin-4-yl]oxy} pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide



Step 1: tert-butyl 4-[(6-nitropyridin-3-yl)oxy]piperidine-1-carboxylate

A mixture of 5-fluoro-2-nitropyridine (2.0 g, 14.0 mmol), NaH (671 mg, 28.0 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (2.81 g, 14.0 mmol) in THF (10 mL) was stirred at 0 °C under N_2 overnight. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to afford the title compound (2.6 g, 58%) as a yellow oil.

Step 2: 2-nitro-5-(piperidin-4-yloxy)pyridine

A solution of tert-butyl 4-[(6-nitropyridin-3-yl)oxy]piperidine-1-carboxylate (2.6 g, 8.04 mmol) in 4M HCl/dioxane (3ml) was stirred at RT for 1 h. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to afford the title compound (2.0 g, >100%) as a yellow oil.

Step 3: tert-butyl 2-{4-[(6-nitropyridin-3-yl)oxy]piperidin-1-yl}acetate

A mixture of 2-nitro-5-(piperidin-4-yloxy)pyridine (2.2 g, 9.89 mmol), Cs_2CO_3 (3.22 g, 9.89 mmol) and *tert*-butyl bromoacetate (1.93 g, 9.89 mmol) in MeCN (20 mL) was heated at reflux overnight. The mixture was concentrated, diluted with water, and extracted with EtOAc. The organic phase was dried over Na2SO4 and concentrated. The residue was purified by flash chromatography (50:1 to 10:1 PE:EtOAc) to afford the title compound (2.3 g, 69%). LCMS (Method A): 4.25 min, m/z: 338.0 $[M+H]^+$.

Step 4: tert-butyl 2-{4-[(6-aminopyridin-3-yl)oxy]piperidin-1-yl}acetate

A mixture of tert-butyl 2-{4-[(6-nitropyridin-3-yl)oxy]piperidin-1-yl}acetate (2.3 g, 6.81 mmol) and zinc (2.22 g, 34.0 mmol) in sat. aq. NH_4Cl (5mL) and MeOH (50 mL) was stirred at 60 °C under N_2 overnight. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (PE/EA 100:1 to 10:1) to afford the title compound (2.1 g, 100%) as a yellow oil. LCMS (method A): 4.25 min, m/z: 308.4 $[M+H]^+$.

Step 5: tert-butyl 2-[4-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)piperidin-1-yl]acetate

A mixture of tert-butyl 2-{4-[(6-aminopyridin-3-yl)oxy]piperidin-1-yl}acetate (2.0 g, 6.50 mmol), AcOK (1.91 g, 19.5 mmol) $Pd_2(dba)_3$ (595 mg, 650 µmol), Xantphos (752 mg, 1.30 mmol) and 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile (**Intermediate B1'**, 2.47 g, 6.50 mmol) in dioxane (30 mL) was heated overnight at 100 °C under N_2. The mixture was concentrated, and the residue was partitioned between water and EtOAc. The organic phase was separated, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (100:1 to 50:1 DCM:MeOH) to afford the title compound (1.3 g, 33%). LCMS (Method A): 4.00 min, m/z: 608.0 $[M+H]^+$.

Step 6: tert-butyl 2-(4-{[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}piperidin-1-yl)acetate

A mixture of tert-butyl 2-[4-({6-[(3-bromo-4-cyano-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl)amino]pyridin-3-yl}oxy)piperidin-1-yl]acetate (350 mg, 576 µmol), 1,1-difluoro-N-{2-[(1S)-1-(4-fluorophenyl)ethoxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl} methanesulfonamide (**Intermediate C5**, 271 mg, 576 µmol), Na_2CO_3 (182 mg, 1.72 mmol) and $Pd(dppf)Cl_2$ (42.1 mg, 57.6 µmol) in 80% aq. dioxane (2.5 mL) was stirred at 100 °C under N_2 overnight. The mixture was concentrated, and the residue was purified by Prep-TLC

(DCM/MeOH = 20/1) to afford the title compound (300 mg, 60%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 873.2 $[M+H]^+$.

Step 7: tert-butyl 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}piperidin-1-yl)acetate

A mixture of tert-butyl 2-(4-{[6-({4-cyano-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}piperidin-1-yl)acetate (300 mg, 344 µmol) and Parkins' catalyst (21.7 mg, 51.5 µmol) in 60% aq. dioxane (5 mL) was stirred at 100 °C under N_2 overnight. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to afford the title compound (230 mg, 75%) as a yellow solid. LCMS (method A): 3.50 min, m/z: 891.1 $[M+H]^+$.

Step 8: 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy} piperidin-1-yl)acetic acid

A mixture of tert-butyl 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino) pyridin-3-yl]oxy}piperidin-1-yl)acetate (100 mg, 112 µmol) and NaOH (4.47 mg, 112 µmol) in 50% aq. MeOH (6 mL) was stirred at 60 °C under N_2 for 2 h. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to afford the title compound (50 mg, 54%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 834.9 $[M+H]^+$.

Step 9: 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl) ethoxy]phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}piperidin-1-yl)acetic acid

A solution of 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluoro phenyl)ethoxy]phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-5-yl}amino)pyridin-3-yl] oxy}piperidin-1-yl)acetic acid (50mg, 59.9 µmol) in formic acid (3 mL) was stirred at RT under N_2 for 20 min. The mixture was concentrated, and the residue was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to afford the title compound (40 mg, 95%) as a yellow solid. LCMS (method A): 4.25 min, m/z: 704.2 $[M+H]^+$.

Step 10: 3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluorophenyl)ethoxy]phenyl]-5-[(5-{[1-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl) pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)piperidin-4-yl]oxy}pyridin-2-yl)amino]-1H-pyrazole-4-carboxamide

A mixture of 2-(4-{[6-({4-carbamoyl-3-[4-(difluoromethanesulfonamido)-3-[(1S)-1-(4-fluoro phenyl)ethoxy]phenyl]-1H-pyrazol-5-yl}amino)pyridin-3-yl]oxy}piperidin-1-yl)acetic acid (40 mg, 56.8 μmol), (2S,4R)-1-[(2S)-2-Amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride (**Intermediate 2**, How much?), Et_3N (28.7 mg, 284 μmol) and HATU (25.8 mg, 68.1 μmol) in MeCN (3 mL) was stirred at 0 °C under N_2 for 3 h. The mixture was concentrated, and the residue was purified by HPLC (method) to afford the title compound (10 mg, 16%) as a yellow solid. LCMS (method A): 4.25 min, 1117.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.97 (d, *J* = 7.4 Hz, 1H), 8.66 (t, *J* = 6.0 Hz, 1H), 7.97-7.88 (m, 2H), 7.75-7.68 (m, 1H), 7.63-7.57 (m, 1H), 7.54 (dt, *J* = 5.6, 3.3 Hz, 1H), 7.43-7.37 (m, 5H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.14 (td, *J* = 8.8, 4.1 Hz, 2H), 7.01 (s, 1H), 5.68-5.62 (m, 1H), 5.23 (d, *J* = 3.4 Hz, 1H), 4.56-4.48 (m, 1H), 4.44 (t, *J* = 8.1 Hz, 1H), 4.40-4.33 (m, 2H), 4.26 (dd, *J* = 15.5, 5.8 Hz, 1H), 3.70-3.57 (m, 2H), 2.79 (s, 2H), 2.44 (d, *J* = 3.7 Hz, 3H), 1.99 (dddd, *J* = 36.2, 30.2, 13.1, 8.1 Hz, 6H), 1.61 (d, *J* = 6.2 Hz, 2H), 1.53 (d, *J* = 6.3 Hz, 2H), 1.45 (d, *J* = 7.8 Hz, 1H), 0.94 (s, 9H).

BIOLOGY

IN VITRO ASSAY

Binding affinity of the test compounds for MLKL (full length), RIP1 and RIP3 was determined using the KINOMEscan™ technology developed by DiscoverX (USA; http://www.discoverx.com). The assay was conducted according to manufacturer instructions.

Protocol Description

Kinase assays. For most assays, kinase-tagged T7 phage strains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32 °C until lysis (90-150 minutes). The lysates were centrifuged (6,000 x g) and filtered (0.2 μm) to remove cell debris. The remaining kinases were produced in HEK293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT)

to remove unbound ligand and to reduce non-specific phage binding. Binding reactions to screen test compounds for kinase binding activity were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17 x PBS, 0.05% Tween 20, 6 mM DTT). All reactions were performed in polypropylene 384-well plates in a final volume of 20 µL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

Compound Handling

An 11-point 3-fold serial dilution of each test compound was prepared in 100% DMSO at 100x final test concentration and subsequently diluted to 1x in the assay (final DMSO concentration = 1%). Most K_Ds were determined using a compound top concentration = 30,000 nM. If the initial K_D determined was < 0.5 nM (the lowest concentration tested in the initial serial dilution), the measurement was repeated with a further 11 point 3-fold serial dilution starting at 3,000 nM.

Binding Constants (K_Ds)

K_D for each test compound was calculated with a standard dose-response curve using the Hill equation (equation (1)):

$$Response = Background + \frac{Signal - Background}{1 + (K_D{}^{Hill\ Slope} / Dose^{Hill\ Slope})} \quad (1)$$

The Hill Slope was set to -1.

Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

Refs:

• Fabian, M.A. et al. A small molecule-kinase interaction map for clinical kinase inhibitors. Nat. Biotechnol. 23, 329-336 (2005).

• Karaman, M.W. et al. A quantitative analysis of kinase inhibitor selectivity. Nat. Biotechnol. 26, 127-132 (2008).

• Hill, A.V. The possible effects of the aggregation of the molecules of hemoglobin on its dissociation curves. J. Physiol. (Lond.). 40, iv-vii (1910).

• Levenberg, K. A method for the solution of certain non-linear problems in least squares. Q. Appl. Math. 2, 164-168 (1944).

Table 35: Results of binding assay for compounds of the invention against MLKL, RIPK1 and RIPK3. Binding affinity is measured by the equilibrium dissociation constant (K_D). The smaller

the K_D value, the greater the binding affinity of the ligand for its target. Activity is provided as follows:

++++ = K_D < 10 nM

+++ = 10 nM < K_D < 1,000 nM

5 ++ = 1,000 nM < K_D < 30,000 nM

+ = K_D > 30,000 nM

Compound No	MLKL (K_D)	RIP1 (K_D)	RIP3 (K_D)
1	++++	+	+
2	+++	+	+
3	++	+	+
4	+++	+	+
5	+++	+	+
6	+++	+	+
7	++	+	+
8	+++	+	+
9	++++	+	+
10	+++	+	+
11	++++	+	+
12	+++	+	+
13	+++	+	+
14	++++	+	+
15	++++	+	+
16	+++	+	+
17	++++	+	+
18	++++	+	++
19	++++	+	+
20	++++	+	+
21	++++	+	+
22	++++	+	+
23	++++	+	+
24	++++	+	+
25	++++	+	+
26	++++	+	+
27	++++	+	+
28	++++	+	+
29	++++	+	+
30	++++	+	+
31	++++	+	+
32	++++	+	+
33	+++	+	++
34	++++	+	+
35	+++	+	+
36	+++	++	+
37	+++	+	+

38	++++	++	+
39	++++	++	+
40	++++	+	+
41	++++	+	+
42	++++	+	+
43	++++	+	++
44	+++	+	+
45	+++	++	+
46	+++	+	+
47	++++	+	+
48	++++	+	+
49	++++	+	++
50	+++	+	+
51	+++	+	+
52	++++	+	++
53	++++	+	++
54	++++	+	++
55	+++	+	++
56	+++	+	++
57	+++	++	+
58	+++	+	++
59	+++	+	++
60	+++	+	+
61	+++	+	++
62	++++	+	+
63	++++	+	+
64	+++	+	+
65	+++	+	+
66	++++	+	++
67	++++	+	+
68	++++	+	+
69	+++	+	+
70	++++	+	+
71	++++	+	++
72	++++	+	+
73	+++	+	+
74	+++	+	++
75	++++	+	+
76	+++	+	+
77	+++	+	++
78	+++	+	+
79	+++	+	+
80	+++	+	+
81	+++	+	+
82	+++	+	+
83	+++	+	+

84	++++	+	++
85	+++	+	++
86	++++	+	++
87	++++	+	+
88	++++	++	++
89	++++	++	++
90	++++	+	+
91	++++	+	+
92	++++	+	++
93	++++	+	+
94	+++	+	++
95	+++	+	++
96	+++	+	++
97	+++	+	+
98	++++	+	+
99	++++	+	+
100	++++	+	+
101	++++	+	+
102	++++	+	+
103	++++	+	++
104	++++	+	+
105	++++	+	+
106	++++	+	+
107	++++	+	++
108	++++	+	+
109	++++	+	++
110	++++	+	+
111	+++	+	+
112	++++	+	+
113	++++	+	+
114	++++	+	++
115	++++	++	+
116	+++	+	+
117	+++	++	+
118	+++	+	+
119	+++	++	+
120	++++	+	+
121	++++	++	++
122	++++	+	++
123	++++	+	+
124	++++	+	+
125	++	+	+
126	++++	+	+
127	++++	+	++
128	++	+	++
129	++	+	++

130	++	+	++
131	++++	+	++
132	+++	+	+
133	++	+	++
134	++	+	++
135	++	n.d.	n.d.
136	++	n.d.	n.d.
137	++++	+	+
138	++	+	+
139	++++	+	+
140	++++	+	+
141	++	+	+
142	++	++	+
143	++++	+	+
144	++++	+	+
145	++++	+	+
146	++++	+	+
147	++++	+	+
148	++++	+	+
149	++++	+	+
150	++++	+	++
151	++++	+	+
152	++++	+	+
153	++++	+	+
154	++++	+	+
155	++++	+	+
156	++++	+	+
157	++++	+	+
158	++++	+	+
159	++++	+	+
160	++++	+	+
161	++++	+	+
162	++++	+	+
163	++++	+	+
164	++++	+	+
165	++++	+	+
166	++++	+	+
167	++++	+	+
168	++++	+	+
169	++++	+	+
170	++++	+	+
171	++++	+	+
172	++++	+	+
173	++++	+	+
174	+++	+	++
175	++++	+	+

176	++++	+	+
177	++++	+	+
178	++++	+	+
179	++++	+	+
180	++++	+	+
181	++++	+	++
182	+++	+	+
183	++++	+	+
184	++++	+	+
185	++++	+	+
186	++++	+	+
187	+++	+	+
188	++++	+	+
189	++++	+	++
190	++++	+	+
191	++++	+	+
192	+++	+	+
193	++++	+	+
194	++++	+	+
195	++++	+	+
196	++++	+	+
197	++++	+	++
198	++++	+	+
199	++++	+	+
200	+++	+	+
201	++++	+	+
202	++++	+	+
203	+++	+	+
204	++++	+	+
205	++++	+	+
206	++++	+	+
207	+++	+	+
208	+++	+	+
209	+++	+	+
210	++++	+	+
211	++++	+	+
212	+++	++	+
213	+++	+	+
214	+++	+	+
215	+++	+	+
216	+++	+	+
217	++++	+	+
218	+++	+	+
219	++++	+	+
220	+++	+	+
221	++++	+	+

222	++++	+	+
223	++++	+	+
224	++++	+	+
225	++++	+	+
226	++++	+	+
227	++++	+	+
228	++++	+	+
229	++++	+	+
230	++++	+	+
231	++++	+	+
232	++++	+	+
233	++++	+	+
234	++++	+	+
235	++++	+	+
236	++++	+	+
237	++++	+	+
238	++++	+	+
239	++++	+	+
240	++++	+	+
241	++++	+	+
242	++++	+	+
243	+++	+	+
244	+++	+	+
245	++++	+	+
246	++++	+	+
247	++++	+	+
248	++++	+	+
249	++++	+	+
250	+++	n.d.	n.d.
251	++++	n.d.	n.d.
252	++++	+	+
253	++++	+	+
254	+++	+	+
255	+++	+	+
256	++++	+	+
257	++++	+	+
258	++++	+	+
259	++++	+	+
260	++++	+	+
261	++++	+	+
262	++++	+	+
263	++++	+	+
264	++++	+	+
265	++++	+	+
266	++++	+	+
267	++++	+	+

268	++++	+	+
269	++++	+	+
270	++++	+	+
271	++++	+	+
272	++++	+	+
273	++++	+	+
274	++++	+	+
275	++++	+	+
276	++++	+	+
277	++++	+	+
278	++++	+	+
279	++++	+	+
280	++++	+	+
281	++++	+	+
282	++++	+	+
283	++++	+	+
284	++++	+	+
285	++++	+	+
286	++++	+	+
287	++++	+	+
288	++++	+	+
289	++++	+	+
290	++++	+	+
291	++++	+	+
292	++++	+	+
293	++++	+	+
294	++++	+	+
295	++++	+	+
296	++++	+	+
297	++++	+	+
298	++++	+	+
299	++++	+	+
300	++++	+	+
301	++++	+	+
302	++++	+	+
303	++++	+	+
304	+++	+	+
305	++++	+	+
306	++++	+	+
307	++++	+	+
308	++++	+	+
309	++++	+	+
310	++++	+	+
311	++++	+	+
312	++++	+	+
313	++++	+	+

314	++++	+	+
315	++++	+	+
316	++++	+	+
317	++++	+	+
318	++++	+	+
319	++++	+	+
320	++++	+	+

Table 36: Results of binding assay for compounds of the invention against MLKL. Binding affinity is measured by the equilibrium dissociation constant (K_D). The smaller the K_D value, the greater the binding affinity of the ligand for its target. Activity is provided as follows:

++++ = K_D < 10 nM

+++ = 10 nM < K_D < 1,000 nM

++ = 1,000 nM < K_D < 30,000 nM

+ = K_D > 30,000 nM

Compound No	MLKL (KD)
1002	nt
1003	nt
1004	nt
1007	++++
1008	++++
1009	++++
1001	++++
1005	++++
1006	++++
1010	+++
1013	++++
1018	+++
1014	++++
1019	++++
1020	++++
1011	++++
1016	++++
1021	++++
1017	++++
1012	++++
1023	++++
1022	++++
1024	++++
1025	++++
1028	++++

1026	++++
1027	++++
1029	++++
1030	nt
1032	++++
1033	++++
1036	++++
1037	++++
1031	nt
1039	+++
1040	++++
1041	++++
1042	++++
1043	++++
1044	+++
1045	++++
1046	+++
1047	+++
1048	++++
1049	++++
1050	+++
1051	+++
1052	++
1053	++++
1055	+++
1056	+++
1057	++++
1058	+++
1059	nt
1060	+++

CELLULAR ASSAY: Screening compounds for inhibition of TSQ induced necroptosis, 384 well plate format.

Cell Line ID: U937 human histiocytic leukemia cell line.

Cell Concentration (cells/well): Final cell density is 20,000 cells per well.

Cell growth medium: HT-RPMI medium + 7.4% Fetal Bovine Serum (FBS). Cells are cultured in Corning 150 cm^2 tissue culture flasks with vented caps at 37 °C/5% CO_2.

Incubation: Plates were incubated at 37 °C/5% CO_2 in a humidified incubator for 48 hours following addition of compounds and death stimuli (TSQ cocktail).

Compound concentration: 36 µM starting concentration, 1:3 dilution, 10 point

DMSO final concentration (% v/v): 0.3%.

Compounds in TSQ cocktail (T: TNF; S: Smac mimetic; Q: Q-VD-OPh) and their final concentrations:

hTNF-Fc (100 ng/ml) – produced by standard procedures as shown in Bossen et al., *J Biol Chem*, 2006, 281(20), 13964-13971.

Compound A (500 nM) - Smac mimetic, Tetralogic and SYNthesis med chem

Q-VD-OPh (10 µM) – MP Biomedicals

Assay experimental outline

The cellular assay was carried out according to the following steps:

1. Each well was prepared by sequential addition of:
    a. DMSO (control; columns 1-2 and 23-24) or compound in DMSO – addition was performed using acoustic transfer of nl volumes of stock compound to give final test concentrations of 36, 12, 4, 1.3, 0.44, 0.148, 0.049, 0.016, 0.005 and 0.002 µM. All wells were backfilled with DMSO to a final total volume in the well of 100 nl.
    b. Following compound/DMSO addition in step (a), 40 µL of cell suspension (5 x 10^5 cells/mL) was added to provide a final cell concentration of 20,000 cells per well, and
    c. Following cell addition in step (b), 10 µL of 5x TSQ cocktail (except to positive controls; columns 1 and 23) was added to each well.
2. After 48 hours, plate was removed from the 37 °C incubator and equilibrated to room temperature for 45 minutes.
3. 15 µL of room temperature CellTitre-Glo2™ (Promega™) was added to each well.
4. Shook plates for 2 minutes (~600 rpm) and incubated at room temperature for 15 minutes to allow signal to stabilise.
5. Read luminescence readout on a plate reader.

Analysis:

Percent viability was calculated for each compound according to equation (2):

$$\%\ viability = 100 \times \frac{(RawData - NSA)}{(TA - NSA)} \quad (2)$$

wherein

RawData is the readout of any cell containing a compound of the invention

TA is the total activity provided by the luminescence readout from DMSO only wells (columns 2 and 24) = 100% viability

NSA is the non-specific activity provided by DMSO+TSQ wells (columns 1 and 23) = 0% viability

Curve fitting: 10-point titration curves are fitted with the 4-parameter logistic nonlinear regression model and the IC_{50} reported is the inflection point of the curve.

Analysis: Data was loaded into Dotmatics™ and visualised using the Tibco® Spotfire™ software. 10 points titration curves were fitted with the 4-parameter logistic nonlinear regression model and the IC_{50} reported reflect the inflection point of the curve for curve fitting.

Interpretation of results:

Assay involving the TSQ cocktail (T: TNF; S: Smac mimetic; Q: Q-VD-OPh): TSQ treatment ensures that cells specifically undergo necroptotic cell death. TNF activates the TNF receptor, Smac mimetic directs the signal away from proinflammatory signaling and toward the RIP1/RIP3-mediated cell death pathways, and Q-VD-OPh ensures that the apoptotic response is blocked leaving only the programmed necrosis response. The compounds' activity (solution in DMSO) tested in this TSQ-induced assay was evaluated by determining the number of viable cells in culture by measuring the amount of ATP present as measured by CelltiterGlo.

Counter screen: In parallel, all compounds were tested for their ability to affect cell viability. The same U937 cells were treated with compound in DMSO without the TSQ cocktail. This counter screen enabled evaluation of off-target effects. In this case, cell viability was measured by CelltiterGlo.

The results of the screening of the compounds described above are shown below in the Table 37.

Table 37: Table showing the results of cell-based assays performed, analysed as the half maximal inhibitory concentration (IC_{50}), being the concentration of the test compound needed

to inhibit TSQ induced necroptosis by 50%. The lower the $IC_{50,}$ the more potent the compound. Activity is provided as follows:

++++ = IC_{50} < 10 nM

+++ = 10 nM < IC_{50} < 1,000 nM

5 ++ = 1,000 nM < IC_{50} < 30,000 nM

+ = IC_{50} > 30,000 nM

Compound No	Inhibition of TSQ-induced necroptosis (IC_{50} cell-based assay)	Off-target effect (IC_{50} cell-based assay)
9	+++	+
14	+++	+
21	++	+
22	+++	+
24	++	+
25	+++	+
34	+++	+
39	++	+
41	++	+
42	+++	+
43	+++	+
53	+++	+
62	+++	+
63	++	+
66	+++	+
68	++	+
71	++	+
84	++	+
88	++	+
90	++	+
92	++	+
93	++	+
101	++	+
102	++	+
108	++	+
113	++	+
115	++	+
123	++	+
124	++	+
127	++	+
128	++	+
139	+++	+
140	+++	++
143	+++	+
144	+++	+

146	++++	+
150	+++	+
152	+++	+
153	+++	+
154	+++	++
155	+++	++
156	++	+
157	+++	+
158	++	+
160	++	+
161	+++	++
162	+++	+
163	+++	+
164	++++	+
165	++++	+
166	+++	+
169	+++	+
170	+++	+
171	+++	+
175	++++	+
176	+++	++
181	++	+
188	+++	+
190	+++	+
191	+++	+
194	+++	++
196	+++	+
198	++	+
199	+++	+
202	+++	+
208	++	+
222	++	+
223	++++	+
229	+++	+
233	+++	+
234	+++	++
235	+++	+
238	+++	+
242	+++	+
245	++++	+
246	+++	+
248	+++	+
249	++	+
251	++	+
252	++	+
253	++	+

256	+	+
259	+	+
260	++++	+
262	+++	+
264	++++	+
265	++	+
266	++	+
271	+++	+
273	+++	+
274	+++	+
275	++	+
276	++++	++
277	++++	+
278	++++	+
279	+++	+
281	+++	+
282	++++	++
283	+++	+
284	+++	+
285	++++	+
286	++	+
288	++++	+
289	++++	+
290	+++	+
291	++++	++
292	+++	+
293	+++	+
294	++	+
295	+++	+
296	++++	+
297	+++	+
298	++++	+
299	++++	+
301	+++	+
302	+++	+
303	+++	+
304	+++	++
305	+++	+
306	+++	+
307	+++	+
308	++++	+
309	+++	+
310	+++	+
311	++	+
312	++++	+
314	+++	+

316	++++	+
317	+++	++
318	++++	+
319	+++	+
320	++++	+

Table 38: Table showing the results of cell-based assays performed, analysed as the half maximal inhibitory concentration (IC_{50}), being the concentration of the test compound needed to inhibit TSQ induced necroptosis by 50%. The lower the $IC_{50,}$ the more potent the compound. Activity is provided as follows:

*** = IC_{50} < 1 μM

** = 1 μM < IC_{50} < 10 μM

* = IC_{50} > 10 μM

Compound No	Inhibition of TSQ-induced necroptosis (IC_{50} cell-based assay)	Off-target effect (IC_{50} cell-based assay)
1002	*	*
1003	*	*
1004	*	*
1007	*	*
1008	*	*
1009	*	*
1001	*	*
1005	*	*
1006	*	*
1010	*	*
1013	**	*
1018	*	*
1014	*	*

1019	***	*
1020	***	*
1011	*	*
1016	**	*
1021	***	*
1017	**	*
1012	*	*
1023	***	*
1022	***	*
1024	***	*
1025	***	*
1028	***	*
1026	**	*
1027	**	*
1029	***	*
1030	***	*
1032	*	*
1033	**	*
1036	**	*
1037	***	*
1031	***	**
1039	***	*
1040	***	*
1041	***	*
1042	***	**
1043	***	*
1044	***	*
1045	***	*
1046	***	*
1047	***	**
1048	***	*

1049	**	*
1050	**	*
1051	**	*
1052	*	*
1053	**	*
1055	***	*
1056	***	*
1057	***	*
1058	***	*
1059	***	**
1060	***	*

DEGRADATION ASSAY: Screening compounds procedure to evaluate the activity of compounds in degrading endogenous MLKL in human cell

The human monocyte cell line (U937) was seeded on the day of the experiment in a 24-well plate at a cell density of 5*10^5 cells per well in a volume of 0.5mL per well.

The compound was diluted in DMSO with a starting concentration of 10mM and titrated stepwise with a dilution of 1:5. 0.5µL of the compound dilution was added to the appropriate well to achieve a final concentration of 10; 2; 0.4; 0.08 and 0.016µM. A DMSO only well was included as control.

The cells were incubated for 24h in the presence of the compound at 37°C and 10% CO_2.

After the 24h incubation period, the medium was removed and cells washed with 0.5mL PBS. The cells were then lysed directly in 60µL of 1x SDS gel loading buffer.

The cell lysate was heat-denatured at 100C for 10min. 10µL of lysate per well were run on 18-well 4-15% Criterion TGX stain free gels (BIO-RAD). The proteins were then transferred onto nitrocellulose membrane with a wet transfer protocol in the Criterion Blotter (BIO-RAD).

Membranes were blocked with 5% skim milk in TBST. Primary antibody against MLKL (clone 3H1, MABC604 Merck) was used at 1:2000 dilution in TBST with 1% BSA and left shaking over night at 4°C. After washes with TBST, the membranes were incubated with goat anti-rat IgG HRP-conjugated antibody (Southern Biotech) in 1% skim milk TBST at 1:10000 dilution for 1h at room temperature. After TBST washes the bands were imaged on the ChemiDoc MP Imaging Systm (BIO-RAD) with Immobilion Western Chemiluminescent HRP Substrate Forte (Millipore). The loading control GAPDH was probed for with rabbit anti-GAPDH (CST 14C10) at 1:2000 dilution in 1% BSA TBST over night at 4°C. TBST washes were followed by

incubation with goat anti-rabbit IgG HRP-conjugated antibody (Southern Biotech) in 1% skim milk TBST at 1:10000 dilution for 1h at room temperature followed by TBST washes. The signal was detected as described above.

The band intensity was measured in the ImageLab Software (BIO-RAD) and the MLKL values adjusted for loading with GAPDH. The percentage of degradation was calculated by normalizing the compound treated values to the DMSO only control.

Table 39: Table showing degradation of endogenous MLKL in U937 (DC_{50} cell-based assay)

+++ = DC_{50} < 1 μM

++ = 1 μM < DC_{50} < 10 μM

+ = DC_{50} > 10 μM

Compound No	**Degradation of endogenous MLKL in U937 (DC_{50} cell-based assay in μM)**
1007	++
1001	++
1005	++
1013	++
1019	+++
1020	+++
1016	++
1021	++
1023	+++
1024	+++
1025	+++
1028	+++
1026	++
1027	++

1029	++
1030	+++
1039	+++
1040	++
1041	+++
1042	++
1043	+++
1045	+++
1048	+++
1050	+++
1051	++
1053	++
1056	+++
1057	+++
1058	+++

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the above-described embodiments, without departing from the broad general spirit and scope of the present disclosure. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS

1. A compound of formula (X):

MLKLi–L–E3L

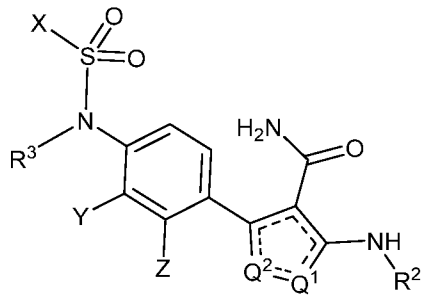
(X)

wherein

E3L is an E3 ligase binding moiety;

L is a linker covalently linking MLKLi to E3L; and

MLKLi is a radical of formula (I)



(I)

wherein

Q^1 and Q^2 are selected from N and NR^1, wherein when Q^1 is N, Q^2 is NR^1 and when Q^2 is N, Q^1 is NR^1;

R^1 and R^3 are independently selected from H and an optionally substituted $C_{1\text{-}6}$-alkyl;

R^2 is an optionally substituted $C_{1\text{-}6}$-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted halo$C_{1\text{-}6}$alkyl, optionally substituted $C_{2\text{-}6}$alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted $C_{1\text{-}6}$alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, R^4, -OR^4, -NR^4R^5 and halo;

wherein at least one of Y and Z is H;

R^4 is selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted C_{1-6}alkylaryl, optionally substituted heterocyclyl, optionally substituted C_{1-6}alkylheterocyclyl, optionally substituted cycloalkyl, optionally substituted C_{1-6}alkylC_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkylaryl, optionally substituted C_{3-10}cycloalkylheterocyclyl, optionally substituted C_{3-10}cycloalkylC_{3-10}cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic heterocyclylC_{3-10}cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

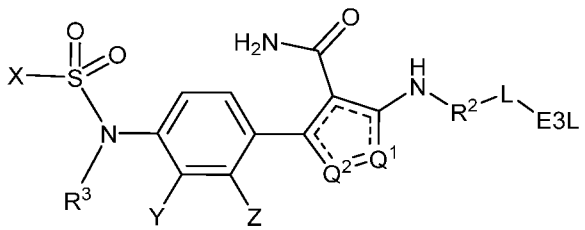
R^5 is H or optionally substituted C_{1-6}alkyl,

or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein R^2 is an optionally substituted aryl or an optionally substituted heterocyclyl.

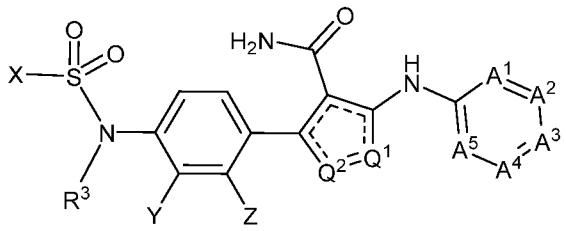
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein R^2 is an optionally substituted 5- or 6-membered heterocyclyl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XI):



(XI).

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XII):



(XII)

wherein A^1-A^5 are independently selected from N, CR^{11} and C–L-E3L,

one of A^1-A^5 is C–L-E3L

wherein not more than 2 of A^1, A^2, A^3, A^4 and A^5 are N;

each R^{11} is independently selected from H and R^{10};

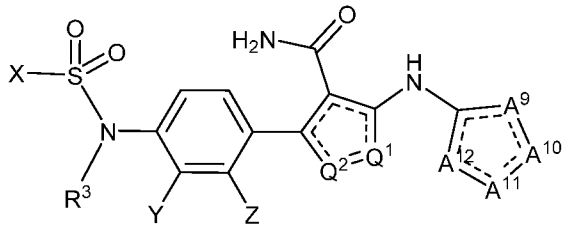
each R^{10} is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

or when two adjacent groups selected from A^1, A^2, A^3, A^4, A^5, are CR^{11}, two R^{11} may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl.

6. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein A^1-A^5 are as defined for any one of embodiments 1-4:

Embodiment No.	A^1	A^2	A^3	A^4	A^5
1	CR^{11}	C-L-E3L	N	CR^{11}	CR^{11}
2	N	CR^{11}	C-L-E3L	CR^{11}	CR^{11}
3	N	CR^{11}	C-L-E3L	N	CR^{11}
4	N	C-L-E3L	N	CR^{11}	CR^{11}

7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XIII):



(XIII)

wherein:

A^9, A^{10}, A^{11} and A^{12} are independently selected from $C(R^{11})_q$, O, S, N, NR^{12}, $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

one of A^9, A^{10}, A^{11} and A^{12} is selected from $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

at least one of A^9, A^{10}, A^{11} and A^{12} is selected from $C(R^{11})_2$, O, S, NR^{12}, $C(R^{11})$–L-E3L;

each R^{11} is independently selected from H and R^{10};

each R^{10} is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

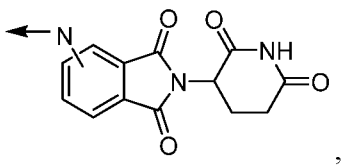
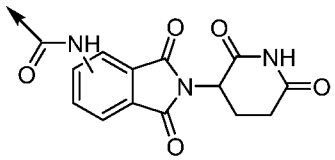
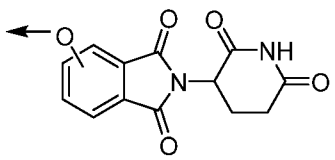
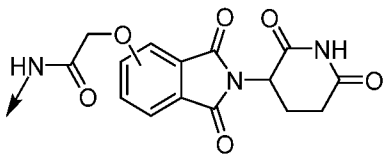
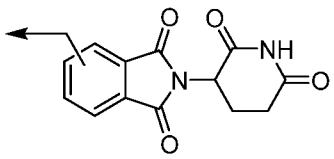
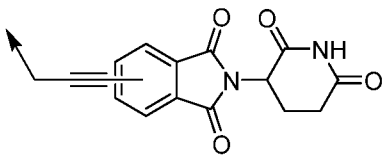
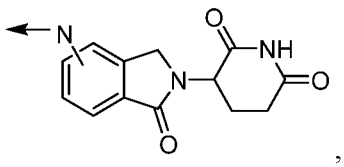
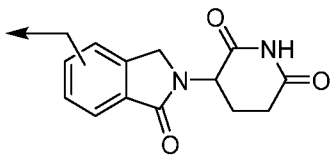
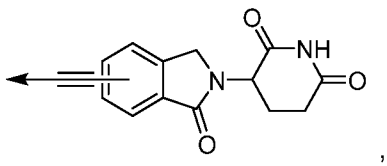
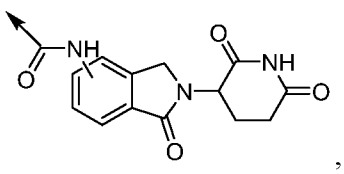
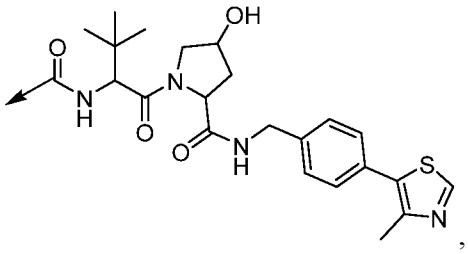
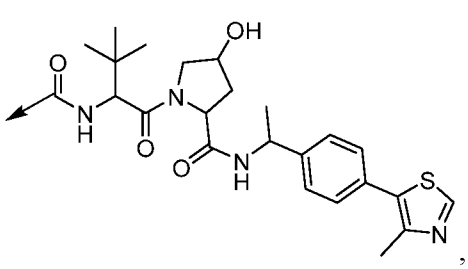
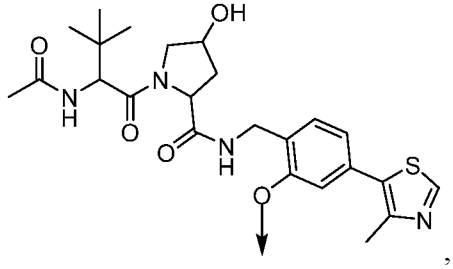
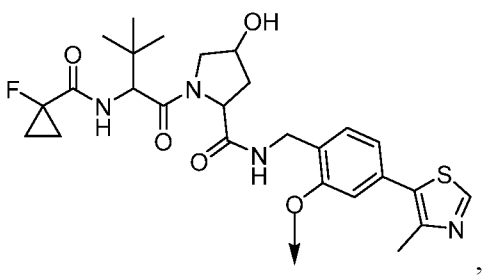
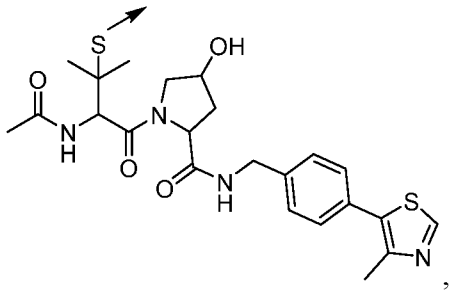
each R^{12} is independently selected from H, $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkylacyl and halo$C_{1\text{-}6}$alkylacyl;

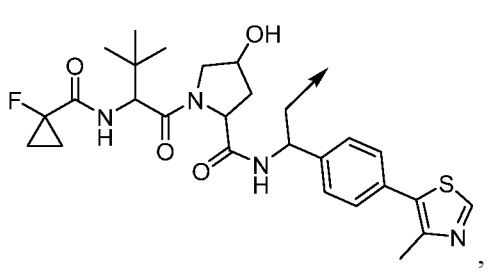
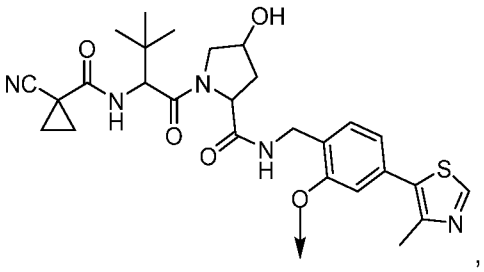
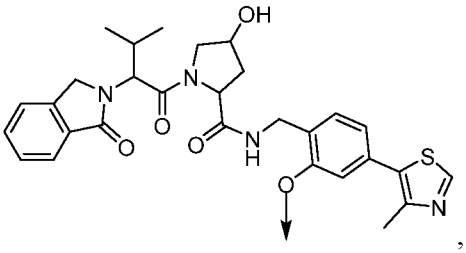
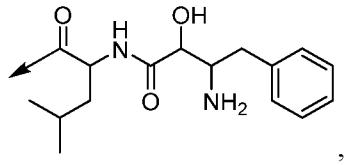
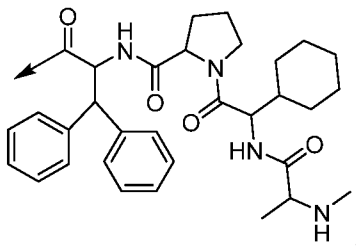
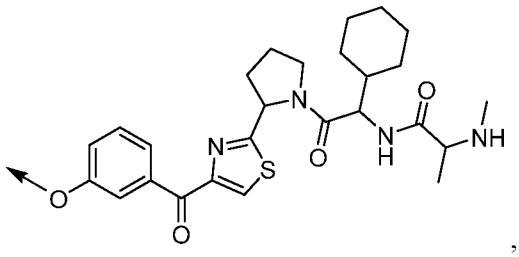
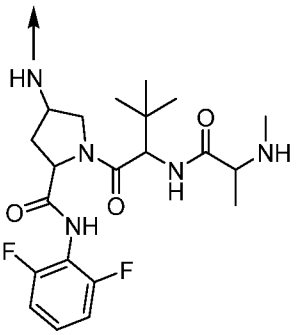
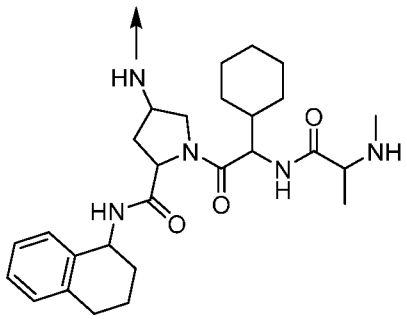
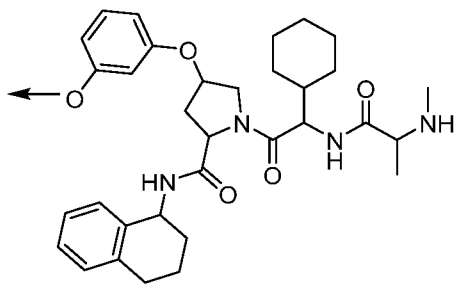
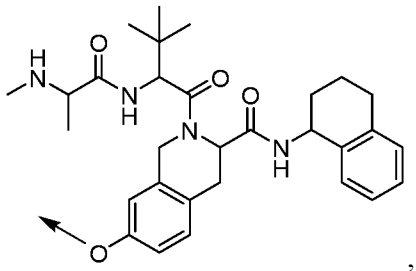
or when two adjacent groups selected from A^9, A^{10}, A^{11} and A^{12} are selected from CR^{11}, $C(R^{11})$–L-E3L and NR^{12}, two R^{11}, two R^{12} or one R^{11} and one R^{12} may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl;

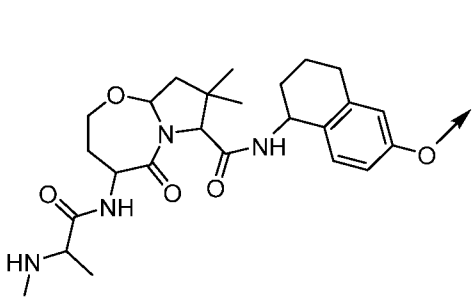
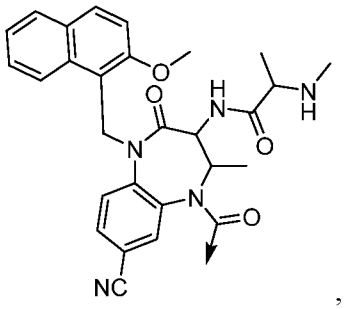
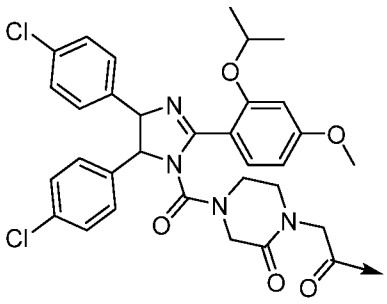
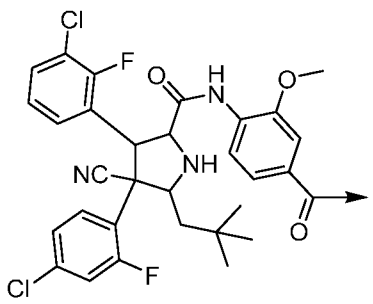
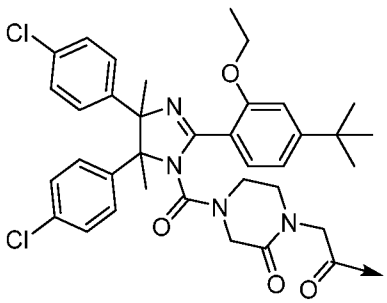
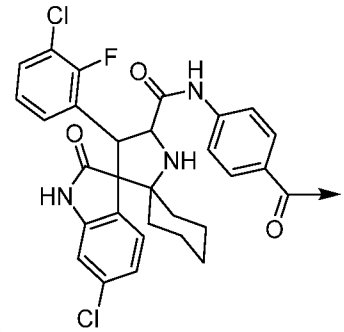
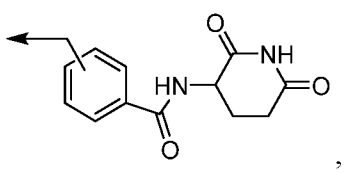
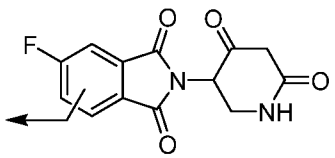
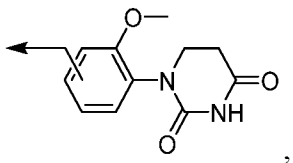
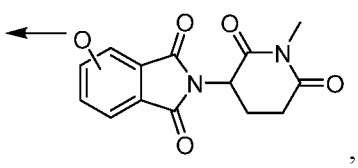
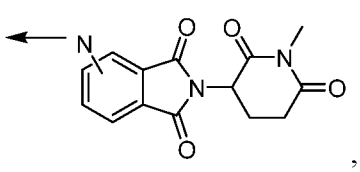
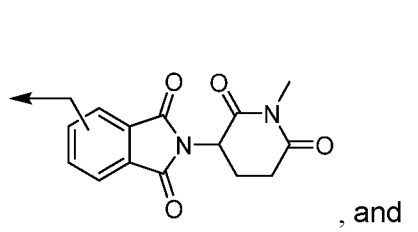
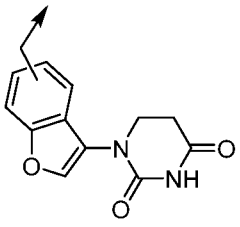
q is 1 or 2.

8. The compound of claim 7, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein A^{12} is N, A^{11} is N-L-E3L, A^{10} is CR^{11} and A^9 is CR^{11}.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the E3 ligase binding moiety is selected from


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

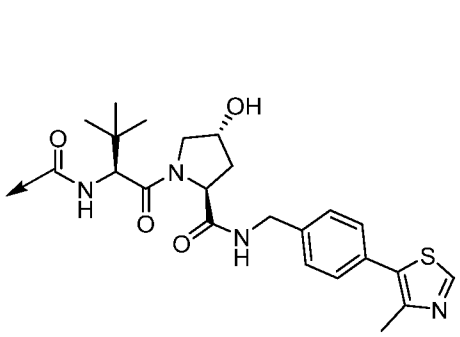
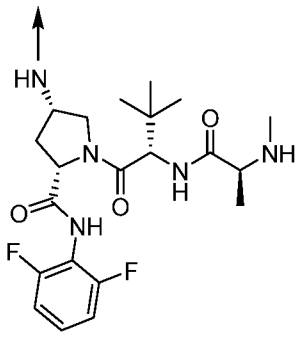
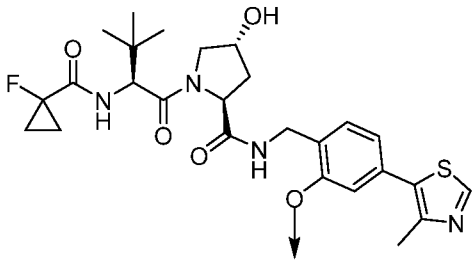
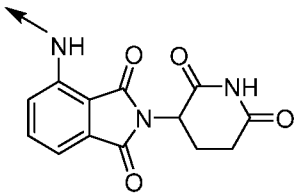
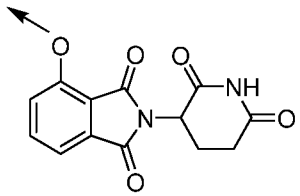
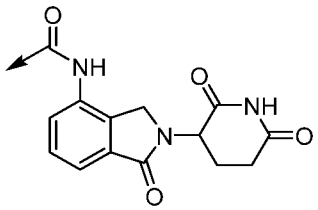
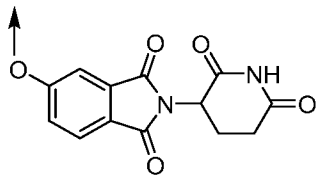
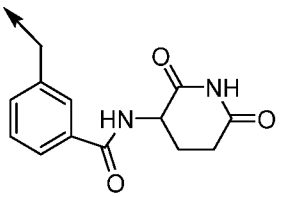
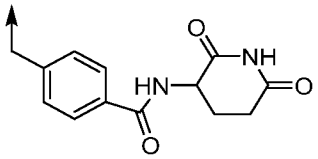
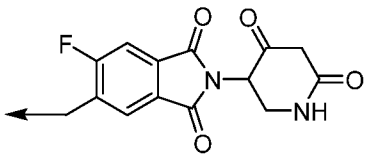
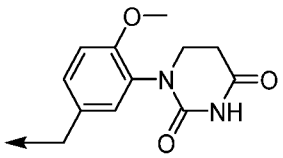
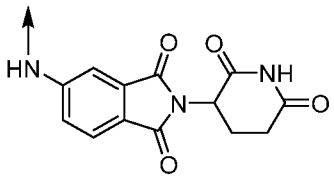
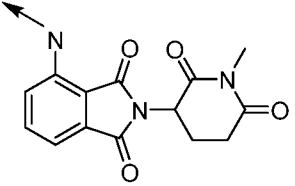












, and

;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

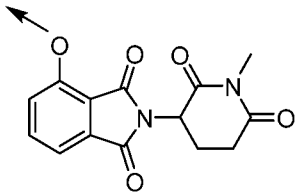
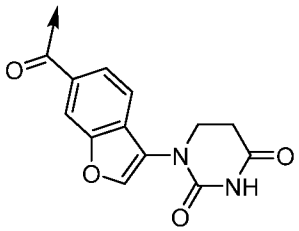
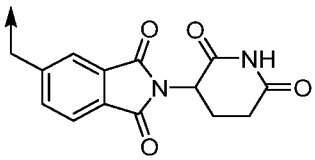
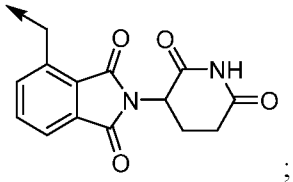
10. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the E3 ligase binding moiety is


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker has a shortest linear chain length of 1 to 50 atoms.

12. The compound of claim 11, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker has a shortest linear chain length of 1 to 10 atoms.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker is a C_{1-50}alkyl optionally interrupted by one or more groups selected from:

a. -O-,

b. -NR^z-,

c. C_{3-8}cycloalkyl,

d. aryl,

e. C_{1-4}alkaryl,

f. heteroaryl,

g. $(C_{1-4}alkoxy)_{1-4}$aryl,

h. haloaryl,

i. 4-8-membered non-aromatic heterocyclyl,

j. -C(O)NR^z-, wherein each R^z is indepedently selected from H and C_{1-4}alkyl,

k. alkenyl,

l. alkynyl,

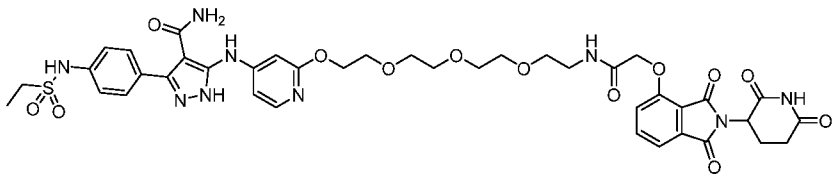
and wherein each of the one or more groups a-l may be further optionally substituted with a group selected from: C_{3-6}cycloalkyl, halo, -OH, -CN, -NR^z_2, C_{1-4}alkyl, C_{1-4}alkoxy, oxo, C_{1-4}alkylketone, -COOH, -$C(O)N(R^z)_2$, and -$NR^zC(O)R^z$.

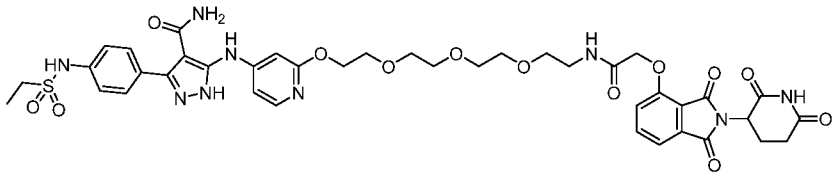
14. The compound of claim 13, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the C_{1-50}alkyl is optionally interrupted by 1-20 of the one or more groups.

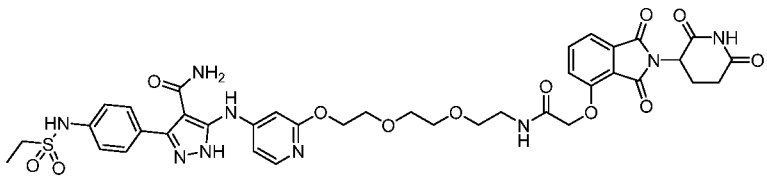
15. The compound of claim 13 or 14, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker comprises the moiety -$(OCH_2CH_2)_v$-, wherein v is an integer from 1 to 15.

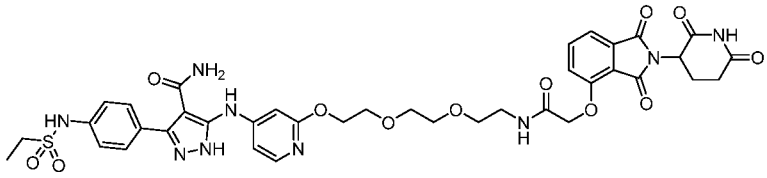
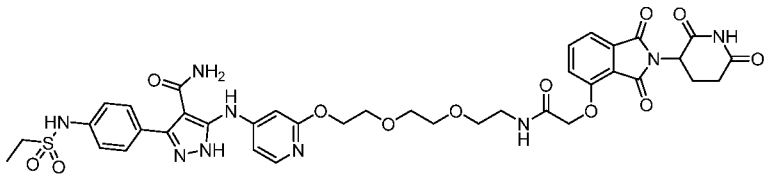
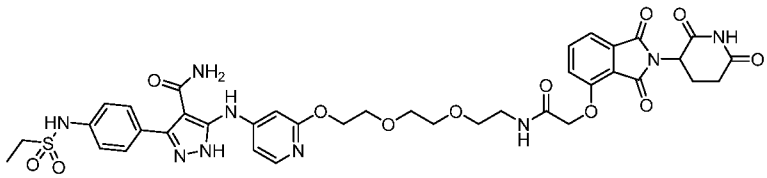
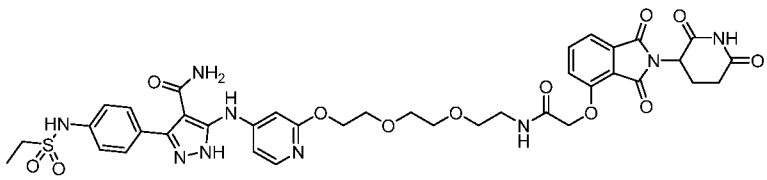
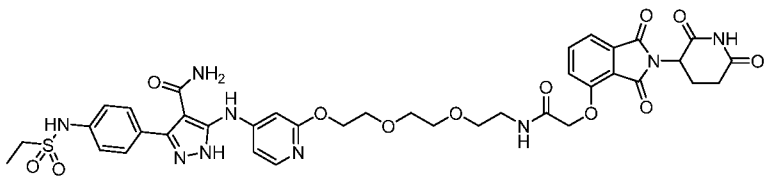
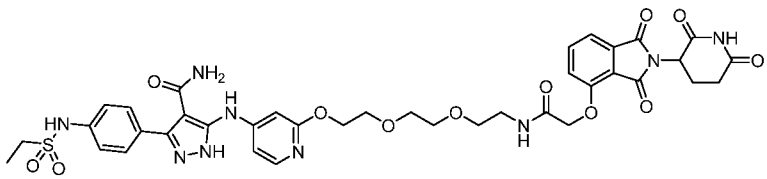
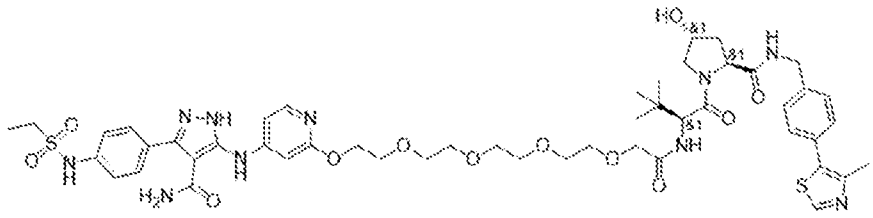
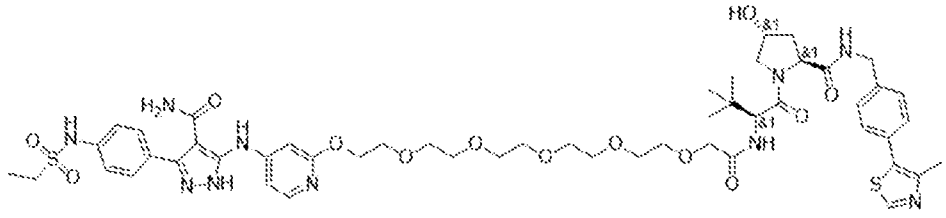
16. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker comprises at least one coupling moiety selected from: -C(O)O-, -$C(O)NR^z$-, -OC(O)O-, -$NR^zC(O)NR^z$-, -$OC(O)NR^z$-, triazolyl, aryl, α,β-unsubstituted ketone, β-hydroxy-ketone, 4-8-membered heteroaryl, unsaturated C_6-cycloalkyl and optionally substituted C_2alkenyl, wherein each R^z is indepedendently selected from H and C_{1-4}alkyl.

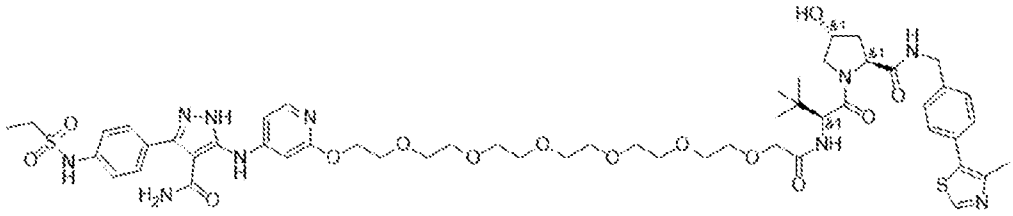
17. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the compound is selected from:


,

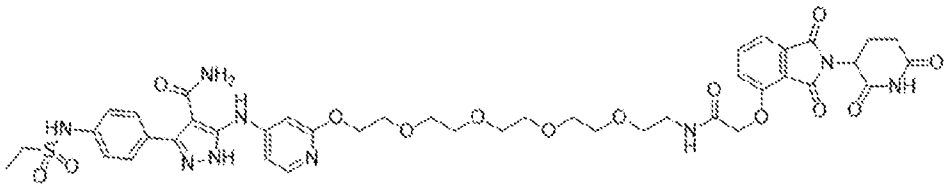

,


,

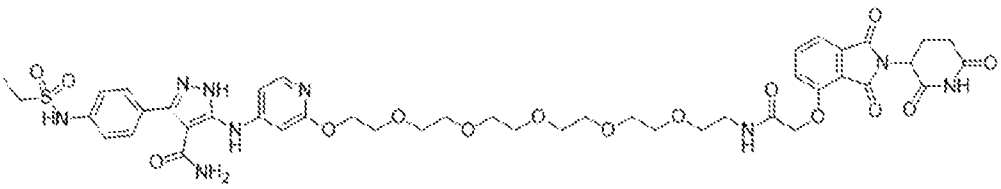

,

,

,

,

,

,

,

,



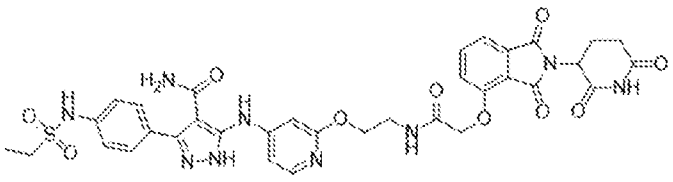
,



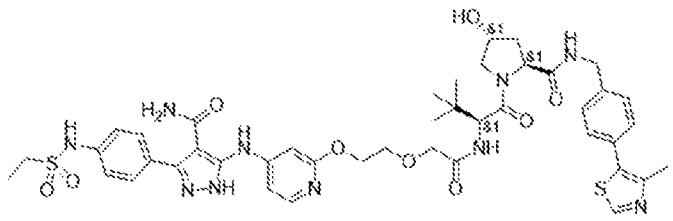
,



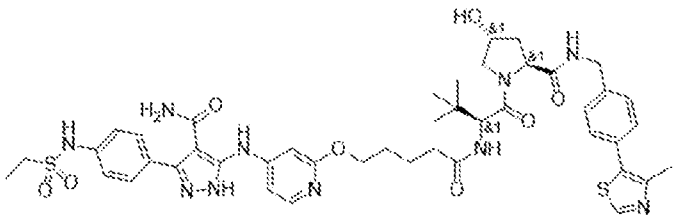
,



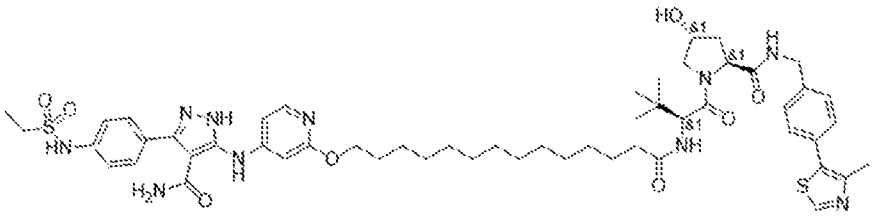
,



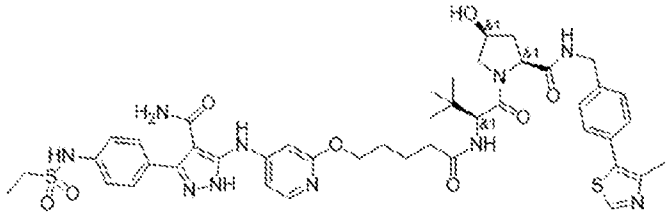
,



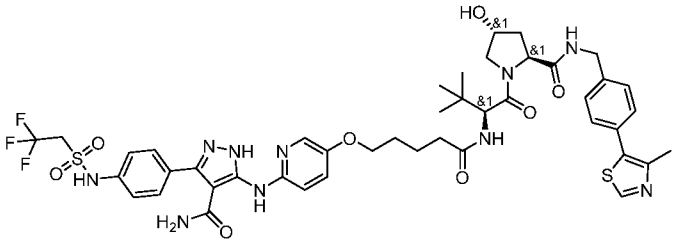
,



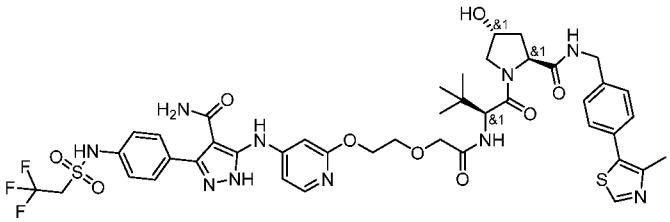
,



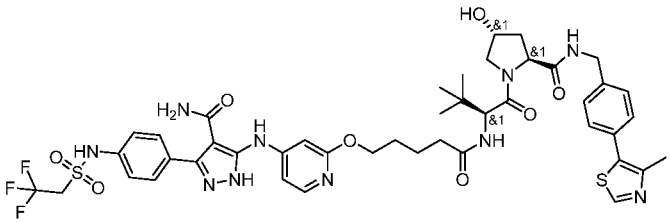
,



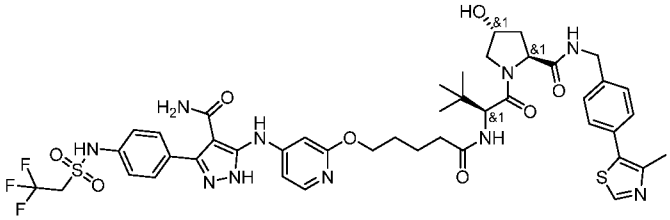
,



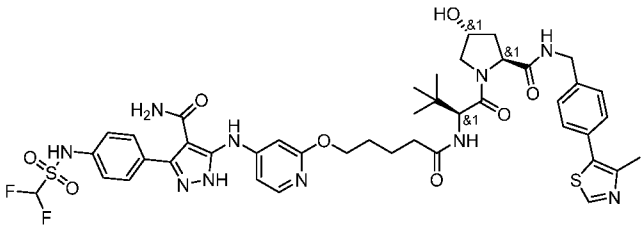
,



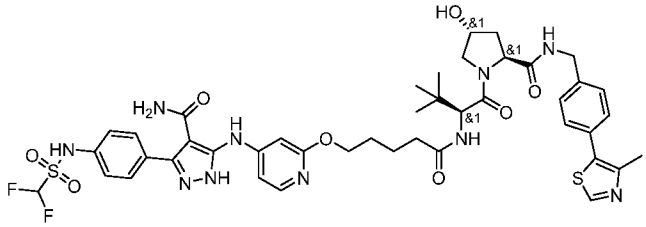
,



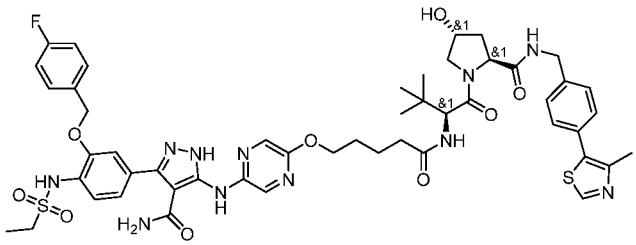
,



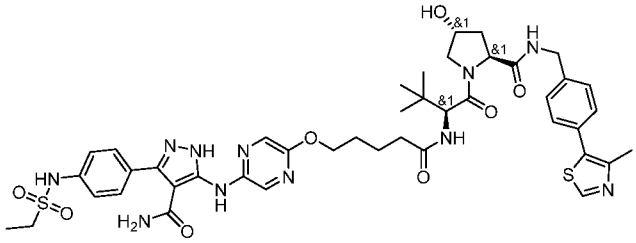
,



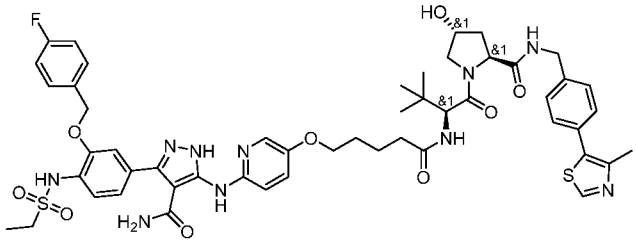
,



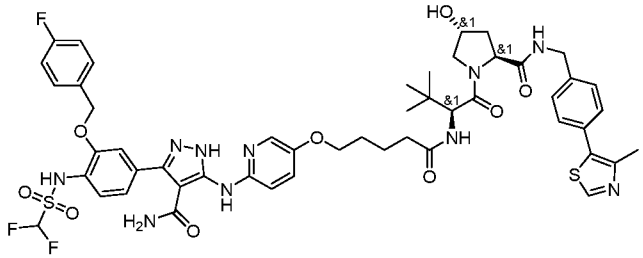
,



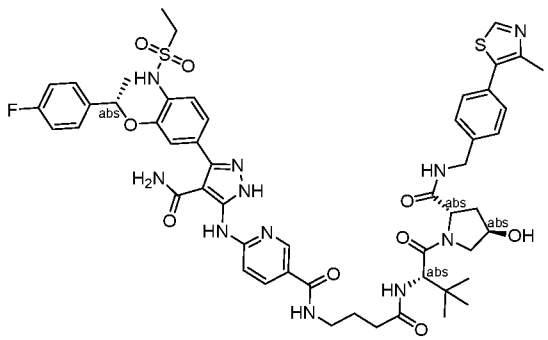
,



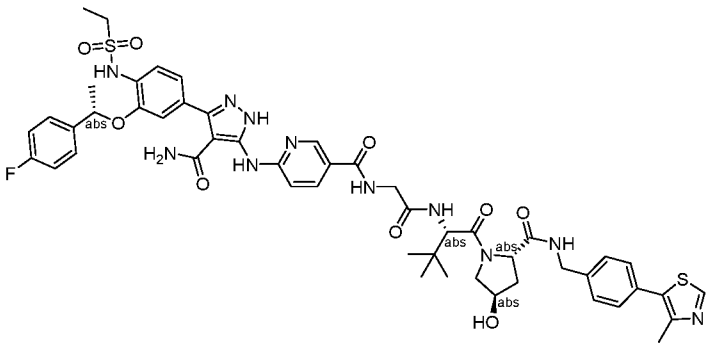
,



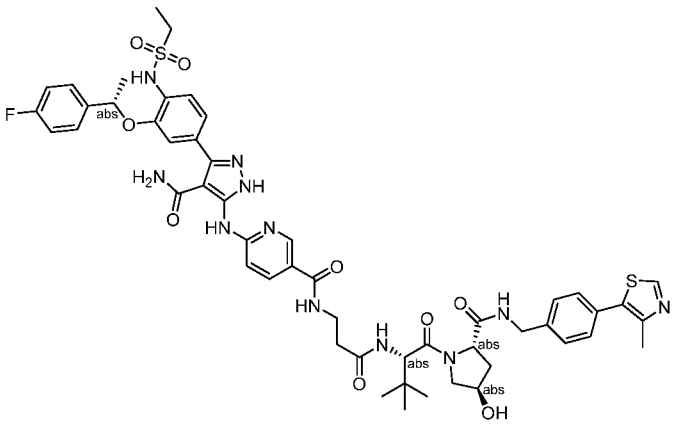
,



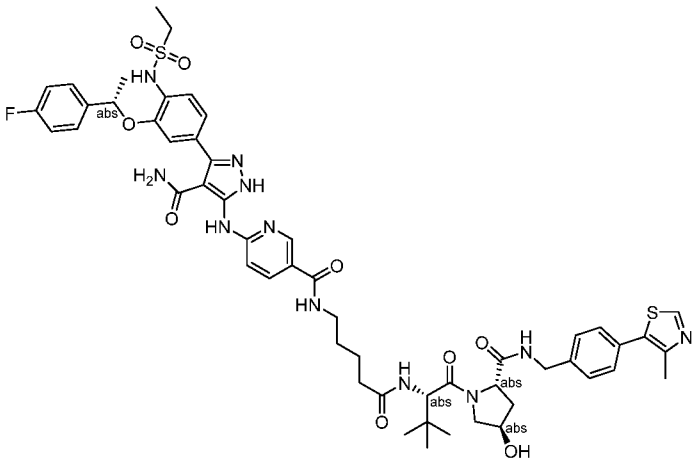
,



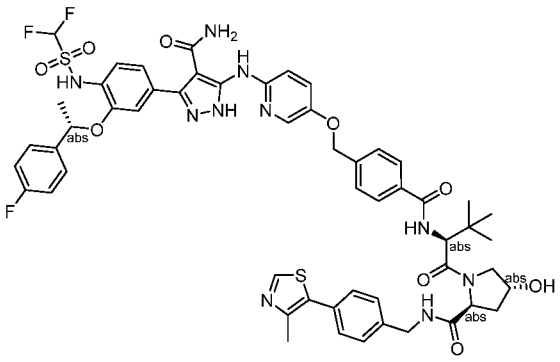
,



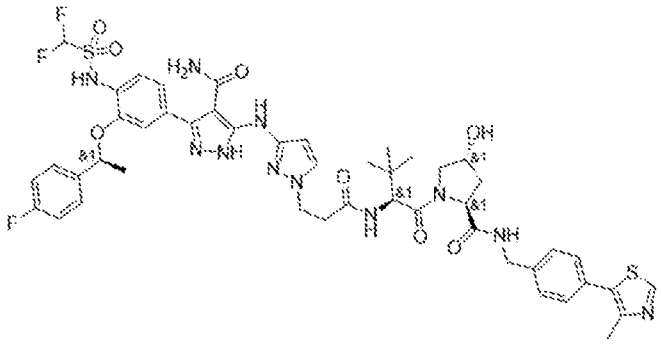
,



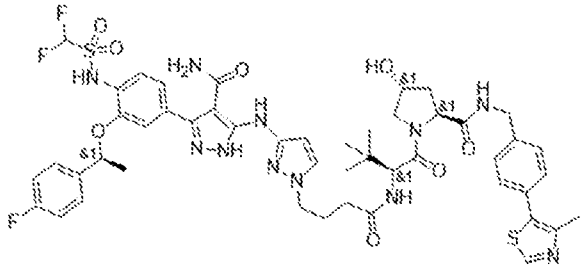
,



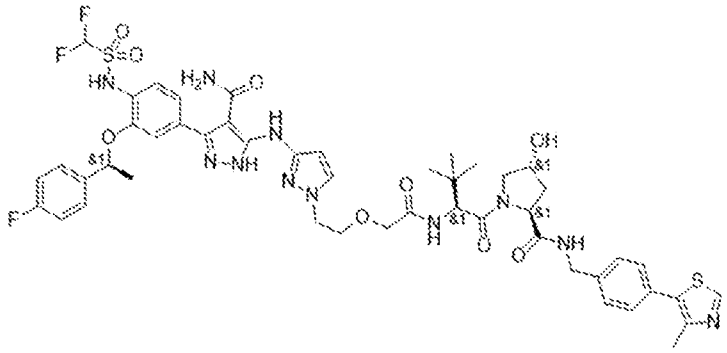
,



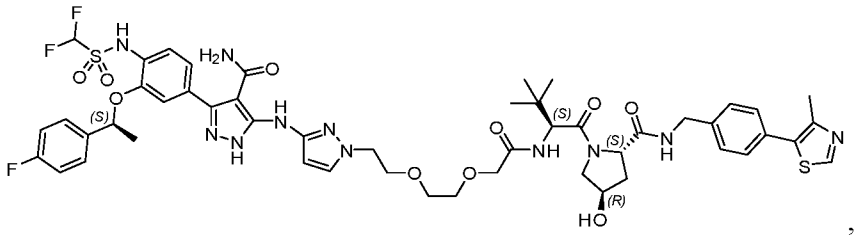
,



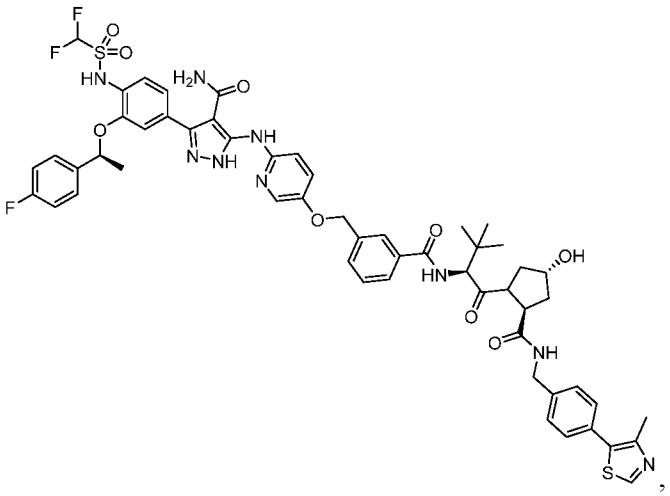
,

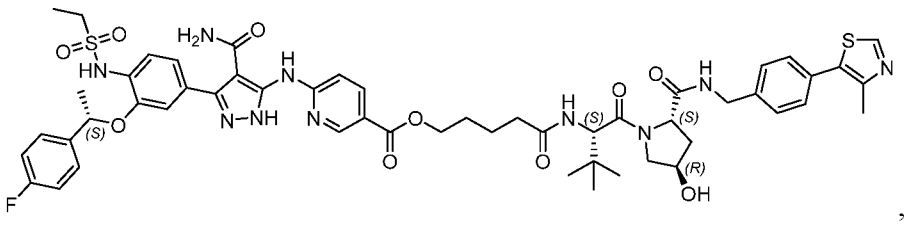


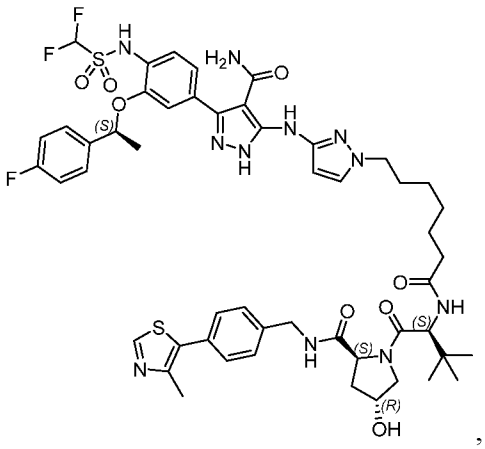
,

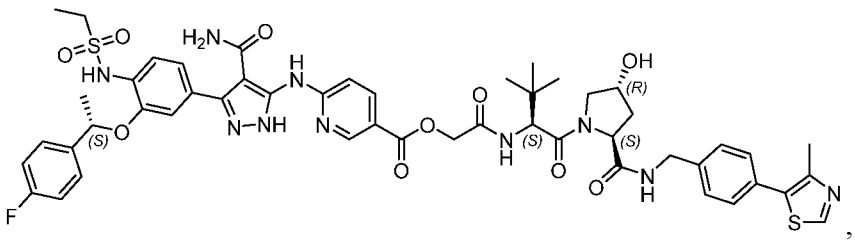


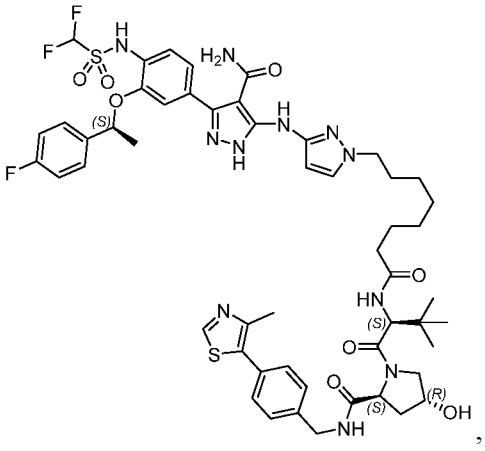
,



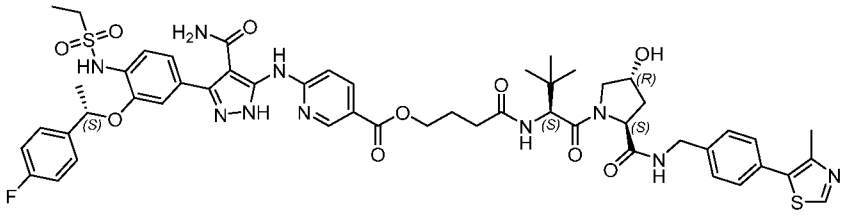


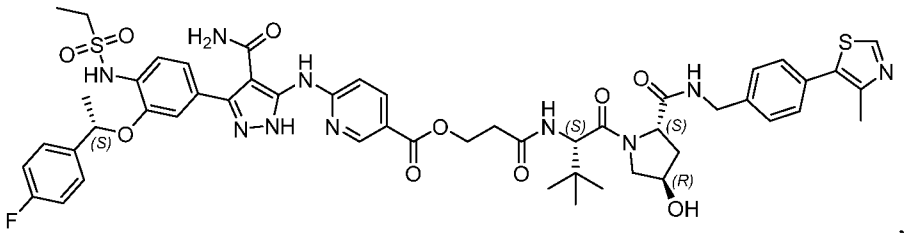




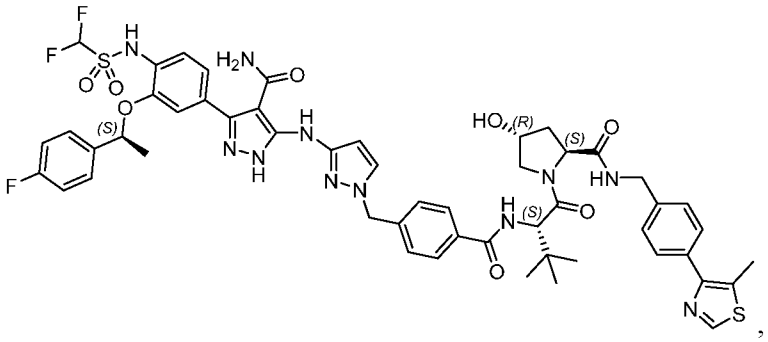


,

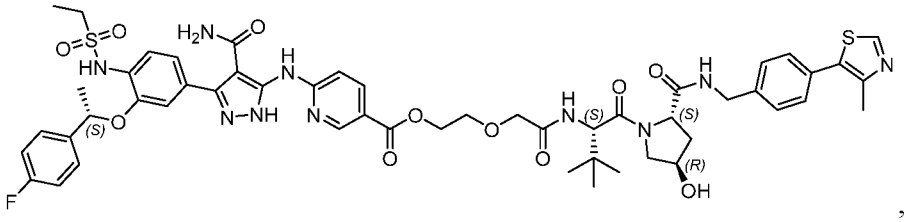




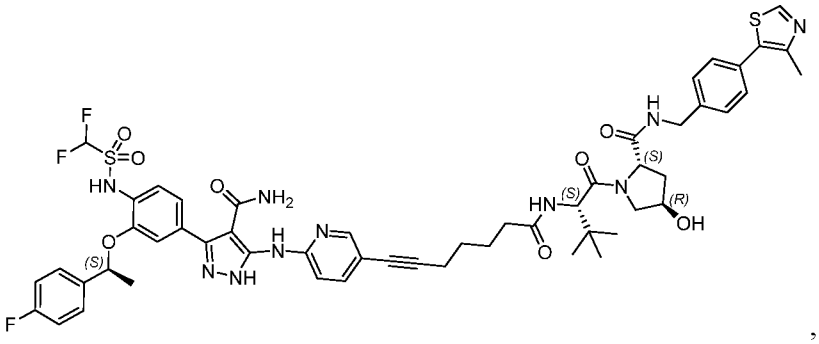
,



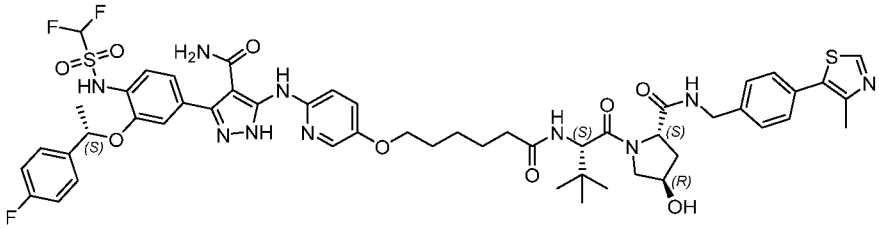
,



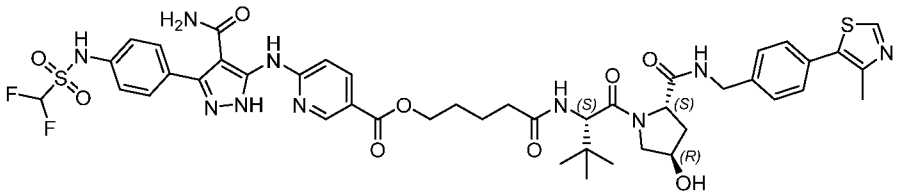
,



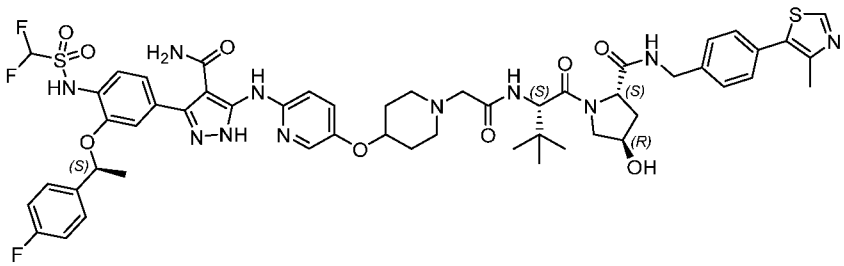
,



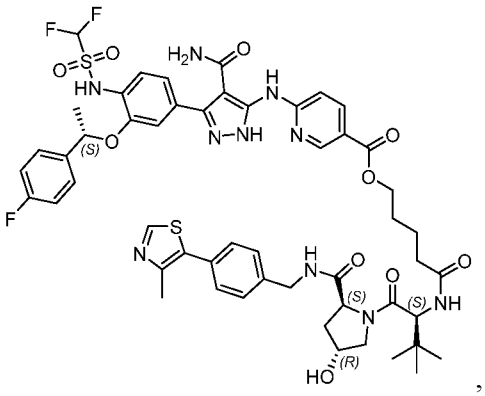
,



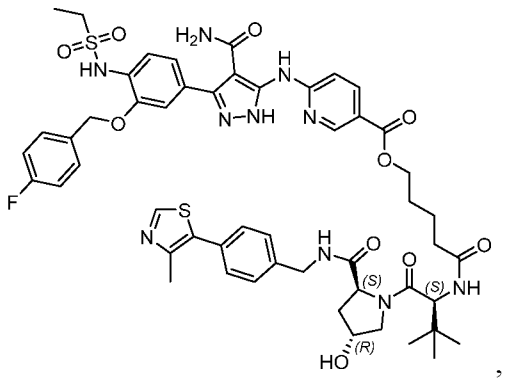
,



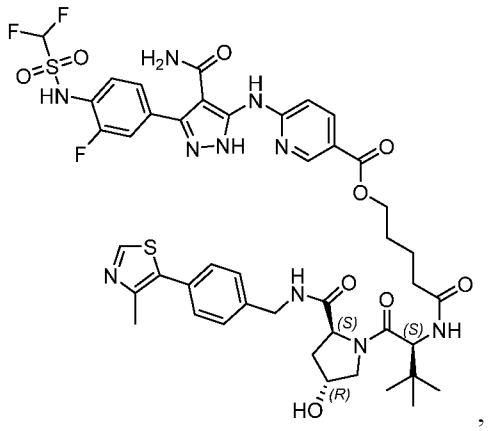
,



,

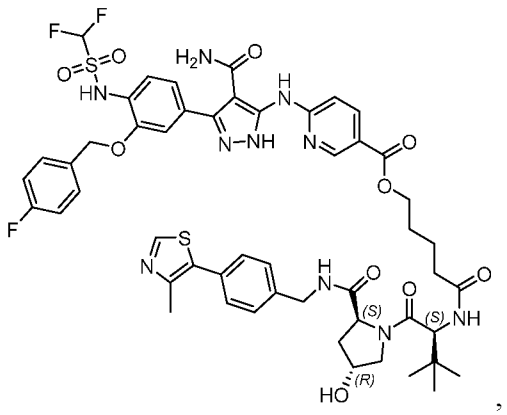


,

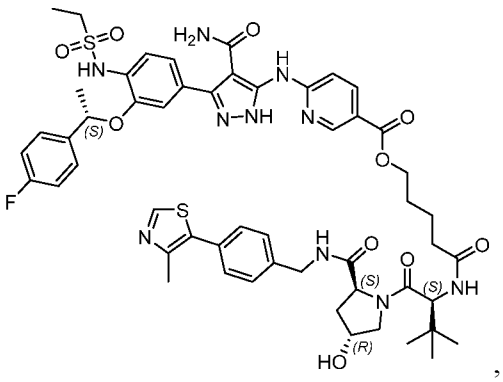


,

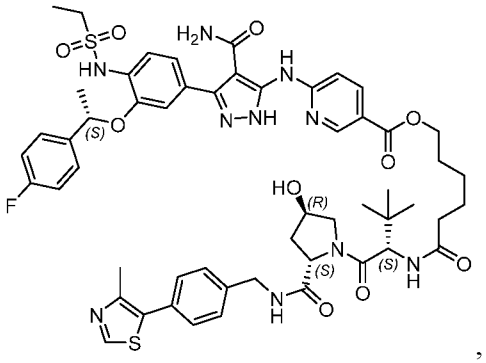
,



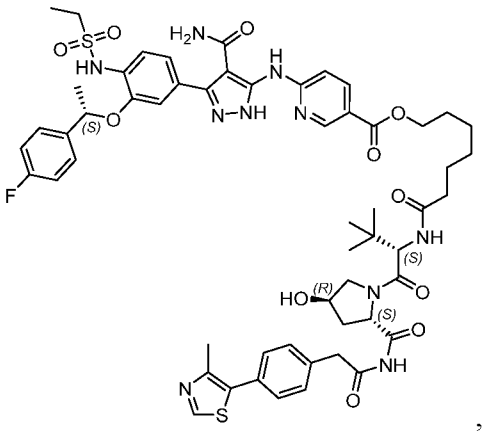
,



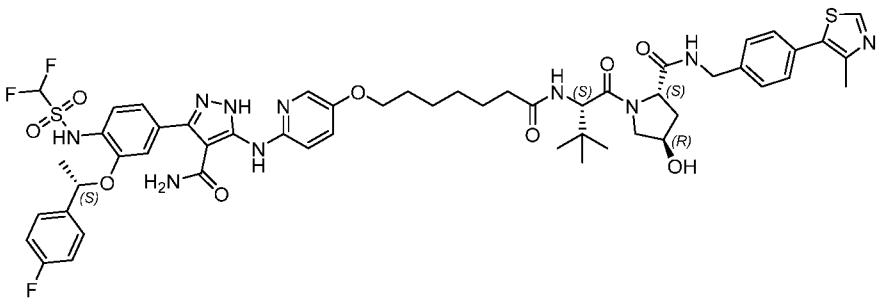
,



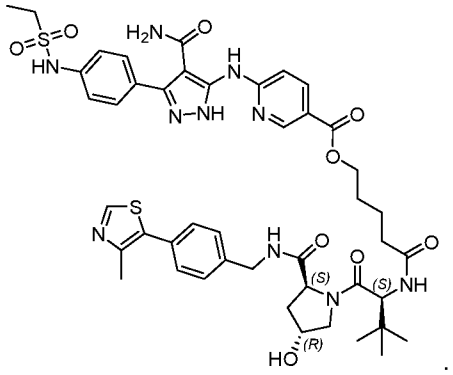
,



,



, and



18. A medicament comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

19. A pharmaceutical composition comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, and a pharmaceutically acceptable excipient.

20. A method of treating necroptosis, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, the medicament of claim 18, or the pharmaceutical composition of claim 19.

21. The method of claim 20, wherein the subject has a disease selected from the group consisting of diseases of the bones, joints, connective tissue and cartilage, muscular diseases, skin diseases, cardiovascular diseases, circulatory diseases, hematological and vascular diseases, diseases of the lung, diseases of the gastro-intestinal tract, diseases of the liver, diseases of the pancreas, metabolic diseases, diseases of the kidneys, viral and bacterial infections, severe intoxications, degenerative diseases associated with the Acquired Immune Deficiency Syndrome (AIDS), disorders associated with aging, inflammatory diseases, auto-immune diseases, dental disorders, ophthalmic diseases or disorders, diseases of the audition tracts, diseases associated with mitochondria, neuronal loss, ischemic reperfusion injury, diseases of the central nervous system, cancer and metastatic cancer.

22. Use of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, in the manufacture of a medicament for treating necroptosis.

23. A compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, for use in the treatment of necroptosis.

24. A method of inhibiting and/or degrading mixed lineage kinase domain-like protein (MLKL), comprising contacting a cell with a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

25. A MLKL degrading agent comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2022/051575

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (Registry and Caplus) Substructure search based on formula (X) and Applicant and Inventor Search (Database searched: DOCDB and DWPI: asn=(ANAXIS NEAR PHARMA NEAR PTY NEAR LTD) AND inn=((BROZOWSKI NEAR Martin) OR (GARNIER NEAR Jean NEAR Marc) OR (GARDNER NEAR Christopher) OR (LESSENE NEAR Guillaume) OR (KERSTEN NEAR Wilco))

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2023	14 February 2023

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
Email address: pct@ipaustralia.gov.au

Authorised officer

Ricky Fung
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. +61 2 6222 3648

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2022/051575**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/172203 A1 (CATALYST THERAPEUTICS PTY LTD) 19 November 2019 See abstract, page 4 line 6 - page 6 line 14, Table 1 pages 124-125	1-25
A	WO 2016/127213 A1 (CATALYST THERAPEUTICS PTY LTD) 18 August 2016 Abstract, page 3 line 1 - page 5 line 22, Tables 1 and 2 pages 124-127	1-25
P,A	WO 2021/253095 A1 (ANAXIS PHARMA PTY LTD) 23 December 2021 See abstract and claims	1-25

INTERNATIONAL SEARCH REPORT	International application No. PCT/AU2022/051575

Supplemental Box – IPC Marks

C07D 401/14 (2006.01)
C07D 417/14 (2006.01)
A61K 31/437 (2006.01)
A61K 31/4545 (2006.01)
A61K 31/513 (2006.01)
A61K 47/55 (2017.01)
A61P 1/00 (2006.01)
A61P 11/00 (2006.01)
A61P 19/00 (2006.01)
A61P 21/00 (2006.01)
A61P 25/00 (2006.01)
A61P 29/00 (2006.01)
A61P 31/00 (2006.01)
A61P 35/00 (2006.01)
A61P 37/00 (2006.01)
A61P 43/00 (2006.01)
A61P 9/00 (2006.01)

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2022/051575**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2015/172203 A1	19 November 2019	WO 2015172203 A1	19 Nov 2015
		AU 2015258781 A1	24 Nov 2016
		BR 112016026544 A2	12 Dec 2017
		CA 2948544 A1	19 Nov 2015
		CN 106456632 A	22 Feb 2017
		EP 3142667 A1	22 Mar 2017
		JP 2017521477 A	03 Aug 2017
		RU 2016144911 A	18 Jun 2018
		SG 11201609350X A	29 Dec 2016
		US 2017114025 A1	27 Apr 2017
WO 2016/127213 A1	18 August 2016	None	
WO 2021/253095 A1	23 December 2021	None	

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.