CYCLIC ETHER PYRAZOL-4-YL-HETEROCYCLYL-CARBOXAMIDE COMPOUNDS AND METHODS OF USE

FIELD OF THE INVENTION

The invention relates generally to cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds for treating disorders mediated by Pim kinase (Pim-1, Pim-2, and/or Pim-3) inhibitors, thus useful as cancer therapeutics. The invention also relates to compositions, more specifically pharmaceutical compositions comprising these compounds and methods of using the same, either alone or in combination, to treat various forms of cancer and hyperproliferative disorders, as well as methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

BACKGROUND OF THE INVENTION

Pim kinases are family of three highly-related serine and threonine protein kinases encoded by the genes Pim-1, Pim-2, and Pim-3. The gene names are derived from the phrase Proviral Insertion, Moloney, frequent integration sites for murine moloney virus wherein the insertions lead to overexpression of Pim kinases and either *de novo* T-cell lymphomas, or dramatic acceleration of tumorigenesis in a transgenic Myc-driven lymphoma model (Cuypers et al. (1984) Cell, vol. 37 (1) pp. 141-50; Selten et al. (1985) EMBO J. vol. 4 (7) pp. 1793-8; van der Lugt et al. (1995) EMBO J. vol. 14 (11) pp. 2536-44; Mikkers et al. (2002) Nature Genetics, vol. 32 (1) pp. 153-9; van Lohuizen et al. (1991) Cell, vol. 65 (5) pp. 737-52). These experiments reveal synergy with the oncogene c-Myc, and suggest that inhibition of the Pim kinases may have therapeutic benefit.

Mouse genetics suggests that antagonizing Pim kinases may have an acceptable safety profile; a Pim 1 -/-; Pim-2 -/-, Pim-3 -/- mouse knockout is viable although slightly smaller than wild type littermates (Mikkers et al. (2004) Mol Cell Biol vol. 24 (13) pp. 6104-154). The three genes give rise to six protein isoforms including a protein kinase domain, and apparently without recognizable regulatory domains. All six isoforms are constitutively active protein kinases that do not require post-translational modification for activity, thus Pim kinases are regulated primarily at the transcriptional level (Qian et al. (2005) J Biol Chem, vol. 280 (7) pp. 6130-7). Pim kinase expression is highly inducible by cytokines and growth factors receptors and Pims are direct transcriptional targets of the Stat proteins, including Stat3 and Stat5. Pim-1, for example, is required for the gp130-mediated Stat3 proliferation signal (Aksoy et al. (2007) Stem Cells, vol. 25 (12) pp. 2996-3004; Hirano et al. (2000) Oncogene vol. 19 (21) pp. 2548-56; Shirogane et al. (1999) Immunity vol. 11 (6) pp. 709-19).

Pim kinases function in cellular proliferation and survival pathways parallel to the PI3k/Akt/mTOR signaling axis (Hammerman et al. (2005) Blood vol. 105 (11) pp. 4477-83). Indeed, several of the phosphorylation targets of the PI3k axis including Bad and eIF4E-BP1 are cell growth and apoptosis regulators and are also phosphorylation targets of the Pim kinases (Fox et al. (2003) Genes Dev vol. 17 (15) pp. 1841-54; Macdonald et al. (2006) Cell Biol vol. 7 pp. 1; Aho et al. (2004) FEBS Letters vol. 571 (1-3) pp. 43-9; Tamburini et al. (2009) Blood vol. 114 (8) pp. 1618-27). Pim kinase may affect cell survival since phosphorylation of Bad increases Bcl-2 activity and therefore promotes cell survival. Likewise, phosphorylation of eIF4E-BP1 by mTOR or Pim kinases causes depression of eIF4E, promoting mRNA translation and cellular growth. In addition, Pim-1 has been recognized to promote cell cycle progression through phosphorylation of CDC25A, p21, and Cdc25C (Mochizuki et al. (1999) J Biol Chemvol. 274 (26) pp. 18659-66; Bachmann et al. (2006) Int J Biochem Cell Biol vol. 38 (3) pp. 430-43; Wang et al. (2002) Biochim Biophys Acta vol. 1593 (1) pp. 45-55.

Pim kinases show synergy in transgenic mouse models with c-Myc-driven and Akt-driven tumors (Verbeek et al. (1991) Mol Cell Biol vol. 11 (2) pp. 1176-9; Allen et al. Oncogene (1997) vol. 15 (10) pp. 1133-41; Hammerman et al. (2005) Blood vol. 105 (11) pp. 4477-83). Pim Kinases are involved in transforming activity of oncogenes identified in acute myeloid leukemia (AML) including Flt3-ITD, BCR-abl, and Tel-Jak2. Expression of these oncogenes in BaF3 cells results in upregulation of Pim-1 and Pim-2 expression, resulting in IL-3 independent growth, and subsequent Pim inhibition results in apoptosis and cell growth arrest (Adam et al. (2006) Cancer Research 66 (7):3828-35). Pim overexpression and dysregulation has also been noted as a frequent event in many hematopoietic cancers, including leukemias and lymphoma (Amson et al. (1989) Proc Natl Acad Sci USA 86 (22):8857-61); Cohen et al. (2004) Leuk Lymphoma 45 (5):951-5; Hüttmann et al. (2006) Leukemia 20 (10):1774-82) as well as multiple myeloma (Claudio et al. (2002) Blood 100 (6):2175-86. Multiple myeloma (MM) is a clonal B-lymphocyte malignancy, which is characterized by the accumulation of terminally differentiated antibody-producing cells in the bone marrow.

Pim 1 has been shown to be overexpressed and correlated to prostate cancer progression (Cibull et al. (2006) J Clin Pathol 59 (3):285-8; Dhanasekaran et al. (2001) Nature vol. 412 (6849):822-6). Pim 1 expression increases in mouse models with disease progression (Kim et al. (2002) Proc Natl Acad Sci USA 99 (5):2884-9). Pim-1 has been reported to be the most highly overexpressed mRNA in the subset of human prostate tumor samples which have a c-Myc-driven gene signature (Ellwood-Yen et al. (2003) Cancer Cell 4(3):223-38). Pim-3 has been also been shown to be overexpressed and to have a functional role in pancreatic cancer and hepatocellular

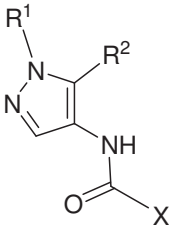
carcinoma (Li et al. (2006) Cancer Research 66 (13):6741-7; Fujii et al. (2005) Int J Cancer 114 (2):209-18.

Beyond oncology therapeutic and diagnostic applications, Pim kinases could play an important role in normal immune system function and Pim inhibition could be therapeutic for a number of different immunologic pathologies including tumorigensis (Nawijn et al (2011) Nature Rev. 11:23-34), inflammation, autoimmune conditions, allergy, and immune suppression for organ transplantation (Aho et al. (2005) Immunology 116 (1):82-8).

SUMMARY

The disclosure relates to cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds for treating disorders mediated by Pim kinase (Pim-1, Pim-2, and/or Pim-3) inhibitors Formula I compounds.

Formula I compounds have the structure:



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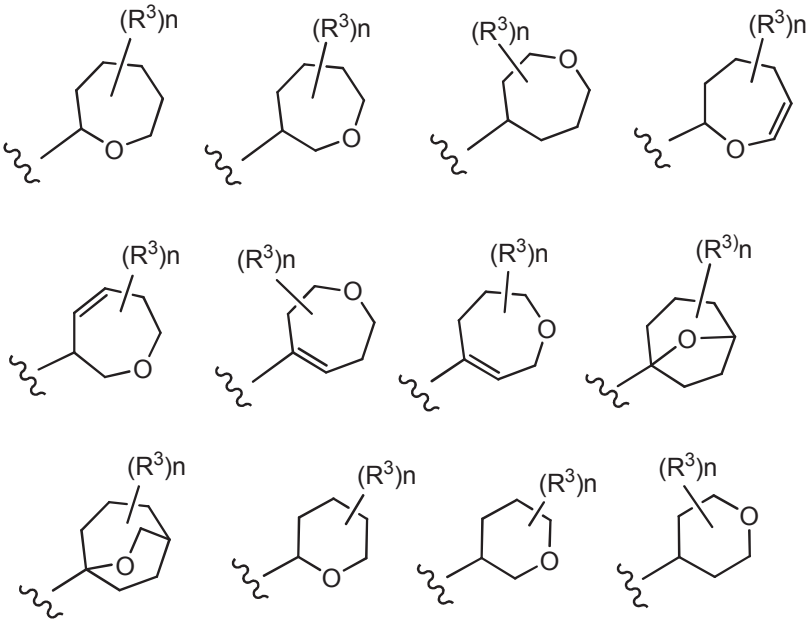
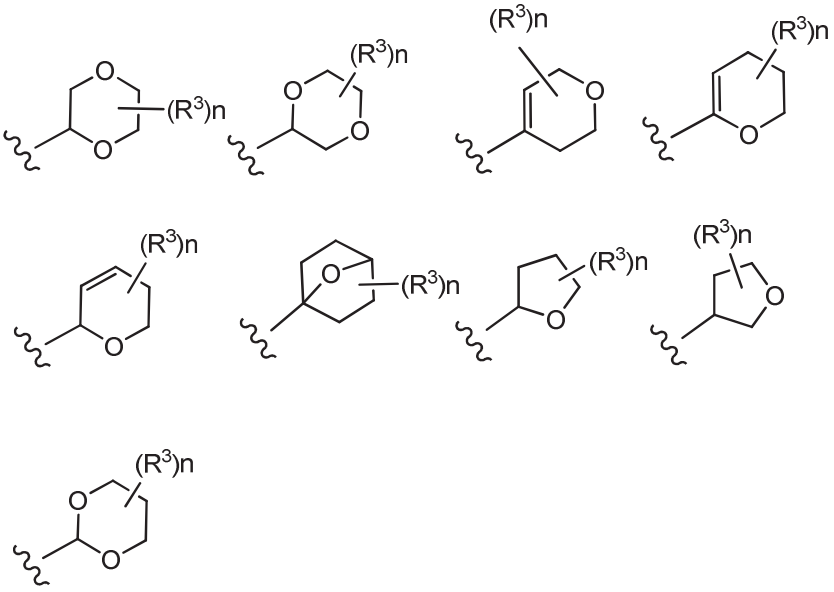
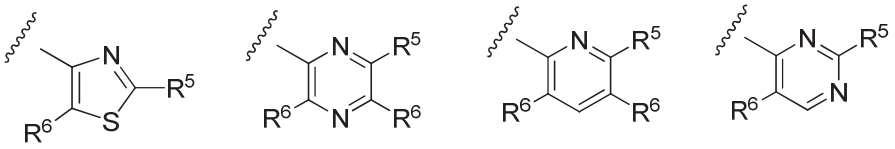
where R^2 is selected from the structures:





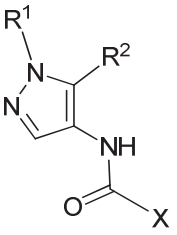
where the wavy line indicates the site of attachment and the dashed line indicates an optional double bond;

X is selected from the structures:



and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof. The various substituents, including R^1, R^2, R^3, R^4, R^5, R^6, R^7, and X are as defined herein.

One aspect of the disclosure is a compound selected from Formula I:



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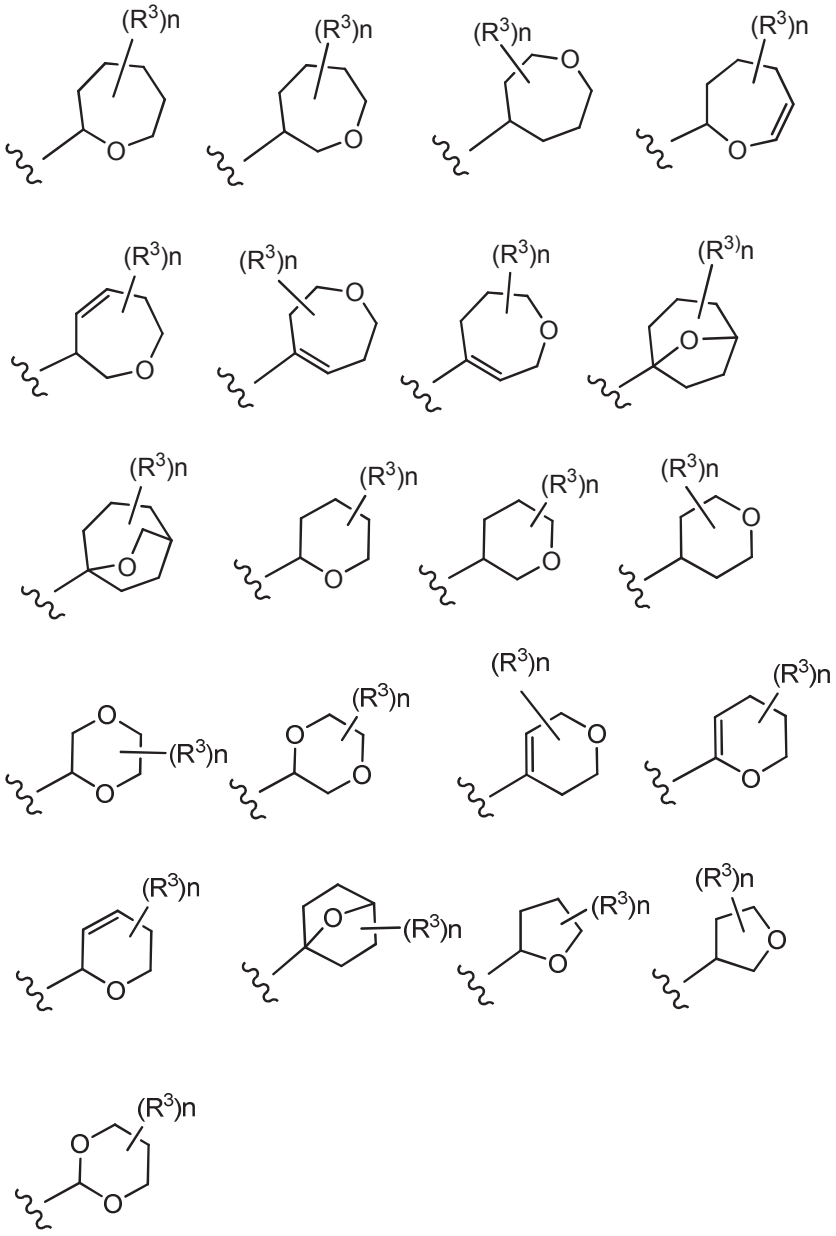
and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_6-C_{20} aryl, C_3-C_{12}carbocyclyl, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, and -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl);

R^2 is selected from the structures:



where the wavy line indicates the site of attachment;

R^3 is independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH=CH_2$, $-CH=C(CH_3)_2$, $=CH_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COCH_2NH_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OC_6H_5$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -

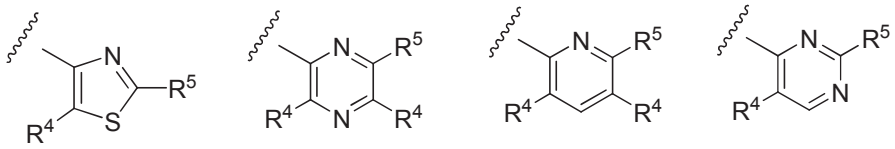
$OCH_2CH(CH_3)_2$, $-OC(CH_3)_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, oxetan-3-ylmethylamino, (3-methyloxetan-3-yl)methylamino, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino;

or where two geminal R^3 groups form a spiro ring selected from a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidinyl, piperazinyl, or piperidinyl ring, where the spiro ring is optionally substituted with one or more groups independently selected from -F, -OH, =O, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

or where two vicinal R^3 groups form a five-membered or six-membered heterocyclyl fused ring, where the heterocyclyl fused ring is optionally substituted with one or more groups independently selected from -F, -OH, =O, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

n is 0, 1, 2, 3, 4, 5, or 6;

X is selected from the structures:



where the wavy line indicates the site of attachment;

R^4 is independently H, F, $-CH_3$, or $-NH_2$; and

R^5 is selected from H, Cl, Br, C_1-C_{12} alkyl, -O-(C_1-C_{12} alkyl), -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_2-C_8 alkenylene)-(C_3-C_{12} carbocyclyl), -(C_2-C_8 alkenylene)-(C_2-C_{20} heterocyclyl), C_6-C_{20} aryl, -(C_6-C_{20} arylene)-(C_2-C_{20} heterocyclyl), -(C_6-C_{20} arylene)-(C_6-C_{20} arylene), -(C_6-C_{20} arylene)-(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_6-C_{20} arylene)-O-(C_2-C_{20} heterocyclyl), -(C_6-C_{20} arylene)-O-(C_1-C_{12} alkyl), C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, -(C_1-C_{20} heteroaryl)-(C_2-C_2o heterocyclyl), and -(C_1-C_{20} heteroaryl)-(C_1-C_{12} alkyl); where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(CH_2OH)_2$, $-C(CH_2OH)_3$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CO_2H$, $-COCH_3$, $-COCH(CH_3)_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, -OH, $-OCH_3$, $-OCF_3$, $-OCH(CH_3)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, -

CH_2OCH_3, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, phenyl, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino.

Another aspect of the disclosure is a pharmaceutical composition comprised of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. The pharmaceutical composition may further comprise a chemotherapeutic agent.

The disclosure includes a method of treating a disease or disorder which method comprises administering a therapeutically effective amount of a Formula I compound to a patient with a disease or disorder selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Pim kinase. The method includes further administering an additional therapeutic agent selected from a chemotherapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

The disclosure includes use of a Formula I compound in the manufacture of a medicament for the treatment of cancer, immune disorders, cardiovascular disease, viral infection,

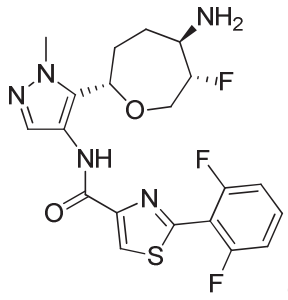
inflammation, metabolism/endocrine function disorders and neurological disorders, wherein the medicament mediates Pim kinase.

The disclosure includes a kit for treating a condition mediated by Pim kinase, comprising: a) a first pharmaceutical composition comprising a Formula I compound; and b) instructions for use.

The disclosure includes a Formula I compound for use as a medicament, and for use in treating a disease or disorder selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Pim kinase.

The disclosure includes methods of making a Formula I compound.

Another aspect of the disclosure is a pharmaceutical composition comprised of a compound having the structure:



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

DEFINITIONS

When indicating the number of substituents, the term “one or more” refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents. The term “substituent” denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule. The term

"substituted" denotes that a specified group bears one or more substituents. Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

The term "alkylene" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkylene radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkylene radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), and the like.

The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations,

or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenyl or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), and the like.

The term "alkenylene" refers to linear or branched-chain divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenylene radical may be optionally substituted substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenylene or vinylene (-CH=CH-), allyl (-CH_2CH=CH-), and the like.

The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynyl (-C≡CH), propynyl (propargyl, -CH_2C≡CH), and the like.

The term "alkynylene" refers to a linear or branched divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynylene radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynylene (-C≡C-), propynylene (propargylene, -CH_2C≡C-), and the like.

The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Spiro moieties are also included within the scope of this definition. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like. Carbocyclyl groups are optionally substituted independently with one or more substituents described herein.

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated

ring, or aromatic carbocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryl groups are optionally substituted independently with one or more substituents described herein.

"Arylene" means a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some arylene groups are represented in the exemplary structures as "Ar". Arylene includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical arylene groups include, but are not limited to, radicals derived from benzene (phenylene), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Arylene groups are optionally substituted with one or more substituents described herein.

The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, azocan-1-yl, azetidin-1-yl, octahydropyrido[1,2-a]pyrazin-2-yl, [1,4]diazepan-1-yl, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl,

pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 2 ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired

physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.,* epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor

antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. Examples of chemotherapeutic agents include: erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo-2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (MEK inhibitor, Exelixis, WO 2007/044515), ARRY-886 (MEK inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), a rapamycin analog, mTOR inhibitor such as everolimus, a MEK inhibitor (GDC-0973), a Bcl-2 inhibitor such as navitoclax, (ABT-263) or ABT-199), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin

1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma1I, calicheamicin omegaI1 (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®,

Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (CAMPATH®), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), and tositumomab (BEXXAR®, Corixa, GlaxoSmithKline).

Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the Formula I compounds of the invention include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lebrikizumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab,

nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a Formula I compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers,

and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. Enantiomers may be separated from a racemic mixture by a chiral separation method, such as supercritical fluid chromatography (SFC). Assignment of configuration at chiral centers in separated enantiomers may be tentative, and depicted in Table 1 structures for illustrative purposes, while stereochemical determination awaits, such as x-ray crystallographic data.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid,

succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid "mesylate", ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and polyamine resins

A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

The term "EC_{50}" is the half maximal effective concentration" and denotes the plasma concentration of a particular compound required for obtaining 50% of the maximum of a particular effect in vivo.

The term "Ki" is the inhibition constant and denotes the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g. a radioligand) was present. Ki values can be converted logarithmically to pKi values (-log Ki), in which higher values indicate exponentially greater potency.

The term "IC_{50}" is the half maximal inhibitory concentration and denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC_{50} values can be converted logarithmically to pIC_{50} values (-log IC_{50}), in which higher values indicate exponentially greater potency. The IC_{50} value is not an absolute value but depends on experimental conditions e.g. concentrations employed, and can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem. Pharmacol. (1973) 22:3099).

The terms "compound of this invention," and "compounds of the present invention" and "compounds of Formula I" include compounds of Formulas I and stereoisomers, geometric

isomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof.

Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

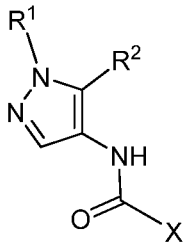
Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to 2H (deuterium, D), 3H (tritium), 11C, 13C, 14C, 15N, 18F, 31P, 32P, 35S, 36Cl, and 125I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent in the compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the

compounds of this invention any atom specifically designated as a deuterium (D) is meant to represent deuterium.

CYCLIC ETHER PYRAZOL-4-YL-HETEROCYCLYL-CARBOXAMIDE COMPOUNDS

The present invention provides cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds of Formula I, including Formulas Ia-i, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by Pim kinases.

Formula I compounds have the structure:

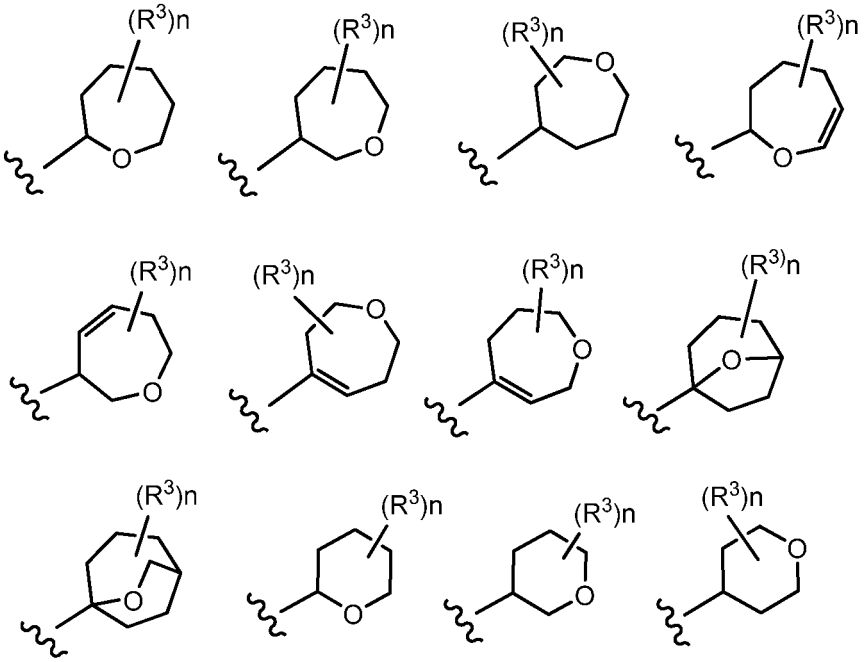


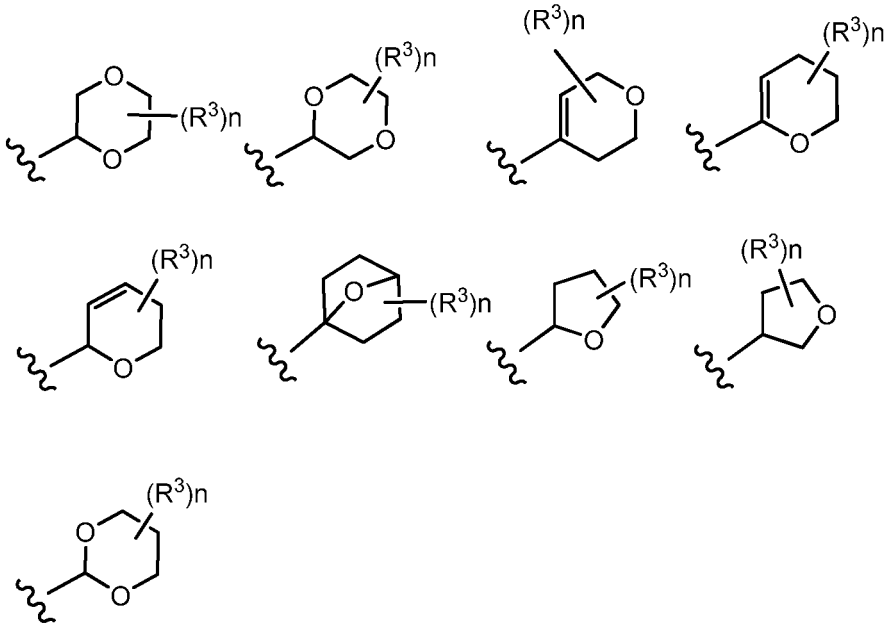
I

and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, C_1–C_{12} alkyl, C_2–C_{12} alkenyl, C_2–C_{12} alkynyl, C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl);

R^2 is selected from the structures:





where the wavy line indicates the site of attachment;

R^3 is independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH=CH_2$, $-CH=C(CH_3)_2$, $=CH_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COCH_2NH_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OCH_2Cl_3$, $-NHC(O)OC_6H_5$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH(CH_3)_2$, $-OC(CH_3)_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, oxetan-3-ylmethylamino, (3-methyloxetan-3-yl)methylamino, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino;

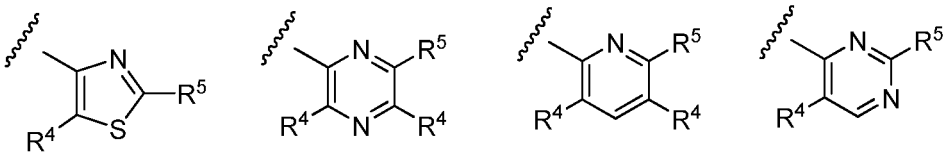
or where two geminal R^3 groups form a spiro ring selected from a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidinyl, piperazinyl, or piperidinyl ring, where the spiro ring is optionally substituted with one or more groups independently selected from $-F$, $-OH$, $=O$, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

or where two vicinal R^3 groups form a five-membered or six-membered heterocyclyl fused ring, where the heterocyclyl fused ring is optionally substituted with one or more groups

independently selected from –F, –OH, =O, $–CH_3$, $–NH_2$, $–CH_2F$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2NH_2$, and $–CF_3$;

n is 0, 1, 2, 3, 4, 5, or 6;

X is selected from the structures:



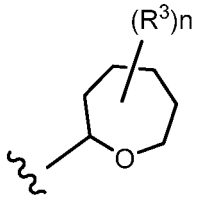
where the wavy line indicates the site of attachment;

R^4 is independently H, F, $–CH_3$, or $–NH_2$; and

R^5 is selected from H, Cl, Br, C_1–C_{12} alkyl, –O–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_2–C_8 alkenylene)–(C_3–C_{12} carbocyclyl), –(C_2–C_8 alkenylene)–(C_2–C_{20} heterocyclyl), C_6–C_{20} aryl, –(C_6–C_{20} arylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–(C_6–C_{20} arylene), –(C_6–C_{20} arylene)–(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_1–C_{12} alkyl), C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl), and –(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl); where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2NH_2$, $–CH_2CH_2NH_2$, $–CH_2CHCH_2NH_2$, $–CH_2CH(CH_3)NH_2$, $–CH_2OH$, $–CH_2CH_2OH$, $–CH(CH_2OH)_2$, $–C(CH_2OH)_3$, $–CH(CH_3)OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, –CN, $–CF_3$, $–CHF_2$, $–CH_2F$, $–CO_2H$, $–COCH_3$, $–COCH(CH_3)_2$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NO_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, –OH, $–OCH_3$, $–OCF_3$, $–OCH(CH_3)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–CH_2OCH_3$, $–S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, phenyl, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino.

Exemplary embodiments of Formula I compounds include wherein R^1 is H, C_1–C_{12} alkyl including $–CH_3$, $–CH_2CH_3$, $–CH_2CHF_2$, and $–CH_2CF_3$, C_3–C_{12} carbocyclyl, or –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl) including oxetan-3-ylmethyl.

Exemplary embodiments of Formula I compounds include wherein R^2 has the structure:



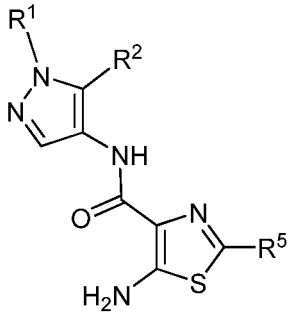
Exemplary embodiments of Formula I compounds include wherein R^3 is independently selected from F, Cl, –OH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCH_2CHF_2$, $–NHCH_2CF_3$, $–CH_2NHCH_3$, and $–OCH_3$; and n is 1, 2, or 3.

Exemplary embodiments of Formula I compounds include wherein R^4 is $–NH_2$.

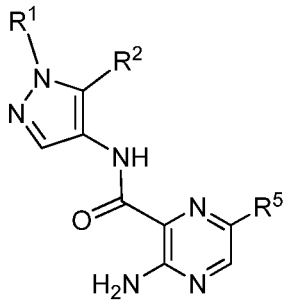
In a particular embodiments of Formula R^4 is –H.

Exemplary embodiments of Formula I compounds include wherein R^5 is C_6–C_{20} aryl including phenyl substituted with one or more F.

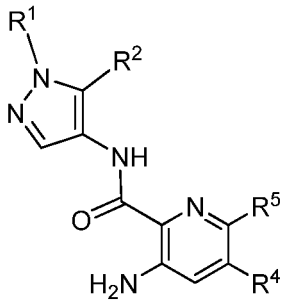
Exemplary embodiments of Formula I compounds include the structures of Formula Ia-d:



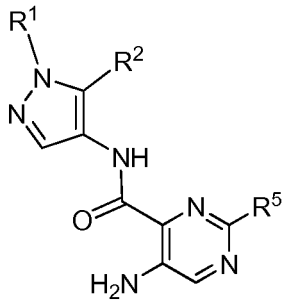
Ia



Ib



Ic



Id

BIOLOGICAL EVALUATION

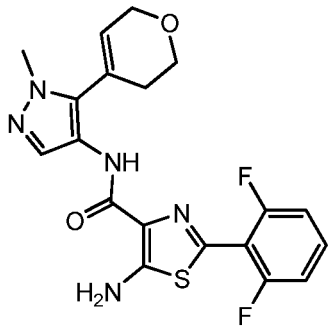
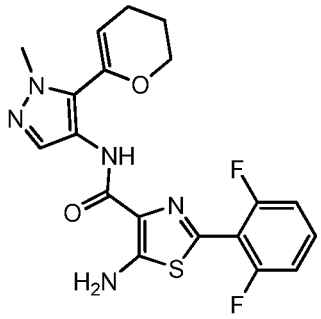
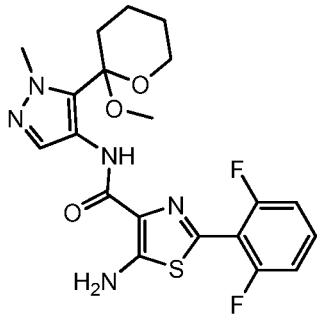
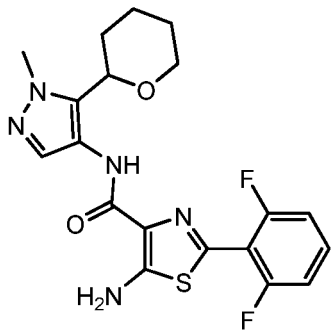
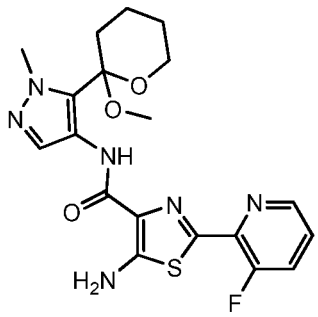
Determination of the Pim kinase activity of a Formula I compound is possible by a number of direct and indirect detection methods. Certain exemplary compounds described herein were assayed for their Pim kinase binding activity, including isoforms Pim-1, Pim-2, and Pim-3, (Example 901) and *in vitro* activity against tumor cells (Example 902). Certain exemplary compounds of the invention had Pim binding activity IC_{50} values less than about 1 micromolar (μM). Certain compounds of the invention had tumor cell-based activity EC_{50} values less than about 1 micromolar (μM), for example against cell line BaF3, a murine interleukin-3 dependent pro-B cell line, useful as a model system for assessing both the potency and downstream signaling of kinase oncogenes ("Ba/F3 cells and their use in kinase drug

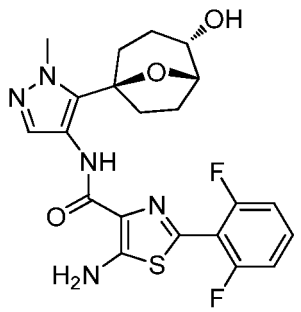
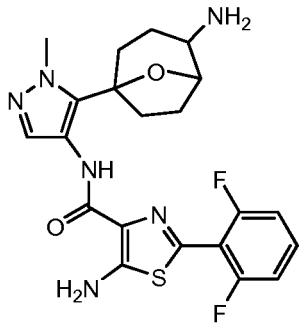
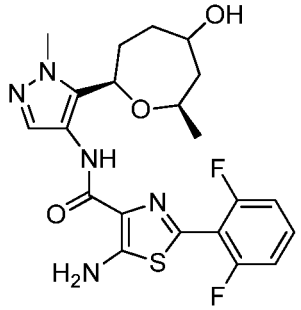
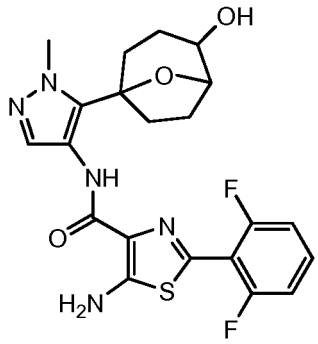
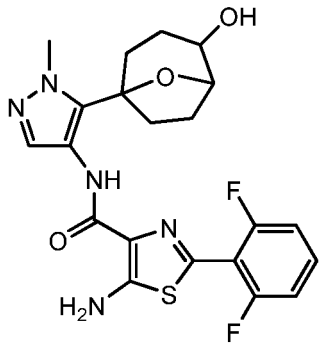
discovery", Warmuth, M, et al, (January 2007) Current Opinion in Oncology, Vol 19(l):55-60), and against MM1.S, a multiple myeloma cell line, useful as a model system for assessing the efficacy of Pim inhibitors in the treatment of multiple myeloma patients (Greenstein et al (2003) Exper. Hematol. 31(4):271-282). Formula I compounds having Ki/IC_{50}/EC_{50} of less than 1 μM in assays described in Examples 901 and 902, may be useful therapeutically as Pim kinase inhibitors (Pim-1, Pim-2 and/or Pim-3).

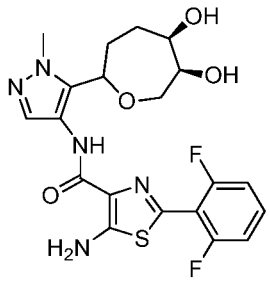
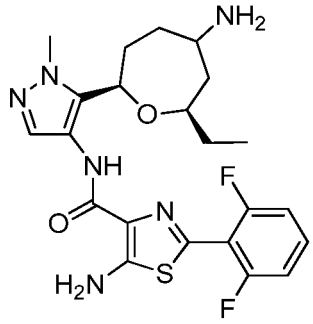
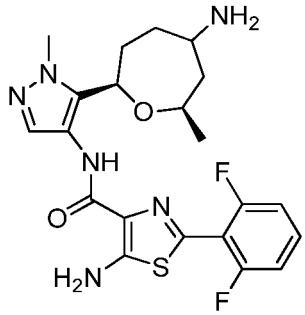
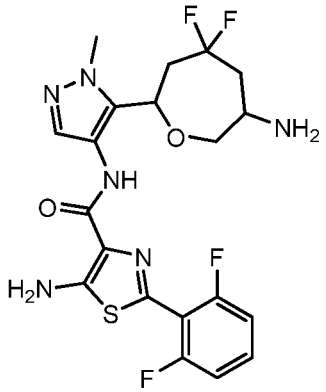
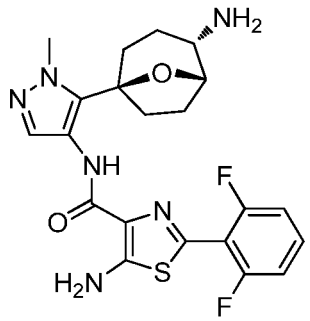
hERG (the human *Ether-à-go-go*-Related Gene) is a gene (*KCNH2*) that codes for a protein known as K_v11.1, the alpha subunit of a potassium ion channel. This ion channel (sometimes simply denoted as 'hERG') is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating (i.e., the hERG channel mediates the repolarizing I_{Kr} current in the cardiac action potential). When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised, either by application of drugs or by rare mutations in some families (Hedley PL et al. (2009) Human Mutation 30 (11): 1486-511), it can result in a potentially fatal disorder called long QT syndrome; a number of clinically successful drugs in the market have had the tendency to inhibit hERG, and create a concomitant risk of sudden death, as a side-effect, which has made hERG inhibition an important antitarget that must be avoided during drug development (Sanguinetti MC, Tristani-Firouzi M (March 2006) Nature 440(7083): 463-9). hERG has also been associated with modulating the functions of some cells of the nervous system (Chiesa N et al (June 1997) J. Physiol. (Lond.). 501 (Pt 2) (2): 313-8; Overholt JL, et al (2000) Adv. Exp. Med. Biol. 475: 241-8) and with establishing and maintaining cancer-like features in leukemic cells. hERG assays were conducted according to Example 903.

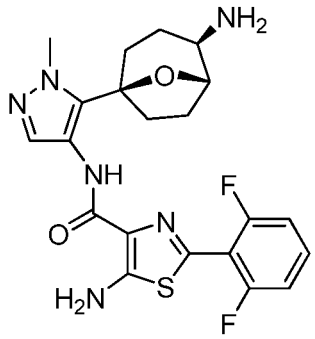
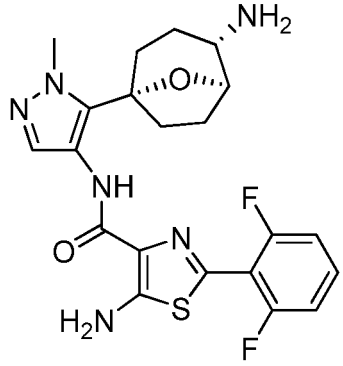
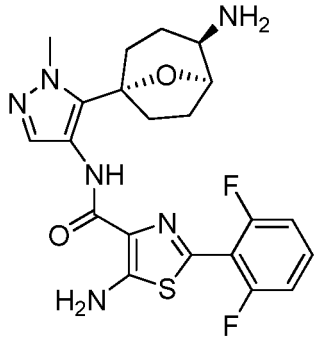
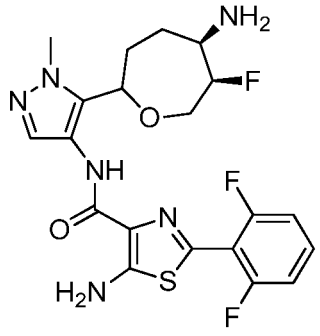
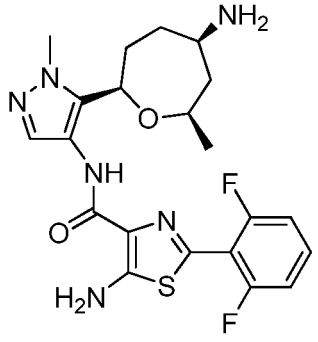
Exemplary Formula I compounds in Tables 1a, 1b, and 1c were made, characterized, and tested for inhibition of Pim kinase according to the methods of this invention, and have the following structures and corresponding names (ChemBioDraw Ultra, Version 11.0, CambridgeSoft Corp., Cambridge MA). Some compounds with chiral atoms in Table 1 have not been fully characterized as to stereochemistry. A tentative assignment of stereochemistry or stereochemical relationship to other groups may be depicted in the structures. Means of separation of stereoisomers and characterization data are given in the Examples.

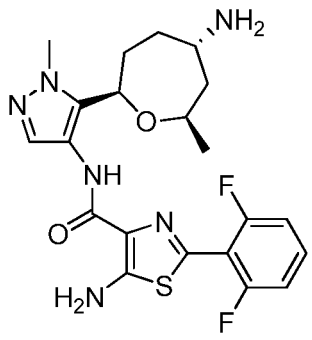
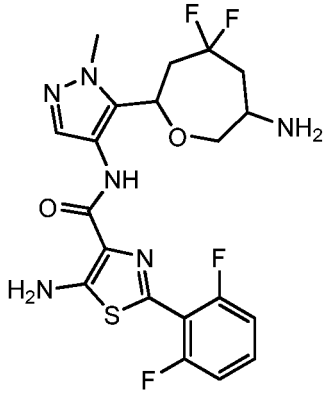
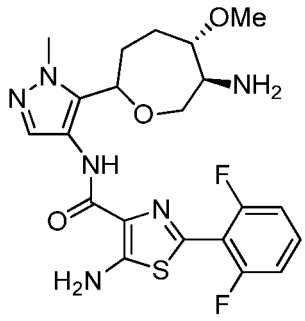
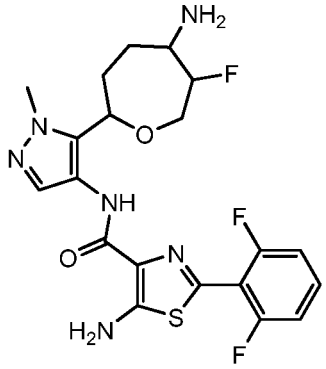
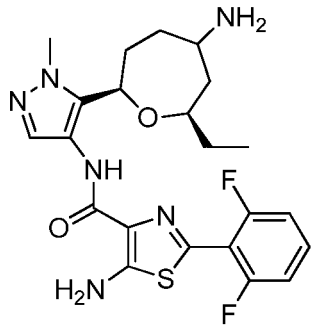
Table 1a.

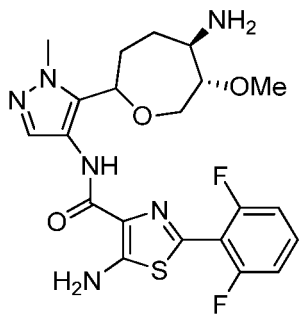
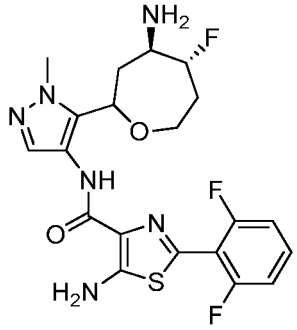
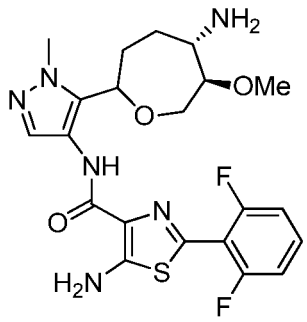
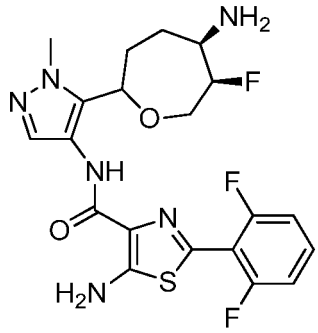
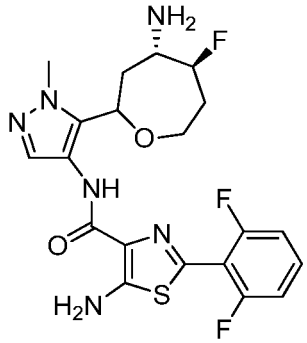
No.	Structure	IUPAC Name	PIM1 LC3K (KI) uM
101		5-amino-2-(2,6-difluorophenyl)-N-[5-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000485
102		5-amino-2-(2,6-difluorophenyl)-N-[5-(3,4-dihydro-2H-pyran-6-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000408
103		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000209
104		5-amino-2-(2,6-difluorophenyl)-N-(1-methyl-5-tetrahydropyran-2-yl-pyrazol-4-yl)thiazole-4-carboxamide	0.000424
105		5-amino-2-(3-fluoro-2-pyridyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000118

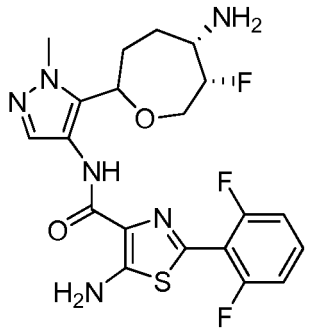
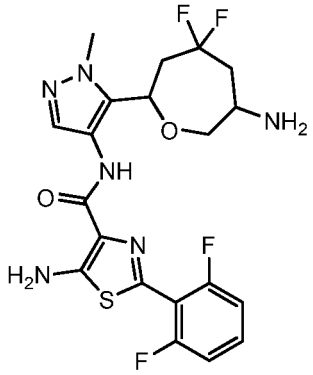
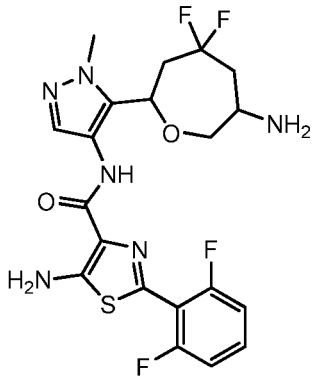
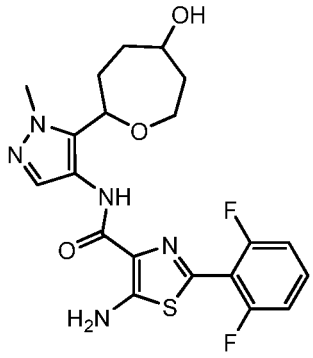
106		5-amino-2-(2,6-difluorophenyl)-N-(5-((1S,4S,5S)-4-hydroxy-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000032
107		5-amino-N-[5-(2-amino-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000008
108		5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,7R)-5-hydroxy-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000049
109		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000034
110		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000017

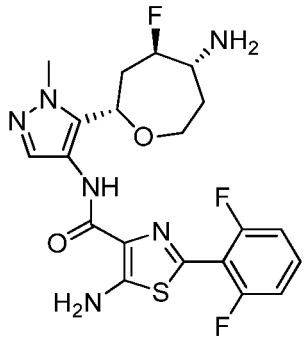
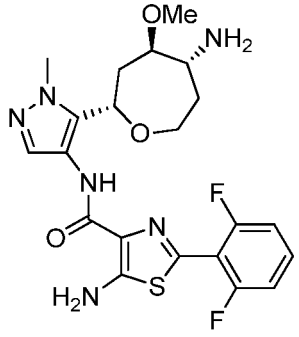
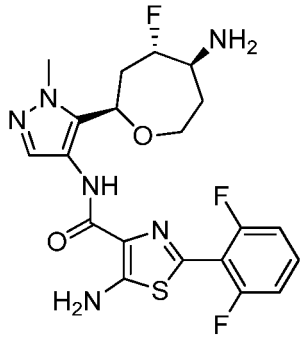
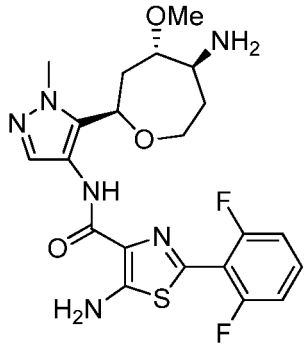
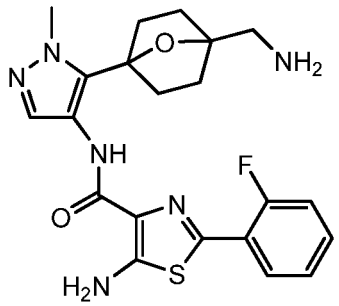
111		5-amino-2-(2,6-difluorophenyl)-N-(5-((5R,6S)-5,6-dihydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000425
112		5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000502
113		5-amino-N-(5-((2R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000019
114		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000032
115		5-amino-N-(5-((1S,4S,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000006

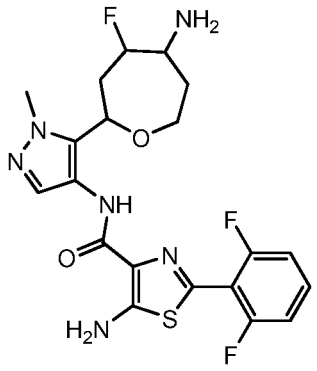
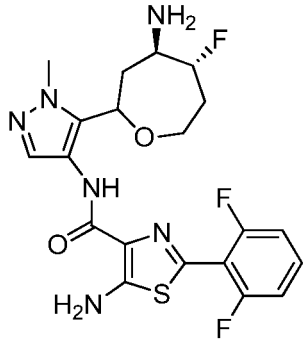
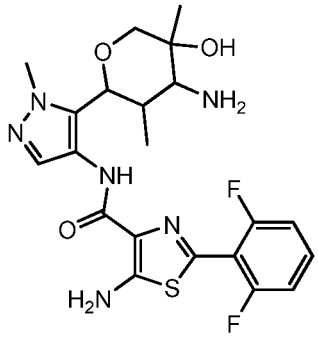
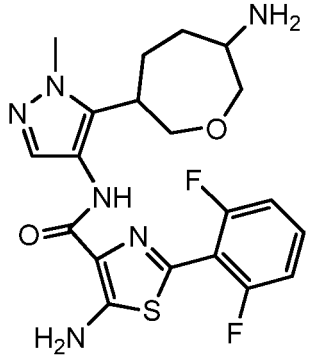
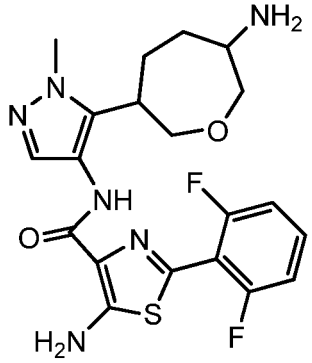
116		5-amino-N-(5-((1S,4R,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000072
117		5-amino-N-(5-((1R,4S,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000002
118		5-amino-N-(5-((1R,4R,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000009
119		5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000021
120		5-amino-N-(5-((2R,5R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000081

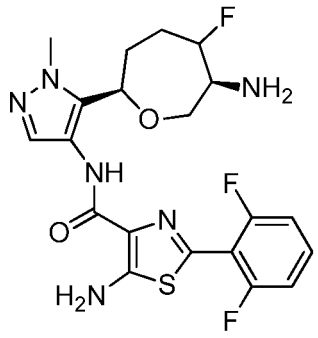
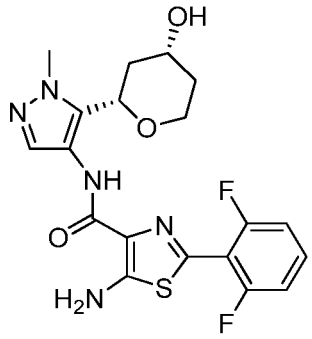
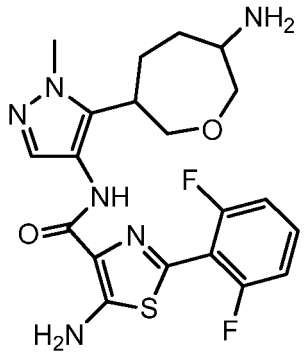
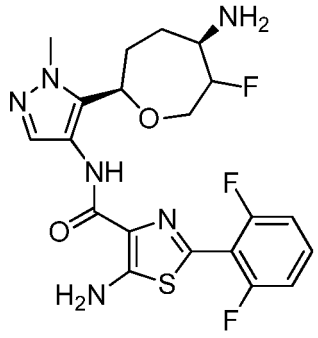
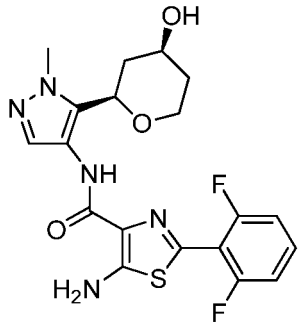
121		5-amino-N-(5-((2R,5S,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000003
122		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014
123		5-amino-N-(5-((5S,6S)-6-amino-5-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000125
124		5-amino-N-[5-(5-amino-6-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000015
125		5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0035

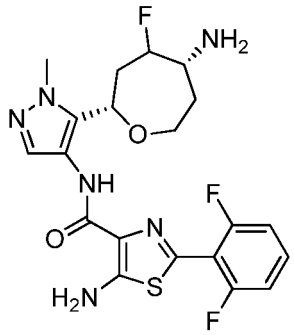
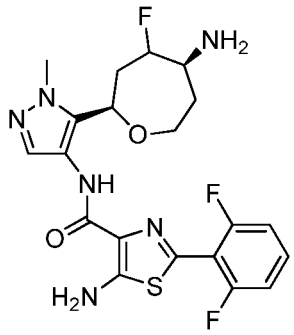
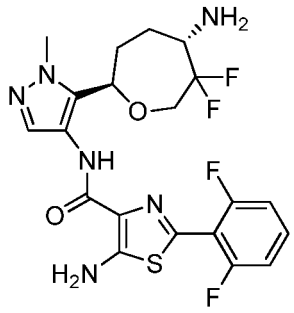
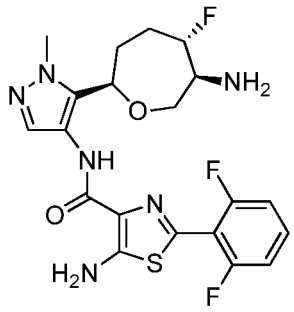
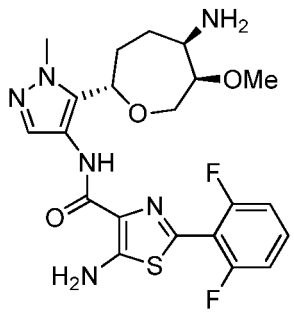
126		5-amino-N-(5-((5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000026
127		5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000112
128		5-amino-N-(5-((5S,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000476
129		5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000006
130		5-amino-N-(5-((4S,5S)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000358

131		5-amino-N-(5-((5S,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00027
132		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014
133		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000076
134		5-amino-2-(2,6-difluorophenyl)-N-[5-(5-hydroxyoxepan-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000054

135		5-amino-N-[5-(5-amino-4-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00001
136		5-amino-N-(5-((2S,4R,5R)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000057
137		5-amino-N-(5-((2R,4S,5S)-5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000099
138		5-amino-N-(5-((2R,4S,5S)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00187
139		5-amino-N-[5-[1-(aminomethyl)-7-oxabicyclo[2.2.1]heptan-4-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000053

140		5-amino-N-(5-(5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000469
141		5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00007
142		5-amino-N-[5-(4-amino-5-hydroxy-3,5-dimethyl-tetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000441
143		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000194
144		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00145

145		5-Amino-*N*-[5-[6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000351
146		5-amino-2-(2,6-difluorophenyl)-N-(5-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000095
147		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000141
148		5-Amino-*N*-[5-[5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000079
149		5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,4S)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000174

150		5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000105
151		5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000068
152		5-Amino-*N*-[5-[(5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000031
153		5-Amino-*N*-[5-[(2*R*,5*S*,6*S*)-6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000114
154		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000080

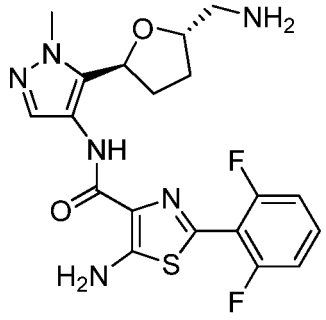
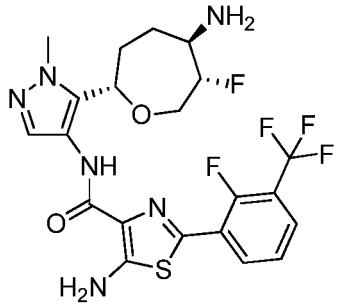
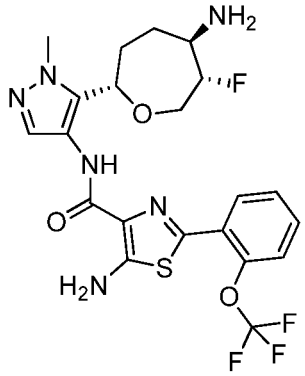
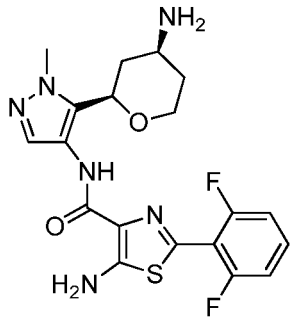
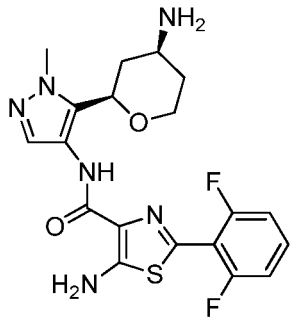
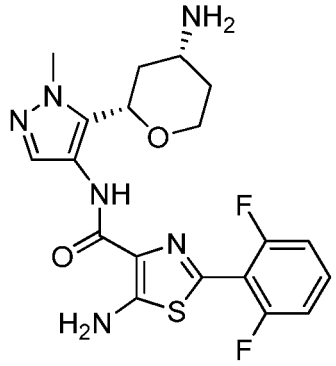
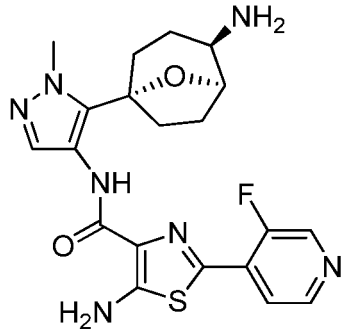
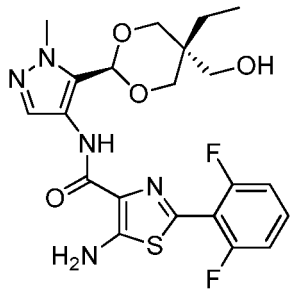
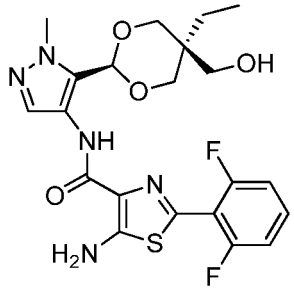
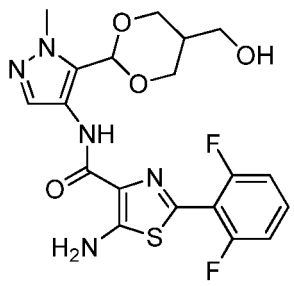
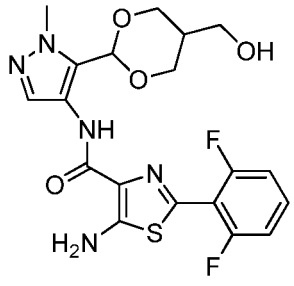
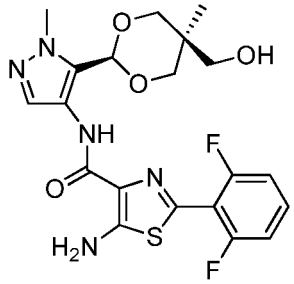
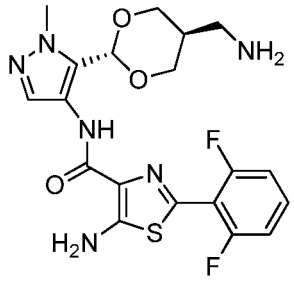
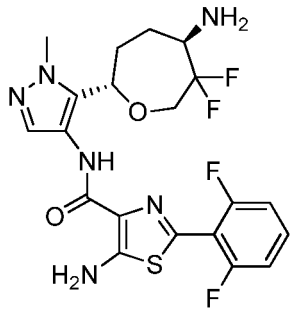
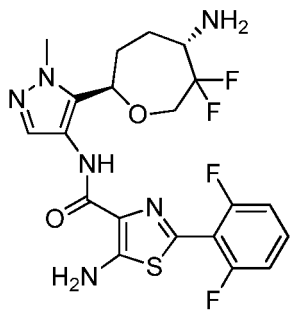
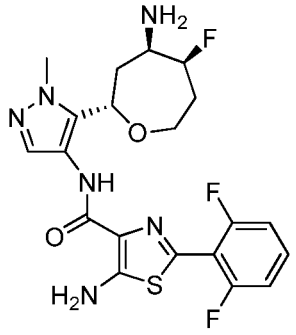
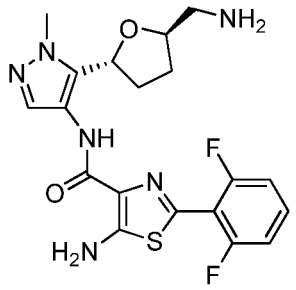
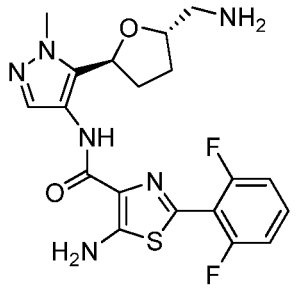
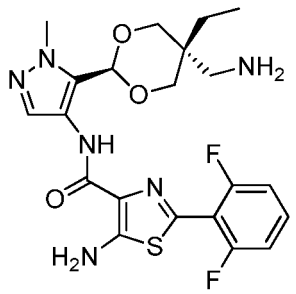
155		5-Amino-*N*-[5-[5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000104

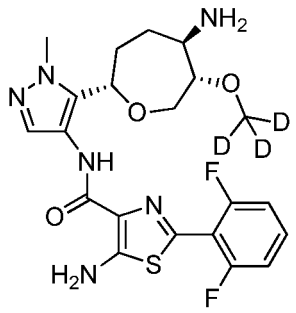
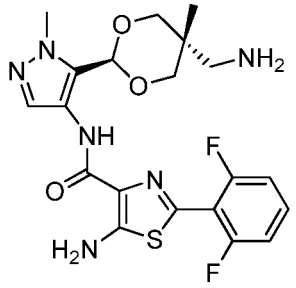
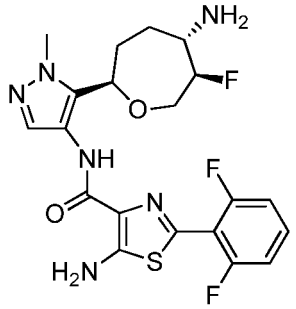
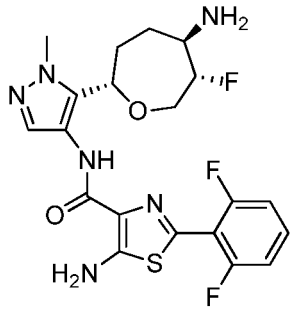
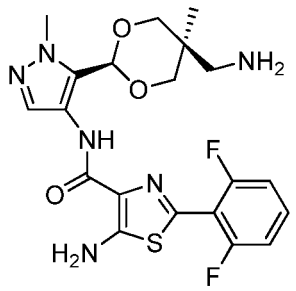
Table 1b.

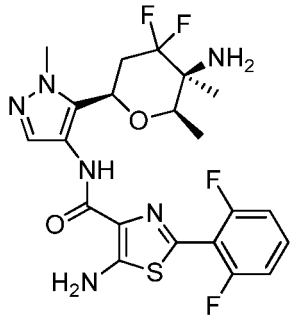
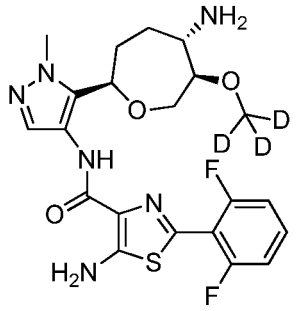
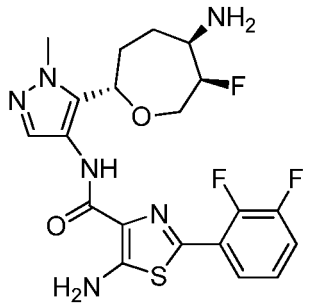
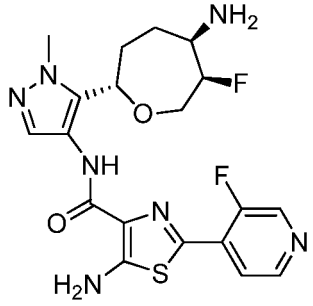
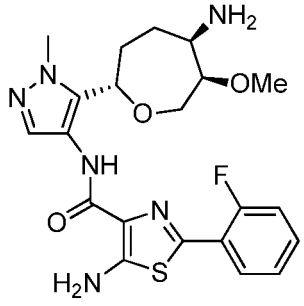
No.	Structure	IUPAC Name	PIM1 LC3K (KI) µM
156		5-amino-N-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000107
157		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide	0.000965
158		Amino-*N*-[5-[4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000032

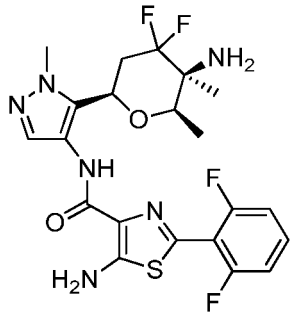
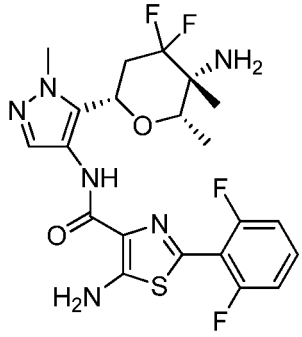
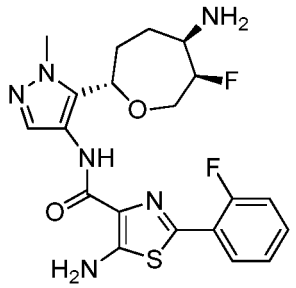
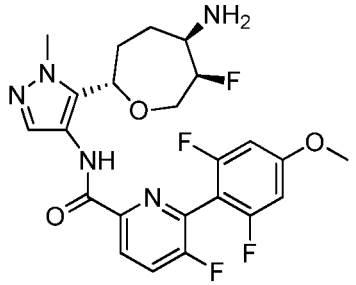
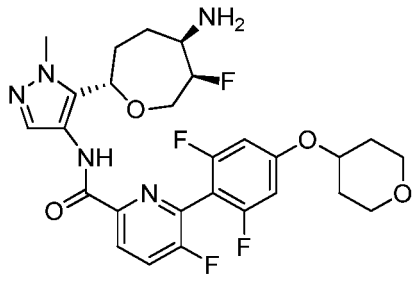
159		5-Amino-*N*-[5-[(2*R*,4*S*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000019
160		5-Amino-*N*-[5-[(2*S*,4*R*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000248
161		5-Amino-*N*-[5-[2-amino-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide	0.000013
162		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000025
163		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.00126

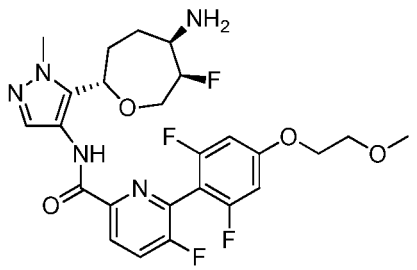
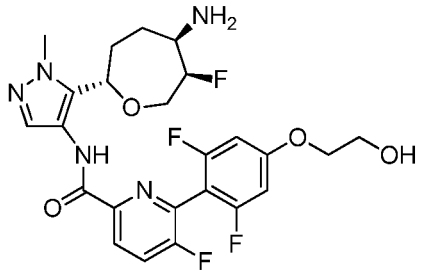
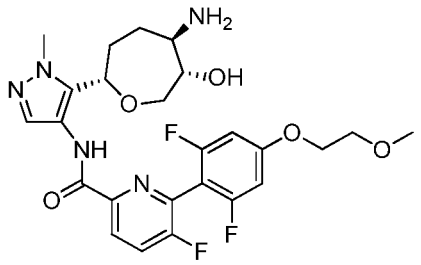
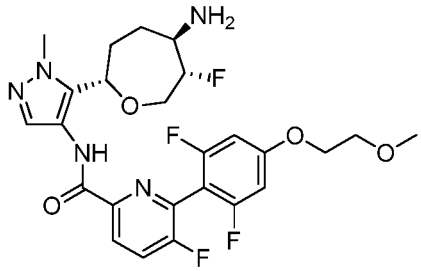
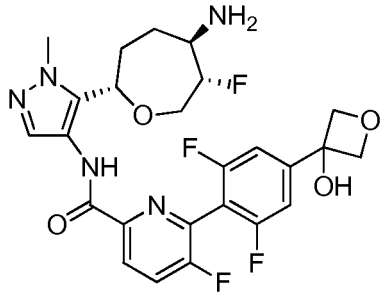
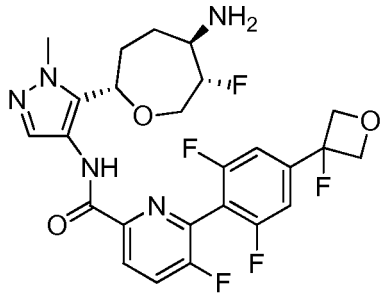
164		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000105
165		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000647
166		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)- 5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000514
167		5-Amino-*N*-[5-[5-(aminomethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000029
168		5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000013

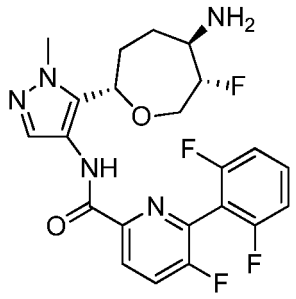
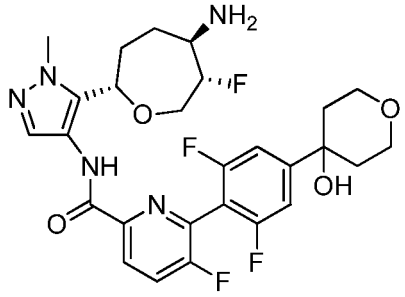
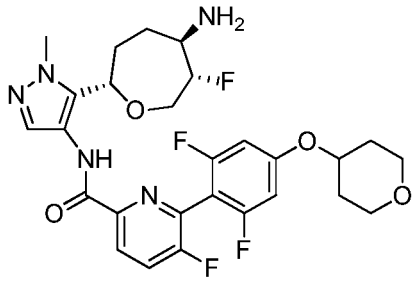
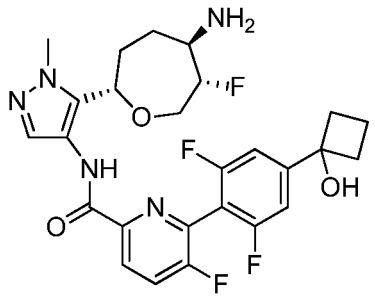
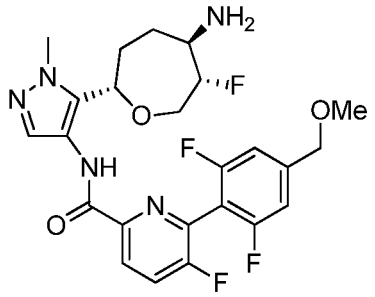
169		5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000341
170		5-Amino-*N*-[5-[4-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000126
171		5-Amino-*N*-[5-[(2*R*,5*R*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000027
172		5-Amino-*N*-[5-[(2*S*,5*S*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00015
173		5-Amino-*N*-[5-[5-(aminomethyl)-5-ethyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000015

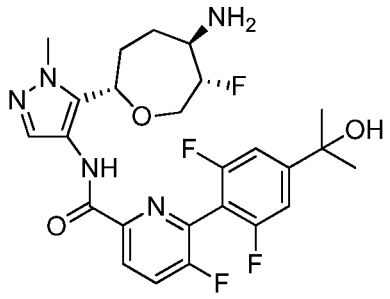
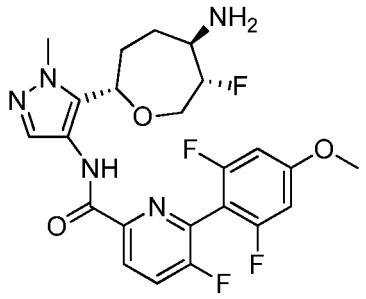
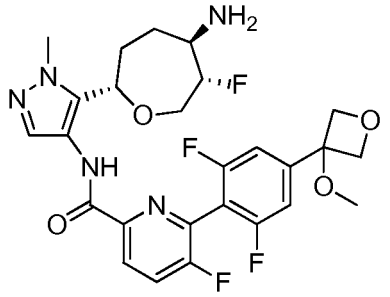
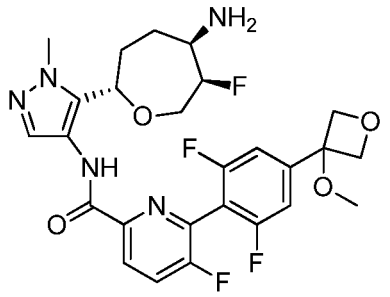
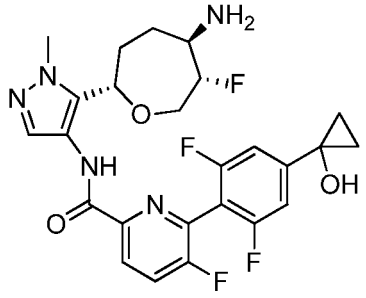
174		5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000135
175		5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000036
176		5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000595
177		5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00000342
178		5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000155

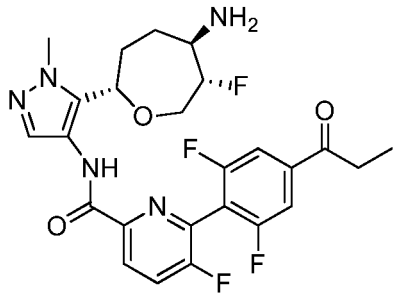
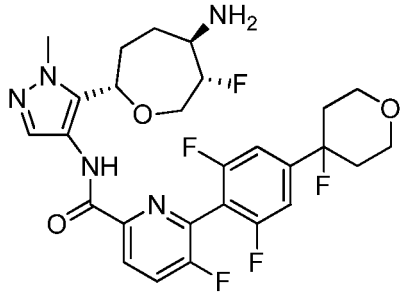
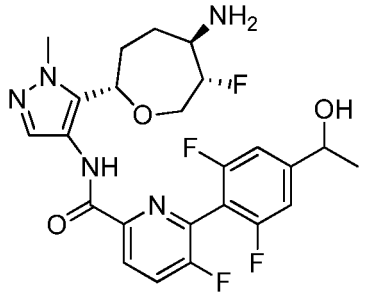
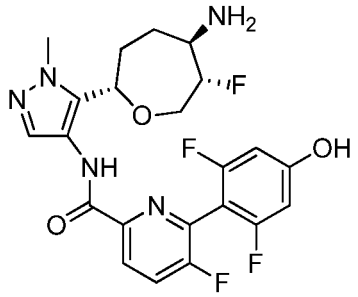
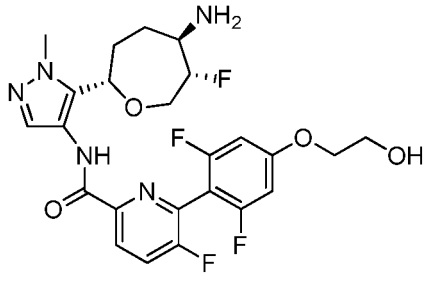
179		5-Amino-*N*-[5-[5-amino-4,4-difluoro-5,6-dimethyl-tetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000456
180		5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000017
181		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000004
182		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide	0.000051
183		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide	0.0000143

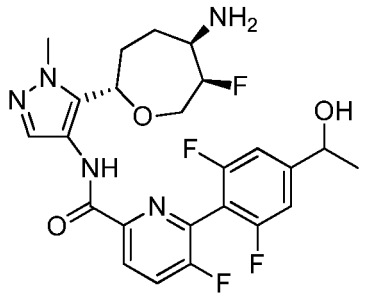
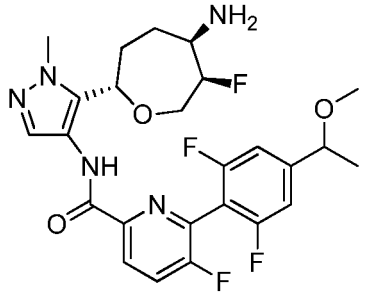
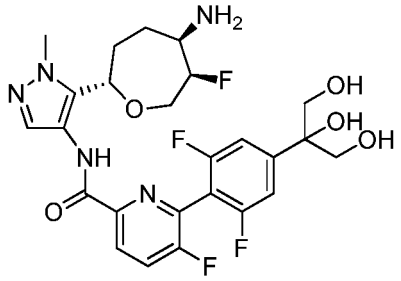
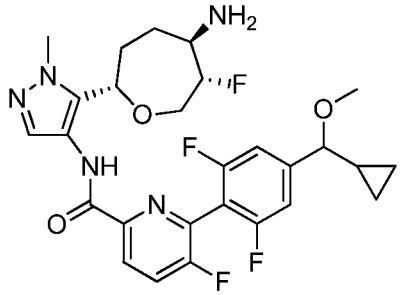
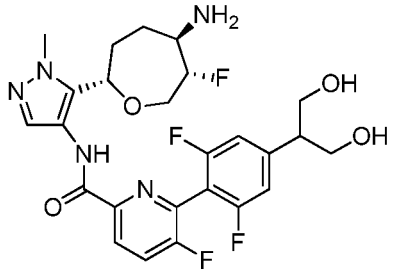
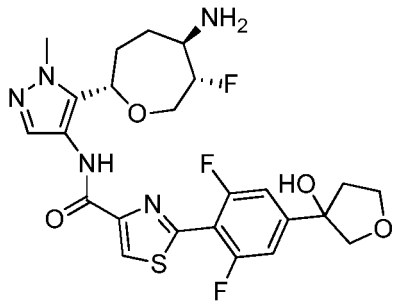
184		5-Amino-*N*-(5-((2*R*,5*S*,6*R*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000484
185		5-Amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00435
186		5-Amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000007
187		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide	0.000027
188		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide	0.00003

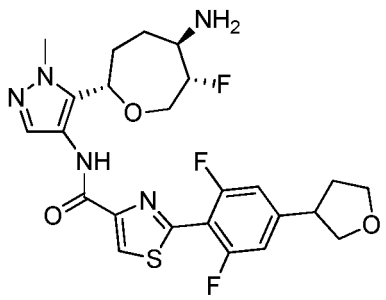
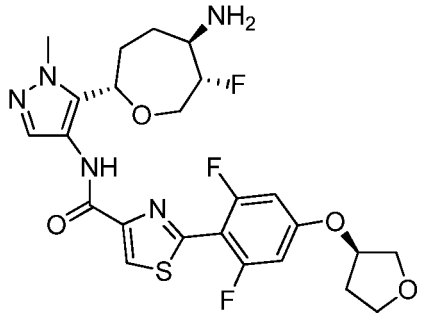
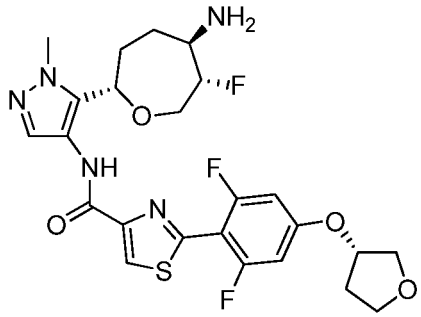
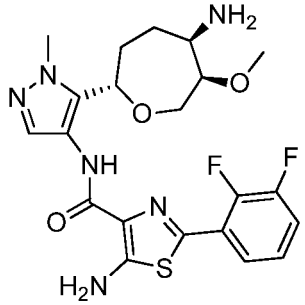
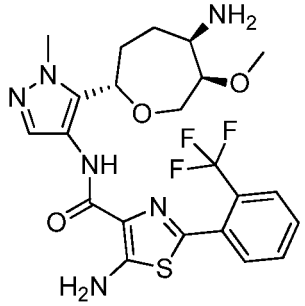
189		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000025
190		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide	0.000014
191		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-hydroxyoxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000056
192		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000023
193		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000034
194		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000022

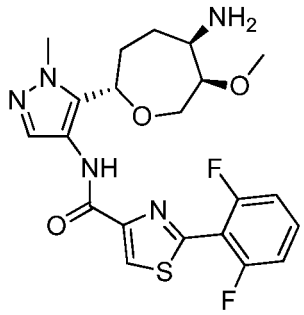
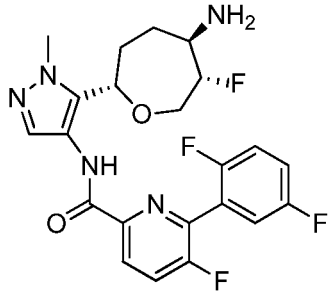
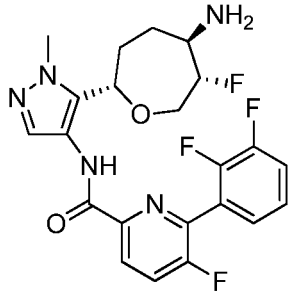
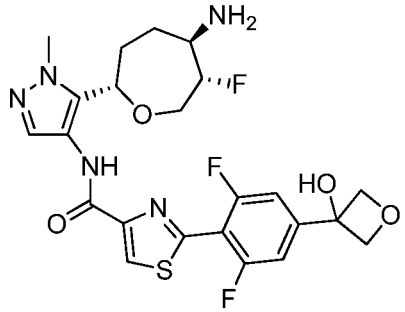
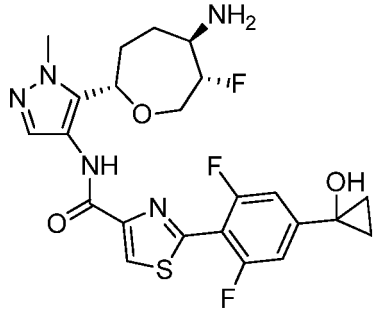
195		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	0.000025
196		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide	0.000006
197		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide	0.000018
198		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide	0.000021
199		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(methoxymethyl)phenyl)-5-fluoropicolinamide	0.000031

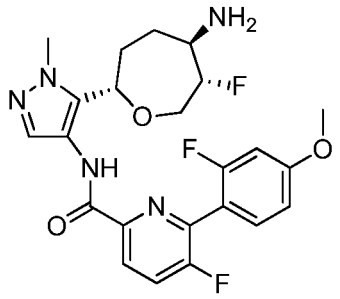
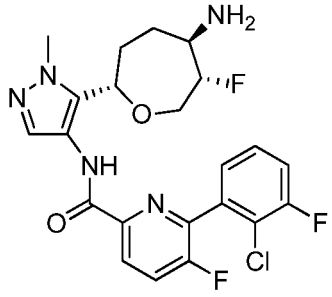
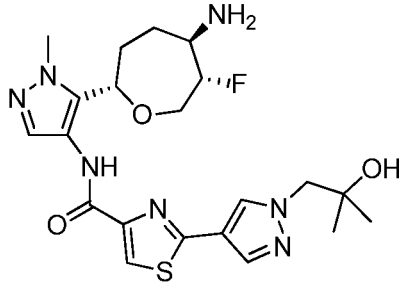
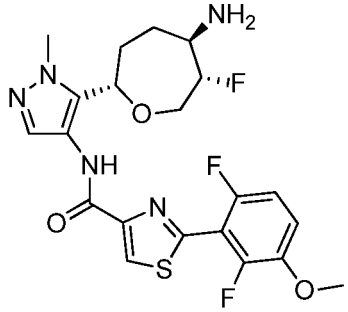
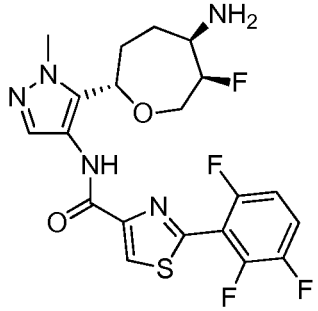
200		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.000011
201		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide	0.000019
202		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000056
203		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000119
204		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)-5-fluoropicolinamide	0.000001

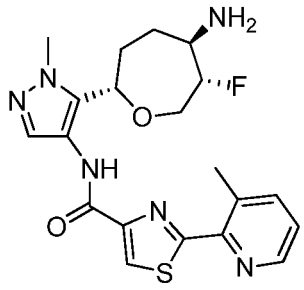
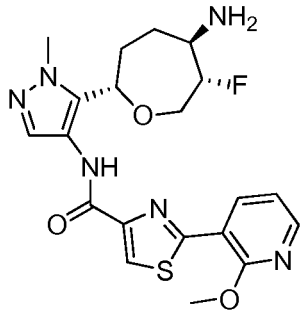
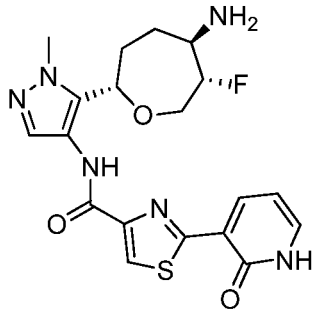
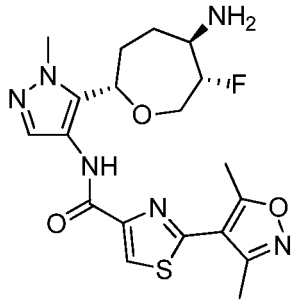
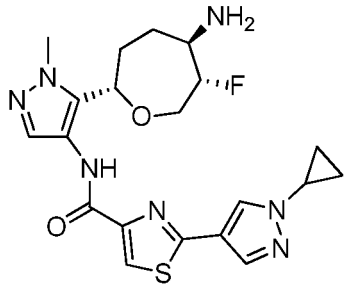
205		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-propionylphenyl)-5-fluoropicolinamide	0.000034
206		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide	0.000016
207		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide	0.000017
208		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide	0.000012
209		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide	0.000016

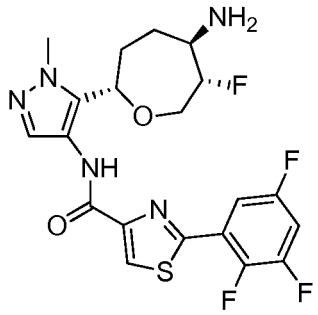
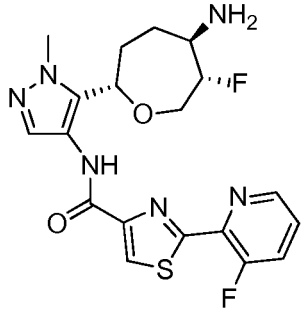
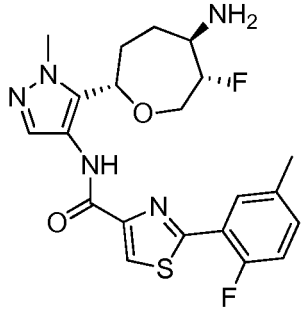
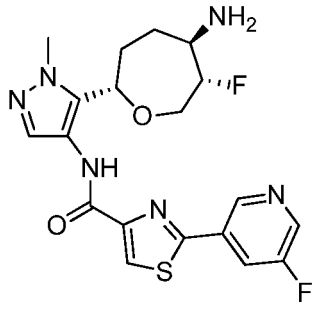
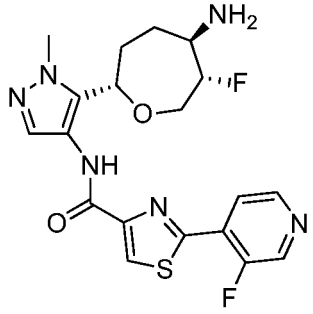
210		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide	0.000053
211		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinamide	0.000037
212		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1,2,3-trihydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.000162
213		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinamide	0.000078
214		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(1,3-dihydroxypropan-2-yl)-2,6-difluorophenyl)-5-fluoropicolinamide	0.000075
215		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide	0.00000762

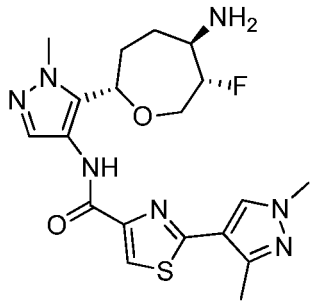
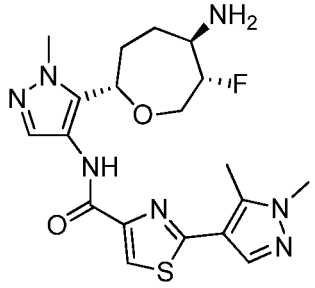
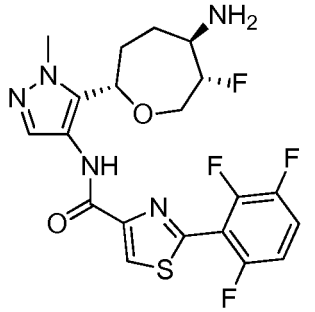
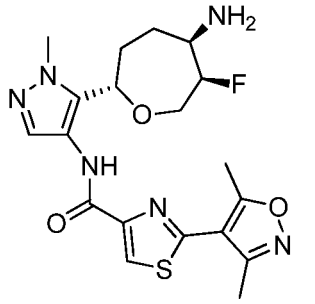
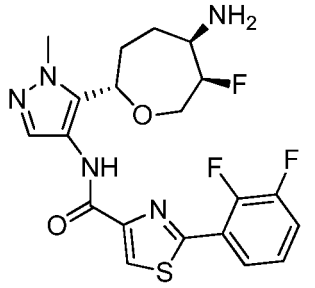
216		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide	0.000011+
217		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*R*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide	0.000003
218		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*S*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide	0.00000224
219		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.00005
220		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000083

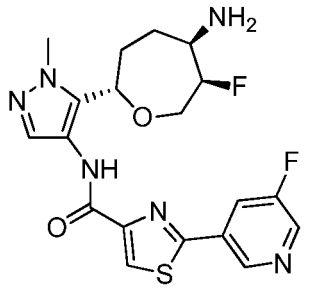
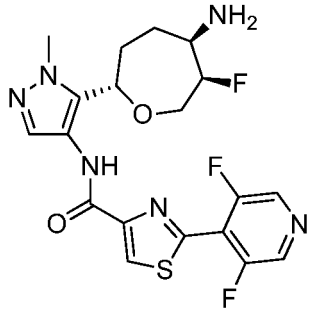
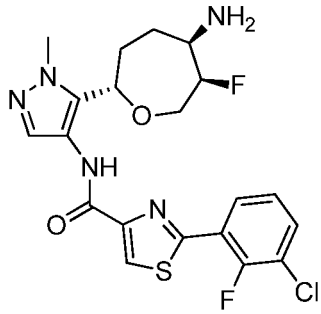
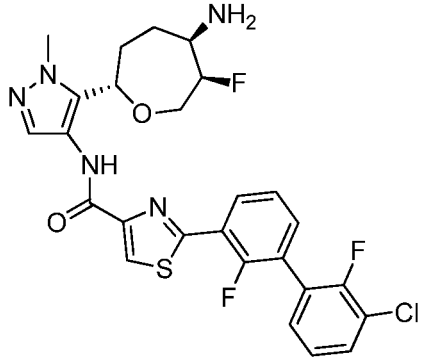
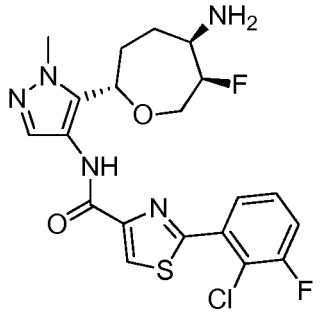
221		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000066
222		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide	0.000161
223		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide	0.000083
224		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000035
225		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)thiazole-4-carboxamide	0.000028

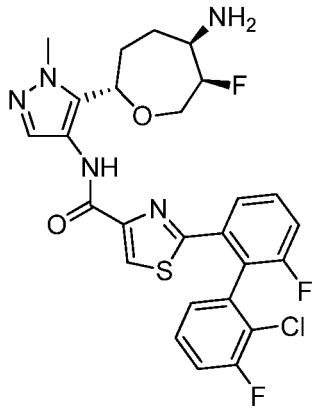
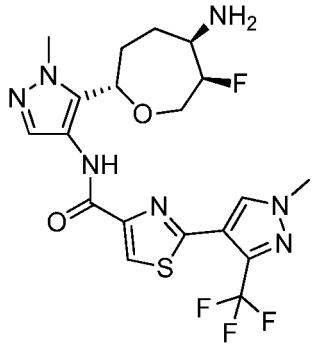
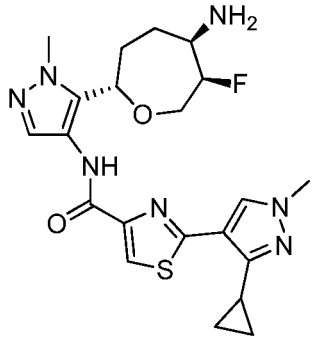
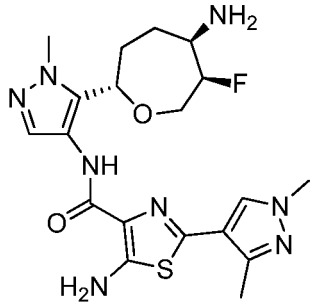
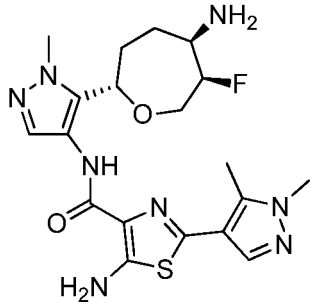
226		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-5-fluoro-6-(2-fluoro-4-methoxyphenyl)picolinamide	0.000036
227		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2-chloro-3-fluorophenyl)-5-fluoropicolinamide	0.00057
228		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000124
229		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000001
230		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000031

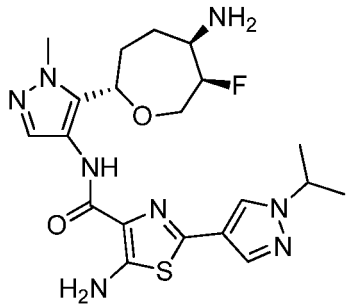
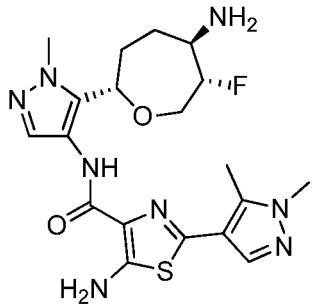
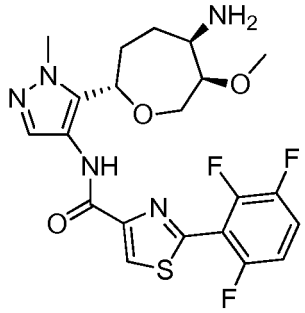
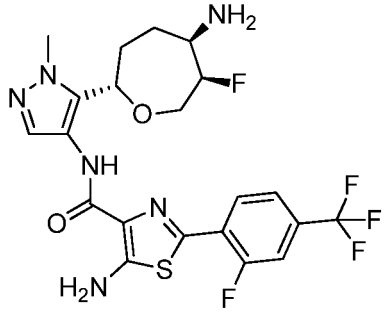
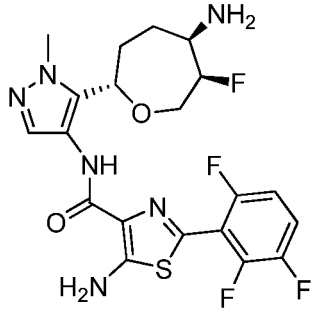
231		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide	0.000045
232		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-methoxypyridin-3-yl)thiazole-4-carboxamide	0.00111
233		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-oxo-1,2-dihydropyridin-3-yl)thiazole-4-carboxamide	0.000103
234		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide	0.000068
235		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-cyclopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000068

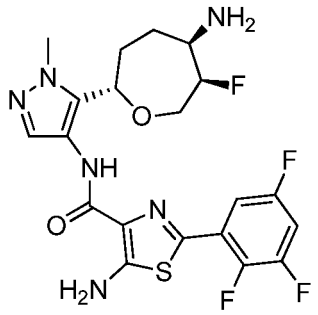
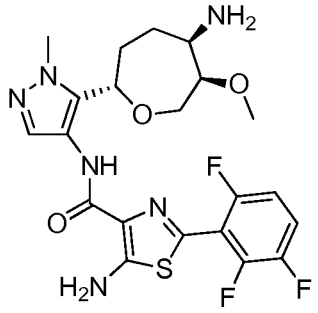
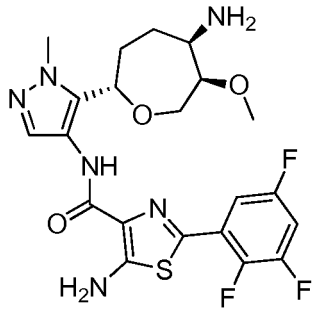
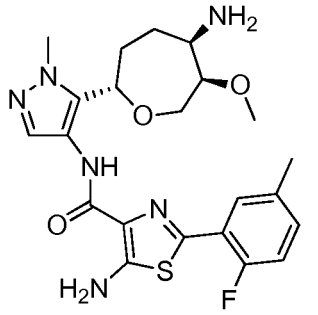
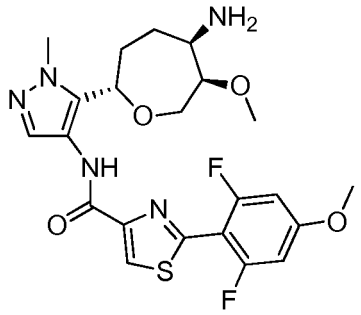
236		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000255
237		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-2-yl)thiazole-4-carboxamide	0.000107
238		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.000048
239		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide	0.00266
240		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide	0.00034

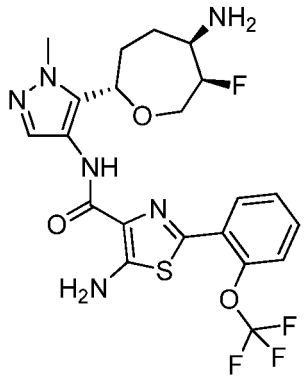
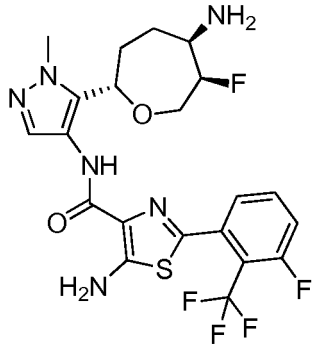
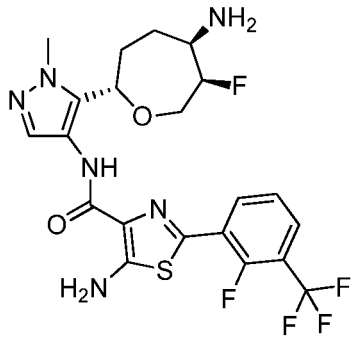
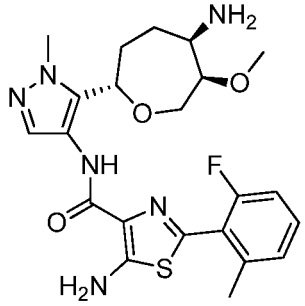
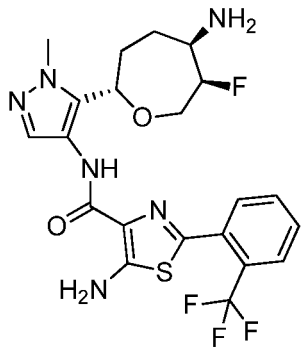
241		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000283
242		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000218
243		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000047
244		N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide	0.00598
245		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000104

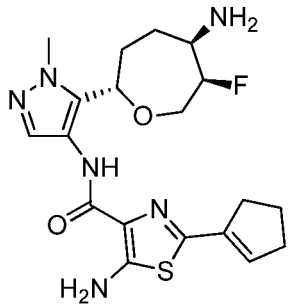
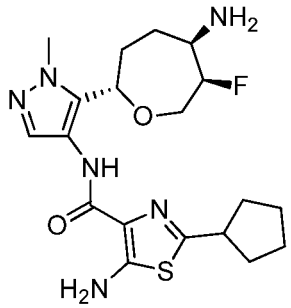
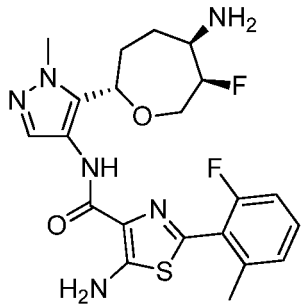
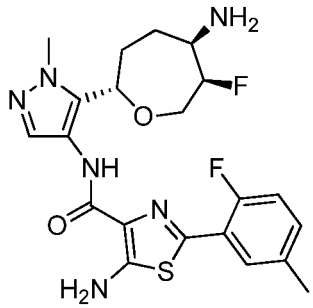
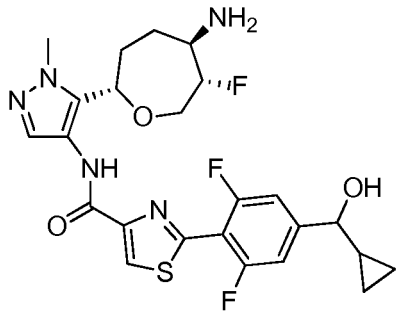
246		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide	0.00576
247		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-difluoropyridin-4-yl)thiazole-4-carboxamide	0.000112
248		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000064
249		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3'-chloro-2,2'-difluoro-[1,1'-biphenyl]-3-yl)thiazole-4-carboxamide	0.000533
250		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000132

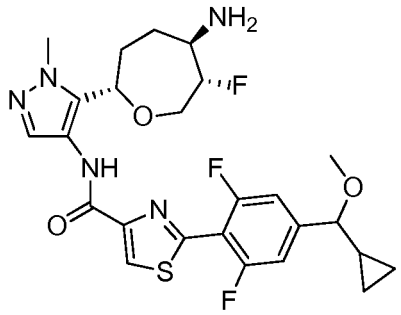
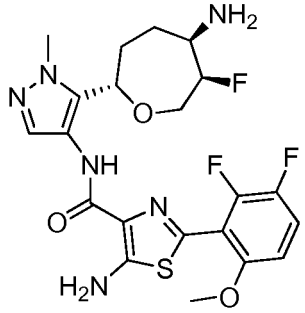
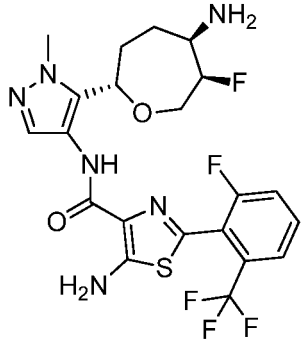
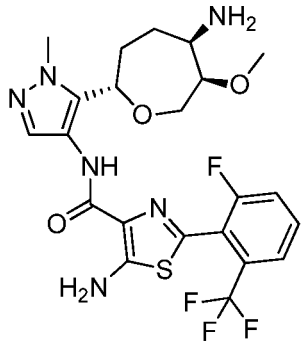
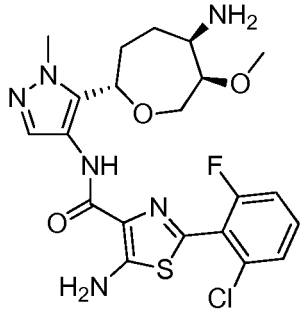
251		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2'-chloro-3',6-difluoro-[1,1'-biphenyl]-2-yl)thiazole-4-carboxamide	0.63
252		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000281
253		N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000253
254		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000026
255		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000007

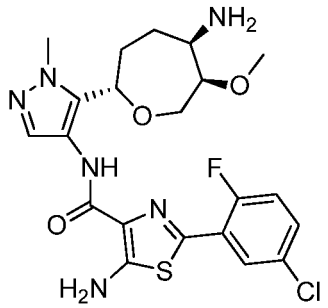
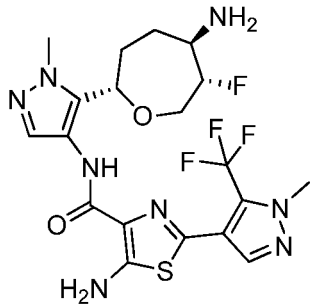
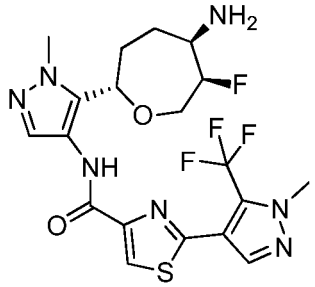
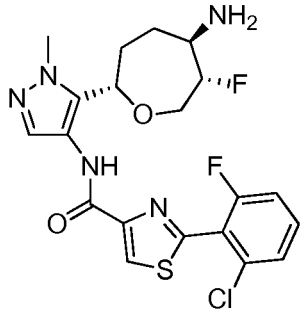
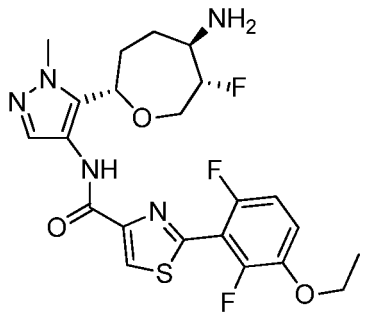
256		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-isopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000093
257		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000025
258		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000145
259		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.00001
260		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000004

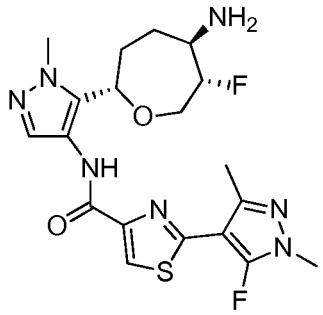
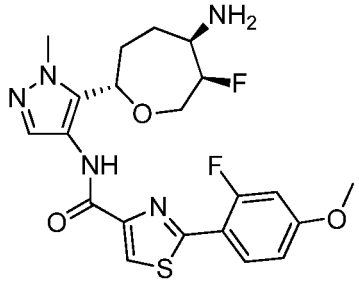
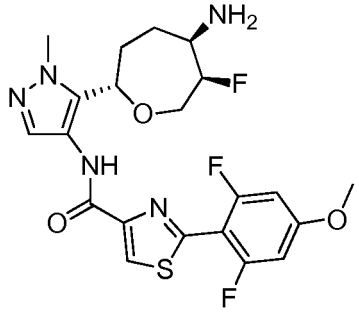
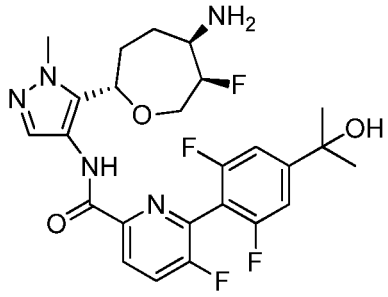
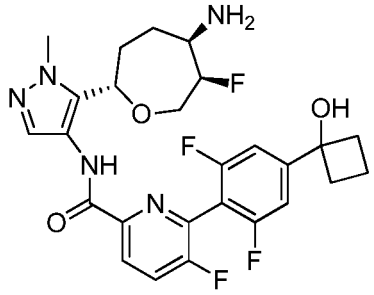
261		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000037
262		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.00001
263		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000127
264		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.00002
265		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000034

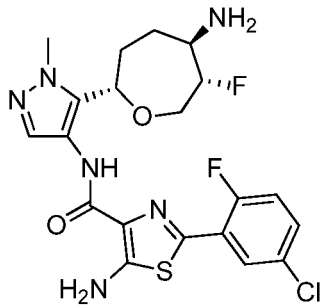
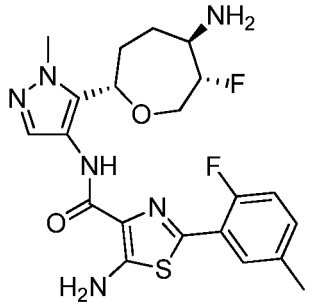
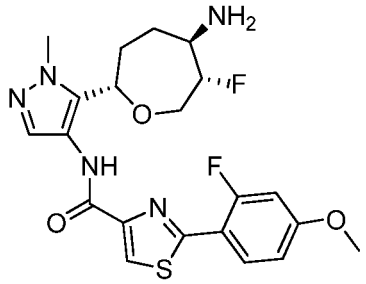
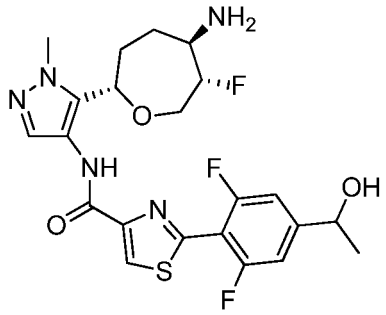
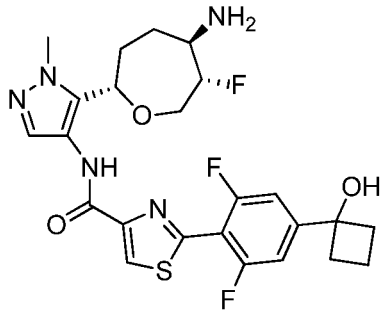
266		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide	0.000155
267		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000098
268		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000028
269		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000052
270		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000053

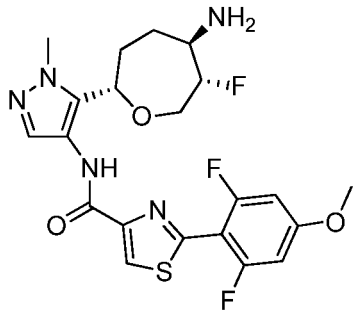
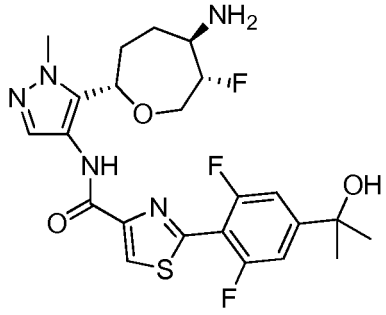
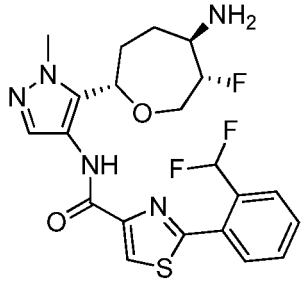
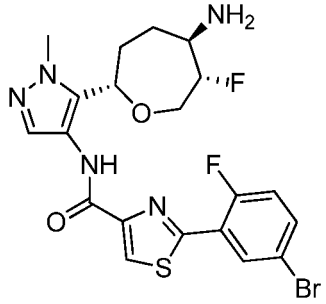
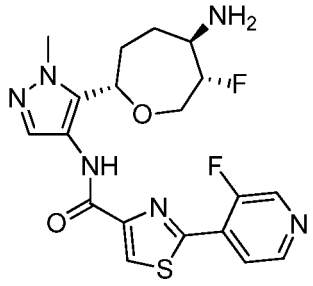
271		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide	0.000062
272		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide	0.000992
273		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000007
274		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.00002
275		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(hydroxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000037

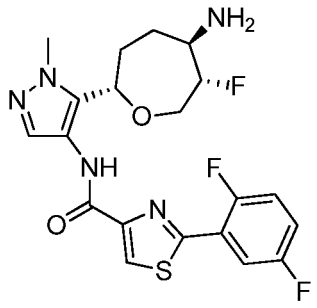
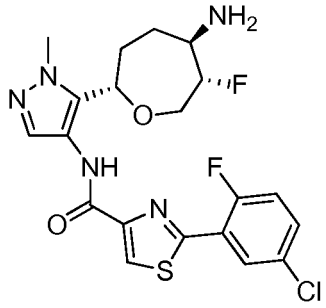
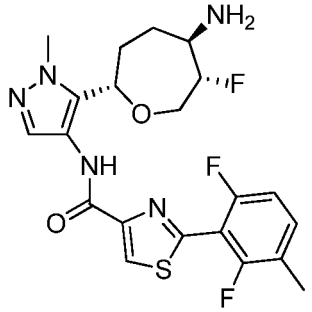
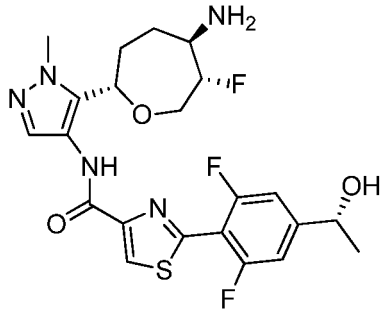
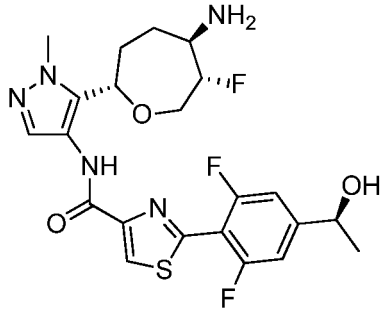
276		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000084
277		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-6-methoxyphenyl)thiazole-4-carboxamide	0.000143
278		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000061
279		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000083
280		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.000014

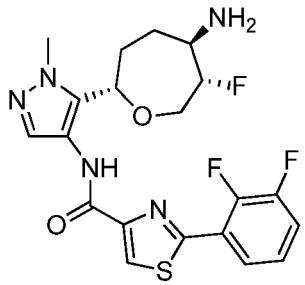
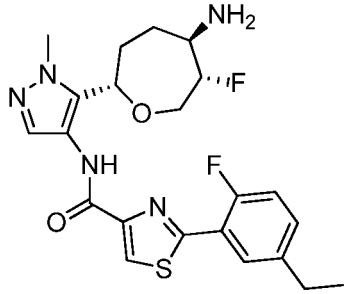
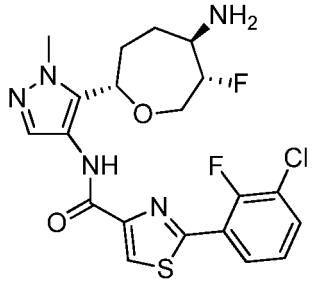
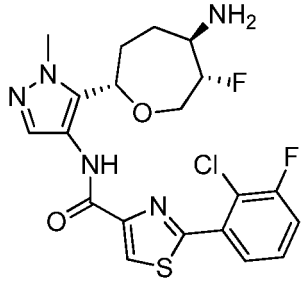
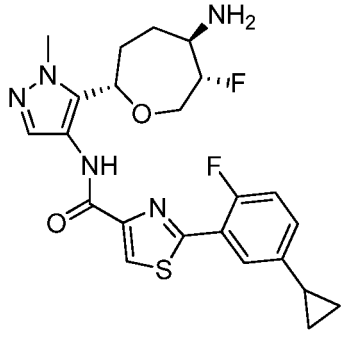
281		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000007
282		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000058
283		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000171
284		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.00022
285		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-ethoxy-2,6-difluorophenyl)thiazole-4-carboxamide	0.000001

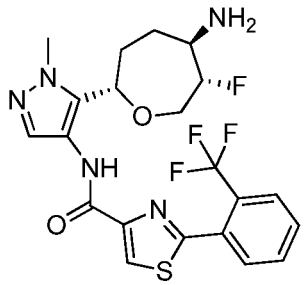
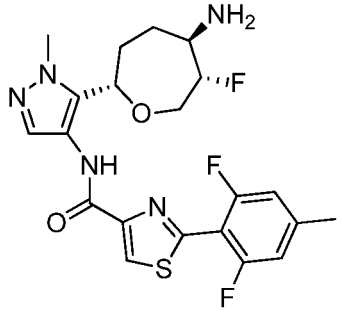
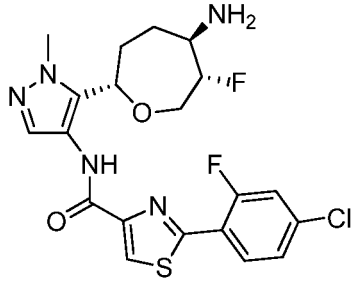
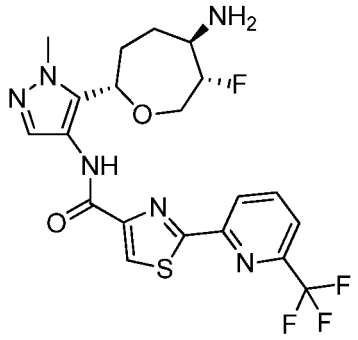
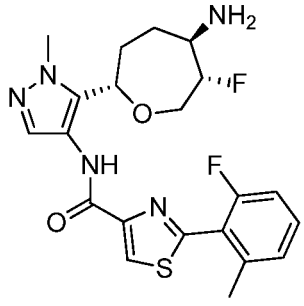
286		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	
287		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000053
288		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000035
289		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.00008
290		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide	0.000131

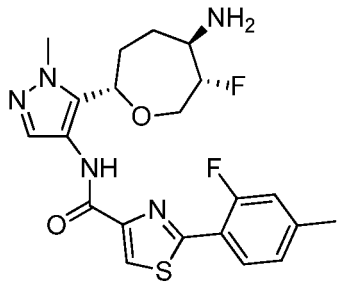
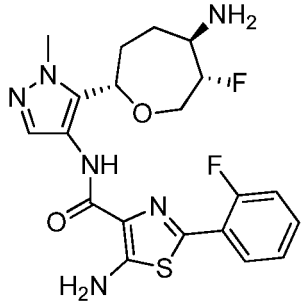
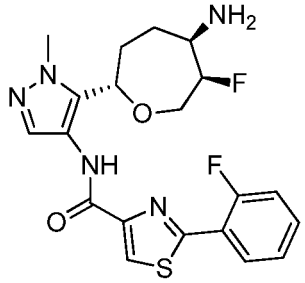
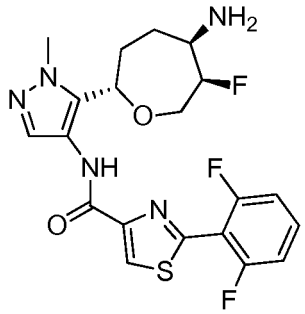
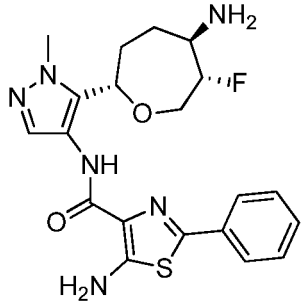
291		5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000018
292		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.000024
293		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000059
294		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000029
295		*N*-(5-((2<u>S</u>,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxamide	0.000027

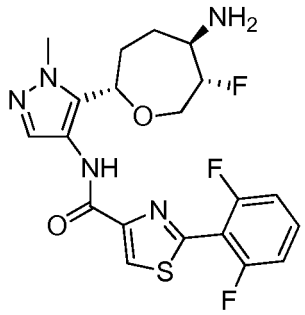
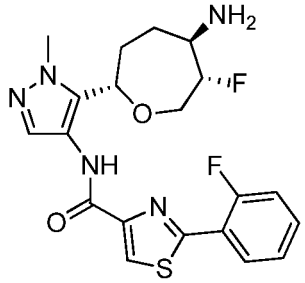
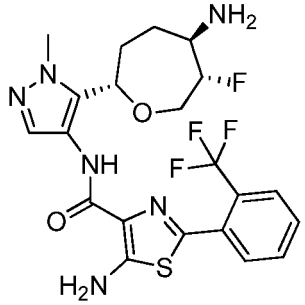
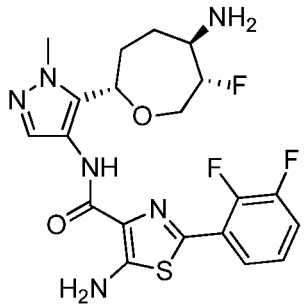
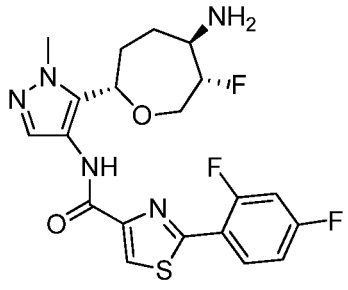
296		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000031
297		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxamide	0.000021
298		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide	0.000783
299		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-bromo-2-fluorophenyl)thiazole-4-carboxamide	0.000023
300		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide	0.000134

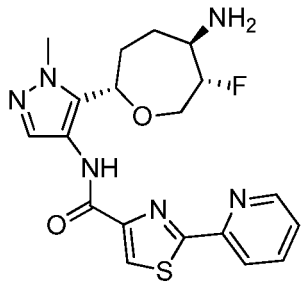
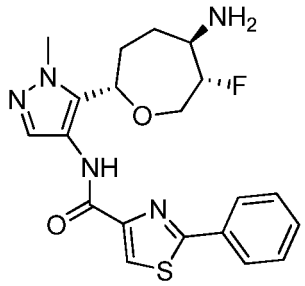
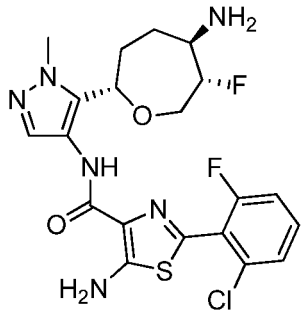
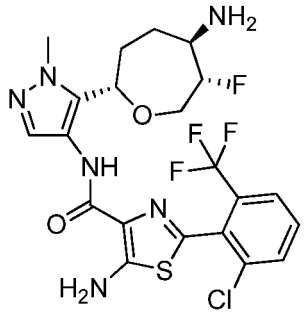
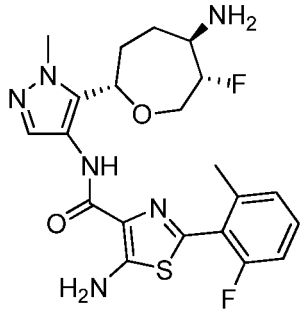
301		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,5-difluorophenyl)thiazole-4-carboxamide	0.000058
302		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000031
303		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxamide	0.000013
304		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*R*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000014
305		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*S*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000008

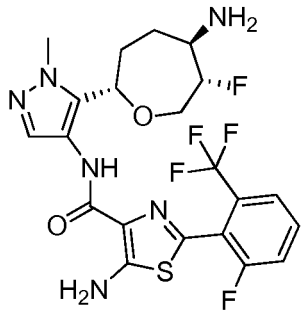
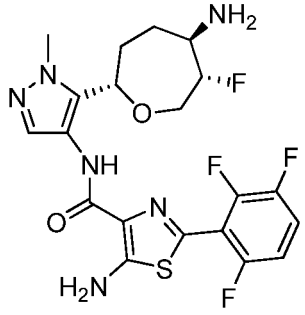
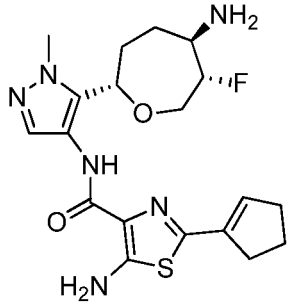
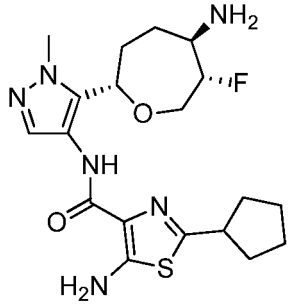
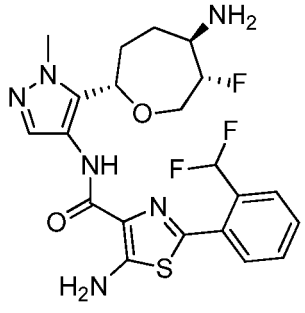
306		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000044
307		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxamide	0.000081
308		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000054
309		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000274
310		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxamide	0.000093

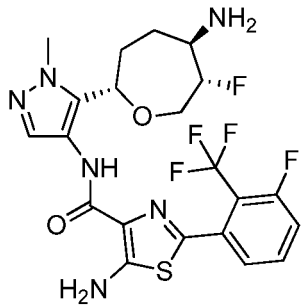
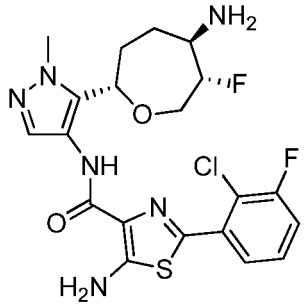
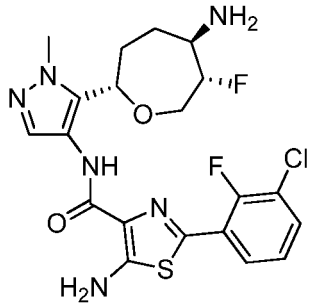
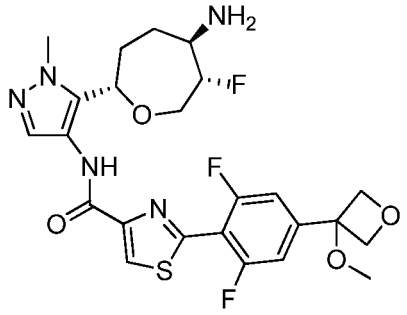
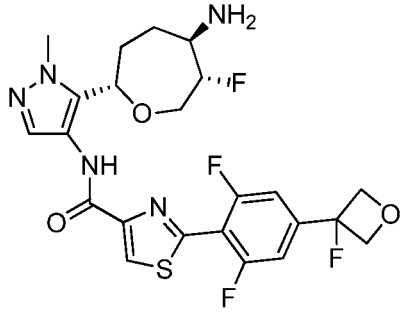
311		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.00165
312		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide	0.000003
313		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000002
314		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxamide	0.00208
315		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000091

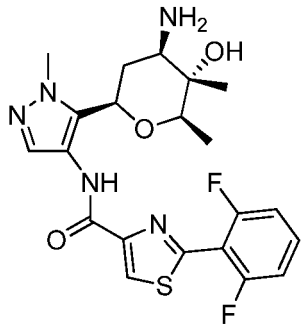
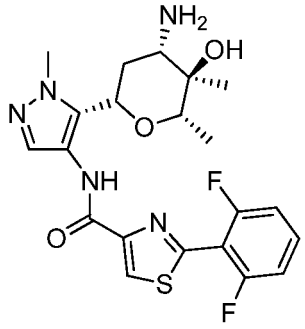
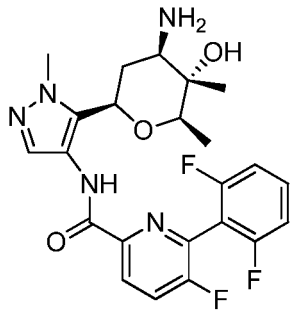
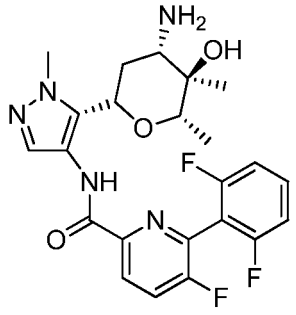
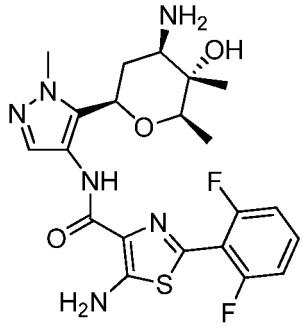
316		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methylphenyl)thiazole-4-carboxamide	
317		5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.00000509
318		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000098
319		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000038
320		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide	0.000036

321		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000137
322		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000072
323		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000283
324		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000019
325		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4-difluorophenyl)thiazole-4-carboxamide	0.00005

326		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide	0.000031
327		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide	0.000021
328		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.000036
329		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000071
330		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000016

331		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000104
332		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000003
333		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide	0.00003
334		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide	0.000453
335		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide	0.000092

336		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000188
337		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000015
338		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000007
339		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000014
340		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000010

341		*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000030
342		*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0023
343		*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	
344		*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	
345		5-amino-*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

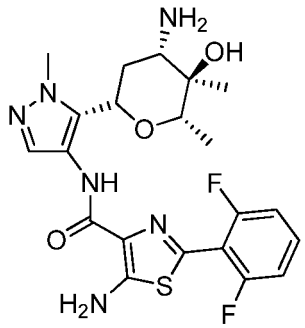
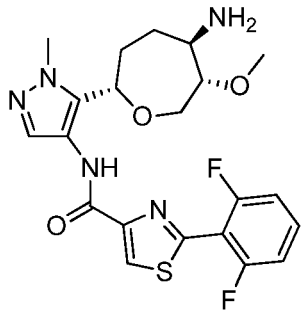
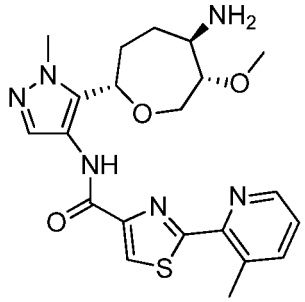
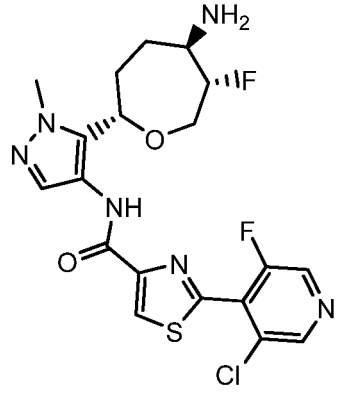
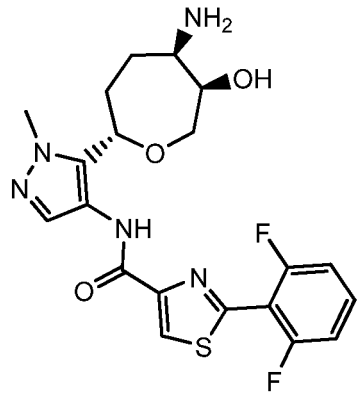
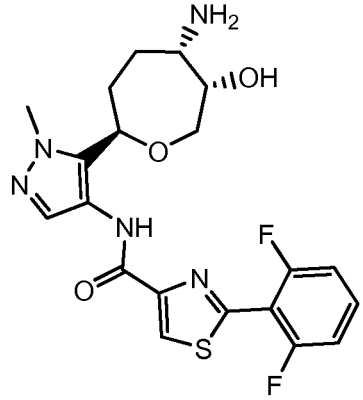
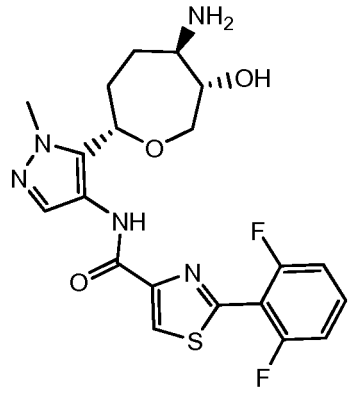
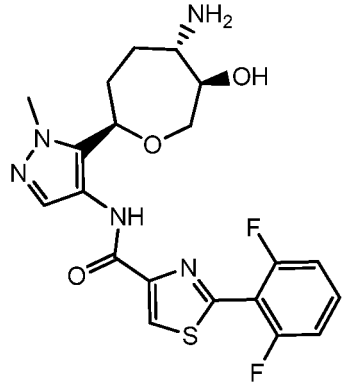
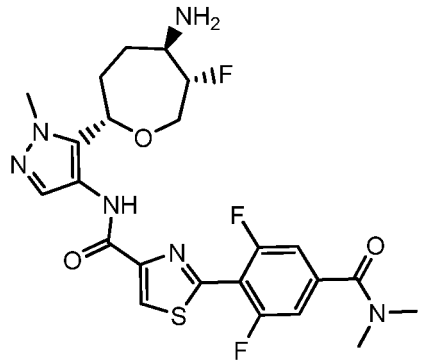
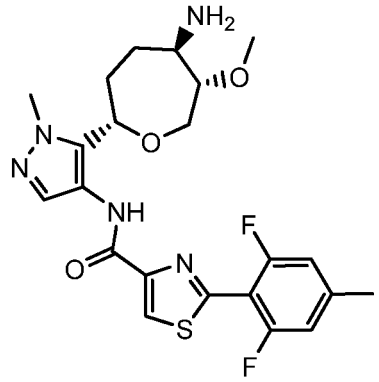
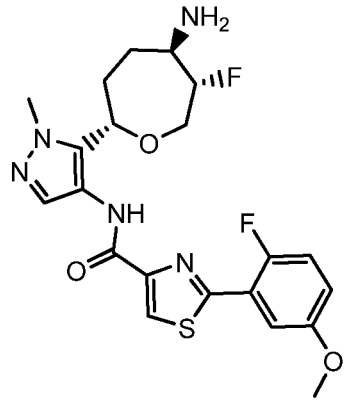
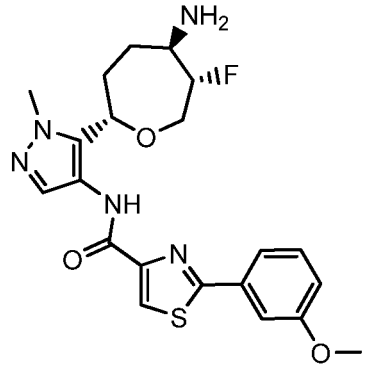
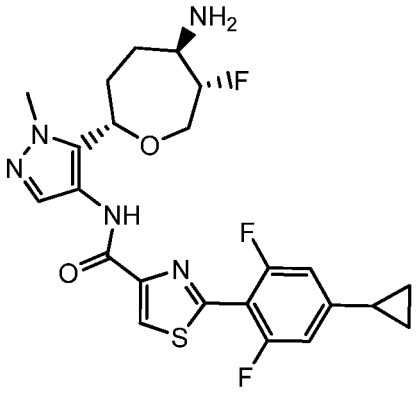
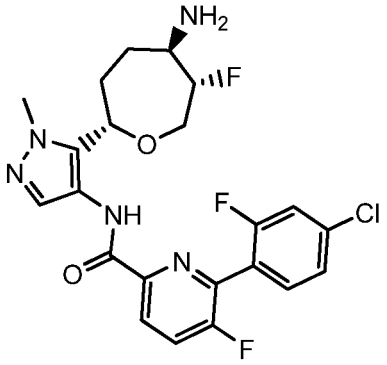
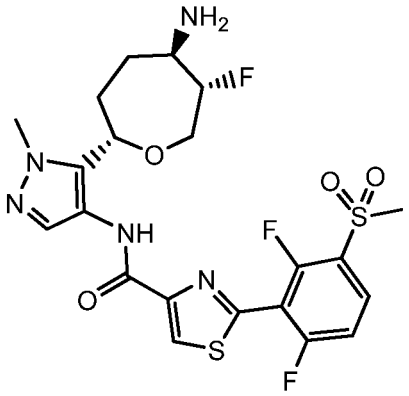
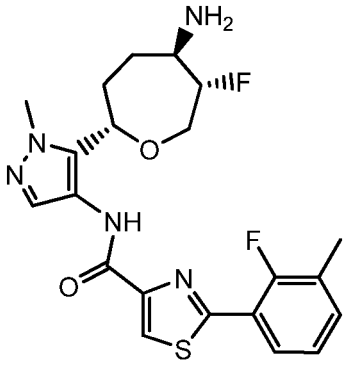
346		5-amino-*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
347		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014
348		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide	0.000014

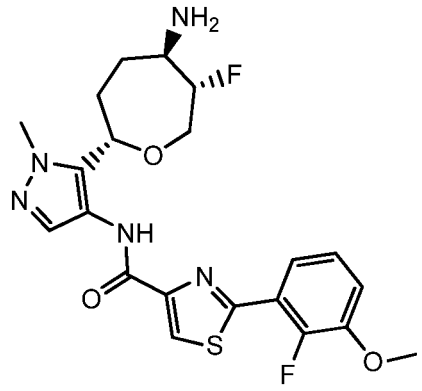
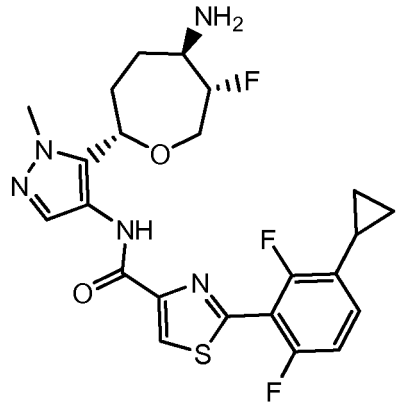
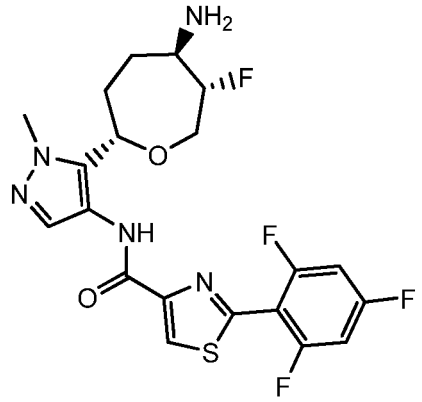
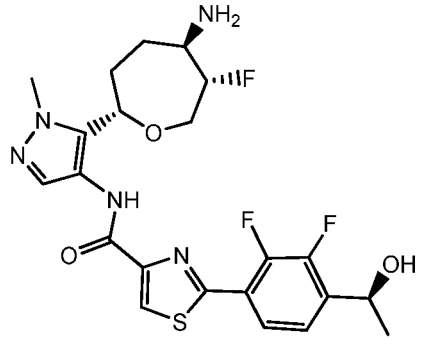
Table 1c

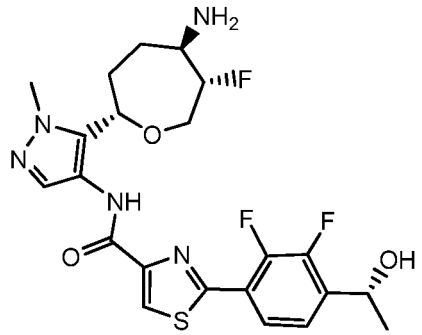
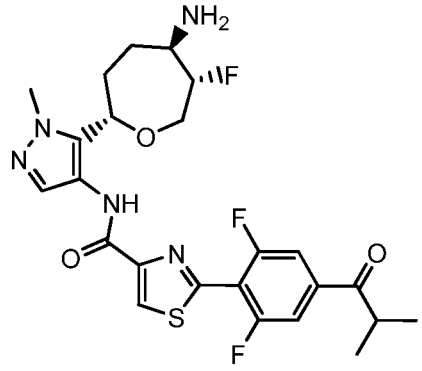
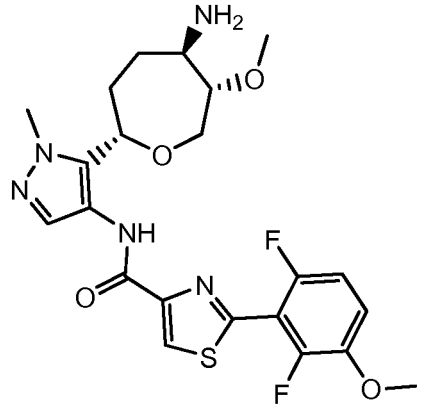
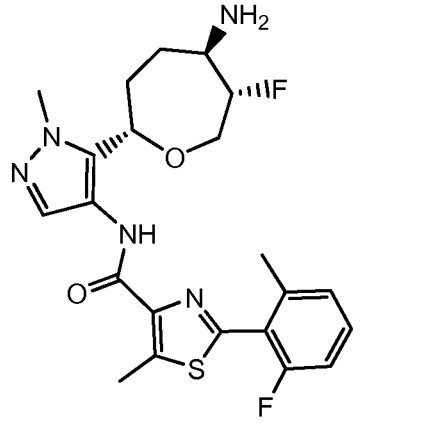
No.	Structure	IUPAC Name	PIM1 LC3K (KI) µM
349		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-5-fluoropyridin-4-yl)thiazole-4-carboxamide	0.00312

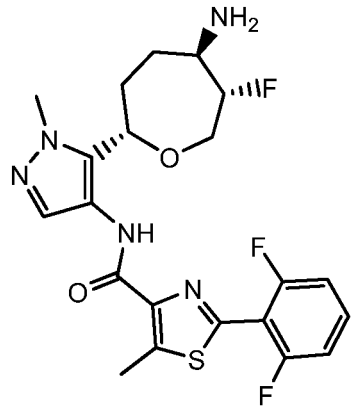
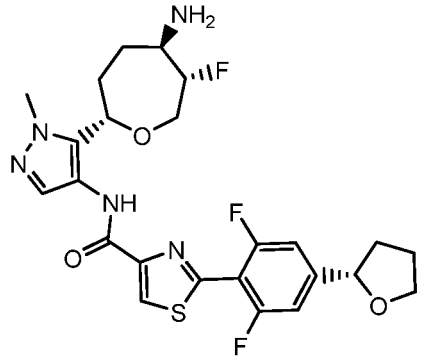
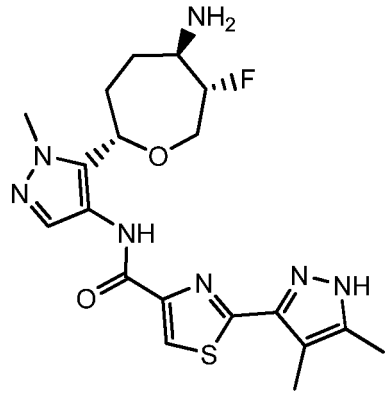
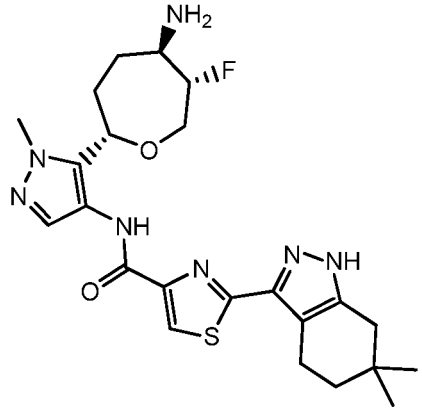
350		N-(5-((2S,5R,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	>0.667
351		N-(5-((2R,5S,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000076
352		N-(5-((2S,5R,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000174
353		N-(5-((2R,5S,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000111

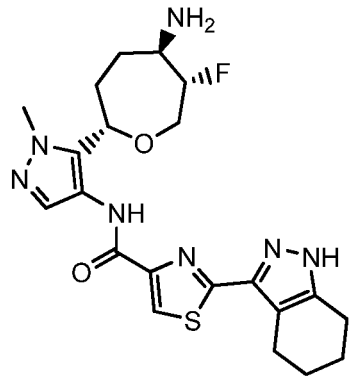
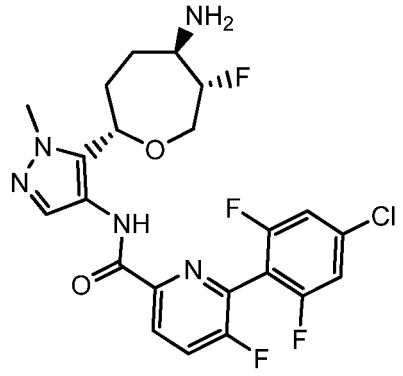
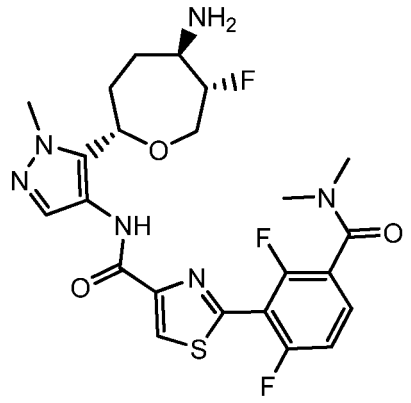
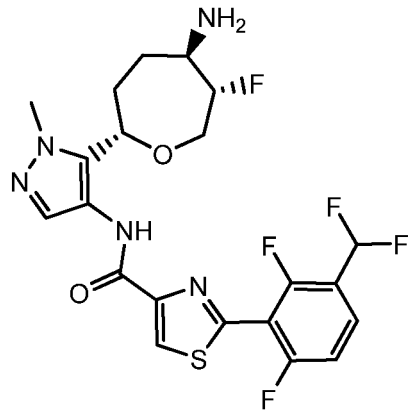
354		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000083
355		N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide	0.000035
356		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methoxyphenyl)thiazole-4-carboxamide	0.000053
357		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methoxyphenyl)thiazole-4-carboxamide	0.000035

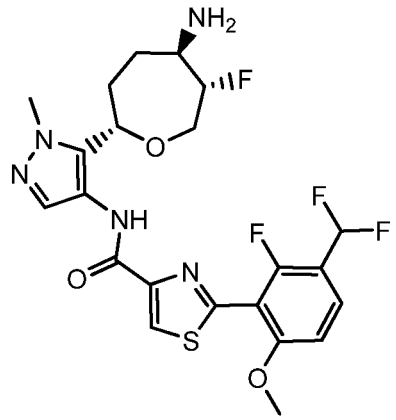
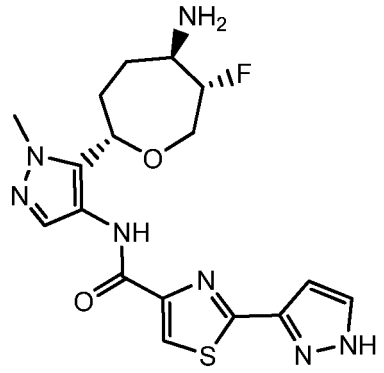
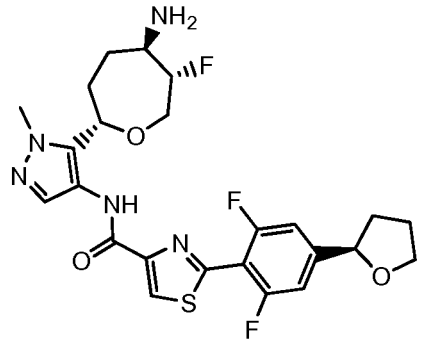
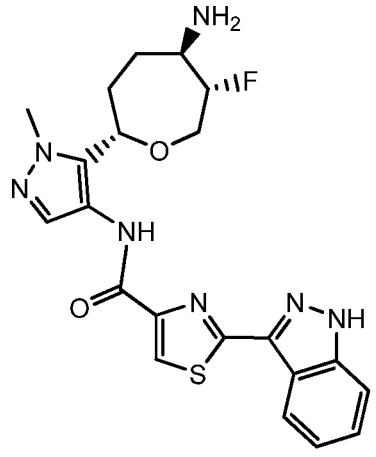
358		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide	0.000009
359		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2-fluorophenyl)-5-fluoropicolinamide	0.000007
360		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluoro-3-methylsulfonyl-phenyl)thiazole-4-carboxamide	0.00185
361		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-3-methyl-phenyl)thiazole-4-carboxamide	0.000068

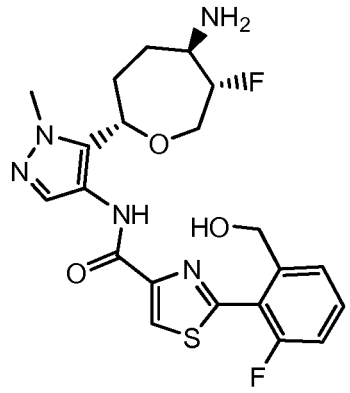
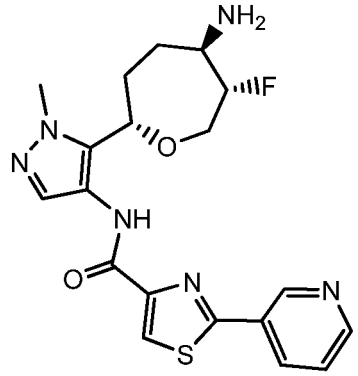
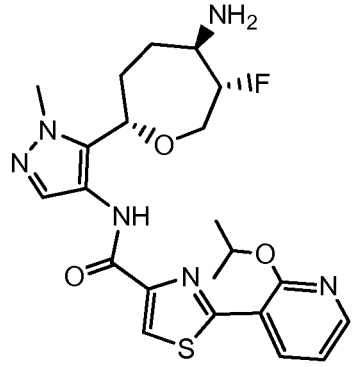
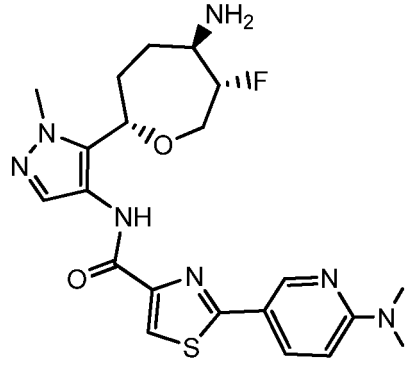
362		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000036
363		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide	0.000034
364		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4,6-trifluorophenyl)thiazole-4-carboxamide	0.000039
365		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((S)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000069

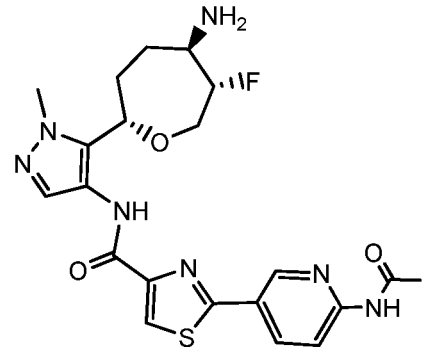
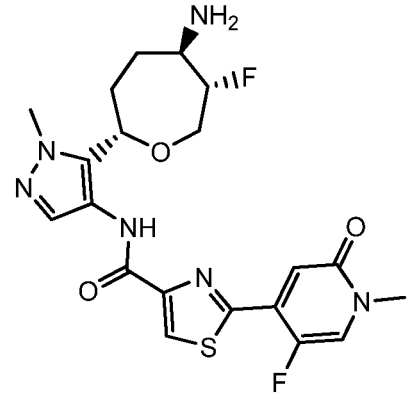
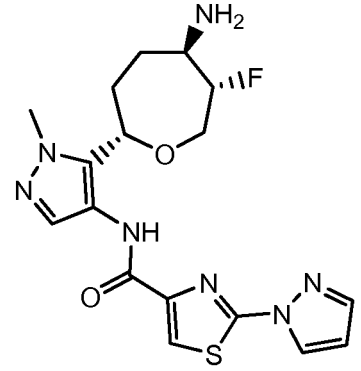
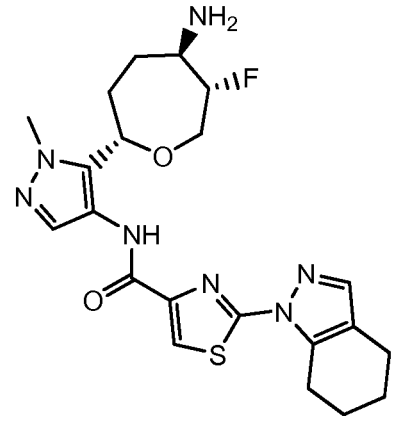
366		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((R)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.00014
367		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-isobutyrylphenyl)thiazole-4-carboxamide	0.000061
368		N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000030
369		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-6-methyl-phenyl)-5-methyl-thiazole-4-carboxamide	0.00359

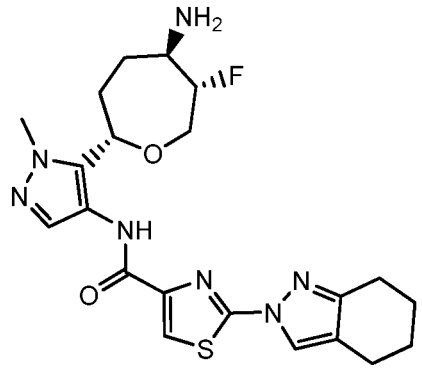
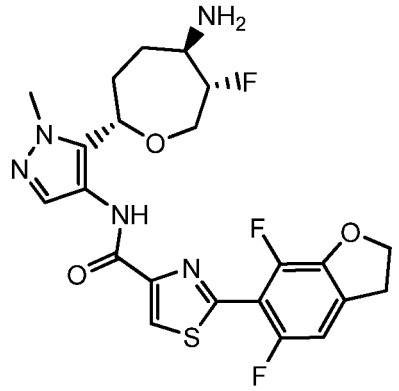
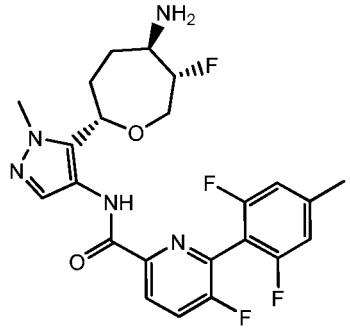
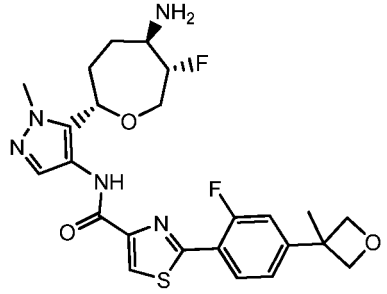
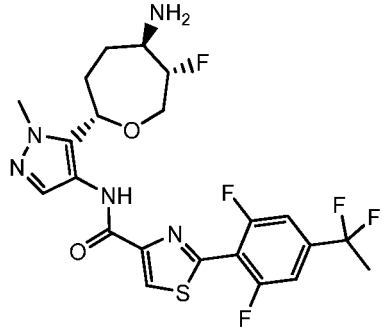
370		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)-5-methyl-thiazole-4-carboxamide	0.000382
371		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((S)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide	0.000057
372		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5-dimethyl-1H-pyrazol-3-yl)thiazole-4-carboxamide	0.000064
373		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide	0.0000090

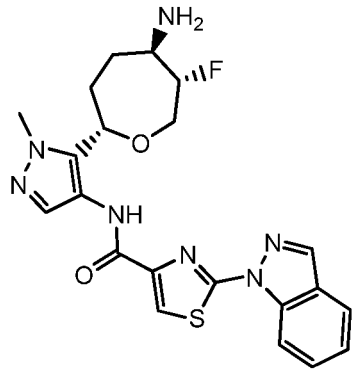
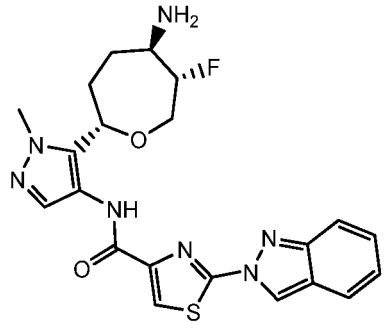
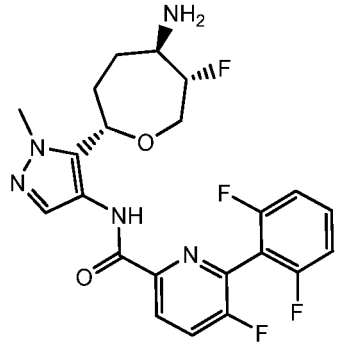
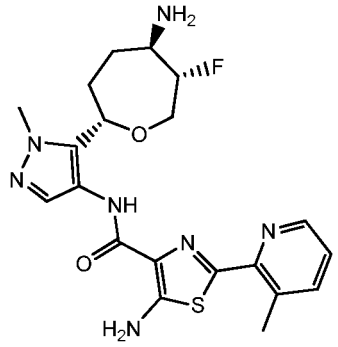
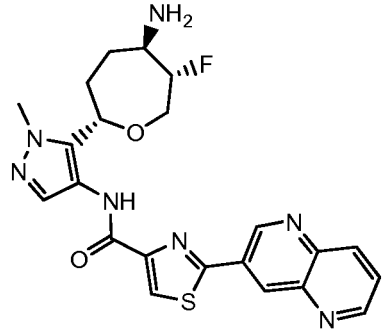
374		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide	0.000023
375		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2,6-difluorophenyl)-5-fluoropicolinamide	0.000036
376		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(dimethylcarbamoyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide	0.000727
377		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide	0.000031

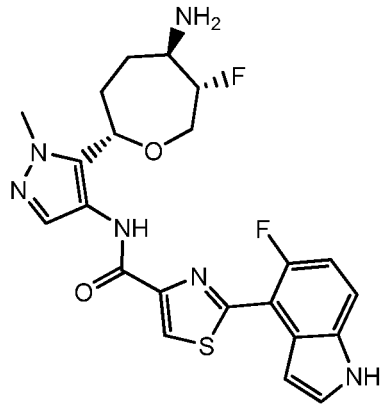
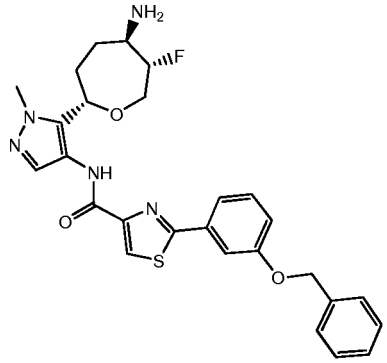
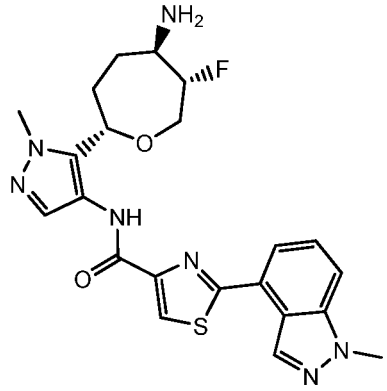
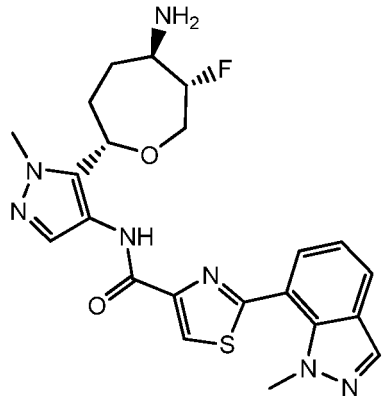
378		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2-fluoro-6-methoxy-phenyl]thiazole-4-carboxamide	0.00148
379		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-pyrazol-3-yl)thiazole-4-carboxamide	0.000129
380		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((R)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide	0.000071
381		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-3-yl)thiazole-4-carboxamide	0.000022

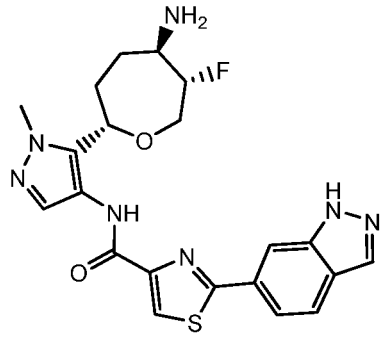
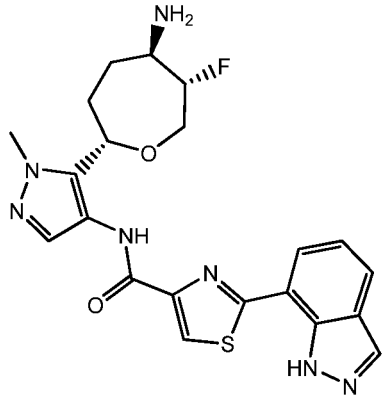
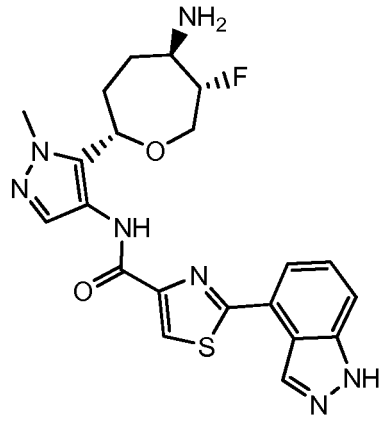
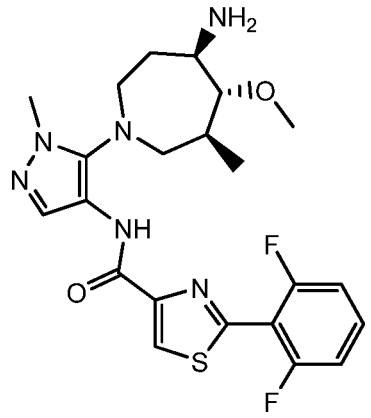
382		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[2-fluoro-6-(hydroxymethyl)phenyl]thiazole-4-carboxamide	0.0072
383		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-pyridyl)thiazole-4-carboxamide	0.000991
384		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-isopropoxy-3-pyridyl)thiazole-4-carboxamide	0.0097
385		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[6-(dimethylamino)-3-pyridyl]thiazole-4-carboxamide	0.0002

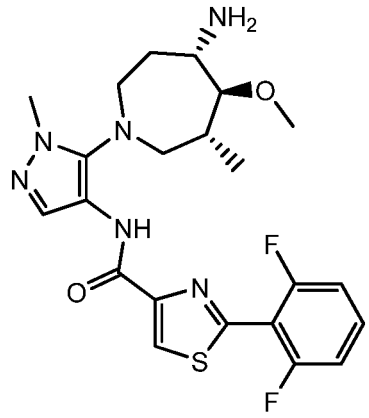
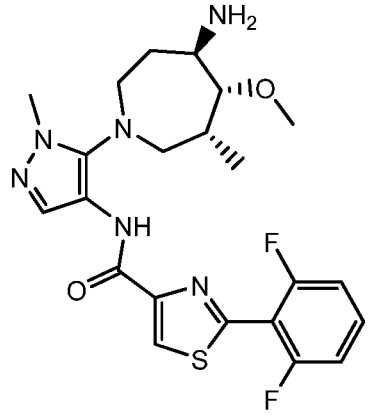
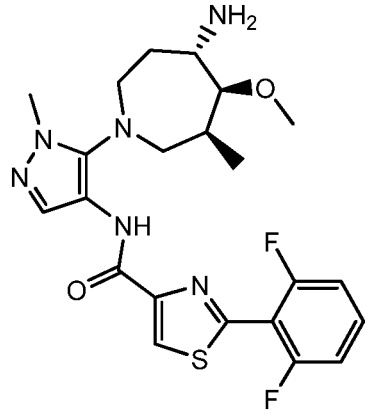
386		2-(6-acetamido-3-pyridyl)-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000389
387		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thiazole-4-carboxamide	0.000954
388		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-pyrazol-1-yl)thiazole-4-carboxamide	0.000157
389		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)thiazole-4-carboxamide	0.000020

390		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazole-4-carboxamide	0.000267
391		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5,7-difluoro-2,3-dihydrobenzofuran-6-yl)thiazole-4-carboxamide	0.000024
392		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinamide	0.000041
393		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(3-methyloxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000003
394		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(1,1-difluoroethyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000018

395		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-1-yl)thiazole-4-carboxamide	0.000085
396		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2H-indazol-2-yl)thiazole-4-carboxamide	0.000002
397		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-6-(2,6-difluorophenyl)-5-fluoro-pyridine-2-carboxamide	0.000016
398		5-amino-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-methyl-2-pyridyl)thiazole-4-carboxamide	0.0000040
399		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1,5-naphthyridin-3-yl)thiazole-4-carboxamide	0.00021

400		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(5-fluoro-1H-indol-4-yl)thiazole-4-carboxamide	0.000011
401		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-benzyloxyphenyl)thiazole-4-carboxamide	0.000447
402		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-4-yl)thiazole-4-carboxamide	0.000117
403		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-7-yl)thiazole-4-carboxamide	0.00591

404		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-6-yl)thiazole-4-carboxamide	
405		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-7-yl)thiazole-4-carboxamide	
406		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-4-yl)thiazole-4-carboxamide	
407		N-(5-((3S,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

408		N-(5-((3R,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
409		N-(5-((3R,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
410		N-(5-((3S,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

The present invention includes a composition (e.g., a pharmaceutical composition) comprising a compound of Formula I, and/or solvates, hydrates and/or salts thereof, and a carrier (a pharmaceutically acceptable carrier). The present invention also includes a composition (e.g., a pharmaceutical composition) comprising a compound of Formula I and/or solvates, hydrates and/or salts thereof, and a carrier (a pharmaceutically acceptable carrier), further comprising a second chemotherapeutic agent such as those described herein. The present compositions are useful for inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human). For example, the present compounds and compositions are useful for treating multiple myeloma, lymphoma, acute myeloid leukemia, prostate cancer, breast

cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human).

The present invention includes a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof. For example, the present invention includes a method of treating multiple myeloma, lymphoma, acute myeloid leukemia, prostate cancer, breast cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human), comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof) or a composition thereof.

The present invention includes a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, in combination with a second chemotherapeutic agent such as those described herein. For example, the present invention includes a method of treating multiple myeloma, lymphoma, acute myeloid leukemia, prostate cancer, breast cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human), comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, in combination with a second chemotherapeutic agent such as those described herein.

The present invention includes a method of treating lymphoma in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as an anti-B-cell antibody therapeutic (e.g., RITUXAN® and/or dacetuzumab), gemcitabine, corticosteroids (e.g., prednisolone and/or dexamethasone), chemotherapy cocktails (e.g., CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and/or ICE (isfosfamide, cytoxan, etoposide)), a combination of biologics and chemotherapy (e.g., RITUXAN®-ICE, dacetuzumab-RITUXAN®-ICE, R-Gem, and/or D-R-Gem), an Akt inhibitor, a PI3K inhibitor (e.g, GDC-0941 (Genentech) and/or GDC-0980 (Genentech)), rapamycin, a rapamycin analog, mTOR inhibitor such as everolimus or sirolimus, a MEK inhibitor (GDC-0973), and a Bcl-2 inhibitor (ABT-263 or ABT-199).

The present invention includes a method of treating multiple myeloma in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as melphalan, "Imids" (immuno-modulators, e.g., thalidomide, lenalidomide, and/or pomolidamide), corticosteroids (e.g., dexamethasone and/or prednisolone), and bortezomib or other proteasome inhibitor.

The present invention includes a method of treating multiple myeloma, chronic lymphocytic leukemia (CLL), or acute myeloid leukemia (AML) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as cytarabine (araC), anthracyclines (e.g., daunorubicin and/or idarubicin), anti-myeloid antibody therapeutics (e.g., SGN-33), anti-myeloid antibody-drug conjugates (e.g., MYLOTARG®).

The present invention includes a method of treating chronic lymphocytic leukemia (CLL) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as fludarabine, cyclophosphamide, anti-B-cell antibody therapeutics (e.g., RITUXAN® and/or dacetuzumab).

The present invention includes a method of treating chronic myeloid leukemia (CML) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as a BCR-abl inhibitor (e.g., imatinib, nilotinib, and/or dasatinib).

The present invention includes a method of treating myelodysplastic diseases (MDS) and myeloproliferative disorders including polycythemia vera (PV), essential thrombocytosis (ET) or myelofibrosis (MF), in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination.

The present invention includes a method of using the present compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection

(including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, inhalation and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or in combination with one or more chemotherapeutic agents, for example those described herein. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension for parenteral injection as a sterile solution, suspension or emulsion for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of Formula I compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When

aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 15.sup.th Edition (1975).

ADMINISTRATION OF FORMULA I COMPOUNDS

The Formula I compounds of the invention may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route may vary with for example the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

A dose to treat human patients may range from about 10 mg to about 1000 mg of Formula I compound. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

METHODS OF TREATMENT WITH FORMULA I COMPOUNDS

Compounds of the present invention are useful for treating hyperproliferative diseases, conditions and/or disorders including, but not limited to, those characterized by over expression of Pim kinases, e.g. Pim-1, Pim-2 and Pim-3 kinases. Accordingly, another aspect of this invention includes methods of treating or preventing diseases or conditions that can be treated or prevented by inhibiting Pim kinase. In one embodiment, the method comprises administering to

a mammal in need thereof a therapeutically effective amount of a compound of Formula I, or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof. In one embodiment, a human patient is treated with a compound of Formula I and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound of Formula I is present in an amount to detectably inhibit Pim kinase activity.

Cancers which can be treated according to the methods of this invention include, but are not limited to, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia.

Another aspect of this invention provides a compound of this invention for use in the treatment of the diseases or conditions described herein in a mammal, for example, a human, suffering from such disease or condition. Also provided is the use of a compound of this invention in the preparation of a medicament for the treatment of the diseases and conditions described herein in a warm-blooded animal, such as a mammal, for example a human, suffering from such disorder.

PHARMACEUTICAL FORMULATIONS

In order to use a Formula I compound for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of this invention in association with a pharmaceutically acceptable diluent or carrier.

A typical formulation is prepared by mixing a Formula I compound and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal.

In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the Formula I compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Pharmaceutical formulations of the compounds of the present invention may be prepared for various routes and types of administration. For example, a compound of Formula I having the desired degree of purity may optionally be mixed with pharmaceutically acceptable diluents, carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation may be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

The compound of this invention for use herein is preferably sterile. In particular, formulations to be used for *in vivo* administration must be sterile. Such sterilization is readily accomplished by filtration through sterile filtration membranes.

The compound ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

The pharmaceutical compositions of the invention comprising a Formula I compound will be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat the coagulation factor mediated disorder. Such amount is preferably below the amount that is toxic to the host or renders the host significantly more susceptible to bleeding.

As a general proposition, the initial pharmaceutically effective amount of the Formula I compound administered parenterally per dose will be in the range of about 0.01-100 mg/kg, namely about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day.

Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). The active pharmaceutical ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and

poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations of Formula I compounds may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of Formula I, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (US 3773919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid.

The formulations include those suitable for the administration routes detailed herein. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of a compound of Formula I suitable for oral administration may be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of Formula I.

Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs may be prepared for oral use. Formulations of compounds of Formula I intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents,

coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or oil, or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

Aqueous suspensions of Formula I compounds contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone,

methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

The pharmaceutical compositions of compounds of Formula I may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis disorders as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

COMBINATION THERAPY

The compounds of Formula I may be employed alone or in combination with other therapeutic agents for the treatment of a disease or disorder described herein, such as a hyperproliferative disorder (e.g., cancer). In certain embodiments, a compound of Formula I is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second compound that has anti-hyperproliferative properties or that is useful for treating a hyperproliferative disorder (e.g., cancer). The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of Formula I such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I, in combination with a chemotherapeutic agent such as described herein.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments.

The combination therapy may provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes, separate pills or capsules, or separate infusions. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

In a particular embodiment of anti-cancer therapy, a compound of Formula I, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with other chemotherapeutic, hormonal or antibody

agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of Formula I, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, and the use of at least one other cancer treatment method. The amounts of the compound(s) of Formula I and the other pharmaceutically active chemotherapeutic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

METABOLITES OF FORMULA I COMPOUNDS

Also falling within the scope of this invention are the *in vivo* metabolic products of Formula I described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of Formula I, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found *in vivo*, may be useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

ARTICLES OF MANUFACTURE

In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. The kit comprises a container comprising a compound of Formula I. The kit may further comprise a label or package insert, on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include,

for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound of Formula I or II or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of Formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder such as a hyperproliferative disorder, neurodegeneration, cardiac hypertrophy, pain, migraine or a neurotraumatic disease or event. In one embodiment, the label or package inserts indicates that the composition comprising a compound of Formula I can be used to treat a disorder resulting from abnormal cell growth. The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

The kit may further comprise directions for the administration of the compound of Formula I and, if present, the second pharmaceutical formulation. For example, if the kit comprises a first composition comprising a compound of Formula I, and a second pharmaceutical formulation, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound of Formula I, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

According to one embodiment, a kit may comprise (a) a first container with a compound of Formula I contained therein; and optionally (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a second compound with anti-hyperproliferative activity. Alternatively, or

additionally, the kit may further comprise a third container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In certain other embodiments wherein the kit comprises a composition of Formula I and a second therapeutic agent, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

PREPARATION OF FORMULA I COMPOUNDS

Compounds of Formula I may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein, and those for other heterocycles described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990), each of which are expressly incorporated by reference. Starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database).

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing Formula I compounds and necessary reagents and intermediates are known in the art and include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G .M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

Compounds of Formula I may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of

Formula I may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds, or pharmaceutically acceptable salts thereof.

The General Procedures and Examples provide exemplary methods for preparing Formula I compounds. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the Formula I compounds. Although specific starting materials and reagents are depicted and discussed in the Figures, General Procedures, and Examples, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In preparing compounds of Formulas I, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

METHODS OF SEPARATION

In the methods of preparing Formula I compounds, it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as

activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like. Selection of appropriate methods of separation depends on the nature of the materials involved, such as, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions, such as on a chiral adsorbent by HPLC or SFC (Supercritical Fluid Chromatography), see White and Burnett (2005) Jour. of Chrom. A1074:175-185; and "Drug Stereochemistry, Analytical Methods and Pharmacology," (1993) Irving W. Wainer, Ed., Marcel Dekker, Inc., New York).

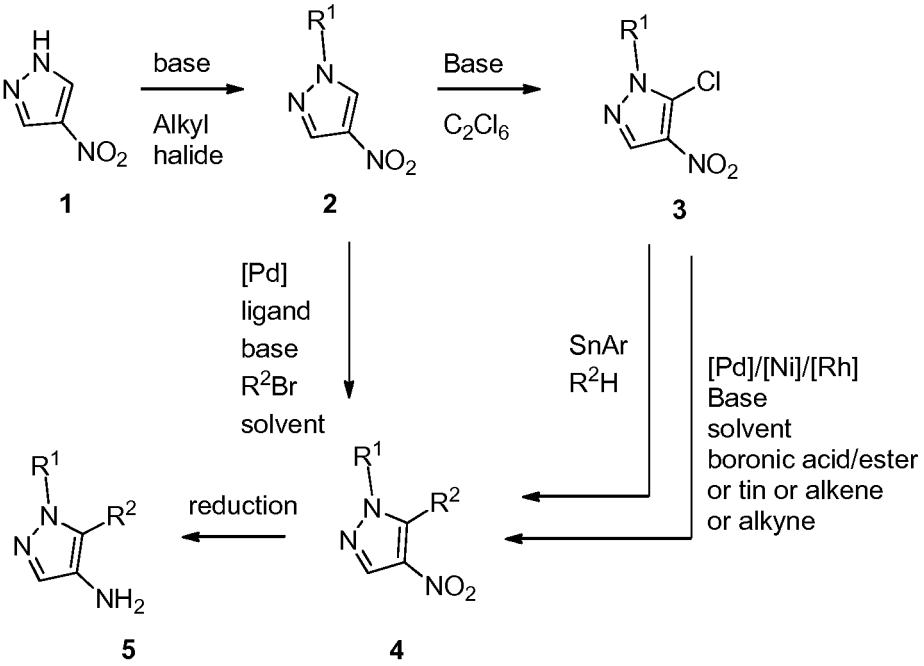
Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of

amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

GENERAL PREPARATIVE PROCEDURES

Scheme 1: synthesis of 4-aminopyrazole compounds **5** from nitro-1H-pyrazole **1**.



wherein R^1 and R^2 are as defined herein.

Scheme 1 shows an exemplary synthesis of 4-aminopyrazole compounds **5**. 4-Nitro-1H-pyrazole **1** is converted to 1-substituted-4-nitro-1H-pyrazole compounds **2** by treatment with a base in a suitable solvent or neat, followed by the addition of an alkylation reagent such as dimethyl sulfate. Compound **2** may be converted to 5-chloro-4-nitro-1H-pyrazole **3** by treatment with a base such as lithium hexamethyldisilazide, or nBuLi in a suitable solvent such as THF (tetrahydrofuran) at an appropriate temperature, such as -78 °C. Compound **3** may be converted to compound **4** by direct SnAr, or transition metal catalyzed cross coupling reactions, e.g. Suzuki, Sonogashira, Heck, Buchwald, Goldberg conditions under known methods. 4-Aminopyrazole **5** may be synthesized from **4** by a suitable reduction method, such as treatment with zinc powder and ammonium formate in tetrahydrofuran, or hydrogenation with H_2 and transitional metal catalysts such as palladium on carbon.

Buchwald coupling reactions may be conducted under Buchwald palladium catalysis conditions with the Buchwald pre-catalyst palladacycle and ligand reagents in the following table and as described in: Biscoe et al (2008) J. Am. Chem. Soc. 130:6686-6687; Kinzel et al (2010) J. Am. Chem. Soc. 132:14073-14075; Molander et al (2012) J. Am. Chem. Soc. 134:11667-11673; Walker et al (2004) Angew. Chem. Int. Ed. 43:1871; Billingsley et al (2007) Angew. Chem. Int. Ed. 46:5359-5363; US 6946560; US 7026498; US 7247731; US 7560582; US 6307087; US 6395916; US 7223879; US 7858784, which are incorporated by reference. Such reagents are commercially available (Johnson Matthey Inc., Wayne, PA; Sigma Aldrich Fine Chemical, St. Louis, MO; Strem Chemicals, Inc., Newburyport, MA).

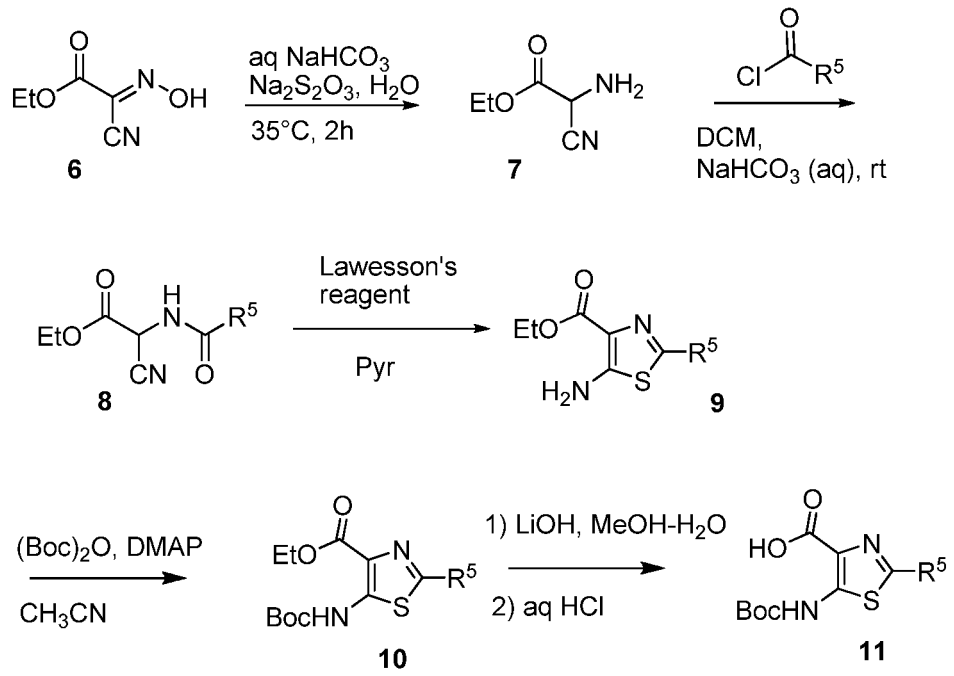
Buchwald Catalysts and Ligands	Name	CAS Reg. No.
2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl	DavePhos	213697-53-1
2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl	XPhos	564483-18-7
2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl	SPhos	657408-07-6
2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl	tBuXPhos	564483-19-8
(2-Biphenyl)dicyclohexylphosphine	CyJohnPhos	247940-06-3
(2-Biphenyl)di-*tert*-butylphosphine	JohnPhos	224311-51-7
Sodium 2′-dicyclohexylphosphino-2,6 dimethoxy-1,1′-biphenyl-3-sulfonate hydrate	SPhos [water soluble]	1049726-96-6
2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl	Tetramethyl tBuXPhos	857356-94-6

2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl	RuPhos	787618-22-8
2′-(Diphenylphosphino)-N,N′-dimethyl-(1,1′-biphenyl)-2-amine, 2-Diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl	PhDave-Phos	240417-00-9
2′-(Di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine	t-BuDavePhos	224311-49-3
2-Dicyclohexylphosphino-2′-methylbiphenyl, 2-Methyl-2′-dicyclohexylphosphinobiphenyl	MePhos	251320-86-2
2-Di-*tert*-butylphosphino-2′-methylbiphenyl	tBuMePhos	255837-19-5
Au(MeCN)SbF_6	JohnPhos	866641-66-9
(2-Biphenyl)di-*tert*-butylphosphine gold(I) chloride, 2-(Di-*tert*-butylphosphino)biphenyl gold(I) chloride	JohnPhos AuCl	854045-93-5
2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl gold(I) chloride	XPhos AuCl	854045-94-6
2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl gold(I) bis(trifluoromethanesulfonyl)imide	XPhos $AuNTf_2$	934506-10-2
2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl	BrettPhos	1070663-78-3
RuPhos Pd G1 Methyl-*t*-Butyl Ether Adduct		
Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl)]palladium(II)	XPhos Palladacycle	1028206-56-5
Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2-aminoethylphenyl)]palladium(II) - methyl-*t*-butyl ether adduct	SPhos Palladacycle	
t-BuXPhos palladium(II) phenethylamine chloride	tBuXPhos Pd G1	1142811-12-8
2-{Bis[3,5-bis(trifluoromethyl)phenyl]phosphino}-3,6-dimethoxy -2′,4′,6′-triisopropyl-1,1′-biphenyl	JackiePhos	1160861-60-8
2-(Di-*tert*-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl	tBuBrettPhos	1160861-53-9
Dicyclohexyl(2′,4′,6′-trimethoxy[1,1′-biphenyl]-2-yl)-phosphine		1000171-05-0
BrettPhos Pd G1 Methyl-*t*-Butyl Ether Adduct		
Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-	Xphos Pd G2	1310584-14-5

biphenyl)]palladium(II)		
Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)	SPhos Pd G2	1375325-64-6
Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)	RuPhos Pd G2	1375325-68-0
Chloro[(2-dicyclohexylphosphino-2′,6′-bis(*N*,*N*-dimethylamino)-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II)	CPhos-Pd-G2	
[(2-Dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate	CPhos-Pd-G3	
[(2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate	*t*BuXPhos-Pd-G3	
(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate	RuPhos-Pd-G3	
(2-Dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate	XPhos-Pd-G3	
[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate	BrettPhos-Pd-G3	
[(2-{Bis[3,5-bis(trifluoromethyl)phenyl]phosphine}-3,6-dimethoxy- 2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate	JackiePhos-Pd-G3	
Me4-tert-butyl XPhos-AuMeCN SbF6		1334547-72-6
tBuXPhos Au(MeCN)SbF_6		1140531-94-7
RuPhos Au(MeCN)SbF_6		
SPhos Au(MeCN)SbF_6		1236160-37-4
XPhos Au(MeCN)SbF_6		1215877-64-7
Me4-*tert*-butyl XPhos-AuCl		1140907-91-0
tBuXPhos AuCl		

RuPhos AuCl		1261452-57-6
SPhos AuCl		854045-95-7
CyJohnPhos AuCl		854045-92-4
BrettPhos AuCl		1334547-75-9
JohnPhos $AuNTf_2$		1036000-94-8
Me_4-tert-butyl XPhos-$AuNTf_2$		
tBuXphos $AuNTf_2$		1190991-33-3
SPhos $AuNTf_2$		1121960-90-4
CyJohnPhos $AuNTf_2$		1016161-75-3
CPhos $AuNTf_2$		
RuPhos $AuNTf_2$		
BrettPhos $AuNTf_2$		1296269-97-0
DavePhos $AuNTf_2$		1188507-66-5
CPhos		1160556-64-8
Chloro(sodium-2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl-3′-sulfonate)[2-(2′-amino-1,1′-biphenyl)]palladium(II)		
Di-Ad-BrettPhos		1160861-59-5
Dicyclohexyl(2-(2-methoxynaphthalen-1-yl)phenyl)phosphine		1309570-98-6
tert-BuBrettPhos-Pd-G3		
di-Ad-Johnphos-G3		

Scheme 2: synthesis of 4-carboxy-thiazoles **11** from hydroxamide compounds **6**

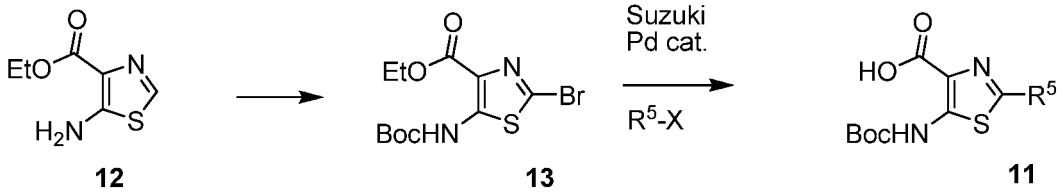


6 7 8 9 10 11

wherein R^5 is as defined herein.

Scheme 2 shows an exemplary synthesis of 4-carboxy-thiazoles **11** from hydroxamide compounds **6**. Reduction of **6** by a reducing reagent in a suitable solvent such as $Na_2S_2O_3$ in water gives **7**, which may be converted to **8** by an acylating reagent in a suitable solvent with a suitable base such as benzoyl chloride in dichloromethane with sodium bicarbonate. Compound **8** may be converted to **9** by a sulfur containing reagent in a suitable reagent such as Lawesson's reagent in pyridine, and protected to **10** by a suitable protecting group such as Boc (*tert*-butyloxycarbonyl). Ester hydrolysis of **10** using a suitable base and solvent, such as LiOH in methanol and water gives **11**.

Scheme 3: synthesis of 2-substituted, 4-carboxy-5-aminothiazoles **11** by C-2 bromination of **12** followed by Suzuki reaction of **13**



12 13 11

wherein R^5 is as defined herein.

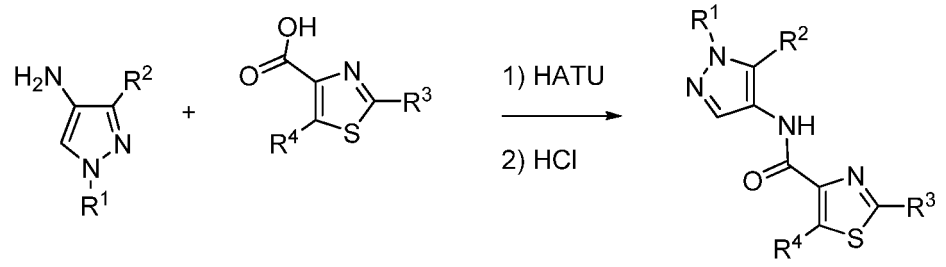
Scheme 3 shows an exemplary synthesis of 2-substituted, 4-carboxy-5-aminothiazoles **11** by C-2 bromination of 5-aminothiazole-4-carboxylate esters such as **12** followed by Suzuki reaction of 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylate esters such as **13**. 5-Aminothiazole-4-carboxylate esters such as **12** may be brominated to give **13** with a brominating reagent in a suitable solvent, such as NBS (N-bromosuccinimide) in dichloromethane. The Suzuki-type coupling reaction is useful to attach a heterocycle or a heteroaryl by displacing a halide at the 2-position of the thiazole, pyridyl, pyrazinyl, or pyrimidinyl ring in the synthesis of

a Formula I compound. For example, 2-bromo (or chloro) thiazole **13** may be reacted with about 1.5 equivalents of an aryl, heterocyclyl or heteroaryl boronic acid or ester reagent and an excess of aqueous sodium carbonate in acetonitrile. A catalytic amount, or more, of a low valent palladium reagent, such as bis(triphenylphosphine)palladium(II) dichloride, is added. A variety of boronic acids or boronic esters can be used. Boronic esters include pinacol esters (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl). Also, a nitrogen atom of a heterocycle or heteroaryl may be protected, for example as N-THP. In some cases potassium acetate is used in place of sodium carbonate to adjust the pH of the aqueous layer. The reaction may be heated to about 140-150 °C under pressure in a microwave reactor such as the Biotage Optimizer (Biotage, Inc.) for 10 to 30 minutes. The contents are extracted with ethyl acetate, or another organic solvent. After evaporation of the organic layer the Suzuki coupling product may be purified on silica or by reverse phase HPLC.

A variety of palladium catalysts can be used during the Suzuki coupling step to form exemplary Formula I compounds. Low valent, Pd(II) and Pd(0) catalysts may be used in the Suzuki coupling reaction, including $PdCl2(PPh_3)_2$, $Pd(t\text{-}Bu)_3$, $PdCl_2$ dppf CH_2Cl_2, $Pd(PPh_3)_4$, $Pd(OAc)/PPh_3$, $Cl_2Pd[(Pet_3)]_2$, $Pd(DIPHOS)_2$, $Cl_2Pd(Bipy)$, $[PdCl(Ph_2PCH_2PPh_2)]_2$, $Cl_2Pd[P(o\text{-}tol)_3]_2$, $Pd_2(dba)_3/P(o\text{-}tol)_3$, $Pd_2(dba)/P(furyl)_3$, $Cl_2Pd[P(furyl)_3]_2$, $Cl_2Pd(PmePh_2)_2$, $Cl_2Pd[P(4\text{-}F\text{-}Ph)_3]_2$, $Cl_2Pd[P(C_6F_6)_3]_2$, $Cl_2Pd[P(2\text{-}COOH\text{-}Ph)(Ph)_2]_2$, $Cl_2Pd[P(4\text{-}COOH\text{-}Ph)(Ph)_2]_2$, and encapsulated catalysts Pd EnCat™ 30, Pd EnCat™ TPP30, and Pd(II)EnCat™ BINAP30 (US 2004/0254066).

A variety of solid adsorbent palladium scavengers can be used to remove palladium after the Suzuki, Suzuki-Miyaura, or Buchwald reactions. Exemplary embodiments of palladium scavengers include FLORISIL®, SILIABOND®Thiol, and SILIABOND® Thiourea. Other palladium scavengers include silica gel, controlled-pore glass (TosoHaas), and derivatized low crosslinked polystyrene QUADRAPURE™ AEA, QUADRAPURE ™ IMDAZ, QUADRAPURE ™ MPA, QUADRAPURE ™ TU (Reaxa Ltd., Sigma-Aldrich Chemical Co.).

Scheme 4: synthesis of coupled pyrazole-thiazole compounds **12** by coupling 4-aminopyrazole compounds **5** and 2-substituted, 4-carboxy-5-aminothiazoles **11**

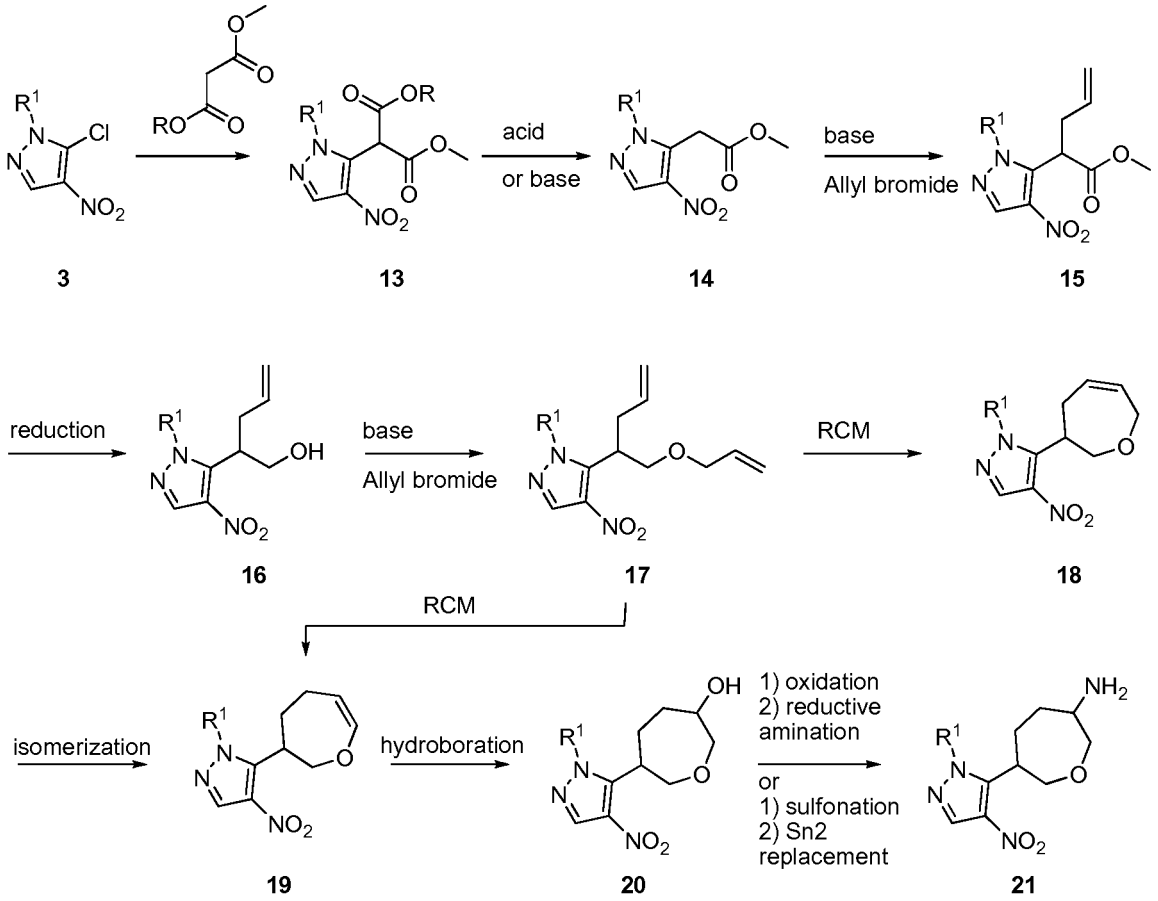


5 **11** **12**

wherein R^1, R^2 and R^3 are as defined herein.

Scheme 4 shows an exemplary synthesis of coupled pyrazole-thiazole compounds **12**. Coupling of 4-aminopyrazole compounds **5** and 2-substituted, 4-carboxy-5-aminothiazoles **11** with an amide-forming (peptide) coupling reagent such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), HATU (O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HBTU (*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, or PyBOP ((Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) in a suitable solvent such as dichloromethane or DMF forms the amide bond in **12** (Hermanson, G. in Bioconjugate Techniques, 2nd Edition (2008) Academic Press, San Diego). Boc and other protecting groups of **12** can be removed under the usual conditions, to remove Boc, Fmoc or other acid-labile protecting groups from the 4-amino group of **5** under conditions such as HCl in dioxane and water or trifluoroacetic acid in dichloromethane.

Scheme 5: synthesis of 6-(4-nitro-1H-pyrazol-5-yl)oxepan-3-amine compounds **21** from 5-chloro-4-nitro-1H-pyrazole compounds **3**



3 **13** **14** **15**

16 **17** **18**

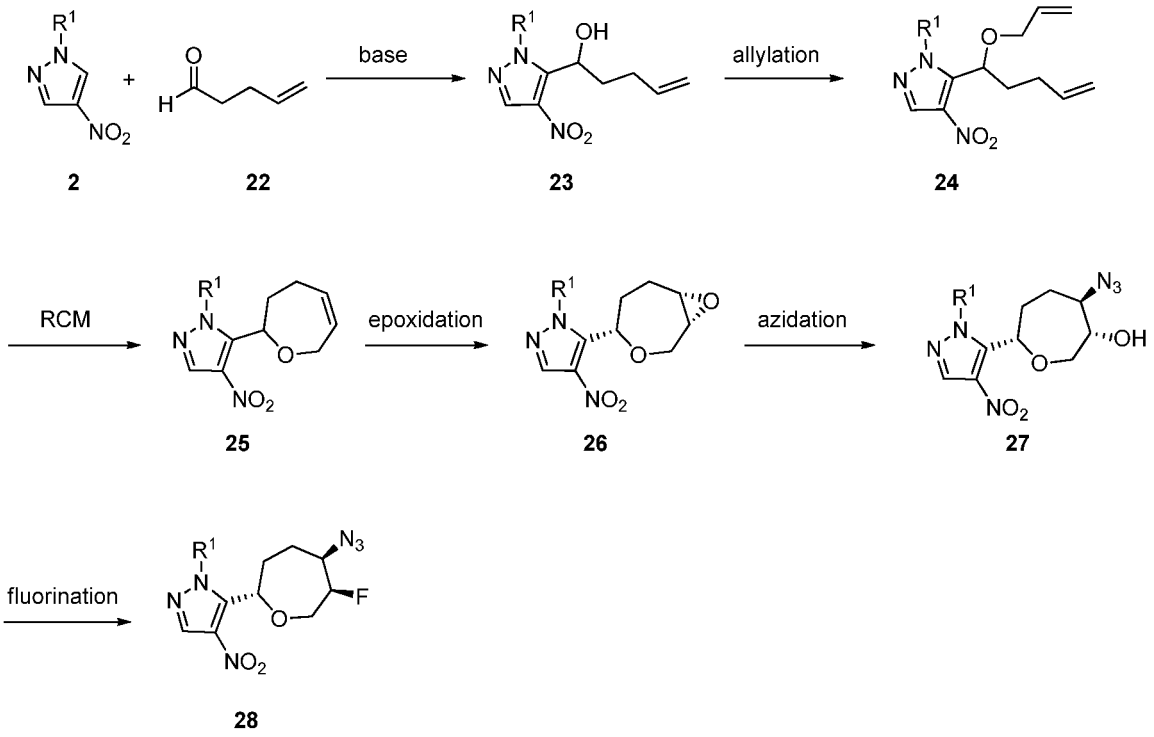
19 **20** **21**

wherein R^1 is as defined herein.

Scheme 5 shows an exemplary synthesis of 6-(4-nitro-1H-pyrazol-5-yl)oxepan-3-amine compounds **21**, such as 6-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-3-amine where R is methyl, from 5-chloro-4-nitro-1H-pyrazole compounds **3**. Displacement of chloro from **3** with dimethyl malonate in the presence of a base such as potassium carbonate in a suitable solvent such as

DMSO or by similar methods described in the literature yield 2-(1-substituted-4-nitro-1H-pyrazol-5-yl)malonate compounds **13**. Decarboxylation of **13** in a basic, acidic or combination of both conditions described in the literature give alkyl 2-(4-nitro-1H-pyrazol-5-yl)acetate ester compounds **14**. Allylation of 14 give alkyl 2-(4-nitro-1H-pyrazol-5-yl)pent-4-enoate ester compounds **15** using a suitable base such as sodium hydride in a suitable solvent such as DMF or by a method described in the literature. Reduction of **15** may be accomplished by a suitable reductive reagent such as DIBAL in a suitable solvent such as THF or by a method described in the literature to yield 2-(4-nitro-1H-pyrazol-5-yl)pent-4-en-1-ol compounds **16**. Allylation of compounds of formula 16 may yield 5-(1-(allyloxy)pent-4-en-2-yl)- 4-nitro-1H-pyrazole compounds **17** using a suitable base such as sodium hydride in a suitable solvent such as DMF or by a method described in the literature. Ring closing metathesis of **17** under suitable condition using Grubb's or related ruthenium catalyst (RCM = ruthenium-catalyzed metathesis) may yield 4-nitro-5-(2,3,4,7-tetrahydrooxepin-3-yl)-1H-pyrazole compounds **18**. Isomerization of 18 with Grubb's or Wilkinson's catalyst may yield 4-nitro-5-(2,3,4,5-tetrahydrooxepin-3-yl)-1H-pyrazole compounds **19**. Compounds **17** may be converted directly to **19** in a one pot procedure using ring closing metathesis conditions described in the literature. Hydroboration of **19** using conditions described in the literature may give 6-(4-nitro-1H-pyrazol-5-yl)oxepan-3-ol compounds **20**, which may be oxidized to ketone followed by reductive amination to yield 6-(4-nitro-1H-pyrazol-5-yl)oxepan-3-amine compounds **21**, or by sulfonation followed by displacement with an amine reagent.

Scheme 6: synthesis of 5-(5-azido-6-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **28** from 1-substituted-4-nitro-1H-pyrazole compounds **2**



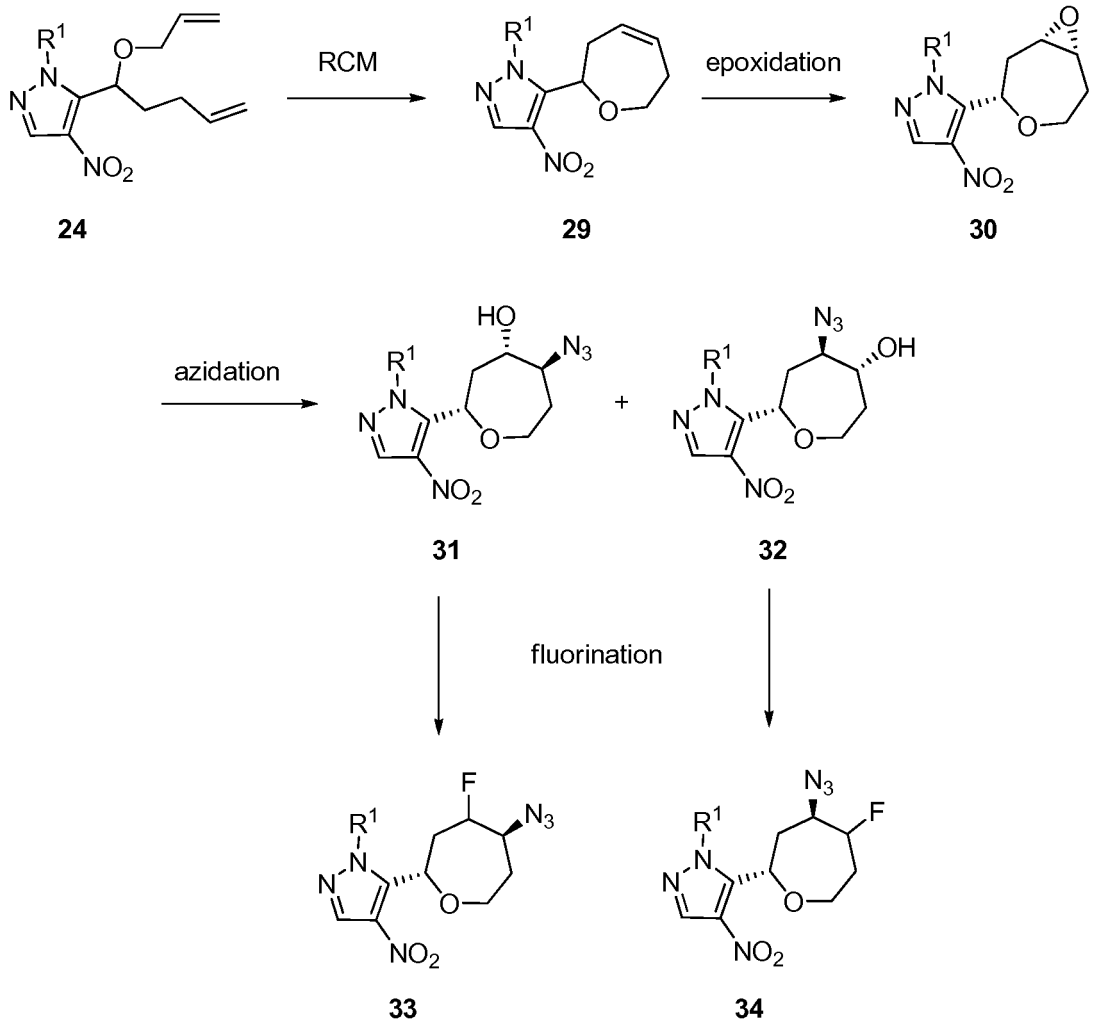
2 22 23 24 25 26 27 28

wherein R^1 is as defined herein.

Scheme 6 shows an exemplary synthesis of 5-(5-azido-6-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **28** from 1-substituted-4-nitro-1H-pyrazole compounds **2**. Reaction of **2** and pent-4-enal **22** with a suitable base such as lithium hexamethyldisilazide in a suitable solvent such as THF at the required temperature or by procedures described in the literature gives 1-(1-substituted-4-nitro-1H-pyrazol-5-yl)pent-4-en-1-ol compounds **23**. Heating **23** with bis-allylcarbonate in the presence of a suitable catalyst such as tris(dibenzylideneacetone)-dipalladium(0) and triphenylphoshine in solvents such as dioxane or using methods described in the literature gives 5-(1-(allyloxy)pent-4-enyl)-1-substituted-4-nitro-1H-pyrazole compounds **24**. Cyclization of **24** by heating in a suitable solvent such as toluene with a suitable catalyst such as Grubbs 1st generation catalyst (RCM) or by methods described in the literature gives 1-substituted-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1H-pyrazole compounds **25**. Treatment of **25** with an epoxidizing reagent such as m-CPBA (meta-chloroperbenzoic acid) in a solvent such as dichloromethane or by similar methods described in the literature gives 5-(3,8-dioxabicyclo[5.1.0]octan-4-yl)-1-substituted-4-nitro-1H-pyrazole compounds **26**. Opening of the epoxide of **26** with sodium azide according to literature methods gives 4-azido-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-3-ol compounds **27**. Fluorination of **27** with a reagent such as deoxo-Fluor® in a suitable solvent such as DCM or by methods described in the literature gives **28**.

Scheme 7: synthesis of 5-(5-azido-4-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **33** and 5-(4-azido-5-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole

compounds **34** from 5-(1-(allyloxy)pent-4-enyl)-1-substituted-4-nitro-1H-pyrazole compounds **24**



24 **29** **30**

31 **32**

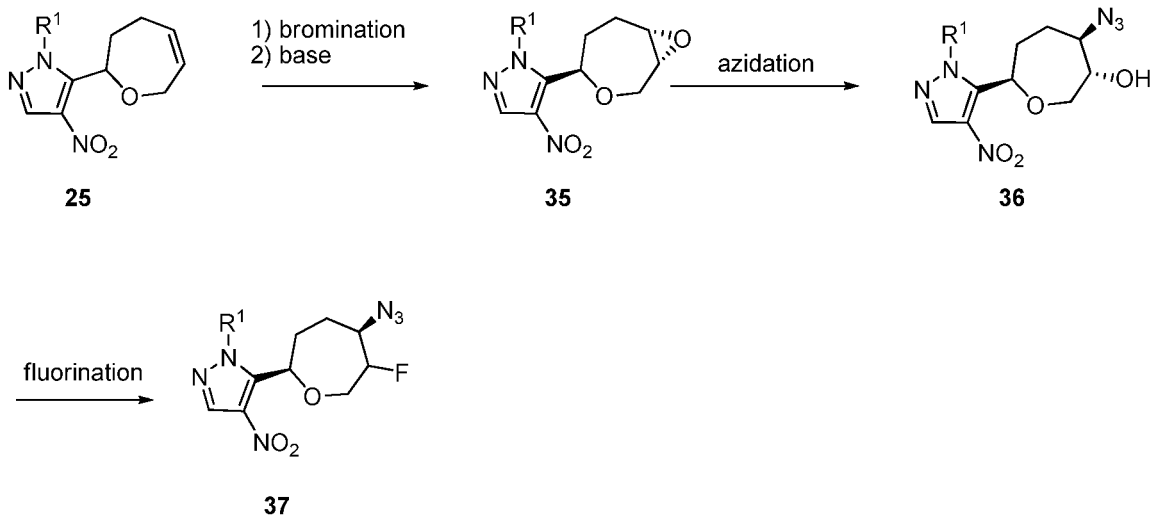
33 **34**

wherein R^1 is as defined herein.

Scheme 7 shows an exemplary synthesis of 5-(5-azido-4-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **33** and 5-(4-azido-5-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **34** from 5-(1-(allyloxy)pent-4-enyl)-1-substituted-4-nitro-1H-pyrazole compounds **24**. Cyclization of 24 by heating in a suitable solvent such as dichloromethane with a suitable catalyst such as Grubbs 2nd generation catalyst (RCM) or by methods described in the literature gives 1-substituted-4-nitro-5-(2,3,6,7-tetrahydrooxepin-2-yl)-1H-pyrazole compounds **29**. Epoxidation of **29** with an epoxidizing reagent such as m-CPBA in a solvent such as dichloromethane or by similar methods described in the literature gives 5-(4,8-dioxabicyclo[5.1.0]octan-3-yl)-1-substituted-4-nitro-1H-pyrazole compounds **30**. Treatment of 30 with an azide reagent (azidation) may give a mix of ring opened compounds 5-azido-2-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-4-ol **31** and 5-azido-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-4-ol **32**. Fluorination of **31** and **32** with a fluorinating reagent such as

deoxo-Fluor® in a suitable solvent such as DCM or by methods described in the literature gives **33** and **34**, respectively.

Scheme 8: synthesis of 5-(5-azido-6-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **37** from 1-substituted-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1H-pyrazole compounds **25**



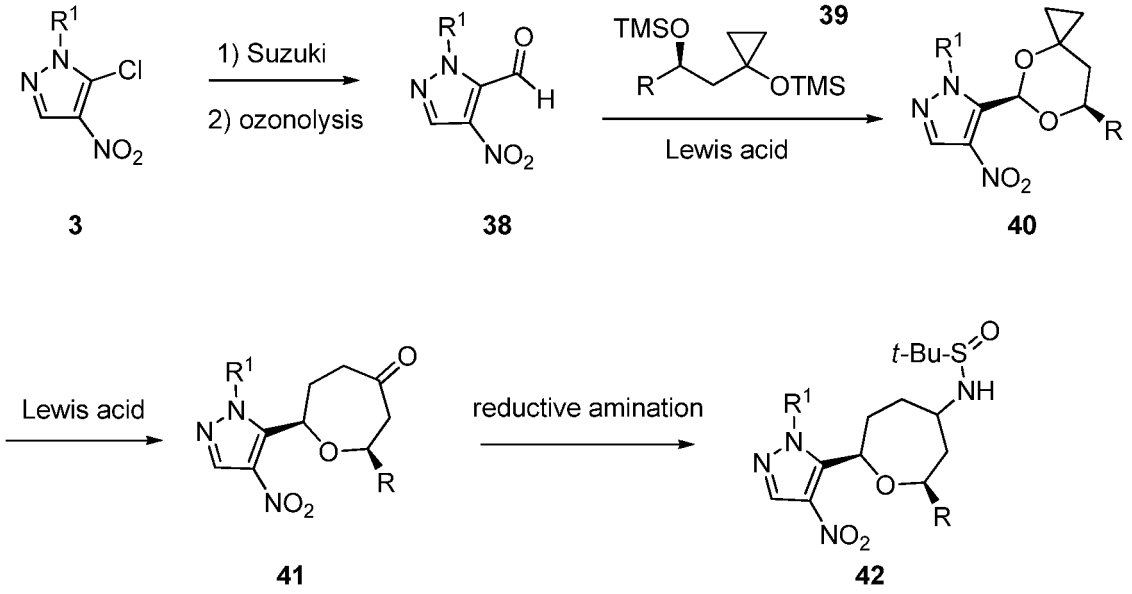
25 **35** **36**

37

wherein R^1 is as defined herein.

Scheme 8 shows an exemplary synthesis of 5-(5-azido-6-fluorooxepan-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **37** from 1-substituted-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1H-pyrazole compounds **25**. Treatment of **25** with *N*-bromosuccinimide and acetic acid in the presence of molecular sieves in a suitable solvent such as dichloromethane followed by treatment with potassium carbonate in a suitable solvent such as methanol or by methods described in the literature gives 5-(3,8-dioxabicyclo[5.1.0]octan-4-yl)-1-substituted-4-nitro-1H-pyrazole compounds **35**. Epoxide ring opening of **25** sodium azide according to literature methods gives 4-azido-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-3-ol compounds **36**. Fluorination of **36** with a fluorinating reagent such as deoxo-Fluor® in a solvent such as DCM or by methods described in the literature gives **37**.

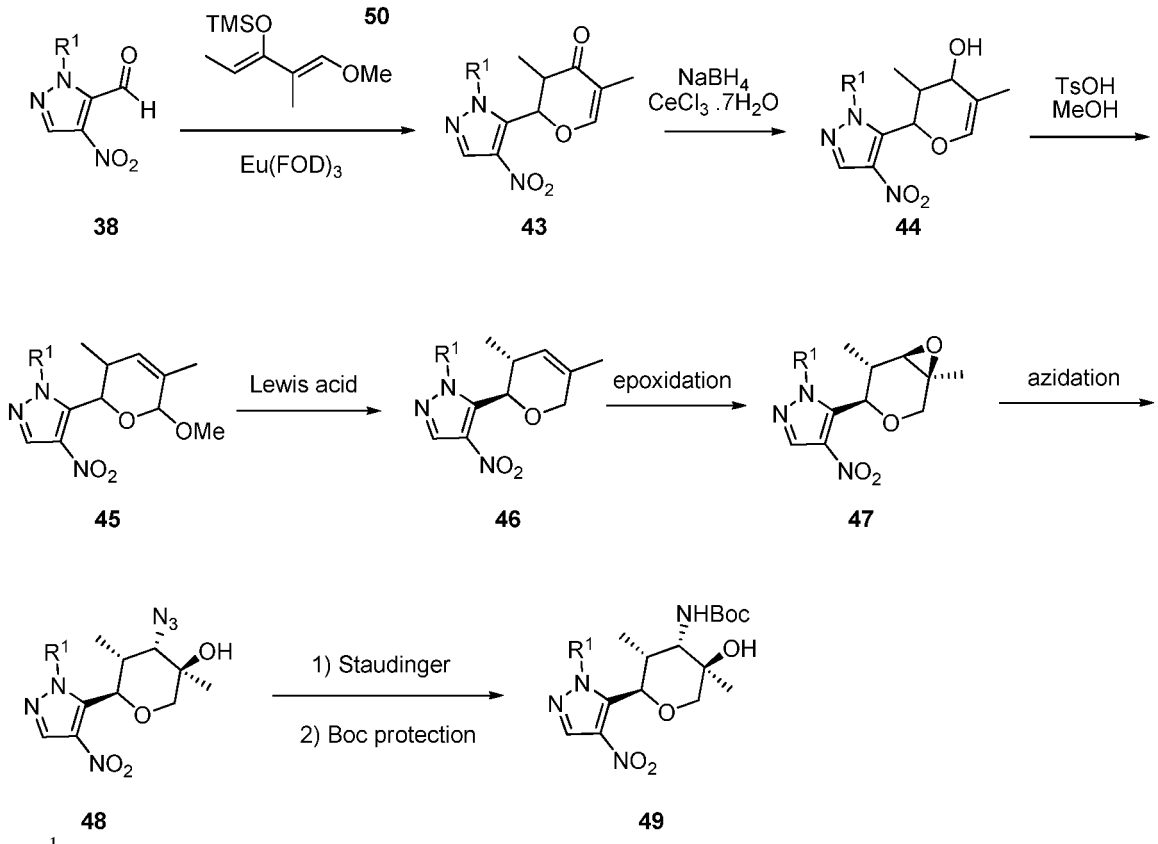
Scheme 9: synthesis of 2-methyl-N-(2-substituted-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)propane-2-sulfinamide compounds **42** from 5-chloro-4-nitro-1H-pyrazole compounds **3**



wherein R^1 is as defined herein.

Scheme 9 shows an exemplary synthesis of 2-methyl-N-(2-substituted-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)propane-2-sulfinamide compounds **42** from 5-chloro-4-nitro-1H-pyrazole compounds **3**. Suzuki reaction of **3** by heating with potassium vinyltrifluoroborate and cesium carbonate in solvents such as DMF and water in the presence of a suitable catalyst such as 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex followed by treatment of the resulting alkene with ozone in a suitable solvent such as dichloromethane or using methods described in the literature gives 1-substituted-4-nitro-1H-pyrazole-5-carbaldehyde compounds **38**. Treatment of **38** with (R)-trimethyl(1-(1-(trimethylsilyloxy)cyclopropyl)propan-2-yloxy)silane compounds **39** and trimethylsilyl triflate in a suitable solvent such as dichloromethane or using methods described in the literature (Minbiole et al (2005) Org. Lett. 7:515) gives 5-((5R,7R)-7-substituted-4,6-dioxaspiro[2.5]octan-5-yl)-1-substituted-4-nitro-1H-pyrazole compounds **40**. Treatment of **40** with a suitable Lewis acid such as titanium tetrachloride in a solvent such as dichloromethane or using methods described in the literature gives rearranged product, (2R,7R)-2-substituted-7-(1-substituted-4-nitro-1H-pyrazol-5-yl)oxepan-4-one compounds **41**. Reductive amination of **41** by heating with (R)-2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid such as titanium(IV) ethoxide in a solvent such as THF followed by treatment with sodium borohydride in a suitable solvent or using methods described in the literature gives **42**.

Scheme 10: synthesis of tert-butyl (2R,3R,4S,5R)-5-hydroxy-3,5-dimethyl-2-(1-substituted-4-nitro-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-ylcarbamate compounds **49** from 1-substituted-4-nitro-1H-pyrazole-5-carbaldehyde compounds **38**

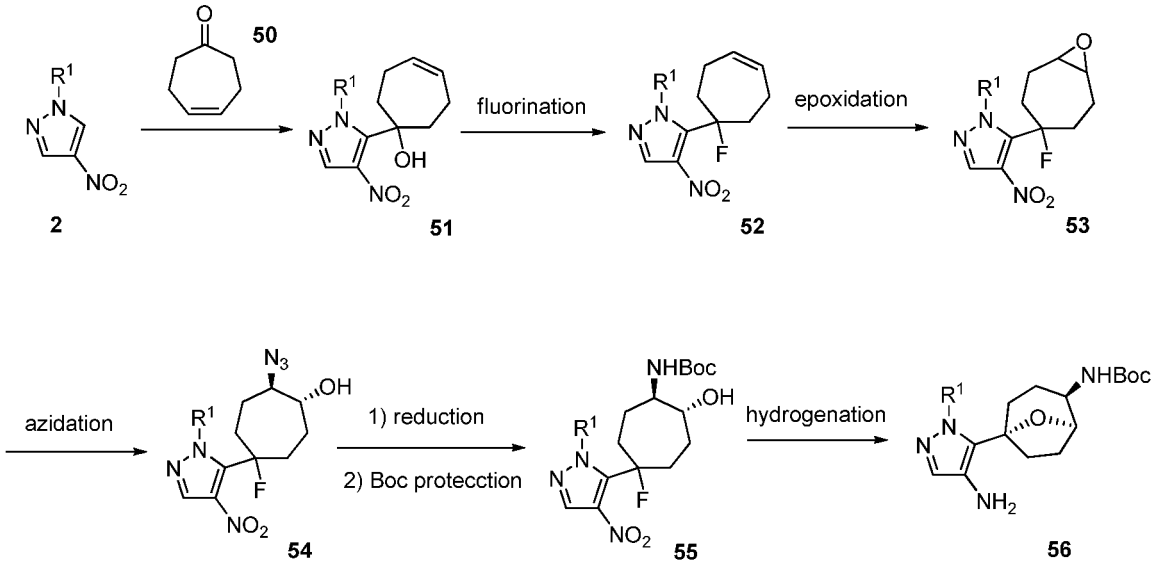


wherein R^1 is as defined herein.

Scheme 10 shows an exemplary synthesis of tert-butyl (2R,3R,4S,5R)-5-hydroxy-3,5-dimethyl-2-(1-substituted-4-nitro-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-ylcarbamate compounds **49** from 1-substituted-4-nitro-1H-pyrazole-5-carbaldehyde compounds **38**. Heating **38** with diene ((1E,3Z)-1-methoxy-2-methylpenta-1,3-dien-3-yloxy)trimethylsilane **50** in the presence of Resolve-Al™ EuFOD (Europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate), Sievers' Reagent, Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium, Sigma-Aldrich Product No. 160938, CAS No. 17631-68-4) in a suitable solvent such as chloroform or using methods described in the literature gives 3,5-dimethyl-2-(1-substituted-4-nitro-1H-pyrazol-5-yl)-2H-pyran-4(3H)-one compounds **43**. Treatment of **43** with a suitable reducing agent such as sodium borohydride in the presence of cerium(III) chloride heptahydrate in an appropriate solvent such as methanol or using similar methods described in the literature gives 3,5-dimethyl-2-(1-substituted-4-nitro-1H-pyrazol-5-yl)-3,4-dihydro-2H-pyran-4-ol compounds **44**. Heating **44** with p-toluene sulfonic acid in methanol or using methods described in the literature gives rearranged product, 5-(6-methoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **45**. Treatment of 45 with a Lewis acid such as boron trifluoride diethyl etherate and reducing agent such as triethylsilane in a suitable solvent such as dichloromethane or using methods described in the literature gives 5-(3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)-1-substituted-4-nitro-1H-pyrazole compounds **46**. Epoxidation of 46 with an epoxidizing reagent such as m-CPBA or by

similar procedures reported in the literature gives 5-(1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)-1-substituted-4-nitro-1H-pyrazole compounds **47**. Opening of the epoxide of **47** with sodium azide according to literature methods gives 4-azido-3,5-dimethyl-6-(1-substituted-4-nitro-1H-pyrazol-5-yl)tetrahydro-2H-pyran-3-ol compounds **48**. Staudinger azide reduction of **48** by heating with trimethylphosphine in THF and water followed by protection of the resulting amine with a suitable protecting group such as a Boc-protecting group using the methods outlined or those described in the literature gives **49**.

Scheme 11: synthesis of tert-butyl (5-(4-amino-1-substituted-1H-pyrazol-5-yl)-8-oxabicyclo[3.2.1]octan-2-ylcarbamate compounds **56** from 1-substituted-4-nitro-1H-pyrazole compounds **2**



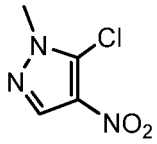
wherein R^1 is as defined herein.

Scheme 11 shows an exemplary synthesis of tert-butyl (5-(4-amino-1-substituted-1H-pyrazol-5-yl)-8-oxabicyclo[3.2.1]octan-2-ylcarbamate compounds **56** from 1-substituted-4-nitro-1H-pyrazole compounds **2**. Reaction of **2** with (Z)-cyclohept-4-enone **50** and a suitable base such as lithium hexamethyldisilazide at an appropriate temperature in a solvent such as THF or by methods described in the literature gives 1-(1-substituted-4-nitro-1H-pyrazol-5-yl)cyclohept-4-enol compounds **51**. Fluorination of **51** with a fluorinating reagent such as deoxo-Fluor® in a suitable solvent such as DCM or by methods described in the literature gives 5-(1-fluorocyclohept-4-enyl)-1-substituted-4-nitro-1H-pyrazole compounds **52**. Epoxidation of **52** with m-CPBA or similar methods described in the literature gives 5-(4-fluoro-8-oxabicyclo[5.1.0]octan-4-yl)-1-substituted-4-nitro-1H-pyrazole compounds **53**. Opening the epoxide of **53** with sodium azide according to literature methods gives 2-azido-5-fluoro-5-(1-substituted-4-nitro-1H-pyrazol-5-yl)cycloheptanol compounds **54**. Staudinger azide reduction of **54** by heating with triphenylphosphine in THF and water followed by protection of the resulting amine with a suitable protecting group such as a Boc-protecting group using the methods

outlined or those described in the literature gives tert-butyl-(5-fluoro-2-hydroxy-5-(1-substituted-4-nitro-1H-pyrazol-5-yl)cycloheptylcarbamate compounds **55**. Hydrogenation of **55** by heating at an appropriate temperature in the presence of a suitable catalyst such as 10% palladium on carbon under an atmosphere of hydrogen gas in suitable solvents such as a mixture of THF and methanol gives **56**.

EXAMPLES

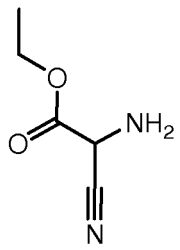
Example 1 5-chloro-1-methyl-4-nitro-1H-pyrazole



To a 500 mL round bottom flask containing 4-nitro-*1-H*-pyrazole (5g, 44.2 mmol) was added sodium hydroxide (1M, 200 mL) and dimethyl sulfate (31 mL, 330 mmol). The mixture was stirred at room temperature for 72 h and the mixture was extracted with CH_2Cl_2 (2 x 150 mL). The organic layer was separated and the solvent was distilled off to yield 1-methyl-4-nitro-1H-pyrazole as a white solid (4.30 g, 76%).

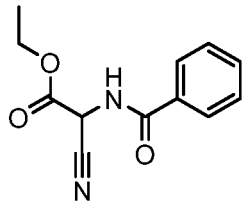
Following WO 2007/99326, to a 500 mL 3-neck-round bottom flask was added 1-methyl-4-nitro-1H-pyrazole (4.30 g, 33.8 mmol) and THF (12 mL). The mixture was cooled to -78 °C and lithium hexamethyldisilazide in THF (1M, 88.4 mL, 90 mmol) was added dropwise via an addition funnel over 20 min. The brown mixture was stirred for 30 min and warmed to -45 °C over 30 min. The mixture was cooled back down to –78 °C and hexachloroethane (10.5 g, 44.2 mmol) dissolved in THF (20 mL) was added via an addition funnel over 15 min. The mixture was stirred for 2.5 h, warmed from -78 °C to -40 °C and the reaction was monitored by LCMS. Upon completion of the reaction, the reaction was quenched with a solution of saturated NH_4Cl (150 mL), and ethyl acetate (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with water (150 mL), dried over Na_2SO_4 and the organic solvent was distilled off. The crude product was purified via flash chromatography (CH_2Cl_2/ 7% MeOH) to yield 5-chloro-1-methyl-4-nitro-1H-pyrazole as a white solid (1.40 g, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 3.92 (s, 3H); ESIMS m/z = 162.0 (M+1)

Example 2 ethyl 2-amino-2-cyanoacetate



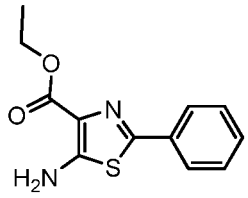
To a stirred solution of (E)-ethyl 2-cyano-2-(hydroxyimino)acetate (20g, 0.14 mol) in water (250 mL) was added a saturated solution of $NaHCO_3$ in water (160 mL), followed by the addition of $Na_2S_2O_4$ (60 g, 0.423 mol). The reaction mixture was warmed up to 35 ^oC and stirred for additional 2 hr. It was then saturated with NaCl (150 g) and extracted with DCM (3 x 350 mL). Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give ethyl 2-amino-2-cyanoacetate as a red oil (7.8 g, 43%) that was used at the next step without additional purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 4.45 (s, 1H), 4.34 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H); MS (ESI) m/z: 129 [M+H$^+$].

Example 3 ethyl 2-benzamido-2-cyanoacetate



To a stirred solution of compound ethyl 2-amino-2-cyanoacetate (0.64 g, 5 mmol) in DCM (15 mL) was added a saturate solution of $NaHCO_3$ in water (15 mL). With vigorously stirring, benzoyl chloride (0.84 g, 6 mmol) was added. The reaction mixture was stirred at ambient temperature for additional 30 min at which time it was extracted with DCM (3 x 15 mL). Combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, concentrated in vacuo. Resulted residue was purified by silica gel column chromatography (5:1 PE/EtOAc) to afford ethyl 2-benzamido-2-cyanoacetate (0.25 g, 22%) as white solid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.83-7.85 (m, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 7.0 Hz, 1H), 5.72 (d, J = 7.5 Hz, 1H), 4.40 (q, J = 7.5 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H); MS (ESI) m/z: 233 [M+H$^+$].

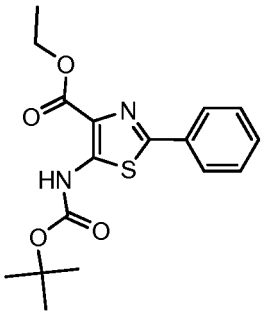
Example 4 ethyl 5-amino-2-phenylthiazole-4-carboxylate



To a stirred solution of compound ethyl 2-benzamido-2-cyanoacetate (0.46 g, 2 mmol) in pyridine (20 mL) was added Lawesson's reagent (0.81 g, 2 mmol). The reaction mixture was heated at reflux for 15 hr. It was then concentrated and diluted with EtOAc (40 mL). The diluted mixture was washed with water (3 x 20 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10:1 PE/EtOAc) to afford ethyl 5-amino-2-phenylthiazole-4-carboxylate (0.2 g, 40%) as yellow solid:

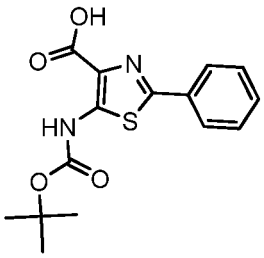
^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.80 (d, J = 6.5 Hz, 1H), 7.36-7.41 (m, 3H), 4.43 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H); MS (ESI) m/z: 249 [M+H$^+$].

Example 5 ethyl 5-(tert-butoxycarbonylamino)-2-phenylthiazole-4-carboxylate



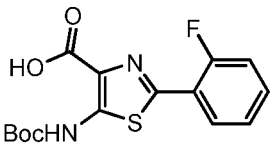
To a solution of compound ethyl 5-amino-2-phenylthiazole-4-carboxylate (248 mg, 1 mmol) in CH_3CN (10 mL) was added DMAP (6 mg, 0.05 mmol) followed by $(Boc)_2O$ (262 mg, 1.2 mmol). The reaction mixture was maintained at ambient temperature for additional 30 min. The mixture was then evaporated in vacuo to give ethyl 5-(tert-butoxycarbonylamino)-2-phenylthiazole-4-carboxylate as a red solid (340 mg, 95%) that was used at the next step without further purification.

Example 6 5-(tert-butoxycarbonylamino)-2-phenylthiazole-4-carboxylic acid



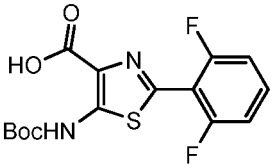
To a solution of compound ethyl 5-(tert-butoxycarbonylamino)-2-phenylthiazole-4-carboxylate (348 mg, 1 mmol) in MeOH/H_2O (10 mL, 1:1) was added $LiOH{\cdot}H_2O$ (20 mg, 5 mmol). The reaction mixture was heated at 50-55 °C until starting material disappeared from TLC. It was cooled at about 0-4 °C and conc. HCl added dropwise until pH of about 5. The resulted mixture was then extracted with DCM (3 x 20 mL). Combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (50:1 DCM:MeOH) to give the 5-(tert-butoxycarbonylamino)-2-phenylthiazole-4-carboxylic acid (0.22 g, 68%) as white solid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.69 (s, 1H), 7.89-7.91 (m, 2H), 7.46-7.47 (m, 3H), 1.57 (s, 9H); MS (ESI) m/z: 321 [M+H$^+$]

Example 7 5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carboxylic acid



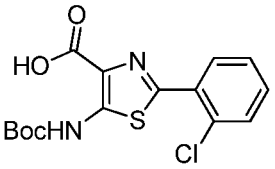
Following procedures from Examples 19-23 and shown in scheme 2, 2-fluorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.70 (s, 1H), 8.19-8.23 (m, 1H), 7.42-7.45 (m, 1H), 7.20-7.30 (m, 2H), 1.57 (s, 9H); MS (ESI) m/z: 339 [M+H$^+$]

Example 8 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



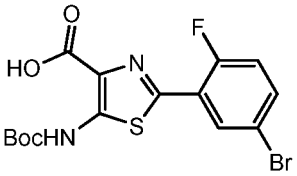
Following procedures from Examples 19-23 and shown in scheme 2, 2, 6-difluorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 7.42-7.46 (m, 1H), 7.06 (t, J = 8.5 Hz, 2H), 1.47 (s, 9H); MS (ESI) m/z: 355 [M+H$^+$].

Example 9 5-(tert-butoxycarbonylamino)-2-(2-chlorophenyl)thiazole-4-carboxylic acid



Following procedures from Examples 19-23 and shown in Scheme 2, 2-chlorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2-chlorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (DMSO, 500 MHz) δ (ppm): 13.57 (s, 1H), 10.05 (s, 1H), 8.14-8.17 (m, 1H), 7.63-7.65 (m, 1H), 7.49-7.51 (m, 2H), 1.53 (s, 9H); MS (ESI) m/z: 355 [M+H$^+$].

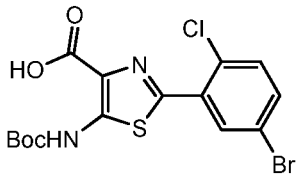
Example 10 2-(5-bromo-2-fluorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



Following procedures from Examples 1-9 and shown in Scheme 2, 5-bromo-2-fluorobenzoyl chloride was converted to 2-(5-bromo-2-fluorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.70 (s,

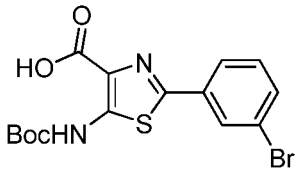
1H), 8.32-8.34 (m, 1H), 7.49-7.52 (m, 1H), 7.09-7.13 (m, 1H), 1.57 (s, 9H); MS (ESI) m/z: 418 [M+H$^+$].

Example 11 2-(5-bromo-2-chlorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



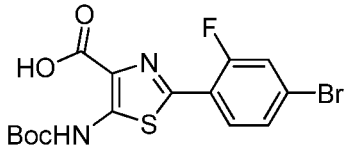
Following procedures from Examples 1-9 and shown in Scheme 2, 5-bromo-2-chlorobenzoyl chloride was converted to 2-(5-bromo-2-chlorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.70 (s, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 1.57 (s, 9H); MS (ESI) m/z: 433 [M+H$^+$].

Example 12 2-(3-bromophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



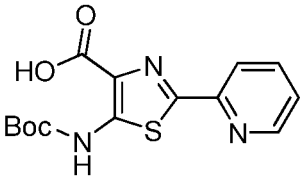
Following procedures from Examples 1-9 and shown in Scheme 2, 3-bromobenzoyl chloride was converted to 2-(3-bromophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.68 (s, 1H), 8.08 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 1.57 (s, 9H); MS (ESI) m/z: 399 [M+H$^+$]

Example 13 2-(4-bromo-2-fluorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



Following procedures from Examples 1-9 and shown in Scheme 2, 4-bromo-2-fluorobenzoyl chloride was converted to 2-(4-bromo-2-fluorophenyl)-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.67 (s, 1H), 8.07 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 9.5 Hz, 1H), 1.57 (s, 9H); MS (ESI) m/z: 417 [M+H$^+$]

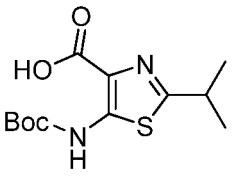
Example 14 5-(tert-butoxycarbonylamino)-2-(yridine-2-yl)thiazole-4-carboxylic acid



To a solution of picolinic acid (1.23 g, 10 mmol), EDC·HCl (1.91 g, 10 mmol) and HOBT (1.35 g, 10 mmol) in THF (80 mL) was added DIPEA (3.6 g, 30 mmol) at ambient temperature. The reaction mixture was maintained at the same temperature for 1 hr at which time a solution of ethyl 2-amino-2-cyanoacetate (1.28 g, 10 mmol) in THF (5 mL) was added. The reaction mixture was stirred at ambient temperature for additional 6 hr. It was then concentrated, and the residue was purified by silica gel column chromatography (5:1 PE/EtOAc) to give ethyl 2-cyano-2-(picolinamido)acetate (0.7 g, 30%) as yellow solid.

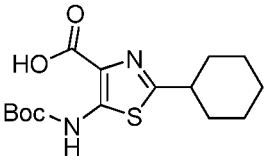
Following procedures from Examples 19-23 and shown in Scheme 2, ethyl 2-cyano-2-(picolinamido)acetate was converted to 5-(tert-butoxycarbonylamino)-2-(pyridine-2-yl)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.72 (s, 1H), 8.61 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.34 (dd, J = 5.5 Hz, J = 7.0 Hz, 1H), 1.57 (s, 9H); MS (ESI) m/z: 322 [M+H$^+$].

Example 15 5-(tert-butoxycarbonylamino)-2-isopropylthiazole-4-carboxylic acid



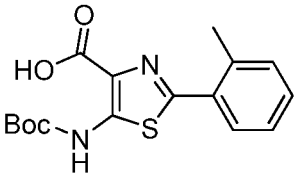
Following procedures from Examples 1-9 and shown in Scheme 2, isobutyryl chloride was converted to 5-(tert-butoxycarbonylamino)-2-isopropylthiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.54 (s, 1H), 3.16-3.21 (m, 1H), 1.54 (s, 9H), 1.37 (d, J = 7.0 Hz, 6H); MS (ESI) m/z: 287 [M+H$^+$].

Example 16 5-(tert-butoxycarbonylamino)-2-cyclohexylthiazole-4-carboxylic acid



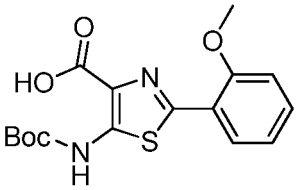
Following procedures from Examples 1-9 and shown in Scheme 2, cyclohexanecarboxylic acid chloride was converted to 5-(tert-butoxycarbonylamino)-2-cyclohexylthiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.53 (s, 1H), 2.84-2.89 (m, 1H), 2.08-2.12 (m, 2H), 1.84 (dd, J = 3.5 Hz, J = 10.0 Hz, 2H), 1.73 (d, J = 13.0 Hz, 1H), 1.53 (s, 9H), 1.35-1.50 (m, 4H), 1.25-1.27 (m, 1H); MS (ESI) m/z: 327 [M+H$^+$].

Example 17 5-(tert-butoxycarbonylamino)-2-o-tolylthiazole-4-carboxylic acid



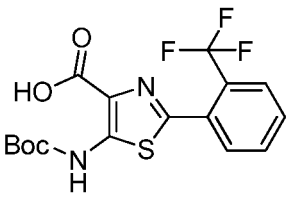
Following procedures from Examples 1-9 and shown in Scheme 2, 2-methylbenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-o-tolylthiazole-4-carboxylic acid: ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 7.34 (s, 1H), 7.13-7.22 (m, 3H), 2.32 (s, 3H), 1.43 (s, 9H); MS (ESI) m/z: 335 [M+H$^+$].

Example 18 5-(tert-butoxycarbonylamino)-2-(2-methoxyphenyl)thiazole-4-carboxylic acid



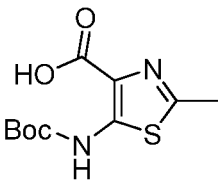
Following procedures from Examples 1-9 and shown in Scheme 2, 2-methoxybenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2-methoxyphenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 9.63 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 1.57 (s, 9H); MS (ESI) m/z: 351 [M+H$^+$]

Example 19 5-(tert-butoxycarbonylamino)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid



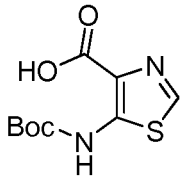
Following procedures from Examples 1-9 and shown in Scheme 2, 2-(trifluoromethyl)benzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 7.76 (d, J = 7.5 Hz, 1H), 7.58-7.64 (m, 3H), 1.46 (s, 9H); MS (ESI) m/z: 389 [M+H$^+$].

Example 20 5-(tert-butoxycarbonylamino)-2-methylthiazole-4-carboxylic acid



Following procedures from Examples 1-9 and shown in Scheme 2, acetyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-methylthiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.62 (s, 1H), 2.62 (s, 3H), 1.54 (s, 9H); MS (ESI) m/z: 259 [M+H$^+$]

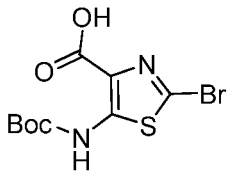
Example 21 5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



Under a nitrogen atmosphere (N_2), HCOOH (2.44 g, 53 mmol) was added to Ac_2O (6.48 g, 63.6 mmol) at 0 °C. After it was allowed to warm to ambient temperature the reaction was heated at 50 °C for 15 hr. It was allowed to cool to ambient temperature. This mixed acid anhydride was then added dropwise to a solution of ethyl 2-amino-2-cyanoacetate (128 mg, 1 mmol) in dry THF (5 mL) at 0 °C. After the cooling bath was removed, the reaction was maintained at ambient temperature for additional 1 hr. The reaction mixture was concentrated and purified by silica gel column chromatography (5:1 PE/EtOAc) to afford ethyl 2-cyano-2-formamidoacetate (110 mg, 70%) as a white solid.

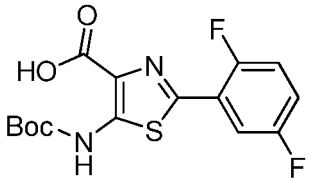
Following procedures from Examples 1-9 and shown in Scheme 2, ethyl 2-cyano-2-formamidoacetate was converted to 5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.70 (s, 1H), 8.29 (s, 1H), 1.55 (s, 9H); MS(ESI) m/z: 245 [M+H$^+$]

Example 22 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



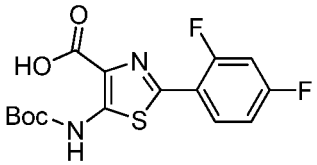
To a solution of 5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid (1.72 g, 10 mmol) in DCM (50 mL) was added in three portions NBS (1.95 g, 11 mmol); the reaction mixture was stirred at ambient temperature for 1 h. Reaction was concentrated in vacuo; resulted residue was purified by silica gel column chromatography (6:1 Pet-ether-EtOAc) to afford 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid (1.75 g, 70%) as white solid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 13.65 (s, 1H), 10.03 (s, 1H), 1.49 (s, 9H). MS(ESI) m/z: 324 [M+H$^+$]

Example 23 5-(tert-butoxycarbonylamino)-2-(2,5-difluorophenyl)thiazole-4-carboxylic acid



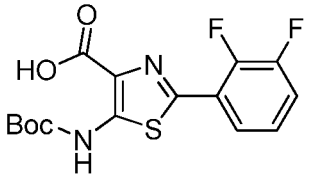
Following procedures from Examples 1-9 and shown in Scheme 2, 2,5-difluorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2,5-difluorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.68 (s, 1H), 7.87-7.91 (m, 1H), 7.15-7.26 (m, 1H), 7.08-7.13 (m, 1H), 1.57 (s, 9H); MS (ESI) m/z: 357 [M+H$^+$]

Example 24 5-(tert-butoxycarbonylamino)-2-(2,4-difluorophenyl)thiazole-4-carboxylic acid



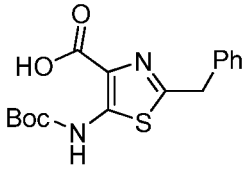
Following procedures from Examples 1-9 and shown in Scheme 2, 2,4-difluorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2,4-difluorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.66 (s, 1H), 8.16-8.21 (m, 1H), 6.95-7.04 (m, 2H), 1.62 (s, 9H); MS (ESI) m/z: 357 [M+H$^+$]

Example 25 5-(tert-butoxycarbonylamino)-2-(2,3-difluorophenyl)thiazole-4-carboxylic acid



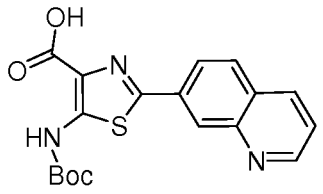
Following procedures from Examples 1-9 and shown in Scheme 2, 2,3-difluorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(2,3-difluorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (CD_3OD, 400 MHz) δ (ppm): 7.45 (s, 1H), 7.07-7.16 (m, 2H), 1.42 (s, 9H); MS (ESI) m/z: 357 [M+H$^+$].

Example 26 2-benzyl-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid



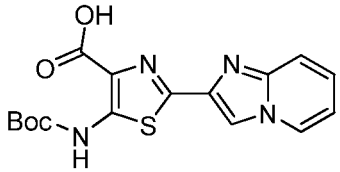
Following procedures from Examples 1-9 and shown in Scheme 2, 2-phenylacetyl chloride was converted to 2-benzyl-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.63 (s, 1H), 7.27-7.35 (m, 5H), 4.25 (s, 2H), 1.50 (s, 9H); MS(ESI) m/z: 335 [M+H$^+$].

Example 27 5-(tert-butoxycarbonylamino)-2-(quinolin-7-yl)thiazole-4-carboxylic acid



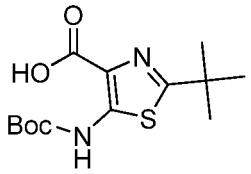
Following procedures from Examples 1-9 and shown in Scheme 2, quinoline-7-carbonyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(quinolin-7-yl)thiazole-4-carboxylic acid: ^{1}H-NMR (DMSO, 500 MHz) δ (ppm): 10.14 (s, 1H), 9.11 (d, J = 5 Hz, 1h), 8.68 (s, 1H), 8.55 (s, 1H), 8.21-8.25 (m, 2H), 7.75-7.77 (m, 1H), 1.54 (s, 9H) ; MS(ESI) m/z: 372 [M+H$^+$]

Example 28 5-(tert-butoxycarbonylamino)-2-(imidazo[1,2-a]yridine-2-yl)thiazole-4-carboxylic acid



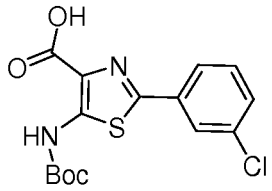
Following procedures from Examples 1-9 and shown in Scheme 2, imidazo[1,2-a]pyridine-2-carbonyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(imidazo[1,2-a]yridine-2-yl)thiazole-4-carboxylic acid: ^{1}H-NMR (DMSO, 500 MHz) δ (ppm): 10.12 (s, 1H), 8.58 (d, 5Hz, 1H), 8.45 (s, 1H), 7.61(d, 5Hz, 1H), 7.31-7.34 (m, 1H), 6.97-6.99 (m, 1H), 1.53 (s, 9H); MS(ESI) m/z: 361 [M+H$^+$].

Example 29 5-(tert-butoxycarbonylamino)-2-tert-butylthiazole-4-carboxylic acid



Following procedures from Examples 1-9 and shown in Scheme 2, pivaloyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-tert-butylthiazole-4-carboxylic acid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.55 (s, 1H), 1.55 (s, 9H), 1.42 (s, 9H); MS(ESI) m/z: 301 [M+H$^+$].

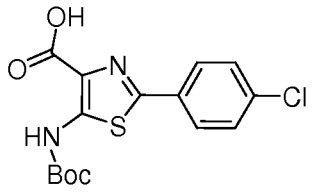
Example 30 5-(tert-butoxycarbonylamino)-2-(3-chlorophenyl)thiazole-4-carboxylic acid



Following procedures from Examples 1-9 and shown in Scheme 2, 3-chlorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(3-chlorophenyl)thiazole-4-carboxylic

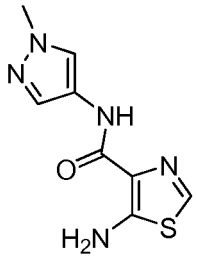
acid: ^{1}H-NMR (DMSO, 500 MHz) δ (ppm): 9.67 (s, 1H), 7.91 (s, 1H), 7.72 (d, J = 7Hz, 1H), 7.38-7.40 (m, 2H), 1.56 s, 9H); MS(ESI) m/z: 355 [M+H$^+$].

Example 31 5-(tert-butoxycarbonylamino)-2-(4-chlorophenyl)thiazole-4-carboxylic acid



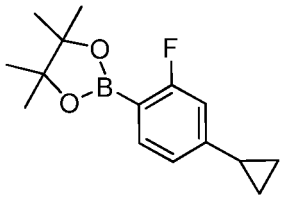
Following procedures from Examples 1-9 and shown in Scheme 2, 4-chlorobenzoyl chloride was converted to 5-(tert-butoxycarbonylamino)-2-(4-chlorophenyl)thiazole-4-carboxylic acid: ^{1}H-NMR (DMSO, 500 MHz) δ (ppm): 9.66 (s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 1.56 (s, 9H); MS(ESI) m/z: 355 [M+H$^+$].

Example 32 5-amino-*N*-(1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide



Following the procedures shown in Scheme 4, 1-methyl-1H-pyrazol-4-amine, 5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid were reacted to give 5-amino-*N*-(1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide as a white solid (13 mg, 32%) over two steps. ESIMS m/z = 336.1 (M+1)

Example 33 2-(4-Cyclopropyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step A: 3-fluoro-4-nitrophenyl trifluoromethanesulfonate

To a stirred solution of 3-fluoro-4-nitrophenol (10.00 g, 63.65 mmol) and trifluoromethanesulfonic anhydride (20.0 mL, 119 mmol, 1.87 eq.) in anhydrous DCM (100.0 mL) at 0 ^{o}C was added dropwise triethylamine (33.27 mL, 238.7 mmol, 3.75 eq.). The resultant brown reaction mixture was stirred at 0 ^{o}C for 2h and then stirred at ambient temperature for 16h. The reaction mixture was slowly quenched with water and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (1x), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude oil was purified *via* flash column chromatography eluted with 0 to 65% DCM/hexane to give 15.67 g (85.1%) of 3-fluoro-4-nitrophenyl trifluoromethanesulfonate as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (t, J = 8.52 Hz, 1H), 7.34-7.27 (m, 2H).

Step B: 4-cyclopropyl-2-fluoro-1-nitrobenzene

A mixture of 3-fluoro-4-nitrophenyl trifluoromethanesulfonate (7.15 g, 24.73 mmol), cyclopropylboronic acid (2.55 g, 29.67 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complexed with dichloromethane (1:1) (1.62 g, 1.98 mmol), and 2M cesium carbonate in water (19.8 mL, 39.56 mmol) in toluene (39.5 mL) was degassed for 20 min. The reaction mixture was stirred at 90 °C under N_2 for 2.5h. The reaction was cooled to RT, diluted with ethyl acetate (200 mL), and filtered through a pad of Celite. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified *via* flash column chromatography eluted with 0 to 75% DCM/hexane to give 4.11 g (91.7%) of 4-cyclopropyl-2-fluoro-1-nitrobenzene as an oil. ^{1}H NMR (400 MHz, MeOD) δ 7.98 (dd, J = 10.2, 6.6 Hz, 1H), 7.12 – 7.02 (m, 2H), 2.11 – 1.97 (m, 1H), 1.20 – 1.11 (m, 2H), 0.89 – 0.82 (m, 2H).

Step C: 4-cyclopropyl-2-fluoroaniline

A mixture of 4-cyclopropyl-2-fluoro-1-nitrobenzene (3.36 g, 18.55 mmol), powdered iron (4.35 g, 77.9 mmol), and 2M ammonium chloride in water (19.8 mL) and 3:2:1 *v/v* EtOH:THF:H_2O (86 mL) was stirred at reflux under N_2 for 17h. The reaction mixture was cooled to RT and filtered through a pad of Celite. The Celite pad was rinsed well with ethyl acetate (~ 50 mL). Saturated aqueous $NaHCO_3$ solution was slowly added to the filtrate to neutralize the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified *via* flash column chromatography eluted with 0 to 75% ethyl acetate/hexane to give 2.80 g (99%) of an orange oil, which solidified at 20°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 – 6.63 (m, 3H), 3.57 (s, 2H), 1.87 – 1.72 (m, 1H), 0.93 – 0.83 (m, 2H), 0.64 – 0.51 (m, 2H) ; MS (ESI) m/z: 152.3 $[M+H]^+$.

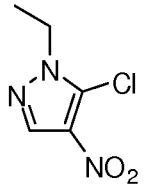
Step D: 4-cyclopropyl-2-fluoro-1-iodobenzene

To a stirred mixture of 4-cyclopropyl-2-fluoroaniline (1.63 g, 10.78 mmol) in water (20 mL) at 0 °C was added concentrated sulfuric acid (8.6 mL, 15.0 eq.) dropwise, while keeping the temperature constant at 0 °C. A solution of sodium nitrite (781.0 mg, 11.32 mmol, 1.05 eq.) in water (2.7 mL) was added and stirred for 5 minutes. This resulting reaction mixture was then added to a solution of potassium iodide (3.76 g, 22.64 mmol, 2.1 eq.) in water (9.7 mL), and the reaction mixture was stirred at 60 °C for 3h. DCM (400 mL) was added to the cooled reaction.

The biphasic layers were separated, and the aqueous layer was extracted with DCM (2 x 150 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_4$, water, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified *via* flash column chromatography eluted with 100% heptane to give 2.01 g (71.28%) of 4-cyclopropyl-2-fluoro-1-iodobenzene as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 6.9 Hz, 1H), 6.76 (dd, *J* = 9.4, 1.9 Hz, 1H), 6.64 (dd, *J* = 8.2, 1.9 Hz, 1H), 1.94 – 1.77 (m, 1H), 1.09 – 0.95 (m, 2H), 0.79 – 0.56 (m, 2H).

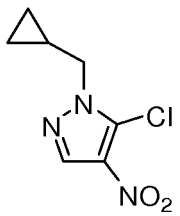
Step E: In a high pressure tube was placed 4-cyclopropyl-2-fluoro-1-iodo-benzene (1.32 g, 5.04 mmol), bispinacol ester boronate (1.53 g, 6.04 mmol), potassium acetate (1.98 g, 20.15 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (368.5 mg, 0.50 mmol), and *N*,*N*-dimethylformamide (35 mL). The reaction mixture was degassed with N_2 for 15 minutes. The vessel was sealed and the reaction mixture was stirred at 90°C for 16h. The cooled reaction mixture was diluted with ethyl acetate (75 mL) and water (25 mL) and then filtered through a pad of Celite. The biphasic layers were separated and the organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified *via* flash column chromatography eluted with 0 to 75% EA/heptane to give 859.0 mg (65.1%) of 2-(4-cyclopropyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.33 (s, 12 H), 0.98 (dd, J = 8.3, 2.0 Hz, 2H), 0.74 – 0.66 (m, 2H)

Example 34 5-Chloro-1-ethyl-4-nitro-1*H*-pyrazole



Following the procedure for Example 1 starting with 1-ethyl-4-nitropyrazole gave 5-chloro-1-ethyl-4-nitro-1*H*-pyrazole as a colorless solid (1.3 g, 74%). ¹H-NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 4.26 (q, *J* = 7Hz, 2H), 1.50 (t, *J* = 7Hz, 3H).

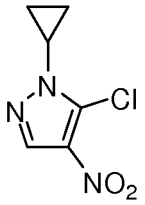
Example 35 5-Chloro-1-cyclopropylmethyl-4-nitro-1*H*-pyrazole



Following the procedure for Example 1 starting with 1-cyclopropylmethyl-4-nitropyrazole gave 5-chloro-1-cyclopropylmethyl-4-nitro-1*H*-pyrazole as a colorless oil (1.16 g,

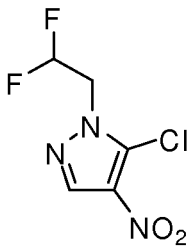
56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 4.07 (d, *J* = 7Hz, 2H), 1.39-1.28 (m, 1H), 0.66-0.59 (m, 2H), 0.50-0.40 (m, 2H).

Example 36 5-Chloro-1-cyclopropyl-4-nitro-1*H*-pyrazole



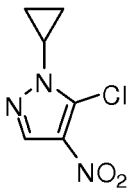
Following the procedure for Example 1 starting with 1-cyclopropyl-4-nitropyrazole gave 5-chloro-1-cyclopropyl-4-nitro-1*H*-pyrazole as a colorless solid (0.23 g, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 3.62-3.54 (m, 1H), 1.38-1.28 (m, 2H), 1.25-1.13 (m, 2H).

Example 37 5-Chloro-1-(2,2-difluoroethyl)-4-nitro-1*H*-pyrazole



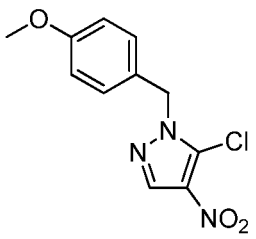
To a stirred solution of 1-(2,2-difluoroethyl)-4-nitro-1*H*-pyrazole (1.0 g, 5.13 mmol) in dry THF (20 mL) cooled to -70 °C was added dropwise a solution of lithium hexamethyldisilazide (1 M in THF, 8.47 mL, 8.47 mmol). After stirring at -70 °C for 40 min, the reaction mixture was allowed to warm to -55 °C over 20 min. After recooling to -70 °C , a solution of perchloroethane (1.74 g, 7.34 mmol) in THF (10 mL) was added slowly and the reaction mixture was stirred at -70 °C for 1.5 hr. Saturated aqueous ammonium chloride solution (30 mL) was added followed by water (15 mL) and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification of the residue by silica gel column chromatography (0-100% EtOAc/isohexane) gave 5-chloro-1-(2,2-difluoroethyl)-4-nitro-1*H*-pyrazole as an off-white solid (438 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 6.18 (tt, *J* = 54.8, 4.2 Hz, 1H), 4.58 (td, *J* = 12.8, 4.2 Hz, 2H).

Example 38 5-Chloro-1-cyclopropyl-4-nitro-1*H*-pyrazole



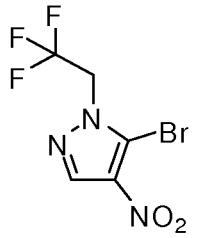
Following Example 37, chlorination of 1-cyclopropyl-4-nitropyrazole gave 5-chloro-1-cyclopropyl-4-nitro-1*H*-pyrazole as a colorless solid (0.23 g, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 3.62-3.54 (m, 1H), 1.38-1.28 (m, 2H), 1.25-1.13 (m, 2H).

Example 39 5-Chloro-1-(4-methoxybenzyl)-4-nitro-1*H*-pyrazole



Following Example 37, chlorination of 1-(4-methoxybenzyl)-4-nitro-1*H*-pyrazole gave 5-chloro-1-(4-methoxybenzyl)-4-nitro-1*H*-pyrazole as a yellow solid (536 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.25 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 5.30 (s, 2H), 3.80 (s, 3H).

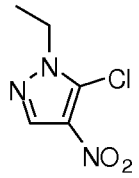
Example 40 5-Bromo-4-nitro-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole



To a stirred solution of 1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-amine (990 mg, 6.0 mmol) in acetic acid (5 mL) was added dropwise acetic anhydride (0.57 mL, 6.0 mmol) and the mixture was stirred at room temperature for 16 hr. More acetic anhydride (0.57 mL, 6.0 mmol) was added to the reaction mixture which was cooled in an ice bath for the addition of fuming nitric acid (0.28 mL, 6 mmol) to take place dropwise. The reaction mixture was stirred at room temperature for 7 hr and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (15 mL) and concentrated hydrochloric acid (10 mL) was added. The mixture was heated at reflux for 16 hr. After concentrating under reduced pressure the residue was partitioned between DCM (50 mL) and 5% aqueous $NaHCO_3$ solution (100 mL). The mixture was filtered and the aqueous layer was extracted with DCM (100 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a pale orange solid (540 mg). This solid (540 mg, 2.57 mmol) was dissolved in bromoform (2.9 mL, 33 mmol) and to the solution was added dropwise *tert*-butyl nitrite (0.92 mL, 7.71 mmol). The reaction mixture was stirred at room temperature for 15 min and then heated at 145 °C for 1.5 hr. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (0-100% EtOAc/isohexane) to give 5-bromo-4-nitro-1-(2,2,2-trifluoroethyl)-

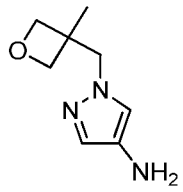
1*H*-pyrazole as a pale yellow solid (536 mg, 33% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 4.86 (q, *J* = 7.8 Hz, 2H).

Example 41 5-Chloro-1-ethyl-4-nitro-1*H*-pyrazole



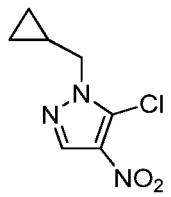
Following the procedure for Intermediate 5 starting with 1-ethyl-4-nitropyrazole gave 5-chloro-1-ethyl-4-nitro-1*H*-pyrazole as a colorless solid (1.3 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 4.26 (q, *J* = 7Hz, 2H), 1.50 (t, *J* = 7Hz, 3H).

Example 42 1-((3-Methyloxetan-3-yl)methyl)-1*H*-pyrazol-4-amine



A mixture of 4-nitropyrazole (1.13 g, 10 mmol) and K_2CO_3 (3.4 g, 25 mmol) in MeCN (50 mL) was stirred at room temperature for 15 min prior to addition of 3-(bromomethyl)-3-methyloxetane (1.8 g, 11 mmol). The reaction mixture was stirred at room temperature for 18 hr, filtered and the filter cake washed with MeCN. The filtrate was concentrated under reduced pressure and the residue purified by silica gel column chromatography (0-100% EtOAc/isohexane) gradient to afford 1-((3-methyloxetan-3-yl)methyl)-4-nitro-1*H*-pyrazole as a colorless solid (1.43 g, 73%). A portion of this solid (206 mg, 1.04 mmol) dissolved in MeOH (20 mL) was treated with ammonium formate (260 mg, 4.13 mmol) and 10% palladium on carbon (50 mg). The mixture was heated at 80 °C for 1.5 hr, cooled, filtered through Celite® and the filtrate concentrated under reduced pressure to afford 1-((3-methyloxetan-3-yl)methyl)-1*H*-pyrazol-4-amine as a pale pink gum (160 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.97 (s, 1H), 4.66 (d, *J* = 6.1 Hz, 2H), 4.37 (d, *J* = 6.1 Hz, 2H), 4.19 (s, 2H), 2.91 (s, 2H), 1.23 (s, 3H).

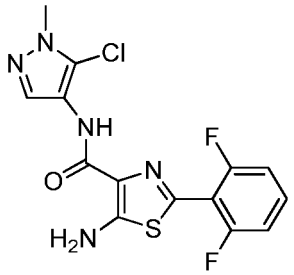
Example 43 5-Chloro-1-cyclopropylmethyl-4-nitro-1*H*-pyrazole



Following the procedure for Intermediate 5 starting with 1-cyclopropylmethyl-4-nitropyrazole gave 5-chloro-1-cyclopropylmethyl-4-nitro-1*H*-pyrazole as a colorless oil (1.16 g,

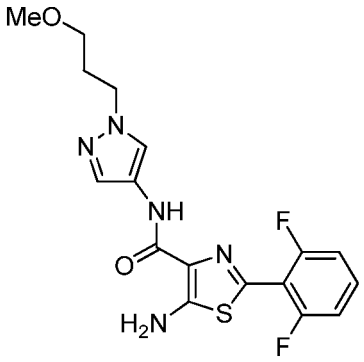
56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 4.07 (d, *J* = 7Hz, 2H), 1.39-1.28 (m, 1H), 0.66-0.59 (m, 2H), 0.50-0.40 (m, 2H).

Example 44 5-Amino-*N*-(5-chloro-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide



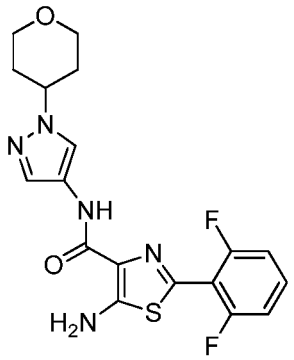
Following the procedure for Intermediate 1starting from 3-chloro-1-methyl-1*H*-pyrazol-4-amine gave 5-Amino-*N*-(5-chloro-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide as an off-white solid (146 mg, 46% over 3 steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.89 (s, 1H), 7.74 (s, 1H), 7.60-7.50 (m, 3H), 7.28 (t, *J* = 8.6 Hz, 2H), 3.80 (s, 3H). LCMS (ES+) m/z 370 (M+1).

Example 45 5-Amino-2-(2,6-difluorophenyl)-*N*-(1-(3-methoxypropyl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide



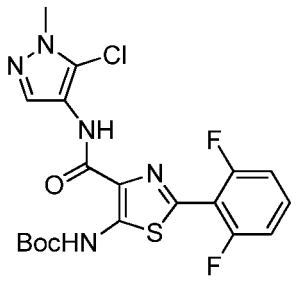
Following the procedure for Intermediate 1gave, after purification *via* preparative HPLC, 5-Amino-2-(2,6-difluorophenyl)-*N*-(1-(3-methoxypropyl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide (0.14 g, 28% over two steps) as a cream solid. ^{1}H (400 MHz, d_6-DMSO) δ 9.75 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.58-7.52 (m, 3H), 7.30-7.25 (m, 2H), 4.09 (t, *J* = 17.0 Hz, 2H), 3.27 (s, 3H), 3.23 (t, *J* = 15.4 Hz, 2H), 1.98 -1.93 (m, 2H). LCMS (ES+) m/z 394 (M+1)

Example 46 5-Amino-2-(2,6-difluorophenyl)-*N*-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide



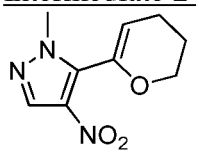
Following the procedure for Intermediate 1 gave, after purification *via* preparative HPLC, 5-Amino-2-(2,6-difluorophenyl)-*N*-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide (0.17 g, 43% over two steps) as a light brown solid. ^{1}H (400 MHz, d_6-DMSO) δ 9.75 (s, 1H), 8.03 (s, 1H), 7.70 (s, 1H), 7.58-7.52 (m, 3H), 7.29-7.25 (m, 2H), 4.40-4.36 (m, 1H), 3.97-3.93 (m, 2H), 3.49-3.43 (m, 2H), 1.97-1.87 (m, 4H) LCMS (ES+) m/z 406 (M+1).

Intermediate 1 *tert*-Butyl 4-(5-chloro-1-methyl-1*H*-pyrazol-4-ylcarbamoyl)-2-(2,6-difluorophenyl)thiazol-5-ylcarbamate



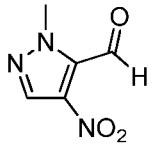
A solution of PyBOP (4.08 g, 7.84 mmol) and 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2.20 g, 6.16 mmol) in DCM (50 mL) was stirred at room temperature for 30 min. A solution of 5-chloro-1-methyl-1*H*-pyrazol-4-amine (737 mg, 5.60 mmol) and DIPEA (1.6 mL, 9.0 mmol) in DCM (50 mL) was then added and the mixture stirred at room temperature for 16 hr. The mixture was diluted with DCM (50 mL) and washed with water (3 x 50 mL). The organic layer was separated, passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-100% EtOAc/isohexane) followed by trituration with MeCN gave *tert*-butyl 4-(5-chloro-1-methyl-1*H*-pyrazol-4-ylcarbamoyl)-2-(2,6-difluorophenyl)thiazol-5-ylcarbamate as an off-white solid (1.71 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.73 (s, 1H), 8.06 (s, 1H), 7.42-7.33 (m, 1H), 7.09-7.01 (m, 2H), 3.87 (s, 3H), 1.54 (s, 9H).

Intermediate 2 5-(3,4-Dihydro-2*H*-pyran-6-yl)-1-methyl-4-nitro-1*H*-pyrazole



A mixture of 5-chloro-1-methyl-4-nitro-1*H*-pyrazole (200 mg, 1.25 mmol), potassium fluoride dihydrate (235 mg, 2.5 mmol) and 3,4-dihydro-2*H*-pyran-6-boronic acid pinacol ester (394 mg, 1.88 mmol) in THF (3 mL) was degassed by bubbling nitrogen through it for 15 min. Tris(dibenzylideneacetone)dipalladium/tri-tert-butyl phosphonium tetrafluoroborate mixture (mole ratio: 1/1.2, 151 mg, 0.13 mmol) was added and the mixture degassed for a further 10 min before being heated in the microwave at 85 °C for 2 hr. Water (10 mL) was added and the mixture extracted with EtOAc (3 x 5 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-5% EtOAc/isohexane) gave 5-(3,4-dihydro-2*H*-pyran-6-yl)-1-methyl-4-nitro-1*H*-pyrazole as a yellow solid (215 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.22 (t, J = 3.9 Hz, 1H), 4.20 (t, J = 5.1 Hz, 2H), 3.88 (s, 3H), 2.31-2.24 (m, 2H), 2.05-1.96 (m, 2H).

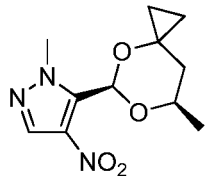
Intermediate 3 2-Methyl-4-nitro-pyrazole-3-carbaldehyde



Nitrogen was bubbled through a solution of 3-chloro-2-methyl-4-nitro-pyrazole (16 g, 100 mmol), potassium vinyltrifluoroborate (18 g, 134 mmol) and cesium carbonate (3.7 M in water, 50 mL, 190 mmol) in DMF (100 mL). 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (900 mg, 1.10 mmol) was added and degassing continued for 30 min. The reaction mixture was heated at 110 °C for 18 hr. More 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (900 mg, 1.10 mmol) was added and heating continued for 24 hr. More 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (400 mg, 0.49 mmol) was added and heating continued for 4 hr. The reaction was cooled to room temperature and brine (200 mL) and EtOAc (500 mL) were added. The organic layer was washed with water (4 x 300 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) gave 1-methyl-4-nitro-5-vinyl-1*H*-pyrazole as a colourless solid (9.1 g). Through a solution of this solid (9.1 g, 59 mmol) in DCM (400 mL) cooled to -78 °C was bubbled ozone. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue colour was discharged. The mixture was allowed to warm to room temperature and flushed with nitrogen for 15 min. Anhydrous dimethyl sulfide (5 mL) was added and the mixture warmed to room temperature. After stirring for 12 hr, the solvents were removed under reduced pressure. DCM (150 mL) was added and the mixture was washed with water (50 mL). The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organic layers were washed with brine

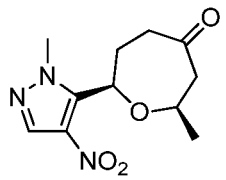
(100 mL), separated, dried over Na_2SO_4 and concentrated to give 2-methyl-4-nitro-pyrazole-3-carbaldehyde as a yellow-orange solid (6.6 g, 43% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.11 (s, 1H), 4.23 (s, 3H).

Intermediate 4 1-Methyl-5-(5-methyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole



To a solution of 1-(2-hydroxypropyl)cyclopropanol (2.0 g, 17.2 mmol) in DCM (35 mL) at 0 °C was added 2,6-lutidine (5 mL, 42.9 mmol) followed by trimethylsilyl trifluoromethanesulfonate (6 mL, 32.9 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hr. Additional amounts of 2,6-lutidine (5 mL, 42.9 mmol) and trimethylsilyl trifluoromethanesulfonate (6 mL, 32.9 mmol) were added at 0 °C. The mixture was stirred for 1 hr and quenched with saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with DCM (50 mL) and the organic layer was washed with aqueous 0.1 M HCl (2 x 15 mL) and passed through a phase separation cartridge. To this solution was added 2-methyl-4-nitro-pyrazole-3-carbaldehyde (1.40 g, 9.03 mmol) and the resulting solution was cooled to -78 °C and trimethylsilyl trifluoromethanesulfonate (4.11 mL, 22.6 mmol) added. The mixture was warmed to 0 °C, stirred for 3 hr, cooled to -78 °C and additional trimethylsilyl trifluoromethanesulfonate (4.11 mL, 22.6 mmol) added. The mixture was warmed to 0 °C and stirred for 1 hr and solid sodium carbonate (2.5 g) added. The reaction mixture was stirred for 10 min before saturated aqueous $NaHCO_3$ (100 mL) was added. The organic layer was washed with water (100 mL) and brine (100 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 1-methyl-5-(5-methyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole as a colourless solid (1.0 g, 44% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.59 (s, 1H), 4.29-4.02 (m, 4H), 2.33-2.23 (m, 1H), 1.33 (d, J = 6.2 Hz, 3H), 1.17-1.12 (m, 1H), 1.02-0.89 (m, 2H), 0.70-0.52 (m, 2H).

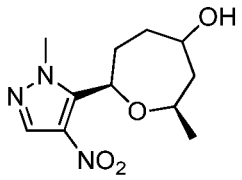
Intermediate 5 2-Methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one



To a solution of 1-methyl-5-(5-methyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole (1.0 g, 3.95 mmol) in DCM (20 mL) at -78 °C was added titanium tetrachloride (6.6 mL, 59.3

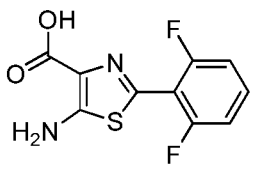
mmol) dropwise. Halfway through the addition, the reaction mixture became harder to stir so more DCM (10 mL) was added. The brown slurry was warmed to 0 °C and stirred for 1 hr. Solid sodium carbonate (5 g) was cautiously added followed by saturated aqueous $NaHCO_3$ (100 mL) and DCM (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, (100 mL) and brine (100 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one as a colourless solid (749 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.69 (dd, J = 11.0, 2.4 Hz, 1H), 4.21-4.14 (m, 1H), 4.01 (s, 3H), 3.07-2.97 (m, 1H), 2.79-2.63 (m, 3H), 2.19-2.07 (m, 1H), 2.07-1.91 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H).

Intermediate 6 2-Methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol



To a solution of 2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one (65 mg, 0.26 mmol) in THF (1 mL) under nitrogen cooled to -78 °C was added dropwise a solution of L-selectride (1 M in THF, 0.28 mL, 0.28 mmol). After 1 hr the mixture was quenched with MeOH (1 mL) and warmed to room temperature. EtOAc (10 mL) and brine (10 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification via silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol as a colourless solid (54 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2s, 1 H), 5.63-5.59 and 5.56-5.50 (2m, 1H), 4.26-4.01 (m, 5H), 3.88-3.73 (m, 1H), 2.21-1.72 (m, 4H), 1.28-1.23 (m, 3H), 0.99-0.81 (m, 2H).

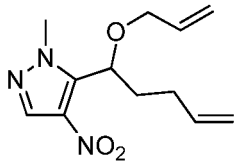
Intermediate 7 5-Amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



To a solution of 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (530 mg, 1.49 mmol) in MeOH (10 mL) was added HCl in dioxane (4 M, 5 mL, 20.0 mmol). The reaction mixture was stirred at room temperature for 48 hr and the solvents removed under reduced pressure to give 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic

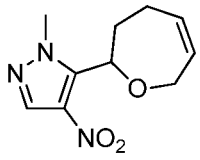
acid as the hydrochloride salt. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.57-7.45 (m, 1H), 7.29-7.18 (m, 2H), 5.30 (br s, 3H).

Intermediate 8 5-(1-Allyloxypent-4-enyl)-1-methyl-4-nitro-pyrazole



To a solution of 1-methyl-4-nitro-pyrazole (9.7 g, 76.7 mmol) and pent-4-enal (10.0 g, 84.4 mmol) in THF (250 mL) at -78 °C was added dropwise a solution of LiHMDS in THF (1 M, 192 mL, 191.7 mmol). The reaction mixture was allowed to warm to -40 °C and stirred for 4 hr. The reaction was quenched with a saturated solution of ammonium chloride (100 mL), warmed to room temperature and the solvents removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with water (30 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave a clear oil. This oil (7.1 g, 33.6 mmol), diallyl carbonate (14.33 g, 100.9 mmol) and triphenylphosphine (880 mg, 3.35 mmol) were dissolved in dioxane (236 mL) under nitrogen before tris(dibenzylideneacetone)-dipalladium(0) (780 mg, 0.84 mmol) was added. The reaction mixture was heated at 50 °C for 1 hr and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) gave 5-(1-allyloxypent-4-enyl)-1-methyl-4-nitro-pyrazole as a yellow oil (8.35 g, 43% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 5.90-5.73 (m, 2H), 5.46 (dd, J = 8.8, 5.1 Hz, 1H), 5.29-5.16 (m, 2H), 5.10-5.00 (m, 2H), 4.04 (s, 3H), 3.92 (d, J = 5.8 Hz, 2H), 2.37-2.25 (m, 1H), 2.22-2.09 (m, 1H), 2.09-1.96 (m, 1H), 1.84 (dddd, J = 13.7, 9.2, 6.9, 5.1 Hz, 1H).

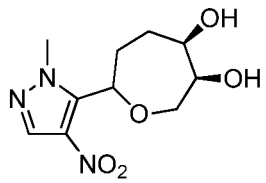
Intermediate 9 1-Methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole



5-(1-Allyloxypent-4-enyl)-1-methyl-4-nitro-pyrazole (5 g, 19.92 mmol) was dissolved in toluene (1 L) and the mixture was degassed for 30 min before Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium, Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride, "Grubbs 1st generation catalyst" CAS No. 172222-30-9, Sigma-Aldrich Product No. 579726, US 6111121, (878 mg, 0.99 mmol) was added. The reaction mixture was further degassed for 20 min, then heated at reflux for 2 hr, cooled to room temperature and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with aqueous 1 M HCl (150 mL), water

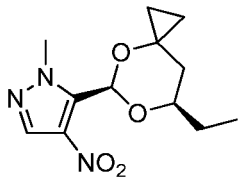
(150 mL), saturated aqueous $NaHCO_3$ (2 x 150 mL) and brine (150 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-20% EtOAc/isohexane) gave 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole as a clear oil (3.3 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.99-5.91 (m, 1H), 5.83-5.76 (m, 1H), 5.59 (dd, J = 9.4, 3.0 Hz, 1H), 4.42 (dd, J = 15.8, 5.5 Hz, 1H), 4.24-4.17 (m, 1H), 4.06 (s, 3H), 2.58-2.48 (m, 1H), 2.46-2.36 (m, 1H), 2.14 (ddt, J = 14.1, 6.8, 3.5 Hz, 1H), 1.99-1.88 (m, 1H).

Intermediate 10 7-(2-Methyl-4-nitro-pyrazol-3-yl)oxepane-3,4-diol



To a solution of AD-mix α (1.51 g) in *tert*-butanol (5.4 mL) and water (5.5 mL) at 0 °C was added a solution of 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole (240 mg, 1.08 mmol) in *tert*-butanol (0.8 mL). The reaction mixture was stirred at 0 °C for 1 hr before solid sodium thiosulfate (1.4 g) was added slowly. The mixture was stirred for a further 1 hr and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL) and the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-2.5% MeOH/EtOAc) gave 7-(2-methyl-4-nitro-pyrazol-3-yl)oxepane-3,4-diol as a colourless solid (30 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.98 (m, 1H), 5.49 (dd, J = 8.9, 5.7 Hz, 1H), 4.20 (dd, J = 13.7, 3.2 Hz, 1H), 4.16-4.10 (m, 1H), 4.09 (s, 3H), 4.04-3.97 (m, 1H), 3.73 (dd, J = 13.7, 2.5 Hz, 1H), 2.53-2.46 (m, 1H), 2.32 (dtd, J = 14.3, 8.8, 4.9 Hz, 1H), 2.23 (d, J = 5.8 Hz, 1H), 2.19-2.01 (m, 2H), 1.84-1.75 (m, 1H).

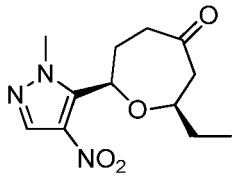
Intermediate 11 1-Methyl-5-(5-ethyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole



To a solution of (3*R*)-ethyl 3-hydroxybutanoate (2.5 g, 18.9 mmol) in THF (100 mL) under nitrogen was added a solution of titanium(IV) isopropoxide (6.02 mL, 19.9 mmol) in THF (15 mL) followed by a solution of ethyl magnesium bromide in diethyl ether (3 M, 30.2 mL, 90.7 mmol) dropwise over a period of 2 hr. The reaction mixture was stirred for a further 2 hr, before being cooled to 0 °C and quenched by the slow addition of a saturated aqueous ammonium chloride (75 mL). The solution was filtered and the filtrate extracted with DCM (3 x 20 mL). The

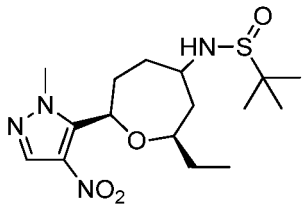
combined organic layers were washed with brine (75 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 1-[(2*R*)-2-hydroxybutyl]-cyclopropanol as a yellow oil (1.50 g). To a solution of this oil (900 mg, 7.76 mmol) in DCM (15 mL) cooled to 0 °C was added 2,6-lutidine (2.26 mL, 19.40 mmol) followed by trimethylsilyl trifluoromethanesulfonate (3.1 mL, 17.10 mmol). The reaction mixture was stirred at 0 °C for 2 hr before additional 2,6-lutidine (2.26 mL, 19.40 mmol) and trimethylsilyl trifluoromethanesulfonate (3.1 mL, 17.10 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 18 hr. The mixture was cooled to 0 °C, quenched with 0.1 M aqueous HCl (15 mL) and extracted with DCM (50 mL). The organic layer was washed with 0.1 M aqueous HCl (2 x 15 mL) and passed through a phase separation cartridge. To this solution was added 2-methyl-4-nitro-pyrazole-3-carbaldehyde (1.90 g, 7.13 mmol) and the resulting solution was cooled to -78 °C before trimethylsilyl trifluoromethanesulfonate (0.64 mL, 3.56 mmol) was added dropwise. The mixture was warmed to 0 °C and stirred for 3 hr before being cooled to -78 °C and additional trimethylsilyl trifluoromethanesulfonate (1 mL, 5.49 mmol) was added. After stirring at 0 °C for 3 hr the procedure was repeated. The reaction mixture was stirred at 0 °C for a further 2 hr before solid sodium carbonate (2.5 g) was added. The reaction mixture was stirred for 10 min and a saturated solution of $NaHCO_3$ (10 mL) was added. The organic layer was washed with water (10 mL) and brine (10 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 1-methyl-5-(5-ethyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole as a colourless solid (655 mg, 4% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.58 (s, 1H), 4.13 (s, 3H), 4.00-3.92 (m, 1H), 2.29 (t, J = 12.4 Hz, 1H), 1.75-1.47 (m, 3H), 1.00-0.87 (m, 5H), 0.67-0.53 (m, 2H).

Intermediate 12 2-Ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one



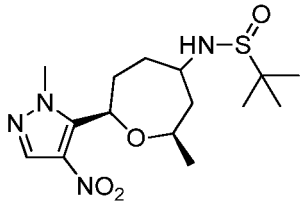
Following the procedure for Intermediate 5 starting from 1-methyl-5-(5-ethyl-6,8-dioxaspiro[2.5]octan-7-yl)-4-nitro-pyrazole gave 2-ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one as a colourless solid (240 mg, 13% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.67 (dd, J = 11.0, 2.4 Hz, 1H), 4.02 (s, 3H), 3.94 (dd, J = 10.2, 5.2 Hz, 1H), 3.04 (td, J = 13.3, 3.3 Hz, 1H), 2.79-2.63 (m, 3H), 2.20-2.12 (m, 1H), 2.05-1.92 (m, 1H), 1.67-1.57 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

Intermediate 13 *N*-(2-Ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide



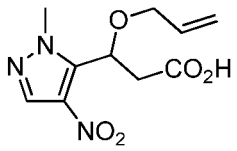
To a solution of 2-ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one (120 mg, 0.45 mmol) in THF (3 mL) was added (*R*)-2-methylpropane-2-sulfinamide (70 mg, 0.58 mmol) followed by titanium(IV) ethoxide (0.30 mL, 1.12 mmol). The reaction mixture was heated at reflux for 4 hr then allowed to cool to room temperature. The crude solution was added dropwise to a solution of sodium borohydride (69 mg, 1.80 mmol) in THF (3 mL) at -60 °C. The reaction mixture was warmed to 0 °C, quenched with MeOH (3 mL) and brine (50 mL), and stirred at room temperature for 18 hr. The mixture was filtered through Celite® washing with EtOAc (200 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (150 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-10% MeOH/DCM) gave *N*-(2-ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide as a mixture of diastereomers (ratio 5:2) as a colourless solid (118 mg, 71% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 and 8.02 (2s, 1H), 5.60-5.51 (m, 1H), 4.08 and 4.06 (2s, 3H), 3.83-3.66 (m, 2H), 3.62-3.50 (m, 1H), 3.22 and 3.15 (d, J = 6.2 and 4.0 Hz, 1H), 2.11-1.96 (m, 4H), 1.76 (s, 1H), 1.63-1.54 (m, 2H), 1.28-1.15 (m, 9H), 0.91 (td, J = 7.4, 2.4 Hz, 3H).

Intermediate 14 *N*-(2-Methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide



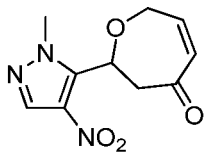
Following the procedure for Intermediate 13 starting from 2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-one gave *N*-(2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide as an off-white solid (208 mg, 40% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.63-5.51 (m, 1H), 4.05 (s, 3H), 3.86-3.72 (m, 2H), 3.19-3.11 (m, 1H), 2.22-1.69 (m, 6H), 1.29-1.20 (m, 12H).

Intermediate 15 3-Allyloxy-3-(2-methyl-4-nitro-pyrazol-3-yl)propanoic acid



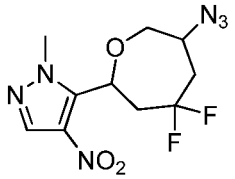
To a suspension of zinc dust (<10 μm, 10.3 g, 159 mmol) in dry Et_2O (120 mL) was added a few drops of trimethysilyl chloride to initiate the reaction. The reaction mixture was then heated at reflux for 5 min and a few drops of 1,2-dibromoethane were carefully added. A solution of *tert*-butyl 2-bromoacetate (18.8 mL, 127 mmol) was added dropwise and the reaction mixture was heated at reflux for 1 hr. A solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (77 wt% in DMSO, 6.4 g, 31.8 mmol) in THF (120 mL) was added at room temperature and stirring continued for 150 min. The reaction mixture was diluted with EtOAc (200 mL) and saturated ammonium chloride/1 M HCl (100 mL/100 mL) and stirred for 18 hr. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave *tert*-butyl 3-hydroxy-3-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)propanoate as a colourless solid (6.52 g, 77%). To a solution of this solid (6.52 g, 24 mmol) in dioxane (168 mL) was added bisallylcarbonate (10.2 g, 72 mmol). The reaction mixture was degassed with nitrogen for 30 min. Tris(dibenzylideneacetone)-dipalladium(0) (557 mg, 0.60 mmol) and triphenylphosphine (630 mg, 2.40 mmol) were added in a single portion and degassing continued for 15 min. The reaction mixture was heated at 65 °C for 1 h and cooled to room temperature. Brine (100 mL) and EtOAc (150 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with brine (100 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave *tert*-butyl 3-(allyloxy)-3-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)propanoate as a colourless solid (7.7 g, 99%). To a solution of this solid (7.7 g, 24 mmol) in DCM (80 mL) was added TFA (40 mL) and the mixture was stirred at room temperature for 18 hr. After cooling to 0 °C, sodium carbonate (5 g), saturated aqueous $NaHCO_3$ (100 mL) and DCM (200 mL) were carefully added until the effervescence stopped. Concentrated HCl was slowly added until the solution was pH4. The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organic layers were separated, dried over Na_2SO_4 and concentrated under reduced pressure to give 3-allyloxy-3-(2-methyl-4-nitro-pyrazol-3-yl)propanoic acid as a yellow oil (4.33 g, 55% over three steps). ^1H NMR (400 MHz, $CDCl_3$) δ 11.5-10.3 (br s, 1H), 8.08 (s, 1H), 5.90-5.78 (m, 3H), 5.28-5.18 (m, 1H), 4.07 (s, 3H), 4.06-3.96 (m, 2H), 2.99 (dd, J = 16.2, 9.3 Hz, 1H), 2.87 (dd, J = 16.2, 4.3 Hz, 1H).

Intermediate 16 2-(2-Methyl-4-nitro-pyrazol-3-yl)-3,7-dihydro-2*H*-oxepin-4-one



To a solution of 3-allyloxy-3-(2-methyl-4-nitro-pyrazol-3-yl)propanoic acid (4.33 g, 17 mmol) in DCM (48 mL) at 0 °C under nitrogen was added oxalyl chloride (4.37 mL, 51 mmol) followed by the cautious addition of DMF (0.05 mL) to initiate the acylation. The reaction mixture was stirred at room temperature for 3 hr and concentrated under reduced pressure. The residue was dissolved in DME (28 mL), vinyltributyltin (2.48 mL, 8.50 mmol) added and the mixture degassed with nitrogen for 30 min. *trans*-Benzyl(chloro)-bis(triphenylphosphine)palladium(II) (129 mg, 0.17 mmol) was added and degassing continued for 10 min. The reaction mixture was heated to 65 °C for 1 hr and cooled to room temperature. Concentration under reduced pressure and purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 5-(allyloxy)-5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-1-en-3-one as a yellow syrup (2.76 g, 61%). A solution of this syrup (250 mg, 0.94 mmol) in toluene (90 mL) was degassed with nitrogen for 30 min at 35 °C. Zhan 1B catalyst (26 mg, 0.04 mmol) dissolved in toluene (2 mL) was added to the reaction mixture and degassing continued for 15 min. After stirring at 35 °C for 1 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-(2-methyl-4-nitro-pyrazol-3-yl)-3,7-dihydro-2*H*-oxepin-4-one as a colourless solid (107 mg, 30% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.44 (ddd, J = 12.8, 3.4, 2.3 Hz, 1H), 6.15 (m, 1H), 6.01 (dd, J = 11.1, 3.4 Hz, 1H), 4.72 (ddd, J = 19.8, 3.4, 1.7 Hz, 1H), 4.61 (ddd, J = 19.6, 2.4 Hz, 1H), 4.08 (s, 3H), 3.20-3.12 (m, 2H).

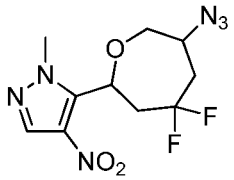
Intermediate 17 5-(6-Azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (Diastereomer 1)



To a solution of 2-(2-methyl-4-nitro-pyrazol-3-yl)-3,7-dihydro-2*H*-oxepin-4-one (440 mg, 0.42 mmol) in MeCN (3 mL) was added Amberlite IRA 900F resin (79 mg, 0.19 mmol) and trimethylsilylazide (1.2 mL, 9.35 mmol). The reaction mixture was heated at 65 °C behind a blast screen for 24 hr, cooled to room temperature and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave pure 6-azido-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-one along with mixed fractions containing product and starting material. These were concentrated under reduced pressure and resubmitted

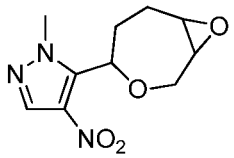
to the same reaction conditions. Final purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 6-azido-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-one as a colourless solid (449 mg). To this solid (449 mg, 1.60 mmol) was added deoxo-Fluor® (50% in THF, 5 mL) and the mixture was stirred at room temperature for 18 hr. DCM (50 mL) was added and the reaction mixture cooled to 0 °C. Saturated aqueous $NaHCO_3$ (30 mL) was then carefully added. The aqueous layer was extracted with DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 5-(6-azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (Diastereomer 1 - major) as a colourless solid (264 mg, 47% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.67-5.58 (m, 1H), 4.18-3.91 (m, 3H), 4.08 (s, 3H), 2.79-2.63 (m, 1H), 2.63-2.40 (m, 3H).

Intermediate 18 5-(6-Azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (Diastereomer 2)



Following the procedure for Intermediate 17 also gave 5-(6-azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (Diastereomer 2 - minor) as a colourless solid (69 mg, 12% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.73 (dd, J = 10.9, 4.5 Hz, 1H), 4.34-4.29 (m, 1H), 4.01 (s, 3H), 4.01-3.93 (m, 1H), 3.53 (dd, J = 11.4, 11.4 Hz, 1H), 2.71-2.49 (m, 4H).

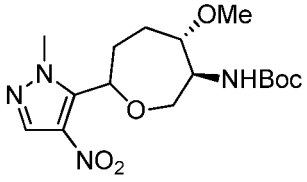
Intermediate 19 5-(5,8-Dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole



To a solution of 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole (1.00 g, 4.74 mmol) in DCM (25 mL) was added *m*-CPBA (70-75%, 1.75 g, 7.11 mmol) and the reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave racemic 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole as a colourless solid (490 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-7.87 (m, 1H), 5.07 (d, J = 9.9 Hz, 1H), 4.50 (dd, J = 14.5, 3.1 Hz, 1H), 4.05 (s, 3H), 3.93 (d, J = 14.4 Hz, 1H), 3.35 (t, J = 4.5 Hz, 1H), 3.13 (t, J =

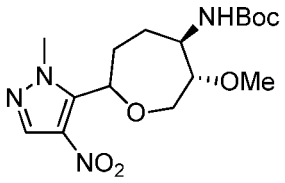
3.6 Hz, 1H), 2.55-2.47 (m, 1H), 2.31-2.21 (m, 1H), 2.16-2.04 (m, 1H), 1.79 (dd, *J* = 14.4, 1.8 Hz, 1H).

Intermediate 20 *tert*-Butyl *N*-(4-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate



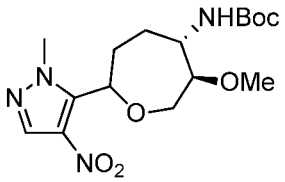
A solution of 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (220 mg, 0.92 mmol) Intermediate 19 in MeOH/water (6 mL/1.2 mL) was treated with ammonium chloride (122 mg, 2.30 mmol) and sodium azide (299 mg, 4.60 mmol) and the mixture was heated at 70 °C behind a blast screen for 16 hr. The reaction mixture was extracted with EtOAc (100 mL) and the organic layer was washed with water (2 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue (500 mg, 1.77 mmol) was dissolved in dry DMF (15 mL), cooled to 0 °C, sodium hydride (60% in mineral oil, 106 mg, 2.66 mmol) was added and the mixture stirred for 15 min. Iodomethane (0.17 mL, 2.66 mmol) was added and the reaction mixure was warmed to room temperature and stirred for 16 hr. Water (20 mL) was added and the mixture was extracted with EtOAc (2 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave 4-azido-5-methoxy-1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)azepane as a yellow oil (280 mg). A solution of this oil (270 mg, 0.91 mmol) in THF/water (13 mL/2.5 mL) was treated with triphenylphosphine (263 mg, 1.00 mmol) and the reaction mixture was heated at 70 °C behind a blast screen for 18 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dry DCM (15 mL) at 0 °C and di-*tert*-butyl-dicarbonate (238 mg, 1.09 mmol) was added followed by DIPEA (0.66 mL, 4.55 mmol). The reaction mixture was warmed to room temperature and stirred for 3 hr before being quenched with water (20 mL) and extracted with DCM (100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) isolated four diastereomers. The minor fraction gave *tert*-butyl *N*-(4-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate (racemate) as a colourless solid (60 mg, 17% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.58-5.51 (m, 1H), 4.82 (br s, 1H), 4.31 (dd, *J* = 12.7, 3.0 Hz, 1H), 4.02 (s, 3H), 3.87 (br s, 1H), 3.62-3.48 (m, 2H), 3.41 (s, 3H), 2.28-2.09 (m, 2H), 2.03-1.83 (m, 2H), 1.47 (s, 9H).

Intermediate 21 *tert*-butyl ((3S,4R,7S)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate



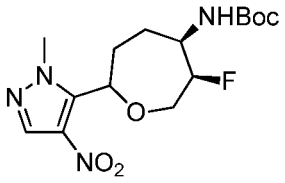
Following the procedure for Intermediate 20, the major fraction isolated (290 mg) was further purified *via* chiral SFC to give *tert*-butyl ((3S,4R,7S)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate as a colourless solid (101 mg, 29% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.39 (dd, J = 10.6, 3.6 Hz, 1H), 4.75 (br s, 1H), 4.33 (dd, J = 14.2, 1.9 Hz, 1H), 4.06 (s, 3H), 3.91-3.83 (m, 1H), 3.75 (dd, J = 14.2, 3.2 Hz, 1H), 3.43 (s, 3H), 3.39-3.34 (m, 1H), 2.22-2.12 (m, 1H), 2.12-2.03 (m, 1H), 2.03-1.82 (m, 2H), 1.47 (s, 9H).

Intermediate 22 *tert*-butyl ((3R,4S,7R)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate



Following the procedure for Intermediate 21 also gave *tert*-butyl ((3R,4S,7R)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate as a colourless solid (101 mg, 29% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.99 (m, 1H), 5.39 (dd, J = 10.6, 3.6 Hz, 1H), 4.75 (br s, 1H), 4.33 (dd, J = 14.2, 1.9 Hz, 1H), 4.06 (s, 3H), 3.90-3.82 (m, 1H), 3.75 (dd, J = 14.2, 3.2 Hz, 1H), 3.43 (s, 3H), 3.42-3.31 (m, 1H), 2.22-2.12 (m, 1H), 2.12-2.03 (m, 1H), 2.03-1.83 (m, 2H), 1.62-1.29 (m, 9H).

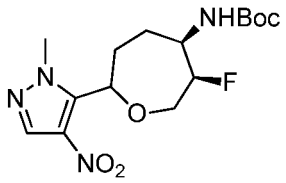
Intermediate 23 *tert*-Butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate



A solution of 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (130 mg, 0.54 mmol) Intermediate 19 in MeOH/water (3 mL/0.6 mL) was treated with ammonium chloride (72 mg, 1.35 mmol) and sodium azide (177 mg, 2.72 mmol) and the mixture was heated at 70 °C behind a blast screen for 18 hrs. The reaction mixture was extracted with EtOAc (100 mL) and the organic layer was washed with water (3 x 20 mL), washed with brine (20 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the

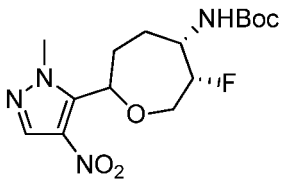
resulting residue (100 mg, 0.35 mmol) in DCM (3 mL) was added deoxo-Fluor® (50% in THF, 0.32 mL, 0.89 mmol) and the mixture was stirred at room temperature for 16 hr. The mixture was diluted with DCM (30 mL), cooled in an ice/water bath and quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (30 mL). The resulting mixture was stirred for 10 min. The organic layer was separated, dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) gave an oil (90 mg). A solution of this oil (90 mg, 0.35 mmol) in THF/water (4 mL/0.8 mL) was treated with triphenylphosphine (92 mg, 0.35 mmol) and the reaction mixture was heated at 70 °C behind a blast screen for 18 hr. The mixture was concentrated under reduced pressure. The resulting residue was dissolved in dry DCM (7 mL) at 0 °C and di-*tert*-butyl-dicarbonate (84 mg, 0.38 mmol) and DIPEA (0.22 mL, 1.6 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 3 hr. Water (10 mL) was added and the mixture extracted with DCM (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) gave *tert*-butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate as a mixture of enantiomers as a mixture of enantiomers as an off-white solid (70 mg, 36% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.55-5.49 (m, 1H), 5.10-4.92 (m, 2H), 4.36-4.09 (m, 2H), 4.02 (s, 3H), 3.97-3.83 (m, 1H), 2.32-2.18 (m, 1H), 2.02-1.89 (m, 2H), 1.83 (d, J = 14.0 Hz, 1H), 1.47 (s, 9H).

Intermediate 24 *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate



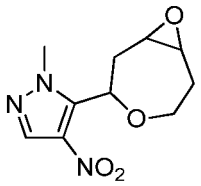
Further purification of *tert*-butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate *via* chiral SFC gave *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate as an off-white solid (52 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.55-5.49 (m, 1H), 5.09-4.91 (m, 2H), 4.36-4.10 (m, 2H), 4.01 (s, 3H), 3.91 (ddd, J = 26.6, 14.4, 2.2 Hz, 1H), 2.31-2.19 (m, 1H), 2.02-1.95 (m, 2H), 1.83 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H).

Intermediate 25 *tert*-butyl ((3S,4S,7R)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate



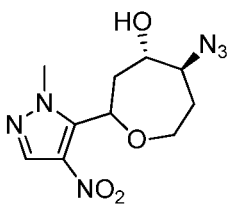
Following the procedure for Intermediate 24 also gave *tert*-butyl ((3S,4S,7R)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate as an off-white solid (61 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.55-5.49 (m, 1H), 5.10-4.92 (m, 2H), 4.36-4.09 (m, 2H), 4.02 (s, 3H), 3.97-3.83 (m, 1H), 2.32-2.18 (m, 1H), 2.02-1.89 (m, 2H), 1.83 (d, J = 14.0 Hz, 1H), 1.47 (s, 9H).

Intermediate 26 5-(4,8-Dioxabicyclo[5.1.0]octan-5-yl)-1-methyl-4-nitro-pyrazole



5-(1-Allyloxypent-4-enyl)-1-methyl-4-nitro-pyrazole (7.08 g, 28.2 mmol) was dissolved in DCM (910 mL) and the mixture degassed for 30 min before Grubbs 2nd generation catalyst (1.19 g, 1.41 mmol) was added. The reaction mixture was heated at 40 °C for 18 hr and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-10% EtOAc/isohexane) followed by reverse-phase preparative HPLC gave a mixture of isomers of 1-methyl-4-nitro-5-(tetrahydrooxepin-2-yl)pyrazole (66/34) as a clear oil (2.3 g). To a solution of this oil (2.3 g, 10.31 mmol) in DCM (50 mL) was added *m*-CPBA (70-75%, 3.56 g, 14.40 mmol) and the reaction mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with DCM (50 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave 5-(4,8-dioxabicyclo[5.1.0]octan-5-yl)-1-methyl-4-nitro-pyrazole as a colourless solid (1.0 g, 14% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.51-5.44 (m, 1H), 4.02 (s, 3H), 3.93 (dt, J = 12.7, 3.4 Hz, 1H), 3.62-3.53 (m, 1H), 3.35-3.27 (m, 2H), 2.58-2.51 (m, 1H), 2.41-2.25 (m, 3H).

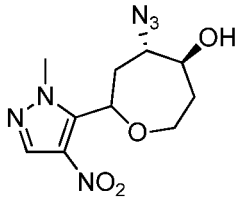
Intermediate 27 5-Azido-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol



To a solution of 5-(4,8-dioxabicyclo[5.1.0]octan-5-yl)-1-methyl-4-nitro-pyrazole (1.04 g, 4.35 mmol) in 4:1 MeOH:water (30 mL) was added ammonium chloride (0.58 g, 10.88 mmol)

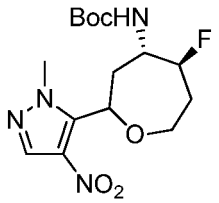
and sodium azide (1.41 g, 21.75 mmol). The mixture was heated at 70 °C behind a blast screen for 16 hr. The MeOH was removed under reduced pressure and EtOAc (20 mL) added. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL), passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-60% EtOAc/isohexane) gave 5-azido-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol as a pale yellow gum (718 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.76 (dd, J = 9.3, 3.2 Hz, 1H), 4.18-4.10 (m, 1H), 4.08-4.04 (m, 4H), 3.91 (ddd, J = 9.4, 6.6, 6.2 Hz, 1H), 3.79 (ddd, J = 12.6, 8.6, 3.5 Hz, 1H), 2.44 (ddd, J = 15.3, 9.4, 3.8 Hz, 1H), 2.37-2.29 (m, 1H), 2.24 (d, J = 3.2 Hz, 1H), 2.12 (ddd, J = 15.3, 5.7, 3.2 Hz, 1H), 2.06-1.96 (m, 1H).

Intermediate 28 5-Azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol



Following the procedure for Intermediate 26 also gave 5-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol as a pale yellow gum (285 mg, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.64 (dd, J = 10.8, 1.4 Hz, 1H), 4.06-3.96 (m, 4H), 3.95-3.83 (m, 2H), 3.72 (ddd, J = 10.8, 9.0, 4.9 Hz, 1H), 2.43 (d, J = 2.5 Hz, 1H), 2.28 (ddd, J = 14.1, 4.9, 1.4 Hz, 1H), 2.21-2.12 (m, 2H), 2.09-2.00 (m, 1H).

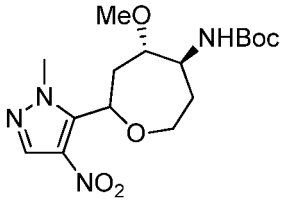
Intermediate 29 *tert*-Butyl *N*-(5-fluoro-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate



To a solution of 5-azido-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol (282 mg, 1.00 mmol) in DCM (6 mL) cooled to 0 °C was added dropwise a solution of deoxo-Fluor® in (50% in THF, 0.46 mL, 1.25 mmol). The mixture was warmed to room temperature and stirred for 16 hr. Additional deoxo-Fluor® (50% in THF, 0.23 mL, 0.63 mmol) was added and the mixture was stirred at room temperature for 5 hr. After cooling in an ice bath saturated aqueous $NaHCO_3$ (10 mL) was added slowly. The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. The residue was purified *via* silica gel chromatography (0-50% EtOAc/isohexane) to yield the fluoro compound as a clear gum (205 mg). To a solution of this gum (200 mg, 0.70 mmol) in THF (5 mL) and water (1 mL) was added triphenylphosphine (202 mg, 0.77 mmol) and the mixture heated at 60 °C for 2 hr. The mixture was diluted with

EtOAc (10 mL) and washed with brine (2 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. The residue was dissolved in DCM (2 mL) and DIPEA (0.24 mL, 1.40 mmol) and di-*tert*-butyl dicarbonate (183 mg, 0.84 mmol) were added. The mixture was stirred at room temperature for 2 hr. Water (2 mL) was added and the mixture was extracted with DCM (3 x 2 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-50% EtOAc/isohexane) gave *tert*-butyl *N*-(5-fluoro-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate as a clear gum (240 mg, 66% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.62 (dd, *J* = 11.3, 2.3 Hz, 1H), 5.28-4.79 (m, 2H), 4.29-4.19 (m, 1H), 4.15-4.07 (m, 1H), 4.04 (s, 3H), 3.77 (ddd, *J* = 12.9, 8.1, 4.5 Hz, 1H), 2.41-2.07 (m, 3H), 2.04 (d, *J* = 10.8 Hz, 1H), 1.44 (s, 9H).

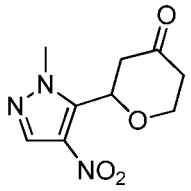
Intermediate 30 *tert*-Butyl *N*-(5-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate



To a solution of 5-azido-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol (352 mg, 1.25 mmol) in dry THF (6 mL) under nitrogen cooled to 0 °C was added sodium hydride (60% in mineral oil, 55 mg, 1.38 mmol). After stirring for 20 min, iodomethane (0.09 mL, 1.38 mmol) was added and the reaction mixure was allowed to warm to room temperature and stirred for 90 min. The mixture was re-cooled to 0 °C and more sodium hydride (60% in mineral oil, 55 mg, 1.38 mmol) was added. After stirring for 20 min, more iodomethane (0.09 mL, 1.38 mmol) was added and the reaction mixure was allowed to warm to room temperature and stirred for 5 hr. Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave the intermediate methyl ether as a clear gum (155 mg). A solution of this gum (154 mg, 0.52 mmol) in THF/water (5 mL/1 mL) was treated with triphenylphosphine (150 mg, 0.57 mmol) and the reaction mixture was heated at 60 °C behind a blast screen for 2 hr. The mixture was diluted with EtOAc (10 mL) and washed with brine (2 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. The residue was dissolved in dry DCM (2 mL) and DIPEA (0.18 mL, 1.04 mmol) and di-*tert*-butyl-dicarbonate (136 mg, 0.62 mmol) were added. The reaction mixture was stirred at room temperature for 3 hr. Water (2 mL) was added and the mixture was extracted with DCM (3 x 2 mL). The organic layer was

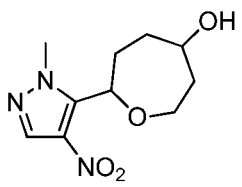
passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave *tert*-butyl *N*-(5-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate as a clear gum (190 mg, 41% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.67 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.96 (s, 1H), 4.33 (s, 1H), 4.06 (s, 3H), 4.02-3.84 (m, 2H), 3.62 (d, *J* = 5.2 Hz, 1H), 3.44 (s, 3H), 2.52 (dddd, *J* = 15.1, 9.9, 7.5, 2.1 Hz, 1H), 2.20-2.01 (m, 2H), 1.90-1.78 (m, 1H), 1.48 (s, 9H).

Intermediate 30 2-(2-Methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-one



To a solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (600 mg, 3.87 mmol) in $CDCl_3$ (20 mL) was added Danishefsky's diene (836 mg, 5.81 mmol) and Resolve-Al™ EuFOD (157 mg, 0.39 mmol). The reaction mixture was heated at 80 °C in a sealed tube for 24 hr. Additional Resolve-Al™ EuFOD (250 mg, 0.62 mmol) was added and heating continued for another 24 hr. The reaction mixture was concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-2*H*-pyran-4(3*H*)-one a yellow solid (710 mg, 82%). A portion of this solid (300 mg, 1.35 mmol) was dissolved in THF (10 mL) under nitrogen and cooled to -78 °C. A solution of L-selectride (1 M in THF, 1.48 mL, 1.48 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 min. The mixture was quenched with MeOH (2 mL) and warmed to room temperature. EtOAc (30 mL) and brine (30 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) then the combined organic layers were washed with brine (30 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-one as a colourless solid (224 mg, 61% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 5.70 (dd, *J* = 11.8, 3.3 Hz, 1H), 4.49 (ddd, *J* = 11.8, 7.5, 1.3 Hz, 1H), 4.15 (s, 3H), 3.94-3.86 (m, 1H), 2.83-2.63 (m, 3H), 2.58-2.50 (m, 1H).

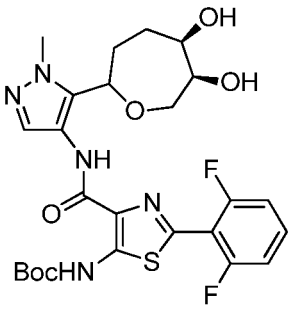
Intermediate 31 7-(2-Methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol



To a solution of 2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-one (300 mg, 1.33 mmol) in DCM (12 mL) at -70 °C was added boron trifluoride etherate (0.75 mL, 1.73 mmol)

dropwise followed by a (trimethylsilyl)diazomethane solution (2 M in hexanes, 0.87 mL, 1.73 mmol). The reaction mixture was stirred at -70 °C for 90 min, quenched with water (10 mL), diluted with DCM (12 mL) and warmed to room temperature. The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-one as a colourless solid (121 mg) and its regioisomer 2-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-one (151 mg). To a solution of 7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-one (121 mg, 0.51 mmol) in MeOH (5 mL) at 0 °C was added portionwise $NaBH_4$ (23 mg, 0.61 mmol). Stirring continued for 1 hr and the reaction mixture was quenched with 1 M HCl (5 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (30 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure to give 7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol as a 1:1 mixture of diastereomers as a colourless oil (85 mg, 27% over two steps). The product was used without further purification as a 1/1 mixture of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 and 8.01 (s, 1H), 5.61-5.56 and 5.54-5.50 (m, 1H), 4.26-4.14 (m, 1H), 4.07 and 4.04 (s, 3H), 3.90-3.80 and 3.81-3.63 (m, 1H), 2.20-1.80 (m, 8H).

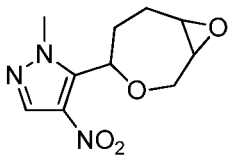
Intermediate 32 *tert*-Butyl *N*-[2-(2,6-difluorophenyl)-4-[[5-[5,6-dihydroxyoxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



To a solution of AD-mix β (1.25 g) in *tert*-butanol (5.1 mL) and water (4.6 mL) at 0 °C was added a solution of 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole (200 mg, 0.89 mmol) in *tert*-butanol (1 mL). The reaction mixture was stirred at 0 °C for 66 hr before solid sodium thiosulfate (1.4 g) was added slowly. The mixture was stirred for a further 1 hr and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-2.5% MeOH/EtOAc) gave 7-(2-methyl-4-nitro-pyrazol-3-yl)oxepane-3,4-diol as a colourless solid. A solution of this diol in MeOH (18 mL) was passed through the H-Cube® (full hydrogen mode, 65 °C, flow rate: 1 mL/min, 30 mm 10% Pd/C cartridge). The solvent was removed under reduced pressure to give the crude amine. To a solution of this amine in DCM (10 mL) was added 5-(*tert*-butoxycarbonylamino)-2-(2,6-

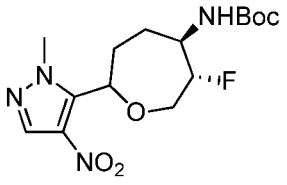
difluorophenyl)thiazole-4-carboxylic acid (348 mg, 0.98 mmol), PyBOP (694 mg, 1.3 mmol) and DIPEA (0.44 mL, 2.67 mmol). The mixture was stirred at room temperature for 18 hr. The mixture was diluted with EtOAc (20 mL) and washed with brine (5 ml). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-10% MeOH/EtOAc) gave *tert*-butyl *N*-[2-(2,6-difluorophenyl)-4-[[5-[5,6-dihydroxyoxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate as an off-white solid (96 mg, 23% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.17-8.14 (m, 1H), 7.39-7.32 (m, 1H), 7.09-7.01 (m, 2H), 6.25 (s, 1H), 5.12 (t, J = 4.5 Hz, 1H), 4.23 (dd, J = 13.7, 4.0 Hz, 1H), 3.87 (d, J = 3.9 Hz, 1H), 3.81-3.66 (m, 5H), 2.12-2.00 (m, 3H), 1.70 (t, J = 14.4 Hz, 3H), 1.55 (s, 9H).

Intermediate 33 5-(5,8-Dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole



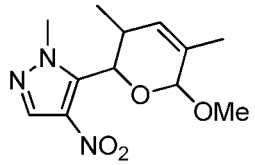
To a solution of 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)pyrazole (1.0 g, 4.5 mmol) in DCM (18 mL) was added 3Å molecular sieves followed by NBS (0.80 g, 4.48 mmol) and acetic acid (0.26 mL, 4.48 mol). The reaction mixture was stirred at room temperature for 60 hr. The mixture was diluted with DCM (30 mL) and washed with water (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave the intermediate bromoacetate as a mixture of regioisomers as a clear oil (1.17 g). The procedure was repeated to provide more material. To a solution of this oil (1.55 g, 4.3 mmol) in MeOH (60 mL) was added K_2CO_3 (2.66 g, 19.2 mmol) in a single portion. This mixture was stired for 1 hr before water (50 mL) was added. EtOAc (150 mL) was added and the layers were separated. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give 5-(5,8-dioxabicyclo[5.1.0]-octan-4-yl)-1-methyl-4-nitro-pyrazole as a clear oil (0.86 g, 61% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.53-5.45 (m, 1H), 4.53 (dd, J = 13.5, 5.2 Hz, 1H), 4.07 (s, 3H), 3.58-3.48 (m, 1H), 3.36-3.25 (m, 2H), 2.55-2.42 (m, 1H), 2.07-1.87 (m, 3H).

Intermediate 34 *tert*-Butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate



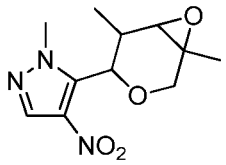
Following the procedure for Intermediate 23 starting from 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (Intermediate 33) gave *tert*-butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (290 mg, 53% over four steps) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.50 (dd, J = 9.9, 3.8 Hz, 1H), 4.96-4.73 (m, 2H), 4.14-3.95 (m, 3H), 4.03 (s, 3H), 2.30-2.16 (m, 3H), 1.95-1.84 (m, 1H), 1.47 (s, 9H).

Intermediate 35 5-(6-Methoxy-3,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-pyrazole



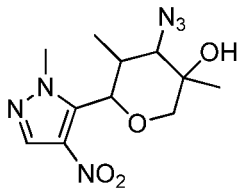
To a solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (487 mg, 3.14 mmol) in $CDCl_3$ (12 mL) was added [(*Z*)-1-[(*E*)-2-methoxy-1-methyl-vinyl]prop-1-enoxy]-trimethyl-silane (944 mg, 4.71 mmol) and Resolve-Al™ EuFOD (127 mg, 0.31 mmol). The reaction mixture was heated at 80 °C in a sealed tube for 18 hr. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 3,5-dimethyl-2-(2-methyl-4-nitro-pyrazol-3-yl)-2,3-dihydropyran-4-one as a mixture of diastereomers as a yellow oil (829 mg). A solution of this oil (829 mg, 3.14 mmol) and cerium(III) chloride heptahydrate (4.8 g, 12.56 mmol) in MeOH (10 mL) was stirred at room temperature for 15 min. After cooling to 0 °C, sodium borohydride (143 mg, 3.8 mmol) was added portionwise and the mixture was stirred at 0 °C for 1 hr. The reaction was quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (50 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (40 mL) and treated with tosic acid monohydrate (87 mg). The mixture was heated at reflux for 18 hr and concentrated under reduced pressure. The residue was dissolved in DCM (30 mL) and the organic layer was washed with aqueous $NaHCO_3$ (2 x 20 mL), washed with brine (20 mL), passed through a phase separation cartridge and concentrated under reduced pressure to give 5-(6-methoxy-3,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-pyrazole as a yellow oil (558 mg, 51% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-7.98 (m, 1H), 5.90 (d, J = 3.6 Hz) and 5.78 (d, J = 3.2 Hz) (1H), 5.72 (d, J = 5.6 Hz) and 5.64 (d, J = 10.8 Hz) (1H), 4.80 and 4.76 (2s, 1H), 4.16 and 4.06 (2s, 3H), 3.42 and 3.40 (2s, 3H), 2.65-2.58 (m, 1H), 1.77 and 1.65 (2s, 3H), 0.90 (d, J = 7.2 Hz) and 0.83 (d, J = 7.2 Hz) (3H).

Intermediate 36 5-(2,6-Dimethyl-4,7-dioxabicyclo[4.1.0]heptan-3-yl)-1-methyl-4-nitro-pyrazole



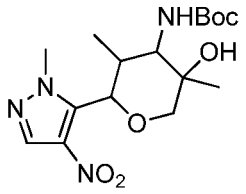
To a solution of 5-(6-methoxy-3,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-pyrazole (100 mg, 0.38 mmol) in DCM (1 mL) cooled to -78 °C was added boron trifluoride diethyl etherate (0.14 mL, 1.13 mmol) and triethylsilane (0.36 mL), 2.68 mmol). After stirring at -78 °C for 1 hr, the reaction mixture was allowed to warm to room temperature and stirred for 18 hr. Saturated aqueous $NaHCO_3$ (5 mL) and DCM (5 mL) were added and the organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave 5-(3,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-pyrazole as a yellow oil. The reaction was repeated to provide more material. To a solution of 5-(3,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-pyrazole (305 mg, 1.29 mmol) in DCM (6.5 mL) cooled to 0 °C was added *m*-CPBA (70-75%, 382 mg, 1.54 mmol) and the mixture was stirred at 0 °C for 90 min. More *m*-CPBA (70-75%, 191 mg, 0.774 mmol) was added and the mixture was slowly warmed to room temperature over 6 hr. The mixture was filtered through Celite® washing with DCM (15 mL) and the filtrate washed with saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave 5-(2,6-dimethyl-4,7-dioxabicyclo[4.1.0]heptan-3-yl)-1-methyl-4-nitro-pyrazole as a single diastereomer as an off-white solid (189 mg, 53% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 5.32-5.28 (m, 1H), 4.15-4.08 (m, 1H), 4.06 (s, 3H), 3.78 (d, J = 12.9 Hz, 1H), 3.30 (d, J = 5.6 Hz, 1H), 2.71-2.61 (m, 1H), 1.38 (s, 3H), 0.92 (d, J = 7.0 Hz, 3H).

Intermediate 37 4-Azido-3,5-dimethyl-6-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-3-ol



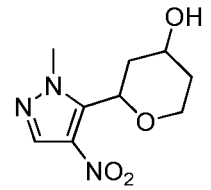
Following the procedure for Intermediate 27 starting from 5-(2,6-dimethyl-4,7-dioxabicyclo[4.1.0]heptan-3-yl)-1-methyl-4-nitro-pyrazole gave 4-azido-3,5-dimethyl-6-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-3-ol as an off-white solid (140 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.74 (d, J = 2.9 Hz, 1H), 4.14 (s, 2H), 3.79-3.64 (m, 3H), 3.58 (s, 1H), 2.58 (qdd, J = 7.6, 2.9, 2.2 Hz, 1H), 1.81 (s, 1H), 1.25 (s, 3H), 1.18 (d, J = 7.6 Hz, 3H).

Intermediate 38 *tert*-Butyl *N*-[5-hydroxy-3,5-dimethyl-2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-yl]carbamate



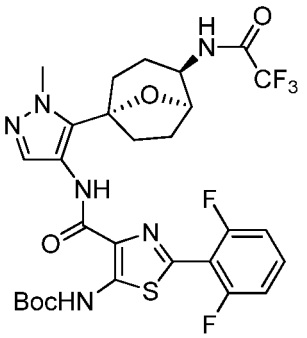
A solution of 4-azido-3,5-dimethyl-6-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-3-ol (140 mg, 0.47 mmol) in THF/water (1 mL/0.2 mL) was treated with triphenylphosphine (373 mg, 1.42 mmol) and the reaction mixture was heated at 65 °C behind a blast screen for 18 hr. More THF (1 mL) was added along with a solution of trimethylphosphine (1 M in toluene, 1 mL, 1.0 mmol). The mixture was heated at 65 °C behind a blast screen for 3 hr. The solvents were removed under reduced pressure and the residue was dissolved in dry DCM (4 mL). Di-*tert*-butyl-dicarbonate (115 mg, 0.53 mmol) was added followed by DIPEA (0.18 mL, 1.05 mmol) and the reaction mixture was stirred at room temperature for 72 hr. The mixture was concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave *tert*-butyl *N*-[5-hydroxy-3,5-dimethyl-2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-yl]carbamate an off-white solid (112 mg, 64% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.52 (d, J = 2.7 Hz, 1H), 4.11-4.01 (m, 6H), 2.67-2.58 (m, 1H), 2.54 (s, 1H), 1.61 (s, 1H), 1.48 (s, 9H), 1.36 (s, 3H), 0.98 (d, J = 7.2 Hz, 3H).

Intermediate 39 2-(2-Methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-ol



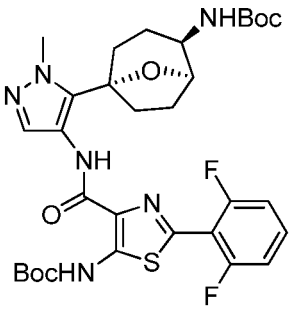
Following the procedure for Intermediate 30 also gave 2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-ol as as a mixture of diastereomers as a yellow gum (91 mg, 12% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 and 8.03 (2s, 1H), 5.88 (dd, J = 8.3, 6.1 Hz) and 5.70 (dd, J = 11.8, 3.2 Hz) (1H), 4.49 (dd, J = 11.8, 7.4 Hz) and 4.40 (s) (1H), 4.15-3.72 (m, 2H), 4.15 and 4.09 (s, 3H), 2.85-2.55 (m, 1H), 2.03-1.89 (m, 3H), 1.79-1.66 (m, 1H).

Intermediate 40 *tert*-Butyl *N*-(2-(2,6-difluorophenyl)-4-((1-methyl-5-(2-((2,2,2-trifluoroacetyl)amino)-8-oxabicyclo[3.2.1]octan-5-yl)pyrazol-4-yl)carbamoyl)thiazol-5-yl)carbamate



To a solution of 2,2,2-trifluoro-*N*-(5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl)acetamide (120 mg, 0.32 mmol) in THF (10 mL) and MeOH (10 mL) was added 10% palladium on carbon (12 mg). The reaction mixture was heated at 40 °C under a 400 psi atmosphere of hydrogen for 3 hr, cooled to room temperature, filtered through Celite®, washing with methanol (50 mL) and concentrated under reduced pressure. The procedure was repeated using the same conditions except with additional aqueous HCl (2 M, 2 mL). To a solution of the residue in DCM (20 mL) was added DIPEA (1.00 mL, 5.74 mmol), 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (123 mg, 0.46 mmol) and PyBOP (409 mg, 0.78 mmol) and the mixture was stirred at room temperature for 16 hr. The reaction was quenched with water (20 mL) and extracted with DCM (150 mL). The organic layer was washed saturated solution of $NaHCO_3$ (30 mL) and water (30 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel chromatography (80-100% EtOAc/isohexane) gave *tert*-butyl *N*-(2-(2,6-difluorophenyl)-4-((1-methyl-5-(2-((2,2,2-trifluoroacetyl)amino)-8-oxabicyclo[3.2.1]octan-5-yl)pyrazol-4-yl)carbamoyl)thiazol-5-yl)carbamate as an off-white solid (58 mg, 27% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 10.39 (s, 1H), 8.33 (s, 1H), 7.39-7.33 (m, 1H), 7.18-7.10 (m, 2H), 5.91 (d, J = 7.7 Hz, 1H), 4.89-4.83 (m, 1H), 4.47-4.38 (m, 1H), 3.86 (s, 3H), 2.47-2.38 (m, 1H), 2.27-1.90 (m, 7H), 1.55 (s, 9H).

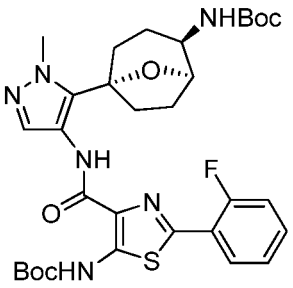
Intermediate 41 *tert*-Butyl *N*-[5-[4-[[5-(*tert*-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate



Following the procedure for Intermediate 1 starting from *tert*-butyl *N*-(5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl)carbamate gave *tert*-butyl *N*-(5-[4-[[5-

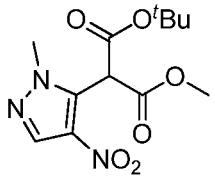
(*tert*-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate as a pale pink solid (172 mg, 17% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 10.45 (s, 1H), 8.29 (s, 1H), 7.35-7.27 (m, 1H), 7.18-7.08 (m, 2H), 4.76 (br s, 1H), 4.29 (br s, 1H), 4.04 (br s, 1H), 3.85 (s, 3H), 2.38-2.33 (m, 1H), 2.19-1.86 (m, 7H), 1.55 (s, 9H), 1.48 (s, 9H).

Intermediate 42 *tert*-Butyl *N*-[5-[4-[[5-(*tert*-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate



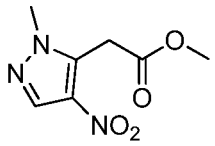
Following the procedure for Intermediate 1 starting from *tert*-butyl *N*-(5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl)carbamate gave *tert*-butyl *N*-(5-[4-((5-(*tert*-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carbonyl)amino)-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate as a pale pink solid (310 mg, 31% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (br s, 1H), 10.48 (s, 1H), 8.39-8.29 (m, 2H), 7.60-7.51 (m, 1H), 7.38-7.31 (m, 1H), 7.18 (dd, *J* = 11.4, 8.3 Hz, 1H), 4.86 (br s, 1H), 4.36 (br s, 1H), 4.07 (br s, 1H), 3.86 (s, 3H), 2.43-2.35 (m, 1H), 2.22-1.92 (m, 7H), 1.55 (s, 9H), 1.50 (s, 9H).

Intermediate 43 1-tert-butyl 3-methyl 2-(1-methyl-4-nitro-1H-pyrazol-5-yl)malonate



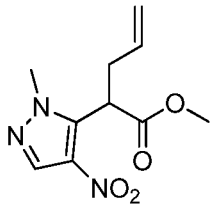
Potassium carbonate (15.40 g, 111.42 mmol) was added in one portion to a stirred, RT solution of 5-chloro-1-methyl-4-nitro-pyrazole (6.0 g, 37.140 mmol) and tert-butyl methyl melonate (8.74 g, 50.139 mmol) in anhydrous DMSO (100 mL) under nitrogen. The mixture was heated at 75 °C for 3 hours before being cooled and allowed to stand at RT overnight. The mixture was poured into water (500 mL), acidified with 2N HCl (80ml, PH 5) and extracted with EtOAc (2 x 250 mL, 2x200ml). The combined organics were dried (MgSO4) and the solvent removed under reduced pressure. The residue was purified via silica gel chromatography (0 - 30% EtOAc/heptane) to afford 1-tert-butyl 3-methyl 2-(1-methyl-4-nitro-1H-pyrazol-5-yl)malonate as a colorless solid (10.3g, 92.7%).

Intermediate 44 methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)acetate



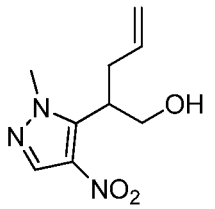
A mixture of 1-tert-butyl 3-methyl 2-(1-methyl-4-nitro-1H-pyrazol-5-yl)malonate (6.92 g, 23.1 mmol) and formic acid (100 mL) was heated at 50 °C for 5 hours before being cooled to room temperature. Formic acid was removed under reduced pressure; the residue was diluted with brine and extracted with DCM 3x. The combined organics were dried (MgSO4) and the solvent removed under reduced pressure. The residue was purified via silica gel chromatography (0 - 60% EtOAc/heptane) to afford methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)acetate (4.15g, 90%).

Intermediate 45 methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-enoate



To a solution of methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)acetate (869 mg, 4.36 mmol) in anhydrous DMF (10 mL) was added at 0°C sodium hydride (218mg, 5.45 mmol, 60 mass%), the mixture became dark red right away. After stirring at 0°C for 15min, allyl bromide (0.57 mL, 6.54 mmol) was added slowly, stirred at 0°C for 10min then room temp for 1h. The reaction was quenched with water (20 mL) and extracted with EA (200 mL, 50 mL). Combined organic layer was washed with water (15x3 mL), brine (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-enoate (713mg, 68%). 1H NMR (400 MHz, CDCl3) δ 8.10 (s, 1H), 5.71 – 5.54 (m, 1H), 5.01 (d, J = 13.1 Hz, 2H), 4.43 (dd, J = 9.8, 5.5 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.14 – 3.02 (m, 1H), 2.79 – 2.62 (m, 1H).

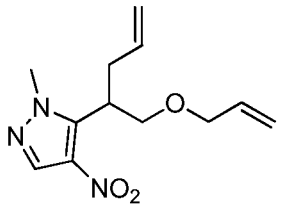
Intermediate 46 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-en-1-ol



DIBAL-H (1.0 mol/L) in toluene (16.03 mmol, 16 mL) was added to a solution of methyl 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-enoate (959 mg, 4.01 mmol) in THF (16 mL) under nitrogen atmosphere at 0°C. The mixture was stirred for 30 min at 0°C. 1N HCl (25 mL) solution was slowly added to the reaction mixture at 0°C, followed by ethyl acetate (30 mL). After separation, the organic layer was washed by saturated $NaHCO_3$ solution (30 mL) and saline (30

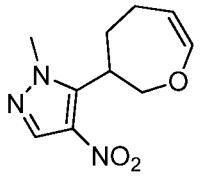
mL). The combined aqueous layers were extracted with ethyl acetate till there was no desired product in the aqueous layer. The organic layers were combined and subsequently dried (Na_2SO_4), filtered and evaporated to yield a light brown oil (610 mg). The crude material was purified on silica gel using 0-100% ethyl acetate in heptane to give 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-en-1-ol as a light yellow solid (676 mg, 80%).

Intermediate 47 5-[1-(allyloxymethyl)but-3-enyl]-1-methyl-4-nitro-pyrazole



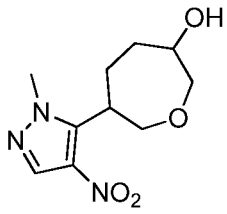
To a solution of 2-(2-methyl-4-nitro-pyrazol-3-yl)pent-4-en-1-ol (91 mg, 0.43) in anhydrous DMF (5 mL) was added at 0°C sodium hydride (20mg, 0.49 mmol, 60 mass%). After stirring at 0°C for 15min, allyl bromide (79, 0.64 mmol) was added slowly, stirred at 0°C for 10min then warm to room temperature for 2h. The reaction was quenched with water (10ml) and extracted with EA (3x50ml). Combined organic layer was washed with brine (10ml) and concentrated to dryness. The residue was purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford 5-[1-(allyloxymethyl)but-3-enyl]-1-methyl-4-nitro-pyrazole (84mg, 78%).

Intermediate 48 1-methyl-4-nitro-5-(2,3,4,5-tetrahydrooxepin-3-yl)pyrazole



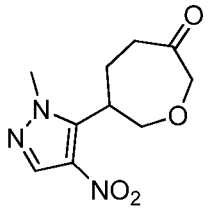
A solution of 1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium, "Grubb's catalyst 2nd generation", CAS Reg. No. 246047-72-3, Sigma-Aldrich Product No. 569747, US 6111121, US 7329758 (375mg, 0.42 mmol) in toluene (15ml) was added to a solution of 5-[1-(allyloxymethyl)but-3-enyl]-1-methyl-4-nitro-pyrazole (527 mg, 2.10 mmol) in toluene (115 mL). The resulting solution was heated at reflux (120°C) for 2.5h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford 1-methyl-4-nitro-5-(2,3,4,5-tetrahydrooxepin-3-yl)pyrazole (133mg, 30%).

Intermediate 49 6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol



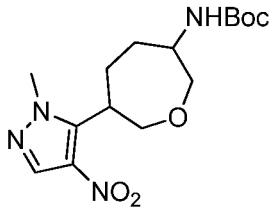
Borane dimethyl sulfide complex (2.0 mol/L) in THF (0.91 mL, 1.82 mmol) was added to a solution of 1-methyl-4-nitro-5-(2,3,4,5-tetrahydrooxepin-3-yl)pyrazole (204 mg, 0.91 mmol) in anhydrous THF (8 mL) at 0°C. The mixture was stirred at 0°C for 15min then warm to RT for 2h. 1M NaOH (1.5 mL) and hydrogen peroxide (30 mass% in water) (0.8 mL) were added and the mixture was stirred at RT for 2h. The reaction was quenched with water and extracted with DCM (2x) and EA (1x). Combined organic layers were washed with brine (10ml) and concentrated to dryness. The residue was purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford 6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol (53mg, 24%).

Intermediate 50 6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one



To a solution of 6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol (53 mg, 0.22 mmol) in DCM (6 mL) was added Dess-Martin periodinane (192mg, 0.44 mmol) and sodium bicarbonate (93mg, 1.10 mmol). The mixture was stirred at room temperature overnight, quenched with water, and extracted with DCM (3x). Combined organic layers were concentrated to dryness and purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford 6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one (53mg, quant.).

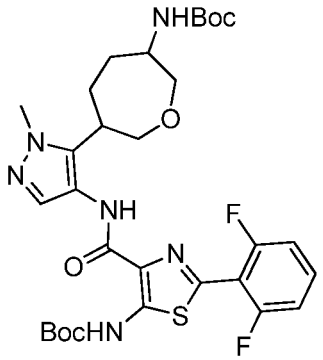
Intermediate 51 tert-butyl N-[6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate



6-(2-Methyl-4-nitro-pyrazol-3-yl)oxepan-3-one (53 mg, 0.23 mmol) , ammonium acetate (219mg, 2.76 mmol) , sodium cyanoborohydride (38mg, 0.57 mmol) and a few pettets of 4A molecular seives were dissolved in methanol (2 mL). Acetic acid (35mg, 0.57 mmol) was added and the mixture was stirred at RT under N2 atmosphere for three days. The reaction was quenched with sat. sodium bicarbonate and extracted with DCM (3x). Combined organic layers were dried (MgSO4) and the solvent removed under reduced pressure. The residue was dissolved

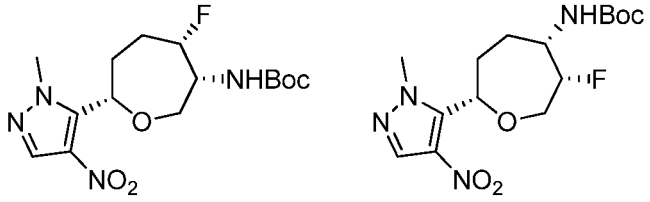
in DCM (5 mL) and di-tert-butyl-dicarbonate (63mg, 0.69 mmol) and DIPEA (0.067 mL, 0.38 mmol) were added. The mixture was stirred at room temperature overnight and then purified purified via silica gel chromatography (0 - 100% EtOAc/heptane) to afford tert-butyl N-[6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate (53mg, 81%).

Intermediate 52 tert-butyl N-[6-[4-[[5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]oxepan-3-yl]carbamate



A solution of tert-butyl N-[6-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate (53 mg, 0.16 mmol) in MeOH (25 mL) was passed through the H-Cube® (50 bar, 50°C, flow rate: 1 mL/min, 30 mm 10% Pd/C cartridge). The solvent was removed under reduced pressure to afford tert-butyl N-[6-(4-amino-2-methyl-pyrazol-3-yl)oxepan-3-yl]carbamate as a brown oil. To a solution of this oil in DCM (5 mL) was added 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (72 mg, 0.20 mmol), PyBOP (133 g, 0.25mmol) and DIPEA (0.17 mL, 0.94 mmol) and the mixture was stirred at room temperature for 16 hr. The reaction was quenched with water and extracted with EA (3x). The organic layers were combined and the solvent was removed under reduced pressure. Purification via silica gel column chromatography (0-100% EtOAc/heptane) gave tert-butyl N-[6-[4-[[5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]oxepan-3-yl]carbamate (100mg, 99%).

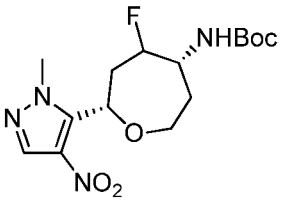
Intermediate 53 *tert*-Butyl *N*-[4-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate and *tert*-Butyl *N*-[3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



Following the procedure for Intermediate 23 starting from 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (Intermediate 33) gave an inseparable mixture of *tert*-butyl *N*-[4-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate and

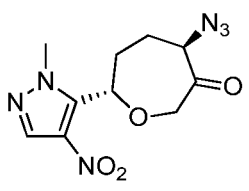
tert-butyl *N*-[3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as an oil (290 mg, 53% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.58-5.47 (m, 1H), 4.96-4.73 (m, 2H), 4.14-3.93 (m, 5H), 2.30-2.16 (m, 3H), 2.04-1.83 (m, 2H), 1.47 (s, 9H).

Intermediate 54 *tert*-Butyl *N*-[5-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



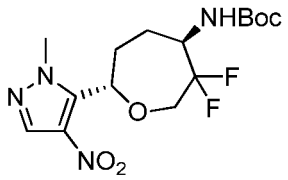
A solution of deoxo-Fluor (50% in THF, 0.576 mL, 1.56 mmol) was added dropwise to an ice-cooled solution of 5-azido-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol (353 mg, 1.25 mmol, intermediate 27) in DCM (6 mL). The mixture was allowed to warm to room temperature whilst stirring for 16 hr before being cooled in an ice bath and saturated aqueous $NaHCO_3$ (10 mL) slowly added. The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-50% EtOAc/isohexane) gave 5-(5-azido-4-fluorooxepan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a clear gum. To a solution of this gum (145 mg, 0.51 mmol) in THF (5 mL) and water (1 mL) was added triphenylphosphine (147 mg, 0.56 mmol) and the mixture heated at 60 °C for 2 hr. The mixture was diluted with EtOAc (10 mL) and washed with brine (2 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. The residue was dissolved in DCM (2 mL) and DIPEA (0.178 mL, 1.02 mmol) and di-*tert*-butyl dicarbonate (134 mg, 0.61 mmol) were added. The mixture was stirred at room temperature for 2 hr. Water (2 mL) was added and the mixture extracted with DCM (3 x 2 mL). The combined organic layers were passed though a phase separation cartridge, concentrated under reduced pressure and the residue purified *via* silica gel chromatography (0-50% EtOAc/isohexane) to give *tert*-butyl *N*-[5-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as a clear gum (180 mg, 39% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.54 (dd, J = 10.5, 4.2 Hz, 1H), 5.10-4.92 (m, 2H), 4.21-4.09 (m, 2H), 4.05 (s, 3H), 3.74-3.62 (m, 1H), 2.57-2.38 (m, 1H), 2.35-2.15 (m, 2H), 1.91-1.81 (m, 1H), 1.46 (s, 9H).

Intermediate 55 4-Azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one



To a solution of 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (2.85 g, 11.9 mmol, intermediate 19) in MeOH (60 mL) and water (11.5 mL) was added NH_4Cl (1.58 g, 29.8 mmol) followed by sodium azide (3.87 g, 59.5 mmol). The reaction mixture was heated at 70 °C for 18 hr then allowed to cool to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with brine (50 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure to give the azido alcohol as an orange oil as a 80/20 mixture of regioisomers. To a solution of this oil (1.9 g, 6.7 mmol) in DCM (40 mL) was added Dess-Martin periodinane (1.8 g, 4.26 mmol) and the mixture stirred at room temperature for 3 hr. Aqueous saturated $NaHCO_3$ (50 mL) and 20% sodium thiosulfate solution (50 mL) were added and the reaction mixture was stirred for 30 min until full dissolution of salts was observed. The mixture was diluted with DCM (50 mL) and the organic layer was separated, dried over $MgSO_4$ and cancentrated under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave 4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one as an oil (1.05 g, 86% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.38 (dd, J = 10.1, 2.7 Hz, 1H), 4.63-4.51 (m, 2H), 4.30-4.20 (m, 1H), 4.08 (s, 3H), 2.29-2.16 (m, 4H).

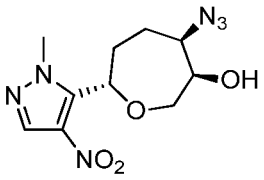
Intermediate 56 *tert*-Butyl *N*-[3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



To a solution of 4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one (440 mg, 1.57 mmol, intermediate 55) in DCM (10 mL) was added deoxo-Fluor® (50% in THF, 1.42 mL, 3.92 mmol) and the mixture stirred at room temperature for 18 hr. DCM (20 mL) was added, the mixture was cooled to 0 °C and saturated aqueous $NaHCO_3$ (20 mL) was carefully added. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave 5-(5-azido-6,6-difluorooxepan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as an oil (280 mg). A solution of this oil (280 mg, 0.93 mmol) in THF/water (10 mL/1.8 mL) was treated with triphenylphosphine (267 mg, 1.02 mmol) and the reaction mixture was heated at 70 °C behind a blast shield for 18 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dry DCM (15 mL), cooled to 0 °C and di-*tert*-butyl-dicarbonate (243 mg, 1.12 mmol) was added followed by DIPEA (0.15 mL, 1.12 mmol). The reaction mixture was allowed to warm to room temperature and stirred for

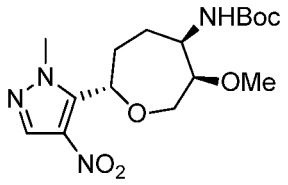
72 hr. Water (20 mL) was added and the mixture was extracted with DCM (100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-35% EtOAc/isohexane) gave *tert*-butyl *N*-[3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as a clear oil (310 mg, 59% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.48-5.42 (m, 1H), 5.10-5.01 (m, 1H), 4.49-4.35 (m, 2H), 4.04 (s, 3H), 3.99-3.80 (m, 1H), 2.17-1.98 (m, 4H), 1.48 (s, 9H).

Intermediate 57 4-Azido-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-3-ol



To a solution of 4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one (Intermediate 55) (1 g, 3.57 mmol) in dry THF (25 mL) under nitrogen cooled to -78 °C was added L-selectride (1 M in THF, 4.3 mL, 4.3 mmol) and the mixture was stirred at -78 °C for 45 min. The mixture was allowed to warm to room temperature and water (10 mL) was added. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave racemic 4-azido-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-3-ol (relative stereochemistry as shown above) as a yellow oil (580 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.63 (dd, J = 10.6, 3.5 Hz, 1H), 4.21-4.14 (m, 3H), 4.01 (s, 3H), 3.69-3.58 (m, 1H), 2.45-2.33 (m, 1H), 2.27-2.08 (m, 2H), 2.01-1.84 (m, 2H).

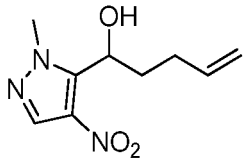
Intermediate 58 *tert*-Butyl *N*-[3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



To a solution of 4-azido-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-3-ol, (Intermediate 57) (182 mg, 0.65 mmol) in anhydrous DMF (5 mL) under nitrogen was added sodium hydride (60% dispersion in mineral oil, 39 mg, 0.97 mmol) portionwise over 10 min. After a further 45 min, methyl iodide (0.06 mL, 0.97 mmol) was added dropwise and the mixture stirred for 18 hr at room temperature. Further sodium hydride (60% dispersion in mineral oil, 39 mg, 0.97 mmol) was added followed by methyl iodide (0.06 mL, 0.97 mmol) and the mixture stirred at room temperature for 48 hr. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL),

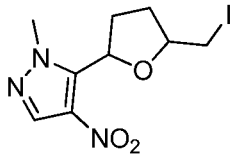
separated, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave 5-(5-azido-6-methoxyoxepan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as an oil (100 mg). A solution of this oil (100 mg, 0.37 mmol) in THF/water (5 mL/1 mL) was treated with triphenylphosphine (97 mg, 0.37 mmol) and the reaction mixture heated at 70 °C behind a blast shield for 18 hr. The mixture was concentrated under reduced pressure. The residue was dissolved in dry DCM (3 mL) at 0 °C and di-*tert*-butyl-dicarbonate (89 mg, 0.4 mmol) and DIPEA (0.18 mL, 1.02 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 3 hr. Water (10 mL) was added and the mixture extracted with DCM (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave racemic *tert*-butyl-(3-methoxy-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate (relative stereochemistry as shown above) as a clear oil (119 mg, 47% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.39 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.75 (br s, 1H), 4.33 (dd, *J* = 14.2, 1.9 Hz, 1H), 4.06 (s, 3H), 3.91-3.83 (m, 1H), 3.75 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.43 (s, 3H), 3.39-3.34 (m, 1H), 2.22-2.12 (m, 1H), 2.12-2.03 (m, 1H), 2.03-1.82 (m, 2H), 1.47 (s, 9H).

Intermediate 59 1-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-ol



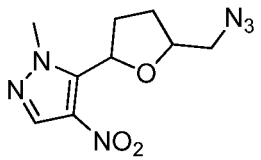
A solution of 1-methyl-4-nitro-1*H*-pyrazole (9.7 g, 76.7 mmol) and 4-pentenal (10 g, 84.4 mmol) in dry THF (250 mL) was cooled to -78 °C and stirred under nitrogen. A solution of LiHMDS (1 M in THF, 192 mL, 191.7 mmol) was added dropwise over a period of 3 hr. The reaction mixture was allowed to warm and to -40 °C and stirred for 2 hr, quenched by dropwise addition of saturated ammonium chloride solution (100 mL), warmed to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with saturated ammonium chloride solution (50 mL), separated, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* silica gel chromatography (0-100% EtOAc/DCM) followed by silica gel chromatography (0-100% EtOAc/isohexane) to gave 1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-ol as a pale yellow oil (5.75 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 5.85-5.78 (m, 1H), 5.32-5.26 (m, 1H), 5.12-5.04 (m, 2H), 3.98 (s, 3H), 3.45 (d, *J* = 8.7 Hz, 1H), 2.92-2.09 (m, 3H), 1.90-1.86 (m, 1H).

Intermediate 60 5-(5-(Iodomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole



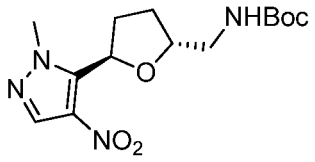
To a stirred solution of 1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-ol (0.84 g, 3.98 mmol, intermediate 59) in dry THF (25 mL) under nitrogen was added iodine (1.52 g, 5.97 mmol). After stirring for 5 min, Na_2CO_3 (0.63 g, 5.97 mmol) was added followed by silver triflate (3.07 g, 11.94 mmol) and the dark red solution turned yellow. The mixture was stirred at room temperature for 1 hr, diluted with THF (25 mL) and filtered through celite. The yellow solid was washed with THF/DCM and the filtrate concentrated under reduced pressure. Purification *via* silica gel chromatography (0-40% EtOAc/DCM) gave 5-(5-(iodomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a pale yellow gum (640 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.91-5.87 (m, 1H), 4.39-4.35 (m, 1H), 4.02 (s, 3H), 3.37-3.30 (m, 2H), 2.69-2.67 (m, 1H), 2.45-2.41 (m, 1H), 2.05-1.89 (m, 2H).

Intermediate 61 5-(5-(Azidomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1H-pyrazole



To a solution of 5-(5-(iodomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (640 mg, 1.90 mmol, intermediate 60) in dry DMF (10 mL) was added sodium azide (250 mg, 3.80 mmol) and the mixture stirred at room temperature for 36 hr. The mixture was diluted with EtOAc (25 mL) and washed with water (2 x 10 mL) and brine (20 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure to give 5-(5-(azidomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a yellow oil (480 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.84-5.70 (m, 1H), 4.49-4.45 (m, 1H), 4.03 (s, 3H), 3.56-3.39 (m, 2H), 2.66-2.65 (m, 1H), 2.29-2.22 (m, 1H), 2.02-1.92 (m, 2H).

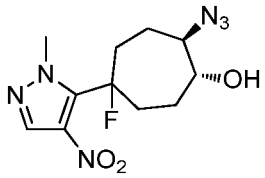
Intermediate 62 *tert*-Butyl ((5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydrofuran-2-yl)methyl)carbamate



A solution of 5-(5-(azidomethyl)tetrahydrofuran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (520 mg, 2.07 mmol, intermediate 61) in THF/water (20 mL/4 mL) was treated with triphenylphosphine (600 mg, 2.28 mmol) and the reaction mixture heated at 70 °C behind a blast

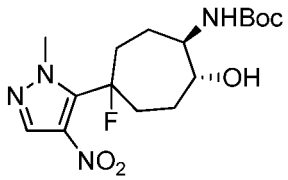
shield for 1.5 hr. The mixture was allowed to cool to room temperature and the organic solvent was removed under reduced pressure. The aqueous layer was extracted witn DCM (40 mL) and the organic layer was passed through a phase separation cartridge and concentrated under reduced pressure to give a pale yellow oil. This oil was dissolved in DCM (20 mL) and DIPEA (0.72 mL, 4.14 mmol) was added followed by a solution of di-*tert*-butyl-dicarbonate (540 mg, 2.48 mmol) in DCM (1 mL) in two portions. The reaction mixture was stirred at room temperature for 1 hr. Water (10 mL) was added and the organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave *tert*-butyl ((5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydrofuran-2-yl)methyl)carbamate as a colourless gum (145 mg, 21% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.80-5.76 (m, 1H), 4.85 (br s, 1H), 4.35 (br s, 1H), 4.01 (s, 3H), 3.50-3.40 (m, 1H), 3.25-3.19 (m, 1H), 2.65-2.55 (m, 1H), 2.25-2.20 (m, 1H), 2.00-1.80 (m, 2H), 1.46 (s, 9H).

Intermediate 63 2-Azido-5-fluoro-5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)cycloheptanol



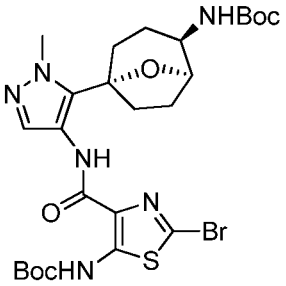
A solution of 5-(4-fluoro-8-oxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-1*H*-pyrazole (2.75 g, 10.8 mmol, Intermediate 155) in DMF/water (35 mL/10 mL) was treated with ammonium chloride (1.43 g, 27.0 mmol) and sodium azide (3.5 g, 53.9 mmol) and the mixture was heated at 100 °C behind a blast shield for 18 hr. The reaction mixture was extracted with EtOAc (200 mL) and the organic layer was washed with water (8 x 30 mL), washed with brine (30 mL), separated, dried over $MgSO_4$, and concentrated under reduced pressure. Purification *via* silica gel column chromatography (30-40% EtOAc/isohexane) gave 2-azido-5-fluoro-5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)cycloheptanol as the second eluting isomer as a white solid (2.16 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 and 8.05 (2s, 1H), 4.08 and 4.06 (2s, 3H), 3.88-3.78 (m, 1H), 3.65-3.58 (m, 1H), 2.87-2.55 (m, 2H), 2.31-2.21 (m, 2H), 2.18-2.00 (m, 3H), 1.98-1.85 (m, 2H).

Intermediate 64 *tert*-Butyl *N*-[5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl]carbamate



A solution of 2-azido-5-fluoro-5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)cycloheptanol (300 mg, 1.05 mmol, intermediate 63) in THF/water (15 mL/3 mL) was treated with triphenylphosphine (290 mg, 1.11 mmol) and the mixture heated at 60 °C behind a blast shield for 18 hr. Brine (5 mL) was added and the mixture extracted with EtOAc (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the resulting oil in dry DCM (20 mL) under nitrogen was added slowly DIPEA (0.88 mL, 5.03 mmol) followed by a solution of di-*tert*-butyl-dicarbonate (263 mg, 1.21 mmol) in dry DCM (10 mL). The reaction mixture was stirred at room temperature for 4 days. Water (30 mL) was added and the mixture was extracted with DCM (80 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (40-50% EtOAc/isohexane) gave *tert*-butyl *N*-[5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl]carbamate as a colourless oil (218 mg, 58% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 and 8.05 (2s, 1H), 4.86 (br s, 1H), 4.08 and 4.06 (2s, 3H), 3.88-3.79 (m, 1H), 3.75-3.67 (m, 2H), 2.77-2.48 (m, 2H), 2.40-2.30 (m, 1H), 2.21-1.95 (m, 3H), 1.95-1.67 (m, 2H), 1.47 (s, 9H).

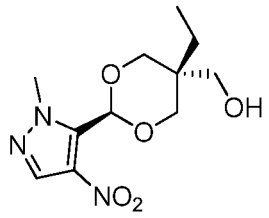
Intermediate 65 *tert*-Butyl *N*-[2-bromo-4-[[5-[2-(tert-butoxycarbonylamino)-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



To a solution of *tert*-butyl *N*-[5-fluoro-2-hydroxy-5-(2-methyl-4-nitro-pyrazol-3-yl)cycloheptyl]carbamate (210 mg, 0.565 mmol, intermediate 64) in THF (20 mL) and MeOH (20 mL) was added 10% palladium on carbon (20 mg). The reaction mixture was heated at 40 °C under a 400 psi atmosphere of hydrogen for 3 hr. After cooling to room temperature, the mixture was filtered through Celite®, washing with MeOH (50 mL) and concentrated under reduced pressure. To a solution of the residue in DCM (30 mL) was added DIPEA (2 mL, 1.40 mmol), 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid (208 mg, 0.62 mmol, Example 22) and PyBOP (727 mg, 1.40 mmol) and the mixture was stirred at room temperature for 18 hr. Water (20 mL) was added and the mixture was extracted with DCM (100 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (80-100% EtOAc/isohexane) gave *tert*-butyl *N*-[2-bromo-4-[[5-[2-(*tert*-butoxycarbonylamino)-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (120 mg, 34% over two steps). ^{1}H NMR (400 MHz,

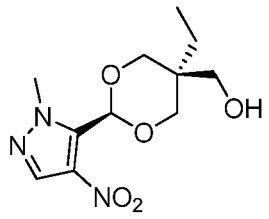
$CDCl_3$) δ 10.40 (br s, 1H), 9.86 (br s, 1H), 8.12 (br s, 1H), 4.70-4.63 (m, 1H), 4.36-4.22 (m, 1H), 3.97-3.86 (m, 1H), 3.86 (s, 3H), 2.40-2.31 (m, 1H), 2.21-1.93 (m, 7H), 1.55 (s, 9H), 1.52 (s, 9H).

Intermediate 66 (5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer)



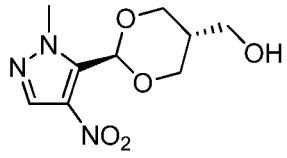
To a solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (370 mg, 2.39 mmol, intermediate 3) in toluene (50 mL) was added 2-ethyl-2-(hydroxymethyl)propane-1,3-diol (315 mg, 2.35 mmol) followed by *p*-toluenesulfonic acid (20 mg, 0.10 mmol). The reaction mixture was heated at reflux for 36 hr whilst azeotropically removing the water. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave (5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer) as the first eluting isomer as a colourless solid (244 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.38 (s, 1H), 4.16 (s, 3H), 4.02 (d, J = 11.5 Hz, 2H), 3.97 (d, J = 5.2 Hz, 2H), 3.42 (d, J = 3.8 Hz, 2H), 1.90 (m, 3H), 0.99 (t, J = 7.6 Hz, 3H).

Intermediate 67 (5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer)



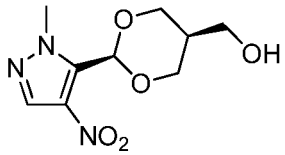
Following the procedure for Intermediate 66 also gave (5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer) as the second eluting isomer as a colourless solid (118 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.37 (s, 1H), 4.13 (s, 3H), 4.12 (d, J = 12.8 Hz, 2H), 3.98 (d, J = 3.9 Hz, 2H), 3.73 (d, J = 11.8 Hz, 2H), 1.74 (br s, 1H), 1.31 (q, J = 7.7 Hz, 2H), 0.89 (t, J = 7.7 Hz, 3H).

Intermediate 68 (2-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer)



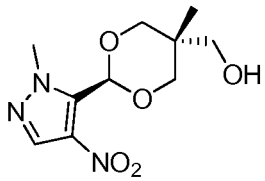
To a solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (718 mg, 4.63 mmol, intermediate 3) in toluene (100 mL) was added 2-(hydroxymethyl)propane-1,3-diol (700 mg, 6.73 mmol) followed by *p*-toluenesulfonic acid (88 mg, 0.463 mmol). The reaction mixture was heated at reflux for 18 hr whilst azeotropically removing the water. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with DCM (50 mL) and washed with a saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with water (20 mL) and brine (20 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave (2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer) as the first eluting isomer as a colourless solid (220 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.42 (s, 1H), 4.34 (dd, *J* = 11.6, 4.7 Hz, 2H), 4.12 (s, 3H), 3.81 (t, *J* = 11.5 Hz, 2H), 3.56 (t, *J* = 5.1 Hz, 2H), 2.53-2.38 (m, 1H), 1.67 (t, *J* = 4.6 Hz, 1H).

Intermediate 69 (2-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (cis isomer)



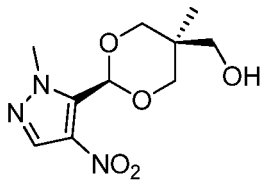
Following the procedure for Intermediate 68 also gave (2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer) as a colourless solid (268 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.49 (s, 1H), 4.28 (d, *J* = 11.9 Hz, 2H), 4.20 (d, *J* = 3.3 Hz, 2H), 4.12 (s, 3H), 4.06 (dd, *J* = 7.8, 3.7 Hz, 2H), 1.82 (t, *J* = 4.9 Hz, 1H), 1.78-1.71 (m, 1H).

Intermediate 70 (5-Methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer)



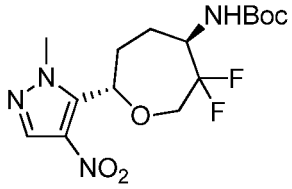
Following the procedure for Intermediate 68 starting from 2-methyl-2-(hydroxymethyl)propane-1,3-diol gave (5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol as the first eluting isomer as a colourless solid (167 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.38 (s, 1H), 4.19 (s, 3H), 4.02 (d, *J* = 11.3 Hz, 2H), 3.89 (d, *J* = 11.3 Hz, 2H), 3.43 (d, *J* = 4.5 Hz, 2H), 1.65-1.40 (m, 1H), 1.36 (s, 3H).

Intermediate 71 (5-Methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer)



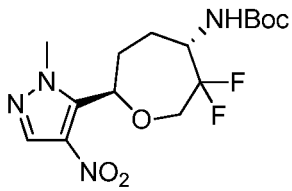
Following the procedure for Intermediate 70 also gave (5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer) as the second eluting isomer (480 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.40 (s, 1H), 4.16-4.06 (m, 5H), 3.91 (s, 2H), 3.72 (d, J = 11.9 Hz, 2H), 0.85 (s, 3H). OH not observed.

Intermediate 72 *tert*-Butyl *N*-[(4*R*,7*S*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



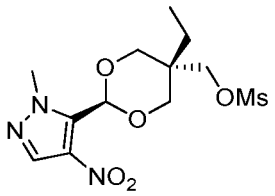
tert-Butyl *N*-[3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 56) was further purified *via* chiral SFC to give *tert*-butyl *N*-[(4*R*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as the second eluting isomer as an off-white solid (57 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.48-5.42 (m, 1H), 5.06 (d, J = 9.5 Hz, 1H), 4.49-4.38 (m, 2H), 4.05 (s, 3H), 3.98-3.82 (m, 1H), 2.18-2.00 (m, 4H), 1.48 (s, 9H).

Intermediate 73 *tert*-Butyl *N*-[(4*S*,7*R*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



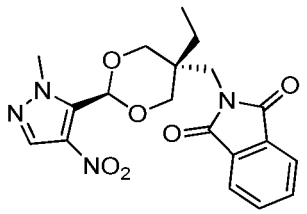
Following the procedure for Intermediate 72 also gave *tert*-butyl *N*-[(4*S*,7*R*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as the first eluting isomer as an off-white solid (65 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.48-5.42 (m, 1H), 5.05 (d, J = 9.2 Hz, 1H), 4.50-4.36 (m, 2H), 4.05 (s, 3H), 3.98-3.84 (m, 1H), 2.18-2.00 (m, 4H), 1.48 (s, 9H).

Intermediate 74 (5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl methanesulfonate



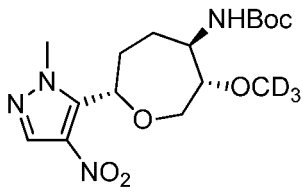
To a solution of (5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer) (610 mg, 2.25 mmol, intermediate 66) in dry DCM (15 mL) at 0 °C was added Et_3N (0.45 mL, 3.38 mmol) followed by methanesulfonyl chloride (0.21 mL, 2.70 mmol). The reaction mixture was slowly warmed to room temperature over 1.5 hr. The mixture was re-cooled to 0 °C and diluted with aqueous 1 M HCl (10 mL) and DCM (20 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (15 mL) and water (15 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure to give (5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl methanesulfonate as a white solid (816 mg, quantitative). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.38 (s, 1H), 4.14 (s, 3H), 4.05-3.88 (m, 6H), 3.22-2.92 (m, 3H), 1.96 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H).

Intermediate 75 2-((5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)isoindoline-1,3-dione



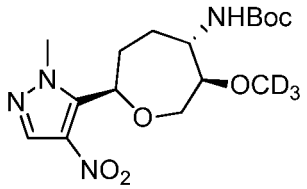
To a solution of (5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl methanesulfonate (816 mg, 2.25 mmol, intermediate 74) in dry DMSO (10 mL) was added potassium phthalamide (2.1 g, 11.3 mmol) in a single portion. The reaction mixture was heated at 180 °C for 5 hr, cooled to room temperature and diluted with EtOAc (50 mL) and water (30 mL). The organic layer was washed with water (3 x 30 mL), 2 N NaOH (2 x 20 mL) and water (20 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-((5-ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)isoindoline-1,3-dione as a colourless solid (317 mg, 35%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.93-7.88 (m, 2H), 7.82-7.76 (m, 2H), 6.31 (s, 1H), 4.14 (s, 3H), 4.06 (d, J = 11.8 Hz, 2H), 3.85 (d, J = 11.8 Hz, 2H), 3.51 (s, 2H), 1.92 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).

Intermediate 76 *tert*-Butyl *N*-[7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate



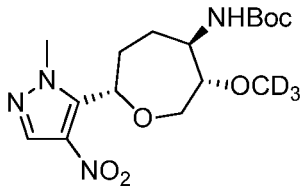
A solution of 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (400 mg, 1.67 mmol, intermediate 19) in MeOH/water (9 mL/1.7 mL) was treated with ammonium chloride (221 mg, 4.2 mmol) and sodium azide (544 mg, 8.37 mmol) and the mixture was heated at 70 °C behind a blast shield for 18 hr. The reaction mixture was extracted with EtOAc (100 mL) and the organic layer washed with water (3 x 20 mL) and brine (20 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the residue (310 mg, 1.1 mmol) in anhydrous DMF (5 mL) under nitrogen at room temperature was added sodium hydride (60% dispersion in mineral oil, 53 mg, 1.32 mmol) portionwise over 10 min. After a further 45 min, trideuteromethyl iodide (0.21 mL, 3.3 mmol) was added dropwise and the mixture stirred at room temperature for 18 hr. More sodium hydride (60% dispersion in mineral oil, 310 mg, 1.1 mmol) was added followed by more trideuteromethyl iodide (0.21 mL, 3.3 mmol) and the mixture stirred at room temperature for 48 hr. Water (20 mL) was added and the mixture extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isohexane) gave 5-[5-azido-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-4-nitro-pyrazole as an oil (140 mg). A solution of this oil (140 mg, 0.47 mmol) in THF/water (5 mL/0.9 mL) was treated with triphenylphosphine (135 mg, 0.52 mmol) and the reaction mixture was heated at 70 °C behind a blast shield for 18 hr. The mixture was concentrated under reduced pressure. The resulting residue was dissolved in dry DCM (9 mL) at 0 °C and di-*tert*-butyl-dicarbonate (123 mg, 0.56 mmol) and DIPEA (0.25 mL, 1.41 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 3 hr. Water (10 mL) was added and the mixture extracted with DCM (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-60% EtOAc/isohexane) gave racemic *tert*-butyl *N*-[7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate (relative stereochemistry as shown above) as an off-white solid (125 mg, 28% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.39 (dd, J = 10.6, 3.6 Hz, 1H), 4.85-4.67 (m, 1H), 4.32 (dd, J = 14.2, 1.9 Hz, 1H), 4.06 (s, 3H), 3.90-3.82 (m, 1H), 3.75 (dd, J = 14.2, 3.2 Hz, 1H), 3.40-3.33 (m, 1H), 2.20-1.82 (m, 4H), 1.46 (m, 9H).

Intermediate 77 *tert*-Butyl *N*-[(3*R*,4*S*,7*R*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate



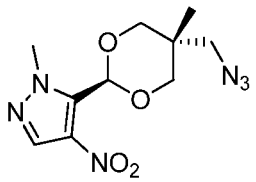
Further purification of *tert*-butyl *N*-[7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate *via* chiral SFC gave *tert*-butyl *N*-[(3*R*,4*S*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate as the first eluting isomer as an off-white solid (54 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.39 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.85-4.68 (m, 1H), 4.32 (dd, *J* = 14.2, 1.9 Hz, 1H), 4.06 (s, 3H), 3.90-3.82 (m, 1H), 3.75 (dd, *J* = 14.0, 3.2 Hz, 1H), 3.40-3.33 (m, 1H), 2.20-1.83 (m, 4H), 1.46 (s, 9H).

Intermediate 78 *tert*-Butyl *N*-[(3*S*,4*R*,7*S*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate



Following the procedure for Intermediate 77 also gave *tert*-butyl *N*-[(3*S*,4*R*,7*S*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate as the second eluting isomer as an off-white solid (52 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.39 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.85-4.66 (m, 1H), 4.33 (dd, *J* = 14.2, 1.9 Hz, 1H), 4.07 (s, 3H), 3.90-3.83 (m, 1H), 3.75 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.40-3.33 (m, 1H), 2.21-1.83 (m, 4H), 1.47 (m, 9H).

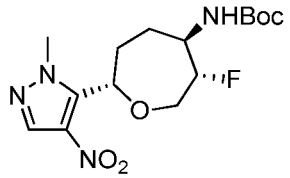
Intermediate 79 5-(5-(Azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (*trans* isomer)



To a solution of (5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer) (248 mg, 1.02 mmol, intermediate 66) in dry DCM at 0 °C (10 mL) was added Et_3N (0.20 mL, 1.53 mmol) followed by methanesulfonyl chloride (0.10 mL, 1.22 mmol). The reaction mixture was slowly warmed to room temperature over 1.5 hr. The mixture was re-cooled to 0 °C and 1 M aqueous HCl (5 mL) and DCM (20 mL) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure to yield a colourless oil. This oil was dissolved in DMF (20 mL) and sodium azide (400 mg, 6.12 mmol) was added. The reaction mixture was heated at 140 °C for 18 hr behind a blast shield. The reaction mixture was cooled to

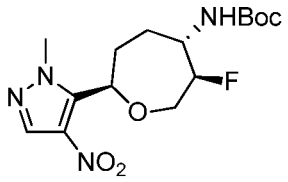
room temperature and diluted with water (20 mL) and EtOAc (50 mL). The organic layer was washed with water (3 x 20 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure to give 5-(5-(azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a colourless solid (300 mg, quantitative over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.36 (s, 1H), 4.17 (s, 3H), 3.88 (s, 4H), 3.20 (s, 2H), 1.40 (s, 3H).

Intermediate 80 *tert*-Butyl *N*-[(3*S*,4*R*,7*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



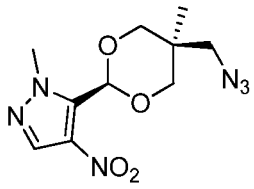
To a solution of 4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol (660 mg, 2.34 mmol, intermediate 57) in DCM (12 mL) was added deoxo-Fluor® (50% in THF, 2.12 mL) and the mixture was stirred at room temperature for 18 hr. The mixture was diluted with DCM (22 mL), cooled to 0 °C and saturated aqueous $NaHCO_3$ (20 mL) was carefully added. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-30% EtOAc/isohexane) gave 5-(5-azido-6-fluorooxepan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as an oil (440 mg). A solution of this oil (440 mg, 1.54 mmol) in THF/water (15 mL/2.8 mL) was treated with triphenylphosphine (487 mg, 1.86 mmol) and the reaction mixture was heated at 70 °C behind a blast shield for 18 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dry DCM (15 mL), cooled to 0 °C and di-*tert*-butyl-dicarbonate (402 mg, 1.84 mmol) was added followed by DIPEA (0.8 mL, 4.62 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 hr. Water (20 mL) was added and the mixture extracted with DCM (100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-35% EtOAc/isohexane) followed by chiral prep SFC gave *tert*-butyl *N*-[(3*S*,4*R*,7*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as a white solid (223 mg, 27% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.37 (dd, J = 10.5, 3.0 Hz, 1H), 4.89 (br s, 1H), 4.61 (ddd, J = 49.1, 7.7, 3.2 Hz, 1H), 4.44 (dd, J = 22.2, 15.0 Hz, 1H), 4.07 (s, 3H), 3.98-3.80 (m, 1H), 3.49 (d, J = 5.3 Hz, 1H), 2.15-1.90 (m, 4H), 1.47 (s, 9H).

Intermediate 81 *tert*-Butyl *N*-[(3*R*,4*S*,7*R*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



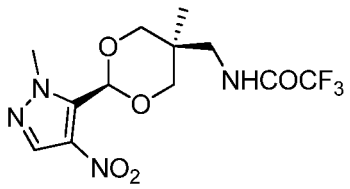
Following the procedure for Intermediate 80 also gave *tert*-butyl *N*-[(3*R*,4*S*,7*R*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as a white solid (247 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.39 (dd, *J* = 10.7, 2.9 Hz, 1H), 4.85 (br s, 1H), 4.61 (ddd, *J* = 49.3, 7.7, 3.17 Hz, 1H), 4.52-4.40 (m, 1H), 4.07 (s, 3H), 3.97-3.84 (m, 1H), 3.49 (d, *J* = 5.3 Hz, 1H), 2.15-1.88 (m, 4H), 1.49 (s, 9H).

Intermediate 82 5-(5-(Azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (*cis* isomer)



Following the procedure for Intermediate 79 starting from (5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer, intermediate 67) gave 5-(5-(azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a colourless solid (519 mg, 87% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.39 (s, 1H), 4.14 (s, 3H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.73 (d, *J* = 12.0 Hz, 2H), 3.70 (s, 2H), 0.87 (s, 3H).

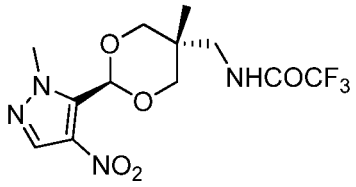
Intermediate 83 2,2,2-Trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide (*cis* isomer)



To a solution of 5-(5-(azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (*cis* isomer) (519 mg, 1.84 mmol, intermediate 82) in dry MeOH (25 mL) and THF (10 mL) was added ammonium formate (300 mg, 4.76 mmol) and 10% Pd/C (300 mg, 0.28 mmol). The mixture was heated at reflux for 30 min and then cooled to room temperature. The suspension was filtered through celite and the cake washed with EtOAc (200 mL). The filtrate was concentrated under reduced pressure and the crude residue was dissolved in dry THF (11 mL) and DCM (2 mL) and cooled to 0 °C. Et_3N (0.38 mL, 2.86 mmol) was added followed by trifluoroacetic anhydride (0.30 mL, 2.10 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 hr. The mixture was recooled to 0 °C and quenched with water (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (10

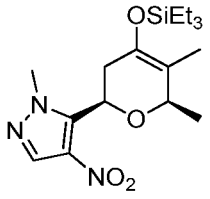
mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2,2,2-trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide as a colourless oil (410 mg, 63 % over two steps).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.24 (s, 1H), 6.33 (s, 1H), 4.17 (s, 3H), 3.92 (d, J = 12.0 Hz, 2H), 3.75 (d, J = 6.8 Hz, 2H), 3.71 (d, J = 12.0 Hz, 2H), 0.80 (s, 3H).

Intermediate 84 2,2,2-Trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide (*trans* isomer)



To a solution of 5-(5-(azidomethyl)-5-methyl-1,3-dioxan-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (*trans* isomer; 300 mg, 1.02 mmol, intermediate 79) in THF (3 mL) and water (0.3 mL) was added triphenylphosphine (322 mg, 1.22 mmol). The reaction mixture was heated at 70 °C for 1 hr. The mixture was cooled to room temperature and concentrated under reduced pressure. To a solution of the crude residue in dry THF (10 mL) at 0 °C was added Et_3N (0.20 mL, 1.53 mmol) followed by trifluoromethanesulfonic anhydride (0.16 mL, 1.12 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 18 hr. The mixture was re-cooled to 0 °C and more Et_3N (0.20 mL, 1.53 mmol) and trifluoromethanesulfonic anhydride (0.16 mL, 1.12 mmol) were added. The reaction mixture was slowly warmed to room temperature and stirred for 6 hr. The mixture was re-cooled to 0 °C, quenched with water (10 mL) and extracted with DCM (20 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2,2,2-trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide as a colourless solid (171 mg, 0.49 mmol).

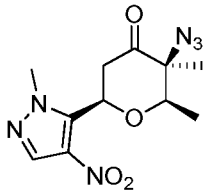
Intermediate 85 5-(5,6-Dimethyl-4-((triethylsilyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole



To a solution of (*E*)-3-methylpent-3-en-2-one (2.69 mL, 24.1 mmol) in DCM (200 mL) cooled to 0 °C was added Et_3N (10.5 mL, 79.5 mmol) followed by TESOTf (6.0 mL, 26.5 mmol). The mixture was warmed to room temperature and stirred for 18 hr. Saturated aqueous $NaHCO_3$

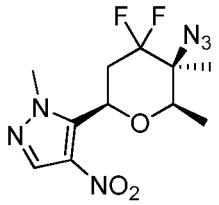
solution (100 mL) and DCM (200 mL) were added. The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organic layers were washed with brine (100 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure to give (*E*)-triethyl((3-methylpenta-1,3-dien-2-yl)oxy)silane. To a solution of 2-methyl-4-nitro-pyrazole-3-carbaldehyde (1.0 g, 8 mmol, intermediate 3) in $CDCl_3$ (28 mL) was added (*E*)-triethyl((3-methylpenta-1,3-dien-2-yl)oxy)silane (1.6 g, 7.55 mmol) followed by EuFOD (220 mg, 0.50 mmol). The reaction mixture was heated at 65 °C behind a blast shield for 18 hr in a pressure tube. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 5-(5,6-dimethyl-4-((triethylsilyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole as a colourless oil (2.92 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.64 (dd, *J* = 10.9, 3.6 Hz, 1H), 4.33-4.28 (m, 1H), 4.25-3.94 (m, 3H), 2.50-2.41 (m, 1H), 2.31 (m, 1H), 1.61 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.05-0.97 (m, 6H), 0.73-0.61 (m, 9H).

Intermediate 86 3-Azido-2,3-dimethyl-6-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)dihydro-2*H*-pyran-4(3*H*)-one



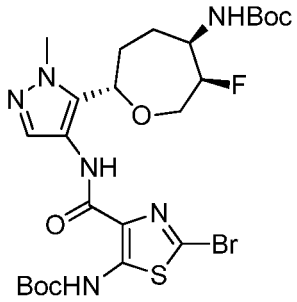
To a solution of 5-(5,6-dimethyl-4-((triethylsilyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (507 mg, 1.38 mmol, intermediate 85) in dry MeCN (3.5 mL) cooled to -20 °C was added sodium azide (404 mg, 6.22 mmol) followed by a solution of cerium ammonium nitrate (2.27 g, 4.15 mmol) in CH_3CN (10.4 mL) dropwise. The reaction mixture was stirred at -20 °C for 1 hr, slowly warmed to 0 °C over 1 hr then quenched with water (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 3-azido-2,3-dimethyl-6-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)dihydro-2*H*-pyran-4(3*H*)-one as a white solid (187 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.78 (dd, *J* = 12.3, 3.2 Hz, 1H), 4.21 (s, 3H), 3.73 (dd, *J* = 12.3, 6.2 Hz, 1H), 3.13 (dd, *J* = 14.6, 12.3 Hz, 1H), 2.73 (dd, *J* = 14.6, 3.2 Hz, 1H), 1.44 (s, 3H), 1.41 (d, *J* = 6.1 Hz, 3H).

Intermediate 87 5-(5-Azido-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole



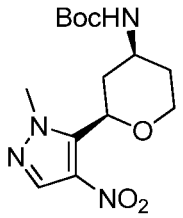
To a solution of 3-azido-2,3-dimethyl-6-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)dihydro-2*H*-pyran-4(3*H*)-one (335 mg,1.14 mmol, intermediate 86) in dry DCM (10 ml) was added a solution of deoxo-Fluor® (50% in THF, 830 mg, 1.88 mmol) and the mixture stirred at room temperature for 18 hr. Saturated aqueous $NaHCO_3$ solution (20 mL) and DCM (20 mL) were added. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (20% EtOAc/isohexane) gave 5-(5-azido-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (contaminated with some vinyl fluoride) as a pale yellow oil (157 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.69 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.13 (s, 3H), 3.76 (qd, *J* = 6.3, 1.6 Hz, 1H), 2.59-2.40 (m, 1H), 2.38-2.28 (m, 1H), 1.48 (s, 3H), 1.32 (d, *J* = 6.2 Hz, 3H).

Intermediate 88 *tert*-Butyl *N*-[2-bromo-4-[[5-[(2*S*,5*R*,6*R*)-5-(*tert*-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



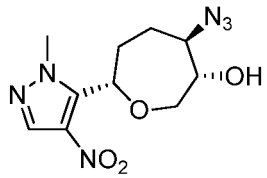
Following the procedure for Intermediate 65 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24) gave *tert*-butyl *N*-[2-bromo-4-[[5-[(2*S*,5*R*,6*R*)-5-(*tert*-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate as a solid (350 mg, 73% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 9.31 (s, 1H), 7.98 (s, 1H), 5.15-4.98 (m, 1H), 4.93 (d, *J* = 9.0 Hz, 1H), 4.77 (d, *J* = 8.7 Hz, 1H), 4.39-3.94 (m, 2H), 3.80 (s, 3H), 2.12-1.93 (m, 4H), 1.85 (d, *J* = 11.0 Hz, 1H), 1.52 (s, 9H), 1.46 (s, 9H).

Intermediate 89 *tert*-Butyl (2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydro-2*H*-pyran-4-yl)carbamate



To a solution of 2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-ol (450 mg, 1.98 mmol, Intermediate 39) in dry DCM (24 mL) at 0 °C was added Et_3N (0.33 mL, 2.97 mmol) followed by MsCl (0.44 mL, 4.0 mmol). The reaction mixture was stirred at 0 °C for 30 min then at room temperature for 18 hr. The mixture was re-cooled to 0 °C and quenched with aqueous saturated $NaHCO_3$ (10 mL). The organic layer was washed with 0.1 M HCl (5 mL), passed through a phase separation cartridge and concentrated under reduced pressure to give a colourless oil. This oil was dissolved in DMF (10 mL) and sodium azide (660 mg, 10 mmol) was added. The reaction mixture was heated at 110 °C for 2 hr behind a blast shield. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was washed with water (3 x 20 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure to give a colourless solid (220 mg). To a solution of this solid (220 mg, 0.87 mmol) in THF (2.5 mL) and water (0.5 mL) was added triphenylphosphine (344 mg, 1.31 mmol). The reaction mixture was heated at 65 °C behind a blast shield for 4 hr. The mixture was re-cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), treated with di-*tert*-butyl-dicarbonate (287 mg, 1.31 mmol) and DIPEA (0.44 mL, 2.62 mmol) and the reaction mixture stirred at room temperature for 16 hr. The mixture was concentrated under reduced pressure. Purification *via* silica gel column chromatography (30% EtOAc/isohexane) gave *tert*-butyl (2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydro-2*H*-pyran-4-yl)carbamate as a yellow oil (155 mg, 24% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.44 (d, J = 11.6 Hz, 1H), 4.52 (s, 1H), 4.19 (dd, J = 11.9, 4.6 Hz, 1H), 4.06 (s, 3H), 3.68-3.60 (m, 1H), 2.29 (d, J = 12.6 Hz, 1H), 2.03 (d, J = 8.4 Hz, 1H), 1.75 (s, 1H), 1.61-1.47 (m, 2H), 1.45 (s, 9H).

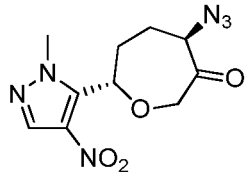
Intermediate 90 (3S,4R,7S)-4-azido-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-3-ol



To a solution of 5-(5,8-dioxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-pyrazole (2.7 g, 11.3 mmol, intermediate 19) in MeOH/water (60 mL/15 mL) was added ammonium chloride (1.51 g, 28.3 mmol) and sodium azide (3.67 g, 56.5 mmol). The mixture was heated at 70 °C

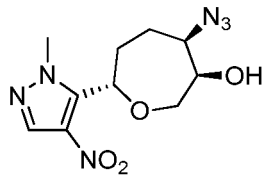
behind a blast shield for 4 hr. The MeOH was removed under reduced pressure and the aqueous residue extracted with EtOAc (100 mL). The organic layer was washed with aqueous $NaHCO_3$ (3 x 20 mL), passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) followed by chiral SFC chromatography gave (3S,4R,7S)-4-azido-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-3-ol as the second eluting isomer as a clear gum (1.4 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.43-5.37 (m, 1H), 4.18 (dd, J = 13.9, 2.1 Hz, 1H), 4.06 (s, 3H), 3.97-3.77 (m, 3H), 2.45 (d, J = 3.9 Hz, 1H), 2.32-2.09 (m, 2H), 2.10-1.85 (m, 2H).

Intermediate 91 (4*R*,7*S*)-4-Azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one



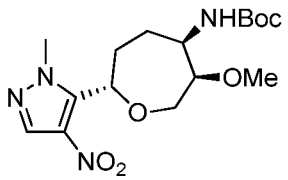
To a solution of (3S,4R,7S)-4-azido-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-3-ol (1.4 g, 4.96 mmol, intermediate 90) in DCM (35 mL) was added Dess-Martin peridionane (2.52 g, 5.96 mmol) and the mixture stirred at room temperature for 2 hr. Aqueous saturated $NaHCO_3$ (60 mL) and 20% sodium thiosulfate solution (50 mL) were added and the reaction mixture was stirred for 30 min until full dissolution of salts was observed. The organic layer was separated, dried over $MgSO_4$ and solvents removed under reduced pressure. Purification *via* silica gel column chromatography (0-40% EtOAc/isoHexane) gave (4*R*,7*S*)-4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one as an off-white solid (1.1 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.38 (dd, J = 10.2, 2.7 Hz, 1H), 4.62-4.49 (m, 2H), 4.31-4.22 (m, 1H), 4.08 (s, 3H), 2.31-2.17 (m, 3H), 2.15-2.04 (m, 1H).

Intermediate 92 (3*R*,4*R*,7*S*)-4-Azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol



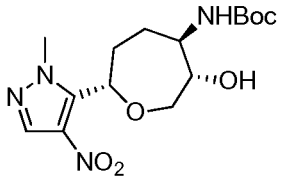
Following the procedure for Intermediate 57 starting from (4*R*,7*S*)-4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-one gave (3*R*,4*R*,7*S*)-4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol as a dark orange oil (850 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.68-5.60 (m, 1H), 4.24-4.14 (m, 3H), 4.01 (s, 3H), 3.72-3.58 (m, 1H), 2.45-2.31 (m, 1H), 2.30-2.09 (m, 2H), 2.01-1.81 (m, 2H).

Intermediate 93 *tert*-Butyl *N*-[(3*R*,4*R*,7*S*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate



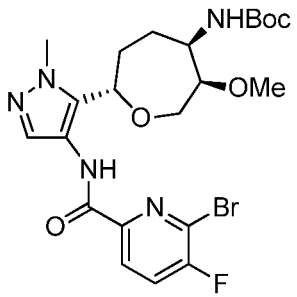
Following the procedure for Intermediate 58 starting from (3*R*,4*R*,7*S*)-4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol gave *tert*-butyl *N*-[(3*R*,4*R*,7*S*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate as a colourless oil (357 mg, 32% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 5.60-5.53 (m, 1H), 5.12-5.02 (m, 1H), 4.21-4.08 (m, 2H), 4.01 (s, 3H), 3.79 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.75-3.70 (m, 1H), 3.41 (s, 3H), 2.28-2.07 (m, 1H), 1.97-1.89 (m, 2H), 1.80-1.72 (m, 1H), 1.47 (s, 9H).

Intermediate 94 *tert*-Butyl ((3*S*,4*R*,7*S*)-3-hydroxy-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate



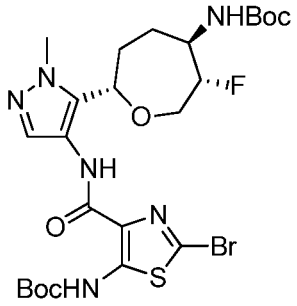
To a solution of (3*S*,4*R*,7*R*)-4-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-ol (Intermediate 90) (1.19 g, 4.22 mmol) in THF (50 mL) and water (10 mL) was added triphenylphosphine (1.22 g, 4.64 mmol) and the mixture heated at 70 °C for 24 hr. The mixture was diluted with EtOAc (100 mL) and washed with brine (2 x 25 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through an SCX column washing with MeOH and eluting with 3% 7 N NH_3 in MeOH/DCM to give an oil. This oil was dissolved in DCM (13.5 mL) and DIPEA (1.08 mL, 6.21 mmol) and di-*tert*-butyl-dicarbonate (1.36 g, 6.21 mmol) were added. The mixture was stirred at room temperature for 3 hr then concentrated under reduced pressure. Purification *via* silica gel chromatography (0-60% EtOAc/isohexane) gave *tert*-butyl ((3*S*,4*R*,7*S*)-3-hydroxy-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate (contaminated with some triphenylphosphine oxide) as a clear gum (895 mg, 60% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.42-5.36 (m, 1H), 4.83 (d, *J* = 6.7 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 2H), 4.08 (s, 3H), 3.86-3.76 (m, 3H), 2.18-2.07 (m, 1H), 2.02-1.89 (m, 3H), 1.47 (s, 9H).

Intermediate 95 *tert*-Butyl *N*-[(3*R*,4*R*,7*S*)-7-[4-[(6-bromo-5-fluoro-pyridine-2-carbonyl)amino]-2-methyl-pyrazol-3-yl]-3-methoxy-oxepan-4-yl]carbamate



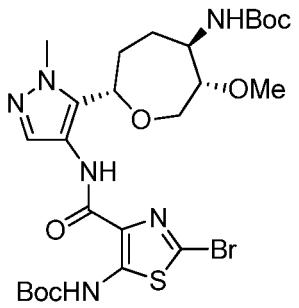
Following the procedure for Example 65, starting from *tert*-butyl *N*-[(3*R*,4*R*,7*S*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 93) and replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 6-bromo-5-fluoro-pyridine-2-carboxylic acid (see US2010/56576 A1) gave *tert*-butyl *N*-[(3*R*,4*R*,7*S*)-7-[4-[(6-bromo-5-fluoro-pyridine-2-carbonyl)amino]-2-methyl-pyrazol-3-yl]-3-methoxy-oxepan-4-yl]carbamate (contaminated with tetramethylurea) as a clear oil (169 mg, 30% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.26-8.17 (m, 2H), 7.63-7.55 (m, 1H), 5.02 (br s, 1H), 4.96 (dd, *J* = 9.0, 3.6 Hz, 1H), 4.32 (dd, *J* = 13.2, 4.4 Hz, 1H), 4.05-3.94 (m, 2H), 3.85-3.80 (m, 1H), 3.78 (s, 3H), 3.47 (s, 3H), 2.10-1.91 (m, 3H), 1.86-1.78 (m, 1H), 1.45 (s, 9H).

Intermediate 96 *tert*-Butyl *N*-[2-bromo-4-[[5-[(2*S*,5*R*,6*S*)-5-(*tert*-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



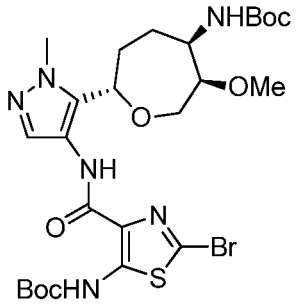
Following the procedure for Intermediate 65, starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80) gave *tert*-butyl *N*-[2-bromo-4-[[5-[(2*S*,5*R*,6*S*)-5-(*tert*-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate.

Intermediate 97 *tert*-Butyl N-[2-bromo-4-[[5-[(2*S*,5*R*,6*S*)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



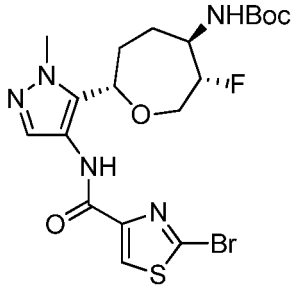
Following the procedure for Intermediate 65, starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 21) gave *tert*-Butyl N-[2-bromo-4-[[5-[(2*S*,5*R*,6*S*)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate.

Intermediate 98 *tert*-Butyl N-[2-bromo-4-[[5-[(2*S*,5*R*,6*R*)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate



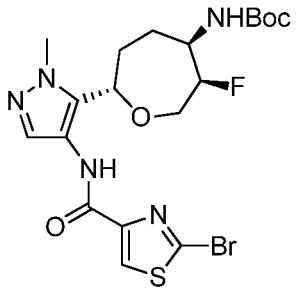
Following the procedure for Intermediate 65, starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 93) gave *tert*-Butyl N-[2-bromo-4-[[5-[(2*S*,5*R*,6*R*)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate.

Intermediate 99 *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate



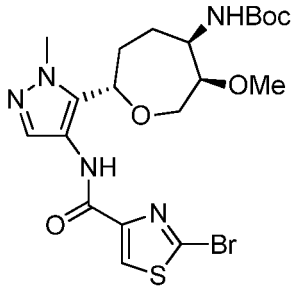
Following the procedure for Intermediate 65, starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80) and replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 2-bromothiazole-4-carboxylic acid (commercial) gave *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate.

Intermediate 100 *tert*-butyl ((3*R*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate



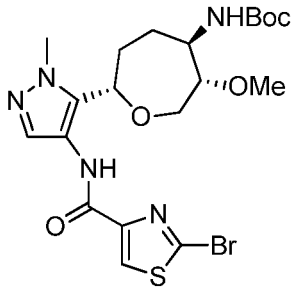
Following the procedure for Intermediate 65, starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24) and replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 2-bromothiazole-4-carboxylic acid (commercial) gave *tert*-butyl ((3*R*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate.

Intermediate 101 *tert*-butyl ((3*R*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate



Following the procedure for Intermediate 65, starting from *tert*-butyl ((3R,4R,7S)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 93) and replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 2-bromothiazole-4-carboxylic acid (commercial) gave *tert*-butyl ((3*R*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate.

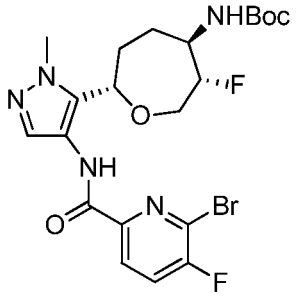
Intermediate 102 *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate



Following the procedure for Intermediate 65, starting from *tert*-butyl ((3S,4R,7S)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 21) and

replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 2-bromothiazole-4-carboxylic acid (commercial) gave *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate.

Intermediate 103 *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate



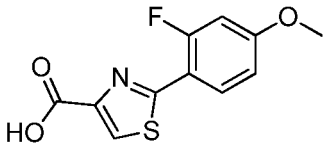
Following the procedure for Example 65, starting from *tert*-butyl *N*-[(3*S*,4*R*,7*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 80) and replacing 2-bromo-5-(tert-butoxycarbonylamino)thiazole-4-carboxylic acid with 6-bromo-5-fluoro-pyridine-2-carboxylic acid (see US2010/56576 A1) gave *tert*-butyl ((3*S*,4*R*,7*S*)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate.

Intermediate 104 2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxylic acid

To a solution of methyl 2-bromothiazole-4-carboxylate (3.27 mmol, 741 mg) in tetrahydrofuran (15 mL) and water (1.5 mL) was added 2,6-difluoro-4-methoxyphenylboronic acid (1.8 equiv., 5.88 mmol, 1160 mg) and potassium fluoride (3.3 equiv., 10.8 mmol, 627 mg). The mixture was degassed with nitrogen, then tris(dibenzylideneacetone)dipalladium(0) (0.2 equiv., 0.654 mmol, 617 mg) and tri-tert-butylphosphine (1.0 M in toluene; 0.4 equiv., 1.31 mmol, 1.3 mL) were added and the reaction mixture was heated under microwave at 100 °C for 30 minutes. The reaction mixture was concentrated and the residue was purified on silica eluted with 0 to 50% EtOAc in heptane to afford methyl 2-(2,6-difluoro-4-methoxy-phenyl)thiazole-4-carboxylate (2.40 mmol, 685 mg, 74% yield).

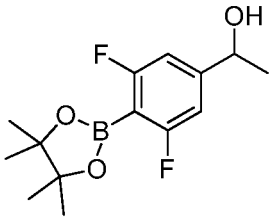
To a solution of methyl 2-(2,6-difluoro-4-methoxy-phenyl)thiazole-4-carboxylate (2.403 mmol, 685.5 mg) in methanol (15 mL) and water (5 mL) was added lithium hydroxide (1.9 equiv., 4.54 mmol, 111 mg) . The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with 1N HCl(aq.), then partitioned between EtOAc and brine. The organic layer was concentrated. The residue was dried on highvac to afford 2-(2,6-difluoro-4-methoxy-phenyl)thiazole-4-carboxylic acid (650 mg, quant.) as a brown solid.

Intermediate 105 2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxylic acid



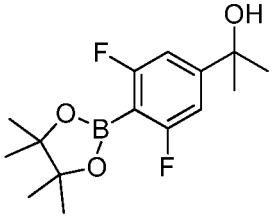
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 2-fluoro-4-methoxyphenylboronic acid gave the title compound.

Intermediate 106 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanol



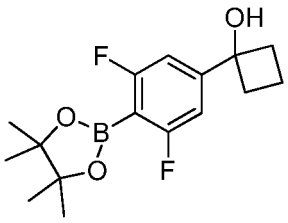
To a solution of 1-(3,5-difluorophenyl)ethanol (10.2 mmol, 1660 mg, commercial) in tetrahydrofuran (100 mL) at -78 °C was added n-butyllithium (2.5 mol/L) in hexane (2.4 equiv., 24.4 mmol, 9.8 mL) dropwise. The mixture was stirred at -78 °C for 2 hours. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.50 equiv., 25.4 mmol, 5.29 mL) was added, and the reaction mixture was stirred over night allowing to warm to room temperature. The reaction mixture was quenched with saturated $NaHCO_3$(aq.) And extracted with etoac. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and the filtrated was concentrated to afford the desired product which was used without further purification.

Intermediate 107 2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol



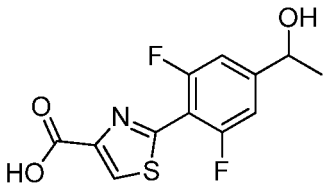
Following the procedure of Intermediate 106, replacing 1-(3,5-difluorophenyl)ethanol with 2-(3,5-difluorophenyl)propan-2-ol (see US2012/225062) provided the title compound.

Intermediate 108 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol



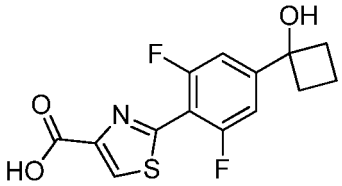
Following the procedure of Intermediate 106, replacing 1-(3,5-difluorophenyl)ethanol with 1-(3,5-difluorophenyl)cyclobutanol (see US2012/225062) provided the title compound.

Intermediate 109 2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid



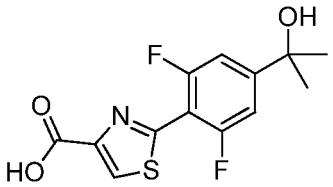
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanol (Intermediate 106) gave the title compound.

Intermediate 110 2-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxylic acid



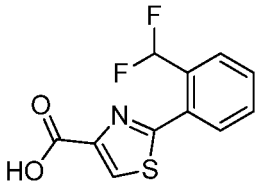
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol (Intermediate 108) gave the title compound.

Intermediate 111 2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxylic acid



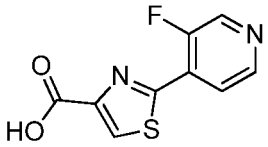
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (Intermediate 107) gave the title compound.

Intermediate 112 2-(2-(difluoromethyl)phenyl)thiazole-4-carboxylic acid



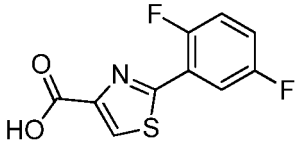
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2-(difluoromethyl)phenyl)boronic acid gave the title compound.

Intermediate 113 2-(3-fluoropyridin-4-yl)thiazole-4-carboxylic acid



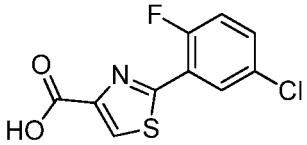
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (3-fluoropyridin-4-yl)boronic acid gave the title compound.

Intermediate 114 2-(2,5-difluorophenyl)thiazole-4-carboxylic acid



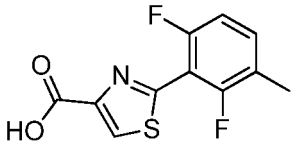
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2,5-difluorophenyl)boronic acid gave the title compound.

Intermediate 115 2-(5-chloro-2-fluorophenyl)thiazole-4-carboxylic acid



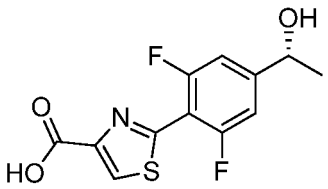
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (5-chloro-2-fluorophenyl)boronic acid gave the title compound.

Intermediate 116 2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxylic acid



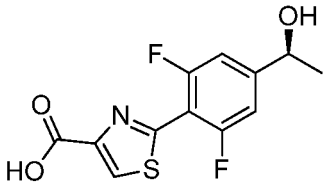
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2,6-difluoro-3-methylphenyl)boronic acid gave the title compound.

Intermediate 117 (R)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid



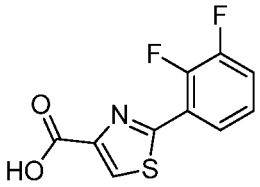
Following the procedure of Intermediate 109, replacing 1-(3,5-difluorophenyl)ethanol in step 1 (Intermediate 106) with (R)-1-(3,5-difluorophenyl)ethanol (commercial).

Intermediate 118 (S)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid



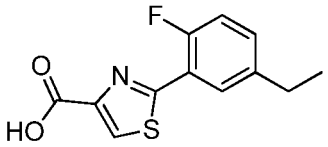
Following the procedure of Intermediate 109, replacing 1-(3,5-difluorophenyl)ethanol in step 1 (Intermediate 106) with (S)-1-(3,5-difluorophenyl)ethanol (commercial source).

Intermediate 119 2-(2,3-difluorophenyl)thiazole-4-carboxylic acid



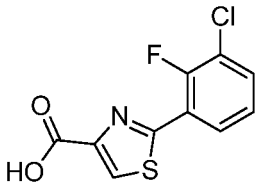
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2,3-difluorophenyl)boronic acid gave the title compound.

Intermediate 120 2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxylic acid



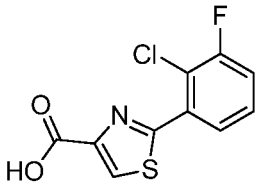
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (5-ethyl-2-fluorophenyl)boronic acid gave the title compound.

Intermediate 121 2-(3-chloro-2-fluorophenyl)thiazole-4-carboxylic acid



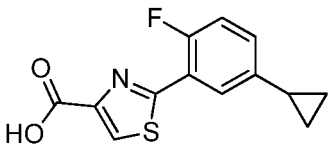
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (3-chloro-2-fluorophenyl)boronic acid gave the title compound.

Intermediate 122 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylic acid



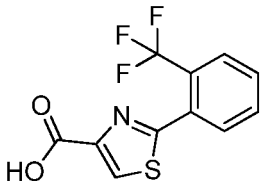
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2-chloro-3-fluorophenyl)boronic acid gave the title compound.

Intermediate 123 2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxylic acid



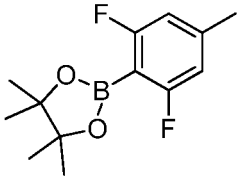
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (5-cyclopropyl-2-fluorophenyl)boronic acid gave the title compound.

Intermediate 124 2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid



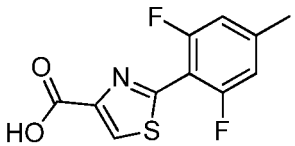
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2-(trifluoromethyl)phenyl)boronic acid gave the title compound.

Intermediate 125 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



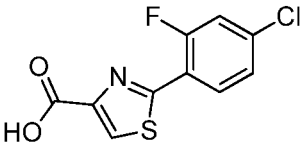
Following the procedure of Intermediate 106, replacing 1-(3,5-difluorophenyl)ethanol with 1,3-difluoro-5-methylbenzene, and reducing the number of equivalents of butyl lithium to 1.05 provided the title compound.

Intermediate 126 2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxylic acid



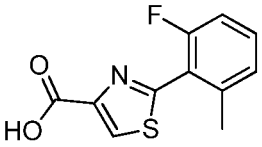
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 125) gave the title compound.

Intermediate 127 2-(4-chloro-2-fluorophenyl)thiazole-4-carboxylic acid



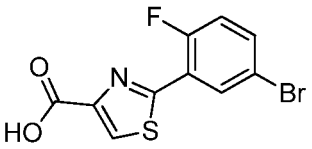
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (4-chloro-2-fluorophenyl)boronic acid gave the title compound.

Intermediate 128 2-(2-fluoro-6-methylphenyl)thiazole-4-carboxylic acid



Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2-fluoro-6-methylphenyl)boronic acid gave the title compound.

Intermediate 129 2-(5-bromo-2-fluorophenyl)thiazole-4-carboxylic acid



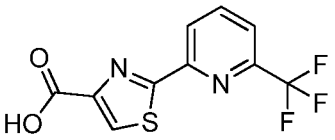
5-bromo-2-fluoro-benzonitrile (12.4 mmol, 2470 mg) in pyridine (6.5 mL) was treated with ammonium sulfide (40 mass% in water, 1.1 equiv., 13.6 mmol, 2.32 mL) and triethylamine (1.1 equiv. , 13.6 mmol, 1.90 mL). The reaction mixture was heated at 50 °C for 3 hours, then cooled to room temperature. The reaction mixture was partitioned between EtOAc and water. The organic later was washed with water (3x), and brine (3x), dried with $MgSO_4$, then concentrated. The residue was purified on silica eluted with 0 to 50% EtOAc in Heptane to provide 5-bromo-2-fluoro-benzenecarbothioamide (2.84 g, 94% yield).

A mixture of 5-bromo-2-fluoro-benzenecarbothioamide (11.8 mmol, 2840 mg) and ethyl bromopyruvate (1.05 equiv., 12.4 mmol, 1.56 mL) in ethanol (30 mL) was heated at 80 °C overnight. The mixture was concentrated and the residue was purified on silica eluted with 0 to 20% EtOAc in Heptane to afford ethyl 2-(5-bromo-2-fluoro-phenyl)thiazole-4-carboxylate (2960 mg, 76.14% Yield) as a clear oil.

To a solution of ethyl 2-(5-bromo-2-fluoro-phenyl)thiazole-4-carboxylate (8.97 mmol, 2960 mg) in methanol (40 mL) and water (10 mL) was added lithium hydroxide (1.6 equiv., 14.2 mmol, 347 mg) . The reaction mixture was stirred at 50 °C for 2 hours. The reaction

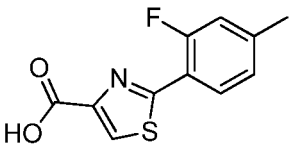
mixture was cooled to room temperature, concentrated, suspended in water, and then quenched with 2N HCl(aq.). The solid was collected, washed with water, and dried under high vacuum to afford 2-(5-bromo-2-fluoro-phenyl)thiazole-4-carboxylic acid (2410 mg, 89% Yield) as a white solid.

Intermediate 130 2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxylic acid



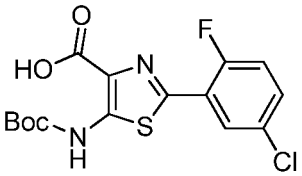
Following the procedure of Intermediate 129, replacing 5-bromo-2-fluoro-benzonitrile with 6-(trifluoromethyl)picolinonitrile gave the title compound.

Intermediate 131 2-(2-fluoro-4-methylphenyl)thiazole-4-carboxylic acid



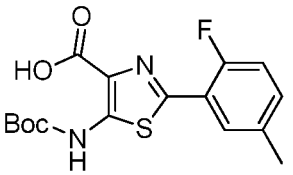
Following the procedure of Intermediate 129, replacing 5-bromo-2-fluoro-benzonitrile with 2-fluoro-4-methylbenzonitrile gave the title compound.

Intermediate 132 5-((tert-butoxycarbonyl)amino)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxylic acid



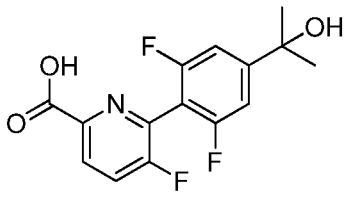
Following procedures from Examples 1-9, 5-chloro-2-fluorobenzoyl chloride was converted to the title compound.

Intermediate 133 5-((tert-butoxycarbonyl)amino)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxylic acid



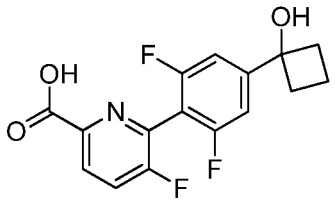
Following procedures from Examples 1-9, 2-fluoro-5-methylbenzoyl chloride was converted to the title compound.

Intermediate 134 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinic acid



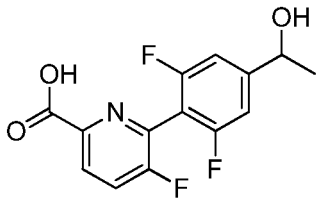
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (Intermediate 107) and replacing methyl 2-bromothiazole-4-carboxylate with methyl 6-bromo-5-fluoropicolinate (see US2012/225062) gave the title compound.

Intermediate 135 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinic acid



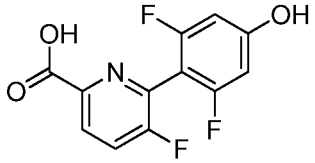
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol (Intermediate 108) and replacing methyl 2-bromothiazole-4-carboxylate with methyl 6-bromo-5-fluoropicolinate (see US2012/225062) gave the title compound.

Intermediate 136 6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinic acid



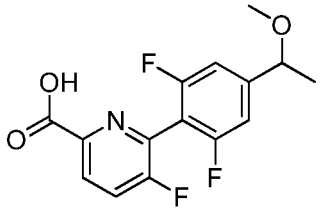
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanol (Intermediate 106) and replacing methyl 2-bromothiazole-4-carboxylate with methyl 6-bromo-5-fluoropicolinate (see US2012/225062) gave the title compound.

Intermediate 137 6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinic acid



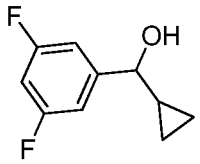
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with (2,6-difluoro-4-hydroxyphenyl)boronic acid and replacing methyl 2-bromothiazole-4-carboxylate with methyl 6-bromo-5-fluoropicolinate (see US2012/225062) gave the title compound.

Intermediate 138 6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinic acid



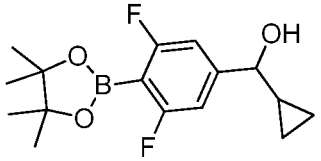
To a solution of methyl 6-[2,6-difluoro-4-(1-hydroxyethyl)phenyl]-5-fluoro-pyridine-2-carboxylate (1.21 mmol, 376 mg; penultimate intermediate en route to Intermediate 136) in N,N-dimethylformamide (50 mL) at 0 °C was added sodium hydride (60 mass% in mineral oil, 1.5 equiv., 1.81 mmol, 72.5 mg). The mixture was stirred for 2 minutes, then iodomethane (3.0 equiv., 3.62 mmol, 0.226 mL) was added. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica eluted with 0 to 50% EtOAc in Heptane to provide methyl 6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinate (392 mg, 63%). This ester was diluted with MeOH (15 mL) and water (5 mL) and lithium hydroxide (60 mg) was added. The mixture was stirred overnight at rt. The reaction was quenched by the addition of 1 N HCl(aq), then the mixture was diluted with EtOAc and washed with brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to provide the title compound (quant) which was used without purification.

Intermediate 139 cyclopropyl(3,5-difluorophenyl)methanol



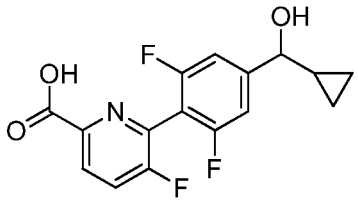
A solution of 3,5-difluorobenzaldehyde (1.0 g, 7.0 mmol) was dissolved in tetrahydrofuran (10 mL) was cooled in an ice bath. cyclopropylmagnesium bromide (0.5 M in THF, 1.2 equiv., 8.4 mmol) was added slowly and the mixture was stirred at 0 °C for 60 min. The reaction was quenched with sat. ammonium chloride and extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the title compound of sufficient purity to be used directly.

Intermediate 140 cyclopropyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



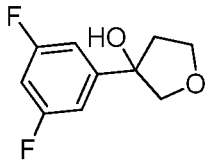
Following the procedure of Intermediate 106, replacing 1-(3,5-difluorophenyl)ethanol with cyclopropyl(3,5-difluorophenyl)methanol (Intermediate 139) provided the title compound.

Intermediate 141 6-(4-(cyclopropyl(hydroxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinic acid



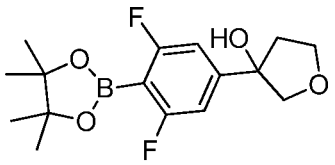
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with cyclopropyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (Intermediate 141) and replacing methyl 2-bromothiazole-4-carboxylate with methyl 6-bromo-5-fluoropicolinate (see US2012/225062) gave the title compound.

Intermediate 142 3-(3,5-difluorophenyl)tetrahydrofuran-3-ol



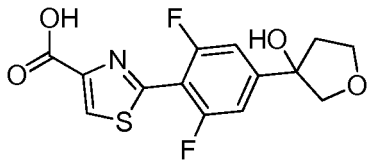
to a solution of 1-bromo-3,5-difluoro-benzene (4.00 g, 20.7 mmol) in tetrahydrofuran (70 mL) under nitrogen was added magnesium (6.0 equiv., 124 mmol) and the solution was heated at 85 °C for three hours. The solution was cooled to rt and 3-oxotetrahydrofuran (1 equiv., 20.726 mmol) in THF (20 mL) was added via syringe. The mixture was stirred at rt for three days. The reaction was quenched with sat $NaHCO_3$, extracted with EtOAc and washed with brine. Purification by CombiFlash (0 to 100% EtOAc in heptane) provided the title compound (405 mg, 9.7%).

Intermediate 143 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydrofuran-3-ol



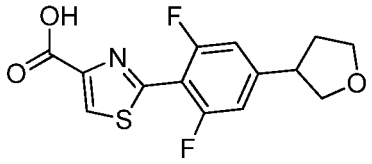
Following the procedure of Intermediate 106, replacing 1-(3,5-difluorophenyl)ethanol with 3-(3,5-difluorophenyl)tetrahydrofuran-3-ol methanol (Intermediate 142) provided the title compound.

Intermediate 144 2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxylic acid



Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydrofuran-3-ol (Intermediate 143) gave the title compound.

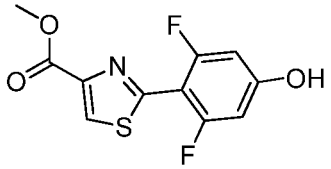
Intermediate 145 2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxylic acid



To a solution of methyl 2-[2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl]thiazole-4-carboxylate (250 mg, 0.732 mmol, precursor to Intermediate 144) in dichloromethane (1 mL) was added TRIFLUOROACETIC ACID (1 mL) The mixture was heated at 120 °C in microwave for 2 h. After in vacuo concentration, purification by CombiFlash (0 to 100% EtOAC in heptane) provided methyl 2-(4-(2,5-dihydrofuran-3-yl)-2,6-difluorophenyl)thiazole-4-carboxylate (57 mg, 24% yield) as a mixture of olefin isomers.

This mixture was diluted with 30 mL MeOH and ran through an H-cube hydrogenator (1 mL/min, 60 bar, 70 deg C) to provide, after concentration, methyl 2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxylate (44 mg). This ester was diluted with THF (3 mL) and water (1.5 mL) and LiOH (6.5 mg, 2.0 equiv.) was added. After stirring for 2.5 hours at rt, the mixture was neutralized with 1 N HCl(aq), diluted with EtOAc and washed with brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to provide the title compound (42 mg, quant).

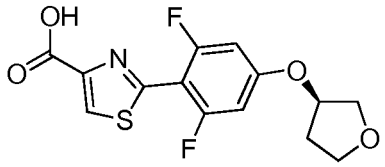
Intermediate 146 methyl 2-(2,6-difluoro-4-hydroxyphenyl)thiazole-4-carboxylate



To a suspension of methyl 2-bromothiazole-4-carboxylate (500 mg, 2.16 mmol) , 2,6-difluoro-4-hydroxyphenylboronic acid (2 equiv., 767 mg) and potassium fluoride (3.3 equiv., 414 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added bis(tri-tert-butylphosphine)palladium(0) (0.1 equiv., 110 mg) and the mixture was heated to 120 °C for 15 min in the microwave reactor. After in vacuo concentration, the reaction mixture was purified by CombiFlash (0 to 100% EtOAc in heptane) to provide 241 mg of the title compound as a ~1:1

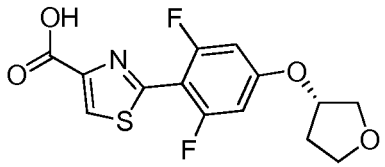
mixture with methyl 2-bromothiazole-4-carboxylate, which was used directly without further purification.

Intermediate 147 (R)-2-(2,6-difluoro-4-((tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxylic acid



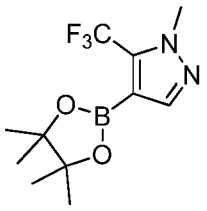
To a solution of methyl 2-(2,6-difluoro-4-hydroxy-phenyl)thiazole-4-carboxylate (207 mg, 0.763 mmol) and (R)-3-hydroxytetrahydrofuran (3 equiv., 206 mg) in tetrahydrofuran (5 mL) was added triphenylphosphine (3 equiv., 600 mg) and diisopropyl azodicarboxylate (3 equiv., 0.45 mL) The mixture was stirred at RT for 2 days. The mixture was concentrated and partitioned between EtOAc and water. The organic layer was washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. This residue was diluted with THF (3 mL) and water (1 mL) and LiOH (36 mg) was added. After stirring at rt for 2.5 hours, the reaction was neutralized with 1 N HCl(aq), diluted with EtOAc and washed with brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to provide the title compound, contaminated with triphenylphosphine oxide, and other by-products, which was used without further purification.

Intermediate 148 (S)-2-(2,6-difluoro-4-((tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxylic acid



Following the procedure for Intermediate 147, replacing (R)-3-hydroxytetrahydrofuran with (S)-3-hydroxytetrahydrofuran provided the title compound.

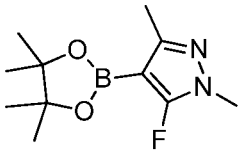
Intermediate 149 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-pyrazole



In a microwave reaction vial, 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (520 mg, 2.27 mmol, commercial), bis(pinacolato)diboron (1.3 equiv., 749 mg), bis(triphenylphosphine)palladium(II) dichloride (0.05 equiv., 79 mg) and POTASSIUM ACETATE (2 equiv., 4445 mg) were dissolved in toluene (15 mL). The mixture was heated in a

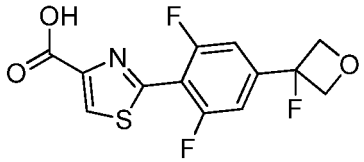
microwave reactor to 150 °C for 10 min. After cooling to rt, the mixture was filtered over celite (EtOAc rinse). The filtrate was concentrated to give the title compound of sufficient purity to be used directly.

Intermediate 150 5-fluoro-1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



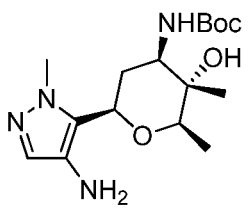
Following the procedure of Intermediate 149, replacing 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole with 4-bromo-5-fluoro-1,3-dimethyl-1H-pyrazole (commercial) provided the title compound.

Intermediate 151 2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxylic acid



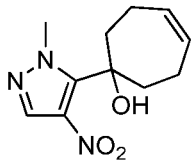
Following the procedure of Intermediate 104, replacing 2,6-difluoro-4-methoxyphenylboronic acid with 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-ol (see US2012/225062) gave the title compound, after adding the following fluorination step prior to ester hydrolysis: A solution of methyl 2-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)thiazole-4-carboxylate (50 mg) in dichloromethane (5 mL) was cooled to -78 °C, then deoxo-fluor (1.5 equiv., 50 wt% solution in toluene) was added. The mixture was allowed to slowly warm to rt over 30 minutes. The reaction was then quenched by the addition of sat. $NaHCO_3$(aq), then the mixture was diluted with EtOAc and washed with brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by CombiFlash (0 to 100% EtOAc in heptane) provided methyl 2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxylate.

Intermediate 152 tert-butyl ((2R*,3S*,4R*,6R*)-6-(4-amino-1-methyl-1H-pyrazol-5-yl)-3-hydroxy-2,3-dimethyltetrahydro-2H-pyran-4-yl)carbamate (racemic)



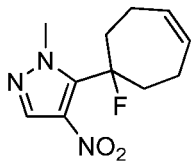
Prepared in an analogous manner to tert-butyl ((2R*,3S*,4R*,6R*)-6-(3-aminopyridin-4-yl)-3-hydroxy-2,3-dimethyltetrahydro-2H-pyran-4-yl)carbamate (WO2012/004217), replacing 3-nitroisonicotinaldehyde with 1-methyl-4-nitro-1H-pyrazole-5-carbaldehyde (Intermediate 3).

Intermediate 153 (*Z*)-1-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)cyclohept-4-enol



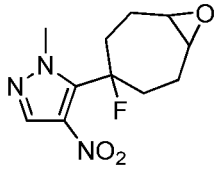
To a solution of 1-methyl-4-nitro-1*H*-pyrazole (1.5 g, 11.8 mmol) and (*Z*)-cyclohept-4-enone (1.4 g, 13.0 mmol) in dry THF (30 mL) under nitrogen cooled to -78 °C was added dropwise a solution of lithium hexamethyldisilazide (1.0 M in THF, 30 mL, 29.5 mmol). The reaction mixture was allowed to warm to -40 °C and stirred for 90 min. Saturated aqueous ammonium chloride solution (30 mL) was added (dropwise initially) and the mixture was allowed to warm to room temperature and extracted with EtOAc (150 mL). The organic layer was washed with water (30 mL), washed with brine (20 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel column chromatography (20-25% EtOAc) gave (*Z*)-1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)cyclohept-4-enol as a tan oil (1.37 g, 49%).

Intermediate 154 (*Z*)-5-(1-Fluorocyclohept-4-enyl)-1-methyl-4-nitro-1*H*-pyrazole



To a solution of (*Z*)-1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)cyclohept-4-enol (1.35 g, 5.70 mmol) in dry DCM (60 mL) was added dropwise a solution of deoxo-Fluor® (50% in THF, 6.2 mL, 17.1 mmol) and the reaction mixture was stirred at room temperature for 90 min. The mixture was cooled to 0 °C and saturated aqueous $NaHCO_3$ solution (70 mL) was added, dropwise initially, and extracted with DCM (100 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. Purification *via* silica gel column chromatography (15-20% EtOAc/hexane) gave (*Z*)-5-(1-fluorocyclohept-4-enyl)-1-methyl-4-nitro-1*H*-pyrazole as an off-white solid (615 mg, 45%).

Intermediate 155 5-(4-Fluoro-8-oxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-1*H*-pyrazole



To a solution of (*Z*)-5-(1-fluorocyclohept-4-enyl)-1-methyl-4-nitro-1*H*-pyrazole (900 mg, 3.77 mmol) in DCM (30 mL) at 0 °C was added portionwise *meta*-chloroperoxybenzoic acid (1.0 g, 4.14 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 90 min before being quenched with a saturated solution of sodium hydrogencarbonate (30 mL). The mixture was extracted with DCM (100 mL), washed with aqueous 2 M NaOH (2 x 50 mL) and brine (30 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to give 5-(4-fluoro-8-oxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-1*H*-pyrazole as a colourless solid (982 mg, quantitative) as a 2:5 ratio of diastereomers.

TABLE 1a and 1b FORMULA I COMPOUNDS

Example 101 5-amino-2-(2,6-difluorophenyl)-N-[5-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **101**

A mixture of *tert*-butyl (4-((5-chloro-1-methyl-1*H*-pyrazol-4-yl)carbamoyl)-2-(2,6-difluorophenyl)thiazol-5-yl)carbamate (234 mg, 0.5 mmol), potassium fluoride dihydrate (155 mg, 1.65 mmol) and 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (210 mg, 1.0 mmol) in THF (5 mL) was degassed by bubbling nitrogen through it for 15 min. Tris(dibenzylideneacetone)dipalladium/tri-*tert*-butyl phosphonium tetrafluoroborate mixture (mole ratio: 1/1.2, 60 mg, 0.05 mmol) was added and the mixture degassed for a further 10 min before being heated in a microwave at 110 °C for 8 hr. Water (10 mL) was added and the mixture extracted with EtOAc (3 x 5 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. The residue was purified *via* silica gel chromatography (isohexane then 0-5% MeOH/EtOAc). The resulting intermediate was dissolved in MeOH (5 mL) and treated with a solution of HCl in dioxane (4 M, 5 mL). The mixture was stirred at room temperature for 16 hr and the solvent removed under reduced pressure. Purification *via* preparative HPLC gave **101** as a brown solid (37 mg, 17% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.05 (s, 1H), 7.38-7.26 (m, 1H), 7.06-6.97 (m, 2H), 6.13 (s, 2H), 6.03-6.00 (m, 1H), 4.41 (d, J = 2.8 Hz, 1H), 4.39 (d, J = 2.8 Hz, 1H), 3.96 (t, J = 5.3 Hz, 2H), 3.83 (s, 3H), 2.45-2.41 (m, 2H). LCMS (ES+) m/z 418 (M+1).

Example 102 5-amino-2-(2,6-difluorophenyl)-N-[5-(3,4-dihydro-2H-pyran-6-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **102**

Following the procedure for Example 101 starting from *tert*-butyl (4-((5-chloro-1-methyl-1*H*-pyrazol-4-yl)carbamoyl)-2-(2,6-difluorophenyl)thiazol-5-yl)carbamate and 3,4-dihydro-2*H*-pyran-6-boronic acid pinacol ester gave **102** as a white solid (25 mg, 8% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.18 (s, 1H), 7.34-7.28 (m, 1H), 7.06-6.98 (m,

2H), 6.13 (s, 2H), 5.11 (t, J = 3.9 Hz, 1H), 4.25 (t, J = 5.1 Hz, 2H), 3.89 (s, 3H), 2.32-2.26 (m, 2H), 2.03-1.96 (m, 2H). LCMS (ES+) m/z 418 (M+1).

Example 103 5-amino-2-(2,6-difluorophenyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **103**

A mixture of *tert*-butyl (4-((5-chloro-1-methyl-1*H*-pyrazol-4-yl)carbamoyl)-2-(2,6-difluorophenyl)thiazol-5-yl)carbamate (234 mg, 0.5 mmol), potassium fluoride dihydrate (155 mg, 1.65 mmol) and 3,4-dihydro-2*H*-pyran-6-boronic acid pinacol ester (210 mg, 1.0 mmol) in THF (5 mL) was degassed by bubbling nitrogen through it for 15 min. Tris(dibenzylideneacetone)dipalladium/tri-*tert*-butyl phosphonium tetrafluoroborate mixture (mole ratio: 1/1.2, 60 mg, 0.05 mmol) was then added and the mixture degassed for a further 10 min before being heated in a microwave at 85 °C for 6 hr. Water (10 mL) was added and the mixture extracted with EtOAc (3 x 5 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-100% EtOAc/isohexane) gave a white solid (269 mg, 0.52 mmol). This was dissolved in DCM (20 mL) and EtOH (10 mL) and passed through the H-Cube® (full H_2, 100 °C, flow rate: 1 mL/min, 30 mm 10% Raney Nickel cartridge). Removal of the solvent under reduced pressure gave *tert*-butyl 2-(2,6-difluorophenyl)-4-(5-(2-ethoxytetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-ylcarbamoyl)thiazol-5-ylcarbamate as a white solid (250 mg, 92%). This solid was dissolved in MeOH (5 mL) and a solution of HCl in dioxane (4 M, 5 mL) and stirred at room temperature for 16 hr. Purification *via* silica gel chromatography (0-5% MeOH/DCM) and preparative HPLC gave **103** as a white solid (31 mg, 10% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.34 (s, 1H), 7.35-7.26 (m, 1H), 7.05-6.97 (m, 2H), 6.19 (s, 2H), 4.03 (dd, J = 11.1, 4.5 Hz, 1H), 3.92 (s, 3H), 3.92-3.78 (m, 1H), 3.16 (s, 3H), 2.15-2.05 (m, 1H), 2.03-1.89 (m, 1H), 1.92-1.64 (m, 4H). LCMS (ES+) m/z 450 (M+1).

Example 104 5-amino-2-(2,6-difluorophenyl)-N-(1-methyl-5-tetrahydropyran-2-yl-pyrazol-4-yl)thiazole-4-carboxamide **104**

10% Palladium on carbon (43 mg, 0.4 mmol) was added to a solution of 5-(3,4-dihydro-2*H*-pyran-6-yl)-1-methyl-4-nitro-1*H*-pyrazole (209 mg, 1.0 mmol) and ammonium formate (465 mg, 8.0 mmol) in MeOH (20 mL) under nitrogen and the mixture heated at 80 °C for 2 hr. The mixture was filtered through Celite® to remove the catalyst and the resulting solution passed through the H-Cube (70 bar H_2, 70 °C, flow rate: 1 mL/min, 10% Pt/C cartridge). The solvent was removed under reduced pressure to give a red gum (170 mg). This was dissolved in DCM (5 mL) and DIPEA (0.13 mL, 0.74 mmol) and added to a solution of PyBOP (335 mg, 0.64 mmol) and 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (180 mg, 0.506 mmol) in DCM (5 mL), which had been stirring at room temperature for 30 min. The

mixture was stirred at room temperature for 16 hr before being diluted with DCM (5 mL) and washed with water (3 x 5 mL). The organic layer was separated, passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-100% EtOAc/isohexane) gave a yellow gum (40 mg). This gum was dissolved in a solution of HCl in dioxane (4 M, 5 mL) and MeOH (5 mL) and stirred at room temperature for 3 hr. The solvents were removed under reduced pressure and the residue purified *via* preparative HPLC to give **104** as a white solid (15 mg, 7% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.14 (s, 1H), 7.34-7.24 (m, 1H), 7.04-6.96 (m, 2H), 6.18 (s, 2H), 4.66-4.56 (m, 1H), 4.29 (dd, J = 11.4, 4.2 Hz, 1H), 3.81 (s, 3H), 3.59 (ddd, J = 12.2, 11.4, 2.1 Hz, 1H), 1.98-1.92 (m, 1H), 1.90-1.71 (m, 3H), 1.71-1.58 (m, 2H). LCMS (ES+) m/z 420 (M+1).

Example 105 5-amino-2-(3-fluoro-2-pyridyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **105**

A solution of 5-(3,4-dihydro-2*H*-pyran-6-yl)-1-methyl-4-nitro-1*H*-pyrazole (209 mg, 1.0 mmol) in MeOH (20 mL) was passed through the H-Cube (Full H_2 mode, 70 °C, flow rate: 1 mL/min, 30 mm 10% Pd/C cartridge). No reaction occurred so to the solution was added 10% palladium on carbon (43 mg, 0.4 mmol) and ammonium formate (465 mg, 8.0 mmol). The mixture was heated at 80 °C under nitrogen for 2 hr. The mixture was filtered through Celite® to remove the catalyst and the resulting solution passed through the H-Cube (70 bar H_2, 70 °C, flow rate: 1 mL/min, 10% Pt/C cartridge). The solvent was removed under reduced pressure to give a red gum (170 mg). This gum (170 mg, 0.48 mmol) was dissolved in DCM (5 mL) and DIPEA (0.13 mL, 0.77 mmol) and added to a solution of PyBOP (350 mg, 0.67 mmol) and 5-(*tert*-butoxycarbonylamino)-2-(3-fluoro-2-pyridyl)thiazole-4-carboxylic acid (179 mg, 0.53 mmol) in DCM (5 mL), which had been stirring at room temperature for 30 min. The mixture was stirred at room temperature for 60 hr, diluted with DCM (5 mL) and washed with water (3 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-100% EtOAc/isohexane) gave a yellow gum. This gum was dissolved in a solution of HCl in dioxane (4 M, 5 mL) and MeOH (5 mL) and stirred at room temperature for 60 hr. The solvents were removed under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave **105** as a pale yellow solid (27 mg, 12% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.39-8.34 (m, 2H), 7.50 (t, J = 9.5 Hz, 1H), 7.33-7.20 (m, 1H), 6.36 (s, 2H), 4.15 (dd, J = 11.1, 4.3 Hz, 1H), 3.95-3.84 (m, 4H), 3.17 (s, 3H), 2.11 (d, J = 12.9 Hz, 1H), 2.04-1.66 (m, 5H). LCMS (ES+) m/z 433 (M+1).

Example 106 5-amino-2-(2,6-difluorophenyl)-N-(5-((1S,4S,5S)-4-hydroxy-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **106**

To a solution of 5-(4-fluoro-8-oxabicyclo[5.1.0]octan-4-yl)-1-methyl-4-nitro-1*H*-pyrazole (100 mg, 0.39 mmol) in THF (25 mL) and water (5 mL) was added 10% palladium on carbon (10 mg). The mixture was heated at 40 °C under an atmosphere of H_2 (400 psi) for 3 hr. The mixture was filtered through Celite® washing with MeOH (30 mL) and concentrated under reduced pressure to give 5-(4-amino-1-methyl-1*H*-pyrazol-5-yl)-8-oxabicyclo[3.2.1]octan-2-ol as an orange solid (105 mg, quantitative). This solid (105 mg, 0.44 mmol) was dissolved in DCM (20 mL) and DIPEA (1 mL, 5.74 mmol) was added, followed by 5-(*tert*-butoxycarbonylamino)-2-(2,6-difluorophenyl)-thiazole-4-carboxylic acid (161 mg, 0.45 mmol) and PyBOP (535 mg, 1.03 mmol). The reaction mixture was stirred at room temperature for 18 hr before being quenched with water (20 mL), extracted with DCM (100 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (80-100% EtOAc/isohexane) gave *tert*-butyl 2-(2,6-difluorophenyl)-4-(5-(4-hydroxy-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1*H*-pyrazol-4-ylcarbamoyl)thiazol-5-ylcarbamate as a colourless oil (635 mg, 54%). To a solution of this oil (160 mg, 0.28 mmol) in MeOH (5 mL) was added HCl in dioxane (4 M, 3.6 mL, 14.4 mmol). The reaction mixture was stirred at room temperature for 18 hr. The solvents were removed under reduced pressure before being purified *via* preparative HPLC, then dissolved in $CHCl_3$/MeOH mixture (10 mL) and passed through an SCX cartridge, eluting with 3N NH_3 in MeOH. The solvents were removed under reduced pressure to give **106** as a pale pink solid (31 mg, 24% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.25 (s, 1H), 7.32-7.26 (m, 1H), 7.02 (t, J = 8.8 Hz, 2H), 6.12 (s, 2H), 4.59-4.55 (m, 1H), 4.12-4.05 (m, 1H), 3.85 (s, 3H), 2.42-2.33 (m, 1H), 2.22-1.89 (m, 6H), 1.62-1.56 (m, 1H), 1.50-1.45 (m, 1H). LCMS (ES+) m/z 462 (M+1).

Example 107 5-amino-N-(5-((1S,4S,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **107**

To a solution of *tert*-butyl *N*-(2-(2,6-difluorophenyl)-4-((1-methyl-5-(2-((2,2,2-trifluoroacetyl)amino)-8-oxabicyclo[3.2.1]octan-5-yl)pyrazol-4-yl)carbamoyl)thiazol-5-yl)carbamate (58 mg, 0.08 mmol) in MeOH (2 mL) was added a solution of HCl in dioxane (4 M, 1.1 mL, 4.42 mmol). The reaction mixture was stirred at room temperature for 16 hr and concentrated under reduced pressure to give a beige solid. This solid was dissolved in MeOH (5 mL) and water (5 mL) and potassium carbonate (61 mg, 0.44 mmol) added. The reaction mixture was heated at reflux for 3 hr, cooled to room temperature and the MeOH was removed under reduced pressure. The aqueous layer was extracted with 5% MeOH in DCM (2 x 25 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* preparative HPLC gave the formate salt of **107** as a white solid (11 mg, 27% over two steps). ^{1}H NMR (400 MHz, d_4-MeOD) δ 8.53 (s, 1H), 8.11 (s, 1H), 7.47-7.43 (m, 1H),

7.18 (t, J = 8.9 Hz, 2H), 4.68 (s, 1H), 3.89 (s, 3H), 3.52-3.41 (m, 1H), 2.65-2.52 (m, 1H), 2.29-2.04 (m, 5H), 2.00-1.92 (m, 1H), 1.82-1.76 (m, 1H). LCMS (ES+) m/z 461 (M+1).

Example 108 5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,7R)-5-hydroxy-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **108**

A solution of 2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol (79 mg, 0.30 mmol) in MeOH (20 mL) was passed through the H-Cube® (full H_2, 70 °C, flow rate: 1 mL/min, 30 mm 20% $Pd(OH)_2$/C cartridge). The solvent was removed under reduced pressure and the crude residue was re-dissolved in MeOH (1 mL). 5-Amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (94 mg, 0.37 mmol) and DIPEA (0.24 mL, 1.40 mmol) were added. Propylphosphonic anhydride solution (0.19 mL, 50% wt in EtOAc, 0.39 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL). The organic layer was washed with 1 M aqueous NaOH (3 x 10 mL), 1 M aqueous HCl (2 x 10 mL) and brine (10 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-5% 7 M NH_3 in MeOH/DCM) gave **108** as a white solid (4 mg, 3% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 11.8 Hz, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.37-7.30 (m, 1H), 7.04-6.97 (m, 2H), 6.15 (s, 2H), 5.00-4.93 (m, 1H), 4.17 (s, 1H), 4.03 (dd, J = 8.0, 6.9 Hz, 1H), 3.77 (s, 3H), 2.11-1.74 (m, 5H), 1.28 (d, J = 3.3 Hz, 1H), 1.21 (dd, J = 9.2, 6.3 Hz, 3H). Alkyl OH not observed. LCMS (ES+) m/z 464 (M+1).

Example 109 5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **109**

Chiral separation of **106** by SFC gave **109**. 1H NMR (400 MHz, DMSO) δ 10.03 (s, 1H), 8.00 (s, 1H), 7.56 – 7.41 (m, 3H), 7.28 (t, J = 8.9 Hz, 2H), 4.92 (d, J = 4.5 Hz, 1H), 4.40 – 4.30 (m, 1H), 3.77 (s, 3H), 3.76 – 3.69 (m, 1H), 2.49 – 2.38 (m, 1H), 2.17 – 2.08 (m, 1H), 2.05 – 1.74 (m, 4H), 1.71 – 1.43 (m, 2H). LCMS (ES+) m/z 462 (M+1).

Example 110 5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **110**

Chiral separation of **106** by SFC gave **110**. 1H NMR (400 MHz, DMSO) δ 10.03 (s, 1H), 8.00 (s, 1H), 7.59 – 7.41 (m, 3H), 7.28 (t, J = 8.9 Hz, 2H), 4.92 (d, J = 4.4 Hz, 1H), 4.42 – 4.29 (m, 1H), 3.77 (s, 3H), 3.76 – 3.66 (m, 1H), 2.49 – 2.37 (m, 1H), 2.17 – 2.06 (m, 1H), 2.04 – 1.75 (m, 4H), 1.71 – 1.43 (m, 2H). LCMS (ES+) m/z 462 (M+1)

Example 111 5-amino-2-(2,6-difluorophenyl)-N-(5-((5R,6S)-5,6-dihydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **111**

A solution of 7-(2-methyl-4-nitro-pyrazol-3-yl)oxepane-3,4-diol (Intermediate 10) (165 mg, 0.64 mmol) in MeOH (13 mL) was passed through the H-Cube (full H_2 mode, 80 °C, flow

rate: 1 mL/min, 30 mm 10% Pd/C cartridge). The solvent was removed under reduced pressure. To a solution of the resulting amine in DCM (10 mL) was added DIPEA (0.33 mL, 1.92 mmol), PyBOP (499 mg, 0.96 mmol) and 5-(*tert*-butoxycarbonylamino)-2-(2,6-difluorophenyl)-thiazole-4-carboxylic acid (249 mg, 0.70 mmol). The mixture was stirred at room temperature for 18 hr, diluted with DCM (5 mL) and washed with water (3 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-10% MeOH/EtOAc) gave a pink solid. This solid (65 mg, 0.11 mmol) was dissolved in a solution of HCl in dioxane (4 M, 8.6 mL) and MeOH (2 mL) and stirred at room temperature for 18 hr. The solvents were removed under reduced pressure. Purification *via* preparative HPLC gave **111** as an off-white solid (28 mg, 9% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (br s, 1H), 8.17 (s, 1H), 7.39-7.32 (m, 1H), 7.10-7.00 (m, 2H), 6.25 (br s, 2H), 5.14-5.10 (m, 1H), 4.23 (dd, J = 13.7, 4.0 Hz, 1H), 3.90-3.85 (m, 1H), 3.79 (s, 3H), 3.75-3.56 (m, 2H), 2.12-2.00 (m, 3H), 1.76-1.70 (m, 1H). OH protons not observed. LCMS (ES+) m/z 466 (M+1).

Example 112 5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **112**

A solution of *N*-(2-ethyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide (118 mg, 0.31 mmol) in MeOH (20 mL) was passed through the H-Cube® (full H_2, 60 °C, flow rate: 1 mL/min, 30 mm 20% $Pd(OH)_2$/C cartridge). The solvent was removed under reduced pressure and the crude residue was re-dissolved in MeOH (1 mL). 5-(*tert*-Butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (119 mg, 0.33 mmol) was added followed by DIPEA (0.16 mL, 0.95 mmol) and the reaction mixture was heated at 50 °C for 15 min. After cooling to room temperature, propylphosphonic anhydride solution (0.17 mL, 50% wt in EtOAc, 0.34 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL), washed with 1 M aqueous NaOH (3 x 10 mL), 1 M aqueous HCl (2 x 10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure and purified *via* silica gel chromatography (0-10% 7 M ammonia in MeOH/DCM) to give an oil as a mixture of isomers. This oil was dissolved in MeOH (2 mL) and HCl in dioxane (4 M, 4.0 mmol, 1 mL) was added. The reaction mixture was stirred at room temperature for 18 hr and the solvents removed under reduced pressure. Purification *via* chiral preparative HPLC gave **112** as a white solid (9 mg, 5% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.15 (s, 1H), 7.34 (tt, J = 8.4, 6.1 Hz, 1H), 7.05-6.97 (m, 2H), 6.16 (s, 2H), 4.80 (dd, J = 8.2, 3.9 Hz, 1H), 3.77 (s, 3H), 3.71-3.62 (m, 1H), 3.39-3.32

(m, 1H), 2.18-2.09 (m, 1H), 2.08-1.98 (m, 1H), 1.93-1.74 (m, 2H), 1.71-1.57 (m, 3H), 1.46-1.33 (m, 3H), 0.81 (t, J = 7.4 Hz, 3H). LCMS (ES+) m/z 477 (M+1).

Example 113 5-amino-N-(5-((2R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **113**

Following the procedure for Example 112 starting from *N*-(2-methyl-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)-2-methyl-propane-2-sulfinamide gave, after silica gel column chromatography (0-10% MeOH/DCM, 1% 7 M NH_3 in MeOH) and preparative HPLC, **113** as an off-white solid (45 mg, 17% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.13 (s, 1H), 7.36-7.29 (m, 1H), 7.05-6.96 (m, 2H), 6.17 (s, 2H), 4.84-4.79 and 4.71-4.67 (m, 1H), 4.04-3.96 (m, 1H), 3.78 and 3.74 (s, 3H), 3.40-3.33 (m, 1H), 2.15-1.51 (m, 8H), 1.26-1.16 (m, 3H). LCMS (ES+) m/z 463 (M+1).

Example 114 5-Amino-*N*-(5-(6-amino-4,4-difluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **114**

To a solution of 5-(6-azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (69 mg, 0.23 mmol) in EtOH (2.3 mL) was added ammonium chloride (61 mg 1.14 mmol) and water (0.23 mL) followed by iron powder (51 mg, 0.91mmol). The reaction mixture was heated at 80 °C for 6 hr and then recharged with the same amounts of iron and ammonium chloride. Heating was continued for 60 min and the reaction mixture was cooled to room temperature. The crude slurry was filtered through Celite® washing with DCM (20 mL). The solution was passed through a phase separation cartridge and concentrated under reduced pressure. The crude residue was dissolved in MeOH (1 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (94 mg, 0.37 mmol) and DIPEA (0.24 mL, 1.40 mmol) were added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.19 mL, 0.39 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure and the residue dissolved in EtOAc (10 mL). The organic layer was washed with 1 M aqueous NaOH (3 x 10 mL), 1 M aqueous HCl (2 x 10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-5% 7 M NH_3 in MeOH/DCM) and preparative HPLC gave 5-amino-*N*-(5-(6-azido-4,4-difluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide as a colourless oil. The compound was dissolved in MeOH (10 mL) and passed through the H-Cube® (full H_2, 70 °C, flow rate: 1 mL/min, 30 mm 10% Pd/C cartridge). Purification *via* silica gel column chromatography (0-10% MeOH/DCM, 1% 7 M NH_3 in MeOH) gave **114** (Diastereomer 1) as a colourless solid (2 mg, 2% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.07 (s, 1H), 7.45-7.18 (m, 1H), 7.05-6.98 (m, 2H), 6.16 (s, 2H), 4.97-4.88 (m, 1H), 4.32-4.23 (m, 1H),

3.83 (s, 3H), 3.54-3.42 (m, 2H), 2.74-2.44 (m, 3H), 2.36-2.20 (m, 1H), 1.31-1.14 (m, 2H). LCMS (ES+) m/z 485 (M+1).

Example 115 5-amino-N-(5-((1S,4S,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **115**

Chiral separation of the racemic mixture tert-butyl N-[5-[4-[[5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate by SFC followed by deprotection with 4N HCl in dioxane gave **115** as a single enantiomer. 1H NMR (400 MHz, DMSO) δ 10.07 (s, 1H), 8.00 (s, 1H), 7.57 – 7.39 (m, 3H), 7.38 – 7.22 (m, 2H), 4.27 (dd, J = 7.1, 3.4 Hz, 1H), 3.77 (s, 3H), 3.01 – 2.90 (m, 1H), 2.44 – 2.30 (m, 1H), 2.22 – 2.07 (m, 1H), 2.04 – 1.55 (m, 5H), 1.44 – 1.27 (m, 1H). LCMS (ES+) m/z 461 (M+1).

Example 116 5-amino-N-(5-((1S,4R,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **116**

Chiral separation of the racemic mixture tert-butyl N-[5-[4-[[5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate by SFC followed by deprotection with 4N HCl in dioxane gave **116** as a single enantiomer. 1H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 8.00 (s, 1H), 7.57 – 7.40 (m, 3H), 7.36 – 7.24 (m, 2H), 4.27 (dd, J = 7.0, 3.4 Hz, 1H), 3.77 (s, 3H), 2.93 (dd, J = 10.0, 5.7 Hz, 1H), 2.43 – 2.34 (m, 1H), 2.20 – 2.08 (m, 1H), 2.04 – 1.50 (m, 5H), 1.42 – 1.29 (m, 1H). LCMS (ES+) m/z 461 (M+1).

Example 117 5-amino-N-(5-((1R,4S,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **117**

Chiral separation of the racemic mixture tert-butyl N-[5-[4-[[5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate by SFC followed by deprotection with 4N HCl in dioxane gave **117** as a single enantiomer. 1H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 8.18 – 8.09 (m, 1H), 7.97 (s, 1H), 7.51 – 7.29 (m, 5H), 4.37 (dd, J = 7.0, 3.6 Hz, 1H), 3.79 (s, 3H), 3.07 – 2.96 (m, 1H), 2.45 – 2.34 (m, 1H), 2.23 – 2.12 (m, 1H), 2.09 – 1.97 (m, 1H), 1.94 – 1.83 (m, 2H), 1.80 – 1.59 (m, 4H), 1.47 – 1.30 (m, 1H). LCMS (ES+) m/z 443 (M+1).

Example 118 5-amino-N-(5-((1R,4R,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **118**

Chiral separation of the racemic mixture tert-butyl N-[5-[4-[[5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-8-oxabicyclo[3.2.1]octan-2-yl]carbamate by SFC followed by deprotection with 4N HCl in dioxane gave **118** as a single enantiomer. 1H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 8.19 –

8.09 (m, 1H), 7.97 (s, 1H), 7.54 – 7.27 (m, 5H), 4.37 (dd, J = 7.2, 3.4 Hz, 1H), 3.79 (s, 3H), 3.09 – 2.96 (m, 1H), 2.46 – 2.36 (m, 1H), 2.23 – 2.13 (m, 1H), 2.12 – 1.98 (m, 1H), 1.96 – 1.82 (m, 2H), 1.79 – 1.58 (m, 3H), 1.45 – 1.29 (m, 1H). LCMS (ES+) m/z 443 (M+1).

Example 119 5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **119**

Following the procedure for Example 111 starting from *tert*-butyl *N*-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 23) gave **119** as a colourless solid (7 mg, 9% over three steps). ^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 7.87 (s, 1H), 7.60-7.44 (m, 3H), 7.32-7.23 (m, 2H), 5.01-4.83 (m, 2H), 4.12-3.90 (m, 2H), 3.72 (s, 3H), 3.36-3.19 (m, 1H), 2.22-2.14 (m, 1H), 1.92-1.57 (m, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 120 5-amino-N-(5-((2R,5R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **120**

Chiral separation of **113** by SFC gave **120**. 1H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 7.91 (s, 1H), 7.61 – 7.50 (m, 1H), 7.46 (s, 2H), 7.26 (t, J = 8.5 Hz, 2H), 5.05 – 4.94 (m, 1H), 4.07 – 3.90 (m, 1H), 3.70 (s, 3H), 3.15 – 3.03 (m, 1H), 2.23 – 2.11 (m, 1H), 1.91 – 1.64 (m, 3H), 1.64 – 1.46 (m, 3H), 1.05 (d, J = 6.3 Hz, 3H). LCMS (ES+) m/z 463 (M+1).

Example 121 5-amino-N-(5-((2R,5S,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **121**

Chiral separation of **113** by SFC gave **121**. 1H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 7.90 (s, 1H), 7.61 – 7.52 (m, 1H), 7.48 (s, 2H), 7.27 (t, J = 8.5 Hz, 2H), 4.99 (dd, J = 9.0, 2.9 Hz, 1H), 4.05 (dd, J = 11.5, 6.5 Hz, 1H), 3.72 (s, 3H), 2.09 (d, J = 14.1 Hz, 1H), 1.98 – 1.51 (m, 6H), 1.09 (d, J = 6.3 Hz, 3H). LCMS (ES+) m/z 463 (M+1).

Example 122 5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **122**

To a solution of 5-(6-azido-4,4-difluoro-oxepan-2-yl)-1-methyl-4-nitro-pyrazole (264 mg, 0.87 mmol) in EtOH (8.8 mL) was added ammonium chloride (360 mg 6.73 mmol) water (0.88 mL) and iron powder (51 mg, 0.91 mmol). The reaction mixture was heated at 80 °C for 16 hr and then cooled to room temperature. The crude slurry was filtered through Celite® washing with DCM (200 mL). The solution was passed through a phase separation cartridge and concentrated under reduced pressure. The residue was dissolved in isopropanol (10 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (255 mg, 0.92 mmol) and DIPEA (0.59 mL, 3.50 mmol) were added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.46 mL, 0.96 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure. Purification *via* silica gel

chromatography (0-5% 7 M NH_3 in MeOH/DCM) followed by preparative HPLC gave **122** (Diastereomer 2) as a colourless solid (24 mg, 6 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 and 9.39 (2s, 1H), 8.09 and 8.07 (2s, 1H), 7.32 (tt, *J* = 8.4, 6.1Hz, 1H), 7.06-6.96 (m, 2H), 6.19 (s, 2H), 4.92 and 4.81 (d, *J* = 11.4 Hz, 1H), 4.27 and 4.08 (2dd, *J* = 12.5, 5.2 Hz, 1H), 3.88 (dd, *J* = 12.5, 6.4 Hz, 1H), 3.83 and 3.81 (2s, 3H), 3.46-3.36 (m, 1H), 2.65-2.46 (m, 1H), 2.45-2.27 (m, 2H), 1.25 (s, 3H). LCMS (ES+) m/z 485 (M+1).

Example 123 5-amino-N-(5-((5S,6S)-6-amino-5-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **123**

Following the procedure for Example 111 starting from *tert*-butyl *N*-(4-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-3-yl]carbamate (Intermediate 20) gave the formate salt of **123** as a colorless solid (9 mg, 11% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.61 (s, 1H), 8.23 (s, 1H), 7.91 (s, 1H), 7.57-7.48 (m, 3H), 7.30 (t, *J* = 8.8 Hz, 2H), 5.13 (dd, *J* = 6.0, 3.4 Hz, 1H), 3.80 (dd, *J* = 12.6, 3.8 Hz, 1H), 3.71 (s, 3H), 3.18 (s, 3H), 3.05-2.97 (m, 1H), 2.93 (t, *J* = 8.6 Hz, 1H), 2.34 (s, 1H), 2.07-1.96 (m, 1H), 1.94-1.82 (m, 2H), 1.53-1.42 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

Example 125 5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **125**

Following the procedure for Example 112 gave another stereoisomer **125** as a colorless oil (1.3 mg, 1% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.73 (s, 1H), 7.89 (s, 1H), 7.53-7.44 (m, 2H), 7.41 (s, 2H), 7.23-7.14 (m, 3H), 5.09 (t, *J* = 5.0 Hz, 1H), 3.62 (s, 3H), 3.49-3.39 (m, 1H), 3.09-2.96 (m, 1H), 2.10-1.96 (m, 1H), 1.84-1.71 (m, 2H), 1.68-1.60 (m, 1H), 1.54-1.35 (m, 3H), 1.27-1.16 (m, 1H), 0.66 (t, *J* = 7.3 Hz, 3H). LCMS (ES+) m/z 477 (M+1).

Example 126 5-amino-N-(5-((5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **126**

Following the procedure for Example 111 starting from *tert*-butyl *N*-((3*S*,4*R*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 21) gave **126** as an off-white solid (33 mg, 25% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.23 (s, 1H), 7.77 (s, 1H), 7.59-7.47 (m, 3H), 7.31-7.23 (m, 2H), 4.79 (dd, *J* = 10.9, 3.6 Hz, 1H), 4.04 (dd, *J* = 13.8, 3.1 Hz, 1H), 3.84-3.75 (m, 1H), 3.75 (s, 3H), 3.09 (s, 3H), 3.08-2.94 (m, 2H), 2.06-1.97 (m, 1H), 1.84-1.67 (m, 2H), 1.64-1.55 (m, 1H), Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

Example 127 5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **127**

Following the procedure for Example 130 also gave **127** as a white solid (5 mg, 1% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 7.96 (s, 1H), 7.36-7.26 (m, 1H), 7.05-6.96 (m, 2H), 6.22 (s, 2H), 4.89 (t, *J* = 6.1 Hz, 1H), 4.82-4.76 and 4.70-4.64 (m, 1H), 4.13 (dq, *J*

= 12.9, 4.2 Hz, 1H), 3.85 (s, 3H), 3.60-3.47 (m, 2H), 2.72-2.62 (m, 1H), 2.33-2.18 (m, 1H), 2.18-1.97 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 128 5-amino-N-(5-((5S,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **128**

Following the procedure for Example 111 from *tert*-butyl *N*-((3*R*,4*S*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 22) gave **128** as a white solid (28 mg, 21% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.23 (s, 1H), 7.77 (s, 1H), 7.59-7.47 (m, 3H), 7.31-7.23 (m, 2H), 4.79 (dd, *J* = 11.0, 3.6 Hz, 1H), 4.04 (dd, *J* = 13.8, 3.1 Hz, 1H), 3.82 (dd, *J* = 13.9, 3.4 Hz, 1H), 3.75 (s, 3H), 3.09 (s, 3H), 3.08-2.93 (m, 2H), 2.07-1.97 (m, 1H), 1.85-1.69 (m, 2H), 1.66-1.55 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

Example 129 5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **129**

Following the procedure for Example 111 starting from *tert*-butyl *N*-((3*R*,4*R*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 24) gave **129** as a colourless solid (30 mg, 38% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.49 (s, 1H), 7.86 (s, 1H), 7.55-7.48 (m, 3H), 7.28 (t, *J* = 8.9 Hz, 2H), 4.98-4.78 (m, 2H), 4.08-3.93 (m, 2H), 3.72 (s, 3H), 3.28-3.20 (m, 1H), 2.22-1.92 (m, 3H), 1.91-1.58 (m, 3H). LCMS (ES+) m/z 467 (M+1).

Example 130 5-amino-N-(5-((4S,5S)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **130**

Following the procedure for Example 111 starting from *tert*-butyl *N*-(5-fluoro-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate gave **130** as a white solid (13 mg, 4% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 7.96 (s, 1H), 7.36-7.26 (m, 1H), 7.05-6.96 (m, 2H), 6.22 (s, 2H), 4.89 (t, *J* = 6.1 Hz, 1H), 4.82-4.76 and 4.70-4.64 (m, 1H), 4.13 (dq, *J* = 12.9, 4.2 Hz, 1H), 3.85 (s, 3H), 3.60-3.47 (m, 2H), 2.72-2.62 (m, 1H), 2.33-2.18 (m, 1H), 2.18-1.97 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 131 5-amino-N-(5-((5S,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **131**

Following the procedure for Example 111 from *tert*-butyl *N*-((3*S*,4*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 25) gave **131** as a colorless solid (30 mg, 38% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.49 (s, 1H), 7.86 (s, 1H), 7.55-7.48 (m, 3H), 7.31-7.22 (m, 2H), 4.95-4.76 (m, 2H), 4.08-3.91 (m, 2H), 3.72 (s, 3H), 3.30-3.22 (m, 1H), 2.22-1.57 (m, 6H). LCMS (ES+) m/z 467 (M+1).

Example 134 5-amino-2-(2,6-difluorophenyl)-N-[5-(5-hydroxyoxepan-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **134**

Following the procedure for Example 108 starting from 7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-ol (85mg 0.35 mmol), using a Raney Nickel cartridge, gave, after preparative HPLC, **134** as a light pink solid and a 1/1 mixture of diastereoisomers (15 mg, 9% over two steps). ^{1}H NMR δ (ppm) ($CDCl_3$) 9.72 (2s, 1H), 8.15 (2s, 1H), 7.37-7.26 (m, 1H), 7.06-6.96 (m, 2H), 6.17 (s, 2H), 5.01-4.92 (m, 1H), 4.23-4.15 (m, 1H), 4.06 (dt, J = 12.7, 4.6 Hz, 1H), 4.01-3.62 (m, 5H), 2.42-2.25 (m, 1H), 2.17-1.90 (m, 5H). LCMS (ES+) m/z 450 (M+1).

Example 135 5-amino-N-(5-((2S,4R,5R)-5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **135**

To a solution of 5-azido-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-ol (353 mg, 1.25 mmol) in DCM (6 mL) at 0 °C was added Bis(2-methoxyethyl)aminosulfur trifluoride, Sigma-Aldrich Product No. 494119, CAS No. 202289-38-1, deoxo-Fluor®, (50% in THF, 0.58 mL, 1.56 mmol) and the mixture was stirred at room temperature for 16 hr. The mixture was cooled in an ice/water bath and quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was passed through a phase separation cartridge and the solvent removed under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave a clear gum. A solution of this gum (145 mg, 0.51 mmol) in THF/water (2.5 mL/0.5 mL) was treated with triphenylphosphine (147 mg, 0.56 mmol) and the reaction mixture was heated at 60 °C behind a blast screen for 2 hr. The mixture was diluted with EtOAc (10 mL) and washed with brine (2 x 5 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. The resulting residue was dissolved in dry DCM (2 mL) and DIPEA (0.18 mL, 1.02 mmol) and di-*tert*-butyl-dicarbonate (134 mg, 0.61 mmol) was added. The reaction mixture was stirred at room temperature for 2 hr. Water (2 mL) was added and the mixture extracted with DCM (3 x 2 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-50% EtOAc/isohexane) gave the intermediate nitro-pyrazole as a clear gum (180 mg). To a solution of this gum (179 mg, 0.5 mmol) was added 10% palladium on carbon (27 mg, 0.25 mmol) and 1-methyl-1,4-cyclohexadiene (0.56 mL, 5.0 mmol). The mixture was heated at 70 °C for 1 hr. No reaction occurred so the mixture was filtered and to the filtrate added 10% palladium on carbon (27 mg, 0.25 mmol) and ammonium formate (126 mg, 2.0 mmol). The mixture was heated at 80 °C under nitrogen for 2 hr. The mixture was cooled to room temperature, filtered through Celite® and concentrated under reduced pressure to give the amino-pyrazole as a pale yellow gum (132 mg). This gum (131 mg, 0.40 mmol) was dissolved in DCM (2 mL) and DIPEA (0.10 mL, 0.56

mmol) and added to a solution of PyBOP (255 mg, 0.49 mmol) and 5-(*tert*-butoxycarbonylamino)-2-(3-fluoro-2-pyridyl)thiazole-4-carboxylic acid (131 mg, 0.37 mmol) in DCM (2 mL) which had been stirring at room temperature for 30 min. The mixture was stirred at room temperature for 16 hr, diluted with DCM (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was passed through a phase separation cartridge and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-3% MeOH/DCM) gave a pale yellow gum (65 mg). Further purification *via* chiral preparative HPLC gave an off-white solid (22 mg). This solid (22 mg, 0.033 mmol) was dissolved in a solution of HCl in dioxane (4 M, 5 mL) and MeOH (2 mL) and stirred at room temperature for 16 hr. The solvents were removed under reduced pressure and residue was passed through an SCX cartridge washing with MeOH and eluting with 3% 7 M NH_3 in MeOH/DCM. Purification *via* silica gel column chromatography (0-5% 7 M NH_3 in MeOH/DCM) gave **135** as a white solid (10 mg, 1% over 6 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.19 (s, 1H), 7.35-7.27 (m, 1H), 7.01 (t, J = 8.7 Hz, 2H), 6.16 (s, 2H), 5.07-5.02 (m, 1H), 4.60 (dddd, J = 43.2, 9.0, 6.5, 3.8 Hz, 1H), 4.23 (ddd, J = 12.5, 7.0, 4.4 Hz, 1H), 3.88-3.74 (m, 4H), 3.36-3.26 (m, 1H), 2.46-2.30 (m, 2H), 2.18-2.07 (m, 1H), 1.98-1.87 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 136 5-amino-N-(5-((2S,4R,5R)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **136**

Following the procedure for Example 140 starting from *tert*-butyl *N*-(5-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate gave **136** as an off-white solid (28 mg, 12% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.20 (s, 1H), 7.35-7.26 (m, 1H), 7.01 (t, J = 8.7 Hz, 2H), 6.16 (s, 2H), 5.04 (dd, J = 6.5, 3.7 Hz, 1H), 4.24-4.16 (m, 1H), 3.87-3.69 (m, 4H), 3.34-3.11 (m, 4H), 3.15-3.08 (m, 1H), 2.24-2.04 (m, 3H), 1.94-1.84 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

Example 137 5-amino-N-(5-((2R,4S,5S)-5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **137**

Following the procedure for Example 140 also gave **137** as a white solid (10 mg, 1%, over 6 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.19 (s, 1H), 7.35-7.27 (m, 1H), 7.01 (t, J = 8.7 Hz, 2H), 6.16 (s, 2H), 5.07-5.02 (m, 1H), 4.60 (dddd, J = 43.2, 9.0, 6.5, 3.8 Hz, 1H), 4.23 (ddd, J = 12.5, 7.0, 4.4 Hz, 1H), 3.88-3.74 (m, 4H), 3.36-3.26 (m, 1H), 2.46-2.30 (m, 2H), 2.18-2.07 (m, 1H), 1.98-1.87 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 138 5-amino-N-(5-((2R,4S,5S)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **138**

Following the procedure for Example 137 also gave **138** as an off-white solid (25 mg, 10% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.20 (s, 1H), 7.35-7.26 (m, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.16 (s, 2H), 5.04 (dd, *J* = 6.5, 3.7 Hz, 1H), 4.24-4.16 (m, 1H), 3.87-3.69 (m, 4H), 3.34-3.11 (m, 4H), 3.15-3.08 (m, 1H), 2.24-2.04 (m, 3H), 1.94-1.84 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

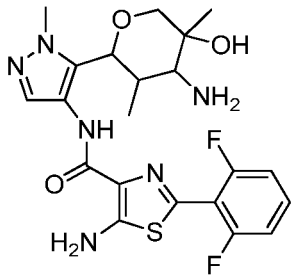
Example 139 5-amino-N-[5-[1-(aminomethyl)-7-oxabicyclo[2.2.1]heptan-4-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide **139**

Following the procedure for Example 106 starting from *tert*-butyl *N*-[[4-fluoro-1-hydroxy-4-(2-methyl-4-nitro-pyrazol-3-yl)cyclohexyl]methyl]carbamate gave, after purification *via* silica gel column chromatography (5% MeOH/DCM with 1% NH_3 in MeOH), **139** as a cream solid (142 mg, 22% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.23 (s, 1H), 8.12 (td, *J* = 7.7, 1.9 Hz, 1H), 7.39-7.33 (m, 1H), 7.29-7.19 (s, 1H), 7.16 (dd, *J* = 11.3, 8.3 Hz, 1H), 6.13 (s, 2H), 3.90 (s, 3H), 3.19 (s, 2H), 2.35-2.26 (m, 2H), 2.07-1.89 (m, 4H), 1.78-1.69 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 443 (M+1).

Example 141 5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **141**

Following the procedure for Example 130 also gave **141** as a white solid (5 mg, 1% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 7.96 (s, 1H), 7.36-7.26 (m, 1H), 7.05-6.96 (m, 2H), 6.22 (s, 2H), 4.89 (t, *J* = 6.1 Hz, 1H), 4.82-4.76 and 4.70-4.64 (m, 1H), 4.13 (dq, *J* = 12.9, 4.2 Hz, 1H), 3.85 (s, 3H), 3.60-3.47 (m, 2H), 2.72-2.62 (m, 1H), 2.33-2.18 (m, 1H), 2.18-1.97 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 142 5-amino-N-[5-(4-amino-5-hydroxy-3,5-dimethyl-tetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **142**



Following the procedure for Example 112 starting from *tert*-butyl *N*-[5-hydroxy-3,5-dimethyl-2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-yl]carbamate gave, after purification *via* preparative HPLC, **142** as an off-white solid (15 mg, 10% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.22 (s, 1H), 7.31 (ddd, *J* = 8.5, 6.1, 2.3 Hz, 1H), 7.07-6.97 (m, 2H), 6.14 (s, 2H), 5.31 (d, *J* = 3.3 Hz, 1H), 4.00 (d, *J* = 12.1 Hz, 1H), 3.83 (d, *J* = 12.1 Hz, 1H), 3.77 (s, 3H), 3.09 (s, 1H), 1.79-1.72 (m, 1H), 1.13 (s, 3H), 1.11 (d, *J* = 7.6 Hz, 3H). Alkyl NH_2 and OH not observed. LCMS (ES+) m/z 479 (M+1).

Example 143 5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **143**

tert-Butyl N-[6-[4-[[5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]oxepan-3-yl]carbamate was stirred with 4N HCl in dioxane (5 mL) and methanol (2 mL) at room temperature for 3h. The solvent was removed under reduced pressure, basified with saturated $NaHCO_3$, and extracted with ethyl acetate (3x). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure and the residue purified by preparative HPLC to afford **143** (24 mg, 32%). 1H NMR (400 MHz, DMSO) δ 9.73, 9.56 (s, 1H), 7.83, 7.78 (s, 1H), 7.62 – 7.42 (m, 3H), 7.36 – 7.18 (m, 2H), 3.96 – 3.71 (m, 6H), 3.59 (ddd, J = 71.3, 12.2, 4.1 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.94 – 2.79 (m, 1H), 2.10 – 1.89 (m, 1H), 1.85-1.68 (m, 1H), 1.68 – 1.56 (m, 1H), 1.54 – 1.39 (m, 1H). LCMS (ES+) m/z 449 (M+1).

Example 144 5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **144**

Chiral separation of **143** by SFC afforded **144** as a mixture of enantiomers. 1H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 7.78 (s, 1H), 7.60 – 7.52 (m, 1H), 7.50 (s, 2H), 7.26 (t, J = 8.6 Hz, 2H), 3.91 – 3.79 (m, 2H), 3.77 (s, 3H), 3.68 (dd, J = 12.3, 3.8 Hz, 1H), 3.50 (dd, J = 12.2, 4.0 Hz, 1H), 2.97 (s, 1H), 2.13 – 2.00 (m, 1H), 1.81 – 1.66 (m, 2H), 1.66 – 1.53 (m, 1H). LCMS (ES+) m/z 449 (M+1).

Example 145 5-amino-N-(5-((5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **145**

Following the procedure for Example 111 starting from *tert*-butyl *N*-(3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (Intermediate 34) gave the formate salt of **145** as a colorless solid (5 mg, 5% over three steps). ^{1}H NMR (400 MHz, DMSO) δ 9.31 (s, 1H), 8.20 (s, 1H), 7.80 (s, 1H), 7.59-7.50 (m, 3H), 7.32-7.22 (m, 2H), 4.93 (dd, *J* = 8.8, 4.2 Hz, 1H), 4.58-4.39 (m, 1H), 3.90 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.78-3.72 (m, 1H), 3.75 (s, 3H), 3.08-2.98 (m, 1H), 2.17-1.91 (m, 3H), 1.88-1.78 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 146 5-amino-2-(2,6-difluorophenyl)-N-(5-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **146**

Following the procedure for Example 108 starting from 2-(2-methyl-4-nitro-pyrazol-3-yl)tetrahydropyran-4-ol gave, after purification *via* chiral SFC, **146** (Enantiomer 1) as an off-white solid (4 mg, 2% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.13 (s, 1H), 7.41-7.14 (m, 1H), 7.06-6.96 (m, 2H), 6.15 (s, 2H), 5.13 (dd, *J* = 11.8, 2.5 Hz, 1H), 4.37-4.34 (m,

1 H), 4.11-4.06 (m, 2H), 3.82 (s, 3H), 2.18-2.00 (m, 2 H), 1.92-1.83 (m, 1H), 1.68-1.60 (m, 1H). OH not observed. LCMS (ES+) m/z 436 (M+1).

Example 147 5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **147**

Chiral separation of **143** by SFC afforded **147** as a mixture of enantiomers. 1H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 7.83 (s, 1H), 7.62 – 7.51 (m, 1H), 7.47 (s, 2H), 7.27 (t, J = 8.5 Hz, 2H), 3.94 – 3.75 (m, 3H), 3.73 (s, 3H), 3.03 – 2.93 (m, 1H), 2.93 – 2.81 (m, 1H), 2.02 – 1.90 (m, 1H), 1.85 – 1.71 (m, 1H), 1.71 – 1.54 (m, 1H), 1.52 – 1.39 (m, 1H). LCMS (ES+) m/z 449 (M+1).

Example 148 5-Amino-*N*-[5-[5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **148**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (from Intermediate 53) gave **148** as a formate salt as a solid (3 mg, 22%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.64 (s, 1H), 7.94 (s, 1H), 7.57-7.45 (m, 4H), 7.29-7.20 (m, 3H), 5.21-5.16 (m, 1H), 4.06-4.01 (m, 1H), 3.82-3.69 (m, 4H), 2.96 (s, 1H), 2.21-2.15 (m, 2H), 2.03-1.74 (m, 1H), 1.79-1.55 (m, 1H), 1.42-1.37 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 149 5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,4S)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **149**

Following the procedure for Example 146 also gave **149** (Enantiomer 2) as an off-white solid (4 mg, 2% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.13 (s, 1H), 7.34-7.27 (m, 1H), 7.05-6.96 (m, 2H), 6.15 (s, 2H), 5.14 (d, *J* = 2.5 Hz, 1H), 5.11 (d, *J* = 2.5 Hz, 1H), 4.36 (s, 1H), 4.11-4.07 (m, 2H), 3.82 (s, 3H), 2.62 (s, 1H), 2.19-2.01 (m, 2H), 1.91-1.85 (m, 1H), 1.73-1.63 (m, 1H). OH not observed. LCMS (ES+) m/z 436 (M+1).

Example 150 5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **150**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[5-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (Intermediate 54) gave **150** as a white solid (28 mg, 12% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.52 (s, 1H), 7.85 (s, 1H), 7.56-7.48 (m, 3H), 7.27 (t, *J* = 8.8 Hz, 2H), 4.99 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.93-4.76 (m, 1H), 4.08-3.99 (m, 1H), 3.79-3.67 (m, 4H), 3.33-3.20 (m, 1H), 2.31-2.12 (m, 2H), 1.89-1.83 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 151 5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **151**

Following the procedure for Example 150 also gave **151** as a white solid (24 mg, 17%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.52 (s, 1H), 7.85 (s, 1H), 7.56-7.48 (m, 3H), 7.27 (t, J = 8.8 Hz, 2H), 4.99 (dd, J = 9.9, 3.0 Hz, 1H), 4.93-4.76 (m, 1H), 4.08-3.99 (m, 1H), 3.79-3.67 (m, 4H), 3.33-3.20 (m, 1H), 2.31-2.12 (m, 2H), 1.89-1.83 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 152 5-Amino-*N*-[5-[(5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **152**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (Intermediate 56) gave **152** as a pale brown solid (60 mg, 73%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.28 (s, 1H), 7.81 (s, 1H), 7.57-7.48 (m, 3H), 7.30-7.20 (m, 2H), 5.06-5.00 (m, 1H), 4.19-3.98 (m, 2H), 3.76 (s, 3H), 2.22-2.14 (m, 1H), 1.92-1.76 (m, 4H). 2H partially masked by water peak. LCMS (ES+) m/z 485 (M+1).

Example 153 5-Amino-*N*-[5-[(2*R*,5*S*,6*S*)-6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **153**

Prior to Boc deprotection of Example 150, SFC purification of *tert*-butyl *N*-[(3*S*,4*S*,7*R*)-7-[4-[[5-(*tert*-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carbonyl]amino]-2-methyl-pyrazol-3-yl]-4-fluoro-oxepan-3-yl]carbamate on a chiral stationary phase gave **153** as a golden solid (25 mg, 59%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.34 (s, 1H), 7.84 (s, 1H), 7.62-7.53 (m, 3H), 7.34-7.26 (m, 2H), 4.97 (dd, J = 8.8, 4.2 Hz, 1H), 4.61-4.44 (m, 1H), 3.96-3.88 (m, 1H), 3.86-3.68 (m, 4H), 3.10-3.01 (m, 1H), 2.18-1.92 (m, 3H), 1.93-1.78 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 154 5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **154**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[(3*R*,4*R*,7*S*)-3-methoxy-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (Intermediate 93) gave **154** as the hydrochloride salt as a beige solid (33 mg, 89%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.41 (s, 1H), 8.06 (s, 3H), 7.84 (s, 1H), 7.60-7.48 (m, 3H), 7.38-7.29 (m, 2H), 4.97-4.92 (m, 1H), 4.15 (dd, J = 13.4, 4.7 Hz, 1H), 3.93 (dd, J = 13.3, 5.4 Hz, 1H), 3.86-3.82 (m, 1H), 3.80-3.62 (m, 4H), 3.29 (s, 3H), 2.13-1.98 (m, 2H), 1.86-1.73 (m, 2H). LCMS (ES+) m/z 479 (M+1).

Example 155 5-Amino-*N*-[5-[5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **155**

Following the procedure for Example 111 starting from *tert*-Butyl ((5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydrofuran-2-yl)methyl)carbamate (Intermediate 62) gave **155** as a cream solid (19 mg, 90%). ^{1}H NMR (400 MHz, d_4-MeOD) δ 7.95 (s, 1H), 7.52-7.45 (m, 1H), 7.20-7.14 (m, 2H), 5.33-5.29 (m, 1H), 4.50-4.47 (m, 1H), 3.85 (s, 3H), 2.96-2.87 (m, 2H), 2.54-2.49 (m,

1H), 2.31-2.25 (m, 1H), 2.08-2.00 (m, 1H), 1.91-1.86 (m, 1H). LCMS (ES+) m/z 435 (M+1). Exchangeable protons not observed.

Example 156 5-amino-N-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide **156**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-3-(trifluoromethyl)phenyl)boronic acid gave **156**. 1H NMR (400 MHz, DMSO-d6) δ 9.37 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H), 7.85 (s, 1H), 7.79 (t, J = 7.3 Hz, 1H), 7.57 (s, 2H), 7.49 (t, J = 7.9 Hz, 1H), 4.91 – 4.82 (m, 1H), 4.67 – 4.49 (m, 1H), 4.42 – 4.26 (m, 1H), 4.21 – 4.00 (m, 1H), 3.77 (s, 3H), 2.13 – 2.01 (m, 1H), 1.90 – 1.67 (m, 4H). LCMS (ES+) m/z 517 (M+1).

Example 157 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide **157**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-(trifluoromethoxy)phenyl)boronic acid gave **157**. 1H NMR (400 MHz, DMSO-d6) δ 9.33 (s, 1H), 8.40 (dd, J = 7.9, 2.3 Hz, 1H), 7.84 (s, 1H), 7.54 – 7.44 (m, 5H), 4.89 – 4.80 (m, 1H), 4.69 – 4.53 (m, 1H), 4.41 – 4.28 (m, 1H), 4.21 – 4.02 (m, 1H), 3.77 (s, 3H), 3.48 – 3.38 (m, 1H), 2.13 – 2.02 (m, 1H), 1.91 – 1.72 (m, 3H). LCMS (ES+) m/z 515 (M+1).

Example 158 5-Amino-*N*-[5-[4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **158**

Following the procedure for Example 111 starting from *tert*-Butyl ((5-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)tetrahydrofuran-2-yl)methyl)carbamate (Intermediate 89) gave **158** as a white solid (11 mg, 5% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.12 (s, 1H), 7.34-7.27 (m, 1H), 7.06-6.96 (m, 2H), 6.16 (s, 2H), 4.62 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.31 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.82 (s, 3H), 3.59 (td, *J* = 12.0, 2.1 Hz, 1H), 3.06-2.96 (m, 1H), 2.12-1.98 (m, 1H), 1.89 (ddd, *J* = 13.1, 4.4, 2.2 Hz, 1H), 1.71-1.46 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 435 (M+1).

Example 159 5-Amino-*N*-[5-[(2*R*,4*S*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **159**

Purification of Example 158 *via* chiral preparative HPLC gave **159** as the first eluting isomer as the formate salt as a white solid (5 mg, 13%). ^{1}H NMR (400 MHz, d_6-DMSO) 9.53 (s,

1H), 8.38 (s, 1H), 7.90 (s, 1H), 7.55-7.46 (m, 3H), 7.32-7.23 (m, 2H), 4.81 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.12 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.76 (s, 3H), 3.62-3.50 (m, 1H), 3.19-3.05 (m, 1H), 2.05 (d, *J* = 12.6 Hz, 1H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.51 (qd, *J* = 12.2, 4.6 Hz, 1H), 1.39 (q, *J* = 11.9 Hz, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 435 (M+1).

Example 160 5-Amino-*N*-[5-[(2*S*,4*R*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **160**

Following the procedure for Example 159 also gave **160** as the seond eluting isomer as the formate salt as a white solid (5 mg, 13%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.53 (s, 1H), 8.38 (s, 1H), 7.90 (s, 1H), 7.55-7.46 (m, 3H), 7.32-7.23 (m, 2H), 4.81 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.12 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.76 (s, 3H), 3.62-3.50 (m, 1H), 3.19-3.05 (m, 1H), 2.05 (d, *J* = 12.6 Hz, 1H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.51 (qd, *J* = 12.2, 4.6 Hz, 1H), 1.39 (q, *J* = 11.9 Hz, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 435 (M+1).

Example 161 5-Amino-*N*-[5-[2-amino-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide **161**

A solution of *tert*-butyl *N*-[2-bromo-4-[[5-[2-(*tert*-butoxycarbonylamino)-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (110 mg, 0.175 mmol, Intermediate 65) in dry dioxane (15 mL) was treated with 3-fluoro-4-(tributylstannyl)-pyridine (0.053 mL, 0.246 mmol), lithium chloride (22 mg, 0.526 mmol), copper(I) iodide (10 mg, 0.053 mmol) and tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.011 mmol). Nitrogen gas was bubbled through the mixture for 10 min and the mixture was heated at 120 °C under microwave irradiation for 90 min. Water (20 mL) was added and the mixture was extracted with EtOAc (60 mL). The organic layer was washed with brine (20 mL), separated, dried over $MgSO_4$, and concentrated under reduced pressure. Purification *via* silica gel chromatography (75% EtOAc/isohexane) gave the desired intermediate as a peach solid (59 mg). This solid was suspended in MeOH (3 mL), treated with a solution of HCl in dioxane (4 M, 2.2 mL, 9.18 mmol) and stirred at room temperature for 18 hr. More HCl in dioxane (4 M, 1.1 mL, 4.59 mmol) was added and the mixture was stirred for 6 hr. The solvent was removed under reduced pressure and the residue was passed through an SCX column washing with MeOH and eluting with 3 N NH_3 in MeOH. Further purification *via* silica gel chromatography (5% MeOH/CH_2Cl_2 with 1% 7 N NH_3 in MeOH) gave **161** as a yellow solid (26 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.57 (d, *J* = 2.6 Hz, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.24 (s, 1H), 8.03-7.97 (m, 1H), 6.28 (s, 2H), 4.51-4.44 (s, 1H), 3.86 (s, 3H), 3.31-3.23 (m, 1H), 2.40-2.33 (m, 1H), 2.21-2.05 (m, 3H), 1.98-1.86 (m, 3H), 1.67-1.29 (m, 3H). LCMS (ES+) m/z 444 (M+1).

Example 162 5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **162**

Following the procedure for Example 111 starting from (5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer, Intermediate 66) gave **162** as a colourless solid (25 mg, 12% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.24 (s, 1H), 7.32-7.30 (m, 1H), 7.04-6.97 (m, 2H), 6.15 (s, 2H), 5.72 (s, 1H), 4.07 (d, *J* = 11.3 Hz, 2H), 3.91 (d, *J* = 11.3 Hz, 2H), 3.85 (s, 3H), 3.44 (d, *J* = 4.9 Hz, 2H), 1.81 (q, *J* = 7.6 Hz, 1H), 1.27 (t, *J* = 5.0 Hz, 2H), 0.83 (t, *J* = 7.6 Hz, 3H). LCMS (ES+) m/z 480 (M+1).

Example 163 5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **163**

Following the procedure for Example 111 starting from (5-Ethyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer, Intermediate 67) gave **163** as a colourless solid (42 mg, 10% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.24 (s, 1H), 7.36-7.28 (m, 1H), 7.07-6.97 (m, 2H), 6.18 (s, 2H), 5.73 (s, 1H), 4.19 (d, *J* = 11.5 Hz, 2H), 3.93 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 3H), 3.66 (d, *J* = 11.6 Hz, 2H), 1.73 (t, *J* = 5.8 Hz, 1H), 1.28 (q, *J* = 7.6 Hz, 2H), 0.92-0.83 (m, 3H). LCMS (ES+) m/z 480 (M+1).

Example 164 5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **164**

Following the procedure for Example 111 starting from (2-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*trans* isomer, Intermediate 68) gave **164** as a 91/9 ratio of *trans*/*cis* isomers as a colourless solid (79 mg, 19% over two steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.73 (s, 1H), 7.99 (s, 1H), 7.54-7.46 (m, 3H), 7.32-7.22 (m, 2H), 5.89 (s, 1H), 4.67 (t, *J* = 5.2 Hz, 1H), 4.21 (dd, *J* = 11.2, 4.6 Hz, 2H), 3.80-3.70 (m, 5H), 3.35-3.30 (m, 2H), 2.28-2.16 (m, 1H). LCMS (ES+) m/z 452 (M+1).

Example 165 5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **165**

Following the procedure for Example 111 starting from (2-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer, Intermediate 69) gave **164** as a 86/14 ratio of *cis*/*trans* isomers of **48** as a colourless solid (45 mg, 9% over two steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.63 (s, 1H), 7.98 (s, 1H), 7.56-7.47 (m, 3H), 7.31-7.22 (m, 2H), 5.97 (s, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.12 (s, 4H), 3.90-3.60 (m, 3H), 3.67 (dd, *J* = 7.8, 5.1 Hz, 2H), 1.57 (t, *J* = 7.8 Hz, 1H). LCMS (ES+) m/z 452 (M+1).

Example 166 5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)- 5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **166**

Following the procedure for Example 111 starting from (5-Methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (*cis* isomer, Intermediate 71) gave **166** as a colourless solid (83 mg, 10% over two steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.65 (s, 1H), 7.98 (s, 1H), 7.57-7.46 (m, 3H), 7.33-7.25 (m, 2H), 5.90 (s, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 2H), 3.77 (s, 3H), 3.68 (d, *J* = 11.2 Hz, 2H), 3.53 (d, *J* = 5.2 Hz, 2H), 0.70 (s, 3H). LCMS (ES+) m/z 466 (M+1).

Example 167 5-Amino-*N*-[5-[5-(aminomethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **167**

To a solution of (2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methanol (360 mg, 1.48 mmol, intermediate 68) in dry THF (12 mL) was added polymer supported triphenylphosphine (~3 mmol/g, 1.5 g, 4.44 mmol) and phthalamide (326 mg, 2.22 mmol) followed by diisopropylazodicarboxylate (450 mg, 2.22 mmol). The reaction mixture was stirred at room temperature for 18 hr then heated at 35 °C for 4 hr. The reaction mixture was filtered and the filtrate diluted with DCM (50 mL) and washed with a saturated aqueous $NaHCO_3$ (25 mL). The organic layer was washed with water (25 mL) and brine (25 mL), separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-100% EtOAc/isohexane) gave 2-((2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)isoindoline-1,3-dione as a colourless solid (226 mg) contaminated with diisopropyl azodicarboxylate byproduct. To a suspension of this solid (165 mg, 0.44 mmol) in MeOH (150 mL) and THF (20 mL) was added ammonium formate (300 mg, mmol) and 10% Pd/C (300 mg). The mixture was heated at reflux for 2 hr. The mixture was quickly filtered whilst hot and the cake washed with DCM (50 mL) and EtOAC (50 mL). The filtrate was concentrated under reduced pressure and the crude residue was dissolved in IPA (5 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (134 mg, 0.46 mmol) and DIPEA (0.31 mL, 1.76 mmol) were then added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.33 mL, 0.48 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The mixture was concentrated under reduced pressure and purified *via* silica gel chromatography (0-5% 7 N NH_3 in MeOH/DCM) to give an oil. This oil was dissolved in EtOH (1 mL), hydrazine (1 mL) was added and the mixture heated at reflux for 16 hr. The solvents were removed under reduced pressure and the residue was dissolved in MeOH and passed through an SCX column eluting with 0-5% 7 N NH_3 in MeOH/DCM. Purification *via* preparative HPLC gave **167** as a colourless solid (4 mg, 1% over four steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.25 (s, 1H), 7.36-7.29 (m, 1H), 7.07-6.99 (m, 2H), 6.18 (s, 2H), 5.74 (s, 1H), 4.46 (dd, *J* = 11.4, 4.5 Hz, 2H), 3.88 (s, 3H), 3.67 (t, *J* = 11.3 Hz, 2H), 2.64 (d, *J* = 6.7 Hz, 2H), 2.41-2.32 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 451 (M+1).

Example 168 5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **168**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[(4*R*,7*S*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 72) gave **168** as the hydrochloride salt as a pale brown solid (57 mg, 79% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.22 (s, 1H), 8.78-8.64 (m, 3H), 7.79 (s, 1H), 7.59-7.48 (m, 2H), 7.34-7.25 (m, 3H), 5.10-5.04 (m, 1H), 4.53-4.07 (m, 2H), 3.97-3.77 (m, 1H), 3.79 (s, 3H), 2.26-1.94 (m, 4H). LCMS (ES+) m/z 485 (M+1).

Example 169 5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **169**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[(4*S*,7*R*)-3,3-difluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 73) gave **168** as the hydrochloride salt as a pale brown solid (13 mg, 16% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.22 (s, 1H), 8.69 (s, 3H), 7.79 (s, 1H), 7.59-7.48 (m, 2H), 7.34-7.25 (m, 3H), 5.06 (d, J = 10.9 Hz, 1H), 4.48-4.36 (m, 1H), 4.47-3.72 (m, 2H), 3.79 (s, 3H), 2.27-2.17 (m, 1H), 2.14-1.93 (m, 3H). LCMS (ES+) m/z 485 (M+1).

Example 170 5-Amino-*N*-[5-[4-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **170**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-(5-fluoro-2-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl)carbamate (intermediate 29) gave **170** as a pink solid (8 mg, 100%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.71 (s, 1H), 7.96 (s, 1H), 7.57-7.49 (m, 3H), 7.31-7.22 (m, 2H), 5.22 (t, J = 4.5 Hz, 1H), 4.46-4.28 (m, 1H), 3.97-3.90 (m, 1H), 3.75-3.60 (m, 4H), 3.06 (q, J = 8.4 Hz, 1H), 2.16-1.99 (m, 5H), 1.85 (d, J = 15.6 Hz, 1H). LCMS (ES+) m/z 467 (M+1).

Example 171 5-Amino-*N*-[5-[(2*R*,5*R*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **171**

Purification of 5-Amino-*N*-[5-[5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide Example 157) by chiral SFC gave **171** as an off-white solid (34 mg). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.40 (s, 1H), 7.88 (s, 1H), 7.57-7.50 (m, 3H), 7.31-7.25 (m, 2H), 5.23-5.20 (m, 1H), 4.30-4.27 (m, 1H), 3.75 (s, 3H), 2.71-2.70 (m, 2H), 2.42-2.41 (m, 1H), 2.10-2.07 (m, 1H), 1.87-1.79 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 435 (M+1).

Example 172 5-Amino-*N*-[5-[(2*S*,5*S*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **172**

Following the procedure for Example 171 also gave **172** as an off-white solid (33 mg). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.42 (s, 1H), 7.88 (s, 1H), 7.57-7.50 (m, 3H), 7.31-7.25 (m, 2H), 5.24-5.20 (m, 1H), 4.29-4.25 (m, 1H), 3.74 (s, 3H), 2.69-2.68 (m, 2H), 2.42-2.41 (m, 1H), 2.08-2.04 (m, 1H), 1.88-1.80 (m, 2H). Alkyl NH_2 not observed. LCMS (ES+) m/z 435 (M+1).

Example 173 5-Amino-*N*-[5-[5-(aminomethyl)-5-ethyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **173**

To a solution of 2-((2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)isoindoline-1,3-dione (317 mg, 0.793 mmol, intermediate 75) in MeOH (10 mL) and THF (10 mL) was added ammonium formate (300 mg, 4.76 mmol) and 10% Pd/C (300 mg, 0.28 mmol) and the mixture was heated at reflux for 2 hr. The mixture was quickly filtered whilst hot and the cake washed with DCM (50 mL) and EtOAC (50 mL). The solvent was removed under reduced pressure and the crude residue was dissolved in EtOAc (10 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (170 mg, 0.66 mmol) and *N*-methylmorpholine (0.4 mL, 1.89 mmol) were added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.32 mL, 0.695 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The solvent was removed under reduced pressure and the residue purified *via* silica gel chromatography (0-5% 7 N NH_3 in MeOH/DCM) to give a colourless solid. To a solution of this solid in EtOH (2 mL) was added hydrazine hydrate (64-65% solution, 2 mL) and the mixture was heated at 70 °C for 16 hr. After concentration under reduced pressure, MeOH was added to the residue and the solids filtered off. The filtrate was concentrated under reduced pressure. Purification *via* K-NH column (0-5% 7 N NH_3 in MeOH/DCM) followed by preparative HPLC gave **173** as a colourless solid (18 mg, 17% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.26 (s, 1H), 7.36-7.29 (m, 1H), 7.06-6.99 (m, 2H), 6.18 (s, 2H), 5.73 (s, 1H), 4.11 (d, J = 11.2 Hz, 2H), 3.87 (s, 3H), 3.78 (d, J = 11.2 Hz, 2H), 2.53 (s, 2H), 1.83 (q, J = 7.6 Hz, 2H), 0.84 (t, J = 7.6 Hz, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 479 (M+1).

Example 174 5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **174**

Following the procedure for Example 111 starting from *tert*-Butyl *N*-[(3*S*,4*R*,7*S*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate (intermediate 78) gave **170** as a pale brown solid (32 mg, 79% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.22 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.58-7.49 (m, 2H), 7.33-7.24 (m, 2H), 4.82-4.77 (m, 1H), 4.08 (dd, J = 13.9, 3.1 Hz, 1H), 3.86 (dd, J = 13.9, 3.7 Hz, 1H), 3.76 (s, 3H), 3.20-3.15 (m, 1H), 3.12-3.04 (m, 1H), 2.09-2.01 (m, 1H), 1.85-1.66 (m, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 482 (M+1).

Example 175 5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **175**

2,2,2-trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide (171 mg, 0.49 mmol, intermediate 84) was dissolved in MeOH (30 mL) and ammonium formate (170 mg, 2.69 mmol) and 10% Pd/C (140 mg, 0.13 mmol) were added. The mixture was heated at reflux for 18 hr before being cooled to room temperature. The suspension was filtered, the cake washed with EtOAc (100 mL) and the filtrate concentrated under reduced pressure. The crude residue was dissolved in EtOAc (10 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (131 mg, 0.51 mmol) was then added followed by *N*-methylmorpholine (0.11 mL, 1.46 mmol). Propylphosphonic anhydride solution (50% wt in EtOAc, 338 mg, 0.53 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure and purified *via* silica gel chromatography (0-5% 7 N NH_3 in MeOH/DCM) to give 5-amino-2-(2,6-difluorophenyl)-*N*-(1-methyl-5-(5-methyl-5-((2,2,2-trifluoroacetamido)methyl)-1,3-dioxan-2-yl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide as a white solid (102 mg, 18% over three steps). A mixture of 5-amino-2-(2,6-difluorophenyl)-*N*-(1-methyl-5-(5-methyl-5-((2,2,2-trifluoroacetamido)methyl)-1,3-dioxan-2-yl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide (101 mg, 0.18 mmol) in MeOH (6 mL) and aqueous saturated K_2CO_3 solution (0.6 mL) was heated in a microwave at 100 °C for 1 hr. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and purified *via* silica gel chromatography (0-20% MeOH/DCM) to give **175** as a white solid (4 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.24 (s, 1H), 7.34-7.27 (m, 1H), 7.05-6.97 (m, 2H), 6.15 (s, 2H), 5.70 (s, 1H), 3.98-3.91 (m, 2H), 3.86 (s, 3H), 3.80 (d, J = 11.0 Hz, 2H), 2.54 (s, 2H), 1.26 (s, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 465 (M+1).

Example 176 5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **176**

Following the procedure for Example 111 starting from *tert*-butyl *N*-[(3*S*,4*R*,7*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 81) gave **176** as a beige solid (17 mg, 11% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.29 (s, 1H), 7.80 (s, 1H), 7.56-7.46 (m, 3H), 7.29-7.19 (m, 2H), 4.78 (dd, J = 10.90, 3.48 Hz, 1H), 4.44-4.26 (m, 1H), 4.21-3.91 (m, 2H), 3.76 (s, 3H), 3.40-3.15 (m, 1H), 2.08-2.00 (m, 1H), 1.88-1.60 (m, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 467 (M+1).

Example 177 5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **177**

Following the procedure for Example 111 starting from *tert*-butyl *N*-[(3*R*,4*S*,7*R*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (intermediate 80) gave **177** as a beige solid (37 mg, 19% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.29 (s, 1H), 7.80 (s, 1H), 7.56-7.46 (m, 3H), 7.29-7.19 (m, 2H), 4.78 (dd, *J* = 10.87, 3.53 Hz, 1H), 4.44-4.26 (m, 1H), 4.20-3.89 (m, 2H), 3.77 (s, 3H), 3.40-3.15 (m, 1H), 2.10-1.60 (m, 6H). LCMS (ES+) m/z 467 (M+1).

Example 178 5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **178**

To a solution of 2,2,2-trifluoro-*N*-((5-methyl-2-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-1,3-dioxan-5-yl)methyl)acetamide (410 mg, 1.16 mmol, intermediate 83) in MeOH (20 mL) was added ammonium formate (400 mg, 6.34 mmol) and 10% Pd/C (400 mg). The mixture was heated at reflux for 5 hr then cooled to room temperature. The suspension was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in IPA (10 mL) and 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (312 mg, 1.22 mmol) and DIPEA (0.62 mL, 3.47 mmol) were then added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.61 mL, 1.28 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. Saturated aqueous $NaHCO_3$ solution (10 mL) and DCM (20 mL) were added. The organic layer was washed with 1 N HCl (10 mL), separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* silica gel chromatography (0-5% 7 N NH_3 in MeOH/DCM) gave 5-amino-2-(2,6-difluorophenyl)-*N*-(1-methyl-5-(5-methyl-5-((2,2,2-trifluoroacetamido)methyl)-1,3-dioxan-2-yl)-1*H*-pyrazol-4-yl)thiazole-4-carboxamide as an oil. To a solution of this oil in IPA (2 mL), THF (2 mL) and water (1 mL) was added K_2CO_3 (31 mg, 0.22 mmol) and the mixture heated at 50 °C for 18 hr. More K_2CO_3 (300 mg, 2.2 mmol) was added and the mixture heated in a microwave at 120 °C for 2.5 hr. The reaction mixture was cooled to room temperature, filtered washing with EtOAc (20 mL) and the filtrate concentrated under reduced pressure. The residue was passed through an SCX column eluting with 0-5% 7 N NH_3 in MeOH/DCM) and purified by preparative HPLC to give **178** as a colourless solid (1 mg, 0.2 % over three steps). ^{1}H NMR (400 MHz, d_4-MeOD) δ 8.45 (s, 2H), 8.01 (s, 1H), 7.39-7.32 (m, 1H), 7.06 (t, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 3.98 (d, *J* = 11.6 Hz, 2H), 3.74-3.65 (m, 5H), 2.86 (s, 2H), 0.69 (s, 3H). LCMS (ES+) m/z 465 (M+1).

Example 179 5-Amino-*N*-[5-[5-amino-4,4-difluoro-5,6-dimethyl-tetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **179**

A solution of 5-(5-azido-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-4-nitro-1*H*-pyrazole (152 mg, 0.481 mmol, intermediate 87) in THF/water (5 mL/0.5 mL) was treated with triphenylphosphine (190 mg, 0.72 mmol) and the mixture was heated at 65 °C

behind a blast shield for 18 hr. The mixture was concentrated under reduced pressure to give a colourless oil (74 mg). A solution of this oil (74 mg, 0.255 mmol) in MeOH (20 mL) was passed through the H-Cube® (full H_2, 85 °C, flow rate: 1 mL/min, 30 mm RaNi cartridge). The solvent was removed under reduced pressure and the residue dissolved in EtOAc (1 mL). 5-Amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (69 mg, 0.268 mmol) and *N*-methylmorpholine (0.08 mL, 0.765 mmol) were added. Propylphosphonic anhydride solution (50% wt in EtOAc, 0.1 mL, 0.281 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure and purified *via* silica gel chromatography (0-5% 7 N NH_3 in MeOH/DCM) to give **179** as a colourless solid (33 mg, 13% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.00 (s, 1H), 7.40-7.31 (m, 1H), 7.06-6.96 (m, 2H), 6.16 (s, 2H), 4.87 (dd, J = 12.1, 2.7 Hz, 1H), 3.84 (s, 3H), 3.77-3.71 (m, 1H), 2.68-2.50 (m, 1H), 2.18-2.08 (m, 1H), 1.34 (s, 2H), 1.22 (d, J = 6.4 Hz, 3H), 1.08 (d, J = 1.8 Hz, 3H). LCMS (ES+) m/z 499 (M+1).

Example 180 5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide **180**

Following the procedure for Example 111 starting from *tert*-butyl *N*-[(3*R*,4*S*)-7-(2-methyl-4-nitro-pyrazol-3-yl)-3-(trideuteriomethoxy)oxepan-4-yl]carbamate (intermediate 77) gave **180** as a solid (15 mg, 22% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.24 (s, 1H), 7.77 (s, 1H), 7.57-7.48 (m, 3H), 7.31-7.23 (m, 2H), 4.79 (dd, J = 10.8, 3.6 Hz, 1H), 4.02 (dd, J = 13.8, 3.0 Hz, 1H), 3.80 (dd, J = 13.8, 3.1 Hz, 1H), 3.75 (s, 3H), 3.01-2.93 (m, 2H), 2.00 (s, 1H), 1.83-1.54 (m, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 482 (M+1).

Example 181 5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,3-difluorophenyl)thiazole-4-carboxamide **181**

Following the procedure for Example 111 starting from *tert*-butyl *N*-[(3*S*,4*R*,7*S*)-3-fluoro-7-(2-methyl-4-nitro-pyrazol-3-yl)oxepan-4-yl]carbamate (Intermediate 88), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-(tert-butoxycarbonylamino)-2-(2,3-difluorophenyl)thiazole-4-carboxylic acid (Example 25) gave **181** as the hydrochloride salt as a pale pink solid (30 mg, 38% over three steps). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.42 (s, 1H), 8.54-8.41 (m, 4H), 7.96-7.89 (m, 1H), 7.67 (s, 1H), 7.50-7.39 (m, 3H), 5.28 (m, 1H), 4.84 (d, J = 10.4 Hz, 1H), 4.33-4.17 (m, 1H), 4.11-3.99 (m, 1H), 3.78 (s, 3H), 3.74-3.52 (m, 1H), 2.16-1.81 (m, 4H). LCMS (ES+) m/z 467 (M+1).

Example 182 5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide **182**

A mixture of *tert*-butyl *N*-[2-bromo-4-[[5-[(2*S*,5*R*,6*R*)-5-(*tert*-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (100 mg, 0.16 mmol, intermediate 88), 3-fluoro-4-tri-*n*-butylstannyl pyridine (93 mg, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (9.3 mg, 0.008 mmol), copper (I) iodide (9 mg, 0.047 mmol) and lithium chloride (21 mg, 0.48 mmol) in dioxane (1.5 mL) was degassed by bubbling nitrogen gas through it for 5 min. The mixture was heated at 135 °C under microwave irradiation for 45 min. After cooling to room temperature, more 3-fluoro-4-tri-*n*-butylstannyl pyridine (93 mg, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (9.3 mg, 0.008 mmol), copper (I) iodide (9 mg, 0.047 mmol) and lithium chloride (21 mg, 0.48 mmol) were added and the mixture was degassed by bubbling nitrogen gas through it for 5 min. The mixture was heated at 135 °C for 45 min, cooled to room temperature, filtered through celite and the filtrate concentrated under reduced pressure. Purification *via* silica gel column chromatography (0-80% EtOAc/isohexane) gave *tert*-butyl *N*-[4-[[5-[(2*S*,5*R*,6*R*)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]-2-(3-fluoro-4-pyridyl)thiazol-5-yl]carbamate as a pale brown solid. This solid was stirred in a solution of HCl (4.0 M in dioxane, 3 mL) and MeOH (0.5 mL) at room temperature for 18 hr. The solvents were removed under reduced pressure. Purification *via* preparative HPLC gave **182** as the formate salt as a pale pink solid (26 mg, 33%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.27 (s, 1H), 8.43 (d, *J* = 2.8 Hz, 1H), 8.28-8.23 (m, 1H), 8.00 (s, 1H), 7.78-7.72 (m, 1H), 7.47 (s, 1H), 7.42 (br s, 2H), 4.78-4.58 (m, 2H), 3.99-3.85 (m, 1H), 3.79-3.67 (m, 1H), 3.49 (s, 3H), 3.17-3.02 (m, 1H), 1.90-1.80 (m, 1H), 1.67-1.51 (m, 2H), 1.41 (d, *J* = 13.1 Hz, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 450 (M+1).

Example 183 5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide **183**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-methoxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 93), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carboxylic acid (Example 7) gave **183** as the hydrochloride salt as a dark salmon pink solid (68 mg, 45%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.47 (s, 1H), 8.18-8.09 (m, 5H), 7.74 (s, 1H), 7.52-7.36 (m, 4H), 4.96 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.19 (dd, *J* = 13.6, 5.0 Hz, 1H), 4.00 (dd, *J* = 13.6, 5.3 Hz, 1H), 3.86 (d, *J* = 4.5 Hz, 1H), 3.78 (s, 3H), 3.62-3.49 (m, 1H), 3.33 (s, 3H), 2.14-1.97 (m, 2H), 1.98-1.74 (m, 2H). LCMS (ES+) m/z 461 (M+1).

Example 184 5-Amino-*N*-(5-((2*R*,5*S*,6*R*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **184**

5-Amino-*N*-(5-(5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6 difluorophenyl)thiazole-4-carboxamide (Example 179) was further purified *via* chiral preparative HPLC to give **184** as the first eluting enantiomer as a colourless solid (15 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.00 (s, 1H), 7.35 (d, *J* = 7.81 Hz, 1H), 7.04-6.97 (m, 2H), 6.15 (s, 2H), 4.87 (dd, *J* = 12.1, 2.7 Hz, 1H), 3.84 (s, 3H), 3.76-3.69 (m, 1H), 2.66-2.52 (m, 1H), 2.18-2.08 (m, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 1.8 Hz, 3H). Alkyl NH_2 not observed. LCMS (ES+) m/z 499 (M+1).

Example 185 5-Amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **185**

Following the procedure for Example 184 also gave **185** as the second eluting enantiomer as a colourless solid (15 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.00 (s, 1H), 7.41-7.31 (m, 1H), 7.05-6.95 (m, 2H), 6.16 (s, 2H), 4.87 (dd, *J* = 12.1, 2.6 Hz, 1H), 3.84 (s, 3H), 3.77-3.71 (m, 1H), 2.69-2.51 (m, 1H), 2.18-2.08 (m, 1H), 1.34 (s, 2H), 1.23 (t, *J* = 8.2 Hz, 3H), 1.08 (d, *J* = 1.8 Hz, 3H). LCMS (ES+) m/z 499 (M+1).

Example 186 5-Amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide **186**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carboxylic acid (Example 7) gave **186** as the hydrochloride salt as a white solid (38 mg, 71%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.47 (s, 1H), 8.60-8.40 (m, 3H), 8.19-8.13 (m, 1H), 7.71 (s, 1H), 7.49-7.35 (m, 3H), 5.40-5.23 (m, 1H), 4.87 (d, *J* = 10.5 Hz, 1H), 4.28 (ddd, *J* = 32.0, 14.5, 4.7 Hz, 1H), 4.07 (ddd, *J* = 23.4, 14.5, 2.8 Hz, 1H), 3.80 (s, 3H), 3.78-3.60 (m, 1H), 2.19-1.82 (m, 4H). LCMS (ES+) m/z 449 (M+1). Alkyl NH_2 not observed.

Example 187 *N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide **187**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid (see WO2010/56576) gave **187** as a white solid solid (22 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.31 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.21 (s, 1H), 7.71-7.63 (m, 1H), 6.64 (d, *J* = 10.1 Hz, 2H), 4.84-4.73 (m, 2H), 4.07-3.89 (m,

3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.41 (dd, *J* = 23.1, 9.5 Hz, 1H), 2.67 (br s, 1H), 2.15-2.08 (m, 1H), 2.08-1.94 (m, 1H), 1.95-1.84 (m, 1H), 1.85-1.73 (m, 1H). LCMS (ES+) m/z 494 (M+1).

Example 188 *N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide **188**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **188** as a white solid (12 mg, 27%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.24 (s, 1H), 8.25 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.17-8.09 (m, 1H), 7.85 (s, 1H), 7.40-7.00 (br s, 2H), 7.20 (d, *J* = 11.6 Hz, 2H), 5.30 (d, *J* = 48 Hz, 1H), 4.92-4.86 (m, 2H), 4.11-4.00 (m, 2H), 3.92-3.84 (m, 2H), 3.75 (s, 3H), 3.62-3.50 (m, 3H), 2.07 (m, 4H), 1.95-1.70 (m, 2H), 1.68-1.55 (m, 2H). LCMS (ES+) m/z 564 (M+1).

Example 189 *N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide **189**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **189** as a white solid (19 mg, 50%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.45 (s, 1H), 8.26 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.19-8.09 (m, 1H), 7.95 (s, 1H), 7.03 (d, *J* = 10.5 Hz, 2H), 4.95 (dd, *J* = 8.3, 3.6 Hz, 1H), 4.69 (s, 1H), 4.57 (s, 1 H), 4.24 (t, *J* = 4.2 Hz, 2H), 3.98-3.78 (m, 2H), 3.73 (s, 3H), 3.70 (t, *J* = 4.2 Hz, 2H), 3.30 (s, 3H), 3.15 (m, 1H), 2.20-2.11 (m, 1H), 1.89-1.72 (m, 2H), 1.72-1.62 (m, 1H), 1.59-1.50 (m, 1H). LCMS (ES+) m/z 538 (M+1).

Example 190 *N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide **190**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(4-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinic acid (see US2012/225062) gave **190** as a white solid (29 mg, 62%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.59 (s, 1H), 8.40 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.27 (dd, *J* = 8.6, 8.6 Hz, 1H), 8.10 (s, 1H), 7.15 (d, *J* = 10.5 Hz, 2H), 5.09 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.86-4.83 (d, *J* = 48 Hz, 1H), 4.28 (t, *J* = 4.8 Hz, 2H), 4.12-3.92 (m, 2H), 3.92-3.86 (m, 5H), 3.70-3.38 (br s, 1H), 3.36-3.24 (m, 1H), 2.33-2.25 (m,

1H), 2.02-1.87 (m, 1H), 1.87-1.75 (m, 1H), 1.75-1.63 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 524 (M+1).

Example 191 *N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-hydroxyoxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide **191**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-hydroxy-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 94), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **191** as a white solid (73 mg, 71%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.22 (s, 1H), 8.25 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.12 (t, *J* = 8.9 Hz, 1H), 7.82 (s, 1H), 6.97 (d, *J* = 10.2 Hz, 2H), 4.79 (dd, *J* = 10.8, 3.4 Hz, 2H), 4.26-4.20 (m, 2H), 3.90-3.67 (m, 4H), 3.73-3.67 (m, 2H), 3.63 (dd, *J* = 12.8, 5.8 Hz, 1H), 3.62-3.02 (m, 3H), 2.73-2.64 (m, 1H), 2.00-1.92 (m, 1H), 1.92-1.79 (m, 1H), 1.79-1.72 (m, 1H), 1.55-1.42 (m, 1H). Alkyl NH_2 not observed. LCMS (ES+) m/z 536 (M+1).

Example 192 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide **192**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **192**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.26 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.11 (t, *J* = 8.9 Hz, 1H), 7.91 (s, 1H), 7.01 – 6.91 (m, 2H), 4.82 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.32 – 4.12 (m, 3H), 4.05 – 3.85 (m, 2H), 3.75 (s, 3H), 3.74 – 3.65 (m, 2H), 3.32 (s, 3H), 3.06 (dd, *J* = 16.5, 7.8 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.82 – 1.57 (m, 5H). LCMS (ES+) m/z 538 (M+1).

Example 193 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinamide **193**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **193**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.30 (dd, *J* = 8.7, 4.0 Hz, 1H), 8.23 – 8.12 (m, 1H), 7.90 (s, 1H), 7.49 (d, *J* = 9.7 Hz, 2H), 4.81 (t, *J* = 5.7 Hz, 3H), 4.73 (dd, *J* = 7.0, 1.4 Hz, 2H), 4.41 – 4.17 (m, 1H), 4.10 – 3.87 (m, 2H), 3.76 (s, 3H), 3.19 – 3.09 (m, 1H), 2.11 – 2.02 (m, 1H), 1.69 (s, 3H). LCMS (ES+) m/z 536 (M+1).

Example 194 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinamide **194**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **194**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.32 (dd, J = 8.7, 4.0 Hz, 1H), 8.18 (t, J = 8.9 Hz, 1H), 7.93 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 5.02 (s, 2H), 4.97 (s, 2H), 4.82 (dd, J = 10.3, 3.7 Hz, 1H), 4.31 – 4.05 (m, 1H), 4.07 – 3.84 (m, 2H), 3.75 (s, 3H), 3.09 – 2.95 (m, 1H), 2.10 – 1.99 (m, 1H), 1.80 – 1.57 (m, 5H). LCMS (ES+) m/z 538 (M+1).

Example 195 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide **195**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluorophenyl)-5-fluoropicolinic acid (see US2012/225061) gave **195**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.30 (dd, J = 8.7, 4.0 Hz, 1H), 8.15 (t, J = 8.9 Hz, 1H), 7.91 (s, 1H), 7.72 – 7.59 (m, 1H), 7.30 (t, J = 8.4 Hz, 2H), 4.86 – 4.78 (m, 1H), 4.31 – 4.05 (m, 1H), 4.02 – 3.83 (m, 2H), 3.75 (s, 3H), 3.11 – 2.97 (m, 1H), 2.11 – 2.00 (m, 1H), 1.82 – 1.50 (m, 5H). LCMS (ES+) m/z 464 (M+1).

Example 196 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide **196**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **196**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.29 (dd, J = 8.7, 4.0 Hz, 1H), 8.23 – 8.10 (m, 1H), 7.88 (s, 1H), 7.49 – 7.35 (m, 2H), 4.85 – 4.76 (m, 1H), 4.39 – 4.11 (m, 1H), 4.07 – 3.68 (m, 9H), 3.17 – 3.03 (m, 1H), 2.11 – 1.99 (m, 3H), 1.84 – 1.51 (m, 5H). LCMS (ES+) m/z 564 (M+1).

Example 197 *N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide **197**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-

difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **197**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.25 (dd, J = 8.7, 4.0 Hz, 1H), 8.11 (t, J = 8.9 Hz, 1H), 7.91 (s, 1H), 6.99 (d, J = 10.2 Hz, 2H), 4.82 (dd, J = 10.4, 3.7 Hz, 1H), 4.77 – 4.66 (m, 1H), 4.21 (ddd, J = 49.1, 7.8, 2.9 Hz, 1H), 4.10 – 3.90 (m, 2H), 3.90 – 3.80 (m, 2H), 3.75 (s, 3H), 3.51 (ddd, J = 12.0, 9.4, 2.8 Hz, 2H), 3.14 – 3.01 (m, 1H), 2.10 – 1.97 (m, 3H), 1.85 – 1.55 (m, 5H). LCMS (ES+) m/z 564 (M+1).

Example 198 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide **198**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **198**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.29 (dd, J = 8.7, 4.0 Hz, 1H), 8.14 (t, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.35 (d, J = 9.5 Hz, 2H), 5.89 (br, 1H), 4.80 (dd, J = 10.5, 3.7 Hz, 1H), 4.32 – 4.07 (m, 1H), 4.07 – 3.84 (m, 2H), 3.75 (s, 3H), 3.11 – 3.00 (m, 1H), 2.50 – 2.39 (m, 2H), 2.38 – 2.26 (m, 2H), 2.09 – 1.88 (m, 2H), 1.84 – 1.68 (m, 2H), 1.67 – 1.57 (m, 2H).LCMS (ES+) m/z 534 (M+1).

Example 199 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(methoxymethyl)phenyl)-5-fluoropicolinamide **199**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(methoxymethyl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **199**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.29 (dd, J = 8.6, 4.0 Hz, 1H), 8.15 (t, J = 8.8 Hz, 1H), 7.91 (s, 1H), 7.24 (d, J = 9.0 Hz, 2H), 4.81 (dd, J = 10.3, 3.7 Hz, 1H), 4.53 (s, 2H), 4.31 – 4.07 (m, 1H), 4.02 – 3.83 (m, 2H), 3.75 (s, 3H), 3.36 (s, 3H), 3.11 – 2.98 (m, 1H), 2.10 – 2.00 (m, 1H), 1.82 – 1.57 (m, 3H). LCMS (ES+) m/z 508 (M+1).

Example 200 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide **200**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **200**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.28 (dd, J = 8.7, 4.0 Hz, 1H), 8.14 (t, J = 8.9 Hz, 1H), 7.89 (s, 1H), 7.34 (d, J = 9.8 Hz, 2H), 5.36 (br, 1H), 4.80 (dd, J = 10.4, 3.7 Hz, 1H),

4.37 – 4.06 (m, 1H), 4.02 – 3.87 (m, 2H), 3.75 (s, 3H), 3.13 – 3.00 (m, 1H), 2.10 – 1.99 (m, 1H), 1.85 – 1.57 (m, 3H), 1.47 (s, 6H). LCMS (ES+) m/z 522 (M+1).

Example 201 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide **201**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid (see US2012/225062) gave **201**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.26 (dd, J = 8.7, 4.0 Hz, 1H), 8.11 (t, J = 8.9 Hz, 1H), 7.90 (s, 1H), 6.94 (d, J = 10.2 Hz, 2H), 4.82 (dd, J = 10.4, 3.7 Hz, 1H), 4.40 – 4.14 (m, 1H), 4.08 – 3.91 (m, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.18 – 3.04 (m, 1H), 2.12 – 2.02 (m, 1H), 1.83 – 1.60 (m, 3H). LCMS (ES+) m/z 494 (M+1).

Example 202 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide **202**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **202**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.32 (dd, J = 8.7, 4.0 Hz, 1H), 8.17 (t, J = 8.9 Hz, 1H), 7.94 (s, 1H), 7.42 (d, J = 9.3 Hz, 2H), 4.87 – 4.75 (m, 5H), 4.17 (ddt, J = 49.0, 6.1, 2.6 Hz, 1H), 4.03 – 3.84 (m, 2H), 3.75 (s, 3H), 3.14 (s, 3H), 3.12 – 2.98 (m, 1H), 2.11 – 2.00 (m, 1H), 1.80 – 1.57 (m, 3H). LCMS (ES+) m/z 550 (M+1).

Example 203 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide **203**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid (see WO2012/225062) gave **203**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.31 (dd, J = 8.7, 4.0 Hz, 1H), 8.19 (t, J = 8.9 Hz, 1H), 7.95 (s, 1H), 7.49 (d, J = 9.3 Hz, 2H), 4.96 (dd, J = 8.1, 4.0 Hz, 1H), 4.81 (d, J = 1.7 Hz, 4H), 4.65 – 4.37 (m, 1H), 3.97 – 3.73 (m, 2H), 3.72 (s, 3H), 3.41 – 3.25 (m, 2H), 3.15 (s, 3H), 3.12 – 2.99 (m, 1H), 2.22 – 2.12 (m, 1H), 1.81 – 1.71 (m, 1H), 1.70 – 1.60 (m, 1H), 1.57 – 1.52 (m, 3H). LCMS (ES+) m/z 550 (M+1).

Example 204 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)-5-fluoropicolinamide **204**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **204**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.27 (dd, J = 8.7, 4.0 Hz, 1H), 8.13 (t, J = 8.9 Hz, 1H), 7.90 (s, 1H), 7.09 (d, J = 9.8 Hz, 2H), 6.26 (s, 1H), 4.81 (dd, J = 10.5, 3.7 Hz, 1H), 4.34 – 4.09 (m, 1H), 4.07 – 3.84 (m, 2H), 3.75 (s, 3H), 3.12 – 2.99 (m, 1H), 2.11 – 1.99 (m, 1H), 1.83 – 1.53 (m, 5H), 1.27 – 1.08 (m, 4H). LCMS (ES+) m/z 520 (M+1).

Example 205 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-propionylphenyl)-5-fluoropicolinamide **205**

The title compound **205** was prepared as a second product during the formation of Example 204, and was separated during the final HPLC purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.34 (dd, J = 8.7, 4.1 Hz, 1H), 8.20 (t, J = 8.9 Hz, 1H), 7.93 (s, 1H), 7.84 (d, J = 8.6 Hz, 2H), 4.81 (ddd, J = 10.8, 6.7, 3.7 Hz, 1H), 4.31 – 4.05 (m, 1H), 4.05 – 3.82 (m, 2H), 3.76 (s, 3H), 3.13 (q, J = 7.1 Hz, 2H), 3.07 – 2.97 (m, 1H), 2.10 – 2.01 (m, 1H), 1.79 – 1.56 (m, 3H), 1.54 (br, 2H), 1.12 (t, J = 7.1 Hz, 3H). LCMS (ES+) m/z 520 (M+1).

Example 206 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide **206**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **206**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.30 (dd, J = 8.7, 4.0 Hz, 1H), 8.17 (t, J = 8.9 Hz, 1H), 7.92 (s, 1H), 7.41 (d, J = 9.2 Hz, 2H), 4.81 (dd, J = 10.3, 3.8 Hz, 1H), 4.17 (ddd, J = 49.1, 5.9, 3.1 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.96 – 3.84 (m, 3H), 3.75 (s, 3H), 3.74 – 3.64 (m, 2H), 3.09 – 2.99 (m, 1H), 2.33 – 2.13 (m, 2H), 2.10 – 1.99 (m, 1H), 1.93 – 1.80 (m, 2H), 1.80 – 1.52 (m, 5H). LCMS (ES+) m/z 566 (M+1).

Example 207 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide **207**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinic acid (Intermediate 136) gave **207**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s,

1H), 8.28 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.14 (t, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 5.51 (br, 1H), 4.87 – 4.76 (m, 2H), 4.36 – 4.08 (m, 1H), 4.03 – 3.84 (m, 2H), 3.75 (s, 3H), 3.10 – 3.00 (m, 1H), 2.10 – 2.00 (m, 1H), 1.85 – 1.68 (m, 1H), 1.67 – 1.57 (m, 2H), 1.37 (d, *J* = 6.4 Hz, 3H). LCMS (ES+) m/z 508 (M+1).

Example 208 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide **208**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinic acid (Intermediate 137) gave **208**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.23 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.08 (t, *J* = 8.8 Hz, 1H), 7.91 (s, 1H), 6.62 (d, *J* = 10.1 Hz, 2H), 4.81 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.39 – 4.14 (m, 1H), 4.10 – 3.87 (m, 2H), 3.75 (s, 3H), 3.16 – 3.03 (m, 1H), 2.10 – 1.99 (m, 1H), 1.82 – 1.56 (m, 3H). LCMS (ES+) m/z 480 (M+1).

Example 209 *N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide **209**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(4-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinic acid (see US2012/225062) gave **209**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.26 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.11 (t, *J* = 8.9 Hz, 1H), 7.92 (s, 1H), 6.93 (d, *J* = 10.2 Hz, 2H), 4.98 (br, 1H), 4.82 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.24 (ddt, *J* = 49.2, 6.1, 2.6 Hz, 1H), 4.11 (t, *J* = 4.8 Hz, 2H), 4.07 – 3.84 (m, 2H), 3.80-3.69 (m, 5H), 3.15 – 3.01 (m, 1H), 2.12 – 2.01 (m, 1H), 1.83 – 1.58 (m, 3H). LCMS (ES+) m/z 524 (M+1).

Example 210 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide **210**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinic acid (Intermediate 136) gave **210**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.34 – 8.24 (m, 1H), 8.16 (t, *J* = 8.9 Hz, 1H), 7.91 (s, 1H), 7.38 – 7.28 (m, 2H), 4.94 – 4.79 (m, 2H), 4.76 – 4.49 (m, 1H), 4.02 – 3.77 (m, 2H), 3.73 (s, 3H), 3.20 – 3.04 (m, 1H), 2.16 – 2.04

(m, 1H), 1.91 – 1.77 (m, 1H), 1.74 – 1.55 (m, 2H), 1.39 (d, *J* = 6.5 Hz, 3H). LCMS (ES+) m/z 508 (M+1).

Example 211 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinamide **211**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinic acid (Intermediate 138) gave **211**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.29 (dd, *J* = 8.7, 4.0 Hz, 1H), 8.17 (t, *J* = 8.9 Hz, 1H), 7.94 (s, 1H), 7.35 – 7.26 (m, 2H), 4.95 (dd, *J* = 8.3, 3.9 Hz, 1H), 4.67 – 4.38 (m, 2H), 3.99 – 3.75 (m, 2H), 3.72 (s, 3H), 3.23 (s, 3H), 3.17 – 3.04 (m, 1H), 2.21 – 2.10 (m, 1H), 1.82 – 1.74 (m, 1H), 1.71 – 1.60 (m, 1H), 1.62 – 1.50 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 3H). LCMS (ES+) m/z 522 (M+1).

Example 212 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1,2,3-trihydroxypropan-2-yl)phenyl)-5-fluoropicolinamide **212**

Following the procedure for Example 111 starting from *tert*-butyl ((3*R*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **212**. Oxetane hydrolysis occurs during acidic deprotection. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.26 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.16 (t, *J* = 8.8 Hz, 1H), 7.92 (s, 1H), 7.44 – 7.36 (m, 2H), 4.84 (d, *J* = 9.5 Hz, 1H), 4.76 – 4.50 (m, 1H), 3.88 (d, *J* = 4.5 Hz, 1H), 3.82 (d, *J* = 4.4 Hz, 1H), 3.72 (s, 3H), 3.67 (d, *J* = 11.7 Hz, 1H), 3.57 (dd, *J* = 11.1, 5.4 Hz, 2H), 2.96 (dd, *J* = 26.7, 10.0 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.90 – 1.82 (m, 1H), 1.73 – 1.62 (m, 1H), 1.61 – 1.53 (m, 1H). LCMS (ES+) m/z 554 (M+1).

Example 213 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinamide **213**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinic acid (Intermediate 141) gave **213**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (d, *J* = 4.5 Hz, 1H), 8.30 (dd, *J* = 8.6, 4.0 Hz, 1H), 8.15 (t, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 1.3 Hz, 1H), 7.26 (d, *J* = 9.2 Hz, 2H), 4.82 (ddd, *J* = 10.3, 3.9, 1.5 Hz, 1H), 4.30 – 4.04 (m, 1H), 4.06 – 3.83 (m, 2H), 3.75 (s, 3H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.24 (s, 3H), 3.14 – 3.00 (m,

1H), 2.04 (s, 1H), 1.81 – 1.56 (m, 5H), 1.16 – 1.02 (m, 1H), 0.66 – 0.33 (m, 4H). LCMS (ES+) m/z 548 (M+1).

Example 214 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(1,3-dihydroxypropan-2-yl)-2,6-difluorophenyl)-5-fluoropicolinamide **214**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinic acid (see US2012/225062) gave **214**. Oxetane hydrolysis occurs during acidic deprotection. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.28 (dd, J = 8.7, 4.0 Hz, 1H), 8.14 (t, J = 8.8 Hz, 1H), 7.73 (s, 1H), 7.20 (d, J = 9.7 Hz, 2H), 4.90 – 4.76 (m, 1H), 4.77 – 4.54 (m, 1H), 4.23 – 3.94 (m, 2H), 3.80 (s, 3H), 3.77 – 3.61 (m, 4H), 3.55 – 3.38 (m, 1H), 3.01 – 2.92 (m, 1H), 2.20 – 2.03 (m, 1H), 2.00 – 1.70 (m, 3H). LCMS (ES+) m/z 538 (M+1).

Example 215 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide **215**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxylic acid (Intermediate 144) gave **215**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.62 (s, 1H), 7.81 (s, 1H), 7.43 (d, J = 10.3 Hz, 2H), 5.81 (s, 1H), 4.81 (dd, J = 10.8, 3.7 Hz, 1H), 4.44 – 4.24 (m, 1H), 4.24 – 4.08 (m, 1H), 4.09 – 3.90 (m, 3H), 3.79 (d, J = 8.1 Hz, 5H), 3.34 – 3.16 (m, 2H), 2.54 – 2.49 (m, 1H), 2.39 – 2.27 (m, 1H), 2.21 – 2.01 (m, 2H), 1.88 – 1.76 (m, 1H), 1.72 – 1.62 (m, 4H). LCMS (ES+) m/z 538 (M+1).

Example 216 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide **216**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxylic acid (Intermediate 145) gave **216**. The product was isolated as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 7.27 (d, J = 10.0 Hz, 2H), 4.81 (dd, J = 10.8, 3.7 Hz, 1H), 4.46 – 4.22 (m, 1H), 4.24 – 4.09 (m, 1H), 4.08 – 3.89 (m, 3H), 3.86 – 3.75 (m, 4H), 3.63 (dd, J = 8.4,

6.9 Hz, 1H), 3.58 – 3.45 (m, 1H), 3.34 – 3.16 (m, 3H), 2.42 – 2.29 (m, 1H), 2.11 – 1.91 (m, 2H), 1.87 – 1.79 (m, 1H), 1.72 – 1.62 (m, 4H). LCMS (ES+) m/z 522 (M+1).

Example 217 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*R*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide **217**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with (*R*)-2-(2,6-difluoro-4-((tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxylic acid (Intermediate 147) gave **217**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.56 (s, 1H), 7.80 (s, 1H), 7.44 (s, 3H), 7.06 – 6.95 (m, 2H), 5.18 (td, *J* = 4.6, 2.4 Hz, 1H), 4.95 – 4.59 (m, 2H), 4.37 – 4.04 (m, 2H), 3.95 – 3.72 (m, 8H), 3.55 (dt, *J* = 17.6, 8.8 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.13 (d, *J* = 11.6 Hz, 1H), 2.06 – 1.80 (m, 5H). LCMS (ES+) m/z 538 (M+1).

Example 218 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*S*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide **218**

Following the procedure for Example 111 starting from *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with (*S*)-2-(2,6-difluoro-4-((tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxylic acid (Intermediate 148) gave **218**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.55 (s, 1H), 7.80 (s, 1H), 7.02 – 6.92 (m, 2H), 5.19 (dd, *J* = 6.2, 4.2 Hz, 1H), 4.80 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.46 – 4.07 (m, 2H), 4.08 – 3.72 (m, 8H), 3.30 – 3.14 (m, 1H), 2.36 – 2.22 (m, 1H), 2.02 (ddd, *J* = 19.6, 14.6, 9.1 Hz, 2H), 1.81 (ddd, *J* = 14.3, 10.2, 4.9 Hz, 1H), 1.68 (s, 4H). LCMS (ES+) m/z 538 (M+1).

Example 219 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide **219**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3-difluorophenyl)boronic acid gave **219**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.90 – 7.82 (m, 2H), 7.56 – 7.42 (m, 3H), 7.38 – 7.30 (m, 1H), 5.07 (t, *J* = 5.7 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.88 – 3.80 (m, 1H), 3.71 (s, 3H), 3.50 – 3.45 (m, 1H), 3.14 (d, *J* = 1.5 Hz, 3H), 2.36 – 2.31 (m, 2H), 1.76 – 1.71 (m, 1H), 1.63 – 1.58 (m, 4H), 1.50 – 1.45 (m, 1H). LCMS (ES+) m/z 479 (M+1).

Example 220 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **220**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-(trifluoromethyl)phenyl)boronic acid gave **220**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.93 – 7.86 (m, 2H), 7.81 – 7.63 (m, 3H), 7.44 (s, 2H), 5.04 (t, *J* = 5.1 Hz, 1H), 3.73 – 3.57 (m, 5H), 3.29 – 3.15 (m, 2H), 2.74 (s, 3H), 2.48 – 2.35 (m, 1H), 1.65 – 1.47 (m, 3H), 1.41 (br, 2H). LCMS (ES+) m/z 511 (M+1).

Example 221 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **221**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate (Intermediate 101), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,6-difluorophenyl)boronic acid gave **221**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.65 (s, 1H), 7.92 (s, 1H), 7.74 – 7.62 (m, 1H), 7.38 (t, *J* = 8.8 Hz, 2H), 5.08 (t, *J* = 5.7 Hz, 1H), 3.93 – 3.75 (m, 2H), 3.72 (s, 3H), 3.52 – 3.44 (m, 1H), 3.03 (s, 3H), 2.44 – 2.32 (m, 1H), 1.81 – 1.53 (m, 3H). LCMS (ES+) m/z 464 (M+1).

Example 222 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide **222**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 103), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,5-difluorophenyl)boronic acid gave **222**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.21 (dd, *J* = 8.6, 3.7 Hz, 1H), 8.09 (dd, *J* = 11.0, 8.6 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.43 (tt, *J* = 9.2, 2.4 Hz, 1H), 4.83 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.46 – 4.21 (m, 1H), 4.20 – 3.89 (m, 2H), 3.80 (s, 3H), 3.18 – 3.04 (m, 1H), 2.16 – 2.04 (m, 1H), 1.94 – 1.79 (m, 1H), 1.75 – 1.55 (m, 4H). LCMS (ES+) m/z 464 (M+1).

Example 223 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide **223**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 103), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3-difluorophenyl)boronic acid gave **223**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.27 (dd, *J* = 8.7, 3.9 Hz, 1H), 8.12 (t, *J* = 9.1 Hz, 1H), 7.90 (s, 1H), 7.69 – 7.52 (m, 2H), 7.47 – 7.37 (m,

1H), 4.84 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.39 – 4.16 (m, 1H), 4.12 – 3.86 (m, 2H), 3.76 (s, 3H), 3.15 – 3.02 (m, 1H), 2.12 – 2.01 (m, 1H), 1.84 – 1.70 (m, 1H), 1.70 – 1.56 (m, 4H). LCMS (ES+) m/z 464 (M+1).

Example 224 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)thiazole-4-carboxamide **224**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-ol (see US2012/225062) gave **224**. LCMS (ES+) m/z 524 (M+1).

Example 225 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)thiazole-4-carboxamide **225**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanol (see US2012/225062) gave **225**. LCMS (ES+) m/z 508 (M+1).

Example 226 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-5-fluoro-6-(2-fluoro-4-methoxyphenyl)picolinamide **226**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 103), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-4-methoxyphenyl)boronic acid gave **226**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.18 (dd, *J* = 8.6, 3.8 Hz, 1H), 8.03 (dd, *J* = 9.6, 8.6 Hz, 1H), 7.88 (s, 1H), 7.69 (t, *J* = 8.8 Hz, 1H), 7.04 – 6.95 (m, 2H), 4.83 (dd, *J* = 10.5, 3.7 Hz, 1H), 4.32 (ddt, *J* = 48.7, 6.0, 2.6 Hz, 1H), 4.16 – 3.89 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.20 – 3.06 (m, 1H), 2.13 – 2.01 (m, 1H), 1.88 – 1.74 (m, 1H), 1.73 – 1.56 (m, 4H). LCMS (ES+) m/z 476 (M+1).

Example 227 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2-chloro-3-fluorophenyl)-5-fluoropicolinamide **227**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(6-bromo-5-fluoropicolinamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 103), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-3-fluorophenyl)boronic acid gave **227**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.28 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.12 (t, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.64 – 7.45 (m, 3H), 4.81 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.20 (ddt, *J* = 49.1, 5.7, 2.7 Hz, 1H), 4.05 – 3.80 (m, 2H), 3.75 (s, 3H),

3.09 – 2.95 (m, 1H), 2.10 – 1.99 (m, 1H), 1.82 – 1.64 (m, 1H), 1.66 – 1.56 (m, 2H), 1.53 (br, 2H). LCMS (ES+) m/z 480 (M+1).

Example 228 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide **228**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol (see US2011/76291) gave **228**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 4.88 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.69 – 4.42 (m, 1H), 4.39 – 4.24 (m, 1H), 4.17 – 3.95 (m, 4H), 3.77 (s, 3H), 2.15 – 2.05 (m, 1H), 1.89 – 1.68 (m, 3H), 1.10 (d, *J* = 4.4 Hz, 6H). LCMS (ES+) m/z 478 (M+1).

Example 229 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide **229**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,6-difluoro-3-methoxyphenyl)boronic acid gave **229**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.63 (s, 1H), 7.78 (s, 1H), 7.40 (td, *J* = 9.3, 5.1 Hz, 1H), 7.27 (td, *J* = 9.5, 1.9 Hz, 1H), 4.81 (dd, *J* = 10.9, 3.6 Hz, 1H), 4.37 (d, *J* = 47.9 Hz, 1H), 4.24 – 4.10 (m, 1H), 4.10 – 3.92 (m, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.29 – 3.19 (m, 1H), 2.11 – 2.01 (m, 1H), 1.87 – 1.77 (m, 1H), 1.75 – 1.66 (m, 2H). LCMS (ES+) m/z 482 (M+1).

Example 230 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **230**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **230**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.68 (s, 1H), 7.85 (s, 1H), 7.75 (qd, *J* = 9.4, 4.9 Hz, 1H), 7.43 (tdd, *J* = 9.7, 4.0, 2.1 Hz, 1H), 5.09 – 4.78 (m, 2H), 4.19 – 3.91 (m, 2H), 3.75 (s, 3H), 3.44 – 3.30 (m, 1H), 2.24 – 2.12 (m, 1H), 1.93 – 1.65 (m, 3H). LCMS (ES+) m/z 470 (M+1).

Example 231 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide **231**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate

(Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-methylpyridin-2-yl)boronic acid gave **231**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.53 (dd, J = 4.7, 1.5 Hz, 1H), 8.47 (s, 1H), 7.91 – 7.83 (m, 1H), 7.81 (s, 1H), 7.45 (dd, J = 7.7, 4.6 Hz, 1H), 4.84 (dd, J = 10.7, 3.6 Hz, 1H), 4.53 – 4.30 (m, 1H), 4.25 – 3.94 (m, 2H), 3.79 (s, 3H), 3.29 – 3.12 (m, 1H), 2.85 (s, 3H), 2.51 (s, 1H), 2.13 – 2.02 (m, 1H), 1.94 – 1.79 (m, 1H), 1.76 – 1.62 (m, 4H). LCMS (ES+) m/z 431 (M+1).

Example 232 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-methoxypyridin-3-yl)thiazole-4-carboxamide **232**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-methoxypyridin-3-yl)boronic acid gave **232**. LCMS (ES+) m/z 447 (M+1).

Example 233 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-oxo-1,2-dihydropyridin-3-yl)thiazole-4-carboxamide **233**

The title compound was isolated as a second product formed during the synthesis of Example 232. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.72 (dd, J = 7.1, 2.1 Hz, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 7.70 (dd, J = 6.3, 2.1 Hz, 1H), 6.49 (t, J = 6.7 Hz, 1H), 4.87 (dd, J = 10.4, 3.6 Hz, 1H), 4.50 (ddd, J = 49.4, 7.1, 2.9 Hz, 1H), 4.40 – 4.25 (m, 1H), 4.20 – 3.94 (m, 1H), 3.78 (s, 3H), 3.40 – 3.29 (m, 1H), 2.13 – 2.00 (m, 1H), 1.90 – 1.65 (m, 3H). LCMS (ES+) m/z 433 (M+1).

Example 234 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide **234**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3,5-dimethylisoxazol-4-yl)boronic acid gave **234**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.47 (s, 1H), 7.78 (s, 1H), 4.82 (dd, J = 10.8, 3.6 Hz, 1H), 4.56 – 4.32 (m, 1H), 4.25 – 3.93 (m, 2H), 3.79 (s, 3H), 3.27 – 3.13 (m, 1H), 2.74 (s, 3H), 2.53 (s, 3H), 2.13 – 2.01 (m, 1H), 1.93 – 1.78 (m, 1H), 1.77 – 1.64 (m, 2H). LCMS (ES+) m/z 435 (M+1).

Example 235 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-cyclopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **235**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole gave **235**. ^{1}H NMR

(400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.44 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 4.92 – 4.83 (m, 1H), 4.59 – 4.40 (m, 1H), 4.32 (dd, J = 22.2, 15.0 Hz, 1H), 4.19 – 3.93 (m, 1H), 3.80 (dd, J = 7.4, 3.7 Hz, 1H), 3.77 (s, 3H), 3.38 – 3.31 (m, 1H), 2.12 – 2.03 (m, 1H), 1.87 – 1.66 (m, 5H), 1.17 – 0.96 (m, 4H). LCMS (ES+) m/z 446 (M+1).

Example 236 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide **236**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,5-trifluorophenyl)boronic acid gave **236**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.63 (s, 1H), 8.14 – 8.04 (m, 1H), 7.83 – 7.71 (m, 2H), 4.85 (dd, J = 10.7, 3.5 Hz, 1H), 4.71 – 4.46 (m, 1H), 4.36 – 4.22 (m, 1H), 4.20 – 3.94 (m, 1H), 3.81 (s, 3H), 3.45 – 3.31 (m, 1H), 2.16 – 2.07 (m, 1H), 1.98 – 1.76 (m, 3H). LCMS (ES+) m/z 470 (M+1).

Example 237 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-2-yl)thiazole-4-carboxamide **237**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-fluoropyridin-2-yl)boronic acid gave **237**. LCMS (ES+) m/z 435 (M+1).

Example 238 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide **238**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-5-methylphenyl)boronic acid gave **238**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.52 (s, 1H), 8.22 (dd, J = 7.3, 2.2 Hz, 1H), 7.84 (s, 1H), 7.43 – 7.29 (m, 2H), 4.89 (dd, J = 10.1, 3.9 Hz, 1H), 4.57 – 4.37 (m, 1H), 4.35 – 4.20 (m, 1H), 4.17 – 3.94 (m, 1H), 3.79 (s, 3H), 3.29 – 3.17 (m, 1H), 2.40 (s, 3H), 2.19 – 2.07 (m, 1H), 1.92 – 1.77 (m, 1H), 1.76 – 1.66 (m, 4H). LCMS (ES+) m/z 448 (M+1).

Example 239 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide **239**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (5-fluoropyridin-3-yl)boronic acid gave **239**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.15 (t,

J = 1.7 Hz, 1H), 8.74 (d, *J* = 2.7 Hz, 1H), 8.55 (s, 1H), 8.37 (dt, *J* = 9.5, 2.3 Hz, 1H), 7.84 (s, 1H), 4.87 (dd, *J* = 10.5, 3.9 Hz, 1H), 4.58 – 4.36 (m, 1H), 4.34 – 4.20 (m, 1H), 4.16 – 3.92 (m, 1H), 3.79 (s, 3H), 3.37 – 3.23 (m, 2H), 2.15 – 2.05 (m, 1H), 1.91 – 1.67 (m, 5H). LCMS (ES+) m/z 435 (M+1).

Example 240 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide **240**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-fluoropyridin-4-yl)boronic acid gave **240**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.73 – 8.64 (m, 2H), 8.23 (dd, *J* = 6.4, 5.0 Hz, 1H), 7.78 (s, 1H), 5.04 – 4.77 (m, 2H), 4.25 – 4.09 (m, 1H), 4.06 – 3.92 (m, 1H), 3.78 (s, 3H), 3.27 – 3.20 (m, 1H), 2.19 – 2.08 (m, 1H), 1.91 – 1.76 (m, 3H), 1.69 – 1.59 (m, 1H). LCMS (ES+) m/z 435 (M+1).

Example 241 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **241**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1,3-dimethyl-1H-pyrazol-4-yl)boronic acid gave **241**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 7.84 (s, 1H), 4.95 – 4.83 (m, 1H), 4.83 – 4.62 (m, 1H), 4.42 – 4.28 (m, 1H), 4.24 – 4.05 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.48 (dd, *J* = 17.3, 8.4 Hz, 1H), 2.47 (s, 3H), 2.15 – 2.06 (m, 1H), 1.87 (d, *J* = 14.4 Hz, 4H). LCMS (ES+) m/z 434 (M+1).

Example 242 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **242**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole gave **242**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.83 (s, 1H), 4.84 (dd, *J* = 10.6, 3.8 Hz, 1H), 4.55 – 4.32 (m, 1H), 4.28 – 4.14 (m, 1H), 4.13 – 3.94 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.29 – 3.16 (m, 1H), 2.61 (s, 3H), 2.12 – 2.02 (m, 1H), 1.91 – 1.78 (m, 1H), 1.75 – 1.64 (m, 4H). LCMS (ES+) m/z 434 (M+1).

Example 243 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **243**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **243**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.67 (s, 1H), 7.83 (s, 1H), 7.73 (qd, J = 9.5, 5.0 Hz, 1H), 7.38 (tdd, J = 9.5, 3.9, 2.1 Hz, 1H), 4.83 (dd, J = 10.7, 3.6 Hz, 1H), 4.45 – 4.23 (m, 1H), 4.17 (ddd, J = 21.9, 15.0, 1.8 Hz, 1H), 4.08 – 3.89 (m, 1H), 3.77 (s, 3H), 3.29 – 3.13 (m, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.72 (m, 1H), 1.72 – 1.60 (m, 4H). LCMS (ES+) m/z 470 (M+1).

Example 244 N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide **244**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3,5-dimethylisoxazol-4-yl)boronic acid gave **244**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.47 (s, 1H), 7.83 (s, 1H), 5.01 (d, J = 50.4 Hz, 1H), 4.84 (d, J = 10.2 Hz, 1H), 4.24 – 4.06 (m, 1H), 4.06 – 3.88 (m, 1H), 3.78 (s, 3H), 3.45 – 3.31 (m, 1H), 2.77 (s, 3H), 2.56 (s, 3H), 2.09 – 1.84 (m, 3H), 1.76 – 1.68 (m, 1H). LCMS (ES+) m/z 435 (M+1).

Example 245 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide **245**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3-difluorophenyl)boronic acid gave **245**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.59 (s, 1H), 8.15 – 8.06 (m, 1H), 7.77 (s, 1H), 7.72 – 7.60 (m, 1H), 7.51 – 7.41 (m, 1H), 5.12 – 4.82 (m, 2H), 4.26 – 4.10 (m, 1H), 4.07 – 3.93 (m, 1H), 3.78 (s, 3H), 3.44 – 3.30 (m, 1H), 2.15 (ddd, J = 11.7, 6.2, 3.5 Hz, 1H), 1.97 – 1.79 (m, 2H), 1.69 (d, J = 13.1 Hz, 1H). LCMS (ES+) m/z 452 (M+1).

Example 246 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide **246**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (5-fluoropyridin-3-yl)boronic acid gave **246**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.13 (t, J = 1.7 Hz, 1H), 8.76 (d, J = 2.8 Hz, 1H), 8.55 (s, 1H), 8.40 – 8.32 (m, 1H), 7.72 (s, 1H), 5.05

– 4.73 (m, 2H), 4.21 – 4.05 (m, 1H), 4.05 – 3.91 (m, 1H), 3.79 (s, 3H), 3.29 – 3.24 (m, 1H), 2.21 – 2.10 (m, 1H), 1.94 – 1.77 (m, 2H), 1.71 – 1.61 (m, 1H). LCMS (ES+) m/z 435 (M+1).

Example 247 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-difluoropyridin-4-yl)thiazole-4-carboxamide **247**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3,5-difluoropyridin-4-yl)boronic acid gave **247**. LCMS (ES+) m/z 453 (M+1).

Example 248 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide **248**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-chloro-2-fluorophenyl)boronic acid gave **248**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.59 (s, 1H), 8.30 – 8.21 (m, 1H), 7.86 – 7.77 (m, 2H), 7.52 – 7.43 (m, 1H), 5.05 – 4.77 (m, 2H), 4.16 (ddd, *J* = 24.7, 13.6, 4.7 Hz, 1H), 3.99 (ddd, *J* = 17.9, 13.5, 4.8 Hz, 1H), 3.77 (s, 3H), 3.27 – 3.22 (m, 1H), 2.18 – 2.09 (m, 1H), 1.88 – 1.78 (m, 2H), 1.71 – 1.60 (m, 3H). LCMS (ES+) m/z 468 (M+1).

Example 249 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3'-chloro-2,2'-difluoro-[1,1'-biphenyl]-3-yl)thiazole-4-carboxamide **249**

The title compound was isolated as a second product during the synthesis of Example 248. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.58 (s, 1H), 8.47 – 8.38 (m, 1H), 7.84 – 7.67 (m, 3H), 7.64 – 7.52 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 5.04 – 4.75 (m, 2H), 4.26 – 4.10 (m, 1H), 4.08 – 3.94 (m, 1H), 3.78 (s, 3H), 3.28 – 3.23 (m, 1H), 2.20 – 2.10 (m, 1H), 1.87 – 1.78 (m, 2H), 1.71 – 1.61 (m, 3H). LCMS (ES+) m/z 562 (M+1).

Example 250 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide **250**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-3-fluorophenyl)boronic acid gave **250**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.62 (s, 1H), 8.19 – 8.11 (m, 1H), 7.81 (s, 1H), 7.70 – 7.57 (m, 2H), 5.02 – 4.71 (m, 2H), 4.18 – 3.90 (m, 2H), 3.77 (s, 3H), 3.34 – 3.18 (m, 1H), 2.20 – 2.10 (m, 1H), 1.86 – 1.72 (m, 2H), 1.68 – 1.59 (m, 3H). LCMS (ES+) m/z 468 (M+1).

Example 251 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2'-chloro-3',6-difluoro-[1,1'-biphenyl]-2-yl)thiazole-4-carboxamide **251**

The title compound was isolated as a second product during the synthesis of Example 250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.31 (s, 1H), 8.26 – 8.18 (m, 1H), 7.80 – 7.53 (m, 6H), 7.42 – 7.33 (m, 1H), 5.02 – 4.77 (m, 2H), 4.25 – 4.06 (m, 1H), 4.05 – 3.92 (m, 1H), 3.77 (s, 3H), 3.25 (s, 1H), 2.14 (s, 1H), 1.91 – 1.55 (m, 5H). LCMS (ES+) m/z 562 (M+1).

Example 252 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide **252**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)boronic acid gave **252**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 7.88 (s, 1H), 4.98 – 4.72 (m, 2H), 4.22 – 4.03 (m, 1H), 4.00 (s, 3H), 3.97 – 3.88 (m, 1H), 3.75 (s, 3H), 3.30 – 3.17 (m, 1H), 2.14 – 2.03 (m, 1H), 1.92 – 1.68 (m, 3H), 1.66 – 1.57 (m, 1H). LCMS (ES+) m/z 488 (M+1).

Example 253 N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **253**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 100), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 3-cyclopropyl-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole gave **253**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.27 (s, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 5.02 – 4.76 (m, 2H), 4.16 – 3.90 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.29 – 3.16 (m, 1H), 2.41 – 2.30 (m, 1H), 2.18 – 2.09 (m, 1H), 1.86 – 1.74 (m, 2H), 1.66 – 1.58 (m, 1H), 1.02 – 0.90 (m, 2H), 0.89 – 0.80 (m, 2H). LCMS (ES+) m/z 460 (M+1).

Example 254 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **254**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1,3-dimethyl-1H-pyrazol-4-yl)boronic acid gave **254**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.25 (s, 2H), 5.00 – 4.73 (m, 2H), 4.16 – 3.89 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.22 (dd, J = 25.0, 9.5 Hz, 1H), 2.56 (s, 3H), 2.10 – 2.01 (m, 1H), 1.90 – 1.71 (m, 3H), 1.66 – 1.58 (m, 1H). LCMS (ES+) m/z 449 (M+1).

Example 255 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **255**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1,5-dimethyl-1H-pyrazol-4-yl)boronic acid gave **255**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.25 (s, 2H), 4.96 – 4.76 (m, 2H), 4.16 – 3.89 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.29 – 3.15 (m, 1H), 2.56 (s, 3H), 2.11 – 2.00 (m, 1H), 1.90 – 1.71 (m, 4H), 1.66 – 1.58 (m, 1H). LCMS (ES+) m/z 449 (M+1).

Example 256 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-isopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **256**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1-isopropyl-1H-pyrazol-4-yl)boronic acid gave **256**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.15 (s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.25 (s, 2H), 5.12 – 4.80 (m, 2H), 4.60 – 4.45 (m, 1H), 4.18 – 3.95 (m, 2H), 3.72 (s, 3H), 3.38 – 3.26 (m, 1H), 2.33 – 2.22 (m, 1H), 1.83 – 1.56 (m, 5H), 1.44 (d, J = 6.7 Hz, 6H). LCMS (ES+) m/z 463 (M+1).

Example 257 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **257**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (1,5-dimethyl-1H-pyrazol-4-yl)boronic acid gave **257**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.25 (s, 2H), 4.79 (dd, J = 10.7, 3.6 Hz, 1H), 4.41 (ddd, J = 49.5, 4.9, 2.7 Hz, 1H), 4.26 – 3.94 (m, 2H), 3.76 (d, J = 5.4 Hz, 6H), 3.30 – 3.16 (m, 1H), 2.52 (s, 3H), 2.04 (dq, J = 11.8, 4.1 Hz, 1H), 1.81 (dd, J = 13.6, 10.0 Hz, 1H), 1.73 – 1.64 (m, 2H). LCMS (ES+) m/z 449 (M+1).

Example 258 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **258**

Following the procedure for Example 101 starting from *tert*-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate (Intermediate 101), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **258**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.69 (s, 1H), 7.95 (s, 1H), 7.77 (qd, J = 9.4, 4.9 Hz, 1H), 7.49 – 7.38 (m, 1H), 5.12 (t, J = 5.6 Hz, 1H),

3.91 – 3.76 (m, 2H), 3.71 (s, 3H), 3.46 – 3.36 (m, 1H), 3.32 – 3.21 (m, 1H), 3.01 (s, 3H), 2.49 – 2.36 (m, 1H), 1.73 – 1.49 (m, 3H), 1.41 (br, 2H). LCMS (ES+) m/z 482 (M+1).

Example 259 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)thiazole-4-carboxamide **259**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-4-(trifluoromethyl)phenyl)boronic acid gave **259**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.31 (q, J = 9.1, 8.5 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.83 – 7.71 (m, 2H), 7.61 (s, 2H), 5.17 – 4.82 (m, 2H), 4.31 – 4.14 (m, 1H), 4.08 – 3.93 (m, 1H), 3.77 (s, 3H), 3.51 – 3.37 (m, 1H), 2.19 – 2.05 (m, 1H), 1.98 – 1.81 (m, 2H), 1.75 – 1.67 (m, 1H). LCMS (ES+) m/z 517 (M+1).

Example 260 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **260**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **260**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.85 (s, 1H), 7.65 – 7.52 (m, 3H), 7.39 – 7.27 (m, 1H), 5.03 – 4.83 (m, 2H), 4.16 – 3.90 (m, 2H), 3.73 (s, 3H), 3.39 (dd, J = 7.1, 4.6 Hz, 1H), 2.18 (ddd, J = 15.1, 6.7, 3.5 Hz, 1H), 1.87 (dt, J = 14.1, 10.3 Hz, 1H), 1.69 (dtd, J = 18.1, 13.8, 11.5, 7.4 Hz, 2H). LCMS (ES+) m/z 485 (M+1).

Example 261 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide **261**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,5-trifluorophenyl)boronic acid gave **261**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.67 (s, 1H), 7.60 (d, J = 9.5 Hz, 3H), 5.05 – 4.71 (m, 2H), 4.20 – 3.90 (m, 2H), 3.77 (s, 3H), 3.31 – 3.26 (m, 1H), 2.19 – 2.09 (m, 1H), 1.91 – 1.78 (m, 2H), 1.69 – 1.64 (m, 1H). LCMS (ES+) m/z 485 (M+1).

Example 262 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **262**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-

yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **262**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.91 (s, 1H), 7.66 – 7.53 (m, 3H), 7.37 – 7.26 (m, 1H), 5.08 (t, J = 5.6 Hz, 1H), 3.92 – 3.71 (m, 2H), 3.69 (s, 3H), 3.46 – 3.33 (m, 1H), 3.33 – 3.21 (m, 1H), 3.02 (s, 3H), 2.47 – 2.35 (m, 1H), 1.76 – 1.63 (m, 1H), 1.62 – 1.50 (m, 2H). LCMS (ES+) m/z 497 (M+1).

Example 263 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide **263**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,5-trifluorophenyl)boronic acid gave **263**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.88 – 7.79 (m, 1H), 7.68 – 7.54 (m, 4H), 4.96 (dd, J = 8.7, 3.5 Hz, 1H), 4.06 (dd, J = 13.1, 4.2 Hz, 1H), 3.92 (dd, J = 13.2, 6.0 Hz, 1H), 3.77 (s, 3H), 3.70 – 3.64 (m, 1H), 3.46 – 3.41 (m, 1H), 3.27 (s, 3H), 2.18 – 2.10 (m, 1H), 1.94 – 1.82 (m, 2H), 1.75 – 1.67 (m, 1H). LCMS (ES+) m/z 497 (M+1).

Example 264 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide **264**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-5-methylphenyl)boronic acid gave **264**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.92 – 7.82 (m, 2H), 7.44 (br, 2H), 7.29 – 7.19 (m, 2H), 5.12 (t, J = 5.4 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.71 (s, 3H), 3.53 – 3.44 (m, 1H), 3.34 – 3.23 (m, 1H), 3.04 (s, 3H), 2.37 (s, 3H), 1.78 – 1.50 (m, 4H). LCMS (ES+) m/z 475 (M+1).

Example 265 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide **265**

Following the procedure for Example 101 starting from tert-butyl ((3R,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate (Intermediate 101), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,6-difluoro-4-methoxyphenyl)boronic acid gave **265**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.56 (s, 1H), 7.94 (s, 1H), 7.08 – 6.97 (m, 2H), 5.11 (t, J = 5.5 Hz, 1H), 3.88 (s, 3H), 3.84 – 3.75 (m, 1H), 3.71 (s, 3H), 3.47 – 3.38 (m, 1H), 3.31 – 3.22 (m, 1H), 3.04 (s, 3H), 2.49 – 2.36 (m, 1H), 1.75 – 1.49 (m, 3H), 1.41 (br, 2H). LCMS (ES+) m/z 494 (M+1).

Example 266 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide **266**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-(trifluoromethoxy)phenyl)boronic acid gave **266**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.28 – 8.20 (m, 1H), 7.78 (s, 1H), 7.57 – 7.43 (m, 6H), 5.00 – 4.77 (m, 2H), 4.22 – 4.06 (m, 1H), 4.06 – 3.92 (m, 1H), 3.75 (s, 3H), 3.29 – 3.21 (m, 1H), 2.18 – 2.09 (m, 1H), 1.95 – 1.54 (m, 5H). LCMS (ES+) m/z 515 (M+1).

Example 267 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **267**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-fluoro-2-(trifluoromethyl)phenyl)boronic acid gave **267**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.87 – 7.76 (m, 2H), 7.66 – 7.50 (m, 2H), 7.44 (s, 2H), 4.90 (dd, *J* = 7.6, 3.8 Hz, 1H), 4.82 – 4.50 (m, 1H), 3.95 – 3.75 (m, 2H), 3.70 (s, 3H), 3.13 (dd, *J* = 21.1, 8.4 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.79 – 1.51 (m, 5H). LCMS (ES+) m/z 517 (M+1).

Example 268 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide **268**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-3-(trifluoromethyl)phenyl)boronic acid gave **268**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.38 (t, *J* = 7.5 Hz, 1H), 7.90 – 7.75 (m, 2H), 7.62 – 7.50 (m, 3H), 5.05 – 4.71 (m, 2H), 4.22 – 4.06 (m, 1H), 4.05 – 3.92 (m, 1H), 3.75 (s, 3H), 3.34 – 3.21 (m, 1H), 2.18 – 2.10 (m, 1H), 1.88 – 1.72 (m, 4H), 1.69 – 1.60 (m, 1H). LCMS (ES+) m/z 517 (M+1).

Example 269 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide **269**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-methylphenyl)boronic acid gave **269**. ^{1}H NMR (400

MHz, DMSO-d_6) δ 9.44 (s, 1H), 7.88 (s, 1H), 7.48 – 7.33 (m, 3H), 7.25 – 7.13 (m, 2H), 5.05 (t, J = 5.3 Hz, 1H), 3.77 – 3.63 (m, 5H), 3.34 – 3.25 (m, 1H), 3.26 – 3.17 (m, 1H), 2.83 (s, 3H), 2.44 (s, 3H), 1.68 – 1.50 (m, 4H). LCMS (ES+) m/z 475 (M+1).

Example 270 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **270**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-(trifluoromethyl)phenyl)boronic acid gave **270**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 7.88 (t, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.77 (dd, J = 6.5, 1.5 Hz, 2H), 7.72 – 7.62 (m, 1H), 7.46 (s, 2H), 4.87 (dd, J = 8.5, 3.4 Hz, 1H), 4.82 – 4.60 (m, 1H), 3.97 – 3.83 (m, 2H), 3.71 (s, 3H), 3.17 (ddt, J = 23.0, 9.2, 2.5 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.86 – 1.54 (m, 4H). LCMS (ES+) m/z 499 (M+1).

Example 271 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide **271**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane gave **271**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.80 (s, 1H), 7.35 (br, J = 8.5 Hz, 2H), 6.21 – 6.14 (m, 1H), 5.22 – 4.76 (m, 2H), 4.22 – 3.94 (m, 2H), 3.71 (s, 3H), 3.53 – 3.40 (m, 1H), 2.76 – 2.66 (m, 2H), 2.22 – 2.10 (m, 1H), 2.02 – 1.87 (m, 3H), 1.84 – 1.67 (m, 2H). LCMS (ES+) m/z 421 (M+1).

Example 272 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide **272**

To a solution of 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide (Example 271) in methanol was added 10% palladium on carbon, and the mixture was stirred overnight under an atmosphere of hydrogen. The mixture was then filtered through Celite and concentrated in vacuo. HPLC purification provided **272**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.77 (s, 1H), 7.05 (s, 2H), 5.17 – 4.78 (m, 2H), 4.17 – 3.92 (m, 2H), 3.71 (s, 3H), 3.47 – 3.34 (m, 1H), 3.27 – 3.15 (m, 1H), 2.23 – 2.11 (m, 1H), 2.11 – 1.95 (m, 2H), 1.94 – 1.83 (m, 1H), 1.82 – 1.57 (m, 9H). LCMS (ES+) m/z 423 (M+1).

Example 273 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide **273**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-methylphenyl)boronic acid gave **273**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.74 (s, 1H), 7.45 – 7.33 (m, 3H), 7.26 – 7.14 (m, 2H), 5.02 – 4.77 (m, 2H), 4.10 – 3.85 (m, 2H), 3.75 (s, 3H), 3.37 (s, 3H), 2.15 – 2.04 (m, 1H), 1.98 – 1.75 (m, 2H), 1.72 – 1.63 (m, 1H). LCMS (ES+) m/z 463 (M+1).

Example 274 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide **274**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-5-methylphenyl)boronic acid gave **274**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.82 (s, 1H), 7.41 (br, 2H), 7.24 (d, J = 8.8 Hz, 2H), 5.09 – 4.68 (m, 2H), 4.22 – 3.97 (m, 2H), 3.74 (s, 3H), 2.36 (s, 3H), 2.23 – 2.12 (m, 1H), 1.88 – 1.73 (m, 2H), 1.68 – 1.63 (m, 3H). LCMS (ES+) m/z 463 (M+1).

Example 275 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(hydroxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide **275**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with cyclopropyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (Intermediate 140) gave **275**, which was isolated as a mixture of diastereomers. LCMS (ES+) m/z 522 (M+1).

Example 276 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide **276**

The title compound was isolated as a second compound formed during the synthesis of Example 275. LCMS (ES+) m/z 536 (M+1).

Example 277 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-6-methoxyphenyl)thiazole-4-carboxamide **277**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-

boronic acid pinacol ester with (2,3-difluoro-6-methoxyphenyl)boronic acid gave **277**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.84 (s, 1H), 7.47 (t, J = 9.4 Hz, 1H), 7.39 (s, 2H), 7.01 (ddd, J = 9.4, 4.0, 1.9 Hz, 1H), 5.02 – 4.76 (m, 2H), 4.18 – 3.93 (m, 2H), 3.92 (s, 3H), 3.72 (s, 3H), 2.23 – 2.13 (m, 1H), 1.90 – 1.60 (m, 4H). LCMS (ES+) m/z 497 (M+1).

Example 278 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide **278**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-(trifluoromethyl)phenyl)boronic acid gave **278**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.85 – 7.69 (m, 4H), 7.47 (s, 2H), 5.03 – 4.74 (m, 2H), 4.00 – 3.86 (m, 2H), 3.74 (s, 3H), 2.13 (ddt, J = 14.4, 6.1, 2.8 Hz, 1H), 2.01 – 1.61 (m, 3H). LCMS (ES+) m/z 517 (M+1).

Example 279 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide **279**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-(trifluoromethyl)phenyl)boronic acid gave **279**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 7.90 (s, 1H), 7.84 – 7.68 (m, 3H), 7.47 (s, 2H), 5.03 (t, J = 5.2 Hz, 1H), 3.71 – 3.52 (m, 5H), 3.29 – 3.13 (m, 2H), 2.72 (s, 3H), 2.48 – 2.40 (m, 1H), 1.63 – 1.47 (m, 5H). LCMS (ES+) m/z 529 (M+1).

Example 280 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide **280**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-6-fluorophenyl)boronic acid gave **280**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.89 (s, 1H), 7.61 – 7.46 (m, 4H), 7.40 (ddd, J = 9.6, 8.2, 1.4 Hz, 1H), 5.06 (t, J = 5.2 Hz, 1H), 3.68 (d, J = 2.8 Hz, 5H), 3.33 – 3.17 (m, 2H), 2.82 (s, 3H), 1.66 – 1.49 (m, 4H). LCMS (ES+) m/z 495 (M+1).

Example 281 5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide **281**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-

yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 98), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-5-fluorophenyl)boronic acid gave **281**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.12 (dd, J = 6.4, 2.7 Hz, 1H), 7.79 (s, 1H), 7.55 – 7.39 (m, 4H), 5.07 (dd, J = 7.0, 4.5 Hz, 1H), 3.99 – 3.84 (m, 2H), 3.72 (s, 3H), 3.52 – 3.43 (m, 1H), 3.33 – 3.24 (m, 1H), 3.15 (s, 3H), 2.33 – 2.22 (m, 1H), 1.82 – 1.52 (m, 4H). LCMS (ES+) m/z 495 (M+1).

Example 282 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide **282**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-pyrazole (Intermediate 149) gave **282**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 7.41 (s, 2H), 4.78 (dd, J = 10.8, 3.6 Hz, 1H), 4.54 – 4.27 (m, 1H), 4.24 – 4.10 (m, 1H), 4.04 (s, 3H), 3.95 (dd, J = 14.9, 3.4 Hz, 1H), 3.76 (s, 3H), 3.29 – 3.14 (m, 1H), 2.10 – 1.98 (m, 1H), 1.85 – 1.76 (m, 3H), 1.73 – 1.63 (m, 2H). LCMS (ES+) m/z 503 (M+1).

Example 283 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide **283**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6R)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 88), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-pyrazole (Intermediate 149) gave **283**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.49 (s, 1H), 8.16 (s, 1H), 7.85 (s, 1H), 4.99 – 4.67 (m, 2H), 4.10 (s, 3H), 4.08 – 3.85 (m, 2H), 3.75 (s, 3H), 3.30 – 3.16 (m, 1H), 2.16 – 2.05 (m, 1H), 1.90 – 1.67 (m, 2H), 1.66 – 1.58 (m, 1H). LCMS (ES+) m/z 488 (M+1).

Example 284 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide **284**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-6-fluorophenyl)boronic acid gave **284**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.66 (s, 1H), 7.72 (s, 1H), 7.64 (td, J = 8.3, 6.0 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.50 – 7.40 (m, 1H), 4.77 (dd, J = 10.9, 3.7 Hz, 1H), 4.38 – 4.17 (m, 1H), 4.17 – 4.03 (m, 1H), 4.02 – 3.83 (m, 1H),

3.78 (s, 3H), 3.23 – 3.09 (m, 1H), 2.10 – 1.98 (m, 1H), 1.91 – 1.76 (m, 1H), 1.70 – 1.56 (m, 4H). LCMS (ES+) m/z 468 (M+1).

Example 285 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-ethoxy-2,6-difluorophenyl)thiazole-4-carboxamide **285**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-ethoxy-2,6-difluorophenyl)boronic acid gave **285**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.63 (s, 1H), 7.79 (s, 1H), 7.39 (td, *J* = 9.3, 5.2 Hz, 1H), 7.24 (td, *J* = 9.6, 1.9 Hz, 1H), 4.80 (dd, *J* = 11.0, 3.6 Hz, 1H), 4.49 – 4.25 (m, 1H), 4.16 (q, *J* = 6.9 Hz, 3H), 4.08 – 3.90 (m, 1H), 3.78 (s, 3H), 3.29 – 3.18 (m, 1H), 2.10 – 2.02 (m, 1H), 1.91 – 1.77 (m, 1H), 1.74 – 1.64 (m, 2H), 1.36 (t, *J* = 6.9 Hz, 3H). LCMS (ES+) m/z 496 (M+1).

Example 286 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide **286**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 5-fluoro-1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (Intermediate 150) gave **286**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.33 (s, 1H), 7.81 (s, 1H), 4.82 (dd, *J* = 10.7, 3.6 Hz, 1H), 4.39 (ddt, *J* = 49.2, 6.4, 2.8 Hz, 1H), 4.24 – 3.94 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.25 – 3.12 (m, 1H), 2.54 (s, 3H), 2.12 – 2.01 (m, 1H), 1.92 – 1.56 (m, 4H). LCMS (ES+) m/z 452 (M+1).

Example 287 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide **287**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxylic acid (Intermediate 105) gave **287**. 1H NMR (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.42 (d, J = 4.3 Hz, 1H), 8.21 (t, J = 8.9 Hz, 1H), 7.81 (s, 1H), 7.15 – 7.00 (m, 2H), 5.00 – 4.80 (m, 2H), 4.22 – 3.92 (m, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 2.20 – 2.09 (m, 1H), 1.90 – 1.75 (m, 2H), 1.65 (d, J = 15.7 Hz, 3H). LCMS (ES+) m/z 464 (M+1).

Example 288 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide **288**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-

((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxylic acid (Intermediate 104) gave **288**. 1H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 8.54 (s, 1H), 7.88 (s, 1H), 7.05 – 6.98 (m, 2H), 4.99 – 4.81 (m, 2H), 4.16 – 3.94 (m, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 2.20 – 2.11 (m, 1H), 1.92 – 1.67 (m, 2H), 1.62 (d, J = 14.4 Hz, 1H). LCMS (ES+) m/z 482 (M+1).

Example 289 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide **289**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinic acid (Intermediate 134) gave **289**. 1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.31 – 8.24 (m, 1H), 8.21 – 8.09 (m, 1H), 7.92 (s, 1H), 7.40 (d, J = 10.5 Hz, 2H), 4.91 (dd, J = 8.8, 3.5 Hz, 1H), 3.91 – 3.79 (m, 2H), 3.72 (s, 3H), 3.08 (dd, J = 23.4, 9.4 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.87 – 1.74 (m, 1H), 1.71 – 1.53 (m, 2H). LCMS (ES+) m/z 522 (M+1).

Example 290 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide **290**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinic acid (Intermediate 135) gave **290**. 1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.31 – 8.23 (m, 1H), 8.23 – 8.13 (m, 2H), 7.91 (s, 1H), 7.42 (dd, J = 9.6, 3.6 Hz, 2H), 4.90 (dd, J = 9.2, 3.5 Hz, 1H), 4.67 (d, J = 5.4 Hz, 1H), 3.92 – 3.81 (m, 2H), 3.76 – 3.70 (m, 3H), 3.11 (dd, J = 23.9, 9.5 Hz, 1H), 2.32 (q, J = 9.9 Hz, 2H), 2.14 – 2.05 (m, 1H), 2.03 – 1.91 (m, 1H), 1.88 – 1.54 (m, 4H). LCMS (ES+) m/z 534 (M+1).

Example 291 5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide **291**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-((tert-butoxycarbonyl)amino)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 132) gave **291**. 1H NMR (400 MHz, DMSO-d6) δ 9.41 (s, 1H), 8.29 (dd, J = 6.5, 2.7 Hz, 1H), 7.73 (bs, 1H), 7.51 (s, 2H), 7.48 – 7.36 (m, 2H), 7.08 – 6.53 (m, 1H), 4.85 (dd, J = 9.9, 4.1 Hz, 1H), 4.51 – 4.31 (m, 1H), 4.29 – 3.93 (m, 2H), 3.78 (s, 3H), 2.18 – 2.07 (m, 1H), 1.93 – 1.79 (m, 1H), 1.78 – 1.62 (m, 3H). LCMS (ES+) m/z 483 (M+1).

Example 292 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide **292**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-((tert-butoxycarbonyl)amino)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxylic acid (Intermediate 133) gave **292**. 1H NMR (400 MHz, DMSO-d6) δ 9.29 (s, 1H), 8.03 (d, J = 7.1 Hz, 1H), 7.82 (s, 1H), 7.44 (s, 2H), 7.26 – 7.17 (m, 2H), 4.86 (dd, J = 10.2, 3.8 Hz, 1H), 4.54 – 4.36 (m, 1H), 4.34 – 4.18 (m, 1H), 4.15 – 3.96 (m, 1H), 3.77 (s, 3H), 2.35 (s, 3H), 2.14 – 2.03 (m, 1H), 1.88 – 1.65 (m, 4H). LCMS (ES+) m/z 463 (M+1).

Example 293 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide **293**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxylic acid (Intermediate 105) gave **293**. 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.10 (s, 1H), 8.44 – 8.34 (m, 2H), 7.88 (d, J = 1.0 Hz, 1H), 7.14 – 7.05 (m, 1H), 7.02 – 6.91 (m, 3H), 6.67 – 6.58 (m, 2H), 4.87 (dd, J = 10.5, 3.6 Hz, 1H), 4.58 – 4.39 (m, 1H), 4.38 – 4.23 (m, 1H), 4.18 – 3.99 (m, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 2.13 – 2.02 (m, 1H), 1.88 – 1.67 (m, 5H). LCMS (ES+) m/z 464 (M+1).

Example 294 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxamide **294**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid (Intermediate 109) gave **294** as a mixture of diastereomers. 1H NMR (400 MHz, DMSO-d6) δ 9.88 (s, 1H), 8.61 (s, 1H), 7.81 (s, 1H), 7.31 – 7.24 (m, 2H), 5.57 (d, J = 4.5 Hz, 1H), 4.86 – 4.75 (m, 2H), 4.41 – 4.23 (m, 1H), 4.23 – 3.92 (m, 2H), 3.78 (s, 3H), 3.26 – 3.15 (m, 1H), 2.11 – 2.01 (m, 1H), 1.87 – 1.76 (m, 1H), 1.74 – 1.59 (m, 4H), 1.35 (d, J = 6.5 Hz, 3H). LCMS (ES+) m/z 496 (M+1).

Example 295 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxamide **295**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-

difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxylic acid (Intermediate 110) gave **295**. 1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.62 (s, 1H), 7.80 (s, 1H), 7.44 – 7.35 (m, 2H), 7.01 – 6.57 (m, 1H), 5.95 (s, 1H), 4.82 (dd, J = 10.9, 3.5 Hz, 1H), 4.42 (d, J = 46.7 Hz, 1H), 4.27 – 3.93 (m, 2H), 3.78 (s, 3H), 2.46 – 2.38 (m, 2H), 2.36 – 2.26 (m, 2H), 2.11 – 1.92 (m, 2H), 1.87 – 1.67 (m, 4H). LCMS (ES+) m/z 522 (M+1).

Example 296 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide **296**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxylic acid (Intermediate 104) gave **296**. 1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.55 (s, 1H), 7.80 (s, 1H), 7.02 – 6.94 (m, 2H), 4.80 (dd, J = 10.8, 3.6 Hz, 1H), 4.41 – 4.25 (m, 1H), 4.22 – 3.91 (m, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.26 – 3.15 (m, 1H), 2.11 – 2.01 (m, 1H), 1.88 – 1.75 (m, 1H), 1.67 (q, J = 9.0, 7.7 Hz, 3H). LCMS (ES+) m/z 482 (M+1).

Example 297 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxamide **297**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxylic acid (Intermediate 111) gave **297**. 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 7.41 – 7.31 (m, 2H), 5.43 (s, 1H), 4.80 (dd, J = 10.9, 3.6 Hz, 1H), 4.23 – 4.10 (m, 1H), 4.08 – 3.90 (m, 1H), 3.78 (s, 3H), 3.26 – 3.15 (m, 1H), 2.10 – 2.01 (m, 1H), 1.88 – 1.76 (m, 1H), 1.74 – 1.60 (m, 4H), 1.46 (s, 6H). LCMS (ES+) m/z 510 (M+1).

Example 298 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide **298**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-(difluoromethyl)phenyl)thiazole-4-carboxylic acid (Intermediate 112) gave **298**. 1H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H), 8.54 (s, 1H), 8.11 – 7.80 (m, 3H), 7.76 – 7.67 (m, 3H), 4.78 (dd, J = 10.8, 3.8 Hz, 1H), 4.48 – 4.29 (m, 1H), 4.20 – 3.89 (m, 2H), 3.81 (s, 3H), 2.11 – 2.02 (m, 1H), 1.98 – 1.86 (m, 1H), 1.74 – 1.64 (m, 2H). LCMS (ES+) m/z 466 (M+1).

Example 299 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-bromo-2-fluorophenyl)thiazole-4-carboxamide **299**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(5-bromo-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 129) gave **299**. 1H NMR (400 MHz, DMSO-d6) δ 10.02 (s, 1H), 8.65 (dd, J = 6.6, 2.6 Hz, 1H), 8.57 (s, 1H), 7.81 – 7.74 (m, 1H), 7.71 (s, 1H), 7.48 (dd, J = 11.0, 8.9 Hz, 1H), 4.86 (dd, J = 10.0, 3.9 Hz, 1H), 4.59 – 4.42 (m, 1H), 4.31 – 3.97 (m, 2H), 3.82 (s, 3H), 2.21 – 2.10 (m, 1H), 1.96 – 1.84 (m, 1H), 1.81 – 1.67 (m, 2H). LCMS (ES+) m/z 512 (M+1).

Example 300 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide **300**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(3-fluoropyridin-4-yl)thiazole-4-carboxylic acid (Intermediate 113) gave **300**. 1H NMR (400 MHz, DMSO-d6) δ 9.97 (s, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.72 (s, 1H), 8.66 (dd, J = 5.0, 1.2 Hz, 1H), 8.36 (dd, J = 6.5, 5.0 Hz, 1H), 7.84 (s, 1H), 7.59 (s, 2H), 4.98 – 4.79 (m, 2H), 4.43 (dd, J = 23.7, 15.4 Hz, 1H), 4.27 – 4.09 (m, 1H), 3.81 (s, 3H), 3.68 – 3.54 (m, 1H), 2.19 – 2.10 (m, 1H), 2.03 – 1.83 (m, 3H). LCMS (ES+) m/z 435 (M+1).

Example 301 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,5-difluorophenyl)thiazole-4-carboxamide **301**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,5-difluorophenyl)thiazole-4-carboxylic acid (Intermediate 114) gave **301**. 1H NMR (400 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.58 (s, 1H), 8.27 – 8.20 (m, 1H), 7.79 (s, 1H), 7.59 – 7.52 (m, 1H), 7.51 – 7.42 (m, 1H), 4.85 (dd, J = 10.6, 3.8 Hz, 1H), 4.51 – 4.35 (m, 1H), 4.31 – 4.18 (m, 1H), 4.13 – 3.95 (m, 1H), 3.80 (s, 3H), 3.27 – 3.19 (m, 1H), 2.14 – 2.05 (m, 1H), 1.98 (s, 1H), 1.92 – 1.82 (m, 1H), 1.76 – 1.66 (m, 2H). LCMS (ES+) m/z 452 (M+1).

Example 302 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide **302**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(5-chloro-

2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 115) gave **302**. 1H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 8.58 (s, 1H), 8.52 (dd, J = 6.4, 2.7 Hz, 1H), 7.72 (s, 1H), 7.69 – 7.62 (m, 1H), 7.55 (dd, J = 10.8, 8.9 Hz, 1H), 4.85 (dd, J = 10.3, 3.9 Hz, 1H), 4.60 – 4.44 (m, 1H), 4.32 – 4.20 (m, 1H), 4.13 – 3.98 (m, 1H), 3.82 (s, 3H), 2.19 – 2.10 (m, 1H), 1.96 – 1.83 (m, 1H), 1.80 – 1.69 (m, 2H). LCMS (ES+) m/z 468 (M+1).

Example 303 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxamide **303**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxylic acid (Intermediate 116) gave **303**. 1H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.63 (s, 1H), 7.80 (s, 1H), 7.57 – 7.48 (m, 1H), 7.29 – 7.19 (m, 1H), 4.83 (dd, J = 10.4, 3.7 Hz, 1H), 4.54 (dd, J = 50.8, 6.9 Hz, 1H), 4.30 – 4.17 (m, 1H), 4.15 – 3.97 (m, 1H), 3.78 (s, 3H), 2.30 (s, 3H), 2.13 – 2.04 (m, 1H), 1.89 – 1.72 (m, 3H). LCMS (ES+) m/z 466 (M+1).

Example 304 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*R*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide **304**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with (R)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid (Intermediate 117) gave **304**. 1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 7.29 (d, J = 10.1 Hz, 2H), 5.56 (s, 1H), 4.86 – 4.77 (m, 2H), 4.67 – 4.47 (m, 1H), 4.30 – 3.97 (m, 2H), 3.79 (s, 3H), 2.14 – 2.05 (m, 1H), 1.93 – 1.75 (m, 3H), 1.37 (d, J = 6.5 Hz, 3H). LCMS (ES+) m/z 496 (M+1).

Example 305 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*S*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide **305**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with (S)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxylic acid (Intermediate 118) gave **305**. 1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 7.30 (d, J = 10.1 Hz, 2H), 5.56 (s, 1H), 4.87 – 4.77 (m, 2H), 4.68 – 4.49 (m, 1H), 4.29 – 3.99 (m, 2H), 3.79 (s, 3H), 2.15 – 2.05 (m, 1H), 1.92 – 1.73 (m, 3H), 1.37 (d, J = 6.5 Hz, 3H). LCMS (ES+) m/z 496 (M+1).

Example 306 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide **306**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,3-difluorophenyl)thiazole-4-carboxylic acid (Intermediate 119) gave **306**. 1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.59 (s, 1H), 8.28 – 8.21 (m, 1H), 7.87 (s, 1H), 7.68 – 7.58 (m, 1H), 7.44 – 7.36 (m, 1H), 4.88 (dd, J = 10.5, 3.5 Hz, 1H), 4.67 – 4.49 (m, 1H), 4.41 – 4.29 (m, 1H), 4.20 – 4.03 (m, 2H), 3.79 (s, 3H), 3.45 – 3.35 (m, 1H), 2.15 – 2.05 (m, 1H), 1.91 – 1.73 (m, 3H). LCMS (ES+) m/z 452 (M+1).

Example 307 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxamide **307**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 120) gave **307**. 1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.52 (s, 1H), 8.23 (dd, J = 7.3, 2.3 Hz, 1H), 7.81 (s, 1H), 7.46 – 7.32 (m, 2H), 4.88 (dd, J = 10.2, 4.0 Hz, 1H), 4.51 – 4.33 (m, 1H), 4.30 – 4.17 (m, 1H), 4.15 – 3.95 (m, 1H), 3.80 (s, 3H), 2.71 (q, J = 7.6 Hz, 2H), 2.19 – 2.08 (m, 1H), 1.91 – 1.79 (m, 2H), 1.79 – 1.63 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H). LCMS (ES+) m/z 462 (M+1).

Example 308 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide **308**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(3-chloro-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 121) gave **308**. 1H NMR (400 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.59 (s, 1H), 8.44 – 8.39 (m, 1H), 7.87 (s, 1H), 7.81 – 7.76 (m, 1H), 7.45 – 7.39 (m, 1H), 4.88 (dd, J = 10.4, 3.5 Hz, 1H), 4.63 – 4.47 (m, 1H), 4.40 – 4.27 (m, 1H), 4.20 – 4.03 (m, 1H), 3.79 (s, 3H), 3.43 – 3.37 (m, 1H), 2.15 – 2.06 (m, 1H), 1.91 – 1.70 (m, 3H). LCMS (ES+) m/z 468 (M+1).

Example 309 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide **309**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 122) gave **309**. 1H NMR (400 MHz, DMSO-d6) δ 9.88 (s, 1H), 8.62 (s, 1H), 8.33 – 8.27 (m, 1H), 7.85 (s, 1H), 7.64 – 7.53 (m, 2H),

4.86 (dd, J = 10.7, 3.7 Hz, 1H), 4.54 – 4.34 (m, 1H), 4.27 (ddd, J = 22.1, 15.0, 1.5 Hz, 1H), 4.05 (ddd, J = 39.0, 15.0, 3.3 Hz, 1H), 3.79 (s, 3H), 2.13 – 2.03 (m, 1H), 1.89 – 1.79 (m, 1H), 1.75 – 1.68 (m, 3H). LCMS (ES+) m/z 468 (M+1).

Example 310 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxamide **310**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 123) gave **310**. 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.51 (s, 1H), 8.16 (dd, J = 7.2, 2.4 Hz, 1H), 7.76 (s, 1H), 7.33 (dd, J = 11.2, 8.6 Hz, 1H), 7.28 – 7.20 (m, 1H), 4.86 (dd, J = 10.2, 4.0 Hz, 1H), 4.29 – 4.16 (m, 1H), 4.12 – 3.94 (m, 1H), 3.81 (s, 3H), 3.26 – 3.15 (m, 1H), 2.18 – 2.04 (m, 2H), 1.96 – 1.82 (m, 1H), 1.80 – 1.61 (m, 4H), 1.04 – 0.94 (m, 2H), 0.80 – 0.71 (m, 2H). LCMS (ES+) m/z 474 (M+1).

Example 311 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **311**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid (Intermediate 124) gave **311**. 1H NMR (400 MHz, DMSO-d6) δ 9.75 (s, 1H), 8.58 (s, 1H), 7.97 – 7.93 (m, 1H), 7.89 – 7.75 (m, 4H), 4.78 (dd, J = 10.9, 3.7 Hz, 1H), 4.37 – 4.19 (m, 1H), 4.14 – 4.02 (m, 1H), 4.02 – 3.84 (m, 1H), 3.78 (s, 3H), 3.20 – 3.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.88 – 1.76 (m, 1H), 1.71 – 1.59 (m, 3H). LCMS (ES+) m/z 484 (M+1).

Example 312 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide **312**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxylic acid (Intermediate 126) gave **312**. 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.59 (s, 1H), 7.81 (s, 1H), 7.18 (dd, J = 10.3, 1.2 Hz, 2H), 4.81 (dd, J = 10.8, 3.6 Hz, 1H), 4.43 – 4.27 (m, 1H), 4.23 – 4.11 (m, 1H), 4.08 – 3.90 (m, 1H), 3.78 (s, 3H), 3.24 – 3.17 (m, 1H), 2.41 (s, 3H), 2.11 – 2.02 (m, 1H), 1.99 – 1.76 (m, 3H), 1.73 – 1.62 (m, 2H). LCMS (ES+) m/z 466 (M+1).

Example 313 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-chloro-2-fluorophenyl)thiazole-4-carboxamide **313**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(4-chloro-2-fluorophenyl)thiazole-4-carboxylic acid (Intermediate 127) gave **313**. 1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.55 (s, 1H), 8.47 (t, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.75 (dd, J = 11.3, 2.0 Hz, 1H), 7.48 (dd, J = 8.6, 2.0 Hz, 1H), 4.88 (dd, J = 10.3, 3.5 Hz, 1H), 4.64 – 4.46 (m, 1H), 4.40 – 4.28 (m, 1H), 4.20 – 3.99 (m, 1H), 3.79 (s, 3H), 3.41 – 3.32 (m, 1H), 2.14 – 2.03 (m, 1H), 1.90 – 1.67 (m, 3H). LCMS (ES+) m/z 468 (M+1).

Example 314 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxamide **314**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxylic acid (Intermediate 130) gave **314**. 1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1H), 9.11 (s, 1H), 9.04 (dd, J = 5.1, 0.9 Hz, 1H), 8.66 (s, 1H), 7.98 (d, J = 5.2 Hz, 1H), 7.80 (s, 1H), 4.80 (dd, J = 10.7, 3.8 Hz, 1H), 4.35 – 4.17 (m, 1H), 4.14 – 4.03 (m, 1H), 4.02 – 3.85 (m, 1H), 3.78 (s, 3H), 3.19 – 3.09 (m, 1H), 2.10 – 2.01 (m, 1H), 1.88 – 1.76 (m, 1H), 1.71 – 1.54 (m, 4H). LCMS (ES+) m/z 485 (M+1).

Example 315 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide **315**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluoro-6-methylphenyl)thiazole-4-carboxylic acid (Intermediate 128) gave **315**. 1H NMR (400 MHz, DMSO-d6) δ 9.77 (s, 1H), 8.60 (s, 1H), 7.73 (s, 1H), 7.56 – 7.38 (m, 1H), 7.24 (dd, J = 10.0, 8.0 Hz, 2H), 4.79 (dd, J = 11.1, 3.6 Hz, 1H), 4.52 – 4.27 (m, 1H), 4.22 – 3.87 (m, 2H), 3.79 (s, 3H), 2.42 (s, 3H), 2.10 – 2.01 (m, 1H), 1.93 – 1.80 (m, 1H), 1.71 (td, J = 8.5, 7.7, 3.1 Hz, 2H). LCMS (ES+) m/z 448 (M+1).

Example 316 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methylphenyl)thiazole-4-carboxamide **316**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluoro-

4-methylphenyl)thiazole-4-carboxylic acid (Intermediate 131) gave **316**. 1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.48 (s, 1H), 8.36 (t, J = 8.1 Hz, 1H), 7.89 (s, 1H), 7.34 – 7.18 (m, 2H), 4.87 (dd, J = 10.6, 3.6 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.38 – 4.25 (m, 1H), 4.19 – 4.01 (m, 1H), 3.78 (s, 3H), 2.40 (s, 3H), 2.12 – 2.03 (m, 1H), 1.88 – 1.78 (m, 1H), 1.77 – 1.66 (m, 3H). LCMS (ES+) m/z 448 (M+1).

Example 317 5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide **317**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-(tert-butoxycarbonylamino)-2-(2-fluorophenyl)thiazole-4-carboxylic acid (Example 7) gave **317**. 1H NMR (400 MHz, DMSO-d6) δ 9.34 (s, 1H), 8.30 (td, J = 7.9, 1.8 Hz, 1H), 7.87 (s, 1H), 7.48 – 7.26 (m, 5H), 7.02 – 6.56 (m, 1H), 4.84 (dd, J = 10.6, 3.5 Hz, 1H), 4.58 – 4.39 (m, 1H), 4.36 – 4.22 (m, 1H), 4.20 – 3.98 (m, 1H), 3.76 (s, 3H), 2.09 – 1.91 (m, 2H), 1.87 – 1.67 (m, 3H). LCMS (ES+) m/z 449 (M+1).

Example 318 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide **318**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluorophenyl)thiazole-4-carboxylic acid (see *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1758) gave **318**. 1H NMR (400 MHz, DMSO-d6) δ 10.08 (s, 1H), 8.53 (s, 1H), 8.35 – 8.28 (m, 1H), 7.81 (s, 1H), 7.66 – 7.58 (m, 1H), 7.53 – 7.41 (m, 2H), 5.02 – 4.81 (m, 2H), 4.24 – 4.09 (m, 1H), 4.09 – 3.92 (m, 1H), 3.77 (s, 3H), 2.20 – 2.09 (m, 1H), 2.07 – 1.92 (m, 1H), 1.87 – 1.74 (m, 2H), 1.66 (d, J = 13.1 Hz, 1H). LCMS (ES+) m/z 434 (M+1).

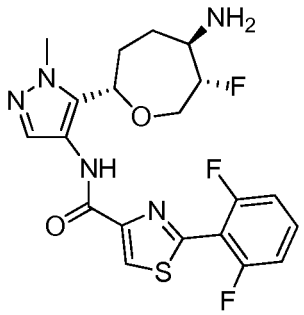
Example 319 *N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **319**

Following the procedure for Example 111 starting from *tert*-butyl ((3R,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 24), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (see US2012/225061) gave **319**. 1H NMR (400 MHz, DMSO-d6) δ 10.02 (s, 1H), 8.63 (s, 1H), 7.86 (s, 1H), 7.74 – 7.59 (m, 1H), 7.38 (t, J = 8.9 Hz, 2H), 5.03 – 4.81 (m, 2H), 4.19 – 3.88 (m, 2H), 3.75 (s, 2H), 2.24 – 2.10 (m, 1H), 1.93 – 1.81 (m, 1H), 1.82 – 1.70 (m, 1H), 1.65 (d, J = 14.0 Hz, 1H). LCMS (ES+) m/z 452 (M+1).

Example 320 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide **320**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-((tert-butoxycarbonyl)amino)-2-phenylthiazole-4-carboxylic acid (Example 6) gave **320**. 1H NMR (400 MHz, DMSO-d6) δ 9.29 (s, 1H), 7.89 – 7.81 (m, 2H), 7.50 – 7.34 (m, 4H), 7.01 – 6.59 (m, 1H), 4.83 (dd, J = 10.7, 3.5 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.37 – 3.99 (m, 2H), 3.80 – 3.70 (m, 3H), 2.04 (d, J = 13.7 Hz, 1H), 2.00 – 1.66 (m, 4H). LCMS (ES+) m/z 431 (M+1).

Example 321 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **321**



Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (see US2012/225061) gave **321**. 1H NMR (400 MHz, DMSO-d6) δ 9.94 – 9.85 (m, 1H), 8.63 (d, J = 1.2 Hz, 1H), 7.81 (d, J = 1.1 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.33 (t, J = 8.7 Hz, 2H), 4.81 (dd, J = 10.9, 3.5 Hz, 1H), 4.44 – 4.24 (m, 1H), 4.23 – 4.10 (m, 1H), 3.99 (ddd, J = 37.2, 14.8, 3.5 Hz, 1H), 3.77 (s, 3H), 2.11 – 2.02 (m, 1H), 1.90 – 1.76 (m, 1H), 1.75 – 1.63 (m, 2H). LCMS (ES+) m/z 452 (M+1).

Example 322 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide **322**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2-fluorophenyl)thiazole-4-carboxylic acid (see *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1758) gave **322**. 1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.53 (s, 1H), 8.52 – 8.44 (m, 1H), 7.89 (s, 1H), 7.63 – 7.56 (m, 1H), 7.51 – 7.37 (m, 2H), 4.88 (dd, J = 10.6, 3.6 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.38 – 4.25 (m, 1H), 4.20 – 3.99 (m, 1H), 3.79 (s, 3H), 2.13 – 2.05 (m, 1H), 1.90 – 1.78 (m, 1H), 1.75 (d, J = 9.6 Hz, 3H). LCMS (ES+) m/z 434 (M+1).

Example 323 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **323**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-((tert-butoxycarbonyl)amino)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid (Example 19) gave **323**. 1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.70 – 7.64 (m, 1H), 7.43 (s, 2H), 4.74 (dd, J = 11.0, 3.4 Hz, 1H), 4.50 – 4.30 (m, 1H), 4.19 – 3.89 (m, 2H), 3.76 (s, 3H), 2.06 – 1.97 (m, 1H), 1.91 – 1.79 (m, 1H), 1.76 – 1.66 (m, 2H). LCMS (ES+) m/z 499 (M+1).

Example 324 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide **324**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-((tert-butoxycarbonyl)amino)-2-(2,3-difluorophenyl)thiazole-4-carboxylic acid (Example 25) gave **324**. 1H NMR (400 MHz, DMSO-d6) δ 9.34 (s, 1H), 8.07 (dd, J = 8.3, 6.5 Hz, 1H), 7.87 (s, 1H), 7.52 (s, 2H), 7.48 – 7.38 (m, 1H), 7.31 – 7.22 (m, 1H), 4.87 – 4.80 (m, 1H), 4.56 – 4.38 (m, 1H), 4.36 – 4.23 (m, 1H), 4.16 – 3.99 (m, 1H), 3.76 (s, 3H), 2.09 – 2.01 (m, 1H), 1.87 – 1.66 (m, 5H). LCMS (ES+) m/z 467 (M+1).

Example 325 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4-difluorophenyl)thiazole-4-carboxamide **325**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,4-difluorophenyl)thiazole-4-carboxylic acid (see US2008/76771) gave **325**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.56 – 8.46 (m, 2H), 7.88 (s, 1H), 7.59 – 7.50 (m, 1H), 7.32 – 7.24 (m, 1H), 4.87 (dd, *J* = 10.4, 3.5 Hz, 1H), 4.57 – 4.38 (m, 1H), 4.38 – 4.23 (m, 1H), 4.18 – 3.98 (m, 1H), 3.78 (s, 3H), 2.14 – 2.02 (m, 1H), 1.88 – 1.66 (m, 4H). LCMS (ES+) m/z 452 (M+1).

Example 326 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide **326**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(pyridin-2-yl)thiazole-4-carboxylic acid (see *Tetrahedron* **2011**, *67*, 267) gave **326**. 1H NMR (400 MHz,

DMSO-d6) δ 9.91 (s, 1H), 8.70 – 8.65 (m, 1H), 8.50 (s, 1H), 8.35 – 8.30 (m, 1H), 8.04 – 7.97 (m, 1H), 7.87 (s, 1H), 7.59 – 7.53 (m, 1H), 4.94 – 4.88 (m, 1H), 4.84 – 4.67 (m, 1H), 4.48 – 4.34 (m, 1H), 4.24 – 4.07 (m, 1H), 3.80 (s, 3H), 3.60 – 3.47 (m, 1H), 2.17 – 2.09 (m, 1H), 1.96 – 1.78 (m, 3H). LCMS (ES+) m/z 417 (M+1).

Example 327 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide **327**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(pyridin-2-yl)thiazole-4-carboxylic acid (see *J. Med. Chem.* (2005), 48:2584) gave **327**. 1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.41 (s, 1H), 8.14 – 8.06 (m, 2H), 7.88 (s, 1H), 7.57 – 7.50 (m, 3H), 4.88 (dd, J = 10.5, 3.6 Hz, 1H), 4.64 – 4.46 (m, 1H), 4.40 – 4.27 (m, 1H), 4.21 – 4.01 (m, 1H), 3.79 (s, 3H), 3.45 – 3.35 (m, 1H), 2.14 – 2.06 (m, 1H), 1.91 – 1.70 (m, 3H). LCMS (ES+) m/z 416 (M+1).

Example 328 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide **328**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-6-fluorophenyl)boronic acid gave **328**. 1H NMR (400 MHz, DMSO-d6) δ 9.26 (s, 1H), 7.69 (s, 1H), 7.58 – 7.51 (m, 1H), 7.49 – 7.45 (m, 1H), 7.40 – 7.33 (m, 1H), 7.00 – 6.60 (m, 2H), 4.74 (dd, J = 11.1, 3.6 Hz, 1H), 4.41 – 4.23 (m, 1H), 4.16 – 3.86 (m, 2H), 3.76 (s, 3H), 2.07 – 1.97 (m, 1H), 1.89 – 1.77 (m, 1H), 1.69 (d, J = 9.1 Hz, 2H). LCMS (ES+) m/z 483 (M+1).

Example 329 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide **329**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-6-(trifluoromethyl)phenyl)boronic acid gave **329**. 1H NMR (400 MHz, DMSO-d6) δ 9.38 (s, 1H), 8.59 – 8.53 (m, 1H), 7.99 – 7.96 (m, 1H), 7.85 (s, 1H), 7.75 – 7.70 (m, 1H), 7.61 (s, 2H), 4.85 (dd, J = 10.4, 3.6 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.37 – 4.24 (m, 1H), 4.16 – 3.97 (m, 2H), 3.76 (s, 3H), 2.11 – 2.03 (m, 1H), 1.89 – 1.67 (m, 4H). LCMS (ES+) m/z 433 (M+1).

Example 330 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide **330**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-methylphenyl)boronic acid gave **330**. 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 7.72 (s, 1H), 7.43 – 7.32 (m, 3H), 7.21 – 7.11 (m, 2H), 4.74 (dd, J = 11.0, 3.6 Hz, 1H), 4.40 – 4.17 (m, 2H), 4.16 – 4.03 (m, 1H), 4.03 – 3.85 (m, 1H), 3.76 (s, 3H), 3.20 – 3.09 (m, 1H), 2.46 (s, 3H), 2.06 – 1.97 (m, 1H), 1.89 – 1.77 (m, 1H), 1.70 – 1.58 (m, 3H). LCMS (ES+) m/z 463 (M+1).

Example 331 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide **331**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-fluoro-6-(trifluoromethyl)phenyl)boronic acid gave **331**. 1H NMR (400 MHz, DMSO-d6) δ 9.18 (s, 1H), 7.81 – 7.68 (m, 3H), 7.42 (s, 2H), 4.78 – 4.68 (m, 1H), 4.45 – 4.26 (m, 1H), 4.14 – 3.86 (m, 2H), 3.76 (s, 3H), 2.07 – 1.97 (m, 1H), 1.88 – 1.76 (m, 1H), 1.76 – 1.65 (m, 2H). LCMS (ES+) m/z 517 (M+1).

Example 332 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide **332**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,3,6-trifluorophenyl)boronic acid gave **332**. 1H NMR (400 MHz, DMSO-d6) δ 9.32 (s, 1H), 7.81 (s, 1H), 7.63 – 7.51 (m, 3H), 7.31 – 7.23 (m, 1H), 4.79 (dd, J = 10.7, 3.5 Hz, 1H), 4.46 – 4.29 (m, 2H), 4.24 – 4.11 (m, 1H), 4.09 – 3.92 (m, 1H), 3.75 (s, 3H), 2.08 – 2.00 (m, 1H), 1.84 – 1.75 (m, 1H), 1.74 – 1.66 (m, 2H). LCMS (ES+) m/z 485 (M+1).

Example 333 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide **333**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane gave **333**. 1H NMR (400 MHz, DMSO-d6) δ 9.09 (s, 1H), 7.85 (s, 1H), 7.34 (s, 2H), 6.20 – 6.15

(m, 1H), 4.80 (dd, J = 10.4, 3.7 Hz, 1H), 4.50 – 4.29 (m, 1H), 4.27 – 4.16 (m, 1H), 4.12 – 3.95 (m, 1H), 3.74 (s, 3H), 2.79 – 2.69 (m, 2H), 2.07 – 1.99 (m, 1H), 1.97 – 1.86 (m, 2H), 1.81 – 1.66 (m, 4H). LCMS (ES+) m/z 421 (M+1).

Example 334 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide **334**

To a solution of 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide (Example 333) in methanol was added 10% palladium on carbon, and the mixture was stirred under an atmosphere of hydrogen overnight. After filtration and in vacuo concentration, purification by HPLC provided the title compound. 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 7.79 (s, 1H), 7.05 (s, 2H), 4.83 – 4.74 (m, 1H), 4.48 – 4.30 (m, 1H), 4.26 – 4.12 (m, 1H), 4.11 – 3.91 (m, 1H), 3.74 (s, 3H), 2.07 – 1.97 (m, 3H), 1.88 – 1.52 (m, 11H). LCMS (ES+) m/z 423 (M+1).

Example 335 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide **335**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-(difluoromethyl)phenyl)boronic acid gave **335**. 1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.09 – 7.80 (m, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.65 – 7.59 (m, 1H), 7.59 – 7.50 (m, 3H), 4.75 (dd, J = 10.6, 3.8 Hz, 1H), 4.42 – 4.26 (m, 1H), 4.19 – 4.07 (m, 1H), 4.04 – 3.87 (m, 1H), 3.79 (s, 3H), 3.21 – 3.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.97 – 1.85 (m, 1H), 1.74 – 1.58 (m, 4H). LCMS (ES+) m/z 481 (M+1).

Example 336 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide **336**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-fluoro-2-(trifluoromethyl)phenyl)boronic acid gave **336**. 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 7.85 – 7.77 (m, 1H), 7.72 (s, 1H), 7.66 – 7.57 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.44 (s, 2H), 4.81 – 4.73 (m, 1H), 4.63 – 4.44 (m, 1H), 4.22 – 4.10 (m, 1H), 4.08 – 3.91 (m, 1H), 3.76 (s, 3H), 2.10 – 2.00 (m, 1H), 1.90 – 1.73 (m, 3H). LCMS (ES+) m/z 517 (M+1).

Example 337 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide **337**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2-chloro-3-fluorophenyl)boronic acid gave **337**. 1H NMR (400 MHz, DMSO-d6) δ 9.32 (s, 1H), 8.20 – 8.12 (m, 1H), 7.84 (s, 1H), 7.52 (s, 2H), 7.50 – 7.39 (m, 2H), 4.82 (dd, J = 10.7, 3.6 Hz, 1H), 4.53 – 4.36 (m, 1H), 4.33 – 4.20 (m, 1H), 4.14 – 3.98 (m, 1H), 3.76 (s, 3H), 2.09 – 2.01 (m, 1H), 1.88 – 1.66 (m, 4H). LCMS (ES+) m/z 483 (M+1).

Example 338 5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide **338**

Following the procedure for Example 101 starting from *tert*-butyl N-[2-bromo-4-[[5-[(2S,5R,6S)-5-(tert-butoxycarbonylamino)-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]carbamoyl]thiazol-5-yl]carbamate (Intermediate 95), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-chloro-2-fluorophenyl)boronic acid gave **338**. 1H NMR (400 MHz, DMSO-d6) δ 9.34 (s, 1H), 8.47 – 8.06 (m, 1H), 7.86 (s, 1H), 7.66 – 7.55 (m, 1H), 7.52 (s, 2H), 7.30 (t, J = 8.1 Hz, 1H), 4.83 (dd, J = 10.5, 3.6 Hz, 1H), 4.58 – 4.37 (m, 1H), 4.36 – 4.22 (m, 1H), 4.18 – 3.97 (m, 1H), 3.76 (s, 3H), 2.10 – 2.00 (m, 1H), 1.89 – 1.60 (m, 4H). LCMS (ES+) m/z 483 (M+1).

Example 339 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)thiazole-4-carboxamide **339**

Following the procedure for Example 101 starting from *tert*-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (Intermediate 99), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with 2-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (US2012/225062) gave **339**. 1H NMR (500 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.65 (s, 1H), 7.88 (s, 1H), 7.46-7.44 (m, 2H), 4.82-4.79 (m, 5H), 4.37-3.93 (m, 3H), 3.78 (s, 3H), 3.24-3.17 (m, 1H), 3.12 (s, 3H), 2.07-1.67 (m, 4H). LCMS (ES+) m/z 538 (M+1).

Example 340 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxamide **340**

Following the procedure for Example 111 starting from *tert*-butyl ((3S,4R,7S)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)carbamate (Intermediate 80), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxylic acid (Intermediate 151) gave **340**. 1H NMR (500 MHz, CDCl3) δ 9.81 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 7.36-7.34 (m, 2H), 5.21-5.16 (m, 2H), 4.86-4.81 (m, 2H), 4.63-4.45 (m, 3H), 4.05-3.86 (m, 1H), 3.85 (s, 3H), 3.52-3.49 (m, 1H), 2.10-2.05 (m, 2H), 1.85-1.72 (m, 2H). LCMS (ES+) m/z 526 (M+1).

Example 341 *N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **341**

Following the procedure for Example 111 (nitro reduction step not necessary) starting from tert-butyl ((2R*,3S*,4R*,6R*)-6-(4-amino-1-methyl-1H-pyrazol-5-yl)-3-hydroxy-2,3-dimethyltetrahydro-2H-pyran-4-yl)carbamate (Intermediate 152), and replacing 5-((*tert*-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (see US2012/225061), and separation of the enantiomers prior to Boc deprotection (SFC; Chiralpak IC) provided **341**. Note: absolute stereochemistry is arbitrary. 1H NMR (500 MHz, CDCl3) δ 9.75 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.46-7.43 (m, 1H), 7.07-7.04 (m, 2H), 4.82-4.79 (d, 1H), 3.79 (s, 3H), 3.47-3.45 (d, 1H), 2.99-2.98 (s, 1H), 2.09-2.05 (m, 1H), 1.92-1.81 (m, 4H), 1.50-1.10 (m, 3H), 1.09 (s, 3H). LCMS (ES+) m/z 464 (M+1).

Example 342 *N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **342**

Following the procedure of Example 341 also provided **342** (absolute stereochemistry is arbitrary). 1H NMR (500 MHz, CDCl3) δ 9.76 (s, 1H), 8.36 (s, 1H), 8.15 (s, 1H), 7.46-7.43 (m, 1H), 7.07-7.04 (m, 2H), 4.82-4.79 (d, 1H), 3.80 (s, 3H), 3.47-3.45 (d, 1H), 2.96-2.95 (s, 1H), 2.08-2.05 (m, 1H), 1.81-1.74 (m, 4H), 1.54-1.52(m, 3H), 1.02 (s, 3H). LCMS (ES+) m/z 464 (M+1).

Example 343 *N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide **343**

Following the procedure for Example 341, replacing 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 6-(2,6-difluorophenyl)-5-fluoropicolinic acid (see US2012/225061), and separation of the enantiomers prior to Boc deprotection (SFC; Chiralpak IC) provided **343**. Note: absolute stereochemistry is arbitrary. 1H NMR (500 MHz, CDCl3) δ 10.10 (s, 1H), 8.43-8.40 (m, 1H), 8.27 (s, 1H), 7.72-7.69 (m, 1H), 7.51-7.47 (m, 1H), 7.07-7.04 (m, 2H), 4.78-4.75 (m, 1H), 3.79-3.78 (m, 3H), 3.37-3.34 (m, 1H), 2.81-2.79 (m, 1H), 2.00-1.94 (m, 1H), 1.64-1.55 (m, 4H), 0.94-0.93 (m, 3H), 0.79 (s, 3H). LCMS (ES+) m/z 476 (M+1).

Example 344 *N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide **344**

Following the procedure of Example 343 also provided **344** (absolute stereochemistry is arbitrary). 1H NMR (500 MHz, CDCl3) δ 10.09 (s, 1H), 8.42-8.40 (m, 1H), 8.26 (s, 1H), 7.72-7.69 (m, 1H), 7.49-7.47 (m, 1H), 7.07-7.04 (m, 2H), 4.78-4.76 (m, 1H), 3.79 (s, 3H), 3.37-3.36 (m, 1H), 2.83-2.81 (m, 1H), 1.98-1.95 (m, 1H), 1.65-1.57 (m, 4H), 0.94-0.93 (m, 3H), 0.80 (s, 3H). LCMS (ES+) m/z 476 (M+1).

Example 345 5-amino-*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **345**

Following the procedure for Example 341, replacing 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 5-(tert-butoxycarbonylamino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (Example 8) and separation of the enantiomers prior to Boc deprotection (SFC; Chiralpak AD-H) provided **345**. Note: absolute stereochemistry is arbitrary. 1H NMR (500 MHz, DMSO-d6) δ 9.39 (s, 1H), 7.90-7.89 (m, 1H), 7.60-7.55 (m, 1H), 7.47 (s, 2H), 7.27-7.24 (m, 2H), 4.89-4.86 (m, 1H), 4.37 (s, 1H), 3.76 (s, 3H), 2.74-2.72 (m, 1H), 1.86-1.83 (m, 1H), 1.46-1.44 (m, 1H), 1.36-1.28 (m, 1H), 1.02 (d, J = 7Hz, 3H), 0.80 (s, 3H). LCMS (ES+) m/z 479 (M+1).

Example 346 5-amino-*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **346**

Following the procedure of Example 345 also provided **346** (absolute stereochemistry is arbitrary). 1H NMR (500 MHz, DMSO-d6) δ 9.39 (s, 1H), 7.90-7.89 (m, 1H), 7.60-7.55 (m, 1H), 7.47 (s, 2H), 7.27-7.24 (m, 2H), 4.89-4.86 (m, 1H), 4.37 (s, 1H), 3.76 (s, 3H), 2.74-2.72 (m, 1H), 1.86-1.83 (m, 1H), 1.46-1.44 (m, 1H), 1.36-1.28 (m, 1H), 1.02 (d, J = 7Hz, 3H), 0.80 (s, 3H). LCMS (ES+) m/z 479 (M+1).

Example 347 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **347**

Following the procedure for Example 101 starting from tert-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate (Intermediate 102), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (2,6-difluorophenyl)boronic acid gave **347**. 1H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 8.65 (s, 1H), 7.94 (s, 1H), 7.69-7.65 (m, 1H), 7.40-7.36 (m, 2H), 5.11-5.09 (m, 1H), 3.85-3.79 (m, 2H), 3.72 (s, 3H), 3.57 (s, 2H), 3.46-3.43 (m, 1H), 3.30 (s, 1H), 3.01 (s, 3H), 2.43-2.37 (m, 1H), 1.74-1.58 (m, 3H). LCMS (ES+) m/z 464 (M+1).

Example 348 *N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide **348**

Following the procedure for Example 101 starting from tert-butyl ((3S,4R,7S)-7-(4-(2-bromothiazole-4-carboxamido)-1-methyl-1H-pyrazol-5-yl)-3-methoxyoxepan-4-yl)carbamate (Intermediate 102), and replacing 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with (3-methylpyridin-2-yl)boronic acid gave **348**. 1H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 8.52-8.51 (m, 1H), 8.27 (s, 1H), 8.23 (s, 1H), 7.67-7.65 (m, 1H), 7.29-7.26 (m, 1H), 5.03-5.00 (m, 1H), 4.04-3.93 (m, 2H), 3.78 (s, 3H), 3.56-3.54 (m, 1H), 3.38-3.36 (m, 1H), 3.33 (s, 3H),

2.88 (s, 3H), 2.61 (s, 2H), 2.13-2.09 (m, 1H), 1.98-1.70 (m, 2H), 1.68-1.56 (m, 1H). LCMS (ES+) m/z 443 (M+1).

Example 349 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-5-fluoropyridin-4-yl)thiazole-4-carboxamide **349**

Following the procedure for Example 101, **349** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.63 (s, 1H), 8.56 (s, 1H), 8.14 (s, 1H), 4.57 (m, 1H), 4.26 (m, 2H), 3.88 (m, 1H), 3.85 (s, 3H), 3.42 (m, 1H), 1.99 (m, 2H), 1.79 (m, 1H), 1.69 (m, 1H), 1.56 (s, 2H). LCMS (ES+) m/z 469.1 (M+1).

Example 350 N-(5-((2S,5R,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **350**

Following the procedure for Example 101, **350** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.63 (s, 1H), 7.90 (s, 1H), 7.68-7.65 (m, 1H), 7.38-7.35 (m, 2H), 5.03-5.00 (m, 1H), 4.79 (bs, 1H), 3.96-3.93 (m, 1H), 3.88-3.87 (m, 1H), 3.73 (s, 3H), 3.63-3.59 (m, 1H), 3.13-3.11 (m, 1H), 2.22-2.18 (m, 1H), 1.83-1.81 (m, 1H), 1.64-1.58 (m, 2H). LCMS (ES+) m/z 450.1 (M+1)

Example 351 N-(5-((2R,5S,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **351**

Following the procedure for Example 101, **351** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.63 (s, 1H), 7.90 (s, 1H), 7.68-7.65 (m, 1H), 7.38-7.35 (m, 2H), 5.04-5.01 (m, 1H), 4.71 (bs, 1H), 3.94-3.90 (m, 1H), 3.85-3.84 (m, 1H), 3.73 (s, 3H), 3.63-3.59 (m, 1H), 3.10-3.08 (m, 1H), 2.24-2.20 (m, 1H), 1.80-1.58 (m, 5H). LCMS (ES+) m/z 450.1 (M+1)

Example 352 N-(5-((2S,5R,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **352**

Following the procedure for Example 101, **352** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.64 (s, 1H), 7.73-7.34 (m, 4H), 4.82-4.79 (d, 2H), 3.84-3.75 (m, 6H), 2.81-2.77 (s, 1H), 2.05-1.51 (m, 6H). LCMS (ES+) m/z 450.1 (M+1)

Example 353 N-(5-((2R,5S,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide **353**

Following the procedure for Example 101, **353** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.64 (s, 1H), 7.74-7.34 (m, 4H), 4.82-4.74 (m, 2H), 3.84-3.76 (m, 6H), 2.80-2.76 (s, 1H), 2.05-1.48 (m, 6H). LCMS (ES+) m/z 450.1 (M+1)

Example 354 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)thiazole-4-carboxamide **354**

Following the procedure for Example 101, **354** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.14 (d, J = 8.5 Hz, 2H), 4.59-4.55(m, 1H), 4.49 – 4.32 (m, 2H), 4.02 – 3.92 (m, 1H), 3.82 (s, 3H), 3.53-3.46 (m, 1H), 2.11 – 1.99 (m, 2H), 1.89 – 1.81 (m, 1H), 1.32-1.26 (m, 1H). LCMS (ES+) m/z 523.2 (M+1)

Example 355 N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide **355**

Following the procedure for Example 101, **355** was prepared. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 6.92 (d, J = 8Hz, 2H), 4.99-4.97 (m, 1H), 4.15 (dd, J = 3.2Hz, 10.4Hz, 1H), 3.94 (dd, J = 6.4Hz, 4Hz, 1H), 3.76 (s, 3H),3.74-3.72 (m, 1H), 3.62-3.54 (m, 1H), 3.32 (s, 3H), 2.39 (s, 3H), 1.90 – 1.87 (m, 1H), 1.87 – 1.85 (m, 1H), 1.75 – 1.67 (m, 2H),1.65-1.57(m, 2H). LCMS (ES+) m/z 478.1 (M+1)

Example 356 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methoxyphenyl)thiazole-4-carboxamide **356**

Following the procedure for Example 101, **356** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.54 (s, 1H), 7.97-7.95(m, 1H),7.72(s, 1H),7.43-7.39(m,1H),7.18-7.15(m,1H) 4.83 – 4.81 (dd, J = 8.0, 2.8Hz, 1H), , 4.44 – 4.33 (dm,, J = 38.8 Hz, 1H), 4.22 – 3.95 (m, 2H), 3.87(s, 3H),3.83(s,3H),3.25-3.19(m,1H), 2.13 – 2.10 (m, 1H), 1.94 – 1.66 (m, 5H). LCMS (ES+) m/z 464.1 (M+1)

Example 357 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methoxyphenyl)thiazole-4-carboxamide **357**

Following the procedure for Example 101, **357** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.16 (s, 2H), 7.68 (d, J=9.0Hz, 1H), 7.50 (t, J = 2.2 Hz, 1H), 7.39 (t, J=7.5Hz, 1H), 7.02-7.00 (m, 1H), 4.63-4.41 (m, 3H), 4.05-3.95 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.65-3.58 (m, 1H), 2.10 – 2.07 (m, 2H), 1.88 – 1.72 (m, 2H), 1.32-1.26 (m, 1H). LCMS (ES+) m/z 446.2 (M+1)

Example 358 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide **358**

Following the procedure for Example 101, **358** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 6.75 (d, *J* = 10.1 Hz, 2H), 4.70 – 4.52 (m, 1H), 4.50 – 4.28 (m, 2H), 3.97 (ddd, *J* = 33.0, 14.6, 4.2 Hz, 1H), 3.83 (s, 3H), 3.49 (dt, *J* = 17.0, 8.6 Hz, 1H), 2.07 (dd, *J* = 10.9, 6.4 Hz, 3H), 1.99 – 1.64 (m, 4H), 1.35 – 0.98 (m, 2H), 0.92 – 0.68 (m, 2H). LCMS (ES+) m/z 492.2 (M+1)

Example 359 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2-fluorophenyl)-5-fluoropicolinamide **359**

Following the procedure for Example 101, **359** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.26-8.23 (m, 1H), 8.12-8.08 (m, 1H), 7.89 (s, 1H), 7.80-7.77 (m, 1H), 7.66-7.64 (m, 1H), 7.52-7.50 (m, 1H), 4.84-4.82 (m, 1H), 4.34-3.93 (m, 3H), 3.76 (s, 3H), 3.10-3.07 (m, 1H), 2.08-2.05 (m, 1H), 1.79-1.63 (m, 5H). LCMS (ES+) m/z 480.1 (M+1)

Example 360 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluoro-3-methylsulfonyl-phenyl)thiazole-4-carboxamide **360**

Following the procedure for Example 101, **360** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.71 (s, 1H), 8.09 (ddd, J = 9.2, 8.0, 5.9 Hz, 1H), 7.80 (s, 1H), 7.60 (t, J = 9.3 Hz, 1H), 4.83 (dd, J = 10.5, 3.8 Hz, 1H), 4.39 – 4.24 (m, 1H), 4.22 – 4.10 (m, 1H), 4.05 – 3.89 (m, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 2.12 – 2.02 (m, 1H), 1.86 – 1.74 (m, 2H), 1.72 – 1.64 (m, 2H). LCMS (ES+) m/z 530.11 (M+1)

Example 361 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-3-methyl-phenyl)thiazole-4-carboxamide **361**

Following the procedure for Example 101, **361** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.52 (s, 1H), 8.29 (t, J = 7.7 Hz, 1H), 7.89 (s, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 4.87 (dd, J = 10.7, 3.6 Hz, 1H), 4.60 – 4.37 (m, 1H), 4.31 (dd, J = 22.4, 14.9 Hz, 1H), 4.20 – 3.95 (m, 1H), 3.78 (s, 3H), 3.39 – 3.29 (m, 1H), 2.36 (d, J = 2.2 Hz, 3H), 2.14 – 2.03 (m, 1H), 1.91 – 1.68 (m, 5H). LCMS (ES+) m/z 448.2 (M+1)

Example 362 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-methoxyphenyl)thiazole-4-carboxamide **362**

Following the procedure for Example 101, **362** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 8.01-7.99 (m, 1H), 7.22-7.19 (m, 1H), 7.08-7.04 (m, 1H), 4.64- 4.55 (m, 3H), 4.20-3.97 (m, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.64-3.60 (m, 1H), 2.09-2.05 (m, 2H), 1.83-1.77 (m, 2H), 1.55 (s, 2H). LCMS (ES+) m/z 464.1 (M+1)

Example 363 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide **363**

Following the procedure for Example 101, **363** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.31 (s, 1H), 8.10 (s, 1H), 7.07 – 6.86 (m, 2H), 4.66 – 4.53 (m, 1H), 4.42 (dd, *J* = 13.6, 6.7 Hz, 1H), 3.97 (ddd, *J* = 32.6, 14.6, 4.1 Hz, 1H), 3.83 (s, 3H), 3.50 (dt, *J* = 18.0, 9.0 Hz, 1H), 2.19 – 2.00 (m, 3H), 1.84 (m, 1H), 1.78 – 1.63 (m, 1H), 1.07 – 0.96 (m, 2H), 0.73 (q, *J* = 5.2 Hz, 2H). LCMS (ES+) m/z 492.2 (M+1)

Example 364 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4,6-trifluorophenyl)thiazole-4-carboxamide **364**

Following the procedure for Example 101, **364** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.63 (s, 1H), 7.81 (s, 1H), 7.48 – 7.45(t, J=7.2 Hz, 2H), 4.82 – 4.79 (m,

1H), 4.37 – 4.27 (m, 1H), 4.20 – 4.12 (m, 1H), 4.03 – 3.92 (m, 1H), 3.77 (s, 3H), 3.21 – 3.19 (m, 1H), 2.07 – 2.03 (m, 1H), 1.80 – 1.67 (m, 5H). LCMS (ES+) m/z 470.1 (M+1)

Example 365 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((S)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide **365**

Following the procedure for Example 101, **365** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.56 (s, 1H), 8.28 – 8.18 (m, 1H), 7.90 (s, 1H), 7.52 – 7.46 (m, 1H), 5.63 – 5.50 (m, 1H), 5.10 – 5.00 (m, 1H), 4.89 (dd, J = 10.4, 3.7 Hz, 1H), 4.58 – 4.41 (m, 1H), 4.39 – 4.26 (m, 1H), 4.18 – 4.00 (m, 1H), 3.78 (s, 3H), 2.13 – 2.04 (m, 1H), 1.89 – 1.68 (m, 5H), 1.39 (d, J = 6.5 Hz, 3H). LCMS (ES+) m/z 496.2 (M+1). Note: benzylic hydroxyl stereochemistry assigned arbitrarily

Example 366 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((R)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide **366**

Following the procedure for Example 101, **366** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.56 (s, 1H), 8.23 (t, J = 7.7 Hz, 1H), 7.90 (s, 1H), 7.54 – 7.45 (m, 1H), 5.58 (d, J = 4.6 Hz, 1H), 5.10 – 5.00 (m, 1H), 4.89 (dd, J = 10.5, 3.7 Hz, 1H), 4.60 – 4.41 (m, 1H), 4.39 – 4.24 (m, 1H), 4.19 – 3.99 (m, 1H), 3.78 (s, 3H), 2.14 – 2.03 (m, 1H), 1.89 – 1.67 (m, 5H), 1.39 (d, J = 6.5 Hz, 3H). LCMS (ES+) m/z 496.2 (M+1). Note: benzylic hydroxyl stereochemistry assigned arbitrarily

Example 367 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-isobutyrylphenyl)thiazole-4-carboxamide **367**

Following the procedure for Example 101, **367** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.39(s, 1H), 8.15 (s, 1H), 7.62 (d, J=9.0 Hz, 1H), 4.61-4.33(m, 3H), 4.06-3.93 (m, 1H), 3.82 (s, 3H), 3.51-3.44 (s, 2H), 2.10 – 1.99 (m, 2H), 1.85 – 1.85 (m, 1H), 1.76-1.70 (m, 1H), 1.26 (d, J=7.0Hz, 6H). LCMS (ES+) m/z 522.2 (M+1)

Example 368 N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide **368**

Following the procedure for Example 101, **368** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.13(s, 1H), 8.65(s, 1H), 7.95(s, 1H), 7.44-7.41(m, 1H), 7.33-7.30(m, 1H), 5,11(t, 1H), 3.91(s, 3H), 3.86-3.83(m, 1H), 3.78-3.74(m, 1H), 3.21(s, 3H), 3.43-3.41(m, 1H), 3.30-3.29(m, 1H), 3.02(s, 3H), 2.46-2.41(m, 1H), 1.71-1.52(m, 5H). LCMS (ES+) m/z 494.2 (M+1)

Example 369 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-6-methyl-phenyl)-5-methyl-thiazole-4-carboxamide **369**

Following the procedure for Example 101, **369** was prepared. ^{1}H NMR (400 MHz, DMSO) δ 9.75 – 9.64 (s, 1H), 7.80 – 7.75 (s, 1H), 7.49 – 7.38 (m, 1H), 7.26 – 7.16 (m, 2H), 4.82 – 4.74 (dd, *J* = 10.9, 3.5 Hz, 1H), 4.41 – 4.23 (m, 1H), 4.17 – 4.04 (m, 1H), 4.03 – 3.86 (ddd, *J* =

37.7, 15.0, 3.4 Hz, 1H), 3.79 – 3.74 (s, 3H), 3.23 – 3.07 (m, 1H), 2.88 – 2.83 (s, 3H), 2.43 – 2.39 (s, 3H), 2.10 – 1.96 (m, 1H), 1.91 – 1.75 (d, *J* = 11.7 Hz, 1H), 1.73 – 1.62 (s, 2H). LCMS (ES+) m/z 462.2 (M+1)

Example 370 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)-5-methyl-thiazole-4-carboxamide **370**

Following the procedure for Example 101, **370** was prepared. ^{1}H NMR (400 MHz, DMSO) δ 9.91 – 9.85 (s, 1H), 7.88 – 7.83 (s, 1H), 7.67 – 7.57 (tt, *J* = 8.4, 6.4 Hz, 1H), 7.36 – 7.25 (m, 2H), 4.85 – 4.78 (dd, *J* = 10.7, 3.5 Hz, 1H), 4.51 – 4.31 (m, 1H), 4.25 – 4.11 (m, 1H), 4.10 – 3.93 (ddd, *J* = 37.0, 14.9, 3.6 Hz, 1H), 3.79 – 3.72 (s, 3H), 3.35 – 3.23 (m, 1H), 2.88 – 2.83 (s, 3H), 2.11 – 2.00 (m, 1H), 1.87 – 1.66 (m, 3H). LCMS (ES+) m/z 466.2 (M+1)

Example 371 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((S)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide **371**

Following the procedure for Example 101, **371** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 7.08 (d, J = 3.0 Hz, 2H), 4.97-4.95 (m, 1H), 4.61-4.44 (m, 3H), 4.14-3.98 (m, 3 H), 3.88 (s, 3H), 3.52-3.50 (m, 1H), 2.43-2.40 (m, 1H), 2.12-1.80 (m, 7H), 1.27-1.23 (m, 2H). LCMS (ES+) m/z 522.2 (M+1). Note: benzylic THF stereochemistry assigned arbitrarily

Example 372 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5-dimethyl-1H-pyrazol-3-yl)thiazole-4-carboxamide **372**

Following the procedure for Example 101, **372** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 9.48 (s, 1H), 8.27 (s, 1H), 7.81(s, 1H), 4.84 – 4.81 (dd, J = 8.4, 3.2, 1H), , 4.46 – 4.33(dm, J = 44.0 Hz, 1H), 4.19 – 3.99 (m, 2H), 3.79 (s, 3H), 3.25-3.14 (m,1H), 2.33 (s,3H), 2.23 (s,3H), 2.10 – 2.06 (m ,1H), 1.91– 1.62 (m, 5H). LCMS (ES+) m/z 434.2 (M+1)

Example 373 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide **373**

Following the procedure for Example 101, **373** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 9.46 (s, 1H), 8.26 (s, 1H), 7.80 (s, 1H), 4.83 (dd, *J*=4.0, 11.0Hz, 1H), 4.44-4.18 (m, 1H), 4.11-4.00 (m, 2H), 3.79 (s, 3H), 3.23-3.15 (m, 1H), 2.94-2.78 (m, 2H), 2.43 (s, 2H), 2.11-2.06 (m, 1H), 1.90-1.82 (m, 1H), 1.77-1.73 (m, 4H), 1.58-1.57 (m, 2H), 1.01 (s, 6H). LCMS (ES+) m/z 488.2 (M+1)

Example 374 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide **374**

Following the procedure for Example 101, **374** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.89 (s, 1H), 9.45 (s, 1H), 8.25 (s, 1H), 7.77 (s, 1H), 4.82-4.77 (m, 1H), 4.44-4.01

(m, 4H), 3.78 (s, 3H), 3.19-3.16 (m, 1H), 2.92-2.78 (m, 2H), 2.63 (s, 2H), 2.08-1.88 (m, 4H), 1.87- 1.76 (m, 4H), 1.30 (s, 1H). LCMS (ES+) m/z 460.2 (M+1)

Example 375 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2,6-difluorophenyl)-5-fluoropicolinamide **375**

Following the procedure for Example 101, **375** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.34-8.31 (m, 1H), 8.20-8.17 (m, 1H), 7.95 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 4.86 – 4.84 (m, 1H), 4.29 – 4.16 (m, 1H), 4.05 -3.88 (m, 2H), 3.76 (s, 3H), 3.08 – 3.02 (m, 1H), 2.09 – 2.05 (m, 1H), 1.75 – 1.64 (m, 5H). LCMS (ES+) m/z 498.1 (M+1)

Example 376 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(dimethylcarbamoyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide **376**

Following the procedure for Example 101, **376** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 – 9.84 (s, 1H), 8.69 – 8.63 (s, 1H), 7.81 – 7.77 (s, 1H), 7.70 – 7.60 (td, J = 8.1, 6.3 Hz, 1H), 7.46 – 7.37 (t, J = 9.2 Hz, 1H), 4.87 – 4.78 (dd, J = 10.8, 3.4 Hz, 1H), 4.59 – 4.37 (dd, J = 51.8, 6.8 Hz, 1H), 4.28 – 4.13 (m, 1H), 4.13 – 3.94 (ddd, J = 37.2, 15.0, 3.5 Hz, 1H), 3.85 – 3.74 (s, 3H), 3.06 – 2.99 (s, 3H), 2.94 – 2.86 (s, 3H), 2.14 – 2.02 (m, 1H), 1.95 – 1.67 (m, 5H). LCMS (ES+) m/z 523.2 (M+1)

Example 377 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide **377**

Following the procedure for Example 101, **377** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 – 9.92 (s, 1H), 8.69 – 8.66 (s, 1H), 7.95 – 7.85 (q, J = 7.6 Hz, 1H), 7.84 – 7.80 (s, 1H), 7.55 – 7.43 (dd, J = 17.7, 8.6 Hz, 1H), 7.41 – 7.13 (m, 1H), 4.89 – 4.79 (d, J = 9.3 Hz, 1H), 4.54 – 4.34 (d, J = 49.6 Hz, 1H), 4.32 – 3.92 (m, 2H), 3.82 – 3.76 (s, 3H), 2.15 – 2.01 (d, J = 13.0 Hz, 1H), 1.93 – 1.65 (m, 5H). LCMS (ES+) m/z 502.1 (M+1)

Example 378 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2-fluoro-6-methoxy-phenyl]thiazole-4-carboxamide **378**

Following the procedure for Example 101, **378** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 – 9.88 (s, 1H), 8.61 – 8.57 (d, J = 1.5 Hz, 1H), 7.83 – 7.75 (t, J = 8.5 Hz, 1H), 7.75 – 7.70 (s, 1H), 7.37 – 6.90 (m, 4H), 4.90 – 4.66 (m, 2H), 4.42 – 4.27 (dd, J = 23.5, 14.9 Hz, 1H), 4.22 – 4.03 (dd, J = 37.7, 15.6 Hz, 1H), 4.02 – 3.96 (s, 3H), 3.83 – 3.78 (s, 3H), 3.64 – 3.49 (s, 1H), 2.22 – 2.09 (d, J = 11.9 Hz, 1H), 2.00 – 1.75 (m, 4H). LCMS (ES+) m/z 514.1 (M+1)

Example 379 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-pyrazol-3-yl)thiazole-4-carboxamide **379**

Following the procedure for Example 101, **379** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.29 (s, 1H), 7.95 – 7.87 (m, 2H), 6.96 (d, J = 2.4 Hz, 1H), 4.88 (dd, J = 10.4, 3.8 Hz, 1H), 4.59 – 4.38 (m, 1H), 4.37 – 4.23 (m, 1H), 4.19 – 3.95 (m, 1H), 3.77 (s, 3H),

3.39 – 3.25 (m, 1H), 2.50 (ddd, J = 23.7, 3.8, 1.9 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.89 – 1.69 (m, 4H). LCMS (ES+) m/z 406.2 (M+1)

Example 380 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((R)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide **380**

Following the procedure for Example 101, **380** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 7.08 (d, J = 9.5 Hz, 2H), 4.98-4.95 (m, 1H), 4.61-4.44 (m, 3H), 4.14-3.98 (m, 3H), 3.85 (s, 3H), 3.55-3.48 (m, 1H), 2.44-2.40 (m, 1H), 2.11-1.73 (m, 8H), 1.28-1.26 (m, 1H). LCMS (ES+) m/z 522.2 (M+1). Note: benzylic THF stereochemistry assigned arbitrarily

Example 381 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-3-yl)thiazole-4-carboxamide **381**

Following the procedure for Example 101, **381** was prepared. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 9.38 (s, 1H), 8.47-8.45 (m, 1H), 8.22 (s, 1H), 8.06 (s, 1H), 7.56-7.54 (m, 1H), 7.50-7.47 (m, 1H), 7.38-7.26 (m, 1H), 4.68-4.65 (m, 1H), 4.47-4.40 (m, 2H), 4.09-4.02 (m, 1H), 3.88 (s, 3H), 3.48-3.47 (m, 1H), 2.17-2.13 (m, 2H), 1.90-1.89 (m, 1H), 1.72-1.70 (m, 1H), 1.59 (s, 2H). LCMS (ES+) m/z 456.1 (M+1)

Example 382 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[2-fluoro-6-(hydroxymethyl)phenyl]thiazole-4-carboxamide **382**

Following the procedure for Example 101, **382** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.60 (s, 1H), 7.71 (s, 1H), 7.63 – 7.52 (m, 2H), 7.36 – 7.27 (m, 1H), 4.79 (dd, J = 11.0, 3.6 Hz, 1H), 4.71 (d, J = 3.3 Hz, 2H), 4.40 (dd, J = 49.4, 6.9 Hz, 1H), 4.23 – 4.11 (m, 1H), 4.05 – 3.89 (m, 1H), 3.80 (s, 3H), 3.26 – 3.19 (m, 1H), 2.11 – 2.03 (m, 1H), 1.96 – 1.84 (m, 1H), 1.76 – 1.66 (m, 2H). LCMS (ES+) m/z 464.2 (M+1)

Example 383 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-pyridyl)thiazole-4-carboxamide **383**

Following the procedure for Example 101, **383** was prepared. LCMS (ES+) m/z 417.1 (M+1)

Example 384 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-isopropoxy-3-pyridyl)thiazole-4-carboxamide **384**

Following the procedure for Example 101, **384** was prepared. ^{1}H NMR (400 MHz, DMSO) δ 9.91 – 9.87 (s, 1H), 8.85 – 8.77 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.48 – 8.45 (s, 1H), 8.36 – 8.30 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.91 – 7.87 (s, 1H), 7.20 – 7.13 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.57 – 5.49 (m, 1H), 4.91 – 4.83 (dd, *J* = 10.5, 3.6 Hz, 1H), 4.58 – 4.39 (m, 1H), 4.39 – 4.25 (dd, *J* = 22.6, 15.0 Hz, 1H), 4.19 – 4.00 (ddd, *J* = 39.7, 15.1, 3.4 Hz, 1H), 3.80 – 3.76 (s, 3H), 3.35 – 3.27

(m, 1H), 2.13 – 2.03 (m, 1H), 1.92 – 1.67 (m, 3H), 1.51 – 1.42 (d, J = 6.2 Hz, 6H). LCMS (ES+) m/z 475.2 (M+1)

Example 385 N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[6-(dimethylamino)-3-pyridyl]thiazole-4-carboxamide **385**

Following the procedure for Example 101, **385** was prepared. LCMS (ES+) m/z 460.2 (M+1)

Example 386 2-(6-acetamido-3-pyridyl)-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide **386**

Following the procedure for Example 101, **386** was prepared. LCMS (ES+) m/z 474.2 (M+1)

Example 387 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thiazole-4-carboxamide **387**

Following the procedure for Example 101, **387** was prepared. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 9.73 (s, 1H), 8.41 (s, 1H), 8.26 (s, 1H), 7.51 (d, J=5.6 Hz,1H), 7.38(d, J=4.8 Hz,1H), 4.48-4.67 (m, 3H), 3.90 – 4.01 (m, 1H), 3.83 (s, 3H), 3.66-3.74 (m, 1H), 3.55 (s, 3H), 2.10-2.14 (m, 2H), 1.83-1.89. LCMS (ES+) m/z 465.1 (M+1)

Example 388 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-pyrazol-1-yl)thiazole-4-carboxamide **388**

Following the procedure for Example 101, **388** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.56(s, 1H), 8.17(s,1H) 7.89-7.93(d, 2H), 6.71-6.72 (t, 1H), 4.89-4.91 (m, 1H), 4.00-4.56 (m, 3H), 3.78 (s, 3H), 2.36-2.36 (s, 1H), 2.08-2.12 (m, 1H), 1.68-1.82 (m, 5H). LCMS (ES+) m/z 406.1 (M+1)

Example 389 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)thiazole-4-carboxamide **389**

Following the procedure for Example 101, **389** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36(s, 1H), 8.10 (s, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 4.82 (dd, J=10.5, 6.5Hz, 1H), 4.45-4.34 (m, 1H), 4.15-4.00 (m, 2H), 3.78 (s, 3H), 3.24-3.09 (m, 3H), 2.09-2.05 (m, 1H), 1.88-1.80 (m, 3H), 1.72-1.65 (m, 6H). LCMS (ES+) m/z 460.2 (M+1)

Example 390 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazole-4-carboxamide **390**

Following the procedure for Example 101, **390** was prepared. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69(s, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.88 (s, 1H), 4.8 (dd, J=10.0, 6.5Hz, 1H), 4.56-4.44 (m, 1H), 4.33 (dd, J=22.5, 7.0Hz, 1H), 4.13-4.01(m, 1), 3.77 (s, 3H), 3.28-3.27 (m, 2H), 2.67-2.65 (m, 2H), 2.57 (s, 2H), 2.10-2.05 (m, 1H), 1.89-1.70 (m, 8H). LCMS (ES+) m/z 460.2 (M+1)

Example 391 N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5,7-difluoro-2,3-dihydrobenzofuran-6-yl)thiazole-4-carboxamide **391**

Following the procedure for Example 101, **391** was prepared. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.63 (s, 1H), 7.76 (s, 1H), 7.31-7.29 (d, J=7.2Hz, 1H), 4.87 – 4.71 (m, 4H), , 4.33 – 4.11 (m, 2H), 3.81 (s, 3H), 3.58-3.55 (m,1H), 3.04-3.01 (m, 2H), 2.16 – 2.14 (m, 1H), 1.96 – 1.73(m, 5H). LCMS (ES+) m/z 494.1 (M+1)

Example 901 Pim kinase binding activity

PIM-1, -2, and -3 enzymes were generated as fusion proteins expressed in bacteria and purified by IMAC column chromatography (Sun, X., Chiu, J.F., and He, Q.Y. (2005) Expert Rev. Proteomics, 2:649-657). A fluorescent-labeled Pim-specific peptide substrate, was custom synthesized by American Peptide Company (Sunnyvale, CA). Reaction Buffer contained 10 mM HEPES, pH 7.2, 10 mM $MgCl_2$, 0.01% Tween 20, 2 mM DTT. Termination Buffer contained 190 mM HEPES, pH 7.2, 0.015% Brij-35, 0.2% Coating Reagent 3 (Caliper Life Sciences, Hopkinton, MA), 20 mM EDTA. Separation Buffer contained 100 mM HEPES, pH 7.2, 0.015% Brij-35, 0.1% Coating Reagent 3, 1:200 Coating Reagent 8 (Caliper Life Sciences, Hopkinton, MA), 10 mM EDTA and 5% DMSO.

PIM reactions were carried out in a final volume of 10 µL per well in a 384-well plate. A standard enzymatic reaction, initiated by the addition of 5 µL 2X ATP and test compound to 5 µL of 2X enzyme and FAM-peptide, contained 20 pM PIM1, 50 pM PIM2, or 55 pM PIM3, 1 µM FAM-peptide, and 10 µM ATP, in Reaction Buffer. After 90 minutes of incubation at room temperature, the phosphorylation reaction was stopped by the addition of 10 µL Termination Buffer. The product and substrate in each independent reaction were separated on a 12-sipper microfluidic chip (Caliper Life Sciences, Hopkinton, MA) run on a Caliper LC3000® (Caliper Life Sciences, Hopkinton, MA). The separation of product and substrate was optimized by choosing voltages and pressure using Caliper's Optimizer software (Hopkinton, MA). The separation conditions used a downstream voltage of –500V, an upstream voltage of –2150V, and a screening pressure of -1.2 psi. The product and substrate fluorophore were excited at 488 nm and detected at 530 nm. Substrate conversion was calculated from the electropherogram using HTS Well Analyzer software (Caliper Life Sciences, Hopkinton, MA). Ki values for the test compound were calculated. See Table 1 for representative PIM1 LC3K Ki in micromolar values of exemplary compounds.

Example 902 In vitro cell proliferation potency assays

BaF3 parental line was obtained from the DSMZ repository. BaF3 lines transfected with PIM1 or PIM2 were generated. Mouse IL-3 was purchased from R&D Systems. G418 was

purchased from Clontech. Media for BaF3 parental line contained RPMI, 10% FBS, 2 mM L-Glutamine, 2 ng/mL mIL-3. Media for BaF3 PIM1 & 2 lines contained RPMI, 10% FBS, 2 mM L-Glutamine, 250 µg/mL. Media for MM1.S (multiple myeloma cells) line contained RPMI, 10% FBS, 2 mM L-Glutamine.

BaF3, a murine interleukin-3 dependent pro-B cell line, parental cells, BaF3 PIM1 cells, BaF3 PIM2 cells, and MM1.S (multiple myeloma) cells were seeded at 2k/well, 5k/well, 5k/well, and 10k/well respectively, in a 384-well plate, at 45 µL/well. Test compound was added at 5 µL/well. BaF3 cells (parental and transfected) were incubated overnight, while MM1.S cells were incubated for 72 hours at 37 °C, 5% CO_2. CELL TITER GLO® Reagent (Promega) was added at 50 µL/well, the plates were incubated for 30 minutes, and their luminescence read on an HT Analyst. IC_{50}/EC_{50} values for the test compound were calculated.

Representative compounds of the present invention were tested as described above and found to exhibit a $Ki/IC_{50}/EC_{50}$ in µM (micromolar) as shown below in Tables 2a, 2b, and 2c.

Table 2a.

No.	Prolif BaF3 IL3 (IC50) µM (micromolar)	Prolif BaF3 PIM1 (IC50) µM (micromolar)	Prolif MM1S ATP (EC50) µM (micromolar)
109	8.3	0.115	9.2
110	9.4	0.0448	2.4
112	6.9	2.1	8.5
115	3.4	0.0192	0.0718
117	3	0.0307	0.122
121	3.5	0.0136	0.0119
126	25	0.0252	0.0217
129	6.9	0.0247	0.109
131	6.8	1.5	10
135	12.7	2.5	4.3
148	25	1.6	7.7

Table 2b.

No.	Prolif BaF3 IL3 (IC50) µM (micromolar)	Prolif BaF3 PIM1 (IC50) µM (micromolar)	Prolif MM1S ATP (EC50) µM (micromolar)
286	11.3	0.947	12.6
316	9.3	0.126	0.686
317	7.9	0.0152	0.0345
319	7.8	0.129	0.875
320	>25	0.0244	0.187
321	4.4+	0.0506	0.385
322	6.3+	0.113	1.5
323	>25	0.186	10
324	>25	0.0453	0.116
325	6.3	0.142	0.735
326	12.4	0.132	0.436
327	16.8	0.176	0.648
328	12.5	0.0214	1.5
329	2.4	0.348	1.7
339	>25	0.0522	1.9
340	20.7	0.0517	>6.2
341	>25	0.0968	6.9
342	10.0	12.7	21.6
343	12.8	0.342	0.781
344	14	9	9.8
345	>25	6.8	>25

346	>25	0.517	4.3
347	5	0.157	3.3
348	10.5	0.359	1

Table 2c

No.	Prolif BaF3+IL3 (IC50) µM (micromolar)	Prolif BaF3_PIM1 (IC50) µM (micromolar)	Prolif MM1S ATP (EC50) µM (micromolar)
351	9.9	0.621	0.52
354	7.3	3.4	5.1
355	3.9	0.0535	1.6
356	6.5	0.108	1.4
358	4.1	0.0682	0.938
359	11.6	0.262	5.8
360	16.5	15.2	9.4
361	2.8	0.25	0.452
362	3.1	0.0507	0.336
363	4.5	0.294	0.937
364	20.2	0.208	1.1
365	15.9	0.408	0.348
366	10.3	0.302	1.7
367	24	0.245	5.4
368	1.9	0.1	2.4
370	6.4	0.675	1.8
371	>25	0.151	4.4
372	20.5	0.602	1.6
373	8.6	0.101	3.4
374	13.1	0.246	1.4
374	10.9	0.0709	4.1

377	9.9	0.0686	4.2
379	>25	0.98	2.9
380	12.2	0.0372	1.7
381	5.8	0.0794	0.64
383	20.8	0.823	5.7
384	7.2	5.6	4.4
385	12	0.118	1.2
387	8.2	3.2	2

Example 903 hERG assays

hERG assays (2-pt) were carried out as follows:

The in vitro potential for hERG (the human *Ether-à-go-go*-Related Gene) potassium channel current inhibition by a selection of the compounds of the invention was assessed according to the study site standard procedures (ChanTest, Cleveland, OH). In brief, hERG-expressing HEK-293 cells (n=2/concentration) were evaluated at 1 and 10 mM in the automated PatchXpress 7000A system (Molecular Devices, Sunnyvale, CA) for 5 minutes after adding the test article. hERG assays (2-pt) data were expressed as percent of maximal current.

hERG assays (IC_{50}) were carried out as follows:

The in vitro potential for hERG potassium channel current inhibition was assessed according to the study site standard procedures (ChanTest, Cleveland, OH). In brief, hERG inhibition (% max) was determined in hERG-expressing HEK-293 cells (n=2 /concentration) using the automated PatchXpress 7000A system (Molecular Devices, Sunnyvale, CA) for 5 minutes after adding the test article. IC_{50} values were calculated based on hERG inhibition at test article concentrations of 0.01, 0.1, 1, 10, 30, and 100 μM.

hERG IC_{50} and IC_{20} values of certain compounds of the invention were measured and compared with a compound, 5-amino-N-(5-((4R,5R)-4-amino-5-fluoroazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, No. 139, from a series of PIM inhibitors where corresponding R^2 is an N-linked heterocyclyl or C-linked carbocyclyl moiety (US 2013/0079321). The $IC_{50/20}$ values for this compound No. 139 of US 2013/0079321 were 2.7 and 0.7 micromolar (μM), respectively. In contrast, the $IC_{50/20}$ values for compound No. **154**, 5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide, from Table 1b of the present invention were 9.1 and 1.6 micromolar, respectively. The $IC_{50/20}$ values for compound No. **177**, 5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-

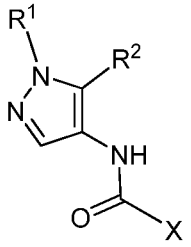
5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide from Table 1b of the present invention were 16 and 3.9 micromolar, respectively. This hERG data indicates the compounds of the invention present diminished susceptibility to QTc prolongation. An excessively prolonged QTc-interval may lead to serious ventricular arrhythmia and sudden death (De Bruin, M.L et al (2005) European Heart Journal, 26:590-597; Redfern, W.S. et al (2003) Cardiovascular Research, 58:32-45).

The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

We Claim:

1. A compound selected from Formula I:

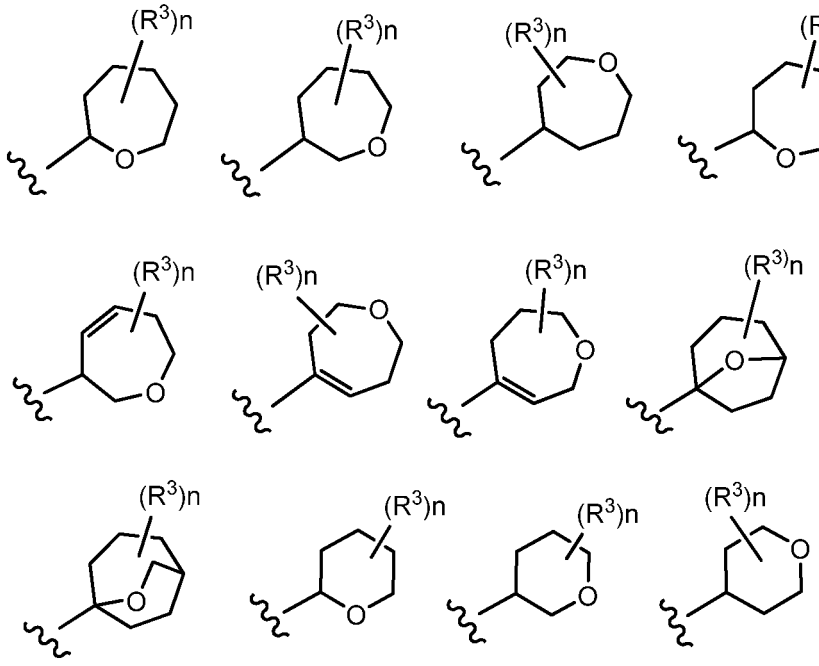


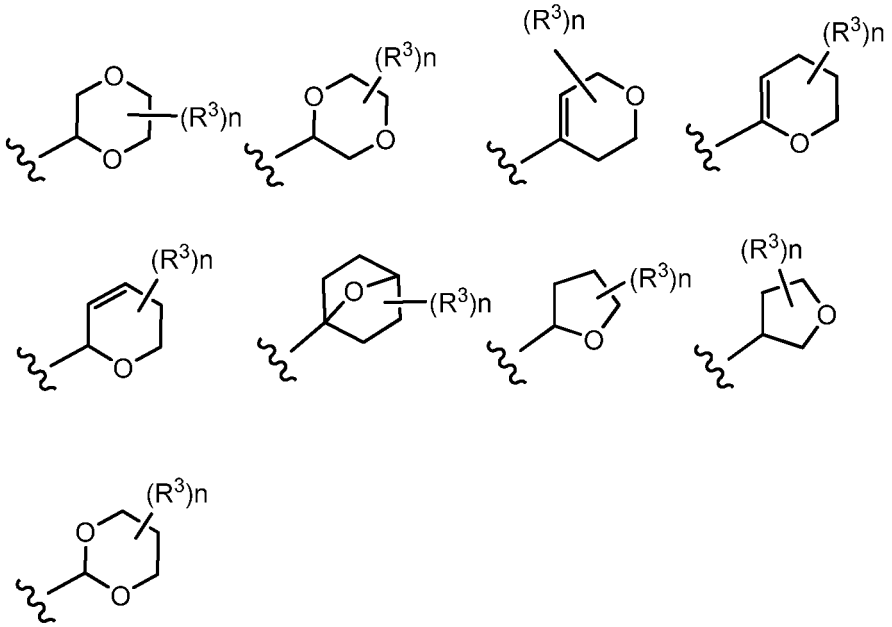
I

and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, C_1–C_{12} alkyl, C_2–C_{12} alkenyl, C_2–C_{12} alkynyl, C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl);

R^2 is selected from the structures:





where the wavy line indicates the site of attachment;

R^3 is independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH=CH_2$, $-CH=C(CH_3)_2$, $=CH_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COCH_2NH_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OCH_2Cl_3$, $-NHC(O)OC_6H_5$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH(CH_3)_2$, $-OC(CH_3)_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, oxetan-3-ylmethylamino, (3-methyloxetan-3-yl)methylamino, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino;

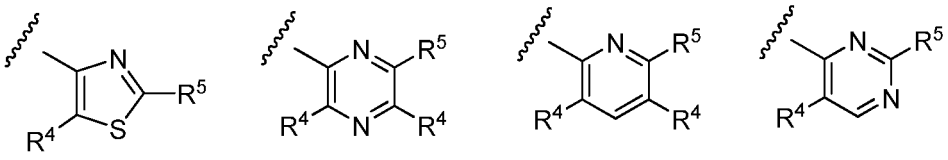
or where two geminal R^3 groups form a spiro ring selected from a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidinyl, piperazinyl, or piperidinyl ring, where the spiro ring is optionally substituted with one or more groups independently selected from $-F$, $-OH$, $=O$, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

or where two vicinal R^3 groups form a five-membered or six-membered heterocyclyl fused ring, where the heterocyclyl fused ring is optionally substituted with one or more groups

independently selected from –F, –OH, =O, $–CH_3$, $–NH_2$, $–CH_2F$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2NH_2$, and $–CF_3$;

n is 0, 1, 2, 3, 4, 5, or 6;

X is selected from the structures:



where the wavy line indicates the site of attachment;

R^4 is independently H, F, $–CH_3$, or $–NH_2$; and

R^5 is selected from H, Cl, Br, C_1–C_{12} alkyl, –O–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_2–C_8 alkenylene)–(C_3–C_{12} carbocyclyl), –(C_2–C_8 alkenylene)–(C_2–C_{20} heterocyclyl), C_6–C_{20} aryl, –(C_6–C_{20} arylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–(C_6–C_{20} arylene), –(C_6–C_{20} arylene)–(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_1–C_{12} alkyl), C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl), and –(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl); where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2NH_2$, $–CH_2CH_2NH_2$, $–CH_2CHCH_2NH_2$, $–CH_2CH(CH_3)NH_2$, $–CH_2OH$, $–CH_2CH_2OH$, $–CH(CH_2OH)_2$, $–C(CH_2OH)_3$, $–CH(CH_3)OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, –CN, $–CF_3$, $–CHF_2$, $–CH_2F$, $–CO_2H$, $–COCH_3$, $–COCH(CH_3)_2$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NO_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, –OH, $–OCH_3$, $–OCF_3$, $–OCH(CH_3)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–CH_2OCH_3$, $–S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, phenyl, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino.

2. The compound of claim 1 wherein R^1 is H.

3. The compound of claim 1 wherein R^1 is C_1–C_{12} alkyl or C_3–C_{12} carbocyclyl.

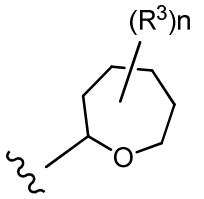
4. The compound of claim 3 wherein R^1 is selected from $–CH_3$, $–CH_2CH_3$, $–CH_2CHF_2$, and $–CH_2CF_3$.

5. The compound of claim 1 wherein R^1 is –(C_1–C_{12} alkylene)–(C_2–C_{20}

heterocyclyl).

6. The compound of claim 5 wherein R^1 is oxetan-3-ylmethyl.

7. The compound of claim 5 wherein R has the structure:



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8. The compound of claim 1 wherein R^3 is independently selected from F, Cl, -OH, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-CH_2NHCH_3$, and $-OCH_3$; and n is 1, 2, or 3.

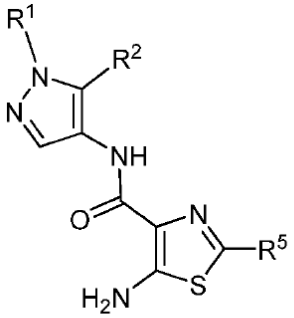
9. The compound of claim 1 wherein R^4 is $-NH_2$.

10. The compound of claim 1 wherein R^4 is H.

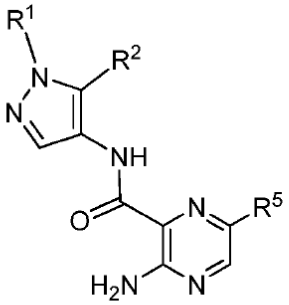
11. The compound of claim 1 wherein R^5 is C_6-C_{20} aryl.

12. The compound of claim 11 wherein R^5 is phenyl substituted with one or more F.

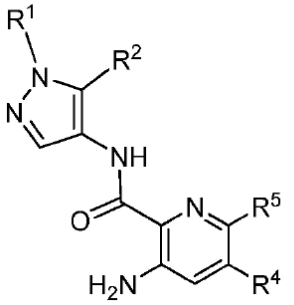
13. The compound of claim 1 having the structure of Formula Ia-Id:



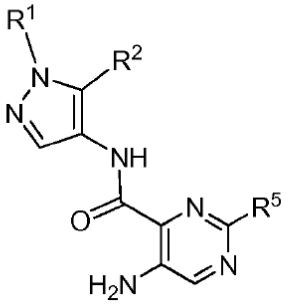
Ia



Ib

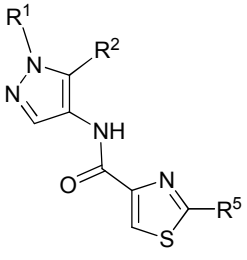


Ic

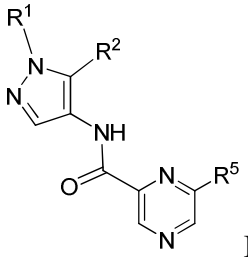


Id

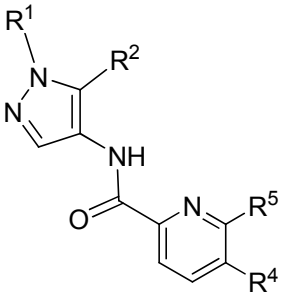
14. The compound of claim 1 selected from Formula Ie-Ih:



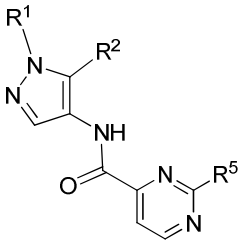
Ie



If



Ig



Ih

15. The compound of claim 1 selected from the group consisting of:

5-amino-2-(2,6-difluorophenyl)-N-[5-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-[5-(3,4-dihydro-2H-pyran-6-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-(1-methyl-5-tetrahydropyran-2-yl-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-2-(3-fluoro-2-pyridyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-(5-((1S,4S,5S)-4-hydroxy-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-N-[5-(2-amino-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,7R)-5-hydroxy-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-(5-((5R,6S)-5,6-dihydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((1S,4S,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((1S,4R,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((1R,4S,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((1R,4R,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-

difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,5R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,5S,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5S,6S)-6-amino-5-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-[5-(5-amino-6-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5S,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((4S,5S)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((5S,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-2-(2,6-difluorophenyl)-N-[5-(5-hydroxyoxepan-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-amino-N-[5-(5-amino-4-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2S,4R,5R)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,4S,5S)-5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-amino-N-(5-((2R,4S,5S)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-

difluorophenyl)thiazole-4-carboxamide
5-amino-N-[5-[1-(aminomethyl)-7-oxabicyclo[2.2.1]heptan-4-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-(5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-[5-(4-amino-5-hydroxy-3,5-dimethyl-tetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-2-(2,6-difluorophenyl)-N-(5-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,4S)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2R,5S)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2R,5S,6S)-6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R,6R)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide; and
5-Amino-N-[5-[5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 selected from the group consisting of:

5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide

5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide

Amino-N-[5-[4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2R,4S)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2S,4R)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[2-amino-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide

5-Amino-2-(2,6-difluorophenyl)-N-[5-[(2R,5R)5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-Amino-2-(2,6-difluorophenyl)-N-[5-[(2S,5S)5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-Amino-2-(2,6-difluorophenyl)-N-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-Amino-2-(2,6-difluorophenyl)-N-[5-[5-(hydroxymethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

5-Amino-N-[5-[5-(aminomethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2S,5R)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2R,5S)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[4-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2R,5R)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2S,5S)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[5-(aminomethyl)-5-ethyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide

5-Amino-N-[5-[(2S,5R,6S)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-

(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2R,5S,6R)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[5-amino-4,4-difluoro-5,6-dimethyl-tetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2R,5S,6R)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R,6R)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,3-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R,6R)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide
5-Amino-N-[5-[(2S,5R,6R)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide
5-Amino-N-(5-((2R,5S,6R)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-(5-((2S,5R,6S)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-Amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-Amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-

methoxyethoxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5 fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(methoxymethyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-propionylphenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-

hydroxyethyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1,2,3-trihydroxypropan-2-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(1,3-dihydroxypropan-2-yl)-2,6-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((R)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((S)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-5-fluoro-6-(2-fluoro-4-methoxyphenyl)picolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2-chloro-3-fluorophenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-(2-hydroxy-2-

methylpropyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-methoxypyridin-3-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-oxo-1,2-dihydropyridin-3-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-cyclopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-2-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-

yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-difluoropyridin-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3′-chloro-2,2′-difluoro-[1,1′-biphenyl]-3-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2′-chloro-3′,6-difluoro-[1,1′-biphenyl]-2-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-isopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-

5-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(hydroxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-6-methoxyphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-

(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-ethoxy-2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-bromo-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-

yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,5-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((R)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((S)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,56R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazol-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-chloro-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methylphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-

fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-

(trifluoromethyl)phenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxamide
N-(5-((2R,4R,5S,6R)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,4S,5R,6S)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2R,4R,5S,6R)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
N-(5-((2S,4S,5R,6S)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
5-amino-N-(5-((2R,4R,5S,6R)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
5-amino-N-(5-((2S,4S,5R,6S)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide; and
N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1 selected from the group consisting of:
N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-5-fluoropyridin-4-yl)thiazole-4-carboxamide
N-(5-((2S,5R,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2R,5S,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((2S,5R,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2R,5S,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methoxyphenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methoxyphenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2-fluorophenyl)-5-fluoropicolinamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluoro-3-methylsulfonyl-phenyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-3-methyl-phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-methoxyphenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4,6-trifluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((S)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((R)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-isobutyrylphenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-6-methyl-phenyl)-5-methyl-thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)-5-methyl-thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((S)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5-dimethyl-1H-pyrazol-3-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2,6-difluorophenyl)-5-fluoropicolinamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(dimethylcarbamoyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2-fluoro-6-methoxy-phenyl]thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-pyrazol-3-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((R)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-3-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[2-fluoro-6-(hydroxymethyl)phenyl]thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-pyridyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-isopropoxy-3-pyridyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[6-(dimethylamino)-3-pyridyl]thiazole-4-carboxamide

2-(6-acetamido-3-pyridyl)-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-pyrazol-1-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5,7-difluoro-2,3-dihydrobenzofuran-6-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(3-methyloxetan-3-yl)phenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(1,1-difluoroethyl)-2,6-difluorophenyl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-1-yl)thiazole-4-carboxamide

N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2H-indazol-2-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-6-(2,6-difluorophenyl)-5-fluoro-pyridine-2-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-methyl-2-pyridyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1,5-naphthyridin-3-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(5-fluoro-1H-indol-4-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-benzyloxyphenyl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-4-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-7-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-6-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-7-yl)thiazole-4-carboxamide

N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-4-yl)thiazole-4-carboxamide

N-(5-((3S,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((3R,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
N-(5-((3R,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide; and
N-(5-((3S,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
or a pharmaceutically acceptable salt thereof.

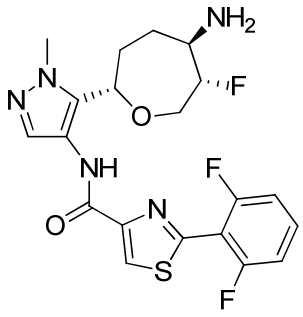
18. A pharmaceutical composition comprised of a compound of claim 1 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

19. The pharmaceutical composition according to claim 18, further comprising a chemotherapeutic agent.

20. The pharmaceutical composition of claim 18 for use in treating a disease or disorder selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Pim kinase.

21. The compound of claim 16, wherein said compound is N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprised of a compound having the structure:



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

23. The pharmaceutical composition of claim 22, further comprising a chemotherapeutic agent.