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(71) Applicant: **KARYOPHARM THERAPEUTICS INC.** [US/US]; 85 Wells Ave., 2nd Floor, Newton, MA 02459 (US).

(72) Inventor: **BALOGLU, Erkan**; 8 Benjamin Terrace, Stoneham, MA 02180 (US).

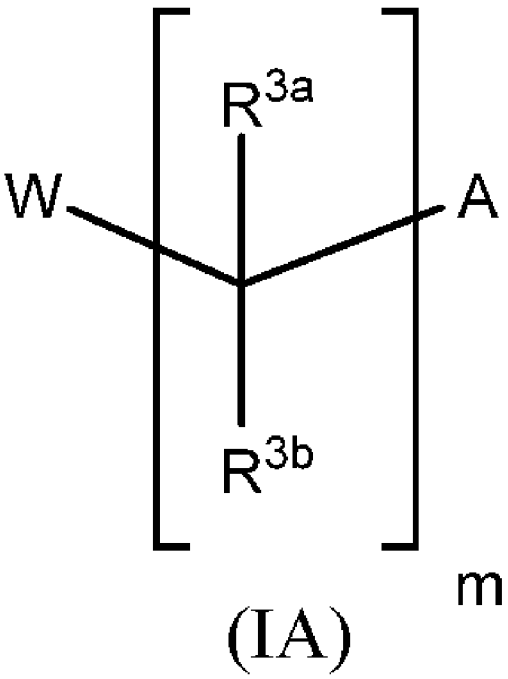
(74) Agents: **ABELLEIRA, Susan, M.** et al.; Foley Hoag LLP, Seaport West, 155 Seaport Blvd., Boston, MA 02210-2600 (US).

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[Continued on next page]

(54) Title: MULTICYCLIC COMPOUNDS AND USES THEREOF



(IA)

(57) Abstract: The present invention relates to multicyclic compounds containing a urea or a guanidine moiety, or pharmaceutically acceptable salts or compositions thereof represented by Structural Formula (IA) or a pharmaceutically acceptable salt thereof and pharmaceutical comopositions comprising the multicyclic compounds. The invention also relates to a method for treating a disease or disorder selected from cancer (e.g., lymphoma, such as mantle cell lymphoma), a neurodegenerative disease, an inflammatory diseases or an immune system disease (e.g., a T-Cell mediated autoimmune disesase) in a subject in need thereof. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof.

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MULTICYCLIC COMPOUNDS AND USES THEREOF

RELATED APPLICATION

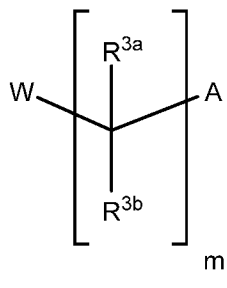
[0001] This application claims the benefit of U.S. Provisional Application No. 62/273,983, filed on December 31, 2015. The entire teachings of the above application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Cancer remains a disease for which existing treatments are insufficient. For example, it is expected that by the end of 2015, more than 1.6 million new cases of cancer will be diagnosed and close to 600,000 people will die from the disease. While major breakthroughs are changing how we prevent, treat, and cure cancer, there is a clear need for additional drug-like compouds that are effective for the treatment of cancer.

SUMMARY OF THE INVENTION

[0003] The present invention relates to multicyclic compounds containing a urea or a guanidine moiety, or pharmaceutically acceptable salts or compositions thereof, useful as, for example, anti-cancer agents. In one embodiment of the invention, the substituted benzofuranyl compounds are represented by Structural Formula (IA):



(IA),

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0004] Another embodiment of the invention is a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0005] Yet another embodiment of the invention is a method for treating a disease or disorder selected from cancer (e.g., lymphoma, such as mantle cell lymphoma), a neurodegenerative disease, inflammatory diseases or an autoimmune system disease (e.g., a T-Cell mediated autoimmune disesase) in a subject in need thereof. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof.

[0006] Without being bound by a particular theory, it is believed that the compounds described herein can modulate (*e.g.*, inhibit) one or more p21-activated kinases (PAK) for example, one or more of PAKs 1-6 (e.g, PAK1, PAK2, PAK3, PAK4, PAK5, PAK6), can inhibit Nicotinamide phosphoribosyltransferase (NAMPT) or can act on both PAK and NAMPT. For example, the compounds described herein can exert their modulatory effect(s) on one or more PAKs by binding to and destabilizing one or more PAKs, can inhibit NAMPT or a combination of these effects.

[0007] As such, in another embodiment, the invention is a method of treating a PAK-mediated disorder, a NAMPT-mediated disorder or a disorder mediated by both PAK and NAMPT in a subject in need thereof, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof.

[0008] Another embodiment of the invention is use of a compound of the invention for the manufacture of a medicament for treating cancer or a PAK-mediated disorder, a NAMPT-mediated disorder or a disorder mediated by both PAK and NAMPT in a subject.

DETAILED DESCRIPTION OF THE INVENTION

[0009] A description of example embodiments of the invention follows.

Definitions

[0010] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles

of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0011] Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford, 1979, which is incorporated by reference herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

[0012] Compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (*e.g.,* as described in: E. L. Eliel and S. H. Wilen, Stereo-chemistry of Carbon Compounds, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers or enantiomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention.

[0013] "Aliphatic" means an optionally substituted, saturated or unsaturated, branched or straight-chain monovalent hydrocarbon radical having the specified number of carbon atoms.

[0014] "Alkyl" means an optionally substituted saturated aliphatic branched or straight-chain monovalent hydrocarbon radical having the specified number of carbon atoms. Thus, "(C_1-C_4) alkyl" means a radical having from 1-4 carbon atoms in a linear or branched arrangement. "(C_1-C_4)alkyl" includes methyl, ethyl, propyl, isopropyl, n-butyl and tert-butyl.

[0015] "Alkylene" means an optionally substituted saturated aliphatic branched or straight-chain divalent hydrocarbon radical having the specified number of carbon atoms. Thus, "(C_1-C_4)alkylene" means a divalent saturated aliphatic radical having from 1-4 carbon atoms in a linear arrangement, e.g., -[(CH_2)$_n$]-, where n is an integer from 1 to 4. "(C_1-C_4)alkylene" includes methylene, ethylene, propylene, and butylene. Alternatively, "(C_1-C_4)alkylene" means a divalent saturated radical having from 1-4 carbon atoms in a branched arrangement, for example: -[($CH_2CH(CH_3)(CH_2)$]-, and the like.

[0016] "Amino" means -NH_2.

[0017] As used herein, the term "dialkylamino" means $(alkyl)_2$-N-, wherein the alkyl groups, which may be the same or different, are as herein defined. Particular dialkylamino groups are $((C_1\text{-}C_4)alkyl)_2$-N-, wherein the alkyl groups may be the same or different. Exemplary dialkylamino groups include dimethylamino, diethylamino and methylethylamino.

[0018] As used herein, the term "monoalkylamino" means a radical of the formula alkyl-NH, wherein the alkyl group is as herein defined. In one aspect, a monoalkylamino is a (C_1-C_6) alkyl-amino-. Exemplary monoalkylamino groups include methylamino and ethylamino.

[0019] "Aryl" or "aromatic" means an aromatic carbocyclic ring system. An aryl moiety can be monocyclic, fused bicyclic, or polycyclic. In one embodiment, "aryl" is a 6-18 membered monocylic or polycyclic system, such as 6-12-membered. Aryl systems include, but are not limited to, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, and anthracenyl.

[0020] Monocyclic aryls are aromatic rings having the specified number of carbon atoms.

[0021] A fused bicyclic aryl has two rings which have two adjacent ring atoms in common.

[0022] Polycyclic aryls have more than two rings (e.g., three rings resulting in a tricyclic ring system) and adjacent rings have at least two ring atoms in common. The first ring is a monocyclic aryl and the remaining ring structures are monocyclic carbocyclyls or monocyclic heterocyclyls. Polycyclic ring systems include fused ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common.

[0023] "Carbocyclyl" means a cyclic group with only ring carbon atoms having the specified number of carbons. "Carbocyclyl" includes 3-18- membered (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,15, 16, 17, 18 or any range therein) saturated, partially saturated or unsaturated aliphatic cyclic hydrocarbon rings or 6-18-membered (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or any range therein) aryl rings, such as C_6-C_{18} or C_6-C_{12}. In certain instances, a carbocyclic moiety can have 3-12 carbon atoms or 3-7 carbon atoms. A carbocyclyl moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic.

[0024] Monocyclic carbocyclyls are saturated or unsaturated aliphatic cyclic hydrocarbon rings or aromatic hydrocarbon rings having the specified number of carbon atoms. Monocyclic carbocyclyls include cycloalkyl, cycloalkenyl, cycloalkynyl and phenyl.

[0025] A fused bicyclic carbocyclyl has two rings which have two adjacent ring atoms in common. The first ring is a monocyclic carbocyclyl and the second ring is a monocyclic carbocyclyl or a monocyclic heterocyclyl.

[0026] A bridged bicyclic carbocyclyl has two rings which have three or more adjacent ring atoms in common. The first ring is a monocyclic carbocyclyl and the second ring is a monocyclic carbocyclyl or a monocyclic heterocyclyl.

[0027] A spiro bicyclic carbocyclyl has two rings which have only one ring atom in common. The first ring is a monocyclic carbocyclyl and the second ring is a monocyclic carbocyclyl or a monocyclic heterocyclyl.

[0028] Polycyclic carbocyclyls have more than two rings (e.g., three rings resulting in a tricyclic ring system) and adjacent rings have at least one ring atom in common. The first ring is a monocyclic carbocyclyl and the remaining ring structures are monocyclic carbocyclyls or monocyclic heterocyclyls. Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common.

[0029] "Cycloalkyl" means a saturated aliphatic cyclic hydrocarbon ring having the specified number of carbons. Thus, "C_3-C_7 cycloalkyl" means a hydrocarbon radical of a (3-7 membered) saturated aliphatic cyclic hydrocarbon ring. A C_3-C_7 cycloalkyl includes, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0030] "Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. "Hetero" also refers to the replacement of at least one carbon atom member in an acyclic system. In some embodiments, a hetero ring system may have 1, 2, 3 or 4 carbon atom members replaced by a heteroatom.

[0031] "Heteroatom" refers to an atom other than carbon. Examples of heteroatoms include nitrogen, oxygen and sulfur.

[0032] "Heterocyclyl" means a cyclic saturated or unsaturated aliphatic or aromatic ring wherein one or more carbon atoms in the ring are independently replaced with a heteroatom having the specified number of ring atoms (i.e., members). Typically the number of ring

atoms of the heterocyclyl ranges from 3-18 atoms (members), such as from 3-15 member atoms or 3-12 member atoms. For aromatic heterocycls the number of ring atoms ranges from 5-18, such as 5-15, 5-12 and typically 5-6-membered rings. When a heteroatom is S, it can be optionally mono- or di-oxygenated (i.e., -S(O)- or -$S(O)_2$-). The heterocyclyl can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic or polycyclic.

[0033] "Saturated heterocyclyl" means an aliphatic heterocyclyl group without any degree of unsaturation (i.e., no double bond or triple bond). It can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic or polycyclic.

[0034] Examples of monocyclic saturated heterocyclyls include, but are not limited to, azetidine, pyrrolidine, piperidine, piperazine, azepane, hexahydropyrimidine, tetrahydrofuran, tetrahydropyran, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine, tetrahydro-2H-1,2-thiazine 1,1-dioxide, isothiazolidine, isothiazolidine 1,1-dioxide.

[0035] A fused bicyclic heterocyclyl has two rings which have two adjacent ring atoms in common. The first ring is a monocyclic heterocyclyl and the second ring is a monocyclic carbocycle (such as a cycloalkyl or phenyl) or a monocyclic heterocyclyl. For example, the second ring is a (C_3-C_6)cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Alternatively, the second ring is phenyl. Examples of fused bicyclic heterocyclyls include, but are not limited to, octahydrocyclopenta[c]pyrrolyl, indoline, isoindoline, 2,3-dihydro-1H-benzo[d]imidazole, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydrobenzo[d]thiazole, octahydrobenzo[d]oxazole, octahydro-1H-benzo[d]imidazole, octahydrobenzo[d]thiazole, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[3.1.0]hexane, and 3-azabicyclo[3.2.0]heptane.

[0036] A spiro bicyclic heterocyclyl has two rings which have only one ring atom in common. The first ring is a monocyclic heterocyclyl and the second ring is a monocyclic carbocycle (such as a cycloalkyl or saturated heterocyclyl) or a monocyclic heterocyclyl. For example, the second ring is a (C_3-C_6)cycloalkyl. Alternatively, the second ring is a (C_3-C_6) saturated heterocyclyl. Examples of spiro bicyclic heterocyclyls include, but are not limited to, azaspiro[4.4]nonane, 7-azaspiro[4.4]nonane, azasprio[4.5]decane, 8-azaspiro[4.5]decane, azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane and 3,9-diazaspiro[5.5]undecane. Further

examples of spiro bicyclic heterocyclyls include 2-oxa-6-azaspiro[3.3]heptane, 1-oxa-6-azaspiro[3.3]heptane and 2-azaspiro[3.3]heptane.

[0037] A bridged bicyclic heterocyclyl has two rings which have three or more adjacent ring atoms in common. The first ring is a monocyclic heterocyclyl and the other ring is a monocyclic carbocycle (such as a cycloalkyl or phenyl) or a monocyclic heterocyclyl. Examples of bridged bicyclic heterocyclyls include, but are not limited to, azabicyclo[3.3.1]nonane, 3-azabicyclo[3.3.1]nonane, azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 6-azabicyclo[3.2.1]octane and azabicyclo[2.2.2]octane, 2-azabicyclo[2.2.2]octane. Further examples of bridged bicyclic heterocyclyls include 6-oxa-3-azabicyclo[3.1.1]heptane, 3-azabicyclo[3.1.0]hexane, 8-oxa-3-azabicyclo[3.2.1]octane and 2-oxa-5-azabicyclo[2.2.1]heptane.

[0038] Polycyclic heterocyclyls have more than two rings, one of which is a heterocyclyl (e.g., three rings resulting in a tricyclic ring system) and adjacent rings having at least one ring atom in common. Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common.

[0039] "Heteroaryl" or "heteroaromatic ring" means a 5-18 membered monovalent heteroaromatic ring radical. Exemplary heteroaryls include, but are not limited to, 5-15-membered, 5-12-memberd or 5-6-membered heteroaryls. A heteroaryl moiety can be monocyclic, fused bicyclic, or polycyclic. In one embodiment, a heteroaryl contains 1, 2, 3 or 4 heteroatoms independently selected from N, O, and S. Heteroaryls include, but are not limited to furan, oxazole, thiophene, 1,2,3-triazole, 1,2,4-triazine, 1,2,4-triazole, 1,2,5-thiadiazole 1,1-dioxide, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,5-triazine, imidazole, isothiazole, isoxazole, pyrazole, pyridazine, pyridine, pyridine-N-oxide, pyrazine, pyrimidine, pyrrole, tetrazole, and thiazole. Bicyclic heteroaryl rings include, but are not limited to, bicyclo[4.4.0] and bicyclo[4.3.0] fused ring systems such as indolizine, indole, isoindole, indazole, benzimidazole, benzthiazole, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine.

[0040] Monocyclic heteroaryls are heteroaromatic rings having the specified number of carbon atoms.

[0041] A fused bicyclic heteroaryl has two rings which have two adjacent ring atoms in common. The first ring is a monocyclic heteroaryl and the second ring is a monocyclic carbocyclyl or a monocyclic heterocyclyl.

[0042] Polycyclic heteroaryls have more than two rings (e.g., three rings resulting in a tricyclic ring system) and adjacent rings have at least two ring atoms in common. The first ring is a monocyclic heteroaryl and the remainding ring structures are monocyclic carbocyclyls or monocyclic heterocyclyls. Polycyclic ring systems include fused ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common.

[0043] "Halogen" and "halo" are used interchangeably herein and each refers to fluorine, chlorine, bromine, or iodine.

[0044] "Chloro" means -Cl.

[0045] "Fluoro" means -F.

[0046] "Cyano" means -CN.

[0047] "Sulfonate" means $-SO_2H$.

[0048] "Alkoxy" means an alkyl radical attached through an oxygen linking atom. "$(C_1$-$C_6)$alkoxy" includes methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

[0049] "Thioalkoxy" means an alkyl radical attached through a sulfur linking atom.

[0050] "Haloalkyl" include mono, poly, and perhaloalkyl groups, where each halogen is independently selected from fluorine, chlorine, and bromine.

[0051] It is understood that substituents and substitution patterns on the compounds of the invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted group" can have a suitable substituent at each substitutable position of the group and, when more than one position in any given structure may be substituted with more than one

substituent selected from a specified group, the substituent can be either the same or different at every position. Alternatively, an "optionally substituted group" can be unsubstitued.

[0052] Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. If a substituent is itself substituted with more than one group, it is understood that these multiple groups can be on the same carbon atom or on different carbon atoms, as long as a stable structure results. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0053] Suitable monovalent substituents on a substitutable atom, for example, a substitutable carbon atom, of an "optionally substituted group" are independently halogen; haloalkyl; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R^o$; $-O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}SR°$; $–(CH_2)_{0–4}Ph$, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$ which may be substituted with R° or halo (*e.g.*, fluoro, chloro, bromo or iodo); –CH=CHPh, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl which may be substituted with R°; -CH(OH)R° (*e.g.*, 3,5-dimethylisoxazol-4-yl, 4-fluorophenyl); $-CH(CH_3)R°$ (*e.g.*, 4,4-difluoropiperidin-1-yl); $–NO_2$; –CN; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $-(CH_2)_{0–4}N(R°)C(O)R°$; $–N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-(CH_2)_{0-4}OC(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0–4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $–(CH_2)_{0–4}C(O)R°$; $–C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $–(CH_2)_{0–4}C(O)SR°$; $-(CH_2)_{0–4}C(O)OSiR°_3$; $–(CH_2)_{0–4}OC(O)R°$; $-OC(O)(CH_2)_{0–4}SR–$, SC(S)SR°; $–(CH_2)_{0–4}SC(O)R°$; $–(CH_2)_{0–4}C(O)NR°_2$; $–(CH_2)_{0–4}C(O)NR°_2$; $–C(S)NR°_2$; $–C(O)NR°NR°_2$; -C(S)SR°; –SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR°_2$; -C(O)N(OR°)R°; –C(O)C(O)R°; –C(O)C(O)NR°$_2$; $-C(O)CH_2C(O)R°$; –C(NOR°)R°; $-(CH_2)_{0–4}SSR°$; $–(CH_2)_{0–4}S(O)_2R°$; $–(CH_2)_{0–4}S(O)_2OR°$; $-(CH_2)_{0–4}OS(O)_2R°$; $–S(O)_2NR°_2$; $-(CH_2)_{0–4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $–N(R°)S(O)_2R°$; -N(OR°)R°; $–C(NH)NR°_2$; $–P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $–OP(O)(OR°)_2$; $SiR°_3$; $–(C_{1–4}$ straight or branched alkylene)O–$N(R°)_2$; or $–(C_{1–4}$ straight or branched alkylene)C(O)O-$N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $C_{1–6}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered carbocyclyl or heterocyclyl, or, notwithstanding the

definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered carbocyclyl or heterocyclyl, which may be substituted as defined below.

[0054] In some embodiments, suitable monovalent substituents on a substitutable atom, for example, a substitutable carbon atom, of an "optionally substituted group" are independently halogen; haloalkyl; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R^o$, $-O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}SR°$; $–(CH_2)_{0–4}Ph$, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl which may be substituted with R°; -CH(OH)(3,5-dimethylisoxazol-4-yl); $–NO_2$; –CN; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $-(CH_2)_{0–4}N(R°)C(O)R°$; –

$N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-(CH_2)_{0-4}OC(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0–4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $–(CH_2)_{0–4}C(O)R°$; $–C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $–(CH_2)_{0–4}C(O)SR°$; $-(CH_2)_{0–4}C(O)OSiR°_3$; $–(CH_2)_{0–4}OC(O)R°$; $-OC(O)(CH_2)_{0–4}SR–$, SC(S)SR°; $–(CH_2)_{0–4}SC(O)R°$; $–(CH_2)_{0–4}C(O)NR°_2$; $–(CH_2)_{0–4}C(O)NR°_2$; $–C(S)NR°_2$; $–C(O)NR°NR°_2$; -C(S)SR°; –

SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR°_2$; -C(O)N(OR°)R°; –C(O)C(O)R°; –

$C(O)C(O)NR°_2$; $-C(O)CH_2C(O)R°$; –C(NOR°)R°; $-(CH_2)_{0–4}SSR°$; $–(CH_2)_{0–4}S(O)_2R°$; $–(CH_2)_{0–4}S(O)_2OR°$; $-(CH_2)_{0–4}OS(O)_2R°$; $–S(O)_2NR°_2$; $-(CH_2)_{0–4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $–N(R°)S(O)_2R°$; -N(OR°)R°; –C(NH)NR°$_2$; $–P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $–OP(O)(OR°)_2$; $SiR°_3$; $–(C_{1–4}$ straight or branched alkylene)O–N(R°)$_2$; or $–(C_{1–4}$ straight or branched alkylene)C(O)O-N(R°)$_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $C_{1–6}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered carbocyclyl or heterocyclyl, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered carbocyclyl or heterocyclyl, which may be substituted as defined below.

[0055] In some embodiments, suitable monovalent substituents on a substitutable atom, for example, a substitutable carbon atom, of an "optionally substituted group" are independently halogen; haloalkyl; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R^o$, $-O–(CH_2)_{0–}$

$_4$C(O)OR°; –$(CH_2)_{0–4}$CH(OR°)$_2$; –$(CH_2)_{0–4}$SR°; –$(CH_2)_{0–4}$Ph, which may be substituted with R°; –$(CH_2)_{0–4}$O$(CH_2)_{0–1}$Ph which may be substituted with R°; –CH=CHPh, which may be substituted with R°; –$(CH_2)_{0–4}$O$(CH_2)_{0–1}$-pyridyl which may be substituted with R°; –NO_2; –CN; –N_3; -$(CH_2)_{0–4}$N(R°)$_2$; -$(CH_2)_{0–4}$N(R°)C(O)R°; –N(R°)C(S)R°; -$(CH_2)_{0-4}$N(R°)C(O)NR°$_2$; -N(R°)C(S)NR°$_2$; -$(CH_2)_{0–4}$N(R°)C(O)OR°; -N(R°)N(R°)C(O)R°; -N(R°)N(R°)C(O)NR°$_2$; -N(R°)N(R°)C(O)OR°; –$(CH_2)_{0–4}$C(O)R°; –C(S)R°; -$(CH_2)_{0-4}$C(O)OR°; –$(CH_2)_{0–4}$C(O)SR°; -$(CH_2)_{0–4}$C(O)OSiR°$_3$; –$(CH_2)_{0–4}$OC(O)R°; -OC(O)$(CH_2)_{0–4}$SR–, SC(S)SR°; –$(CH_2)_{0–4}$SC(O)R°; –$(CH_2)_{0–4}$C(O)NR°$_2$; –$(CH_2)_{0–4}$C(O)NR°$_2$; –C(S)NR°$_2$; –C(O)NR°NR°$_2$; -C(S)SR°; –SC(S)SR°, -$(CH_2)_{0-4}$OC(O)NR°$_2$; -C(O)N(OR°)R°; –C(O)C(O)R°; –C(O)C(O)NR°$_2$; -C(O)CH_2C(O)R°; –C(NOR°)R°; -$(CH_2)_{0–4}$SSR°; –$(CH_2)_{0–4}$S(O)$_2$R°; –$(CH_2)_{0–4}$S(O)$_2$OR°; -$(CH_2)_{0–4}$OS(O)$_2$R°; –S(O)$_2$NR°$_2$; -$(CH_2)_{0–4}$S(O)R°; -N(R°)S(O)$_2$NR°$_2$; –N(R°)S(O)$_2$R°; -N(OR°)R°; –C(NH)NR°$_2$; –P(O)$_2$R°; -P(O)R°$_2$; -OP(O)R°$_2$; –OP(O)(OR°)$_2$; SiR°$_3$; –($C_{1–4}$ straight or branched alkylene)O–N(R°)$_2$; or –($C_{1–4}$ straight or branched alkylene)C(O)O-N(R°)$_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $C_{1–6}$ aliphatic, –CH_2Ph, –O$(CH_2)_{0–1}$Ph, -CH_2-(5-6 membered heteroaryl ring), or a 5–6–membered carbocyclyl or heterocyclyl, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered carbocyclyl or heterocyclyl, which may be substituted as defined below.

[0056] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, haloalkyl, -$(CH_2)_{0-2}$R•, –(haloR•), –$(CH_2)_{0–2}$OH, –$(CH_2)_{0–2}$OR•, –$(CH_2)_{0–2}$CH(OR•)$_2$; -O(haloR•), –CN, –N_3, –$(CH_2)_{0–2}$C(O)R•, –$(CH_2)_{0–2}$C(O)OH, –$(CH_2)_{0–2}$C(O)OR•, –$(CH_2)_{0–2}$SR•, –$(CH_2)_{0–2}$SH, –$(CH_2)_{0–2}$NH$_2$, –$(CH_2)_{0–2}$NHR•, –$(CH_2)_{0–2}$NR•$_2$, –NO_2, –SiR•$_3$, –OSiR•$_3$, -C(O)SR•, –($C_{1–4}$ straight or branched alkylene)C(O)OR•, or –SSR• wherein each R• is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from $C_{1–4}$ aliphatic, –CH_2Ph, –O$(CH_2)_{0–1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0057] "Heteroaryl substituent," as used herein, refers to the suitable monovalent substituents for a substitutable atom, as described above. Preferred heteroaryl substituents include halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R°$, $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-NO_2$; –CN; $-N_3$; or $-(CH_2)_{0-4}N(R°)_2$, wherein each R° is defined above and may be substituted as defined above. Particularly preferred heteroaryl substituents include hydrogen, halogen; (C_1-C_4)alkyl; (C_1-C_4)haloalkyl; (C_1-C_4)alkoxy; (C_1-C_4)thioalkoxy; $-NO_2$; -CN; $-N_3$; or $-N(R°)_2$, wherein each R° is defined above and may be substituted as defined above.

[0058] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted group" include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, and $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0059] Suitable substituents on the aliphatic group of R^* include halogen, $-R^•$, -(halo$R^•$), -OH, $-OR^•$, -O(halo$R^•$), –CN, –C(O)OH, $-C(O)OR^•$, $-NH_2$, $-NHR^•$, $-NR^•_2$, and $-NO_2$, wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0060] Suitable substituents on a substitutable nitrogen of an "optionally substituted group" include $-R^†$, $-NR^†_2$, $-C(O)R^†$, $-C(O)OR^†$, $-C(O)C(O)R^†$, $-C(O)CH_2C(O)R^†$, $-S(O)_2R^†$, $-S(O)_2NR^†_2$, $-C(S)NR^†_2$, $-C(NH)NR^†_2$, and $-N(R^†)S(O)_2R^†$; wherein each $R^†$ is

independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl monocyclic or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0061] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, –$R^{\bullet}$, -(halo$R^{\bullet}$), –OH, –$OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, –C(O)$OR^{\bullet}$, –NH_2, –$NHR^{\bullet}$, –$NR^{\bullet}_2$, or -NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0062] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, the relevant teachings of which are incorporated herein by reference in their entirety. Pharmaceutically acceptable salts of the compounds of this invention include salts derived from suitable inorganic and organic acids and bases that are compatible with the treatment of patients.

[0063] Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable acid addition salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate,

glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0064] In some embodiments, exemplary inorganic acids which form suitable salts include, but are not limited thereto, hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tricarboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid and other sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the mono- or di-acid salts can be formed, and such salts can exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of these compounds are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms.

[0065] In some embodiments, acid addition salts of the compounds of formula I are most suitably formed from pharmaceutically acceptable acids, and include, for example, those formed with inorganic acids, *e.g.,* hydrochloric, sulfuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid.

[0066] Other non-pharmaceutically acceptable salts, *e.g.,* oxalates can be used, for example, in the isolation of compounds of formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt. Also included within the scope of the invention are base addition salts (such as sodium, potassium and ammonium salts), solvates and hydrates of compounds of the invention. The conversion of a given compound salt to a desired compound salt is achieved by applying standard techniques, well known to one skilled in the art.

[0067] A "pharmaceutically acceptable basic addition salt" is any non-toxic organic or inorganic base addition salt of the acid compounds represented by formula I, or any of its intermediates. Illustrative inorganic bases which form suitable salts include, but are not limited thereto, lithium, sodium, potassium, calcium, magnesium or barium hydroxides. Illustrative organic bases which form suitable salts include aliphatic, alicyclic or aromatic organic amines such as methylamine, trimethyl amine and picoline or ammonia. The selection of the appropriate salt may be important so that an ester functionality, if any, elsewhere in the molecule is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

[0068] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxyl, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0069] Pharmaceutically acceptable salts include (C_1-C_6)alkylhalide salts. A (C_1-C_6)alkylhalide salt of a compound described herein can be formed, for example, by treating a compound of Formula II (*e.g.,* wherein q is 0) with a (C_1-C_6)alkylhalide salt, thereby alkylating a nitrogen atom (*e.g.*, the nitrogen atom beta to the group $-[C(R^{4a})(R^{4b})]_n-$ in Formula II) and forming a (C_1-C_6)alkylhalide salt of a compound of Formula II. Examples of (C_1-C_6)alkylhalide salts include methyl iodide and ethyl iodide.

[0070] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.,* enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[0071] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium

or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. For example, in the case of variable R^1, the $(C_1\text{-}C_4)$alkyl or the -O-$(C_1\text{-}C_4)$alkyl can be suitably deuterated (*e.g.*, $-CD_3$, $-OCD_3$).

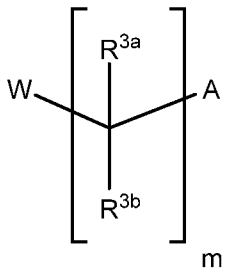
[0072] The term "stereoisomers" is a general term for all isomers of an individual molecule that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric (cis/trans) isomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0073] The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, *i.e.,* a dosage form capable of being administered to a patient. One example of such a carrier is pharmaceutically acceptable oil typically used for parenteral administration. Pharmaceutically acceptable carriers are well known in the art.

[0074] When introducing elements disclosed herein, the articles "a," "an," "the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising," "having" and "including" are intended to be open-ended and mean that there may be additional elements other than the listed elements.

Compounds of the Invention

[0075] A first embodiment of the invention is a compound represented by Structural Formula IA:

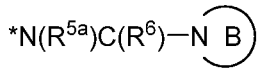


(IA)

or a pharmaceutically acceptable salt thereof, wherein:

W is $-Y(CR^{4a}R^{4b})_nR^2$ or Y';

Y is $*N(R^{5a})C(R^6)N(R^{5b})$-;

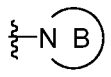
Y' is ;

"*" represents a portion of Y or Y'directly adjacent to $[C(R^{3a})(R^{3b})]_m$;

R^{5a} and R^{5b} are independently hydrogen or $(C_1$-$C_4)$alkyl;

R^6 is =O or $=NR^7$;

R^7 is hydrogen, alkyl, or CN;

 is a 3-18-membered heterocyclyl;

R^2 is 5-18-membered heteroaryl or 6-18-membered aryl;

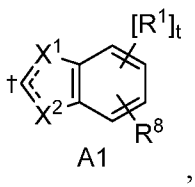
each of R^{3a} and R^{3b} is independently selected from hydrogen and (C_1C_4)alkyl;

m is 1 or 2;

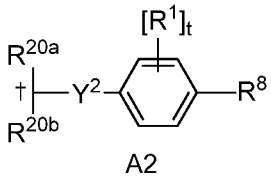
n is 0 or 1;

each of R^{4a} and R^{4b}, if present, is independently selected from hydrogen, $(C_1$-$C_4)$alkyl, and $(C_3$-$C_6)$cycloalkyl;

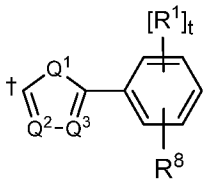
A is selected from:


A1

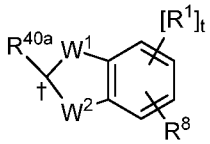
,


A2

,


A3

and


A4

,

wherein:

"†" represents the point of attachment of A to the remainder of the molecule;

one "═══" represents a single bond and the other "═══" represents a double bond;

X^1 is -O-, -S- or $-N(R^{10a})$- and X^2 is $-C(R^{11a})$- or -N-; or

X^1 is -N- and X^2 is $-N(R^{12a})$-, wherein:

R^{10a} is hydrogen or $(C_1$-$C_4)$alkyl;

R^{11a} is hydrogen, deuterium, $(C_1$-$C_4)$alkyl or halo; and

R^{12a} is hydrogen or $(C_1$-$C_4)$alkyl;

Y^2 is -O-, $-S(O)_2$-, -NH- or $-N(C_1$-$C_4)$alkyl-;

each of R^{20a} and R^{20b} is independently hydrogen or $(C_1$-$C_4)$alkyl;

Q^1 is -O-, -S- or -N(R^{30a})-;

Q^2 and Q^3 are each independently -C(R^{31a})- or -N-, wherein:

R^{30a} is hydrogen or (C_1-C_4)alkyl; and

R^{31a} is hydrogen, (C_1-C_4)alkyl or halo;

W^1 is -O- or -S-;

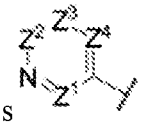
W^2 is -C(O)- or -C(H)$_2$-; and

R^{40a} is hydrogen or (C_1-C_4)alkyl;

each R^1 is independently (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, cyano, sulfonate, -S(O)$_{0-2}$(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, and -O-(3-15-membered)heterocyclyl;

R^8 is carbocyclyl or heterocyclyl (for example, a C3-C18 carbocycle or a 3-18 member heterocycle); and

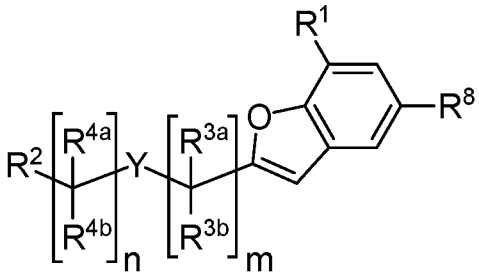
t is 1, 2 or 3;

provided that when Ring A is A2 and W is -Y($CR^{4a}R^{4b}$)$_n$$R^2$, then R^2 is  and R^1 is not a methoxy, wherein each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and C(R^9), wherein no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and each R^9 is independently hydrogen or a 5-18-member heteroaryl substituent; and

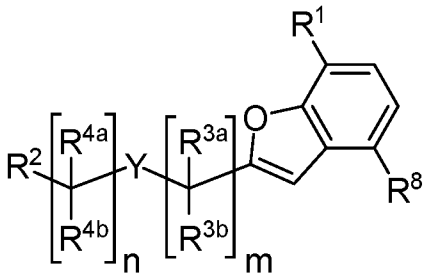
provided that when Ring A is A2 and W is Y', then R^1 is not a trifluoromethyl group;

and further wherein each aryl, heteroaryl, carbocyclyl, heterocyclyl, alkyl or cycloalkyl is optionally and independently substituted.

[0076] A second embodiment of the invention is a compound represented by Structural Formula III-IV:



(III), or



(IV),

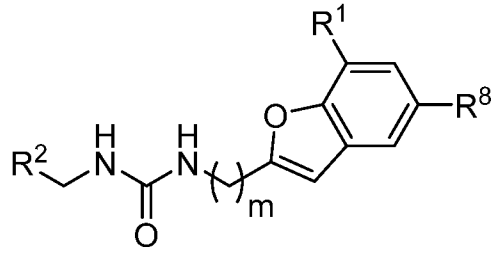
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from each R^1 is independently (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

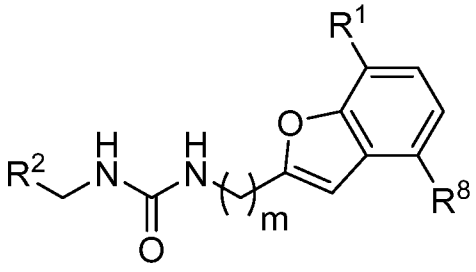
R^8 is optionally substituted (C_3-C_{12})carbocyclyl and optionally substituted 3-15-membered heterocyclyl; and

each carbocyclyl, heterocyclyl, aryl, heteroaryl and alkyl is optionally and independently substituted. The values for the remaining variables are as described in the first embodiment.

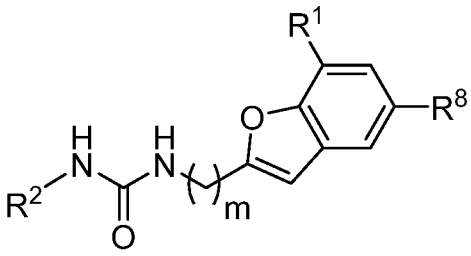
[0077] A third embodiment of the invention is a compound represented represented by Structural Formulas V-VIII:



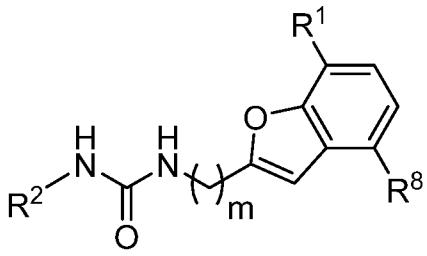
(V),



(VI),



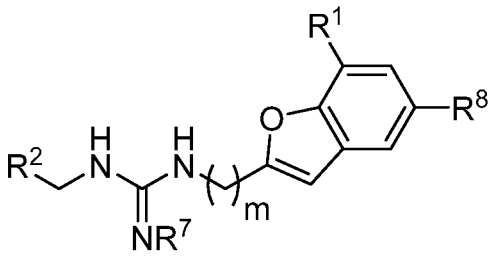
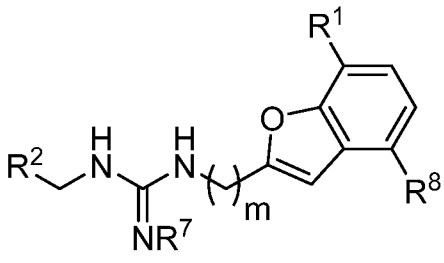
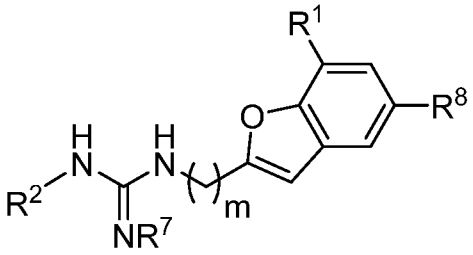
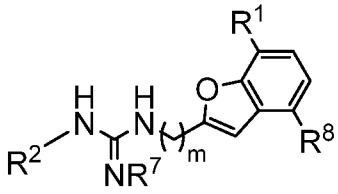
(VII), or



(VIII)

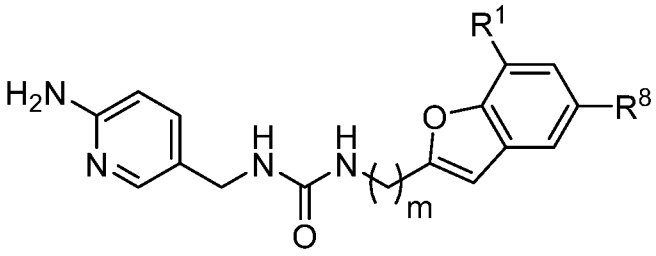
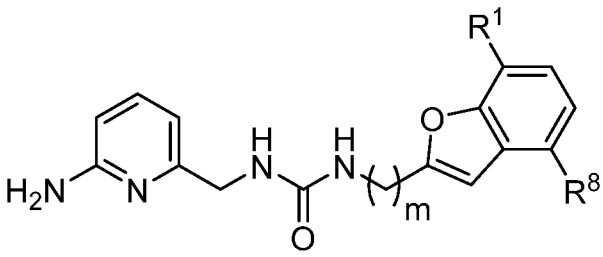
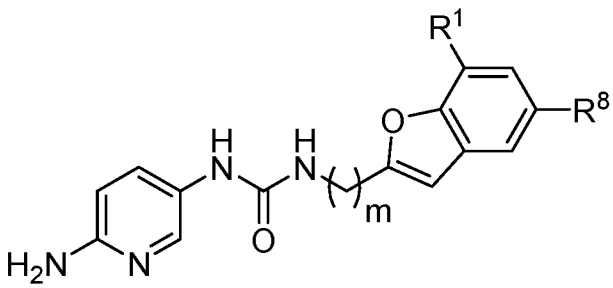
or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2. The values for the remaining variables are as described in the first or second embodiments.

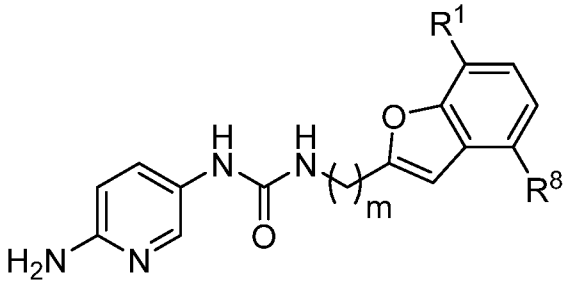
[0078] A fourth embodiment of the invention is a compound represented by Structural Formulas IX-XII:


(IX),

(X),

(XI), or

(XII),

or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2. The values for the remaining variables are as described in the first or second embodiments.

[0079] A fifth embodiment of the invention is a compound represented by Structural Formula XIII-XVI:

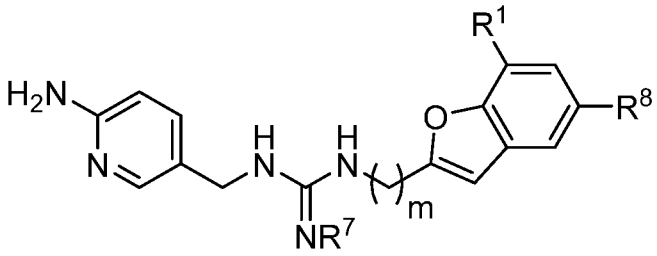

(XIII),

(XIV),

(XV), or



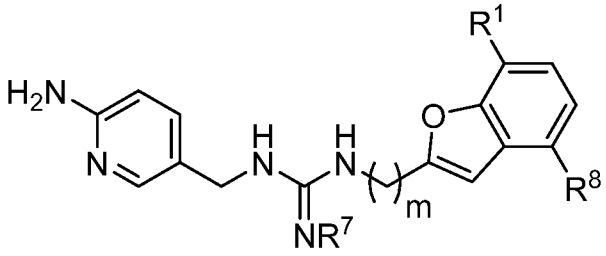
(XVI),

or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2. The values for the remaining variables are as described in the first or second embodiments.

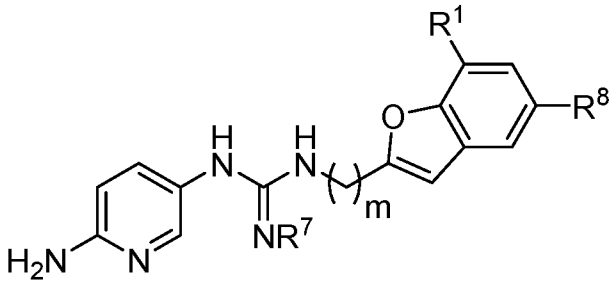
[0080] A sixth embodiment of the invention is a compound represented by Structural Formula XVII-XX:



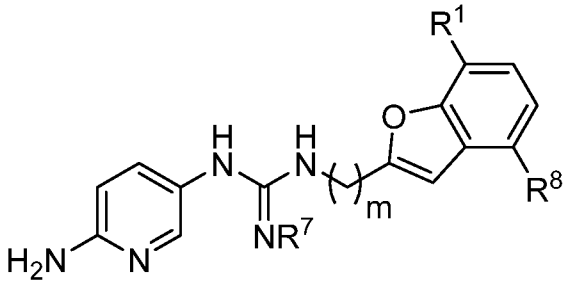
(XVII),



(XVIII),



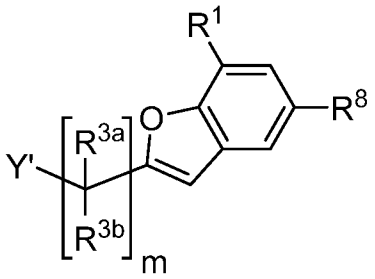
(XIX), or



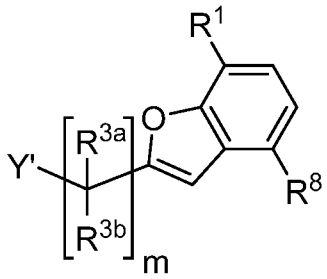
(XX),

or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2. The values for the remaining variables are as described in the first or second embodiments.

[0081] A seventh embodiment of the invention is a compound represented by Structural Formula XXXIII-XXXIV:



(XXXIII), or



(XXXIV)

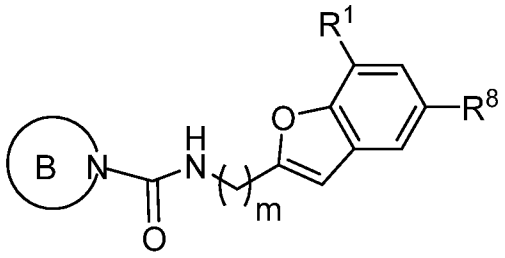
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

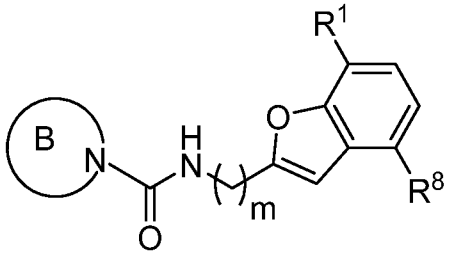
R^8 is optionally substituted (C_3-C_{12})carbocyclyl and optionally substituted (3-15-membered)heterocyclyl; and

each carbocyclyl, heterocyclyl and alkyl is optionally and independently substituted. The values for the remaining variables are as described in the first embodiment.

[0082] In an eighth embodiment the invention is a compound represented by Structural Formula XXXV or XXXVI:



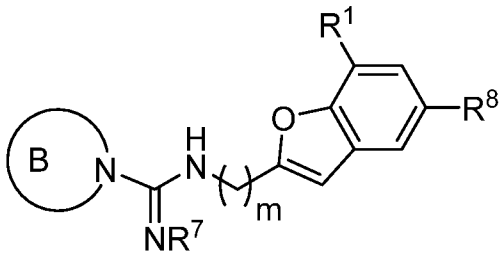
(XXXV), or



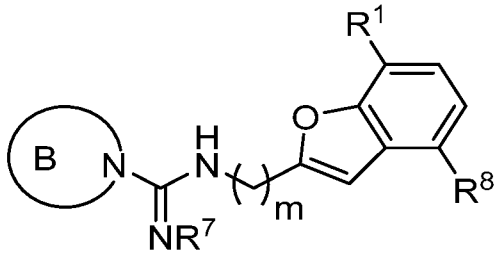
(XXXVI),

or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2. The values for the remaining variables are as described in the first or seventh embodiments.

[0083] In a ninth embodiment the invention is a compound represented by Structural Formula XXXVII-XXXVIII:



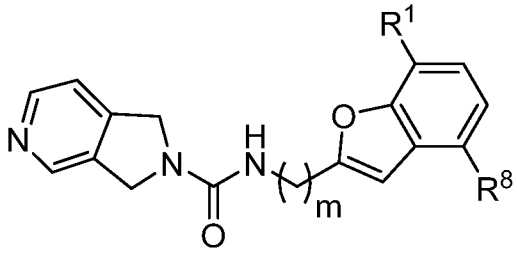
(XXXVII),



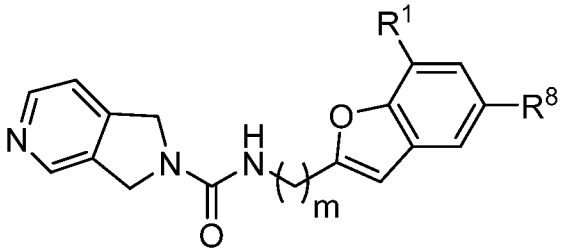
(XXXVIII),

or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as described in the first or seventh embodiments.

[0084] In a tenth embodiment the invention is a compound represented by Structural Formula XXXIX-XL:

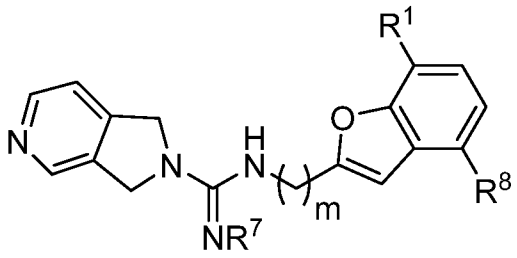


(XXXIX), or

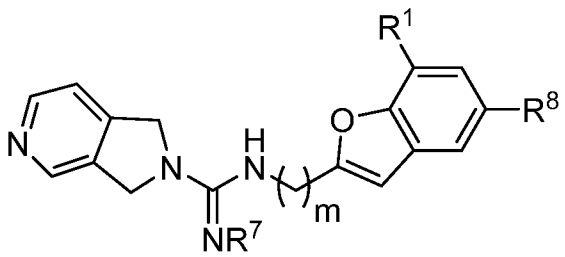


(XL) or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as described in the first or seventh embodiments.

[0085] In an eleventh embodiment the invention is a compound represented by Structural Formula XLI-XLII:



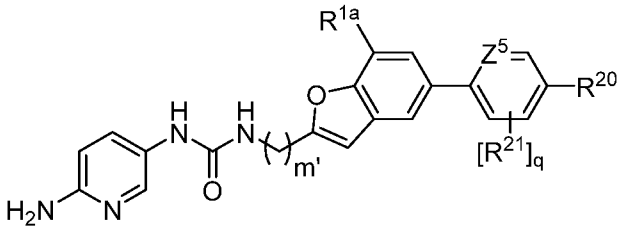
(XLI), or



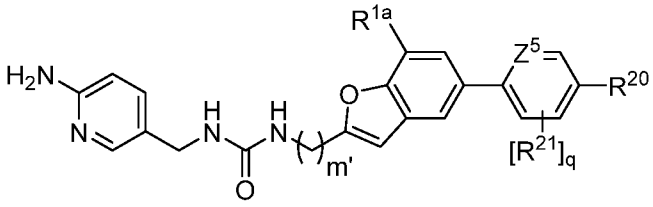
(XLII).

or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as described in the first or seventh embodiments.

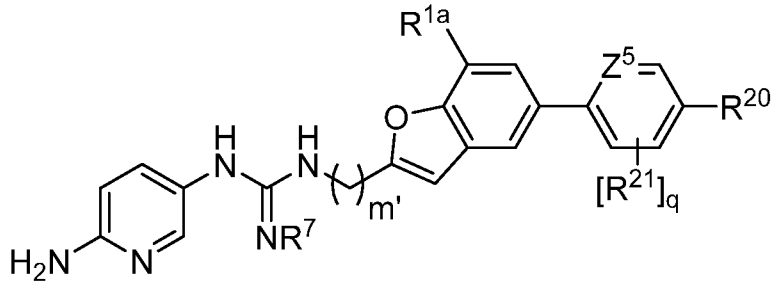
[0086] In a twelfth embodiment the invention is a compound represented by Structural Formula XXI-XXIV:



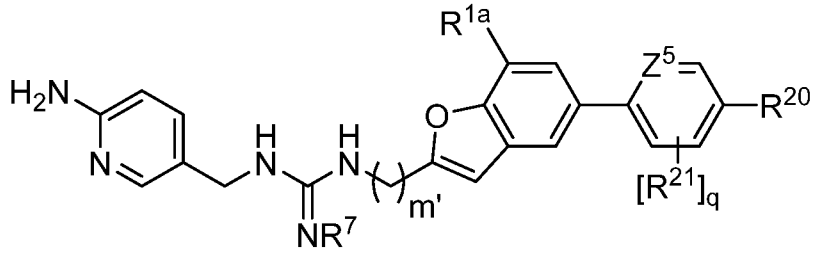
(XXI),



(XXII),



(XXIII), or



(XXIV),

or a pharmaceutically acceptable salt thereof, wherein:

m′ is 1 or 2;

R^{1a} is selected from (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

Z^5 is –N– or –C(H)–;

R^{20} is C(O)(C_0-C_1 alkylene)$NR^{10}R^{11}$, C(S)(C_0-C_1 alkylene)$NR^{10}R^{11}$, wherein:

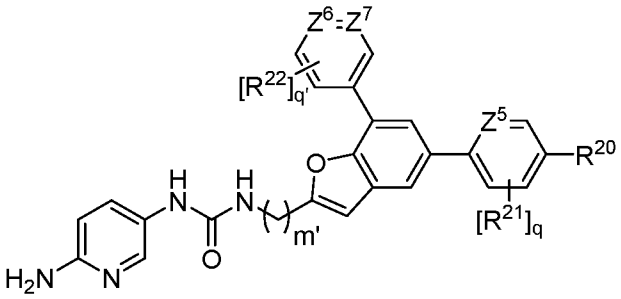
R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl;

each R^{21}, if present, is independently halo;

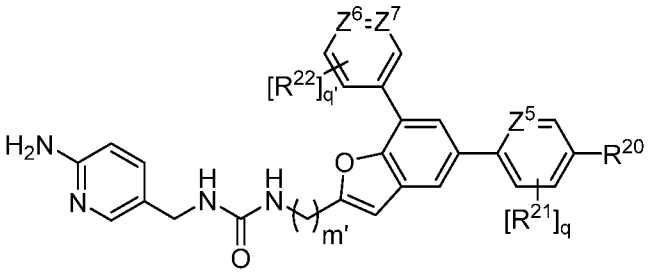
R7 is hydrogen, alkyl or –CN; and

q is 0, 1, 2, 3 or 4 when A is –C(H) – and 0, 1, 2 or 3 when A is –N–.

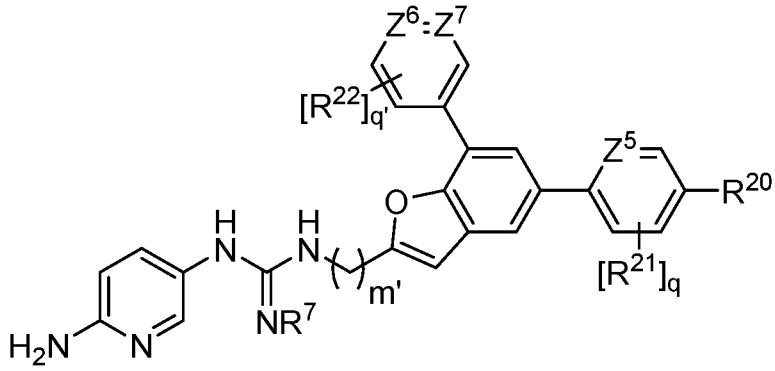
[0087] In a thirteenth embodiment the invention is a compound represented by Structural Formula XXV-XXVIII:



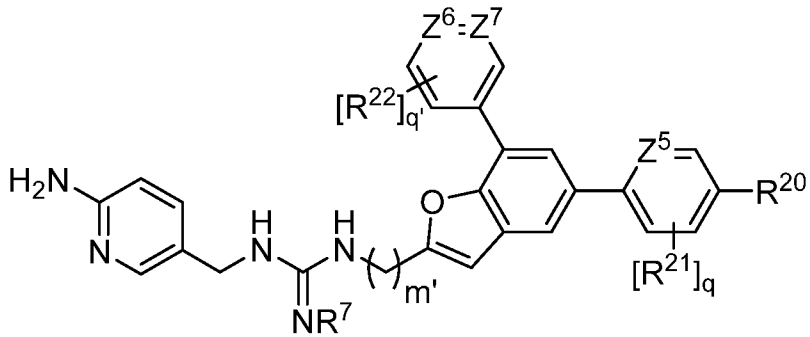
(XXV),



(XXVI),



(XXVII), or



(XXVIII),

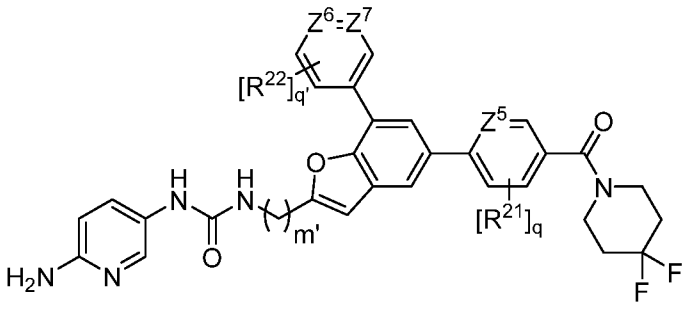
or a pharmaceutically acceptable salt thereof, wherein:

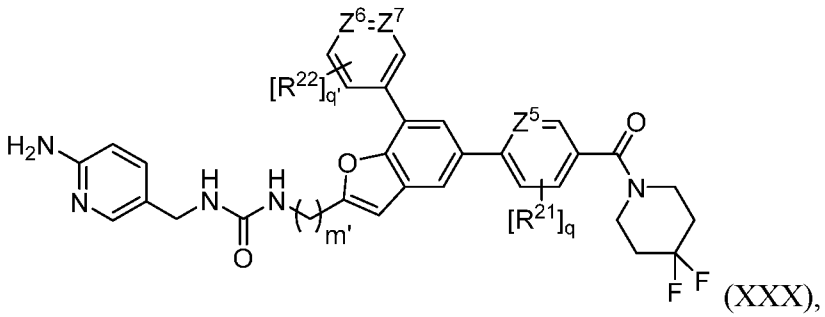
each of Z^6 and Z^7 is independently –N– or –C(H)–, wherein no more than one of Z^6 and Z^7 is nitrogen;

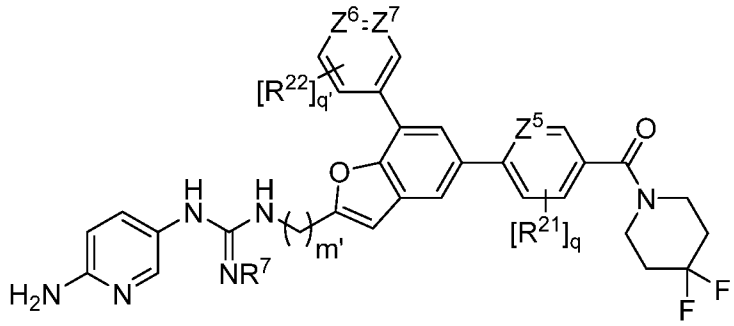
each R^{22}, if present, is independently halo, cyano, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, hydroxy, $(C_1\text{-}C_3)$alkoxy or halo$(C_1\text{-}C_3)$alkoxy ; and

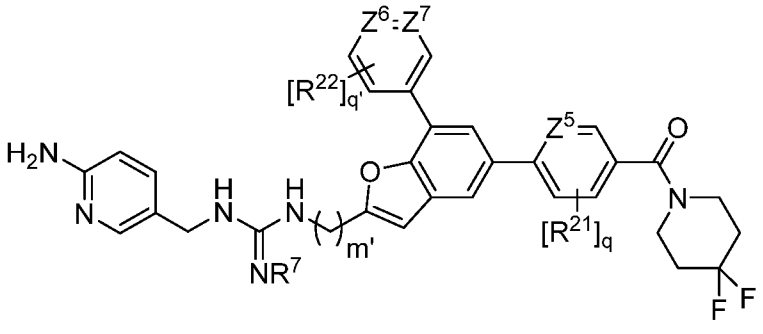
q′ is 0, 1, 2 or 3. The values for the remaining variables are as described in the twelfth embodiment.

[0088] In a fourteenth embodiment, the invention is a compound represented by Structural Formula XXIX-XXXII:


(XXIX),


(XXX),

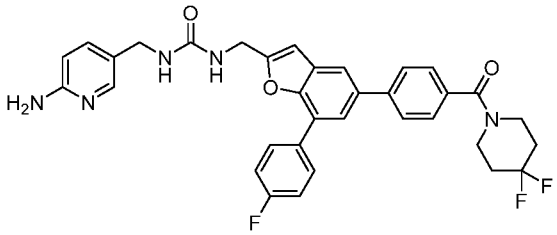
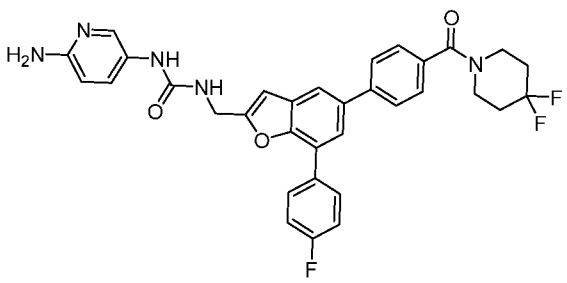
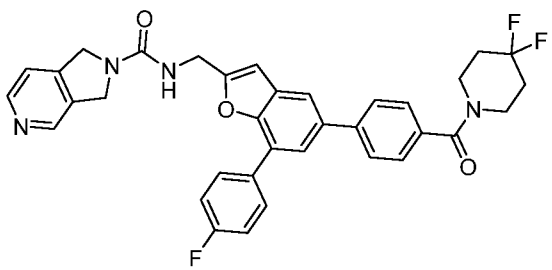

(XXXI), or

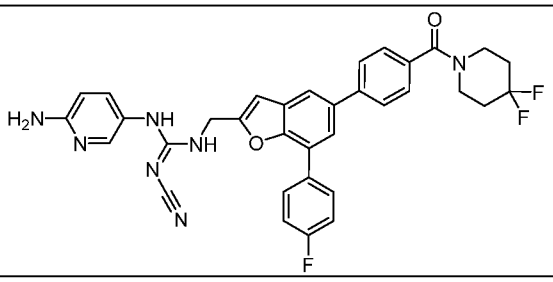
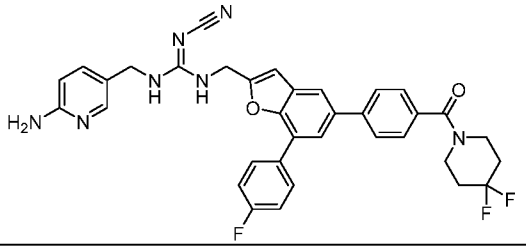
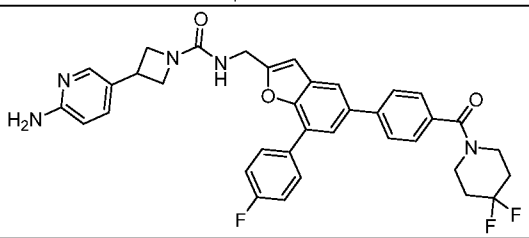
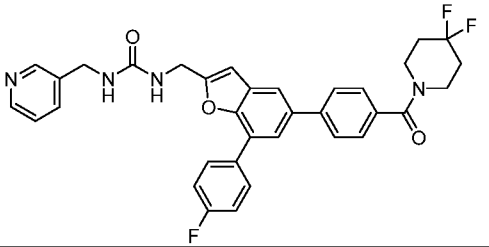
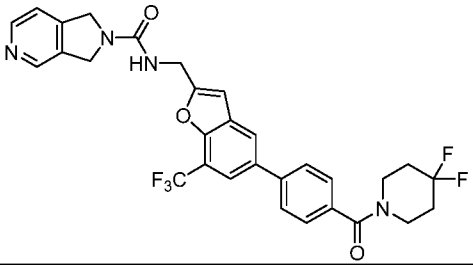
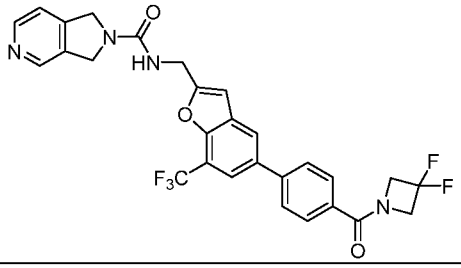


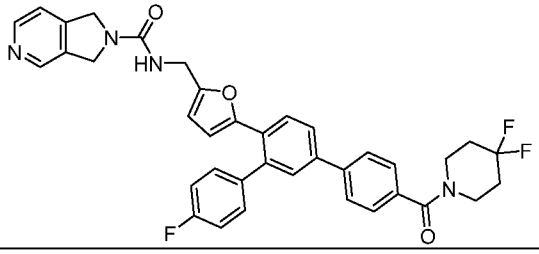
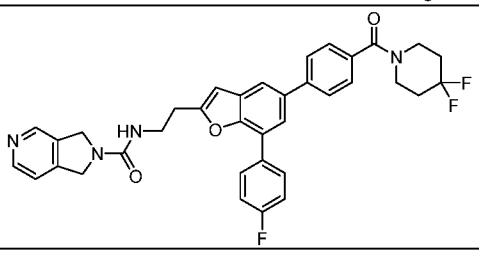
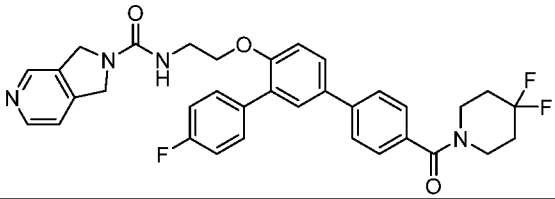
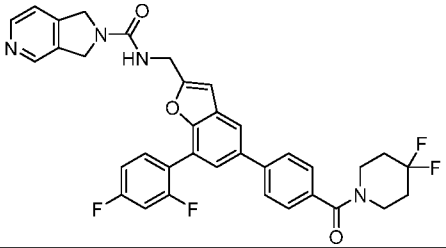
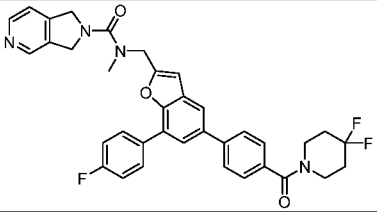
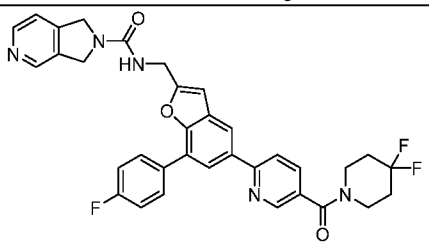
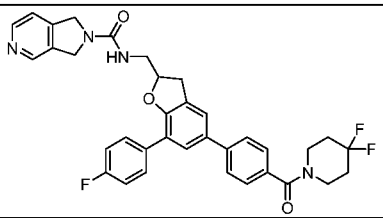
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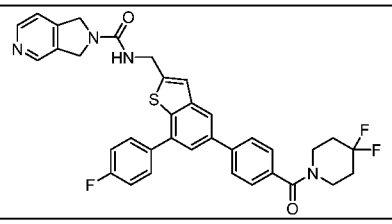
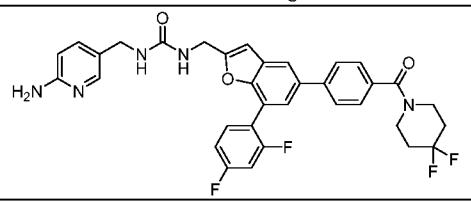
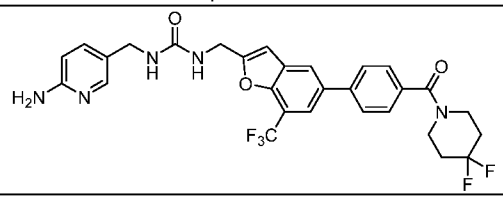
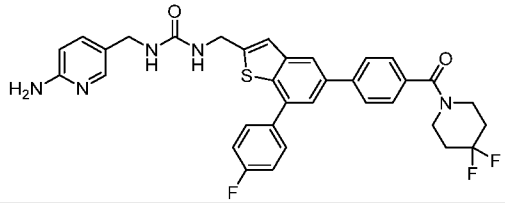
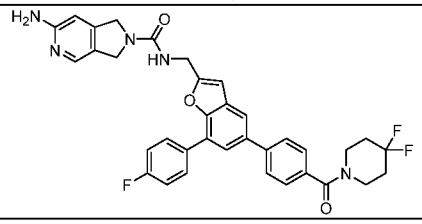
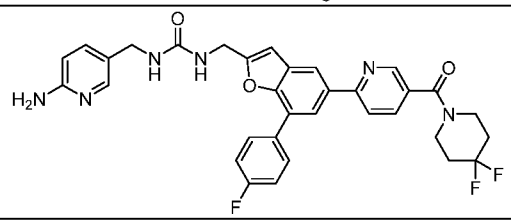
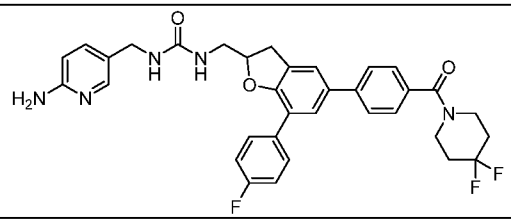
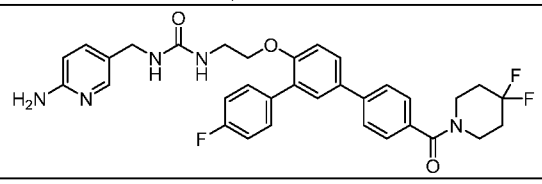
or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as described in the twelfth and thirteenth embodiments.

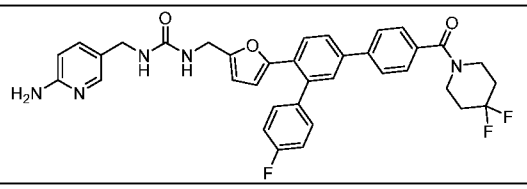
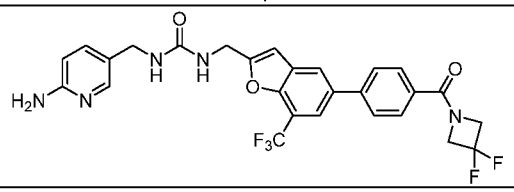
[0089] Exemplary compounds are set forth in Table 1.

Cpd. No.	Structure	Compound Name
100		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
101		1-(6-aminopyridin-3-yl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
102		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

118		(E)-1-(6-aminopyridin-3-yl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
119		(Z)-1-((6-aminopyridin-3-yl)methyl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
103		3-(6-aminopyridin-3-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)azetidine-1-carboxamide
104		1-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-3-(pyridin-3-ylmethyl)urea
105		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
106		N-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

120		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)furan-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
107		N-(2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
121		N-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)oxy)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
108		N-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
109		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-N-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
110		N-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
122		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

111		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
112		1-((6-aminopyridin-3-yl)methyl)-3-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)urea
113		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea
114		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)urea
115		6-amino-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
116		1-((6-aminopyridin-3-yl)methyl)-3-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
123		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)urea
124		1-((6-aminopyridin-3-yl)methyl)-3-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)oxy)ethyl)urea

125		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)furan-2-yl)methyl)urea
117		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea

Formulation and Administration

[0090] Another embodiment of the invention is a composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In certain embodiments, a composition of the invention is formulated for administration to a patient in need of the composition. In some embodiments, a composition of the invention is formulated for oral, intravenous, subcutaneous, intraperitoneal or dermatological administration to a patient in need thereof.

[0091] The term "patient," as used herein, means an animal. In some embodiments, the animal is a mammal. In certain embodiments, the patient is a veterinary patient (i.e., a non-human mammal patient). In some embodiments, the patient is a dog. In other embodiments, the patient is a human.

[0092] "Pharmaceutically or pharmacologically acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards, as required by FDA Office of Biologics standards.

[0093] The phrase "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or

electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0094] Compositions of the present invention may be administered orally, parenterally (including subcutaneous, intramuscular, intravenous and intradermal), by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some embodiments, provided compounds or compositions are administrable intravenously and/or intraperitoneally.

[0095] The term "parenteral," as used herein, includes subcutaneous, intracutaneous, intravenous, intramuscular, intraocular, intravitreal, intra-articular, intra-arterial, intra-synovial, intrasternal, intrathecal, intralesional, intrahepatic, intraperitoneal intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, subcutaneously, intraperitoneally or intravenously.

[0096] Pharmaceutically acceptable compositions of this invention can be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions and/or emulsions are required for oral use, the active ingredient can be suspended or dissolved in an oily phase and combined with emulsifying and/or suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0097] In some embodiments, an oral formulation is formulated for immediate release or sustained/delayed release.

[0098] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders, such as carboxymethylcellulose, alginates, gelatin,

polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium salts, g) wetting agents, such as acetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0099] Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

[00100] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as lactose or milk sugar, as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00101] A compound of the invention can also be in micro-encapsulated form with one or more excipients, as noted above. In such solid dosage forms, the compound of the invention can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, *e.g.,* tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose.

[00102] Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example, by an outer coating of the formulation on a tablet or capsule.

[00103] In another embodiment, a compound of the invention can be provided in an extended (or “delayed” or “sustained”) release composition. This delayed-release

composition comprises a compound of the invention in combination with a delayed-release component. Such a composition allows targeted release of a provided compound into the lower gastrointestinal tract, for example, into the small intestine, the large intestine, the colon and/or the rectum. In certain embodiments, the delayed-release composition comprising a compound of the invention further comprises an enteric or pH-dependent coating, such as cellulose acetate phthalates and other phthalates (*e.g.,* polyvinyl acetate phthalate, methacrylates (Eudragits)). Alternatively, the delayed-release composition provides controlled release to the small intestine and/or colon by the provision of pH sensitive methacrylate coatings, pH sensitive polymeric microspheres, or polymers which undergo degradation by hydrolysis. The delayed-release composition can be formulated with hydrophobic or gelling excipients or coatings. Colonic delivery can further be provided by coatings which are digested by bacterial enzymes such as amylose or pectin, by pH dependent polymers, by hydrogel plugs swelling with time (Pulsincap), by time-dependent hydrogel coatings and/or by acrylic acid linked to azoaromatic bonds coatings.

[00104] In certain embodiments, the delayed-release composition of the present invention comprises hypromellose, microcrystalline cellulose, and a lubricant. The mixture of a compound of the invention, hypromellose and microcrystalline cellulose can be formulated into a tablet or capsule for oral administration. In certain embodiments, the mixture is granulated and pressed into tablets.

[00105] Alternatively, pharmaceutically acceptable compositions of this invention can be administered in the form of suppositories for rectal administration. These can be prepared by mixing the compound of the invention with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00106] Pharmaceutically acceptable compositions of this invention can also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00107] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches can also be used.

[00108] For other topical applications, the pharmaceutically acceptable compositions of the invention can be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water and penetration enhancers. Alternatively, pharmaceutically acceptable compositions of the invention can be formulated in a suitable lotion or cream containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. In some embodiments, suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. In other embodiments, suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water and penetration enhancers.

[00109] For ophthalmic use, pharmaceutically acceptable compositions of the invention can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions can be formulated in an ointment such as petrolatum.

[00110] Pharmaceutically acceptable compositions of this invention can also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00111] In some embodiments, pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[00112] In some embodiments, pharmaceutically acceptable compositions of this invention are formulated for intra-peritoneal administration.

[00113] In some embodiments, pharmaceutically acceptable compositions of this invention are formulated for topical administration.

[00114] The amount of compounds of the present invention that can be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration and the activity of the compound employed. Preferably, compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving the composition.

[00115] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[00116] Other pharmaceutically acceptable carriers, adjuvants and vehicles that can be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-

hydroxypropyl- β-cyclodextrins, or other solubilized derivatives can also be advantageously used to enhance delivery of compounds described herein.

[00117] The pharmaceutical compositions of this invention are preferably administered by oral administration or by injection. The pharmaceutical compositions of this invention can contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation can be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form.

[00118] The pharmaceutical compositions can be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

[00119] When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage

normally administered in a monotherapy regimen. The additional agent(s) can be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, the additional agent(s) can be part of a single dosage form, mixed together with the compound of this invention in a single composition.

[00120] The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, intraocularly, intravitreally, subdermallym, orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight or, alternatively, in a dosage ranging from about 1 mg to about 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of a compound of the invention, or a composition thereof, to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or, alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, a preparation can contain from about 20% to about 80% active compound.

[00121] Doses lower or higher than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

[00122] Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention can be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon recurrence of disease symptoms.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00123] Another embodiment of the present invention relates to treating, for example, lessening the severity of a disease or disorder. The diseases or disorders treatable with the compounds of the invention, include but are not limited to, cancer, neurodegenerative diseases, inflammatory diseases or immune system diseases. Specific examples of these diseases or disorders and other uses (e.g., wound healing) are set forth in detail below.

[00124] In certain embodiments, the invention is a method of treating a PAK-mediated disorder, a NAMPT-mediated disorder or a disorder mediated by both PAK and NAMPT in a subject in need thereof, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof. Specific examples of diseases/disorders that are PAK-mediated, a NAMPT-mediated or mediated by both PAK and NAMPT include the diseases/disorders set forth below.

[00125] Compounds and compositions described herein are useful for treating cancer in a subject in need thereof. Thus, in certain embodiments, the present invention provides a method for treating cancer, comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable salt or composition thereof. The compounds and compositions described herein can also be administered to cells in culture, *e.g., in vitro* or *ex vivo*, or to a subject, *e.g., in vivo*, to treat, prevent, and/or diagnose a variety of disorders, including those described herein below.

[00126] The activity of a compound utilized in this invention as an anti-cancer agent may be assayed in vitro, in vivo or in a cell line. Detailed conditions for assaying a compound utilized in this invention as an anti-cancer agent are set forth in the Exemplification.

[00127] As used herein, the term "treat" or "treatment" is defined as the application or administration of a compound, alone or in combination with a second compound, to a subject, *e.g.,* a patient, or application or administration of the compound to an isolated tissue or cell, *e.g.,* cell line, from a subject, *e.g.,* a patient, who has a disorder (*e.g.,* a disorder as described herein), a symptom of a disorder, or a predisposition toward a disorder, in order to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder, one or more symptoms of the disorder or the predisposition toward the disorder (*e.g.,* to prevent at least

one symptom of the disorder or to delay onset of at least one symptom of the disorder). In the case of wound healing, a therapeutically effective amount is an amount that promotes healing of a wound.

[00128] As used herein, "promoting wound healing" means treating a subject with a wound and achieving healing, either partially or fully, of the wound. Promoting wound healing can mean, e.g., one or more of the following: promoting epidermal closure; promoting migration of the dermis; promoting dermal closure in the dermis; reducing wound healing complications, e.g., hyperplasia of the epidermis and adhesions; reducing wound dehiscence; and promoting proper scab formation.

[00129] As used herein, an amount of a compound effective to treat a disorder, or a "therapeutically effective amount" refers to an amount of the compound which is effective, upon single or multiple dose administration to a subject or a cell, in curing, alleviating, relieving or improving one or more symptoms of a disorder. In the case of wound healing, a therapeutically effective amount is an amount that promotes healing of a wound.

[00130] As used herein, an amount of a compound effective to prevent a disorder, or a "prophylactically effective amount" of the compound refers to an amount effective, upon single- or multiple-dose administration to the subject, in preventing or delaying the onset or recurrence of a disorder or one or more symptoms of the disorder.

[00131] As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, *e.g.,* a disorder described herein or a normal subject. The term "non-human animals" of the invention includes all vertebrates, *e.g.,* non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, *e.g.,* sheep, cow, pig, *etc.*, and companion animals (dog, cat, horse, *etc.*).

[00132] For example, provided herein are methods of treating various cancers in mammals (including humans and non-humans), comprising administering to a patient in need thereof a compound of the invention, or a pharmaceutically acceptable salt thereof. Such cancers include hematologic malignancies (leukemias, lymphomas, myelomas, myelodysplastic and myeloproliferative syndromes) and solid tumors (carcinomas such as oral, gall bladder, prostate, breast, lung, colon, pancreatic, renal, ovarian as well as soft tissue and osteo-sarcomas, and stromal tumors). Breast cancer (BC) can include basal-like breast cancer

(BLBC), triple negative breast cancer (TNBC) and breast cancer that is both BLBC and TNBC. In addition, breast cancer can include invasive or non-invasive ductal or lobular carcinoma, tubular, medullary, mucinous, papillary, cribriform carcinoma of the breast, male breast cancer, recurrent or metastatic breast cancer, phyllodes tumor of the breast and Paget's disease of the nipple. In some embodiments, the present invention provides a method of treating lymphoma, specifically, mantle cell lymphoma.

[00133] In some embodiments, the present invention provides a method of treating inflammatory disorders in a patient, comprising administering to the patient a compound of the invention, or a pharmaceutically acceptable salt thereof. Inflammatory disorders treatable by the compounds of this invention include, but are not limited to, multiple sclerosis, rheumatoid arthritis, degenerative joint disease, systemic lupus, systemic sclerosis, vasculitis syndromes (small, medium and large vessel), atherosclerosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, sepsis, psoriasis and other dermatological inflammatory disorders (such as eczema, atopic dermatitis, contact dermatitis, urticaria, scleroderma, and dermatosis with acute inflammatory components, pemphigus, pemphigoid, allergic dermatitis), and urticarial syndromes.

[00134] Viral diseases treatable by the compounds of this invention include, but are not limited to, acute febrile pharyngitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis, infantile gastroenteritis, Coxsackie infections, infectious mononucleosis, Burkitt lymphoma, acute hepatitis, chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma, primary HSV-1 infection (e.g., gingivostomatitis in children, tonsillitis and pharyngitis in adults, keratoconjunctivitis), latent HSV-1 infection (e.g., herpes labialis and cold sores), primary HSV-2 infection, latent HSV-2 infection, aseptic meningitis, infectious mononucleosis, Cytomegalic inclusion disease, Kaposi's sarcoma, multicentric Castleman disease, primary effusion lymphoma, AIDS, influenza, Reye syndrome, measles, postinfectious encephalomyelitis, Mumps, hyperplastic epithelial lesions (e.g., common, flat, plantar and anogenital warts, laryngeal papillomas, epidermodysplasia verruciformis), cervical carcinoma, squamous cell carcinomas, croup, pneumonia, bronchiolitis, common cold, Poliomyelitis, Rabies, influenza-like syndrome, severe bronchiolitis with pneumonia, German measles, congenital rubella, Varicella, and herpes zoster. Viral diseases treatable by

the compounds of this invention also include chronic viral infections, including hepatitis B and hepatitis C.

[00135] Exemplary ophthalmology disorders include, but are not limited to, macular edema (diabetic and nondiabetic macular edema), aged related macular degeneration wet and dry forms, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epitheliitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, ophthalmic disease associated with hypoxia or ischemia, retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency or cataract.

[00136] Neurodegenerative diseases treatable by compounds of the invention include, but are not limited to, Parkinson's, Alzheimer's, and Huntington's, and Amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease).

[00137] Compounds and compositions described herein may also be used to treat disorders of abnormal tissue growth and fibrosis including dilative cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, pulmonary fibrosis, hepatic fibrosis, glomerulonephritis, polycystic kidney disorder (PKD) and other renal disorders.

[00138] Compounds and compositions described herein may also be used to treat disorders related to food intake such as obesity and hyperphagia.

[00139] In another embodiment, a compound or composition described herein may be used to treat or prevent allergies and respiratory disorders, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD).

[00140] Other disorders treatable by the compounds and compositions described herein include muscular dystrophy, arthritis, for example, osteoarthritis and rheumatoid arthritis, ankylosing spondilitis, traumatic brain injury, spinal cord injury, sepsis, rheumatic disease, cancer atherosclerosis, type 1 diabetes, type 2 diabetes, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, ischemia/reperfusion, stroke, cerebral aneurysm, angina pectoris, pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, asthma, chronic obstructive pulmonary disease, Sjogren's syndrome, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, gut diseases, peritoneal endometriosis, skin diseases, nasal sinusitis, mesothelioma, anhidrotic ecodermal dysplasia-ID, behcet's disease, incontinentia pigmenti, tuberculosis, asthma, crohn's disease, colitis, ocular allergy, appendicitis, paget's disease, pancreatitis, periodonitis, endometriosis, inflammatory bowel disease, inflammatory lung disease, silica-induced diseases, sleep apnea, AIDS, HIV-1, autoimmune diseases, antiphospholipid syndrome, lupus, lupus nephritis, familial mediterranean fever, hereditary periodic fever syndrome, psychosocial stress diseases, neuropathological diseases, familial amyloidotic polyneuropathy, inflammatory neuropathy, parkinson's disease, multiple sclerosis, alzheimer's disease, amyotropic lateral sclerosis, huntington's disease, cataracts, or hearing loss.

[00141] Yet other disorders treatable by the compounds and compositions described herein include head injury, uveitis, inflammatory pain, allergen induced asthma, non-allergen induced asthma, glomerular nephritis, ulcerative colitis, necrotizing enterocolitis, hyperimmunoglobulinemia D with recurrent fever (HIDS), TNF receptor associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes, Muckle-Wells syndrome (urticaria deafness amyloidosis),familial cold urticaria, neonatal onset multisystem inflammatory disease (NOMID), periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome), Blau syndrome, pyogenic sterile arthritis, pyoderma gangrenosum,acne (PAPA), deficiency of the interleukin-1–receptor antagonist (DIRA), subarachnoid hemorrhage, polycystic kidney disease, transplant, organ transplant, tissue transplant, myelodysplastic syndrome, irritant-induced inflammation, plant irritant-induced

inflammation, poison ivy/ urushiol oil-induced inflammation, chemical irritant-induced inflammation, bee sting-induced inflammation, insect bite-induced inflammation, sunburn, burns, dermatitis, endotoxemia, lung injury, acute respiratory distress syndrome, alcoholic hepatitis, or kidney injury caused by parasitic infections.

[00142] The compound and compositions described herein can also be used to trate cocaine addiction.

[00143] Yet another disorder treatable by the compounds and compositions described herein is schizophrenia.

[00144] In further aspects, the present invention provides a use of a compound of the invention, of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer. In some embodiments, the present invention provides a use of a compound of the invention in the manufacture of a medicament for the treatment of any of cancer and/or neoplastic disorders, angiogenesis, autoimmune disorders, inflammatory disorders and/or diseases, epigenetics, hormonal disorders and/or diseases, viral diseases, neurodegenerative disorders and/or diseases, wounds, and ophthamalogic disorders.

Neoplastic Disorders

[00145] A compound or composition described herein can be used to treat a neoplastic disorder. A "neoplastic disorder" is a disease or disorder characterized by cells that have the capacity for autonomous growth or replication, e.g., an abnormal state or condition characterized by proliferative cell growth. Exemplary neoplastic disorders include: carcinoma, sarcoma, metastatic disorders, e.g., tumors arising from prostate, brain, bone, colon, lung, breast, ovarian, and liver origin, hematopoietic neoplastic disorders, e.g., leukemias, lymphomas, myeloma and other malignant plasma cell disorders, and metastatic tumors. Prevalent cancers include: breast, prostate, colon, lung, liver, and pancreatic cancers. Treatment with the compound can be in an amount effective to ameliorate at least one symptom of the neoplastic disorder, e.g., reduced cell proliferation, reduced tumor mass, etc.

[00146] The disclosed methods are useful in the prevention and treatment of cancer, including for example, solid tumors, soft tissue tumors, and metastases thereof, as well as in familial cancer syndromes such as Li Fraumeni Syndrome, Familial Breast-Ovarian Cancer (BRCA1 or BRAC2 mutations) Syndromes, and others. The disclosed methods are also useful in treating non-solid cancers. Exemplary solid tumors include malignancies (e.g.,

sarcomas, adenocarcinomas, and carcinomas) of the various organ systems, such as those of lung, breast, lymphoid, gastrointestinal (e.g., colon), and genitourinary (e.g., renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, and cancer of the small intestine.

[00147] Exemplary cancers described by the National Cancer Institute include: Acute Lymphoblastic Leukemia, Adult; Acute Lymphoblastic Leukemia, Childhood; Acute Myeloid Leukemia, Adult; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer; Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer, Childhood; Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Cerebellar Astrocytoma, Childhood; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma, Childhood; Brain Tumor, Ependymoma, Childhood; Brain Tumor, Medulloblastoma, Childhood; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood; Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood; Brain Tumor, Childhood (Other); Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer, Childhood; Breast Cancer, Male; Bronchial Adenomas/Carcinoids, Childhood; Carcinoid Tumor, Childhood; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Carcinoma of Unknown Primary; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma, Childhood; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer, Childhood; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma, Childhood; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer, Childhood; Ewing's Family of Tumors; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer, Childhood; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian;

Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma, Adult; Hodgkin's Lymphoma, Childhood; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma, Childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney Cancer; Laryngeal Cancer; Laryngeal Cancer, Childhood; Leukemia, Acute Lymphoblastic, Adult; Leukemia, Acute Lymphoblastic, Childhood; Leukemia, Acute Myeloid, Adult; Leukemia, Acute Myeloid, Childhood; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia, Adult Acute; Lymphoblastic Leukemia, Childhood Acute; Lymphocytic Leukemia, Chronic; Lymphoma, AIDS- Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin's, Adult; Lymphoma, Hodgkin's, Childhood; Lymphoma, Hodgkin's During Pregnancy; Lymphoma, Non-Hodgkin's, Adult; Lymphoma, Non- Hodgkin's, Childhood; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Male Breast Cancer; Malignant Mesothelioma, Adult; Malignant Mesothelioma, Childhood; Malignant Thymoma; Mantle Cell Lymphoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Nasopharyngeal Cancer, Childhood; Neuroblastoma; Non-Hodgkin's Lymphoma, Adult; Non-Hodgkin's Lymphoma, Childhood; Non- Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer, Childhood; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; Osteosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer, Childhood; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Childhood; Pancreatic Cancer, Islet Cell;

Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer, Adult; Primary Liver Cancer, Childhood; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell Cancer, Childhood; Renal Pelvis and Ureter, Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Salivary Gland Cancer, Childhood; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Rhabdomyosarcoma, Childhood; Sarcoma, Soft Tissue, Adult; Sarcoma, Soft Tissue, Childhood; Sezary Syndrome; Skin Cancer; Skin Cancer, Childhood; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma, Adult; Soft Tissue Sarcoma, Childhood; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer, Childhood; Supratentorial Primitive Neuroectodermal Tumors, Childhood; T- Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Childhood; Thymoma, Malignant; Thyroid Cancer; Thyroid Cancer, Childhood; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Cancer of, Childhood; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma, Childhood; Vulvar Cancer; Waldenstrom's Macro globulinemia; and Wilms' Tumor. Further exemplary cancers include diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and serous and endometrioid cancer. Yet a further exemplary cancer is alveolar soft part sarcoma.

[00148] Further exemplary cancers include diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Yet further exemplary cancers include endocervical cancer, B-cell ALL, T-cell ALL, B- or T-cell lymphoma, mast cell cancer, glioblastoma, neuroblastoma, follicular lymphoma and Richter's syndrome. Yet further exemplary cancers include glioma.

[00149] Metastases of the aforementioned cancers can also be treated or prevented in accordance with the methods described herein.

Combination therapies

[00150] In some embodiments, a compound described herein is administered together with an additional "second" therapeutic agent or treatment. The choice of second therapeutic agent may be made from any agent that is typically used in a monotherapy to treat the indicated disease or condition. As used herein, the term "administered together" and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of any of the formulas described herein, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00151] In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

Cancer Combination Therapies

[00152] In some embodiments, a compound described herein is administered together with an additional cancer treatment. Exemplary cancer treatments include, for example, chemotherapy, targeted therapies such as antibody therapies, kinase inhibitors, immunotherapy, and hormonal therapy, and anti-angiogenic therapies. Examples of each of these treatments are provided below.

[00153] As used herein, the term "combination," "combined," and related terms refer to the simultaneous or sequential administration of therapeutic agents in accordance with this

invention. For example, a compound of the present invention can be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00154] The amount of both a compound of the invention and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of the invention can be administered.

Chemotherapy

[00155] In some embodiments, a compound described herein is administered with a chemotherapy. Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. "Chemotherapy" usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g., with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

[00156] Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (e.g., folic acid, purine, and pyrimidine derivatives) and alkylating agents (e.g., nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinon, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Atrasentan, Belotecan, Bexarotene, Bendamustine, Bleomycin, Bortezomib, Busulfan, Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine,

Epirubicin, Estramustine, Etoglucid, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

[00157] Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy. In some embodiments, the chemotherapy agents (including combination chemotherapy) can be used in combination with a compound described herein.

Targeted therapy

[00158] Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within a cancer cell. Prominent examples are the tyrosine kinase inhibitors such as axitinib, bosutinib, cediranib, desatinib, erolotinib, imatinib, gefitinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, and vandetanib, and also cyclin-dependent kinase inhibitors such as alvocidib and seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (Herceptin®) typically used in breast cancer, and the anti-CD20 antibody rituximab and tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include

cetuximab, panitumumab, trastuzumab, alemtuzumab, bevacizumab, edrecolomab, and gemtuzumab. Exemplary fusion proteins include aflibercept and denileukin diftitox. In some embodiments, targeted therapy can be used in combination with a compound described herein, *e.g.*, Gleevec (Vignari and Wang 2001).

[00159] Targeted therapy can also involve small peptides as "homing devices" which can bind to cell surface receptors or affected extracellular matrix surrounding a tumor. Radionuclides which are attached to these peptides (*e.g.*, RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell. An example of such therapy includes BEXXAR®.

Angiogenesis

[00160] Compounds and methods described herein may be used to treat or prevent a disease or disorder associated with angiogenesis. Diseases associated with angiogenesis include cancer, cardiovascular disease and macular degeneration.

[00161] Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels. Angiogenesis is a normal and vital process in growth and development, as well as in wound healing and in granulation tissue. However, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. Angiogenesis may be a target for combating diseases characterized by either poor vascularisation or abnormal vasculature.

[00162] Application of specific compounds that may inhibit or induce the creation of new blood vessels in the body may help combat such diseases. The presence of blood vessels where there should be none may affect the mechanical properties of a tissue, increasing the likelihood of failure. The absence of blood vessels in a repairing or otherwise metabolically active tissue may inhibit repair or other essential functions. Several diseases, such as ischemic chronic wounds, are the result of failure or insufficient blood vessel formation and may be treated by a local expansion of blood vessels, thus bringing new nutrients to the site, facilitating repair. Other diseases, such as age-related macular degeneration, may be created by a local expansion of blood vessels, interfering with normal physiological processes.

[00163] Vascular endothelial growth factor (VEGF) has been demonstrated to be a major contributor to angiogenesis, increasing the number of capillaries in a given network. Upregulation of VEGF is a major component of the physiological response to exercise and its

role in angiogenesis is suspected to be a possible treatment in vascular injuries. *In vitro* studies clearly demonstrate that VEGF is a potent stimulator of angiogenesis because, in the presence of this growth factor, plated endothelial cells will proliferate and migrate, eventually forming tube structures resembling capillaries.

[00164] Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (*e.g.,* VEGF). Growth factors such as bFGF and VEGF can induce capillary growth into the tumor, which some researchers suspect supply required nutrients, allowing for tumor expansion.

[00165] Angiogenesis represents an excellent therapeutic target for the treatment of cardiovascular disease. It is a potent, physiological process that underlies the natural manner in which our bodies respond to a diminution of blood supply to vital organs, namely the production of new collateral vessels to overcome the ischemic insult.

[00166] Overexpression of VEGF causes increased permeability in blood vessels in addition to stimulating angiogenesis. In wet macular degeneration, VEGF causes proliferation of capillaries into the retina. Since the increase in angiogenesis also causes edema, blood and other retinal fluids leak into the retina, causing loss of vision.

[00167] Anti-angiogenic therapy can include kinase inhibitors targeting vascular endothelial growth factor (VEGF) such as sunitinib, sorafenib, or monoclonal antibodies or receptor "decoys" to VEGF or VEGF receptor including bevacizumab or VEGF-Trap, or thalidomide or its analogs (lenalidomide, pomalidomide), or agents targeting non-VEGF angiogenic targets such as fibroblast growth factor (FGF), angiopoietins, or angiostatin or endostatin.

Epigenetics

[00168] Compounds and methods described herein may be used to treat or prevent a disease or disorder associated with epigenetics. Epigenetics is the study of heritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence. One example of epigenetic changes in eukaryotic biology is the process of cellular differentiation. During morphogenesis, stem cells become the various cell lines of the embryo which in turn become fully differentiated cells. In other words, a single fertilized egg cell changes into the many cell types including neurons, muscle cells, epithelium, blood

vessels *etc.* as it continues to divide. It does so by activating some genes while inhibiting others.

[00169] Epigenetic changes are preserved when cells divide. Most epigenetic changes only occur within the course of one individual organism's lifetime, but, if a mutation in the DNA has been caused in sperm or egg cell that results in fertilization, then some epigenetic changes are inherited from one generation to the next. Specific epigenetic processes include paramutation, bookmarking, imprinting, gene silencing, X chromosome inactivation, position effect, reprogramming, transvection, maternal effects, the progress of carcinogenesis, many effects of teratogens, regulation of histone modifications and heterochromatin, and technical limitations affecting parthenogenesis and cloning.

[00170] Exemplary diseases associated with epigenetics include ATR-syndrome, fragile X-syndrome, ICF syndrome, Angelman's syndrome, Prader-Wills syndrome, BWS, Rett syndrome, α-thalassaemia, cancer, leukemia, Rubinstein-Taybi syndrome and Coffin-Lowry syndrome.

[00171] The first human disease to be linked to epigenetics was cancer. Researchers found that diseased tissue from patients with colorectal cancer had less DNA methylation than normal tissue from the same patients. Because methylated genes are typically turned off, loss of DNA methylation can cause abnormally high gene activation by altering the arrangement of chromatin. On the other hand, too much methylation can undo the work of protective tumor suppressor genes.

[00172] DNA methylation occurs at CpG sites, and a majority of CpG cytosines are methylated in mammals. However, there are stretches of DNA near promoter regions that have higher concentrations of CpG sites (known as CpG islands) that are free of methylation in normal cells. These CpG islands become excessively methylated in cancer cells, thereby causing genes that should not be silenced to turn off. This abnormality is the trademark epigenetic change that occurs in tumors and happens early in the development of cancer. Hypermethylation of CpG islands can cause tumors by shutting off tumor-suppressor genes. In fact, these types of changes may be more common in human cancer than DNA sequence mutations.

[00173] Furthermore, although epigenetic changes do not alter the sequence of DNA, they can cause mutations. About half of the genes that cause familial or inherited forms of cancer

are turned off by methylation. Most of these genes normally suppress tumor formation and help repair DNA, including O6-methylguanine-DNA methyltransferase (*MGMT*), MLH1 cyclin-dependent kinase inhibitor 2B (*CDKN2B*), and *RASSF1A*. For example, hypermethylation of the promoter of *MGMT* causes the number of G-to-A mutations to increase.

[00174] Hypermethylation can also lead to instability of microsatellites, which are repeated sequences of DNA. Microsatellites are common in normal individuals, and they usually consist of repeats of the dinucleotide CA. Too much methylation of the promoter of the DNA repair gene *MLH1* can make a microsatellite unstable and lengthen or shorten it. Microsatellite instability has been linked to many cancers, including colorectal, endometrial, ovarian, and gastric cancers.

[00175] Fragile X syndrome is the most frequently inherited mental disability, particularly in males. Both sexes can be affected by this condition, but because males only have one X chromosome, one fragile X will impact them more severely. Indeed, fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females. People with this syndrome have severe intellectual disabilities, delayed verbal development, and "autistic-like" behavior.

[00176] Fragile X syndrome gets its name from the way the part of the X chromosome that contains the gene abnormality looks under a microscope; it usually appears as if it is hanging by a thread and easily breakable. The syndrome is caused by an abnormality in the *FMR1* (fragile X mental retardation 1) gene. People who do not have fragile X syndrome have 6 to 50 repeats of the trinucleotide CGG in their *FMR1* gene. However, individuals with over 200 repeats have a full mutation, and they usually show symptoms of the syndrome. Too many CGGs cause the CpG islands at the promoter region of the *FMR1* gene to become methylated; normally, they are not. This methylation turns the gene off, stopping the *FMR1* gene from producing an important protein called fragile X mental retardation protein. Loss of this specific protein causes fragile X syndrome. Although a lot of attention has been given to the CGG expansion mutation as the cause of fragile X, the epigenetic change associated with *FMR1* methylation is the real syndrome culprit.

[00177] Fragile X syndrome is not the only disorder associated with mental retardation that involves epigenetic changes. Other such conditions include Rubenstein-Taybi, Coffin-Lowry, Prader-Willi, Angelman, Beckwith-Wiedemann, ATR-X, and Rett syndromes.

[00178] Epigenetic therapies include inhibitors of enzymes controlling epigenetic modifications, specifically DNA methyltransferases and histone deacetylases, which have shown promising anti-tumorigenic effects for some malignancies, as well as antisense oligonucloetides and siRNA.

Immunotherapy

[00179] In some embodiments, a compound described herein is administered with an immunotherapy. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, prostate cancer vaccine Provenge, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma patients.

[00180] Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a graft-versus-tumor effect. In some embodiments, the immunotherapy agents can be used in combination with a compound described herein.

Hormonal therapy

[00181] In some embodiments, a compound described herein is administered with a hormonal therapy. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers, as well as certain types of leukemia which respond to certain retinoids/retinoic acids. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial. In some embodiments, the hormonal therapy agents can be used in combination with a compound described herein.

[00182] Hormonal therapy agents include the administration of hormone agonists or hormone antagonists and include retinoids/retinoic acid, compounds that inhibit estrogen or testosterone, as well as administration of progestogens.

Inflammation and Autoimmune Disease

[00183] The compounds and methods described herein may be used to treat or prevent a disease or disorder associated with inflammation, particularly in humans and other mammals.

A compound described herein may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the compounds are preferably provided in advance of any inflammatory response or symptom. Administration of the compounds can prevent or attenuate inflammatory responses or symptoms. Exemplary inflammatory conditions include, for example, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, degenerative joint disease, spondouloarthropathies, other seronegative inflammatory arthridities, polymyalgia rheumatica, various vasculidities (e.g., giant cell arteritis, ANCA+ vasculitis), gouty arthritis, systemic lupus erythematosus, juvenile arthritis, juvenile rheumatoid arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), menstrual cramps, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, esophagitis, pancreatitis, peritonitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome. Exemplary inflammatory conditions of the skin include, for example, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, and dermatosis with acute inflammatory components.

[00184] In another embodiment, a compound or method described herein may be used to treat or prevent allergies and respiratory conditions, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD). The compounds may be used to treat chronic hepatitis infection, including hepatitis B and hepatitis C.

[00185] Additionally, a compound or method described herein may be used to treat autoimmune diseases and/or inflammation associated with autoimmune diseases, such as organ-tissue autoimmune diseases (*e.g.,* Raynaud's syndrome), scleroderma, myasthenia gravis, transplant rejection, endotoxin shock, sepsis, psoriasis, eczema, dermatitis, multiple sclerosis, autoimmune thyroiditis, uveitis, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease.

[00186] In a particular embodiment, the compounds described herein can be used to treat multiple sclerosis.

Combination therapy

[00187] In certain embodiments, a compound described herein may be administered alone or in combination with other compounds useful for treating or preventing inflammation. Exemplary anti-inflammatory agents include, for example, steroids (*e.g.,* Cortisol, cortisone, fludrocortisone, prednisone, 6[alpha]-methylprednisone, triamcinolone, betamethasone or dexamethasone), nonsteroidal antiinflammatory drugs (NSAIDS (*e.g.,* aspirin, acetaminophen, tolmetin, ibuprofen, mefenamic acid, piroxicam, nabumetone, rofecoxib, celecoxib, etodolac or nimesulide). In another embodiment, the other therapeutic agent is an antibiotic (*e.g.*, vancomycin, penicillin, amoxicillin, ampicillin, cefotaxime, ceftriaxone, cefixime, rifampinmetronidazole, doxycycline or streptomycin). In another embodiment, the other therapeutic agent is a PDE4 inhibitor (*e.g.*, roflumilast or rolipram). In another embodiment, the other therapeutic agent is an antihistamine (*e.g.*, cyclizine, hydroxyzine, promethazine or diphenhydramine). In another embodiment, the other therapeutic agent is an anti-malarial (*e.g.,* artemisinin, artemether, artsunate, chloroquine phosphate, mefloquine hydrochloride, doxycycline hyclate, proguanil hydrochloride, atovaquone or halofantrine). In one embodiment, the other compound is drotrecogin alfa.

[00188] Further examples of anti-inflammatory agents include, for example, aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alclometasone, alfentanil, algestone, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amcinonide, amfenac, aminochlorthenoxazin, 3-amino-4- hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antrafenine, apazone, beclomethasone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, betamethasone, betamethasone- 17-valerate, bezitramide, [alpha]-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, budesonide, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butorphanol, carbamazepine, carbiphene, caiprofen, carsalam, chlorobutanol, chloroprednisone, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol,

clidanac, clobetasol, clocortolone, clometacin, clonitazene, clonixin, clopirac, cloprednol, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cortisone, cortivazol, cropropamide, crotethamide, cyclazocine, deflazacort, dehydrotestosterone, desomorphine, desonide, desoximetasone, dexamethasone, dexamethasone-21- isonicotinate, dexoxadrol, dextromoramide, dextropropoxyphene, deoxycorticosterone, dezocine, diampromide, diamorphone, diclofenac, difenamizole, difenpiramide, diflorasone, diflucortolone, diflunisal, difluprednate, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, enoxolone, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, fluazacort, flucloronide, flufenamic acid, flumethasone, flunisolide, flunixin, flunoxaprofen, fluocinolone acetonide, fluocinonide, fluocinolone acetonide, fluocortin butyl, fluocoitolone, fluoresone, fluorometholone, fluperolone, flupirtine, fluprednidene, fluprednisolone, fluproquazone, flurandrenolide, flurbiprofen, fluticasone, formocortal, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, halcinonide, halobetasol, halometasone, haloprednone, heroin, hydrocodone, hydro cortamate, hydrocortisone, hydrocortisone acetate, hydrocortisone succinate, hydrocortisone hemisuccinate, hydrocortisone 21-lysinate, hydrocortisone cypionate, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoflupredone, isoflupredone acetate, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levallorphan, levorphanol, levophenacyl-morphan, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, mazipredone, meclofenamic acid, medrysone, mefenamic acid, meloxicam, meperidine, meprednisone, meptazinol, mesalamine, metazocine, methadone, methotrimeprazine, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methylprednisolone suleptnate, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, mometasone, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, nalorphine, 1-naphthyl salicylate, naproxen, narceine,

nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide,norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paramethasone, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenomorphan, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirazolac, piritramide, piroxicam, pirprofen, pranoprofen, prednicarbate, prednisolone, prednisone, prednival, prednylidene, proglumetacin, proheptazine, promedol, propacetamol, properidine, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, proxazole, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylic acid, salicylsulfuric acid, salsalate, salverine, simetride, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tixocortol, tolfenamic acid, tolmetin, tramadol, triamcinolone, triamcinolone acetonide, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac.

[00189] In one embodiment, a compound described herein may be administered with a selective COX-2 inhibitor for treating or preventing inflammation. Exemplary selective COX-2 inhibitors include, for example, deracoxib, parecoxib, celecoxib, valdecoxib, rofecoxib, etoricoxib, and lumiracoxib.

[00190] In some embodiments, a provided compound is administered in combination with an anthracycline or a Topo II inhibitor. In certain embodiments, a provided compound is administered in combination with Doxorubicin (Dox). In certain embodiments, a provided compound is administered in combination with bortezomib (and more broadly including carfilzomib). It was surprisingly found that a provided compound in combination with Dox or bortezomib resulted in a synergystic effect (*i.e.,* more than additive).

Viral infections

[00191] Compounds and methods described herein may be used to treat or prevent a disease or disorder associated with a viral infection, particularly in humans and other mammals. A compound described herein may be administered prior to the onset of, at, or

after the initiation of viral infection. When used prophylactically, the compounds are preferably provided in advance of any viral infection or symptom thereof.

[00192] Exemplary viral diseases include acute febrile pharyngitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis, infantile gastroenteritis, Coxsackie infections, infectious mononucleosis, Burkitt lymphoma, acute hepatitis, chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma, primary HSV-1 infection (*e.g.,* gingivostomatitis in children, tonsillitis and pharyngitis in adults, keratoconjunctivitis), latent HSV-1 infection (*e.g.,* herpes labialis and cold sores), primary HSV-2 infection, latent HSV-2 infection, aseptic meningitis, infectious mononucleosis, Cytomegalic inclusion disease, Kaposi's sarcoma, multicentric Castleman disease, primary effusion lymphoma, AIDS, influenza, Reye syndrome, measles, postinfectious encephalomyelitis, Mumps, hyperplastic epithelial lesions (*e.g.,* common, flat, plantar and anogenital warts, laryngeal papillomas, epidermodysplasia verruciformis), cervical carcinoma, squamous cell carcinomas, croup, pneumonia, bronchiolitis, common cold, Poliomyelitis, Rabies, influenza-like syndrome, severe bronchiolitis with pneumonia, German measles, congenital rubella, Varicella, and herpes zoster.

[00193] Exemplary viral pathogens include Adenovirus, Coxsackievirus, Dengue virus, Encephalitis Virus, Epstein-Barr virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Herpes simplex virus type 1, Herpes simplex virus type 2, cytomegalovirus, Human herpesvirus type 8, Human immunodeficiency virus, Influenza virus, measles virus, Mumps virus, Human papillomavirus, Parainfluenza virus, Poliovirus, Rabies virus, Respiratory syncytial virus, Rubella virus, Varicella-zoster virus, West Nile virus, Dungee, and Yellow fever virus. Viral pathogens may also include viruses that cause resistant viral infections.

[00194] Antiviral drugs are a class of medications used specifically for treating viral infections. Antiviral action generally falls into one of three mechanisms: interference with the ability of a virus to infiltrate a target cell (*e.g.,* amantadine, rimantadine and pleconaril), inhibition of the synthesis of virus (*e.g.,* nucleoside analogues, *e.g.,* acyclovir and zidovudine (AZT), and inhibition of the release of virus (*e.g.,* zanamivir and oseltamivir).

[00195] In some embodiments, the viral pathogen is selected from the group consisting of herpesviridae, flaviviridae, bunyaviridae, arenaviridae, picornaviridae, togaviridae, papovaviridae, poxviridae, respiratory viruses, hepatic viruses, and other viruses.

[00196] Exemplary herpesviridae include herpes simplex virus-1; herpes simplex virus-2; cytomegalovirus, for example, human cytomegalovirus; Varicella-Zoster virus; Epstein-Barr virus; herpes virus-6, for example, human herpes virus-6; and herpes virus-8, for example, human herpes virus-8.

[00197] Exemplary flaviviridae include Dengue virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, and Powassen virus.

[00198] Exemplary bunyaviridae include Rift Valley fever virus, Punta Toro virus, LaCrosse virus, and Marporal virus.

[00199] Exemplary arenaviridae include Tacaribe virus, Pinchinde virus, Junin virus, and Lassa fever virus.

[00200] Exemplary picornaviridae include polio virus; enterovirus, for example, enterovirus-71; and Coxsackie virus, for example, Coxsackie virus B3.

[00201] Exemplary togaviridae include encephalitis virus, for example, Venezuelan equine encephalitis virus, Eastern equine encephalitis virus, and Western equine encephalitis virus; and Chikungunya virus.

[00202] Exemplary papovaviridae include BK virus, JC virus, and papillomavirus.

[00203] Exemplary poxviridae include vaccinia virus, cowpox virus, and monkeypox virus.

[00204] Exemplary respiratory viruses include SARS coronavirus; influenza A virus, for example, H1N1 virus; and respiratory syncytial virus.

[00205] Exemplary hepatic viruses include hepatitis B and hepatitis C viruses.

[00206] Exemplary other viruses include adenovirus, for example, adenovirus-5; rabies virus; measles virus; ebola virus; nipah virus; and norovirus.

Ophthalmology

[00207] Compounds and methods described herein may be used to treat or prevent an ophthalmology disorder. Exemplary ophthalmology disorders include macular edema (diabetic and nondiabetic macular edema), age related macular degeneration wet and dry forms, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis,

episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, ophthalmic disease associated with hypoxia or ischemia, retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency and cataract.

[00208] Other ophthalmology disorders treatable using the compounds and methods described herein include proliferative vitreoretinopathy and chronic retinal detachment.

[00209] Inflammatory eye diseases are also treatable using the compounds and methods described herein.

Neurodegenerative disease

[00210] Neurodegeneration is the umbrella term for the progressive loss of structure or function of neurons, including death of neurons. Many neurodegenerative diseases including Parkinson's, Alzheimer's, and Huntington's occur as a result of neurodegenerative processes. As research progresses, many similarities appear which relate these diseases to one another on a sub-cellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate many diseases simultaneously. There are many parallels between different neurodegenerative disorders including atypical protein assemblies as well as induced cell death.

[00211] Alzheimer's disease is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.

[00212] Huntington's disease causes astrogliosis and loss of medium spiny neurons. Areas of the brain are affected according to their structure and the types of neurons they contain, reducing in size as they cumulatively lose cells. The areas affected are mainly in the striatum, but also the frontal and temporal cortices. The striatum's subthalamic nuclei send control signals to the globus pallidus, which initiates and modulates motion. The weaker signals from

subthalamic nuclei thus cause reduced initiation and modulation of movement, resulting in the characteristic movements of the disorder. Exemplary treatments for Huntington's disease include tetrabenazine, neuroleptics, benzodiazepines, amantadine, remacemide, valproic acid, selective serotonin reuptake inhibitors (SSRIs), mirtazapine and antipsychotics.

[00213] The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models. Exemplary Parkinson's disease therapies include levodopa, dopamine agonists such as include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride, dopa decarboxylate inhibitors, MAO-B inhibitors such as selegilene and rasagilene, anticholinergics and amantadine.

[00214] Amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease) is a disease in which motor neurons are selectively targeted for degeneration. Exemplary ALS therapies include riluzole, baclofen, diazepam, trihexyphenidyl and amitriptyline.

[00215] Other exemplary neurodegenerative therapeutics include antisense oligonucleotides and stem cells.

Wound Healing

[00216] Wounds are a type of condition characterized by cell or tissue damage. Wound healing is a dynamic pathway that optimally leads to restoration of tissue integrity and function. The wound healing process consists of three overlapping phases. The first phase is an inflammatory phase, which is characterized by homeostasis, platelet aggregation and degranulation. Platelets as the first response, release multiple growth factors to recruit immune cells, epithelial cells, and endothelial cells. The inflammatory phase typically occurs over days 0-5. The second stage of wound healing is the proliferative phase during which macrophages and granulocytes invade the wound. Infiltrating fibroblasts begin to produce collagen. The principle characteristics of this phase are epithelialization, angiogenesis,

granulation tissue formation and collagen production. The proliferative phase typically occurs over days 3-14. The third phase is the remodeling phase where matrix formation occurs. The fibroblasts, epithelial cells, and endothelial cells continue to produce collagen and collagenase as well as matrix metalloproteases (MMPs) for remodeling. Collagen crosslinking takes place and the wound undergoes contraction. The remodeling phase typically occurs from day 7 to one year.

[00217] Compounds and compositions described herein can be used for promoting wound healing (*e.g.*, promoting or accelerating wound closure and/or wound healing, mitigating scar fibrosis of the tissue of and/or around the wound, inhibiting apoptosis of cells surrounding or proximate to the wound). Thus, in certain embodiments, the present invention provides a method for promoting wound healing in a subject, comprising administering to the subject a therapeutically effective amount of a compound, or pharmaceutically acceptable salt or composition thereof. The method need not achieve complete healing or closure of the wound; it is sufficient for the method to promote any degree of wound closure. In this respect, the method can be employed alone or as an adjunct to other methods for healing wounded tissue.

[00218] The compounds and compositions described herein can be used to treat wounds during the inflammatory (or early) phase, during the proliferative (or middle) wound healing phase, and/or during the remodeling (or late) wound healing phase.

[00219] In some embodiments, the subject in need of wound healing is a human or an animal, for example, a dog, a cat, a horse, a pig, or a rodent, such as a mouse.

[00220] In some embodiments, the compounds and compositions described herein useful for wound healing are administered topically, for example, proximate to the wound site, or systemically.

[00221] More specifically, a therapeutically effective amount of a compound or composition described herein can be administered (optionally in combination with other agents) to the wound site by coating the wound or applying a bandage, packing material, stitches, *etc*., that are coated or treated with the compound or composition described herein. As such, the compounds and compositions described herein can be formulated for topical administration to treat surface wounds. Topical formulations include those for delivery via the mouth (buccal) and to the skin such that a layer of skin (*i.e.*, the epidermis, dermis, and/or

subcutaneous layer) is contacted with the compound or composition described herein. Topical delivery systems may be used to administer topical formulations of the compounds and compositions described herein.

[00222] Alternatively, the compounds and compositions described herein can be administered at or near the wound site by, for example, injection of a solution, injection of an extended release formulation, or introduction of a biodegradable implant comprising the compound or composition described herein.

[00223] The compounds and compositions described herein can be used to treat acute wounds or chronic wounds. A chronic wound results when the normal reparative process is interrupted. Chronic wounds can develop from acute injuries as a result of unrecognized persistent infections or inadequate primary treatment. In most cases however, chronic lesions are the end stage of progressive tissue breakdown owing to venous, arterial, or metabolic vascular disease, pressure sores, radiation damage, or tumors.

[00224] In chronic wounds, healing does not occur for a variety of reasons, including improper circulation in diabetic ulcers, significant necrosis, such as in burns, and infections. In these chronic wounds, viability or the recovery phase is often the rate-limiting step. The cells are no longer viable and, thus, initial recovery phase is prolonged by unfavorable wound bed environment.

[00225] Chronic wounds include, but are not limited to the following: chronic ischemic skin lesions; scleroderma ulcers; arterial ulcers; diabetic foot ulcers; pressure ulcers; venous ulcers; non-healing lower extremity wounds; ulcers due to inflammatory conditions; and/or long-standing wounds. Other examples of chronic wounds include chronic ulcers, diabetic wounds, wounds caused by diabetic neuropathy, venous insufficiencies, and arterial insufficiencies, and pressure wounds and cold and warm burns. Yet other examples of chronic wounds include chronic ulcers, diabetic wounds, wounds caused by diabetic neuropathy, venous insufficiencies, arterial insufficiencies, and pressure wounds.

[00226] Acute wounds include, but are not limited to, post-surgical wounds, lacerations, hemorrhoids and fissures.

[00227] In a particular embodiment, the compounds and compositions described herein can be used for diabetic wound healing or accelerating healing of leg and foot ulcers secondary to diabetes or ischemia in a subject.

[00228] In one embodiment, the wound is a surface wound. In another embodiment, the wound is a surgical wound (*e.g.*, abdominal or gastrointestinal surgical wound). In a further embodiment, the wound is a burn. In yet another embodiment, the wound is the result of radiation exposure.

[00229] The compounds and compositions described herein can also be used for diabetic wound healing, gastrointestinal wound healing, or healing of an adhesion due, for example, to an operation.

[00230] The compounds and compositions described herein can also be used to heal wounds that are secondary to another disease. For example, in inflammatory skin diseases, such as psoriasis and dermatitis, there are numerous incidents of skin lesions that are secondary to the disease, and are caused by deep cracking of the skin, or scratching of the skin. The compounds and compositions described herein can be used to heal wounds that are secondary to these diseases, for example, inflammatory skin diseases, such as psoriasis and dermatitis.

[00231] In a further embodiment, the wound is an internal wound. In a specific aspect, the internal wound is a chronic wound. In another specific aspect, the wound is a vascular wound. In yet another specific aspect, the internal wound is an ulcer. Examples of internal wounds include, but are not limited to, fistulas and internal wounds associated with cosmetic surgery, internal indications, Crohn's disease, ulcerative colitis, internal surgical sutures and skeletal fixation. Other examples of internal wounds include, but are not limited to, fistulas and internal wounds associated with cosmetic surgery, internal indications, internal surgical sutures and skeletal fixation.

[00232] Examples of wounds include, but are not limited to, abrasions, avulsions, blowing wounds (i.e., open pneumothorax), burn wounds, contusions, gunshot wounds, incised wounds, open wounds, penetrating wounds, perforating wounds, puncture wounds, séton wounds, stab wounds, surgical wounds, subcutaneous wounds, diabetic lesions, or tangential wounds. Additional examples of wounds that can be treated by the compounds and compositions described herein include acute conditions or wounds, such as thermal burns, chemical burns, radiation burns, burns caused by excess exposure to ultraviolet radiation (*e.g.,* sunburn); damage to bodily tissues, such as the perineum as a result of labor and childbirth; injuries sustained during medical procedures, such as episiotomies; trauma-

induced injuries including cuts, incisions, excoriations; injuries sustained from accidents; post-surgical injuries, as well as chronic conditions, such as pressure sores, bedsores, conditions related to diabetes and poor circulation, and all types of acne. In addition, the wound can include dermatitis, such as impetigo, intertrigo, folliculitis and eczema, wounds following dental surgery; periodontal disease; wounds following trauma; and tumor-associated wounds. Yet other examples of wounds include animal bites, arterial disease, insect stings and bites, bone infections, compromised skin/muscle grafts, gangrene, skin tears or lacerations, skin aging, surgical incisions, including slow or non-healing surgical wounds, intracerebral hemorrhage, aneurysm, dermal asthenia, and post-operation infections.

[00233] In preferred embodiments, the wound is selected from the group consisting of a burn wound, an incised wound, an open wound, a surgical or post surgical wound, a diabetic lesion, a thermal burn, a chemical burn, a radiation burn, a pressure sore, a bedsore, and a condition related to diabetes or poor circulation. In more preferred embodiments, the wound is selected from the group consisting of an incised wound, an open wound, a surgical or post surgical wound, a diabetic lesion, a pressure sore, a bedsore, and a condition or wound related to diabetes or poor circulation.

[00234] In some embodiments, the wound is selected from the group consisting of a non-radiation burn wound, an incised wound, an open wound, a surgical or post surgical wound, a diabetic lesion, a thermal burn, a chemical burn, a pressure sore, a bedsore, and a condition related to diabetes or poor circulation. In some embodiments, the wound is selected from the group consisting of an incised wound, an open wound, a surgical or post surgical wound, a diabetic lesion, a pressure sore, a bedsore, and a condition related to diabetes or poor circulation.

[00235] The present disclosure also relates to methods and compositions of reducing scar formation during wound healing in a subject. The compounds and compositions described herein can be administered directly to the wound or to cells proximate the wound at an amount effective to reduce scar formation in and/or around the wound. Thus, in some embodiments, a method of reducing scar formation during wound healing in a subject is provided, the method comprising administering to the subject a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof.

[00236] The wound can include any injury to any portion of the body of a subject. According to embodiments, methods are provided to ameliorate, reduce, or decrease the formation of scars in a subject that has suffered a burn injury. According to preferred embodiments, methods are provided to treat, reduce the occurrence of, or reduce the probability of developing hypertrophic scars in a subject that has suffered an acute or chronic wound or injury.

Other disorders

[00237] Compounds and compositions described herein may also be used to treat disorders of abnormal tissue growth and fibrosis including dilative cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, pulmonary fibrosis, hepatic fibrosis, glomerulonephritis, and other renal disorders.

Combination Radiation Therapy

[00238] Compounds and compositions described herein are useful as radiosensitizers. Therefore, compounds and compositions described herein can be administered in combination with radiation therapy. Radiation therapy is the medical use of high-energy radiation (*e.g.*, x-rays, gamma rays, charged particles) to shrink tumors and kill malignant cells, and is generally used as part of cancer treatment. Radiation therapy kills malignant cells by damaging their DNA.

[00239] Radiation therapy can be delivered to a patient in several ways. For example, radiation can be delivered from an external source, such as a machine outside the patient's body, as in external beam radiation therapy. External beam radiation therapy for the treatment of cancer uses a radiation source that is external to the patient, typically either a radioisotope, such as ^{60}Co, ^{137}Cs, or a high energy x-ray source, such as a linear accelerator. The external source produces a collimated beam directed into the patient to the tumor site. External-source radiation therapy avoids some of the problems of internal-source radiation therapy, but it undesirably and necessarily irradiates a significant volume of non-tumorous or healthy tissue in the path of the radiation beam along with the tumorous tissue.

[00240] The adverse effect of irradiating of healthy tissue can be reduced, while maintaining a given dose of radiation in the tumorous tissue, by projecting the external radiation beam into the patient at a variety of "gantry" angles with the beams converging on the tumor site. The particular volume elements of healthy tissue, along the path of the

radiation beam, change, reducing the total dose to each such element of healthy tissue during the entire treatment.

[00241] The irradiation of healthy tissue also can be reduced by tightly collimating the radiation beam to the general cross section of the tumor taken perpendicular to the axis of the radiation beam. Numerous systems exist for producing such a circumferential collimation, some of which use multiple sliding shutters which, piecewise, can generate a radio-opaque mask of arbitrary outline.

[00242] For administration of external beam radiation, the amount can be at least about 1 Gray (Gy) fractions at least once every other day to a treatment volume. In a particular embodiment, the radiation is administered in at least about 2 Gray (Gy) fractions at least once per day to a treatment volume. In another particular embodiment, the radiation is administered in at least about 2 Gray (Gy) fractions at least once per day to a treatment volume for five consecutive days per week. In another particular embodiment, radiation is administered in 10 Gy fractions every other day, three times per week to a treatment volume. In another particular embodiment, a total of at least about 20 Gy is administered to a patient in need thereof. In another particular embodiment, at least about 30 Gy is administered to a patient in need thereof. In another particular embodiment, at least about 40 Gy is administered to a patient in need thereof.

[00243] Typically, the patient receives external beam therapy four or five times a week. An entire course of treatment usually lasts from one to seven weeks depending on the type of cancer and the goal of treatment. For example, a patient can receive a dose of 2 Gy/day over 30 days.

[00244] Internal radiation therapy is localized radiation therapy, meaning the radiation source is placed at the site of the tumor or affected area. Internal radiation therapy can be delivered by placing a radiation source inside or next to the area requiring treatment. Internal radiation therapy is also called brachytherapy. Brachytherapy includes intercavitary treatment and interstitial treatment. In intracavitary treatment, containers that hold radioactive sources are put in or near the tumor. The sources are put into the body cavities. In interstitial treatment, the radioactive sources alone are put into the tumor. These radioactive sources can stay in the patient permanently. Typically, the radioactive sources are removed from the patient after several days. The radioactive sources are in containers.

[00245] There are a number of methods for administration of a radiopharmaceutical agent. For example, the radiopharmaceutical agent can be administered by targeted delivery or by systemic delivery of targeted radioactive conjugates, such as a radiolabeled antibody, a radiolabeled peptide and a liposome delivery system. In one particular embodiment of targeted delivery, the radiolabelled pharmaceutical agent can be a radiolabelled antibody. See, for example, Ballangrud A. M., *et al. Cancer Res.*, 2001; 61:2008-2014 and Goldenber, D.M. *J. Nucl. Med.*, 2002; 43(5):693-713, the contents of which are incorporated by reference herein.

[00246] In another particular embodiment of targeted delivery, the radiopharmaceutical agent can be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. See, for example, Emfietzoglou D, Kostarelos K, Sgouros G. An analytical dosimetry study for the use of radionuclide-liposome conjugates in internal radiotherapy. J Nucl Med 2001; 42:499-504, the contents of which are incorporated by reference herein.

[00247] In yet another particular embodiment of targeted delivery, the radiolabeled pharmaceutical agent can be a radiolabeled peptide. See, for example, Weiner RE, Thakur ML. Radiolabeled peptides in the diagnosis and therapy of oncological diseases. Appl Radiat Isot 2002 Nov;57(5):749-63, the contents of which are incorporated by reference herein.

[00248] In addition to targeted delivery, brachytherapy can be used to deliver the radiopharmaceutical agent to the target site. Brachytherapy is a technique that puts the radiation sources as close as possible to the tumor site. Often the source is inserted directly into the tumor. The radioactive sources can be in the form of wires, seeds or rods. Generally, cesium, iridium or iodine are used.

[00249] Systemic radiation therapy is another type of radiation therapy and involves the use of radioactive substances in the blood. Systemic radiation therapy is a form of targeted therapy. In systemic radiation therapy, a patient typically ingests or receives an injection of a radioactive substance, such as radioactive iodine or a radioactive substance bound to a monoclonal antibody.

[00250] A "radiopharmaceutical agent," as defined herein, refers to a pharmaceutical agent which contains at least one radiation-emitting radioisotope. Radiopharmaceutical agents are routinely used in nuclear medicine for the diagnosis and/or therapy of various diseases. The radiolabelled pharmaceutical agent, for example, a radiolabelled antibody, contains a radioisotope (RI) which serves as the radiation source. As contemplated herein, the term "radioisotope" includes metallic and non-metallic radioisotopes. The radioisotope is chosen based on the medical application of the radiolabeled pharmaceutical agents. When the radioisotope is a metallic radioisotope, a chelator is typically employed to bind the metallic radioisotope to the rest of the molecule. When the radioisotope is a non-metallic radioisotope, the non-metallic radioisotope is typically linked directly, or via a linker, to the rest of the molecule.

[00251] As used herein, a "metallic radioisotope" is any suitable metallic radioisotope useful in a therapeutic or diagnostic procedure *in vivo* or *in vitro*. Suitable metallic radioisotopes include, but are not limited to: Actinium-225, Antimony-124, Antimony-125, Arsenic-74, Barium-103, Barium-140, Beryllium-7, Bismuth-206, Bismuth-207, Bismuth212, Bismuth213, Cadmium-109, Cadmium-115m, Calcium-45, Cerium-139, Cerium-141, Cerium-144, Cesium-137, Chromium-51, Cobalt-55, Cobalt-56, Cobalt-57, Cobalt-58, Cobalt-60, Cobalt-64, Copper-60, Copper-62, Copper-64, Copper-67, Erbium-169, Europium-152, Gallium-64, Gallium-67, Gallium-68, Gadolinium153, Gadolinium-157 Gold-195, Gold-199, Hafnium-175, Hafnium-175-181, Holmium-166, Indium-110, Indium-111, Iridium-192, Iron 55, Iron-59, Krypton85, Lead-203, Lead-210, Lutetium-177, Manganese-54, Mercury-197, Mercury203, Molybdenum-99, Neodymium-147, Neptunium-237, Nickel-63, Niobium95, Osmium-185+191, Palladium-103, Palladium-109, Platinum-195m, Praseodymium-143, Promethium-147, Promethium-149, Protactinium-233, Radium-226, Rhenium-186, Rhenium-188, Rubidium-86, Ruthenium-97, Ruthenium-103, Ruthenium-105, Ruthenium-106, Samarium-153, Scandium-44, Scandium-46, Scandium-47, Selenium-75, Silver-110m, Silver-111, Sodium-22, Strontium-85, Strontium-89, Strontium-90, Sulfur-35, Tantalum-182, Technetium-99m, Tellurium-125, Tellurium-132, Thallium-204, Thorium-228, Thorium-232, Thallium-170, Tin-113, Tin-114, Tin-117m, Titanium-44, Tungsten-185, Vanadium-48, Vanadium-49, Ytterbium-169, Yttrium-86, Yttrium-88, Yttrium-90, Yttrium-91, Zinc-65, Zirconium-89, and Zirconium-95.

[00252] As used herein, a "non-metallic radioisotope" is any suitable nonmetallic radioisotope (non-metallic radioisotope) useful in a therapeutic or diagnostic procedure *in vivo* or *in vitro*. Suitable non-metallic radioisotopes include, but are not limited to: Iodine-131, Iodine-125, Iodine-123, Phosphorus-32, Astatine-211, Fluorine-18, Carbon-11, Oxygen-15, Bromine-76, and Nitrogen-13.

[00253] Identifying the most appropriate isotope for radiotherapy requires weighing a variety of factors. These include tumor uptake and retention, blood clearance, rate of radiation delivery, half-life and specific activity of the radioisotope, and the feasibility of large-scale production of the radioisotope in an economical fashion. The key point for a therapeutic radiopharmaceutical is to deliver the requisite amount of radiation dose to the tumor cells and to achieve a cytotoxic or tumoricidal effect while not causing unmanageable side-effects.

[00254] It is preferred that the physical half-life of the therapeutic radioisotope be similar to the biological half-life of the radiopharmaceutical at the tumor site. For example, if the half-life of the radioisotope is too short, much of the decay will have occurred before the radiopharmaceutical has reached maximum target/background ratio. On the other hand, too long a half-life could cause unnecessary radiation dose to normal tissues. Ideally, the radioisotope should have a long enough half-life to attain a minimum dose rate and to irradiate all the cells during the most radiation sensitive phases of the cell cycle. In addition, the half-life of a radioisotope has to be long enough to allow adequate time for manufacturing, release, and transportation.

[00255] Other practical considerations in selecting a radioisotope for a given application in tumor therapy are availability and quality. The purity has to be sufficient and reproducible, as trace amounts of impurities can affect the radiolabeling and radiochemical purity of the radiopharmaceutical.

[00256] The target receptor sites in tumors are typically limited in number. As such, it is preferred that the radioisotope have high specific activity. The specific activity depends primarily on the production method. Trace metal contaminants must be minimized as they often compete with the radioisotope for the chelator and their metal complexes compete for receptor binding with the radiolabeled chelated agent.

[00257] The type of radiation that is suitable for use in the methods of the present invention can vary. For example, radiation can be electromagnetic or particulate in nature. Electromagnetic radiation useful in the practice of this invention includes, but is not limited to, x-rays and gamma rays. Particulate radiation useful in the practice of this invention includes, but is not limited to, electron beams (beta particles), protons beams, neutron beams, alpha particles, and negative pi mesons. The radiation can be delivered using conventional radiological treatment apparatus and methods, and by intraoperative and stereotactic methods. Additional discussion regarding radiation treatments suitable for use in the practice of this invention can be found throughout Steven A. Leibel et al., Textbook of Radiation Oncology (1998) (publ. W. B. Saunders Company), and particularly in Chapters 13 and 14. Radiation can also be delivered by other methods such as targeted delivery, for example by radioactive "seeds," or by systemic delivery of targeted radioactive conjugates. J. Padawer *et al.*, Combined Treatment with Radioestradiol lucanthone in Mouse C3HBA Mammary Adenocarcinoma and with Estradiol lucanthone in an Estrogen Bioassay, Int. J. Radiat. Oncol. Biol. Phys. 7:347-357 (1981). Other radiation delivery methods can be used in the practice of this invention.

[00258] For tumor therapy, both α and β-particle emitters have been investigated. Alpha particles are particularly good cytotoxic agents because they dissipate a large amount of energy within one or two cell diameters. The β-particle emitters have relatively long penetration range (2-12 mm in the tissue) depending on the energy level. The long-range penetration is particularly important for solid tumors that have heterogeneous blood flow and/or receptor expression. The β-particle emitters yield a more homogeneous dose distribution even when they are heterogeneously distributed within the target tissue.

[00259] In a particular embodiment, therapeutically effective amounts of the compounds and compositions described herein are administered in combination with a therapeutically effective amount of radiation therapy to treat cancer (*e.g.*, lung cancer, such as non-small cell lung cancer). The amount of radiation necessary can be determined by one of skill in the art based on known doses for a particular type of cancer. See, for example, Cancer Medicine 5th ed., Edited by R.C. Bast et al., July 2000, BC Decker.

[00260] The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Examples. These

Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

[00261]

EXEMPLIFICATION

Abbreviations

Ac	acetyl
ACN	acetonitrile
Boc	*tert*-butoxy carbonyl
CI	Chemical ionization
DIPEA	N,N-Diisopropyl ethylamine
DMF	Dimethylformamide
DMSO	dimethylsulfoxide
dppf	(diphenylphosphino)ferrocene
EDCI	3-(ethyliminomethyleneamino)-N,N-dimethylpropan-1-amine
EDTA	ethylenediamine tetraacetic acid
EI	electron impact ionization
equiv(s).	equivalent(s)
EtOAc	ethyl acetate
EtOH	Ethanol
Et	Ethyl
g	gram(s)
h	hour(s)
HATU	(Dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
LAH	lithium aluminum hydride
LCMS	liquid chromatography mass spectrometry
LRMS	low resolution mass spectrometry

Me	methyl
mg	milligram(s)
min	Minute(s)
mL	milliliter(s)
Ms	mesityl or mesyl
NMR	Nuclear magnetic resonance
PBS	phosphate-buffered saline
PEG	polyethylene glycol
Ph	phenyl
RT, rt, r.t.	Room temperature
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
T3P	Propylphosphonic anhydride (available from Archimica)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t_R	Retention time

[00262] Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of transformations are given below, and it is to be understood that the described transformations

are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994).

[00263] Techniques for purification of intermediates and final products include for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by the one skilled in the art. The definitions of substituents and groups are as in formula I except where defined differently. The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C. The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent a temperature at or above the boiling point of named solvent.

[00264] A typical LCMS method used to characterize synthesized compounds is described below:

Mobile phase: A: water (0.01% TFA); B: CAN (0.01% TFA

Gradient: 5% B increase to 100% B within 1.2 min, 100% B for 1.3 min

Flow Rate: 2.0 mL/min

Column: SunFire C18, 4.6*50mm, 3.5 μm

Column Temperature: 50 °C

Detection: UV (214, 254 nm) and MS (ESI, Pos mode, 110-1000 amu).

Unless otherwise indicated, retention times reported for synthesized compounds were obtained using this LCMS method.

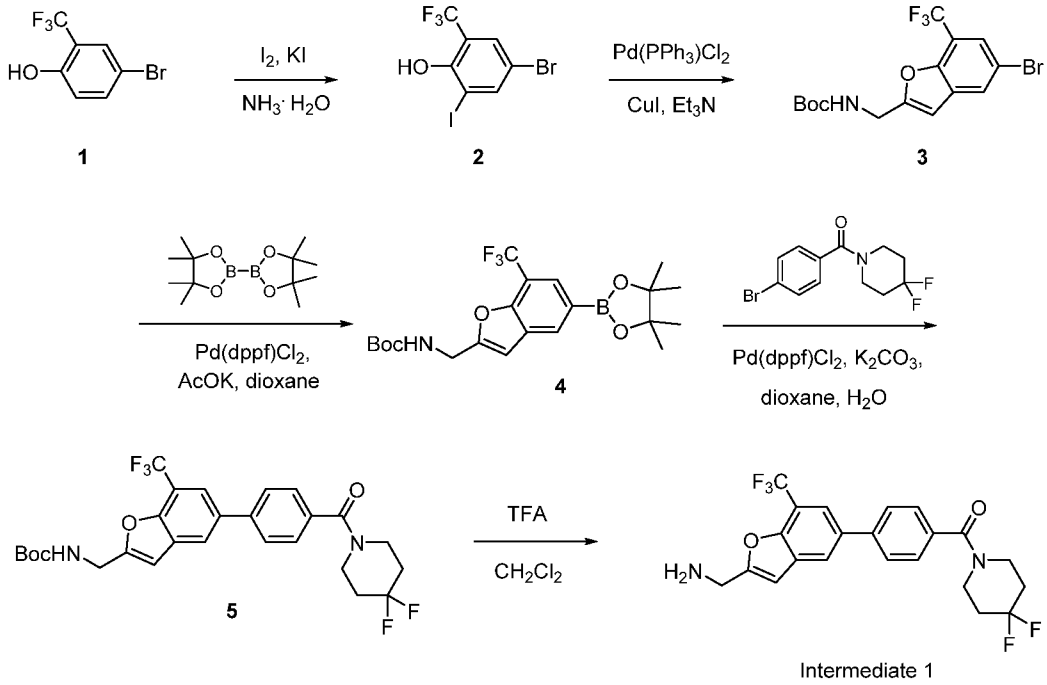
[00265] It is understood that compounds for which a specific synthesis is not shown can be made in accordance with the general procedures disclosed herein.

EXAMPLIFICATION

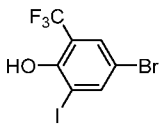
Synthetic Methods

Synthesis of Intermediates.

[00266] Intermediate 1: (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

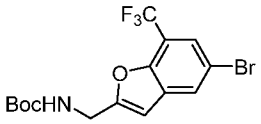


4-Bromo-2-iodo-6-(trifluoromethyl) phenol (2).



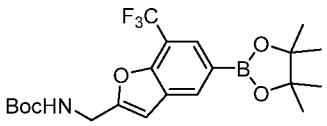
4-Bromo-2-(trifluoromethyl)phenol (250 g, 1041.7 mmol) (1), was dissolved in 3 L of NH_4OH. A solution of KI (518.8 g, 3125.1 mmol) and I_2 (264.6 g, 1041.7 mmol) in 600 mL of H_2O was added to the reaction mixture and stirred at room temperature up to 16 h. The reaction mixture was cooled to 0 °C (ice bath), and neutralized with HCl (conc.) to pH ~ 6-7. The mixture was extracted with EtOAc (1.5 L X 3) and the combined organic fractions were washed with sat. aq. sodium bisulfite solution, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 365 g of the 4-bromo-2-iodo-6-(trifluoromethyl)phenol (2) (96% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.66 (s, 1H), 5.82 (s, 1H). LCMS: t_R = 1.85 min.

tert-Butyl (5-bromo-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (3).



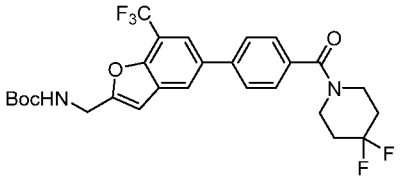
4-Bromo-2-iodo-6-(trifluoromethyl)phenol (260 g, 710 mmol) (2), *tert*-butyl prop-2-ynylcarbamate (110 g, 710 mmol), $Pd(PPh_3)Cl_2$ (30 g, 43 mmol), CuI (8.2 g, 43 mmol), and K_2CO_3 (196 g, 1420 mmol) were added to 1.6 L of ethyl acetate. The reaction mixture was degassed and then heated to reflux under nitrogen atmosphere for 6 h. After cooling to room temperature the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (20% EtOAc/petroleum ether) to yield 140 g of *tert*-butyl (5-bromo-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (3) (50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.76 (s, 1H), 7.60 (s, 1H), 6.83 (s, 1H), 4.34 (d, J = 6 Hz, 2H), 1.35 (s, 9H). LCMS: *m/z* 338 [M-55]$^+$; t_R = 1.99 min.

tert-Butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (4) .



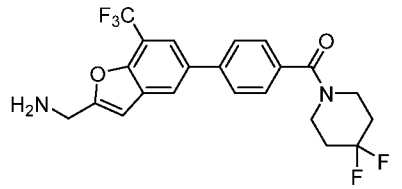
tert-Butyl (5-bromo-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate **(3)** (140 g, 356 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (100 g, 392 mmol), $Pd(dppf)Cl_2$ (30 g, 36 mmol), and potassium acetate (70 g, 712 mmol) were added to of dioxane (1.5 L). The reaction mixture was degassed and then heated at 100 ^{o}C under nitrogen atmosphere for 6 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (5-20% EtOAc/petroleum ether) to yield 143 g of *tert*-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (4) (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.88 (s, 1H), 6.59 (s, 1H), 4.97 (s, 1H), 4.42 (d, J = 5 Hz, 2H), 1.40 (s, 9H), 1.30 (s, 12H). LCMS: *m/z* 464.1 [M+Na]$^+$, t_R = 2.05 min.

tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (5).



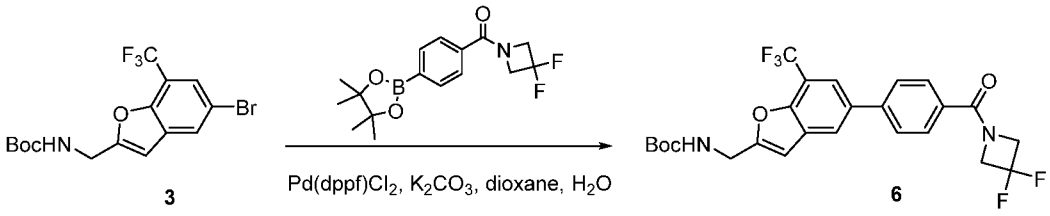
A mixture of *tert*-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (4) (4 g, 9 mmol), (4-bromophenyl)(4,4-difluoropiperidin-1-yl)methanone (prepared as described in WO2007124254) (2.75 g, 9 mmol), $Pd(dppf)Cl_2$ (811 mg, 0.9 mmol) and K_2CO_3 (2.48 g, 18 mmol) in 40 mL of dioxane and 4 mL of H_2O was stirred at 100 °C under nitrogen atmosphere for 4 h. The mixture was extracted with EtOAc (40 mL X 3). The combined organic fraction were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (20-50% EtOAc/petroleum ether) to give 3.3 g of *tert*-butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (5) (68% yield). LCMS: *m/z* 539.2 $[M+H]^+$, t_R = 1.78 min.

Intermediate 1: (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

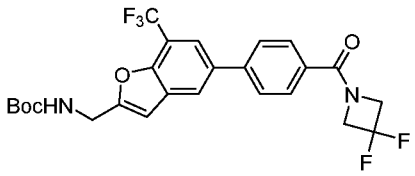


tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (5) (3.3 g, 6.1 mmol) was dissolved in DCM (16 mL). TFA (4 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and concentrated under reduced pressure to give 3.4 g of crude (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 1), which was used without further purification. Yield (100%). LCMS: *m/z* 439.1 $[M+H]^+$; t_R = 1.37 min.

[00267] Intermediate 2: (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(3,3-difluoroazetidin-1-yl)methanone.

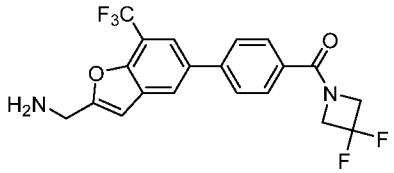


tert-Butyl (5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (6).



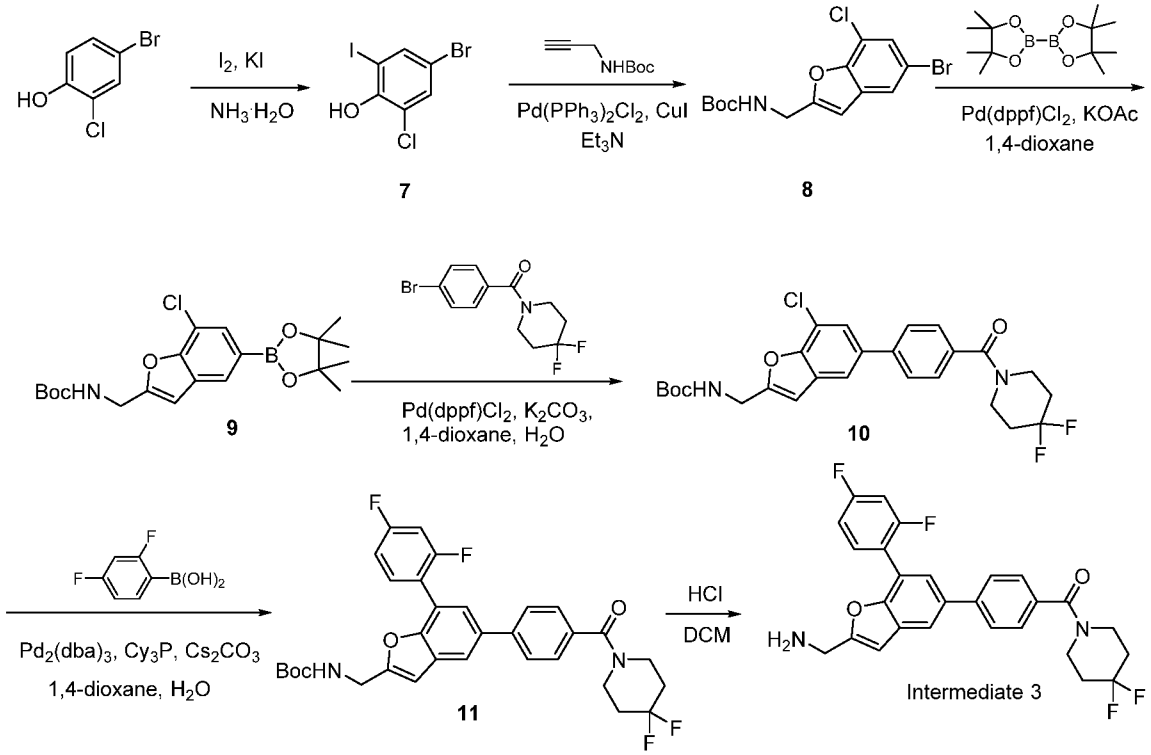
A mixture of (3,3-difluoroazetidin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (prepared as described in WO2014015088) (1.48 g, 4.58 mmol), *tert*-butyl (5-bromo-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (3) (1.8 g, 4.58 mmol), $Pd(dppf)Cl_2$ (375 mg, 0.46 mmol) and K_2CO_3 (1.26 g, 9.2 mmol) in 30 mL of dioxane and 5 mL of H_2O was stirred at 100 °C under nitrogen atmosphere for 1 h. The mixture was extracted with EtOAc (20 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure to give the crude product which was purified by silica gel chromatography (25% EtOAc / petroleum ether) to give 2.1 g of *tert*-butyl (5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate 6) (90% yield). LCMS: *m/z* 511.1 $[M+H]^+$; t_R = 1.87 min.

Intermediate 2: (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(3,3-difluoroazetidin-1-yl)methanone.

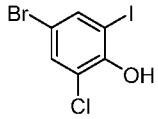


tert-Butyl (5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methylcarbamate (6) (2.1 g, 4.1 mmol) was dissolved in CH_2Cl_2 (20 mL). TFA (3 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and concentrated under reduced pressure to give the crude (4-(2-(aminomethyl)-7-(trifluoromethyl)benzofuran-5-yl)phenyl)(3,3-difluoroazetidin-1-yl)methanone (Intermediate 2), which was used without further purification. Yield (100%). LCMS: *m/z* 411.0 $[M+H]^+$; t_R = 1.31 min.

[00268] Intermediate 3: (4-(2-(aminomethyl)-7-(2,4-difluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

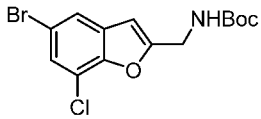


4-Bromo-2-chloro-6-iodophenol (7).



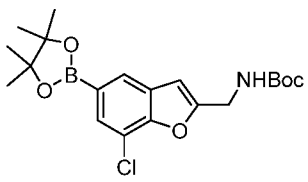
4-Bromo-2-chlorophenol (82.8 g, 400 mmol) was dissolved in 2 L of NH_4OH. A solution of KI (199 g, 1200 mmol) and I_2 (101.2 g, 400 mmol) in 1 L of H_2O was added and the reaction mixture was stirred at 30 °C for 4 h. The mixture was cooled to 0 °C, HCl (conc.) was added to the reaction mixture to a pH = 7. The mixture was extracted with EtOAc (900 mL X 3). The combined organic fractions were washed with sat. sodium bisulfite and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 119 g of 4-bromo-2-chloro-6-iodophenol (7) which was used without further purification (90% yield). LCMS: t_R = 1.76 min.

tert-Butyl (5-bromo-7-chlorobenzofuran-2-yl)methylcarbamate (8).



A mixture of 4-bromo-2-chloro-6-iodophenol (7) (50 g, 0.15 mol), *tert*-butyl prop-2-ynylcarbamate (26 g, 0.17 mol), $Pd(PPh_3)_2Cl_2$ (11 g, 25 mmol) and CuI (5.7 g, 30 mmol) in Et_3N (500 mL) was heated at 80 °C under nitrogen atmosphere for 5 h. After cooling to room temperature the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to yield *tert*-butyl (5-bromo-7-chlorobenzofuran-2-yl)methylcarbamate (35.4 g, 65% yield). LCMS: *m/z* 305.9 $[M-55]^+$; t_R = 1.89 min.

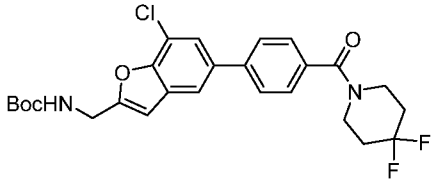
tert-Butyl (7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-2-yl)methylcarbamate (9).



A mixture of *tert*-butyl (5-bromo-7-chlorobenzofuran-2-yl)methylcarbamate (8) (34 g, 94 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (26 g, 102 mmol), $Pd(dppf)Cl_2$ (7.7 g, 9.4 mmol) and potassium acetate (19 g, 189 mmol) in dioxane (100 mL) was heated at 100 °C under nitrogen atmosphere for 8 h. After cooling, the reaction mixture

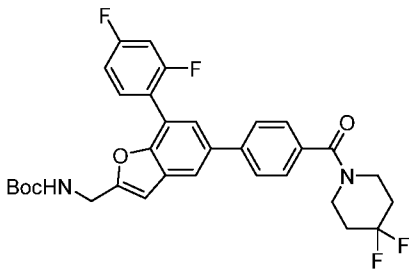
was used directly in the next reaction without further purification. LCMS: *m/z* 430.0 $[M+Na]^+$, t_R = 2.22 min.

tert-Butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (10).



(4-Bromophenyl)(4,4-difluoropiperidin-1-yl)methanone (20 g, 66 mmol) was added to the solution of *tert*-butyl (7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-2-yl)methylcarbamate (9) obtained above. $Pd(dppf)Cl_2$ (4.8 g, 6.6 mmol), potassium carbonate (18 g, 0.13 mol) and water (25 mL) were then added. The reaction mixture was heated at 85 ^oC under nitrogen atmosphere for 16 h. The mixture was extracted with EtOAc (150 mL X 3). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography (40% EtOAc in petroleum ether) to give *tert*-butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (10) (22 g, 66% yield). LCMS: *m/z* 505.2 $[M+H]^+$, t_R = 2.00 min.

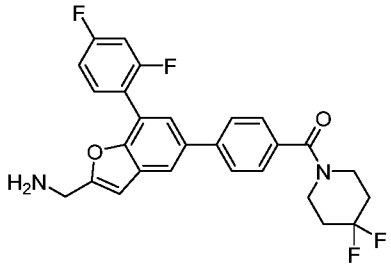
tert-Butyl (7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (11).



tert-Butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (10) (12 g, 23.8 mmol), 2,4-difluorophenylboronic acid (7.5 g, 47.6 mmol), $Pd_2(dba)_3$ (2.5 g, 2.4 mmol), tricyclohexylphosphine (1.3 g, 4.8 mmol) and Cs_2CO_3 (15.5 g, 47.6 mmol) were added to a mixture of 1,4-dioxane (300 mL) and water (30 mL). The mixture was degassed and then heated at 100 °C for 12 h. The reaction mixture was

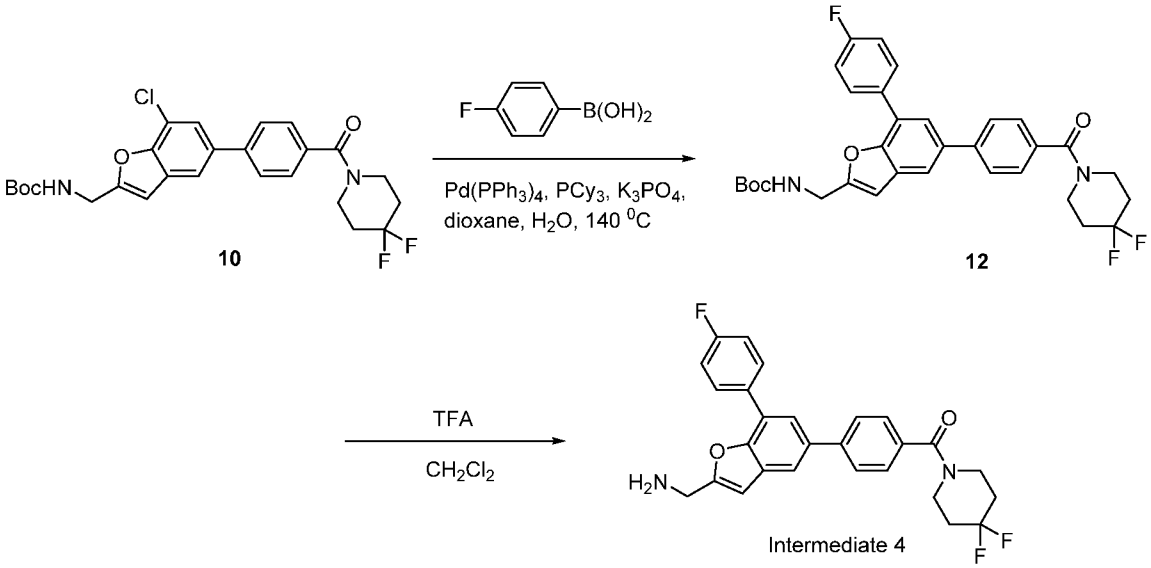
concentrated and purified by silica gel chromatography (30% EtOAc/petroleum ether) to give *tert*-butyl (7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (11) (11 g, 87% yield). LCMS: *m/z* 583.0 $[M+H]^+$; t_R = 1.85 min.

Intermediate 3: (4-(2-(Aminomethyl)-7-(2,4-difluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

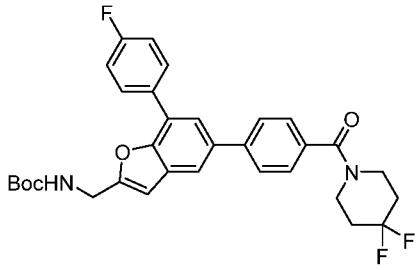


tert-Butyl (7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (11) (11 g, 22.8 mmol) was dissolved in DCM (100 mL) and HCl in dioxane (40 mL, 160 mmol, 4 N) was added dropwise at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to give the crude (4-(2-(aminomethyl)-7-(2,4-difluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 3), which was used without further purification. (10 g, 99% yield). LCMS: *m/z* 483.0 $[M+H]^+$; t_R = 1.67 min.

[00269] Intermediate 4: (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

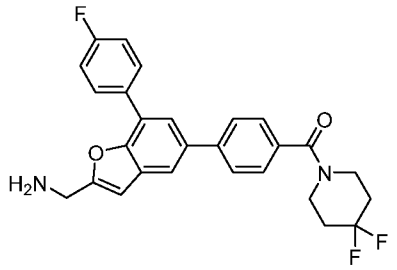


tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (12).



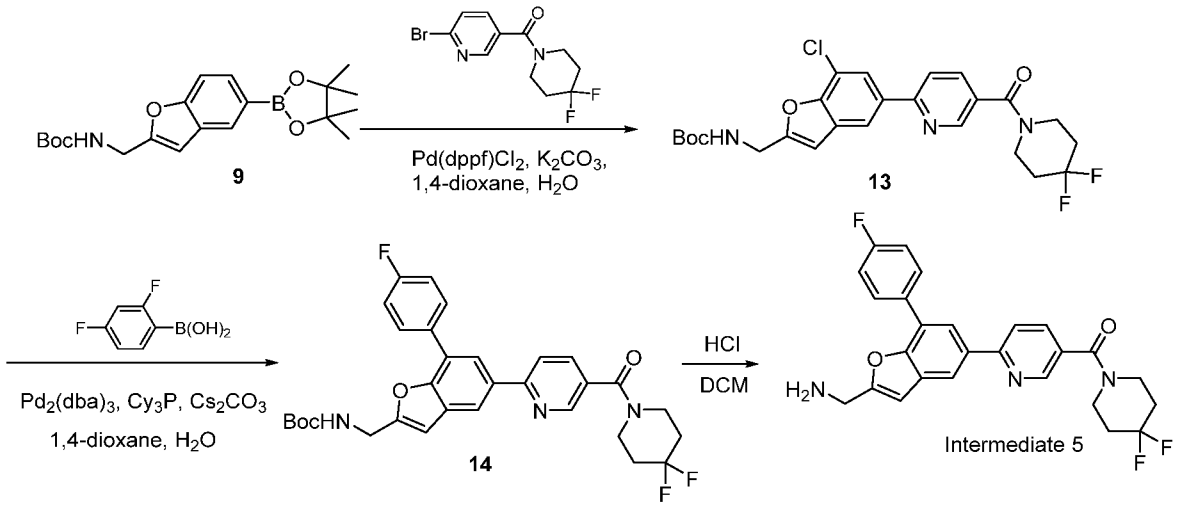
tert-Butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methylcarbamate (10) (400 mg, 0.8 mmol), 4-fluorophenylboronic acid (220 mg, 1.6 mmol), $Pd(PPh_3)_4$ (180 mg, 0.16 mmol), tricyclohexylphosphine (66 mg, 0.24 mmol) and K_3PO_4 (336 mg, 1.6 mmol) were added to a mixture of dioxane (6 mL) and water (0.6 mL). The mixture was degassed and then heated under microwave irradiation at 140 °C for 1 h. The reaction mixture was cooled to room temperature, poured into 10 mL of water, and extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (50% EtOAc/petroleum ether) to give *tert*-butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (12) (230 mg, 50% yield). LCMS: *m/z* 565.2 $[M+H]^+$; t_R = 2.29 min.

Intermediate 4: (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

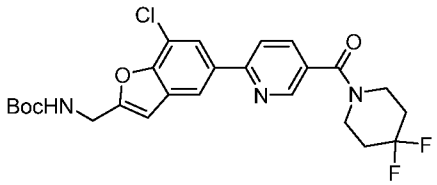


tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (12) (115 mg, 0.25 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added dropwise at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure to give (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 4), which was used without further purification (100 mg, 100% yield). LCMS: *m/z* 465.1 $[M+H]^+$; t_R = 1.61 min.

[00270] Intermediate 5: (6-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)pyridin-3-yl)(4,4-difluoropiperidin-1-yl)methanone.

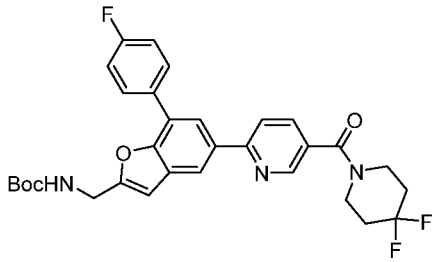


tert-Butyl (7-chloro-5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)benzofuran-2-yl)methylcarbamate (13).



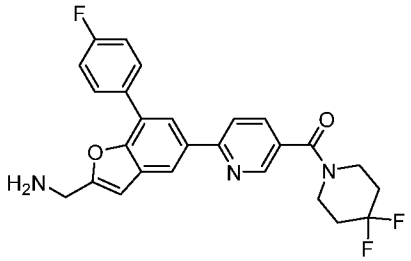
(6-Bromopyridin-3-yl)(4,4-difluoropiperidin-1-yl)methanone (20 g, 66 mmol) was added to a solution of *tert*-butyl (7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-2-yl)methylcarbamate (9). $Pd(dppf)Cl_2$ (4.8 g, 6.6 mmol), potassium carbonate (18 g, 0.13 mol) and water (25 mL) were then added. The reaction mixture was heated at 85 °C under nitrogen atmosphere for 16 h. The mixture was extracted with EtOAc (150 mL X 3). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (40% EtOAc/petroleum ether) to give *tert*-butyl (7-chloro-5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)benzofuran-2-yl)methylcarbamate (13) (20 g, 60% yield). LCMS: *m/z* 506.2 $[M+H]^+$, t_R = 2.00 min.

tert-Butyl (5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (14).



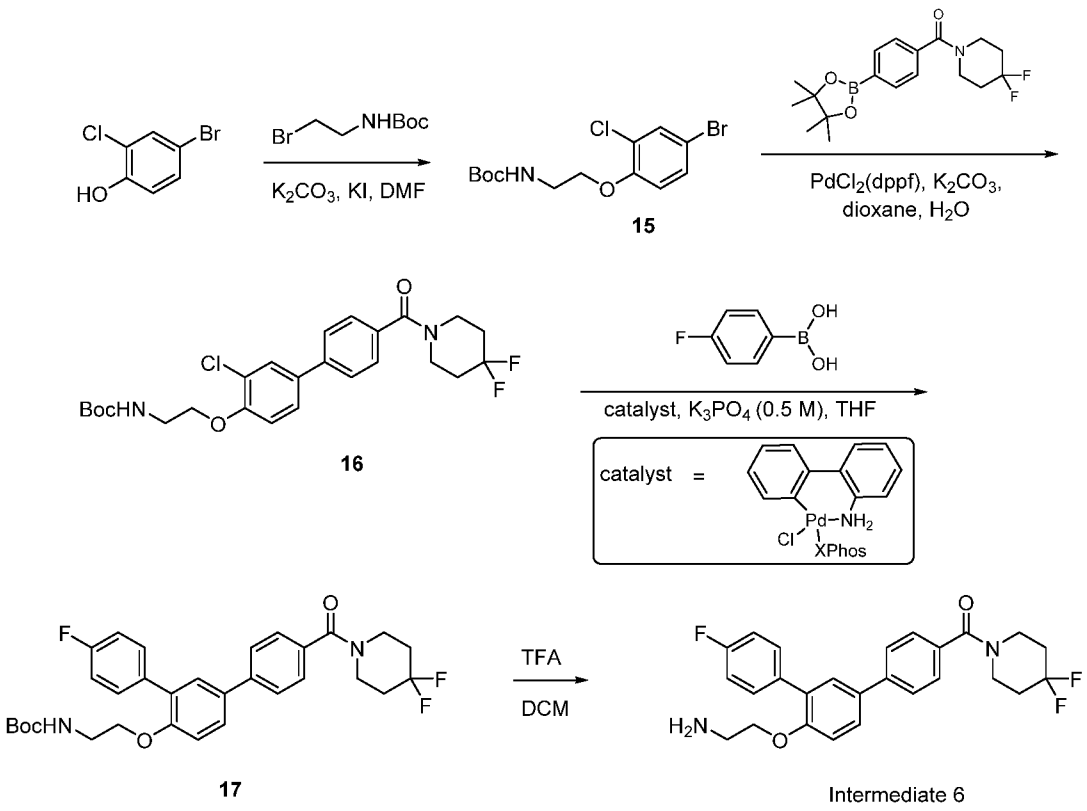
tert-Butyl (7-chloro-5-(5-(morpholine-4-carbonyl)pyridin-2-yl)benzofuran-2-yl)methylcarbamate (13) (200 mg, 0.4 mmol), 4-fluorophenylboronic acid (110 mg, 0.8 mmol), $Pd(PPh_3)_4$ (91 mg, 0.08 mmol), tricyclohexylphosphine (33 mg, 0.12 mmol) and K_3PO_4 (168 mg, 0.8 mmol) were added to a mixture of dioxane (3 mL) and water (0.3 mL). The reaction mixture was degassed and then heated under microwave irradiation to 140 °C for 1 h. The reaction mixture was cooled to room temperature, poured into 5 mL of water, and extracted with EtOAc (10 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (50% EtOAc/petroleum ether) to give *tert*-butyl (5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (14) (115 mg, 51% yield). LCMS: *m/z* 566.1 $[M+H]^+$; t_R = 1.77 min.

Intermediate 5: (6-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)pyridin-3-yl)(4,4-difluoropiperidin-1-yl)methanone.

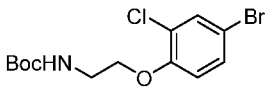


tert-Butyl (5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (14) (115 mg, 0.25 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure to give (6-(2-(aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)pyridin-3-yl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 5) , which was used without further purification (95 mg, 100% yield). LCMS: *m/z* 466.1 $[M+H]^+$; t_R = 1.32 min.

[00271] Intermediate 6: (4'-(2-aminoethoxy)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone.

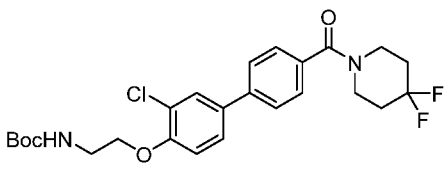


tert-Butyl 2-(4-bromo-2-chlorophenoxy)ethylcarbamate (15).



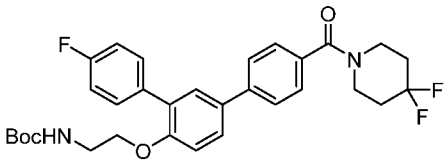
4-Bromo-2-chlorophenol (2.06 g, 10 mmol) was dissolved in DMF (50 mL). K_2CO_3 (2.76 g, 20 mmol), *tert*-butyl 2-bromoethylcarbamate (4.46 g, 20 mmol) and KI (0.33 g, 2 mmol) were added and stirred at 25 °C for 16 h. The reaction mixture was transferred into iced water and extracted with ethyl acetate (50 mL x 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 3.2 g of *tert*-butyl 2-(4-bromo-2-chlorophenoxy)ethylcarbamate (15), which was used without further purification (91% yield). LCMS: *m/z* 252.0 $[M+H\text{-}Boc]^+$, t_R = 2.14 min.

tert-Butyl 2-(3-chloro-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (16).



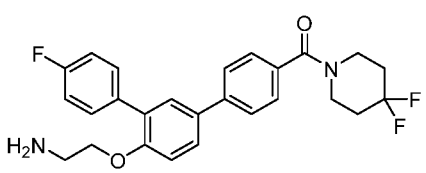
tert-Butyl 2-(4-bromo-2-chlorophenoxy)ethylcarbamate (15) (1.4 g, 4 mmol) was dissolved in a mixture of dioxane (30 mL) and H_2O (8 mL) and (4,4-difluoropiperidin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (1.4 g, 4 mmol), $Pd(dppf)Cl_2$ (650 mg, 0.8 mmol), K_2CO_3 (1.1 g, 8 mmol) were added at room temperature. The mixture was degassed and heated at 90 ^oC under nitrogen atmosphere for 2 h. After cooling to room temperature, the reaction mixture was transferred into water, extracted with ethyl acetate (20 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (10-50% ethyl acetate/petroleum ether) to give 1.2 g of *tert*-butyl 2-(3-chloro-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (16) (51% yield). LCMS: *m/z* 495.1 $[M+H]^+$; t_R = 2.04 min.

tert-Butyl 2-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (17).



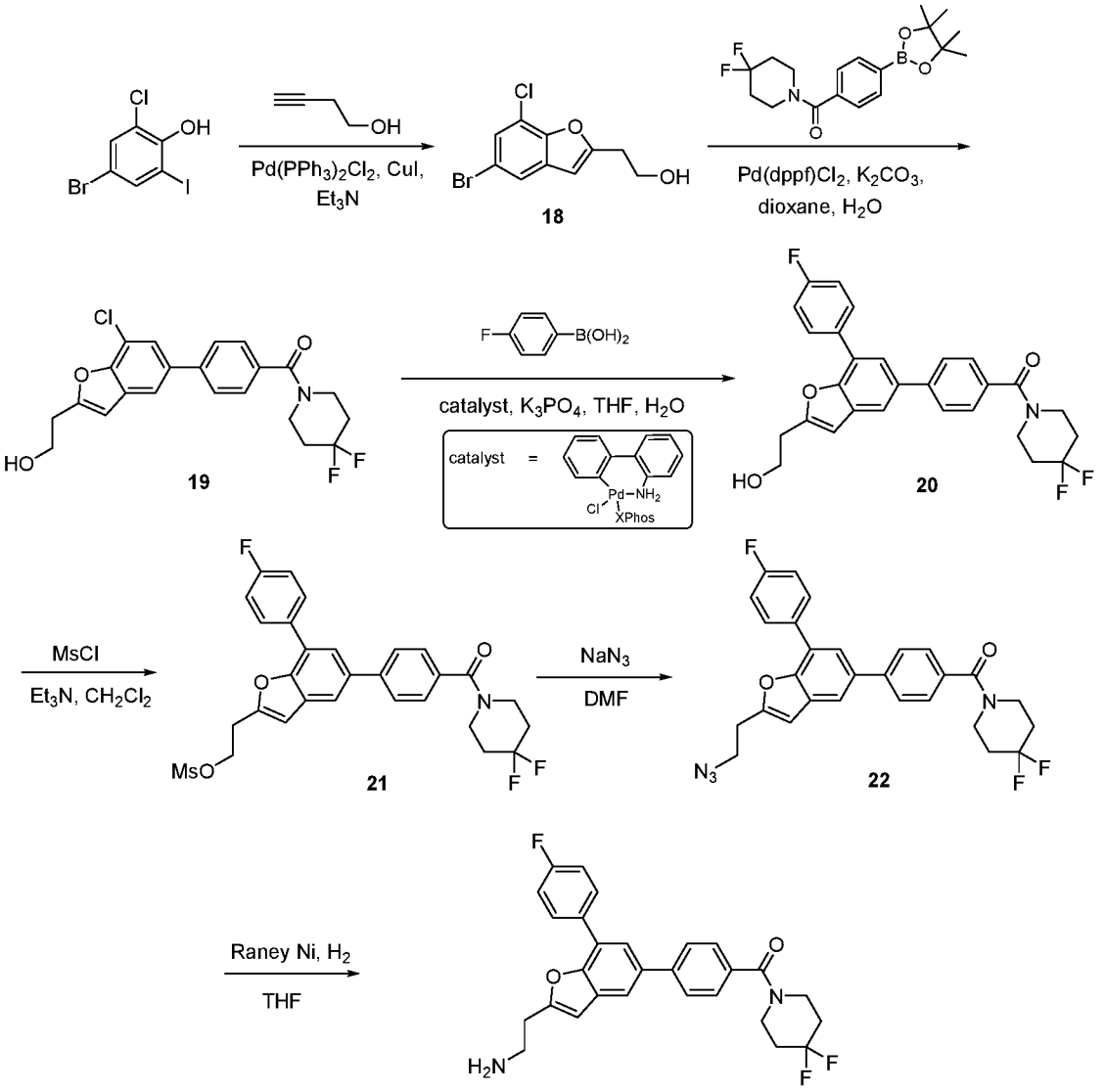
tert-Butyl 2-(3-chloro-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (16) (0.5 g, 1 mmol), 4-fluorophenylboronic acid (210 mg, 1.5 mmol), catalyst (80 mg, 0.1 mmol) and K_3PO_4 (5 mL, 2.5 mmol, 0.5 M aqueous solution) were added to THF (10 mL). The mixture was degassed and then stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to give 472 mg of *tert*-butyl 2-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (17) (84% yield). LCMS: *m/z* 499.2 $[M-55]^+$; t_R = 2.13 min.

Intermediate 6: (4'-(2-aminoethoxy)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone.

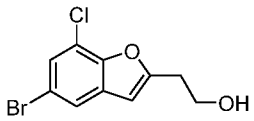


tert-Butyl 2-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethylcarbamate (17) (554 mg, 1 mmol) was dissolved in DCM (32 mL). TFA (8 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, diluted with DCM (50 mL), and neutralized with saturated aqueous $NaHCO_3$ to pH = 7-8. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 450 mg of (4'-(2-aminoethoxy)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 6), which was used without further purification. Yield (99%). LCMS: *m/z* 455.2 $[M+H]^+$; t_R = 1.91 min.

[00272] Intermediate 7: (4-(2-(2-aminoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

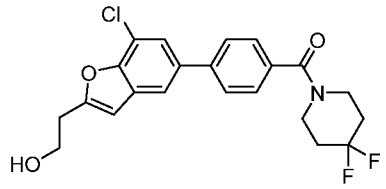


2-(5-Bromo-7-chlorobenzofuran-2-yl)ethanol (18).



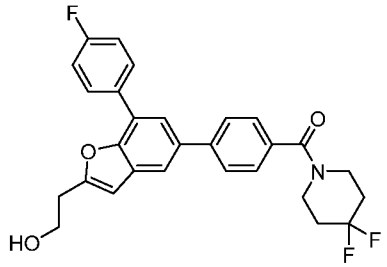
A mixture of 4-bromo-2-chloro-6-iodophenol (5 g, 15 mmol), but-3-yn-1-ol (1.16 g, 16.5 mmol), $Pd(PPh_3)_2Cl_2$ (1 g, 1.5 mmol), CuI (0.28 g, 1.5 mmol) in 50 mL of Et_3N was stirred at 80 °C under nitrogen atmosphere for 7 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (20% EtOAc/petroleum ether) to give 2.6 g of 2-(5-bromo-7-chlorobenzofuran-2-yl)ethanol (18) (63% yield). LCMS: *m/z* 256.7 $[M-OH]^+$; t_R = 1.74 min.

(4-(7-Chloro-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (19).



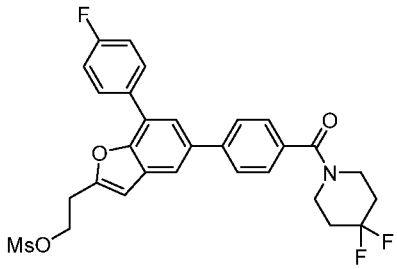
A mixture of 2-(5-bromo-7-chlorobenzofuran-2-yl)ethanol (18) (1.45 g, 5.3 mmol), (4,4-difluoropiperidin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (2.78 g, 7.9 mmol), $Pd(dppf)Cl_2$ (0.38 mg, 0.53 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in dioxane (50 mL) and water (5 mL) was degassed and heated at 100 °C for 3 h. After cooling to room temperature the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (25-100% EtOAc/petroleum ether) to give 1.9 g of (4-(7-chloro-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (19) (86% yield). LCMS: *m/z* 419.8 $[M+H]^+$, t_R = 1.69 min.

(4,4-Difluoropiperidin-1-yl)(4-(7-(4-fluorophenyl)-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)methanone (20).



(4-(7-Chloro-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (19) (1.9 g, 4.5 mmol), 4-fluorophenylboronic acid (0.95 g, 6.8 mmol), catalyst (1 g, 1.36 mmol) and K_3PO_4 (1.9 g, 9 mmol) were added to THF (7 mL) and H_2O (7 mL). The mixture was degassed and stirred at 40 ^oC for 2 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (EtOAc) to give 2.01 g of (4,4-difluoropiperidin-1-yl)(4-(7-(4-fluorophenyl)-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)methanone (20) (93% yield). LCMS: *m/z* 480.8 $[M+H]^+$; t_R = 1.77 min.

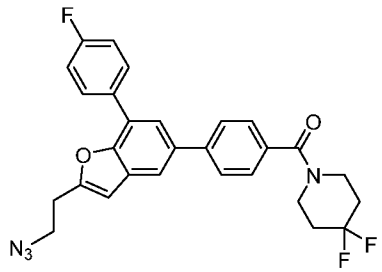
2-(5-(4-(4,4-Difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl methanesulfonate (21).



(4,4-Difluoropiperidin-1-yl)(4-(7-(4-fluorophenyl)-2-(2-hydroxyethyl)benzofuran-5-yl)phenyl)methanone (20) (300 mg, 0.62 mmol) was dissolved in DCM (15 mL). Triethylamine (212 mg, 2.1 mmol) and methane sulfonyl chloride (92 mg, 0.8 mmol) and were added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was transferred into iced water and extracted with DCM (20 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 380 mg of 2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl

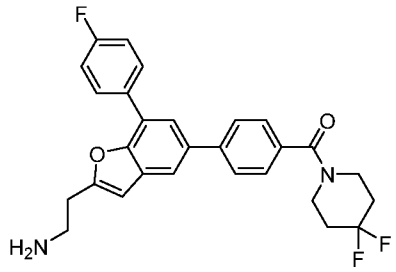
methanesulfonate (21), which was used in the next step without further purification (85% yield). LCMS: *m/z* 558.1 $[M+H]^+$; t_R = 1.81 min.

Synthesis of (4-(2-(2-azidoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (22).



2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl methanesulfonate (21) (380 mg, 0.68 mmol) was dissolved in DMF (15 mL). Sodium azide (53 mg, 0.82 mmol) were added at room temperature. The reaction mixture was stirred at 40 ^oC for 2 h then cooled to room temperature, transferred into ice-water and extracted with ethyl acetate (20 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 316 mg of crude (4-(2-(2-azidoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (22) , which was used without further purification (92% yield). LCMS: *m/z* 505.1 $[M+H]^+$; t_R = 1.94 min.

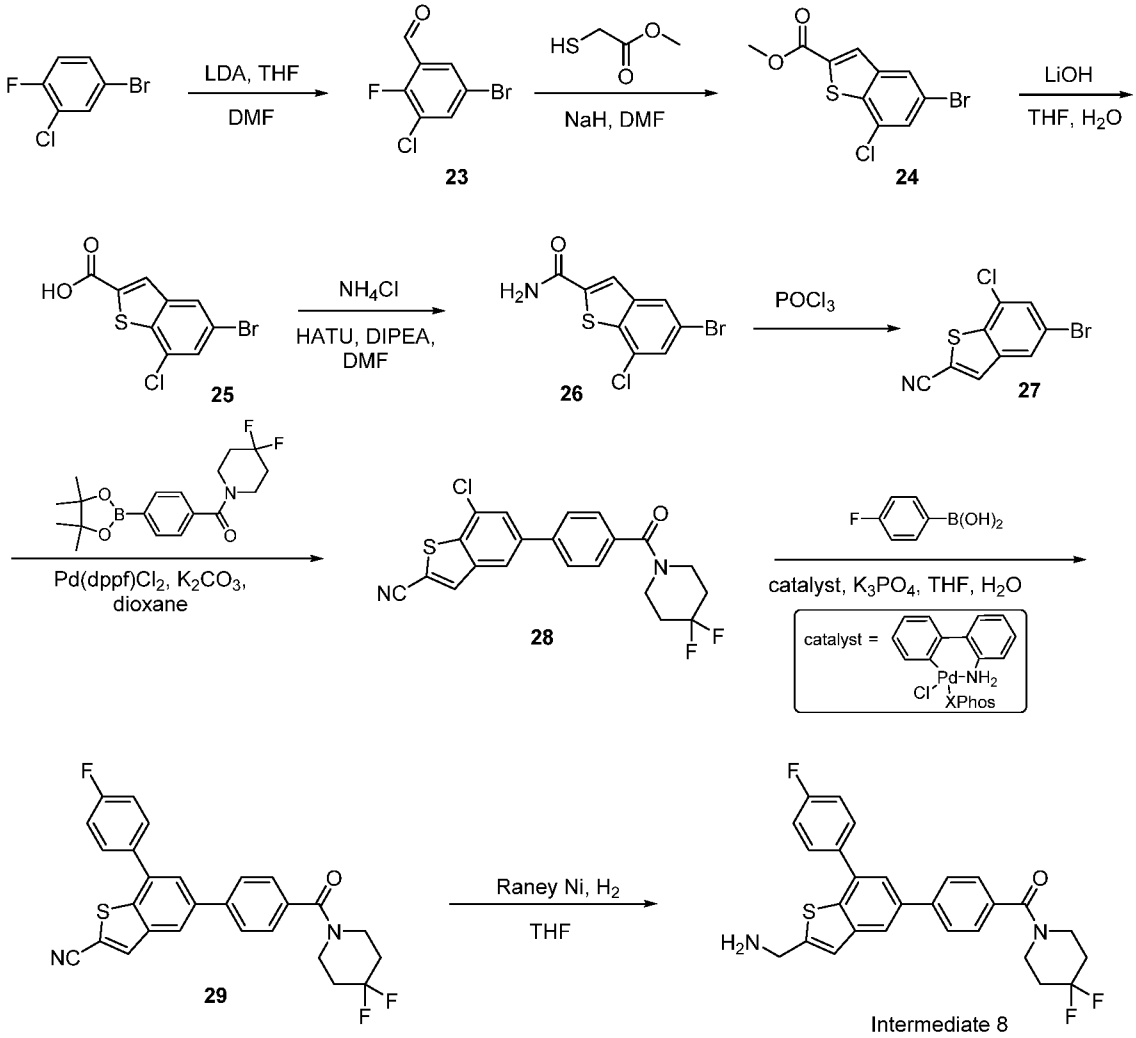
Intermediate 7: (4-(2-(2-Aminoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.



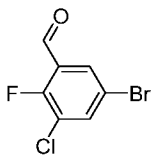
(4-(2-(2-Azidoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (22) (150 mg, 0.3 mmol) was dissolved in THF (15 mL). Raney Ni (50% wet) (100 mg) was added and stirred under a hydrogen gas atmosphere at room temperature for 2 h. The reaction mixture was filtered and the filtrate was concentrated under reduced

pressure to give 131 mg of the crude (4-(2-(2-aminoethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 7), which was used without further purification (yield: 92%). LCMS: *m/z* 479.6 $[M+H]^+$; t_R = 1.32 min.

[00273] Intermediate 8: (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzo[*b*]thiophen-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

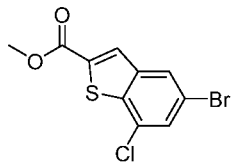


5-Bromo-3-chloro-2-fluorobenzaldehyde (23).



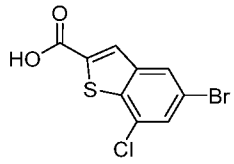
4-Bromo-2-chloro-1-fluorobenzene (16 g, 76.5 mmol) was dissolved in 50 mL of THF. The reaction mixture was cooled to -78 °C. A solution of LDA in THF (2 M, 38.2 mL, 76.4 mmol) was added dropwise over 20 min. The reaction mixture was stirred at -78 oC for 10 min. DMF (8.4 mL) was added dropwise. The reaction mixture was allowed to warm -20 °C. The reaction was quenched with 30 mL of saturated ammonium chloride aqueous solution and the mixture was extracted with methyl tert-butyl ether (50 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na2SO4, and concentrated under reduced pressure to give crude product which was purified by silica gel chromatography (5-10% EtOAc/petroleum ether) to afford 8.4 g of 5-bromo-3-chloro-2-fluorobenzaldehyde (23) (yield: 46%). 1H NMR (400 MHz, DMSO-d6) δ 10.10 (s, 1H), 8.26 (s, 1H), 7.93 (s, 1H).

Methyl 5-bromo-7-chlorobenzo[b]thiophene-2-carboxylate (24).



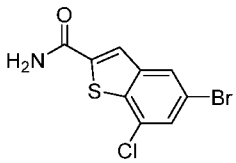
NaH (1.8 g, 45 mmol, 60% dispersion in mineral oil) was suspended in 50 mL of DMF. The mixture was cooled to 0 oC. Methyl 2-mercaptoacetate (3.6 g, 35 mmol) was added dropwise. The reaction mixture was stirred at 0 oC for 30 min. 5-Bromo-3-chloro-2-fluorobenzaldehyde (23) (5.5 g, 23 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated at 140 oC for 16 h. After cooling to room temperature the reaction mixture was poured into ice-water (100 mL), and extracted with EtOAc (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na2SO4, and concentrated under reduced pressure to give crude product which was purified by silica gel chromatography (2% EtOAc/petroleum ether) to afford 2.7 g of methyl 5-bromo-7-chlorobenzo[b]thiophene-2-carboxylate (24) (yield: 39%). 1H NMR (400 MHz, DMSO-d6) δ 8.30 (d, J = 2 Hz, 1H), 8.25 (s, 1H), 7.94 (d, J = 2 Hz, 1H), 3.92 (s, 3H).

5-Bromo-7-chlorobenzo[b]thiophene-2-carboxylic acid (25).



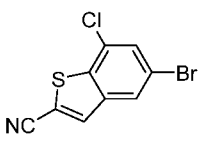
Methyl 5-bromo-7-chlorobenzo[*b*]thiophene-2-carboxylate (24) (2.5 g, 8.2 mmol) and LiOH (383 mg, 16 mmol) were added to THF (30 mL) and H_2O (10 mL). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to remove THF. The pH was neutralized to pH = 6-7 with 2N HCl and extracted with EtOAc (50 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 2.4 g of 5-bromo-7-chlorobenzo[*b*]thiophene-2-carboxylic acid (25) (98% yield). LCMS: t_R = 1.82 min.

5-Bromo-7-chlorobenzo[*b*]thiophene-2-carboxamide (26).



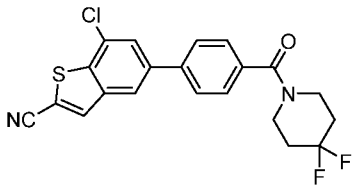
5-Bromo-7-chlorobenzo[*b*]thiophene-2-carboxylic acid (25) (2.4 g, 8.1 mmol) was dissolved in DMF (20 mL) and ammonium chloride (872 mg, 16.2 mmol) was added at 0 °C (ice bath). HATU (4.6 g, 12.3 mmol) was added followed by the dropwise addition of DIPEA (2.1 g, 16.2 mmol). The reaction mixture was allowed to warm to room temperature and heated then at 50 °C for 12 h. After cooling to room temperature the reaction mixture was poured into iced water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product which was purified by silica gel chromatography (25-100% EtOAc/petroleum ether) to afford 1.9 g of 5-bromo-7-chlorobenzo[*b*]thiophene-2-carboxamide (26) (yield: 83%). LCMS: *m/z* 289.9 $[M+H]^+$, t_R = 1.98 min.

5-Bromo-7-chlorobenzo[*b*]thiophene-2-carbonitrile (27).



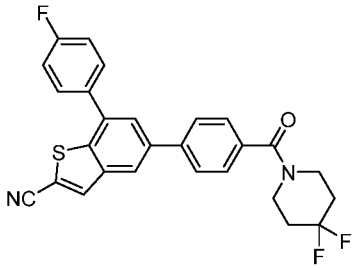
5-Bromo-7-chlorobenzo[*b*]thiophene-2-carboxamide (26) (2.1 g, 7.2 mmol) was dissolved in $POCl_3$ (20 mL). The reaction mixture was heated at 80 °C for 12 h, concentrated under reduced pressure to give a residue which was transferred into iced water (20 mL), extracted with EtOAc (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude 5-bromo-7-chlorobenzo[*b*]thiophene-2-carbonitrile (27), which was used in the next step without further purification (1.9 g, 95% yield). LCMS: t_R = 2.11 min.

7-Chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzo[*b*]thiophene-2-carbonitrile (28).



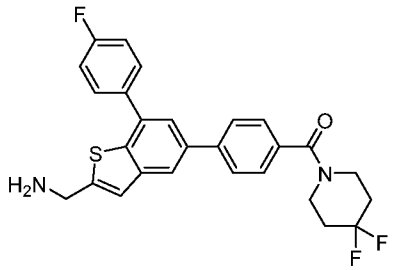
A mixture of 5-bromo-7-chlorobenzo[*b*]thiophene-2-carbonitrile (27) (1.2 g, 4 mmol), (4,4-difluoropiperidin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (1.4 g, 4 mmol), $Pd(dppf)Cl_2$ (293 mg, 0.4 mmol) and K_2CO_3 (1.1 g, 8 mmol) in 50 mL of dioxane and 5 mL of H_2O was degassed. The reaction mixture was heated at 90 °C under nitrogen atmosphere for 4 h. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (0-70% EtOAc/petroleum ether) to give 1.5 g of 7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzo[*b*]thiophene-2-carbonitrile (28). Yield (88%). LCMS: *m/z* 417.0 $[M+H]^+$, t_R = 1.84 min.

5-(4-(4,4-Difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[*b*]thiophene-2-carbonitrile (29).



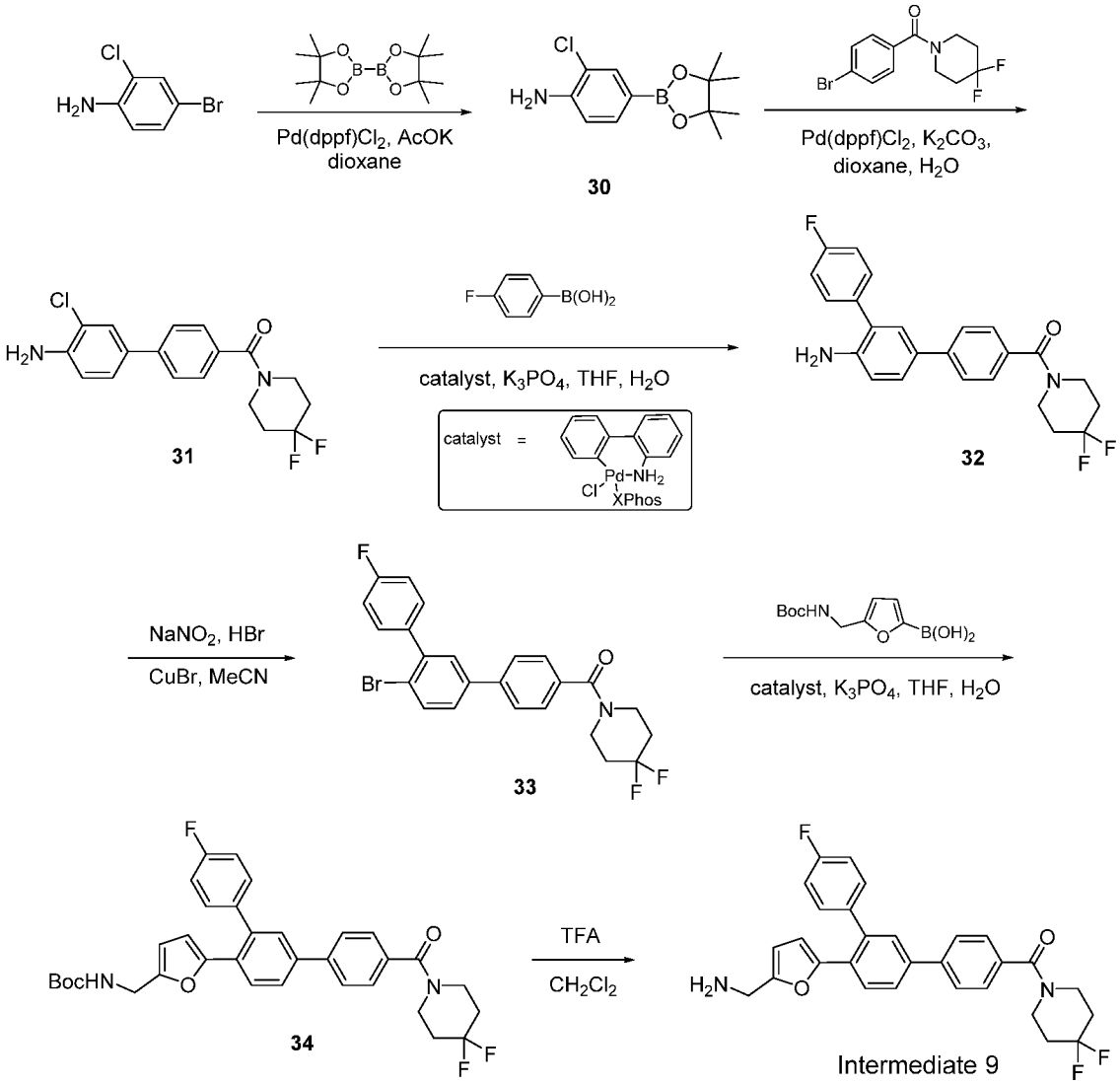
7-Chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzo[*b*]thiophene-2-carbonitrile (28) (150 mg, 0.36 mmol), 4-fluorophenylboronic acid (60 mg, 0.43 mmol), catalyst (26 mg, 0.04 mmol) and K_3PO_4 (4 mL, 2 mmol, 0.5 M) were added to THF (4 mL). The reaction mixture was degassed and heated at 40 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (20-50% EtOAc/petroleum ether) to give 100 mg of 5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[*b*]thiophene-2-carbonitrile (29) (90% yield). LCMS: *m/z* 476.7 $[M+H]^+$; t_R = 1.39 min.

Intermediate 8: (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzo[*b*]thiophen-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.

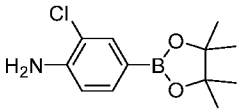


5-(4-(4,4-Difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[*b*]thiophene-2-carbonitrile (100 mg, 0.21 mmol) was dissolved in THF (5 mL). Raney Nickel (100 mg) was added. The reaction mixture was stirred at room temperature under H_2 atmosphere for 0.5 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give crude (4-(2-(aminomethyl)-7-(4-fluorophenyl)benzo[*b*]thiophen-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone, which was used in next step without further purification (70 mg, 60% yield). LCMS: *m/z* 480.7 $[M+H]^+$, t_R = 1.52 min.

[00274] Intermediate 9: (4'-(5-(aminomethyl)furan-2-yl)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone.

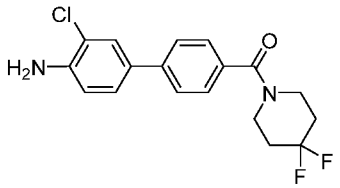


2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (30).



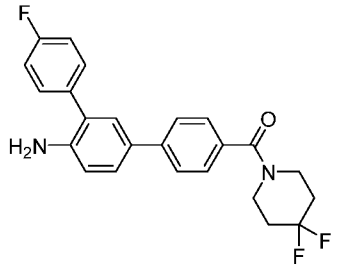
A mixture of 4-bromo-2-chloroaniline (5 g, 24.4 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.8 g, 26.8 mmol), $Pd(dppf)Cl_2$ (1.8 g, 2.4 mmol) and KOAc (4.8 g, 48.8 mmol) in dioxane (80 mL) was degassed and heated at 100 ^{0}C for 6 h. After cooling to room temperature the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (0-25% EtOAc/petroleum ether) to give 4.7 g of 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (30) (63% yield). LCMS: *m/z* 254.1 $[M+H]^+$, $t_R = 2.02$ min.

(4'-Amino-3'-chlorobiphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (31).



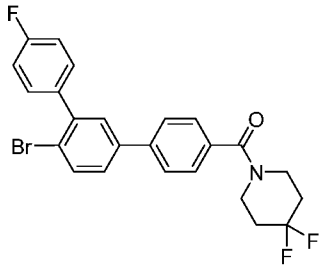
A mixture of 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (30) (7.59 g, 30 mmol), (4-bromophenyl)(4,4-difluoropiperidin-1-yl)methanone (10 g, 33 mmol), $Pd(dppf)Cl_2$ (2 g, 2.4 mmol) and K_2CO_3 (8.3 g, 60 mmol) in dioxane (120 mL) and water (12 mL) was degassed and heated at 100 ^{0}C for 18 h. After cooling to room temperature the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (0-50% EtOAc/petroleum ether) to give 6.6 g of (4'-amino-3'-chlorobiphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (31) (75% yield). LCMS: *m/z* 351.1 $[M+H]^+$, t_R = 1.86 min.

(4'-Amino-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (32).



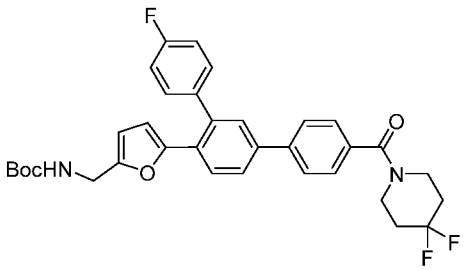
(4'-Amino-3'-chlorobiphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (31) (2.0 g, 5.7 mmol), 4-fluorophenylboronic acid (1 g, 7.4 mmol), catalyst (448 mg, 0.6 mmol) and K_3PO_4 (3.6 g, 17 mmol) were added to a mixture of THF (50 mL) and water (8 mL). The reaction mixture was degassed and then stirred at 40 ^{o}C for 1 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (40% EtOAc/petroleum ether) to give 3.1 g of (4'-amino-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (32) (88% yield). LCMS: *m/z* 411.1 $[M+H]^+$; t_R = 1.71 min.

(4'-Bromo-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (33).



(4'-Amino-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (32) (2 g, 4.9 mmol) was dissolved in acetonitrile (30 mL). The mixture was cooled down to 0 oC, HBr in AcOH (5 mL, 33% w/w) and NaNO2 (504 mg, 7.3 mmol) were added. After stirring at 0 oC for 0.5 h, CuBr (1.0 g, 7.3 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The reaction mixture was diluted with 50 mL of H2O, extracted with EtOAc (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na2SO4, concentrated under reduced pressure and purified by silica gel chromatography (30-50% EtOAc/petroleum ether) to give 2.0 g of (4'-bromo-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (33) (86% yield). LCMS: m/z 474.0 [M+H]+; tR = 1.91 min.

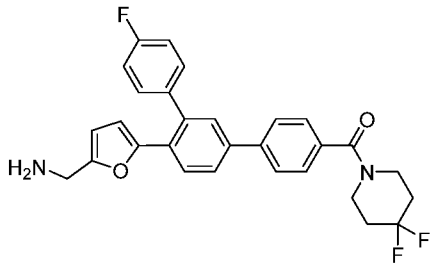
(5-(3-(4-Fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yl)furan-2-yl)methylcarbamate (34).



(4'-Bromo-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone (33) (90 mg, 0.19 mmol), 5-((*tert*-butoxycarbonylamino)methyl)furan-2-ylboronic acid (67 mg, 0.28 mmol), catalyst (15 mg, 0.02 mmol) and K_3PO_4 (0.76 mL, 0.38 mmol, 0.5 M aqueous solution) were added to THF (3 mL). The reaction mixture was degassed and then stirred at 40 ^oC for 3 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (20% EtOAc/petroleum ether) to give 60 mg of *tert*-butyl (5-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-

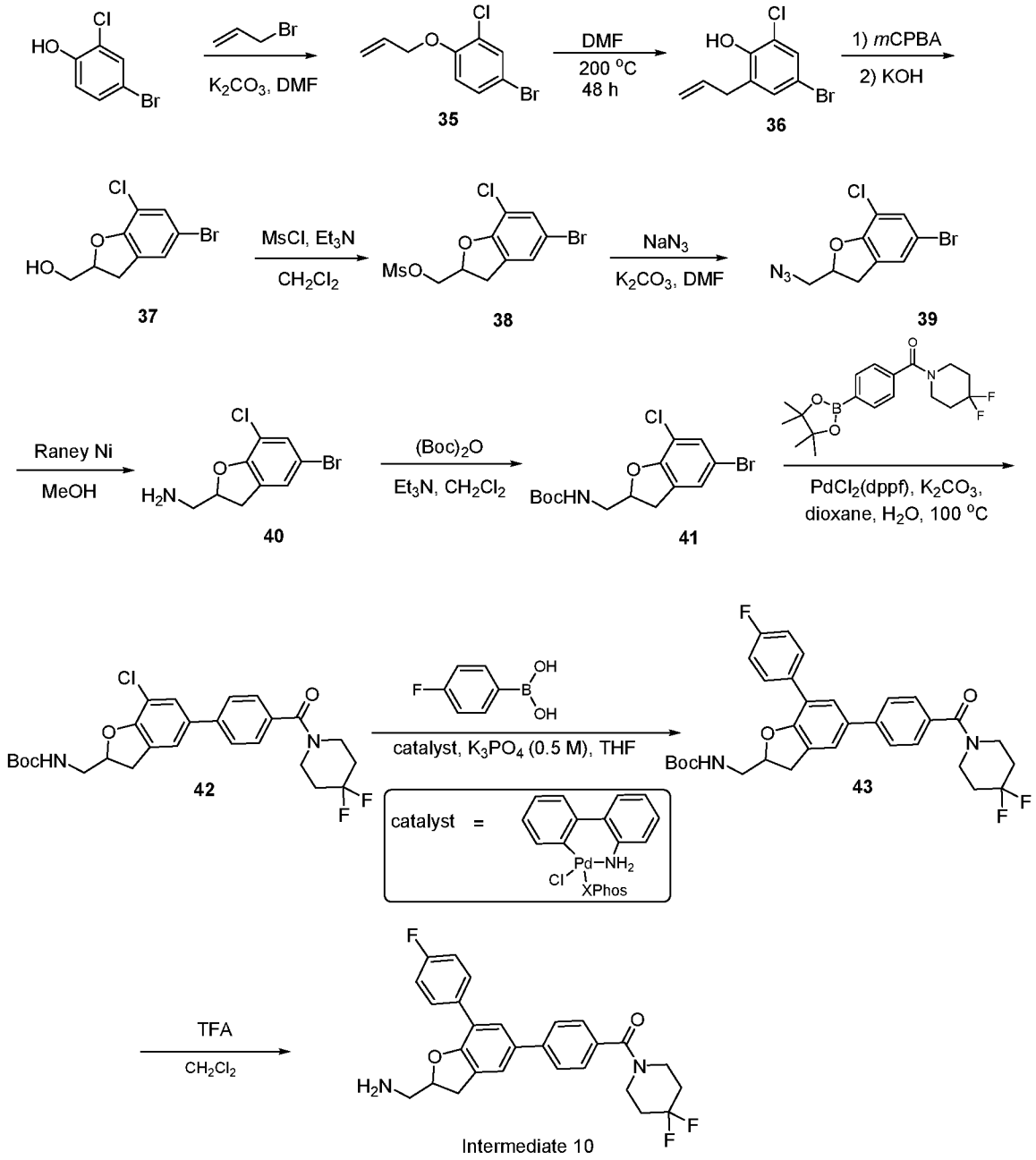
carbonyl)biphenyl-4-yl)furan-2-yl)methylcarbamate (34) (53% yield). LCMS: *m/z* 591.2 $[M+H]^+$; t_R = 1.94 min.

Intermediate 9: (4'-(5-(aminomethyl)furan-2-yl)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone.

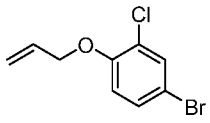


tert-Butyl (5-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yl)furan-2-yl)methylcarbamate (34) (60 mg, 0.1 mmol) was dissolved in DCM (3 mL) and TFA (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give 60 mg of (4'-(5-(aminomethyl)furan-2-yl)-3'-(4-fluorophenyl)biphenyl-4-yl)(4,4-difluoropiperidin-1-yl)methanone, which was used without further purification (99% yield). LCMS: *m/z* 491.0 $[M+H]^+$; t_R = 1.60 min.

[00275] Intermediate 10: (4-(2-(aminomethyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.



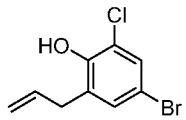
1-(Allyloxy)-4-bromo-2-chlorobenzene (35).



4-Bromo-2-chlorophenol (25 g, 120 mmol) was dissolved in DMF (50 mL). K_2CO_3 (49 g, 360 mmol) and allyl bromide (28 g, 240 mmol) were added at 25 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was transferred into iced

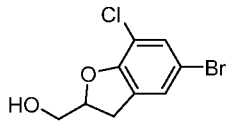
water and extracted with ethyl acetate (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 23 g of 1-(allyloxy)-4-bromo-2-chlorobenzene (35), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.65 (m, 1H), 7.47 (dd, J = 2 Hz, J = 9 Hz, 1H), 7.11 (d, J = 9 Hz, 1H), 6.01-6.09 (m, 1H), 5.29-5.47 (m, 1H), 5.33 (d, J = 15 Hz, 1H), 4.66-4.67 (m, 2H).

2-Allyl-4-bromo-6-chlorophenol (36).



1-(Allyloxy)-4-bromo-2-chlorobenzene (22 g, 89.5 mmol) was dissolved in DMF (20 mL) and the reaction mixture was heated at 200 °C for 48 h. The reaction mixture was cooled to room temperature, transferred into iced water and extracted with ethyl acetate (70 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 20 g of crude 2-allyl-4-bromo-6-chlorophenol which was purified by silica gel chromatography (0-3% ethyl acetate/petroleum ether) to obtain 15 g of pure 2-allyl-4-bromo-6-chlorophenol (36) (68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.40 (d, J = 2 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 5.88-5.98 (m, 1H), 5.08-5.09 (m, 1H), 5.05 (s, 1H), 3.35-3.38 (m, 2H). LCMS: m/z 269.2 $[M+Na]^+$; t_R = 1.92 min.

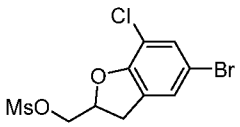
(5-Bromo-7-chloro-2, 3-dihydrobenzofuran-2-yl)methanol (37).



2-Allyl-4-bromo-6-chlorophenol (36) (15 g, 61 mmol) was dissolved in DCM (30 mL). *m*CPBA (15 g, 91.5 mmol) was added at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated sodium bicarbonate solution, saturated sodium thiosulphate solution, followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 13 g of the crude epoxy intermediate. The crude epoxy

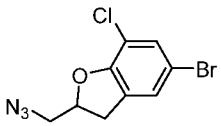
intermediate was then dissolved in DMSO (15 mL) and cooled to 0 °C. KOH (5 g, 91.5 mmol) in 5 mL water was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was transferred into iced water and extracted with ethyl acetate (100 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain 10 g of the crude product which was purified by silica gel chromatography (0-30% ethyl acetate/petroleum ether) to give 8 g of (5-bromo-7-chloro-2,3- dihydrobenzofuran-2-yl)methanol (37) (50% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34-7.37 (m, 2H), 5.05-5.08 (m, 1H), 4.91-4.96 (m, 1H), 3.64-3.69 (m, 2H), 3.10-3.35 (m, 2H). LCMS: *m/z* 284.8 $[M+Na]^+$; t_R = 0.88 min.

(5-Bromo-7-chloro-2, 3-dihydrobenzofuran-2-yl)methyl methanesulfonate (38).



(5-Bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methanol (7.9 g, 30 mmol) was dissolved in DCM (50 mL). Methane sulfonyl chloride (5.1 g, 45 mmol) and triethylamine (6 g, 60 mmol) were added at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was transferred into iced water and extracted with DCM (200 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give (5-bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methyl methanesulfonate (38), which was used without further purification. LCMS: *m/z* 363.0 $[M+Na]^+$; t_R = 0.95 min.

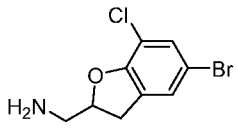
2-(Azidomethyl)-5-bromo-7-chloro-2,3-dihydrobenzofuran (39).



(5-Bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methyl methanesulfonate (38) (30 mmol) was dissolved in DMF (10 mL). Sodium azide (4.1 g, 30 mmol) and K_2CO_3 (4.1 g, 30 mmol) were added at room temperature. The reaction mixture was stirred at 80 °C for 2 h, cooled to room temperature, transferred into iced water, and extracted with ethyl acetate (50 mL X

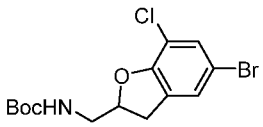
3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 9 g of 2-(azidomethyl)-5-bromo-7-chloro-2,3-dihydrobenzofuran (39), which was used in the next step without further purification.

(5-Bromo-7-chloro-2, 3-dihydrobenzofuran-2-yl)methanamine (40).



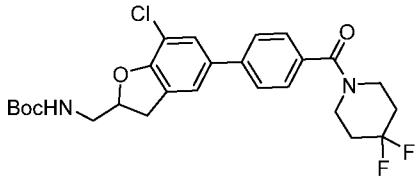
2-(Azidomethyl)-5-bromo-7-chloro-2,3-dihydrobenzofuran (39) (8.9 g, 30.8 mmol) was dissolved in methanol (20 mL). 10% Raney Ni (50% wet) (1 g) the mixture was stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give 6 g of (5-bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methanamine (40), which was used without further purification. LCMS: *m/z* 264.0 $[M+H]^+$; t_R = 0.61 min.

tert-Butyl (5-bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methylcarbamate (41).



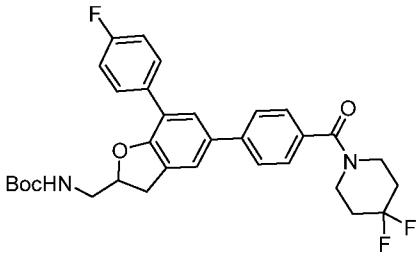
(5-Bromo-7-chloro-2, 3-dihydrobenzofuran-2-yl)methanamine (40) (1.0 g, 3.8 mmol) was dissolved in DCM (20 mL). Di-*tert*-butyl dicarbonate (915 mg, 4.2 mmol) and triethylamine (575 mg, 5.7 mmol) were added at 0 °C and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was transferred into iced water and extracted with DCM (50 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 1.5 g of crude product which was purified by silica gel chromatography (0-10% ethyl acetate/petroleum ether) to give 1.2 g of *tert*-butyl (5-bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methylcarbamate (41)(87% yield). LCMS: *m/z* 306.0 $[M-55]^+$; t_R = 1.05 min.

tert-Butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (42).



tert-Butyl (5-bromo-7-chloro-2,3-dihydrobenzofuran-2-yl)methylcarbamate (41) (600 mg, 1.7 mmol) was dissolved in a mixture of dioxane (15 mL) and H_2O (1.5 mL) and (4,4-difluoropiperidin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (695 mg, 2 mmol), $Pd(dppf)Cl_2$ (139 mg, 0.17 mmol) K_2CO_3 (458 mg, 3.3 mmol) were added at room temperature. The reaction mixture was degassed and then stirred at 80 °C for 2 h. The mixture was transferred into water and extracted with ethyl acetate (50 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to give 600 mg of *tert*-butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (42) (72% yield). LCMS: *m/z* 507.1 $[M+H]^+$; t_R = 1.87 min.

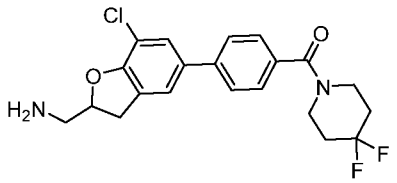
tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (43).



tert-Butyl (7-chloro-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (42) (1 g, 1.98 mmol), 4-fluorophenylboronic acid (415 mg, 2.96 mmol), catalyst (312 mg, 0.4 mmol) and K_3PO_4 (8 mL, 4 mmol, 0.5 M aqueous solution) were added in THF (30 mL). The reaction mixture was degassed and then stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (0-50% EtOAc/petroleum ether) to give 850 mg of *tert*-butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-

fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (43) (76% yield). LCMS: *m/z* 567.2 $[M+H]^+$; t_R = 1.95 min.

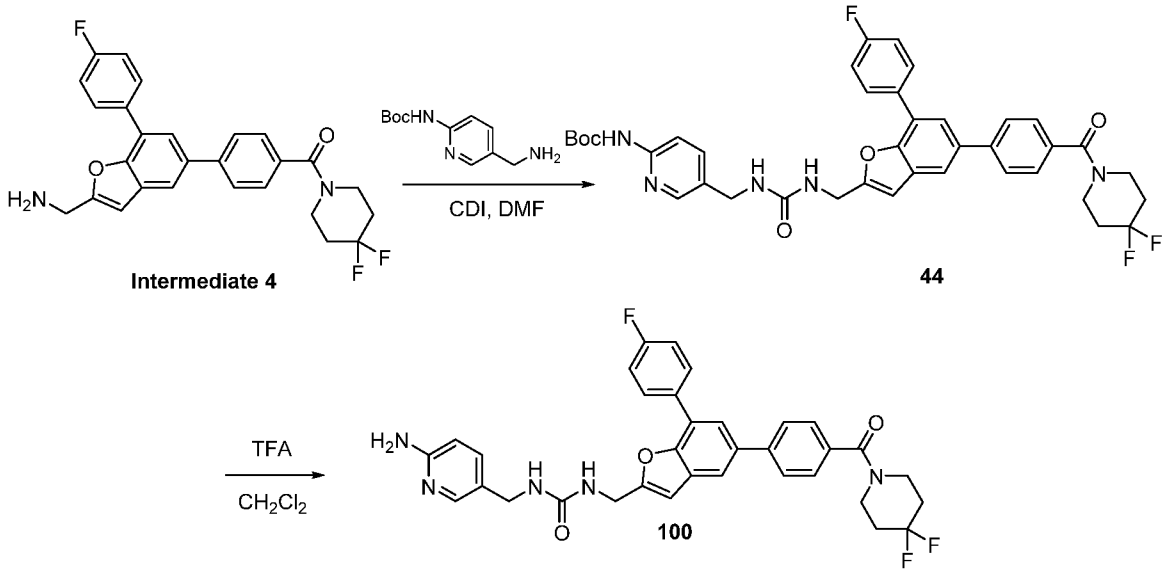
Intermediate 10: (4-(2-(Aminomethyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone.



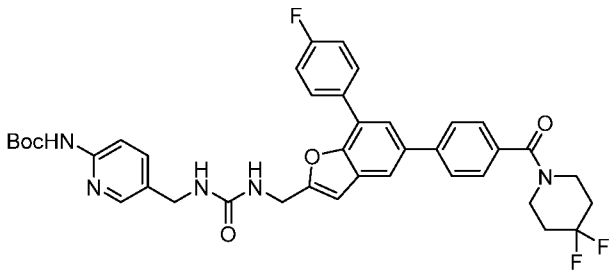
tert-Butyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methylcarbamate (43) (850 mg, 1.5 mmol) was dissolved in DCM (10 mL). TFA (2 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h, diluted with DCM (50 mL), neutralized with saturated aqueous $NaHCO_3$ solution to pH = 7-8. The organic fraction was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 550 mg of (4-(2-(aminomethyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 10), which was used without further purification. Yield (79%). LCMS: *m/z* 467.1 $[M+H]^+$; t_R = 1.47 min.

Synthesis of non-limiting examples of the invention.

[00276] Example 1: Preparation of 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (Compound 100).

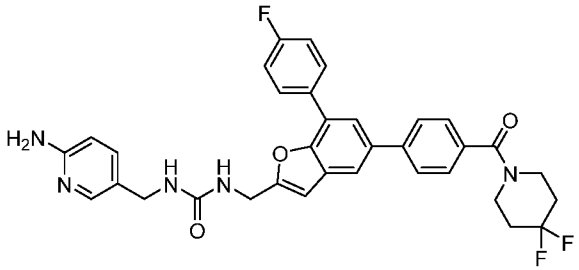


tert-Butyl 5-((3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)ureido)methyl)pyridin-2-ylcarbamate (44).



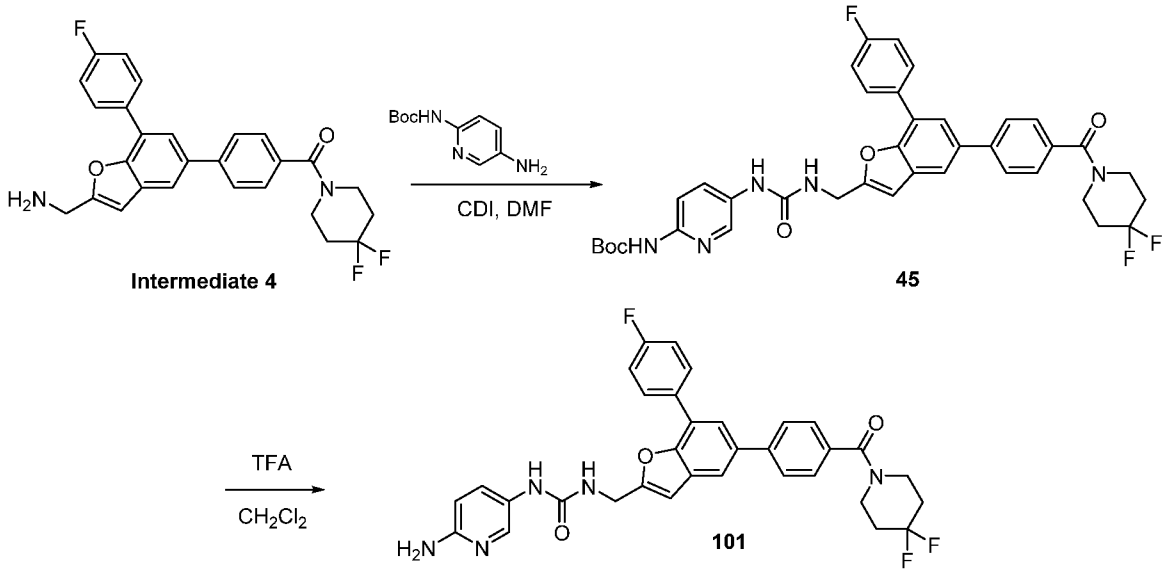
tert-Butyl 5-(aminomethyl)pyridin-2-ylcarbamate (110 mg, 0.5 mmol) was dissolved in 3 mL of DMF. 1,1'-carbonyldiimidazole (122 mg, 0.75 mmol) was added. The mixture was stirred at room temperature for 3 h. (4-(2-(Aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 4) (232 mg, 0.5 mmol) was added. The mixture was stirred at 50 ^{o}C for 3 h, quenched with H_2O (10 mL), extracted with EtOAc (20 mL X 2). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 300 mg of *tert*-butyl 5-((3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)ureido)methyl)pyridin-2-ylcarbamate (44) (82%), which was used directly to next step. LCMS: *m/z* 713.9 $[M+H]^+$, t_R = 2.02 min.

1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (**100**).

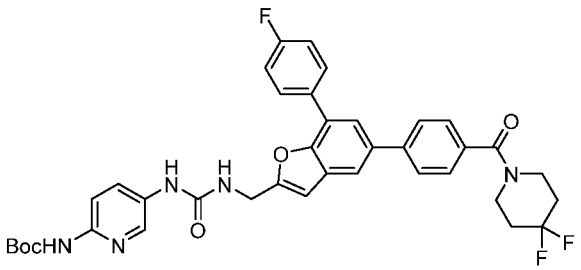


tert-Butyl 5-((3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)ureido)methyl)pyridin-2-ylcarbamate (44) (300 mg, 0.41 mmol) was dissolved in DCM (9 mL). TFA (3 mL) was added. The mixture was stirred at room temperature for 3 h, concentrated under reduced pressure and purified by prep-HPLC to give 25 mg of 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (Compound 100). Yield (10%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06-7.98 (m, 2H), 7.90 (d, J = 2 Hz, 1H), 7.87 (d, J = 8 Hz, 2H), 7.81 (s, 1H), 7.74 (d, J = 2 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.41-7.34 (m, 2H), 7.32-7.27 (m, 1H), 6.76 (s, 1H), 6.56-6.48 (m, 1H), 6.43-6.35 (m, 2H), 5.84 (s, 2H), 4.43 (d, J = 6 Hz, 2H), 4.04 (d, J = 6 Hz, 2H), 3.84-3.43 (m, 4H), 2.15-1.97 (m, 4H). LCMS: m/z 614.0 $[M+H]^+$, t_R = 1.86 min.

[00277] Example 2: Preparation of 1-(6-aminopyridin-3-yl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (Compound 101).

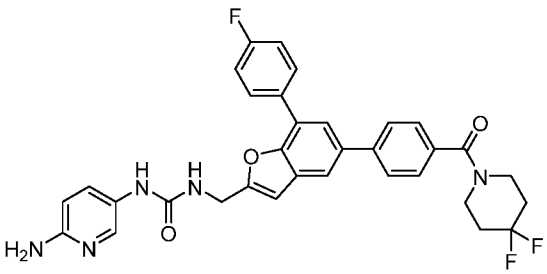


tert-Butyl 5-(3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)ureido)pyridin-2-ylcarbamate (45).



Compound 45 was synthesized in a similar fashion as compound 44 using the indicated reagents. Yield (86%). LCMS: *m/z* 699.8 $[M+H]^+$, $t_R = 2.05$ min.

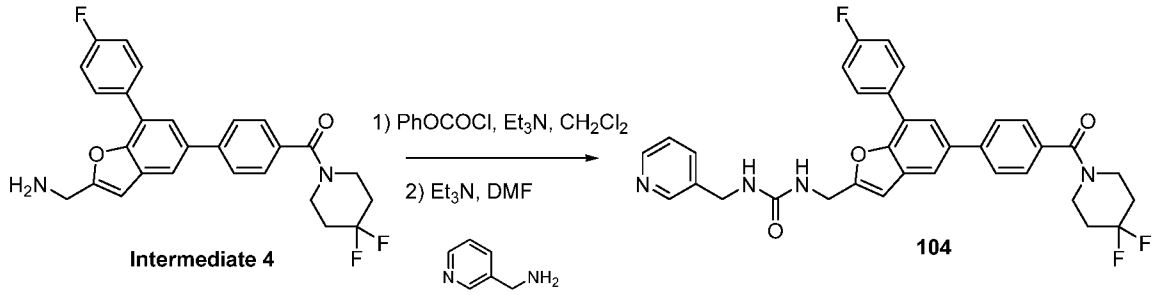
1-(6-Aminopyridin-3-yl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (101).



The title compound was synthesized in a similar fashion as described in Example 1. Yield (20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.08-7.99 (m, 2H), 7.92-7.89

(m, 2H), 7.87 (d, J = 8 Hz, 2H), 7.75 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 7.46-7.41 (m, 1H), 7.40-7.32 (m, 2H), 6.84 (s, 1H), 6.72-6.63 (m, 1H), 6.40 (d, J = 8 Hz, 1H), 5.59 (s, 2H), 4.48 (d, J = 6 Hz, 2H), 3.85-3.46 (m, 4H), 2.14-1.98 (m, 4H). LCMS: m/z 600.0 $[M+H]^+$, t_R = 1.82 min.

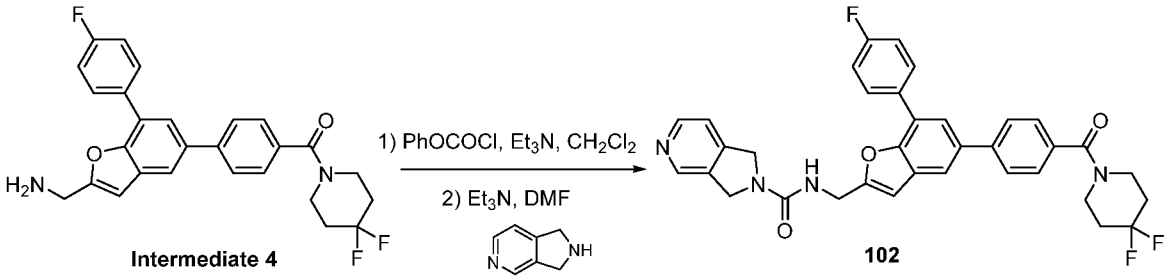
[00278] Example 3: Preparation of 1-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-3-(pyridin-3-ylmethyl)urea (Compound 104).



(4-(2-(Aminomethyl)-7-(4-fluorophenyl)benzofuran-5-yl)phenyl)(4,4-difluoropiperidin-1-yl)methanone (Intermediate 4) (100 mg, 0.22 mmol) was dissolved in DCM (5 mL). The mixture was cooled to 0 °C. Phenyl chloroformate (41 mg, 0.26 mmol) and Et_3N (33 mg, 0.33 mmol) were added. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with H_2O (2 mL) and extracted with DCM (10 mL X 3). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 120 mg of crude phenyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (104). The crude phenyl (5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methylcarbamate (120 mg, 0.2 mmol) was dissolved in 3 mL of DMF. Pyridin-3-ylmethanamine (48 mg, 0.44 mmol) and Et_3N (44 mg, 0.44 mmol) were added. The mixture was stirred at 60 °C for 5 h. The crude mixture was purified by prep-HPLC to give 48 mg of 1-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-3-(pyridin-3-ylmethyl)urea (102). Yield (37%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.43 (d, J = 4 Hz, 1H), 8.05-8.00 (m, 2H), 7.93-7.84 (m, 3H), 7.74 (d, J = 2 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.41-7.29 (m, 3H), 6.78 (s, 1H), 6.70-6.64 (m,

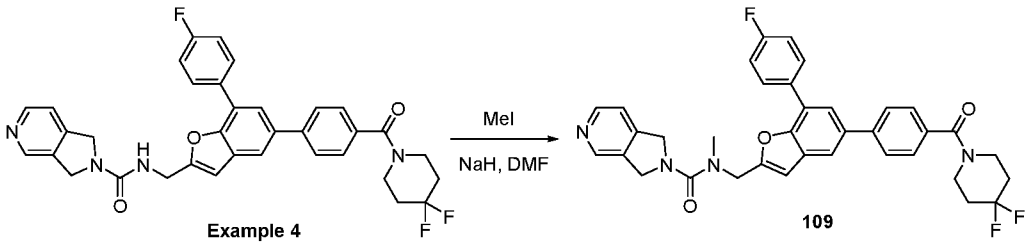
2H), 4.44 (d, J = 6 Hz, 2H), 4.27 (d, J = 6 Hz, 2H), 3.79-3.43 (m, 4H), 2.15-1.98 (m, 4H). LCMS: m/z 599.2 $[M+H]^+$, t_R = 1.86 min.

[00279] Example 4: Preparation of *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 102).



Compound 102 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.70 (s, 1H), 8.08-7.99 (m, 2H), 7.91-7.72 (m, 5H), 7.56 (d, J = 8 Hz, 2H), 7.40-7.30 (m, 3H), 6.86 (s, 1H), 4.82 (s, 2H), 4.79 (s, 2H), 4.51 (d, J = 5 Hz, 2H), 3.82-3.35 (m, 4H), 2.15-1.95 (m, 4H). LCMS: m/z 611.2 $[M+H]^+$, t_R = 1.48 min.

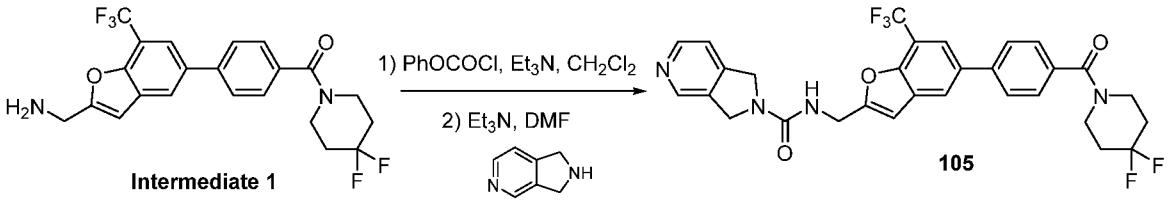
[00280] Example 5: Preparation of *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-*N*-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 109).



N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (102) (126 mg, 0.21 mmol) was dissolved in DMF (5 mL). The mixture was cooled to 0 °C. NaH (15 mg, 0.38 mmol, 60% in mineral oil) was added. After stirring at 0 °C for 0.5 h, MeI (88 mg, 0.63 mmol) was added. The mixture was stirred at 0 °C for further 2 h. The reaction mixture was quenched with water (10 mL), and extracted with EtOAc (20 mL X 3). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, concentrated

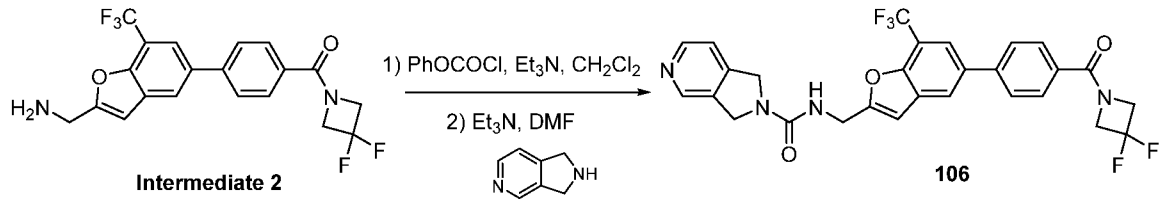
under reduced reduced pressure. The residue was purified by prep-HPLC to give 29 mg of *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-*N*-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (109). Yield (22%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.47 (d, J = 5 Hz, 1H), 8.06-7.99 (m, 2H), 7.93 (d, J = 2 Hz, 1H), 7.87 (d, J = 8 Hz, 2H), 7.76 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 7.38 (d, J = 5 Hz, 1H), 7.34-7.29 (m, 2H), 6.99 (s, 1H), 4.82 (s, 2H), 4.79 (s, 2H), 4.65 (s, 2H), 3.80-3.41 (m, 4H), 2.96 (s, 3H), 2.13-1.99 (m, 4H). LCMS: *m/z* 625.1 $[M+H]^+$, t_R = 1.54 min.

[00281] Example 6: Preparation of *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (105).



Compound 105 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (30%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.49 (d, J = 5 Hz, 1H), 8.23 (s, 1H), 7.86 (s, 1H), 7.83 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.42 (d, J = 5 Hz, 1H), 7.30-7.25 (m, 1H), 6.95 (s, 1H), 4.71 (s, 2H), 4.69 (s, 2H), 4.52 (d, J = 6 Hz, 2H), 3.78-3.44 (m, 4H), 2.14-1.99 (m, 4H). LCMS: *m/z* 585.0 $[M+H]^+$, t_R = 1.49 min.

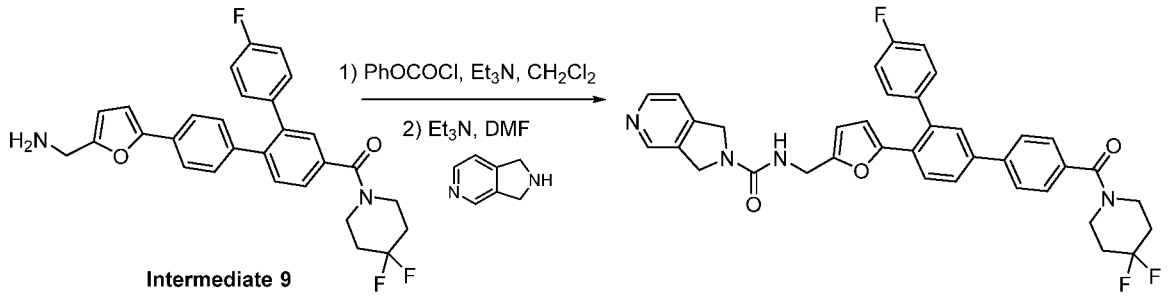
[00282] Example 7: Preparation of *N*-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3H)-carboxamide (Compound 106).



Compound 106 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.49 (d, J =

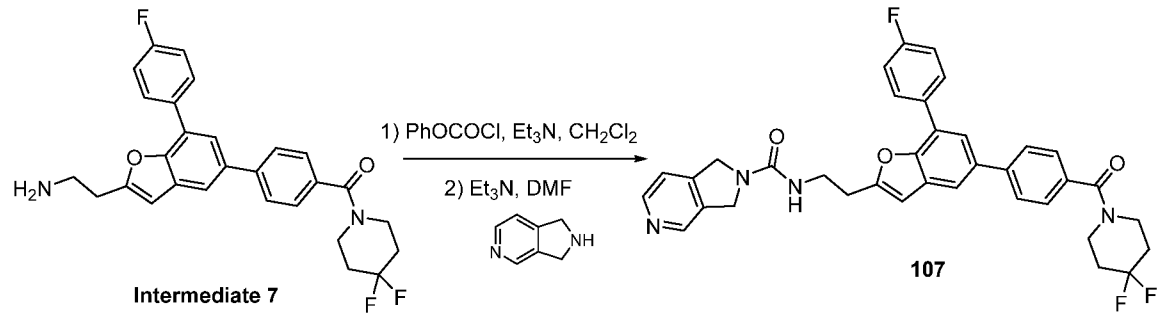
5 Hz, 1H), 8.25 (s, 1H), 7.89-7.77 (m, 5H), 7.42 (d, J = 5 Hz, 1H), 7.29-7.23 (m, 1H), 6.95 (s, 1H), 4.92-4.42 (m, 10H). LCMS: m/z 557.0 $[M+H]^+$, t_R = 1.47 min.

Example 8: *N*-((5-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yl)furan-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide.



The title compound was synthesized in a similar fashion as Example 3 using the indicated reagents. Yield (20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.47 (d, J = 5 Hz, 1H), 7.91-7.79 (m, 4H), 7.59 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 7.42-7.33 (m, 3H), 7.30-7.19 (m, 2H), 6.98-6.89 (m, 1H), 6.19 (d, J = 3 Hz, 1H), 5.61 (d, J = 3 Hz, 1H), 4.64 (d, J = 8 Hz, 4H), 4.25 (d, J = 5 Hz, 2H), 3.85-3.41 (m, 4H), 2.10-1.98 (m, 4H). LCMS: m/z 637.3 $[M+H]^+$, t_R = 1.91 min.

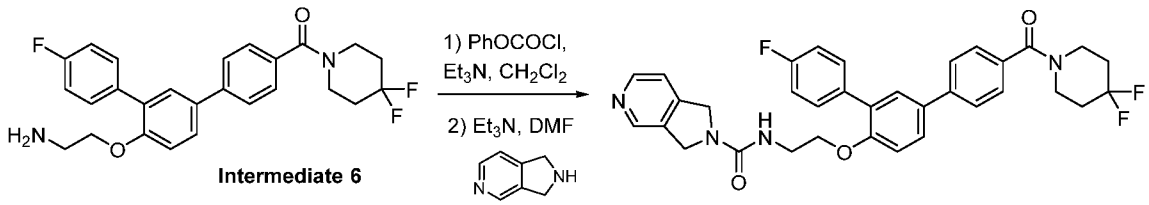
[00283] Example 9: Preparation of *N*-(2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 107).



Compound 107 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.67 (d, J = 5 Hz, 1H), 8.04-7.98 (m, 2H), 7.89-7.83 (m, 3H), 7.74-7.69 (m, 2H), 7.56 (d, J = 8 Hz, 2H),

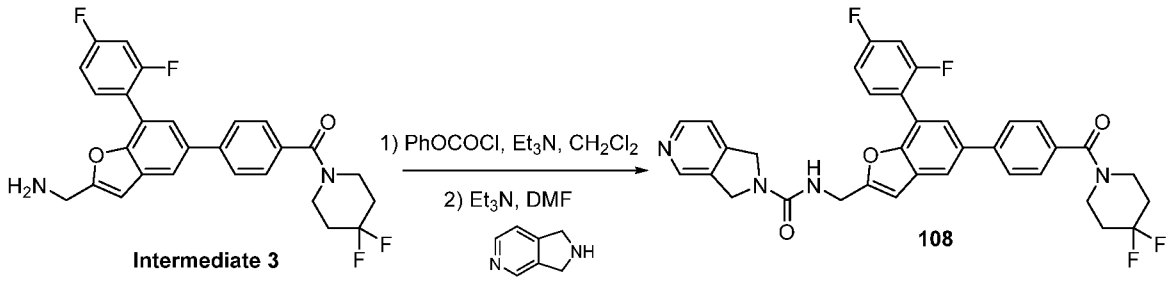
7.34-7.25 (m, 2H), 6.82 (s, 1H), 6.78-6.73 (m, 1H), 4.67 (s, 2H), 4.65 (s, 2H), 3.82-3.68 (s, 6H), 3.04 (t, J = 7 Hz, 2H), 2.15-1.98 (m, 4H). LCMS: m/z 625.3 $[M+H]^+$, t_R = 1.89 min.

Example 10: *N*-(2-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide.



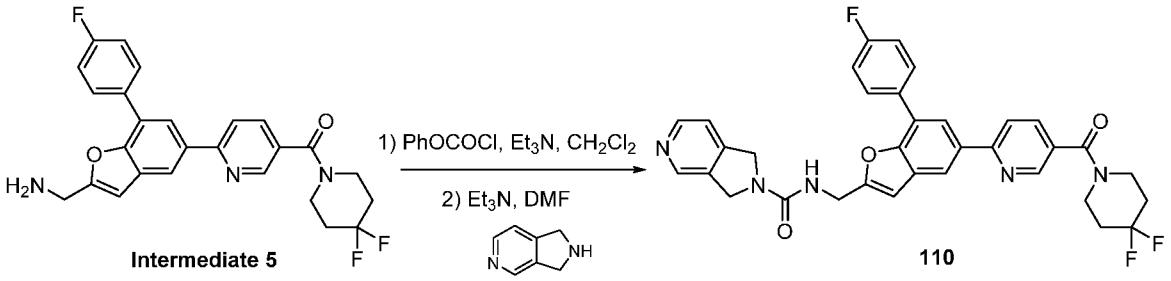
The title compound was synthesized in a similar fashion as Example 3 using the indicated reagents. Yield (25%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.48 (d, J = 5 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 7.71-7.65 (m, 3H), 7.62 (d, J = 2 Hz, 1H), 7.51 (d, J = 8 Hz, 2H), 7.40 (d, J = 5 Hz, 1H), 7.29 (d, J = 9 Hz, 1H), 7.22-7.16 (m, 2H), 6.51 (t, J = 5.2 Hz, 1H), 4.60 (s, 2H), 4.59 (s, 2H), 4.14 (t, J = 6 Hz, 2H), 3.81-3.48 (m, 4H), 3.47-3.41 (m, 2H), 2.13-1.96 (m, 4H). LCMS: m/z 601.3 $[M+H]^+$, t_R = 1.82 min.

[00284] Example 11: Preparation of *N*-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 108).



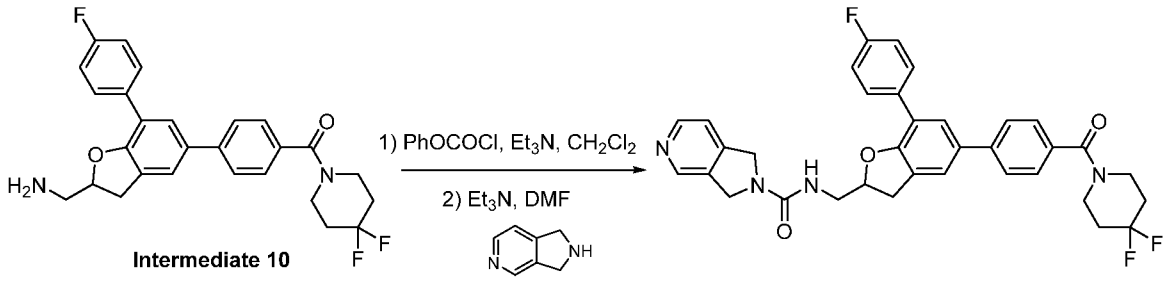
Compound 108 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (10%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.52-8.46 (d, J = 5 Hz, 1H), 7.95 (s, 1H), 7.87-7.76 (m, 3H), 7.63-7.52 (m, 3H), 7.48-7.40 (m, 2H), 7.31-7.23 (m, 1H), 7.22-7.14 (m, 1H), 6.85 (s, 1H), 4.69 (s, 2H), 4.67 (s, 2H), 4.44 (d, J = 5 Hz, 2H), 3.80-3.48 (m, 4H), 2.11-2.00 (m, 4H). LCMS: m/z 629.2 $[M+H]^+$, t_R = 1.87 min.

[00285] Example 12: Preparation of *N*-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 110).



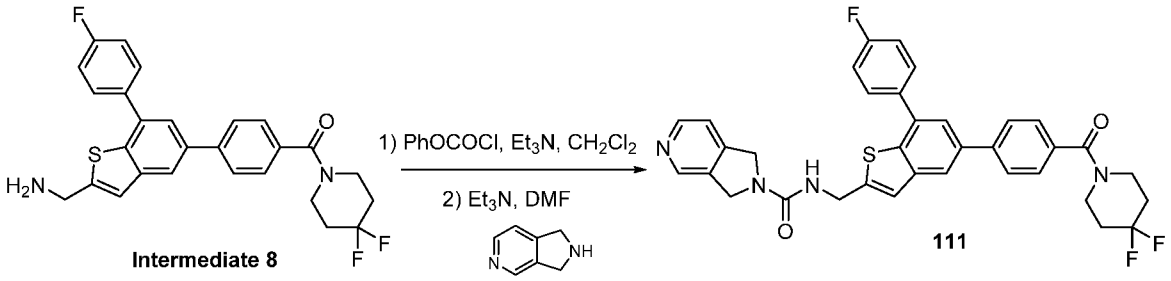
Compound 110 was synthesized in a similar fashion as Example 3 using the indicated reagents. Yield (12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77-8.75 (m, 1H), 8.59 (s, 1H), 8.49 (d, J = 5 Hz, 1H), 8.35 (s, 1H), 8.24-8.19 (m, 2H), 8.05-7.97 (m, 3H), 7.43-7.35 (m, 3H), 7.22-7.19 (m, 1H), 6.90 (s, 1H), 4.71 (s, 2H), 4.69 (s, 2H), 4.50 (s, 2H), 3.79-3.46 (m, 4H), 2.12-2.05 (m, 4H). LCMS: *m/z* 612.2 $[M+H]^+$, t_R = 1.78 min.

Example 13: *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide.



The title compound was synthesized in a similar fashion as Example 3 using the indicated reagents. Yield (11%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.47 (d, J = 5 Hz, 1H), 7.91-7.86 (m, 2H), 7.74 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.39 (d, J = 5 Hz, 1H), 7.27-7.20 (m, 2H), 6.80-6.73 (m, 1H), 5.04-4.96 (m, 1H), 4.63 (s, 2H), 4.61 (s, 2H), 3.79-3.37 (m, 7H), 3.21-3.13 (m, 1H), 2.13-2.00 (m, 4H). LCMS: *m/z* 613.3 $[M+H]^+$, t_R = 1.86 min.

[00286] Example 14: Preparation of *N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[*b*]thiophen-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 111).



Compound 111 was synthesized in a similar fashion as described in Example 3 using the indicated reagents. Yield (24%). 1H NMR (500 MHz, DMSO-d6) δ 8.57 (s, 1H), 8.47 (d, J = 5 Hz, 1H), 8.14 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.86-7.82 (m, 2H), 7.64 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.46 (s, 1H), 7.42-7.37 (m, 3H), 7.32-7.27 (m, 1H), 4.67 (s, 2H), 4.65 (s, 2H), 4.58 (d, J = 6 Hz, 2H), 3.80-3.45 (m, 4H), 2.13-1.99 (m, 4H). LCMS: m/z 627.1 [M+H]+, tR = 1.55 min.

Example 15: 1-((6-aminopyridin-3-yl)methyl)-3-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)urea (Compound 112). Compound 112 was made according to the procedure of Example 1 using Intermediate 3 in place of Intermediate 4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.87-7.75 (m, 4H), 7.60 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 7.48-7.42 (m, 1H), 7.30-7.24 (m, 2H), 6.75 (s, 1H), 6.49-6.45 (m, 1H), 6.40-6.33 (m, 2H), 5.77 (s, 2H), 4.37 (d, J = 6 Hz, 2H), 4.02 (d, J = 6 Hz, 2H), 3.79-3.46 (m, 4H), 2.12-1.98 (m, 4H). LCMS: *m/z* 632.2 $[M+H]^+$, t_R = 1.84 min. Yield (final step): 12%.

Example 16: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea (Compound 113). Compound 113 was made according to the procedure of Example 1 using Intermediate 1 in place of Intermediate 4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.87-7.79 (m, 4H), 7.58 (d, J = 8 Hz, 2H), 7.31-7.25 (m, 1H), 6.84 (s, 1H), 6.60-6.54 (m, 1H), 6.47-6.42 (m, 1H), 6.39 (d, J = 8 Hz, 1H), 5.79 (s, 2H), 4.45 (d, J = 6 Hz, 2H), 4.03 (d, J = 6 Hz, 2H), 3.81-3.43

(m, 4H), 2.13-1.99 (m, 4H). LCMS: *m/z* 588.2 $[M+H]^+$, t_R = 1.79 min. Yield (final step): 50%

Example 17: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[*b*]thiophen-2-yl)methyl)urea (Compound 114).

Compound 114 was made according to Example 14, using appropriate reagents.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, *J* = 2 Hz, 1H), 7.90 (d, *J* = 8 Hz, 2H), 7.87-7.79 (m, 3H), 7.65 (d, *J* = 2 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.44-7.37 (m, 3H), 7.30-7.26 (m, 1H), 6.59 (t, *J* = 6 Hz, 1H), 6.40-6.35 (m, 2H), 5.79 (s, 2H), 4.50 (d, *J* = 6 Hz, 2H), 4.02 (d, *J* = 6 Hz, 2H), 3.81-3.47 (m, 4H), 2.13-2.02 (m, 4H). LCMS: *m/z* 630.2 $[M+H]^+$, t_R = 1.85 min. Yield (final step): 24%.

Example 18: 6-amino-*N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxamide (Compound 115).

Compound 115 was made according to Example 12 using appropriate reagents.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06-8.01 (m, 2H), 7.93-7.83 (m, 4H), 7.73 (d, *J* = 2 Hz, 1H), 7.56 (d, *J* = 8 Hz, 2H), 7.39-7.34 (m, 2H), 7.11-7.04 (m, 1H), 6.84 (s, 1H), 6.39 (s, 1H), 5.84 (s, 2H), 4.53-4.45 (m, 6H), 3.79-3.45 (m, 4H), 2.16-1.99 (m, 4H). LCMS: *m/z* 626.3 $[M+H]^+$, t_R = 1.83 min. Yield (final step): 19%

Example 19: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea (Compound 116).

Compound 116 was made according to Example 1 using Intermediate 5 in place of Intermediate 4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79-8.75 (m, 1H), 8.37 (d, *J* = 2 Hz, 1H), 8.24-8.19 (m, 2H), 8.06-7.97 (m, 5H), 7.89-7.85 (m, 1H), 7.78 (s, 1H), 7.42-7.35 (m, 2H), 6.96 (d, *J* = 9 Hz, 1H), 6.83 (s, 2H), 6.74-6.68 (m, 1H), 4.43 (d, *J* = 5 Hz, 2H), 4.12 (d, *J* = 6 Hz, 2H), 3.61-3.48 (m, 4H), 2.15-2.03 (m, 4H). LCMS: *m/z* 615.1 $[M+H]^+$, t_R = 1.68 min. Yield (final step): 30%.

Example 20: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)urea (Compound 123).

Compound 123 was made according to Example 13 using appropriate reagents. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89-7.83 (m, 2H), 7.79-7.73 (m, 3H), 7.59-7.49 (m, 4H), 7.30-7.23 (m, 3H), 6.37 (d, J = 8 Hz, 1H), 6.29 (t, J = 6 Hz, 1H), 6.12 (t, J = 6 Hz, 1H), 5.76 (s, 2H), 4.98-4.88 (m, 1H), 4.01 (d, J = 6 Hz, 2H), 3.73-3.35 (m, 7H), 3.10-3.03 (m, 1H), 2.11-2.01 (m, 4H). LCMS: m/z 616.3 $[M+H]^+$, t_R = 1.83 min. Yield (final step): 14%.

Example 21: 1-(4-aminobenzyl)-3-(2-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yloxy)ethyl)urea (Compound 124).

Compound 124 was made according to Example 10 using appropriate reagents. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98-7.91 (m, 2H), 7.87-7.83 (m, 1H), 7.78-7.73 (m, 3H), 7.70-7.60 (m, 4H), 7.54-7.48 (m, 2H), 7.25-7.18 (m, 3H), 6.97-6.92 (m, 1H), 6.59 (s, 1H), 6.23-6.17 (m, 1H), 4.10-4.03 (m, 4H), 3.80-3.61 (m, 6H), 2.09-1.99 (m, 4H). LCMS: m/z 604.3 $[M+H]^+$, t_R = 1.81 min. Yield (final step): 42%.

Example 22: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(3-(4-fluorophenyl)-4'-(4,4-difluoropiperidine-1-carbonyl)biphenyl-4-yl)furan-2-yl)methyl)urea (Compound 125).

Compound 125 was made according to Example 8 using appropriate reagents. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87-7.78 (m, 5H), 7.60-7.53 (m, 3H), 7.41-7.36 (m, 2H), 7.30-7.25 (m, 3H), 6.39 (d, J = 8 Hz, 1H), 6.32-6.24 (m, 2H), 6.11 (d, J = 3 Hz, 1H), 5.78 (s, 2H), 5.52 (d, J = 3 Hz, 1H), 4.18 (d, J = 6 Hz, 2H), 4.01 (d, J = 6 Hz, 2H), 3.78-3.44 (m, 4H), 2.10-2.01 (m, 4H). LCMS: m/z 640.3 $[M+H]^+$, t_R = 1.87 min. Yield (final step): 8%.

Example 23: 1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea (Compound 117).

Compound 117 was made according to Example 1 using Intermediate 2 in place of Intermediate 4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.89-7.79 (m, 6H), 7.31-7.28

(m, 1H), 6.84 (s, 1H), 6.61-6.55 (m, 1H), 6.47-6.42 (m, 1H), 6.40 (d, J = 8 Hz, 1H), 5.79 (s, 2H), 4.91-4.78 (m, 2H), 4.59-4.49 (m, 2H), 4.45 (d, J = 6 Hz, 2H), 4.04 (d, J = 6 Hz, 2H). LCMS: m/z 560.2 $[M+H]^+$, t_R = 1.74 min. Yield (final step): 16%.

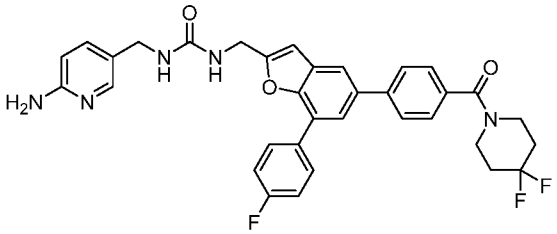
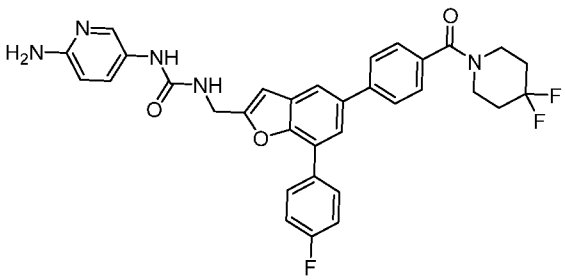
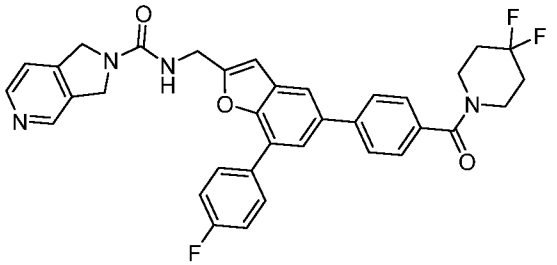
[00287] Example 24. MTT Cell Proliferation Assay

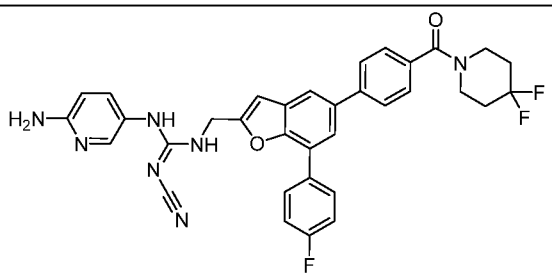
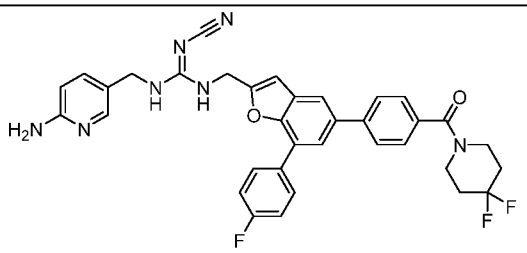
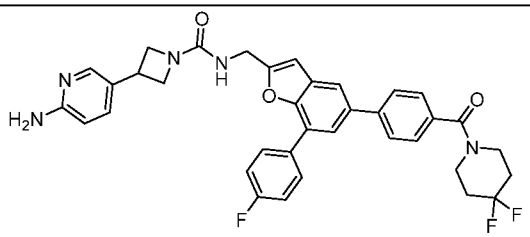
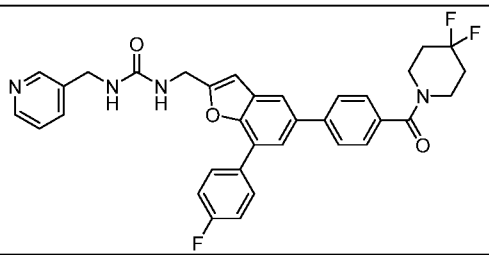
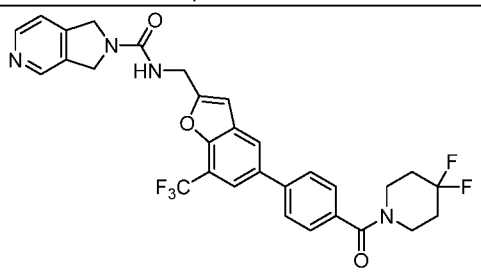
The MTT cell proliferation assay was used to study the cytotoxic properties of the compounds. The assay was performed according to the method described by Roche Molecular Biochemicals, with minor modifications. The assay is based on the cleavage of the tetrazolium salt, MTT, in the presence of an electron-coupling reagent. The water-insoluble formazan salt produced must be solubilized in an additional step. Cells grown in a 96-well tissue culture plate were incubated with the MTT solution for approximately 4 hours. After this incubation period, a water-insoluble formazan dye formed. After solubilization, the formazan dye was quantitated using a scanning multi-well spectrophotometer (ELISA reader). The absorbance revealed directly correlates to the cell number. The cells were seeded at 5,000-10,000 cells in each well of 96-well plate in 100 µL of fresh culture medium and were allowed to attach overnight. The stock solutions of the compounds were diluted in 100 µL cell culture medium to obtain eight concentrations of each test compound, ranging from 1 nM to 30 µM. After incubation for approximately 64–72 hours, 20 uL of CellTiter 96 Aqueous One Solution Reagent (Promega, G358B) was added to each well and the plate was returned to the incubator (37 °C; 5% CO_2) until an absolute OD of 1.5 was reached for the control cells. All optical densities were measured at 490 nm using a Vmax Kinetic Microplate Reader (Molecular Devices). In most cases, the assay was performed in duplicate and the results were presented as a mean percent inhibition to the negative control±SE. The following formula was used to calculate the percent of inhibition: Inhibition (%) = (1-(OD_0/OD)) X 100.

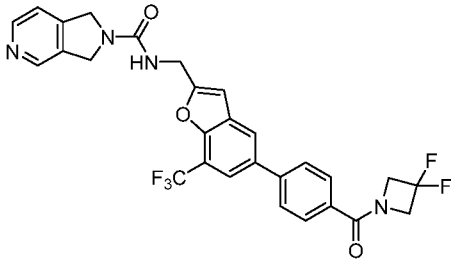
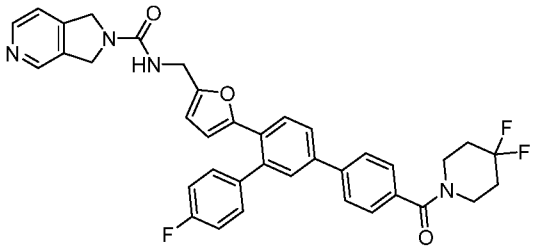
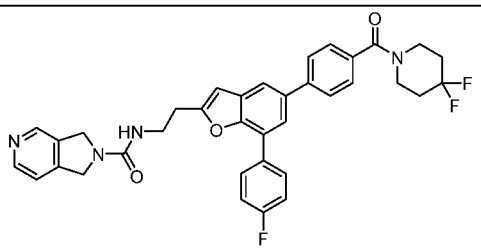
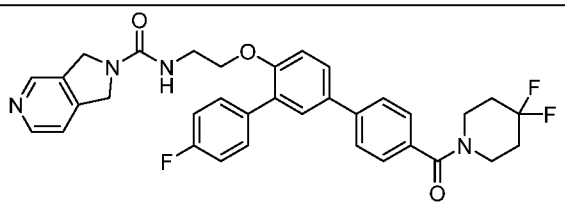
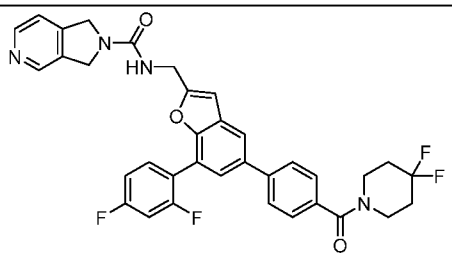
[00288] The compounds were tested against MS751, Z138 and 3T3 cells. The MS751 cell line is derived from a metastasis to lymph node of human cervix from a patient diagnosed with squameous cell carcinoma of the cervix. The Z138 cell line is a mature B-cell acute lymphoblastic leukemia cell line derived from a patient with chronic lumphocytic leukemia. 3T3 cells are standard fibroblast cells; they were originally isolated from Swiss mouse embryo tissue.

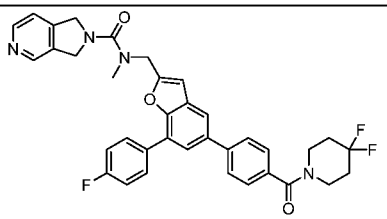
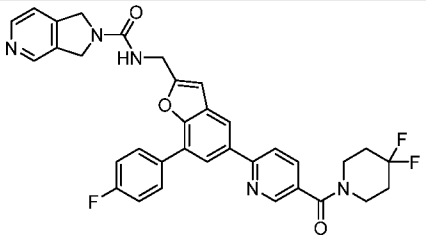
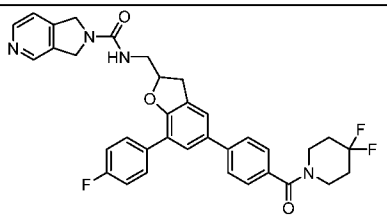
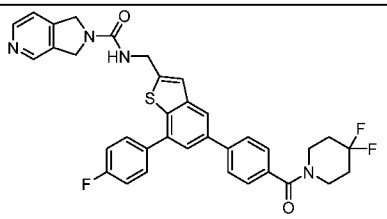
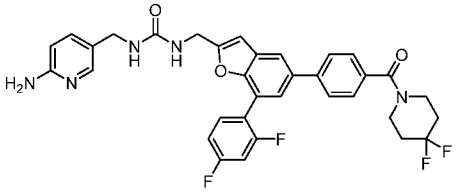
[00289] The results of the MTT assay are reported in Table A.

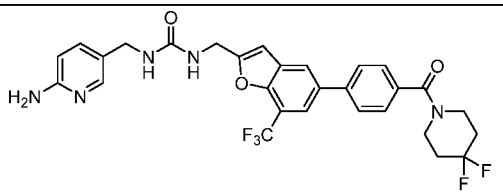
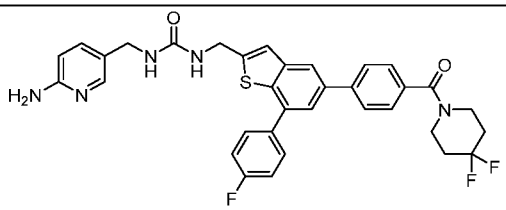
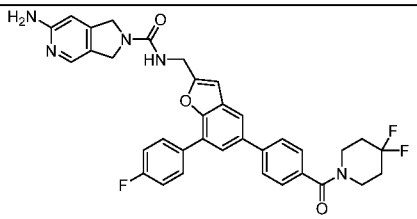
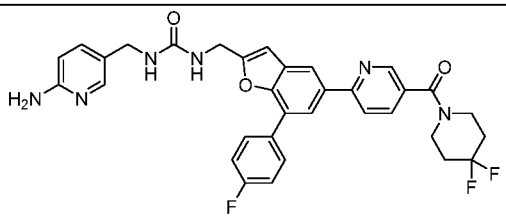
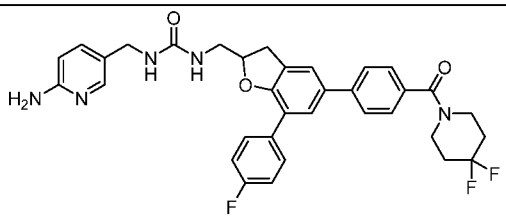
Table A. MTT Assay (IC_{50}: A = <100 nM; B = 100 nM to <5μM; C = 5 μM to 10 μM; D = >10 μM; ND = not determined)

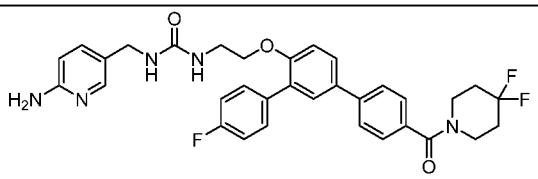
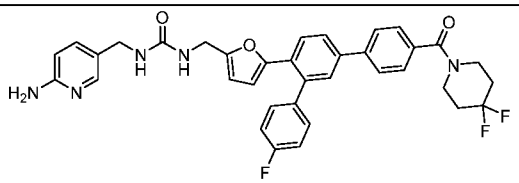
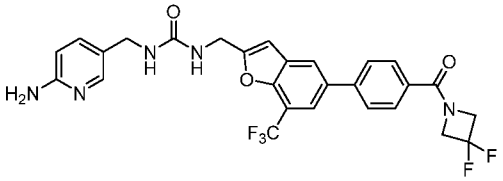
Cpd. No.	Structure	MS751 MTT (IC50; μM)	Z-138 MTT (IC50; μM)	3T3 MTT (IC50; μM)	Compound Name
100		A	A	B	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
101		B	B	D	1-(6-aminopyridin-3-yl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
102		A	A	B	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

118		D	D	D	(E)-1-(6-aminopyridin-3-yl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
119		B	B	D	(Z)-1-((6-aminopyridin-3-yl)methyl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
103		B	A	B	3-(6-aminopyridin-3-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)azetidine-1-carboxamide
104		ND	A	B	1-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-3-(pyridin-3-ylmethyl)urea
105		ND	B	D	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

106		ND	D	D	N-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
120		ND	A	D	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)furan-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
107		A	A	B	N-(2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
121		A	A	D	N-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)oxy)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
108		A	A	D	N-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

109		ND	A	B	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-N-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
110		ND	A	A	N-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
122		ND	A	A	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
111		ND	A	D	N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
112		ND	A	B	1-((6-aminopyridin-3-yl)methyl)-3-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)urea

113		ND	D	D	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea
114		ND	C	D	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)urea
115		ND	A	B	6-amino-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
116		ND	A	B	1-((6-aminopyridin-3-yl)methyl)-3-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
123		ND	A	B	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)urea

124		ND	A	D	1-((6-aminopyridin-3-yl)methyl)-3-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)oxy)ethyl)urea
125		ND	A	D	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)furan-2-yl)methyl)urea
117		ND	C	D	1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea

References

1. Arias-Romano, L.E.; Chernoff, J. *Biol. Cell,* 2008, 100, 97–108.

2. a) Dart, A.E.; Wells, C.M. *European Journal of Cell Biology,* 2013, 92, 129– 138. b) Clairvoyant, F.; Zhu. S. et al. *J Biol Chem,* 2002, 277, 550–8. c) Cammarano, M.S. et al. *Mol Cell Biol.,* 2005, 21, 9532-42. d) Wells, C.M. et al, *J Cell Sci.,* 2010, 123, 1663-73. d) Siu, M.K. et al. *Proc. Natl. Acad. Sci. USA,* 2010, 107(43), 18622-7.

3. a) Guo, C. et al.; *J. Med. Chem.,* 2012, 55, 4728−4739 b) Deacon, S.W. et al. *Chemistry & Biology,* 2008, 15, 322–331 c) Wells, C.M.; Jones, G. E. *Biochem. J.,* 2010, 425, 465–473.

[00290] The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

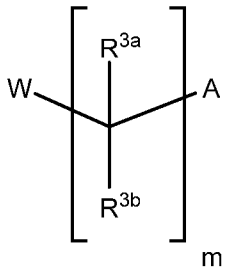
[00291] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various

changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by Structural Formula IA:

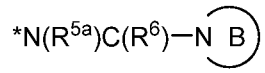


(IA)

or a pharmaceutically acceptable salt thereof, wherein:

W is $-Y(CR^{4a}R^{4b})_nR^2$ or Y';

Y is $*N(R^{5a})C(R^6)N(R^{5b})-$;

Y' is 

;

"*" represents a portion of Y or Y'directly adjacent to $[C(R^{3a})(R^{3b})]_m$;

R^{5a} and R^{5b} are independently hydrogen or $(C_1\text{-}C_4)$alkyl;

R^6 is =O or $=NR^7$;

R^7 is hydrogen, alkyl, or CN;



is a 3-18-membered heterocyclyl;

R^2 is 5-18-membered heteroaryl or 6-18-membered aryl;

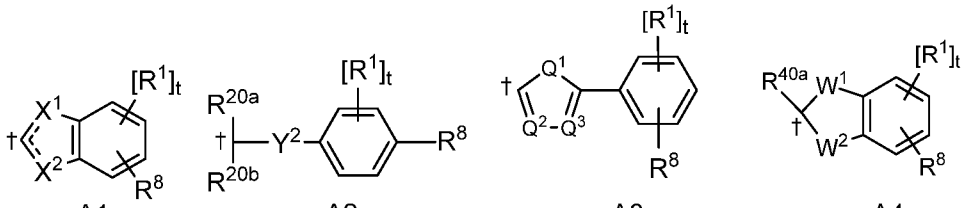
each of R^{3a} and R^{3b} is independently selected from hydrogen and $(C_1\text{-}C_4)$alkyl;

m is 1 or 2;

n is 0 or 1;

each of R^{4a} and R^{4b}, if present, is independently selected from hydrogen, $(C_1\text{-}C_4)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl;

A is selected from:



and ,

wherein:

"†" represents the point of attachment of A to the remainder of the molecule;

one "---" represents a single bond and the other "---" represents a double bond;

X^1 is -O-, -S- or -N(R^{10a})- and X^2 is -C(R^{11a})- or -N-; or

X^1 is -N- and X^2 is -N(R^{12a})-, wherein:

R^{10a} is hydrogen or (C_1-C_4)alkyl;

R^{11a} is hydrogen, deuterium, (C_1-C_4)alkyl or halo; and

R^{12a} is hydrogen or (C_1-C_4)alkyl;

Y^2 is -O-, -$S(O)_2$-, -NH- or -N(C_1-C_4)alkyl-;

each of R^{20a} and R^{20b} is independently hydrogen or (C_1-C_4)alkyl;

Q^1 is -O-, -S- or -N(R^{30a})-;

Q^2 and Q^3 are each independently -C(R^{31a})- or -N-, wherein:

R^{30a} is hydrogen or (C_1-C_4)alkyl; and

R^{31a} is hydrogen, (C_1-C_4)alkyl or halo;

W^1 is -O- or -S-;

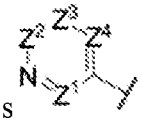
W^2 is -C(O)- or -$C(H)_2$-; and

R^{40a} is hydrogen or (C_1-C_4)alkyl;

each R^1 is independently (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, cyano, sulfonate, -$S(O)_{0-2}$(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, and -O-(3-15-membered)heterocyclyl;

R^8 is a C3-C18 carbocyclyl or a 3-18-member heterocyclyl; and

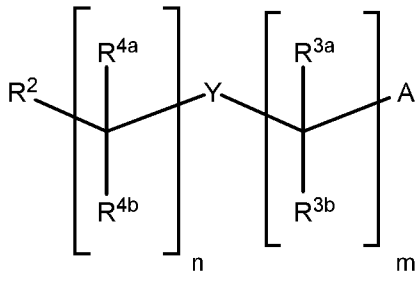
t is 1, 2 or 3;

provided that when Ring A is A2 and W is $-Y(CR^{4a}R^{4b})_nR^2$, then R^2 is  and R^1 is not a methoxy, wherein each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and $C(R^9)$, wherein no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and each R^9 is independently hydrogen or a 5-18-member heteroaryl substituent; and

provided that when Ring A is A2 and W is Y', then R^1 is not a trifluoromethyl group;

and further wherein each aryl, heteroaryl, carbocyclyl, heterocyclyl, alkyl or cycloalkyl is optionally and independently substituted.

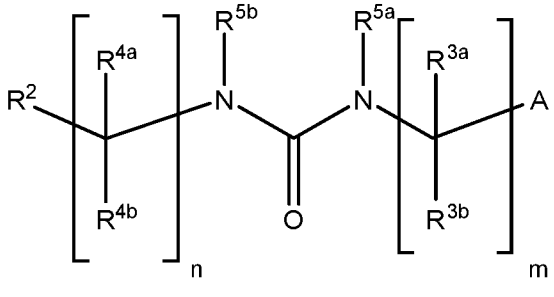
2. The compound of claim 1, represented by Structural Formula IB:



(IB),

or a pharmaceutically acceptable salt thereof.

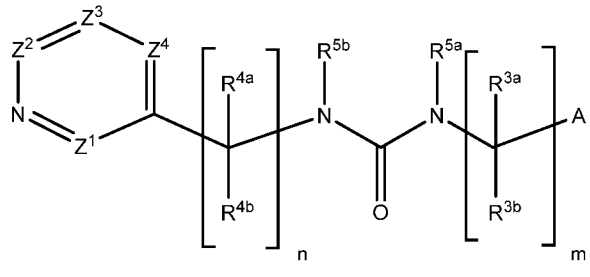
3. The compound of claim 2, represented Structural Formula IC:



(IC),

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of Claims 1-3, represented by Structural Formula ID:



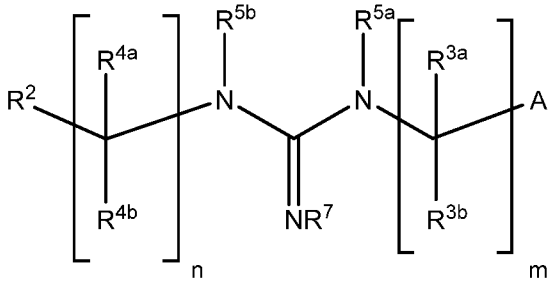
(ID),

or a pharmaceutically acceptable salt thereof, wherein:

each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and C(R^9), wherein:

no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and each R^9 is independently hydrogen or a heteroaryl substituent.

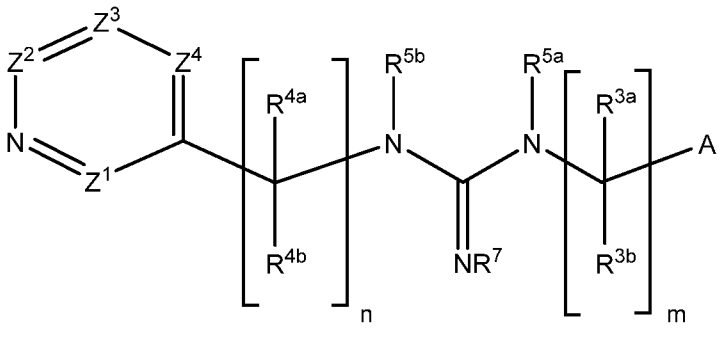
5. The compound of claim 2, represented by Structural Formula IE:



(IE),

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of Claims 1, 2 or 5, represented by Structural Formula IF:



(IF),

or a pharmaceutically acceptable salt thereof, wherein:

each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and C(R^9), wherein:

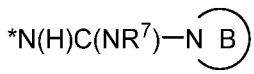
no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and each R^9 is independently hydrogen or a heteroaryl substituent.

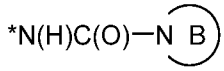
7. The compound of any one of Claims 1, 2, 3 or 5, wherein R^2 is optionally substituted phenyl or optionally substituted 5-15-membered heteroaryl having 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

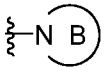
8. The compound of Claim 7, wherein R^2 is optionally substituted and is selected from pyridinyl, isoxazolyl, thiazolyl, pyridazinyl, and phenyl.

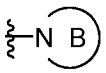
9. The compound of Claim 8, wherein R^2 is selected from 6-aminopyridin-3-yl, 6-trifluoromethylpyridin-3-yl, 6-chloropyridin-3-yl, pyridin-3-yl, pyridin-2-yl, pyridin-4-yl, 3,5-dimethylisoxazol-4-yl, thiazol-4-yl, pyridazin-3-yl, 4-aminophenyl and 6-(dimethylamino)pyridin-3-yl.

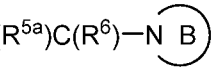
10. The compound of any one of Claims 1, 2, 3, 5, 7 or 8, wherein R^2 is optionally substituted with 1, 2 or 3 substituents independently selected from amino, halogen, (C_1-C_4)alkyl and (C_1-C_4)haloalkyl.

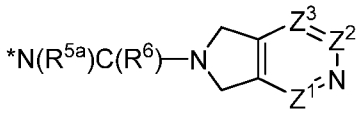
11. The compound of Claim 1, wherein Y' is .

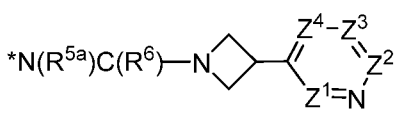
12. The compound of Claim 1, wherein Y' is .

13. The compound of anyone of Claims 1, 11 or 12, wherein  is bicyclic.

14. The compound of anyone of Claims 1, 11 or 12, wherein  is monocylclic.

15. The compound of Claim 1, wherein  is selected from:

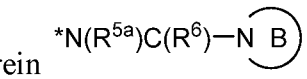


or


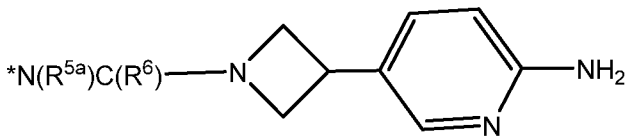
wherein,

each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and $C(R^9)$, wherein: no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and

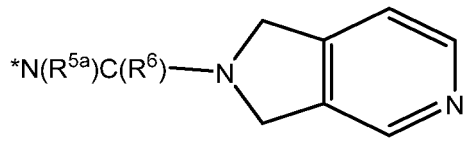
each R^9 is independently hydrogen or a heteroaryl substituent.

16. The compound of claim 15, wherein 

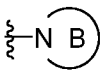
is selected from



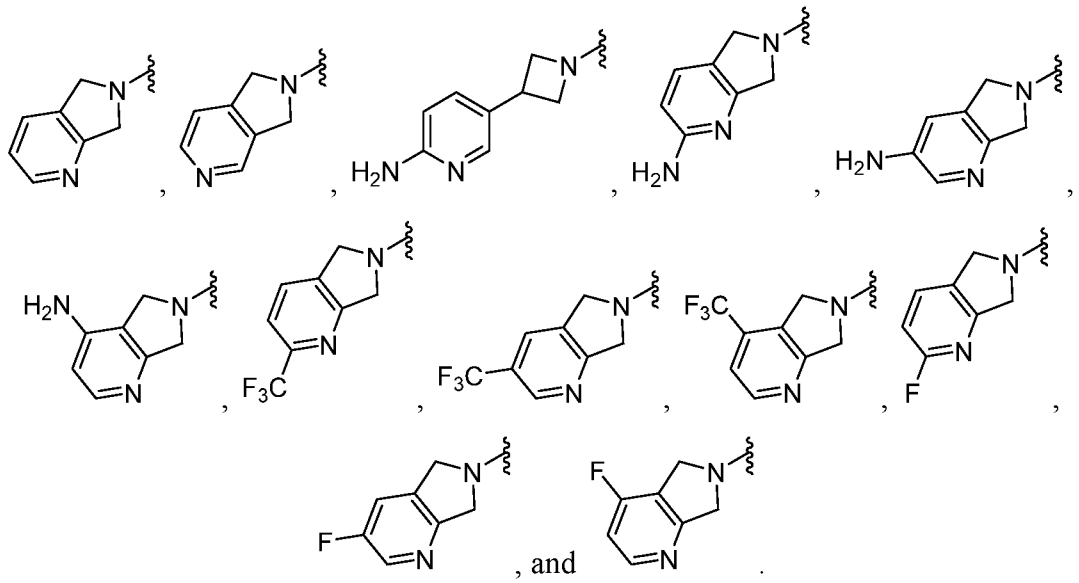
or



.

17. The compound of anyone of claim 1, 11, 12, or 15, wherein 

is selected from

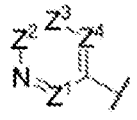
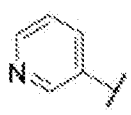
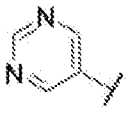
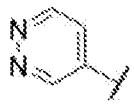
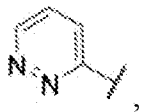
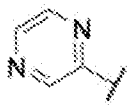


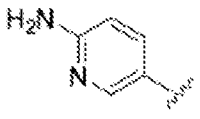
, and .

18. The compound of any one of Claims 1 or 13-16, wherein R^{5a} is hydrogen.

19. The compound of any one of Claims 1, 15, or 16, wherein R^6 is =O.

20. The compound of any one of Claims 1, 15, or 16, wherein R^6 is $=NR^7$.

21. The compound of any one of Claims 4, 6 or 15, wherein the portion of the compound represented by  is selected from: , , , , and , and is optionally substituted with 1, 2 or 3 substituents independently selected from amino, halogen, C1-C4 alkyl or C1-C4 haloakyl.

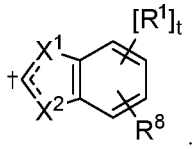
22. The compound of Claim 21, wherein the portion of the compound represented by  is .

23. The compound of any one of claims 1-10, 21 or 22, wherein R^{5a} and R^{5b} are hydrogen.

24. The compound of any one of Claims 1-23, wherein R^{3a} and R^{3b}, if present, are each hydrogen.

25. The compound of any one of Claims 1-24, wherein m is 1.

26. The compound on any one of Claims 1-10 or 21-25, wherein n is 1.

27. The compound of any one of Claims 1-26, wherein A is .

28. The compound of claim 27, wherein X^1 is -O- and X^2 is $-C(R^{11a})-$.

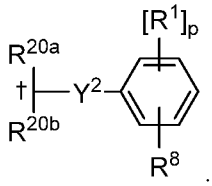
29. The compound of claim 27, wherein X^1 is -O- and X^2 is -N-.

30. The compound of claim 27, wherein X^1 is -S- and X^2 is -C(R^{11a})-.

31. The compound of claim 27, wherein X^1 is -N(R^{10a})- and X^2 is -C(R^{11a})-.

32. The compound of any one of claims 28, 30 or 31 wherein R^{11a} is hydrogen.

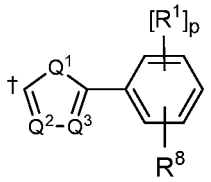
33. The compound of any one of Claim 1-26, wherein A is



34. The compound of Claim 33, wherein Y^2 is –O–.

35. The compound of Claim 33 or 34, wherein each of R^{20a} and R^{20b} is hydrogen.

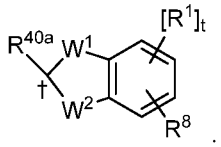
36. The compound of any one of Claims 1-26, wherein A is:



37. The compound of Claim 36, wherein Q^1 is –O–; and Q^2 and Q^3 are each independently –C(R^{31a})–.

38. The compound of claim 37, wherein R^{31a} is hydrogen.

39. The compound of any one of Claims 1-26, wherein A is:

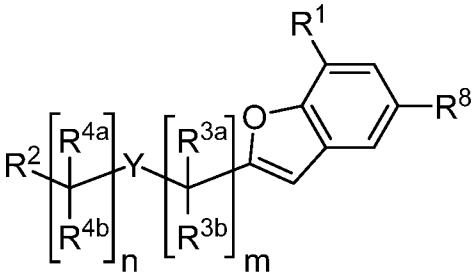


40. The compound of Claim 39, wherein W^1 is –O–.

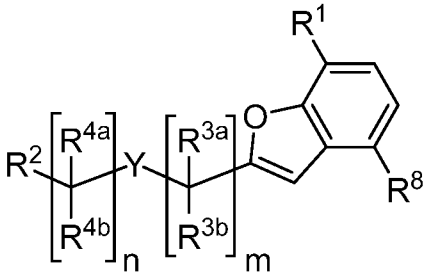
41. The compound of Claim 39 or 40, wherein W^2 is $–CH_2–$.

42. The compound of any one of Claims 39-41, wherein R^{40a} is hydrogen.

43. The compound of Claim 1, represented by Structural Formula III-IV:



(III), or



(IV),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from each R^1 is independently (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

R^8 is optionally substituted (C_3-C_{12})carbocyclyl and optionally substituted 3-15-membered heterocyclyl; and

each carbocyclyl, heterocyclyl, aryl, heteroaryl and alkyl is optionally and independently substituted.

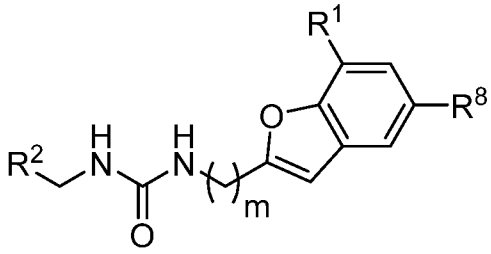
44. The compound of Claim 43, wherein Y is $-N(R^{5a})C(O)N(R^{5b})-$.

45. The compound of Claim 44, wherein Y is –NHC(O)NH-.

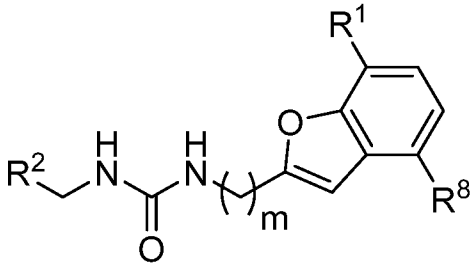
46. The compound of Claim 43, wherein Y is -N(R^{5a})C(NR^7)N(R^{5b})-.

47. The compound of any one of Claims 43-46, wherein n is 1.

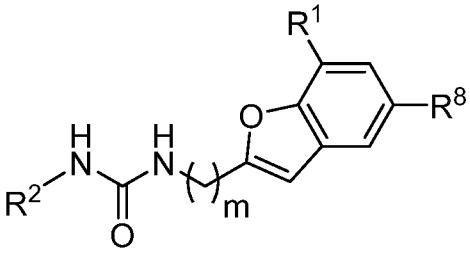
48. The compound of Claim 43, represented by Structural Formulas V-VIII:



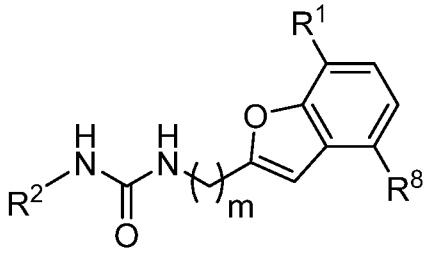
(V),



(VI),



(VII), or

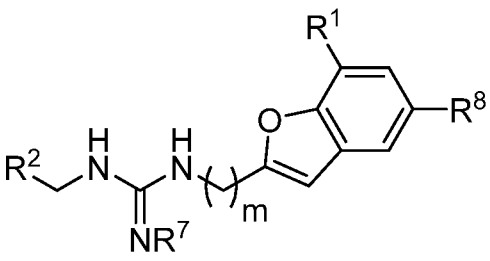


(VIII)

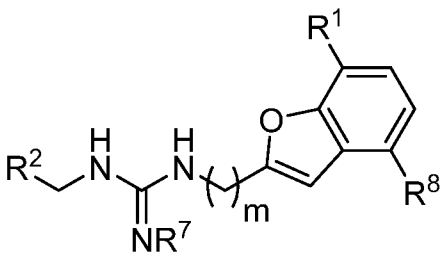
or a pharmaceutically acceptable salt thereof, wherein:

m is 1 or 2.

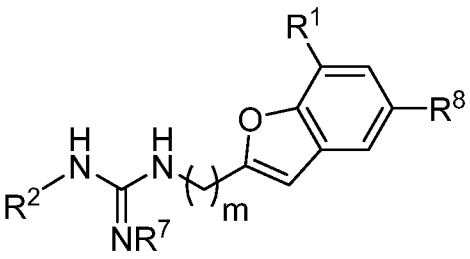
49. The compound of Claim 43, represented by Structural Formulas IX-XII:



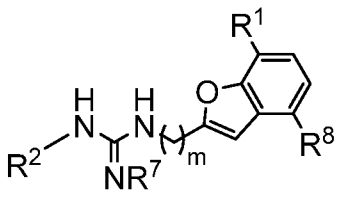
(IX),



(X),



(XI), or



(XII),

or a pharmaceutically acceptable salt thereof, wherein:

m is 1 or 2.

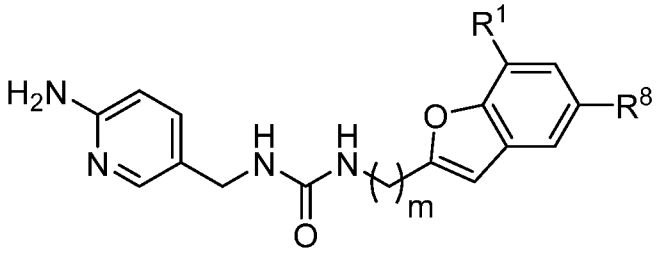
50. The compound of any one of Claims 43-49, wherein R^2 is optionally substituted phenyl or optionally substituted 5-6-membered heteroaryl having 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

51. The compound of Claim 50, wherein R^2 is optionally substituted and is selected from pyridinyl, isoxazolyl, thiazolyl, pyridazinyl, and phenyl.

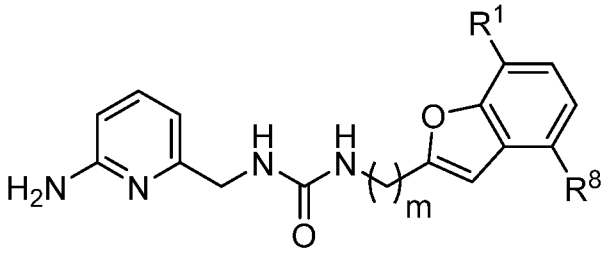
52. The compound of Claim 51, wherein R^2 is selected from 6-aminopyridin-3-yl, 6-trifluoromethylpyridin-3-yl, 6-chloropyridin-3-yl, pyridin-3-yl, pyridin-2-yl, pyridin-4-yl, 3,5-dimethylisoxazol-4-yl, thiazol-4-yl, pyridazin-3-yl, 4-aminophenyl and 6-(dimethylamino)pyridin-3-yl.

53. The compound of any one of Claims 43-51, wherein R^2 is optionally substituted with 1, 2 or 3 substituents independently selected from amino, halogen, $(C_1$-$C_4)$alkyl and $(C_1$-$C_4)$haloalkyl.

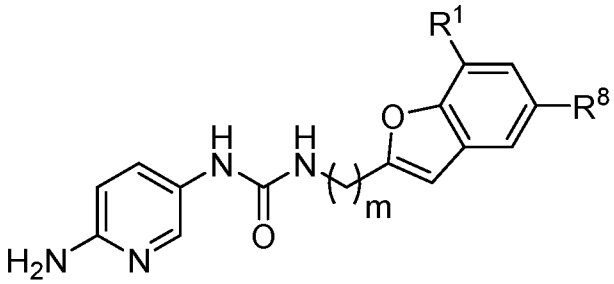
54. The compound of Claim 43, represented by Structural Formula XIII-XVI:



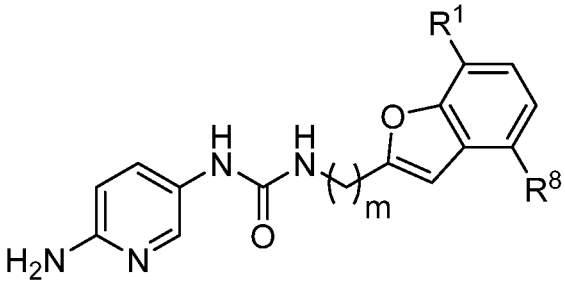
(XIII),



(XIV),



(XV), or

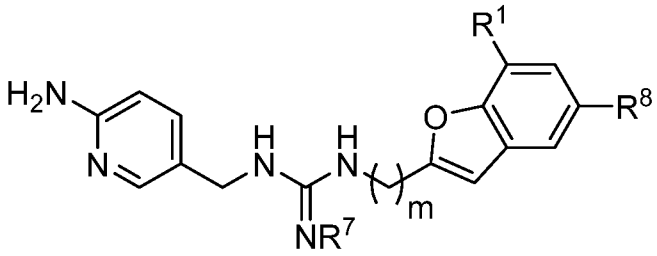


(XVI),

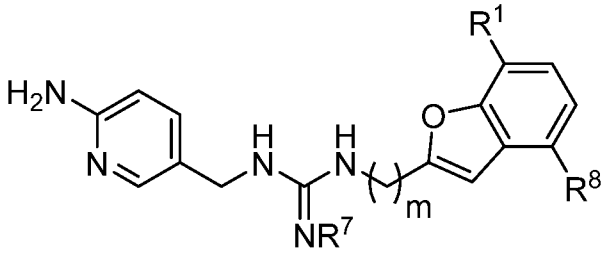
or a pharmaceutically acceptable salt thereof, wherein:

m is 1 or 2.

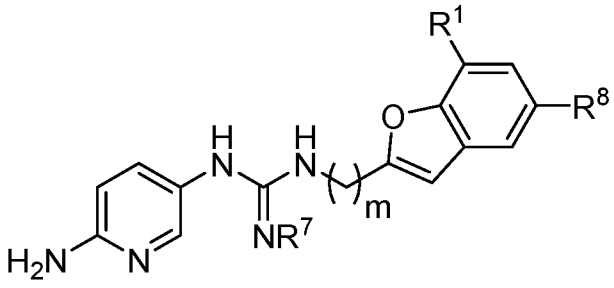
55. The compound of Claim 43, represented by Structural Formula XVII-XX:



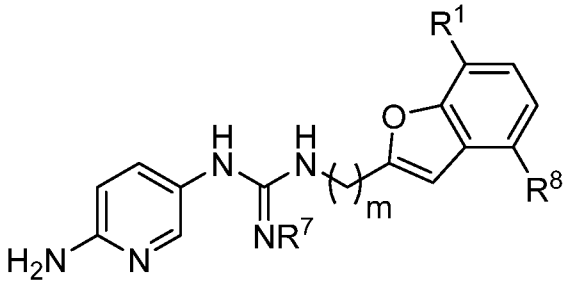
(XVII),



(XVIII),



(XIX), or

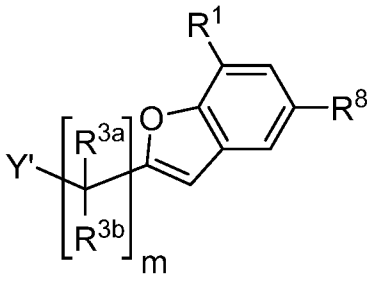


(XX),

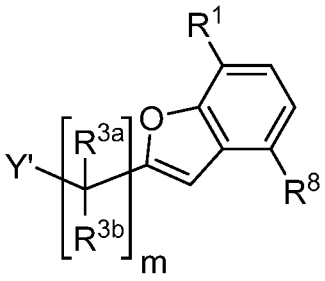
or a pharmaceutically acceptable salt thereof, wherein:

m is 1 or 2.

56. The compound of any one Claim 1, represented by Structural Formula XXXIII-XXXIV:



(XXXIII), or



(XXXIV)

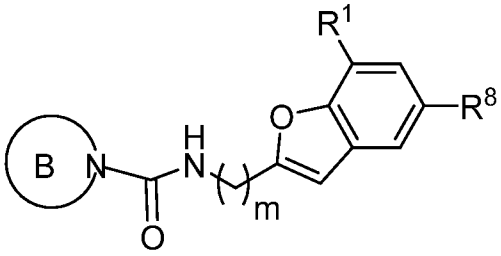
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

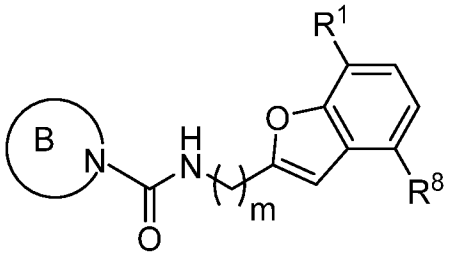
R^8 is optionally substituted (C_3-C_{12})carbocyclyl and optionally substituted (3-15-membered)heterocyclyl; and

each carbocyclyl, heterocyclyl and alkyl is optionally and independently substituted.

57. The compound of Claim 56, represented by Structural Formula XXXV or XXXVI:



(XXXV), or

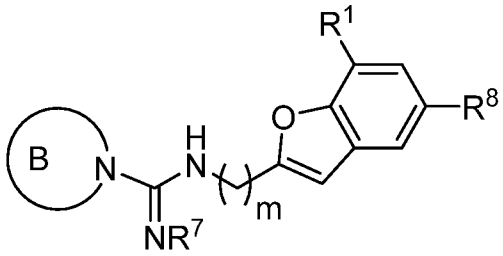


(XXXVI),

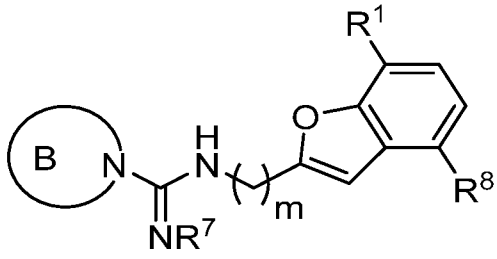
or a pharmaceutically acceptable salt thereof, wherein:

m is 1 or 2.

58. The compound of Claim 56, represented by Structural Formula XXXVII-XXXVIII:

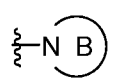


(XXXVII),

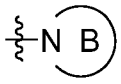


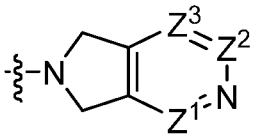
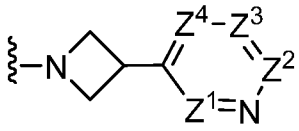
(XXXVIII),

or a pharmaceutically acceptable salt thereof.

59. The compound of anyone of Claims 56-58, wherein  is bicyclic.

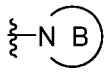
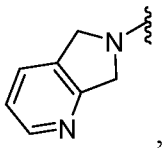
60. The compound of anyone of Claims 56-58, wherein  is monocylclic.

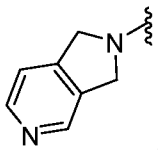
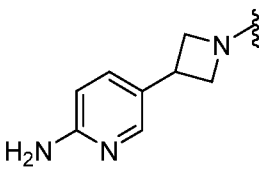
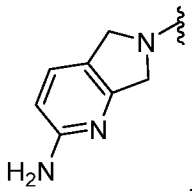
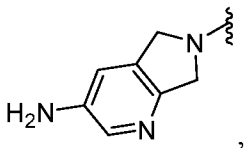
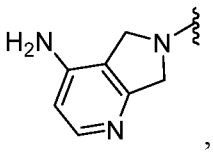
61. The compound of Claim 56-58, wherein  is selected from:

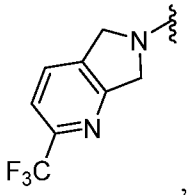
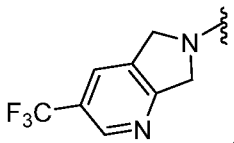
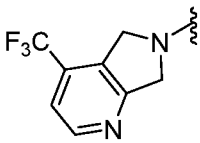
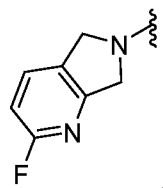
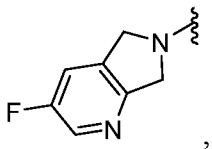
 or  wherein,

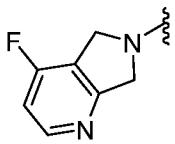
each of Z^1, Z^2, Z^3 and Z^4 is independently selected from N and C(R^9), wherein: no more than one of Z^1, Z^2, Z^3 and Z^4 is nitrogen, and

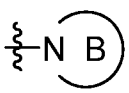
each R^9 is independently hydrogen or a heteroaryl substituent.

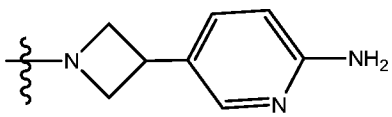
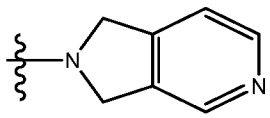
62. The compound of Claim 61, wherein  is selected from ,

, , , , ,

, , , , , and

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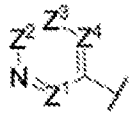
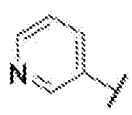
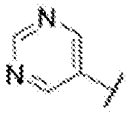
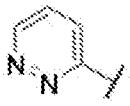
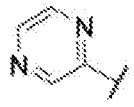
63. The compound of claim 62, wherein  is elected from

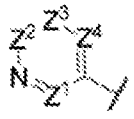
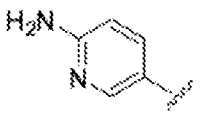
 or .

64. The compound of any one of claim 56, wherein R^{5a} is hydrogen.

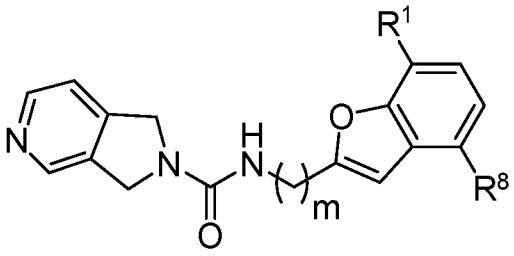
65. The compound of any one of Claims 56, wherein R^6 is =O.

66. The compound of any one of Claims 56, wherein R^6 is $=NR^7$.

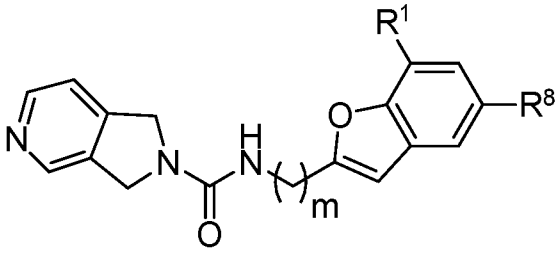
67. The compound of Claim 61, wherein the portion of the compound represented by  is selected from: , , , , and , and is optionally substituted with 1, 2 or 3 substituents independently selected from amino, halogen, (C_1-C_4) alkyl or (C_1-C_4) haloakyl.

68. The compound of Claim 67, wherein the portion of the compound represented by  is .

69. The compound of Claim 56, represented by Structural Formula XXXIX-XL:



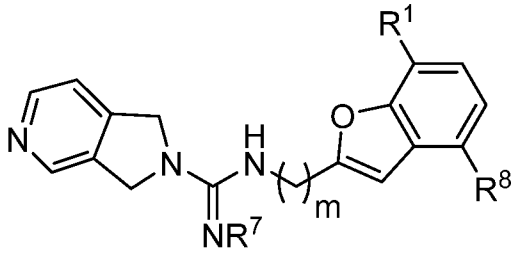
(XXXIX), or



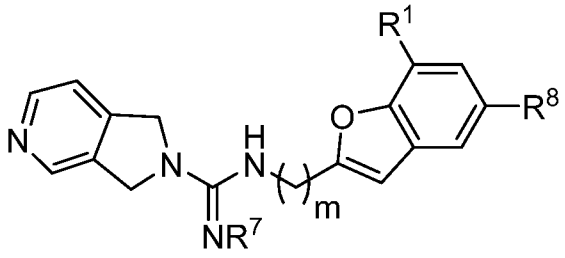
(XL)

or a pharmaceutically acceptable salt thereof.

70. The compound of Claim 56, represented by Structural Formula XLI-XLII:



(XLI), or



(XLII).

or a pharmaceutically acceptable salt thereof.

71. The compound of any one of Claims 1-70, wherein R^1 is selected from halogen, halo(C_1-C_4)alkyl, optionally substituted (C_1-C_4)alkyl, optionally substituted -O-halo(C_1-C_4)alkyl and optionally substituted -O-(C_1-C_4)alkyl.

72. The compound of Claim 71, wherein R^1 is selected from fluoro, chloro, CF_3, CHF_2, OCH_3, OCF_3 and $C(CH_3)_3$.

73. The compound of Claim 72, wherein R^1 is selected from fluoro, chloro, CF_3 and CHF_2.

74. The compound of Claim 73, wherein R^1 is chloro or CF_3.

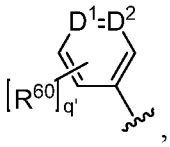
75. The compound of any one of Claims 1-70, wherein R^1 is independently selected from optionally substituted (C_3-C_{12})carbocyclyl, optionally substituted (3-15-membered)heterocyclyl, optionally substituted -O-(C_3-C_{12})carbocyclyl, optionally substituted -O-(3-15-membered)heterocyclyl.

76. The compound of Claim 75, wherein R^1 is selected from optionally substituted (C_6-C_{12})aryl, optionally substituted (5-15-membered)heteroaryl, optionally substituted –O–(C_6-C_{12})aryl and optionally substituted –O–(5-15-membered)heteroaryl.

77. The compound of Claim 76, wherein R^1 is selected from optionally substituted (C_6-C_{12})aryl and optionally substituted (5-15-membered)heteroaryl.

78. The compound of Claim 77, wherein R^1 is independently selected from optionally substituted phenyl or optionally substituted pyridine.

79. The compound of any one of Claims 71-79, wherein R^1 is optionally substituted with 1, 2 or 3 substituents independently selected from halo, cyano, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, hydroxy, (C_1-C_3)alkoxy and halo(C_1-C_3)alkoxy.

80. The compound of any one of Claim 1-70 and 75-78, wherein R^1 is , wherein:

each of D^1 and D^2 is independently -N- or -C(H)-, wherein no more than one of D^1 and D^2 is -N-;

each R^{60}, if present, is independently halo, cyano, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, hydroxy, (C_1-C_3)alkoxy or halo(C_1-C_3)alkoxy; and

q′ is 0, 1, 2 or 3.

81. The compound of claim 80, wherein D^1 and D^2 are each -C(H)-.

82. The compound of claim 80 or 81, wherein each R^{60} is independently fluoro or chloro.

83. The compound of claims 80, 81 or 82, wherein q′ is 1 or 2.

84. The compound of any one of Claims 1-83, wherein R^8 is optionally and independently substituted with 1, 2 or 3 substituents and is phenyl or a 5-6-membered heteroaryl having 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

85. The compound of Claim 84, wherein R^8 is substituted with 1, 2 or 3 substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $C(O)(C_1\text{-}C_4)$alkyl, $C(S)(C_1\text{-}C_4)$alkyl, $C(O)(C_0\text{-}C_4$ alkylene$)NR^{10}R^{11}$, $C(S)(C_0\text{-}C_4$ alkylene$)NR^{10}R^{11}$, $\text{-}S(O)_2NR^{10}R^{11}$ and $C(O)NR^{12}NR^{10}R^{11}$, wherein:

R^{10} and R^{11} are each independently hydrogen, optionally substituted $C_1\text{-}C_4$ alkyl, optionally substituted $(C_3\text{-}C_7)$carbocyclyl, or optionally substituted (3-15-membered)heterocyclyl; or

R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl; and

R^{12} is hydrogen or optionally substituted $(C_1\text{-}C_4)$alkyl.

86. The compound of Claim 85, wherein R^8 is substituted with one substituent selected from $C(O)(C_0\text{-}C_1$ alkylene$)NR^{10}R^{11}$, or $C(S)(C_0\text{-}C_1$ alkylene$)NR^{10}R^{11}$, wherein R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl; and is further optionally substituted with 1 or 2 substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$haloalkyl.

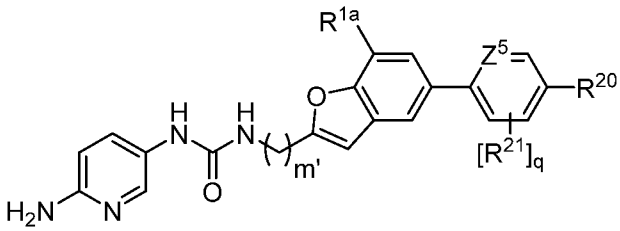
87. The compound of Claim 86, wherein R^8 is:

phenyl or pyridinyl substituted at the para position relative to its attachment point with one substituent selected from $\text{-}C(O)NR^{10}R^{11}$ or $\text{-}C(S)NR^{10}R^{11}$, wherein R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl; and

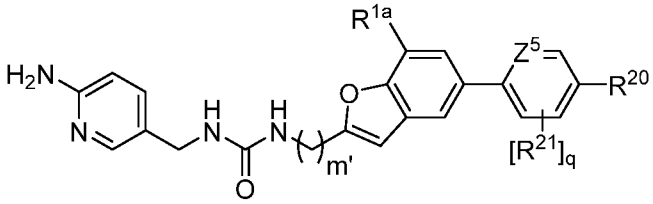
further optionally substituted with 1 or 2 substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$haloalkyl.

88. The compound of any one of Claims 85-87, wherein the heterocyclyl formed by R^{10} and R^{11} taken together with the nitrogen atom to which they are commonly attached is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, hydroxyl, halo(C_1-C_3)alkyl, (C_1-C_3)alkyl and (C_1-C_3)alkoxy.

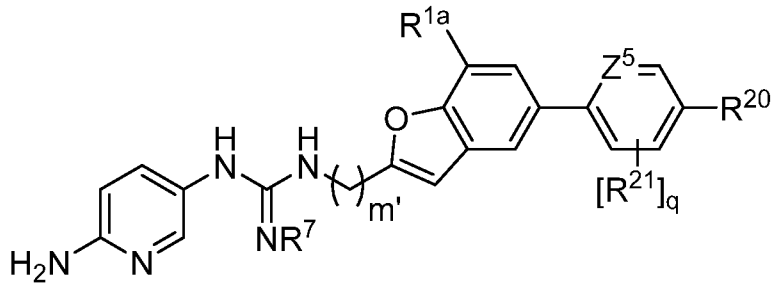
89. A compound represented by Structural Formula XXI-XXIV:



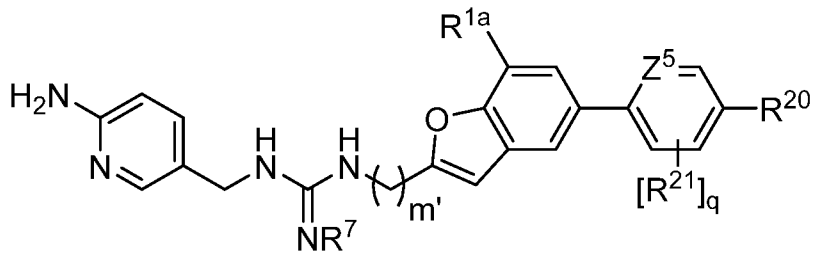
(XXI),



(XXII),



(XXIII), or



(XXIV),

or a pharmaceutically acceptable salt thereof, wherein:

m´ is 1 or 2;

R^{1a} is selected from (C_3-C_{12})carbocyclyl, 3-15-membered heterocyclyl, halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -O-halo(C_1-C_4)alkyl, -O-(C_3-C_{12})carbocyclyl, -O-(3-15-membered)heterocyclyl;

Z^5 is –N– or –C(H)–;

R^{20} is C(O)(C_0-C_1 alkylene)$NR^{10}R^{11}$, C(S)(C_0-C_1 alkylene)$NR^{10}R^{11}$, wherein:

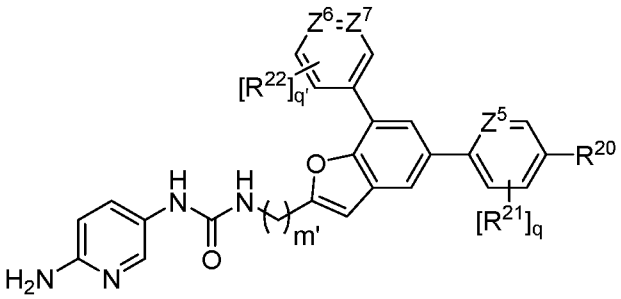
R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl;

each R^{21}, if present, is independently halo;

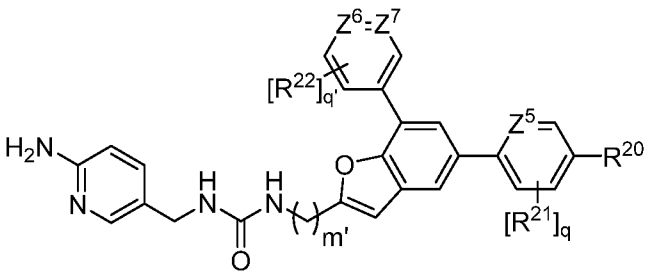
R7 is hydrogen, alkyl or –CN; and

q is 0, 1, 2, 3 or 4 when A is –C(H) – and 0, 1, 2 or 3 when A is –N–.

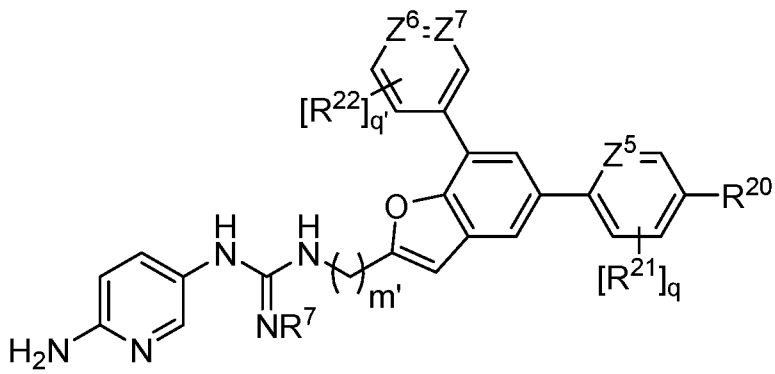
90. The compound of Claim 89, represented by Structural Formula XXV-XXVIII:



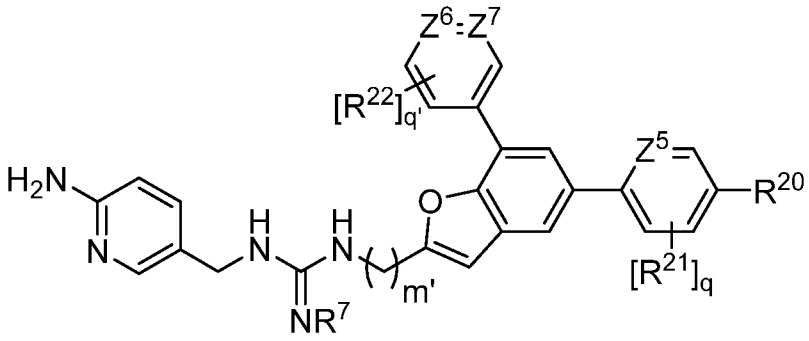
(XXV),



(XXVI),



(XXVII), or



(XXVIII),

or a pharmaceutically acceptable salt thereof, wherein:

each of Z^6 and Z^7 is independently –N– or –C(H)–, wherein no more than one of Z^6 and Z^7 is nitrogen;

each R^{22}, if present, is independently halo, cyano, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, hydroxy, $(C_1\text{-}C_3)$alkoxy or halo$(C_1\text{-}C_3)$alkoxy ; and

q′ is 0, 1, 2 or 3.

91. The compound of Claim 89 or 90, wherein q is 0, 1 or 2.

92. The compound of any one of Claims 89-91, wherein R^{21}, for each occurrence and if present, is fluoro.

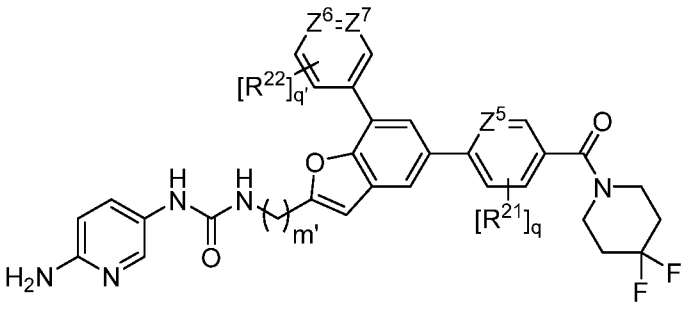
93. The compound of any one of Claims 89-92, wherein R^{20} is $C(O)NR^{10}R^{11}$ or $C(S)NR^{10}R^{11}$, wherein R^{10} and R^{11} are taken together with the nitrogen atom to which they are commonly attached to form an optionally substituted (3-15-membered)heterocyclyl having 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

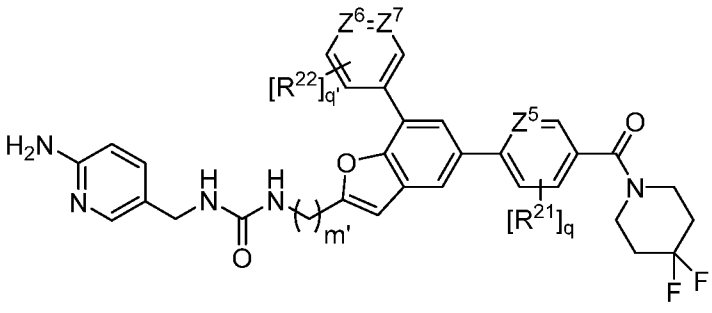
94. The compound of any one of Claims 89-93, wherein the heterocyclyl formed by R^{10} and R^{11} taken together with the nitrogen atom to which they are commonly attached is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, hydroxyl, halo$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkyl and $(C_1\text{-}C_3)$alkoxy.

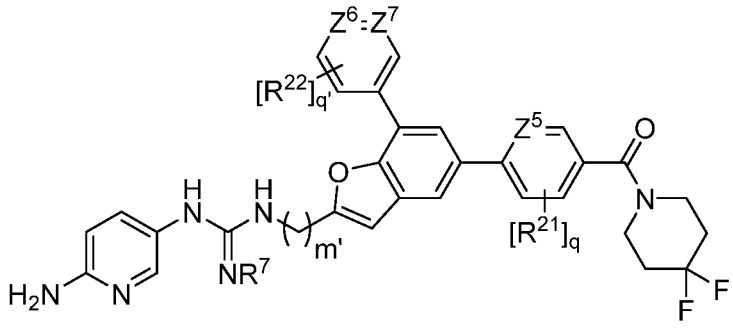
95. The compound of any one of Claims 89-94, wherein Z^5 is C(H).

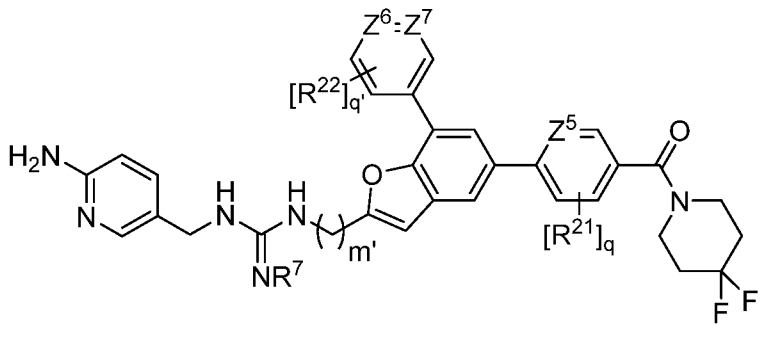
96. The compound of any one of Claims 89-94, wherein Z^5 is N.

97. The compound of any one of Claims 90-96, represented by Structural Formula XXIX-XXXII:


(XXIX),

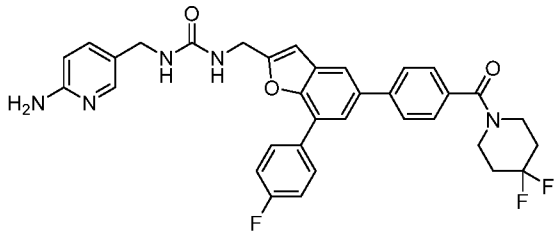
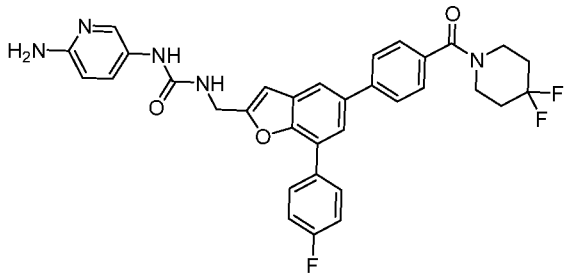
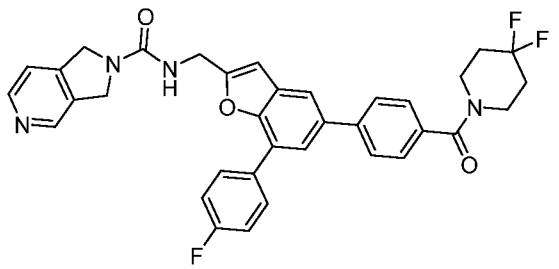

(XXX),

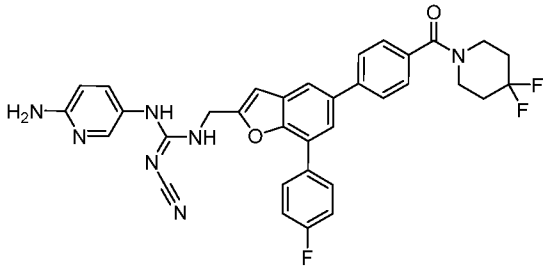
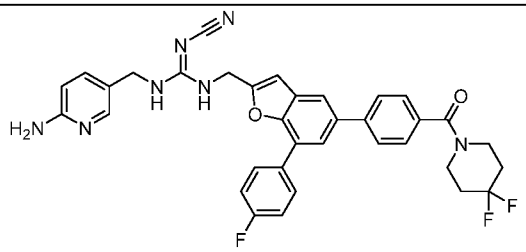
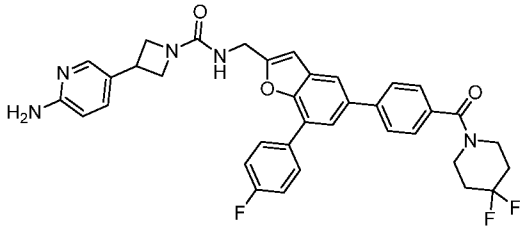
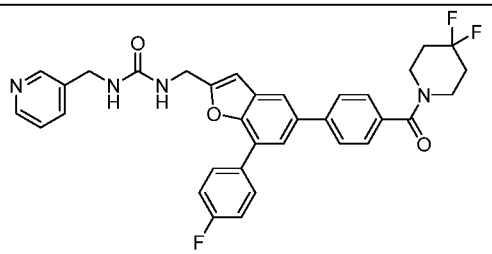
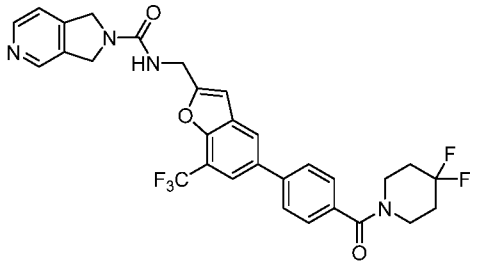

(XXXI), or

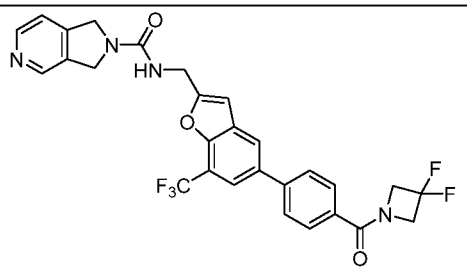
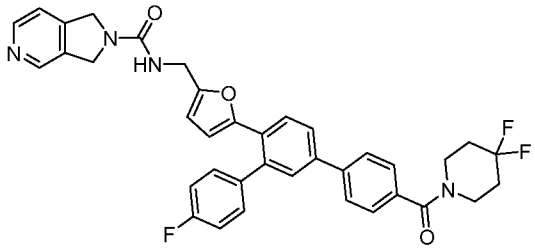
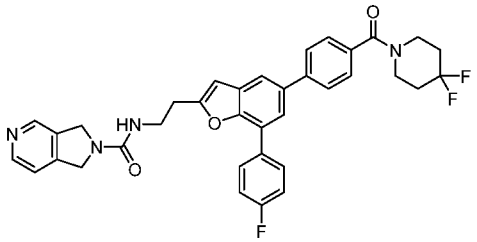
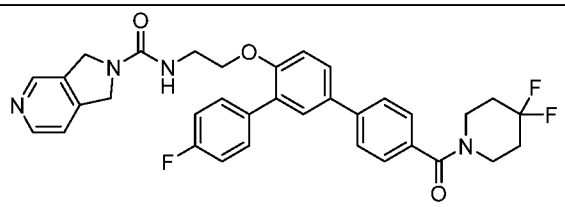
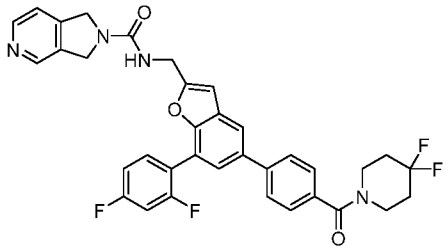

(XXXII),

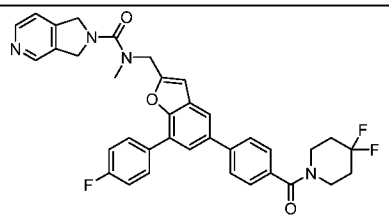
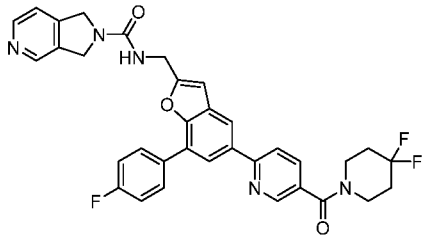
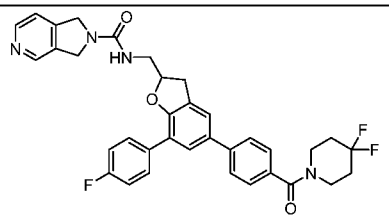
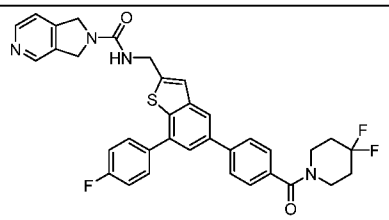
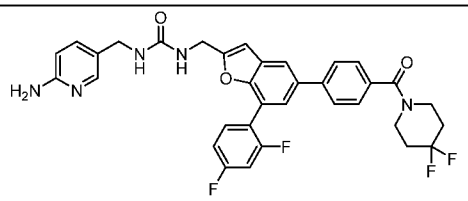
or a pharmaceutically acceptable salt thereof.

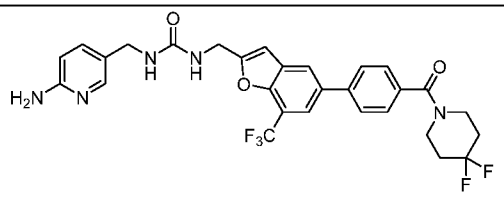
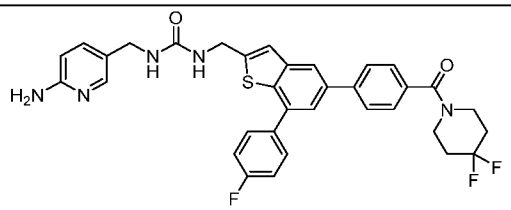
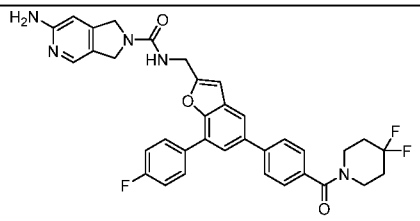
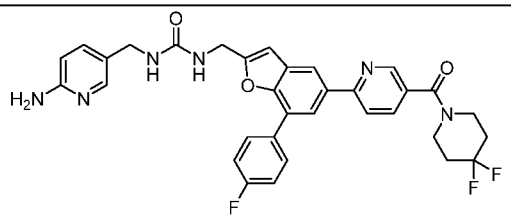
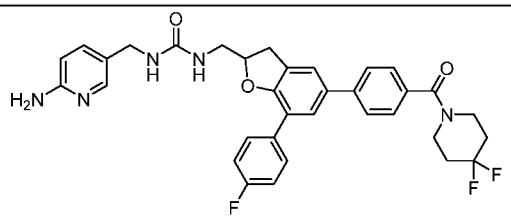
98. A compound represented by any one of the structural formulas below

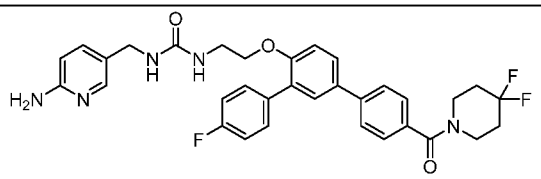
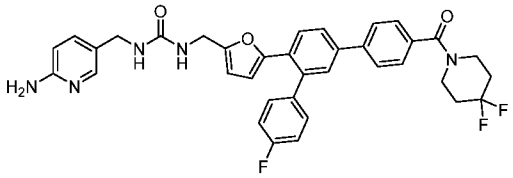
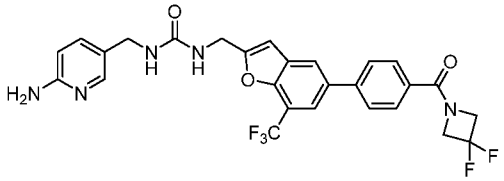
Cpd. No.	Structure	Compound Name
100		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
101		1-(6-aminopyridin-3-yl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
102		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

118		(E)-1-(6-aminopyridin-3-yl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
119		(Z)-1-((6-aminopyridin-3-yl)methyl)-2-cyano-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)guanidine
103		3-(6-aminopyridin-3-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)azetidine-1-carboxamide
104		1-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-3-(pyridin-3-ylmethyl)urea
105		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

106		N-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
120		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)furan-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
107		N-(2-(5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
121		N-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4''-fluoro-[1,1':3',1''-terphenyl]-4'-yl)oxy)ethyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
108		N-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide

109		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-N-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
110		N-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
122		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
111		N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
112		1-((6-aminopyridin-3-yl)methyl)-3-((7-(2,4-difluorophenyl)-5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)benzofuran-2-yl)methyl)urea

113		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea
114		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzo[b]thiophen-2-yl)methyl)urea
115		6-amino-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide
116		1-((6-aminopyridin-3-yl)methyl)-3-((5-(5-(4,4-difluoropiperidine-1-carbonyl)pyridin-2-yl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)urea
123		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl)methyl)urea

124		1-((6-aminopyridin-3-yl)methyl)-3-(2-((4-(4,4-difluoropiperidine-1-carbonyl)-4"-fluoro-[1,1':3',1"-terphenyl]-4'-yl)oxy)ethyl)urea
125		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(4,4-difluoropiperidine-1-carbonyl)-4"-fluoro-[1,1':3',1"-terphenyl]-4'-yl)furan-2-yl)methyl)urea
117		1-((6-aminopyridin-3-yl)methyl)-3-((5-(4-(3,3-difluoroazetidine-1-carbonyl)phenyl)-7-(trifluoromethyl)benzofuran-2-yl)methyl)urea

or a pharmaceutically acceptable salt thereof.

99. A pharmaceutical composition comprising:

(a) a compound of any one of Claims 1-98, or a pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

100. A method of treating a disorder selected from cancer (e.g., lymphoma, such as mantle cell lymphoma), a neurodegenerative disease, inflammatory diseases or an autoimmune system disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of Claims 1-98, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 99.

101. The method of Claim 100, whereing the disorder is cancer.

102. The method of Claim 100, wherein the cancer is lymphoma.

103. The method of Claim 100, wherein the cancer is cervical cancer.

104. The method of Claim 100, wherein the cancer is mantle cell lymphoma.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/069303

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/14 C07D471/04 A61K31/445 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/329786 A1 (WILLARDSEN J ADAM [US] ET AL) 27 December 2012 (2012-12-27) paragraph [0002]; claim 2; examples 274,363,368,401,459,478,519	1
Y	US 2012/053170 A1 (ARIGON JEROME [FR] ET AL) 1 March 2012 (2012-03-01) table I	1-32, 39-104
Y	WO 2015/003166 A1 (KARYOPHARM THERAPEUTICS INC [US]) 8 January 2015 (2015-01-08) pages 370-374; examples 500-767	1-32, 39-104

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2017	26/05/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/069303

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

27-32, 39-70, 89-97(completely); 1-26, 71-88, 98-104(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 27-32, 39-70, 89-97(completely); 1-26, 71-88, 98-104(partially)

Compounds according to claim 1 wherein A is A1 or A4.

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2. claims: 33-35(completely); 1-26, 71-88, 98-104(partially)

Compounds according to claim 1 wherein A is A2.

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3. claims: 36-38(completely); 1-26, 71-88, 98-104(partially)

Compounds according to claim 1 wherein A is A3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/069303

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012329786 A1	27-12-2012	AU 2011223790 A1	30-08-2012
		BR 112012021806 A2	08-09-2015
		CA 2791680 A1	09-09-2011
		CN 102869261 A	09-01-2013
		CN 103819393 A	28-05-2014
		EP 2542086 A1	09-01-2013
		JP 2013522171 A	13-06-2013
		KR 20130044382 A	02-05-2013
		NZ 601788 A	28-11-2014
		US 2012329786 A1	27-12-2012
		US 2015353538 A1	10-12-2015
		WO 2011109441 A1	09-09-2011
US 2012053170 A1	01-03-2012	AR 075920 A1	04-05-2011
		AU 2010227402 A1	20-10-2011
		BR PI1013553 A2	12-04-2016
		CA 2756099 A1	30-09-2010
		CN 102448939 A	09-05-2012
		EP 2411368 A1	01-02-2012
		FR 2943669 A1	01-10-2010
		JP 2012521396 A	13-09-2012
		KR 20110133049 A	09-12-2011
		RU 2011142753 A	27-04-2013
		SG 174902 A1	28-11-2011
		TW 201038554 A	01-11-2010
		US 2012053170 A1	01-03-2012
		UY 32517 A	29-10-2010
		WO 2010109122 A1	30-09-2010
WO 2015003166 A1	08-01-2015	AU 2014285019 A1	21-01-2016
		CA 2917315 A1	08-01-2015
		CN 105492437 A	13-04-2016
		EA 201690153 A1	30-06-2016
		EP 3016946 A1	11-05-2016
		JP 2016523932 A	12-08-2016
		KR 20160029808 A	15-03-2016
		SG 11201510339U A	28-01-2016
		US 2016368904 A1	22-12-2016
		WO 2015003166 A1	08-01-2015