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(54) **IMIDAZOPYRIDINE DERIVATIVES**

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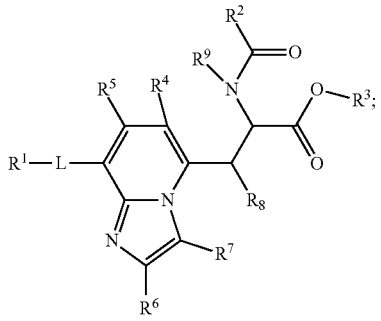
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(57) **ABSTRACT**

The present disclosure provides a compound of Formula (I):

(I)



or a pharmaceutically acceptable salt thereof as described herein. The present disclosure also provides pharmaceutical compositions comprising a compound of Formula (I), processes for preparing compounds of Formula (I), and therapeutic methods for treating inflammatory disease.

IMIDAZOPYRIDINE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/752,848, filed Oct. 30, 2018, which is incorporated herein in its entirety for all purposes.

FIELD

[0002] The present disclosure relates generally to novel compounds that have α4β7 integrin inhibitory action, prodrugs of compounds having α4β7 integrin inhibitory action, and methods of use and manufacture thereof.

BACKGROUND

[0003] Integrins are heterodimeric cell surface proteins involved in numerous cellular processes including cell-cell and cell-extracellular matrix interactions. Upon binding of an extracellular ligand, integrins mediate signal transduction to the cell interior resulting in lymphocyte cell capture, adhesion, and infiltration into the tissue.

[0004] Integrins are heterodimeric proteins consisting of an alpha and a beta subunit. There are 18 known alpha subunits and 8 known beta subunits. The α4β7 integrin is expressed on the surface of lymphocytes and recognizes the extracellular ligand mucosal addressing cell adhesion molecule-1 (MAdCAM-1). α4β7 integrin governs lymphocyte trafficking to and retention in gut tissues through its interaction with MAdCAM-1, which is expressed on venules in the intestinal mucosa and high endothelial venules (HEV) in the gut-associated lymphoid tissues (GALT). Inhibiting the interactions of integrins with their respective ligands has been proposed as an effective method of treating a variety of autoimmune and inflammatory diseases, and blocking the α4β7-MAdCAM-1 interaction has shown therapeutic benefit in inflammatory bowel disease (Crohn's disease and ulcerative colitis).

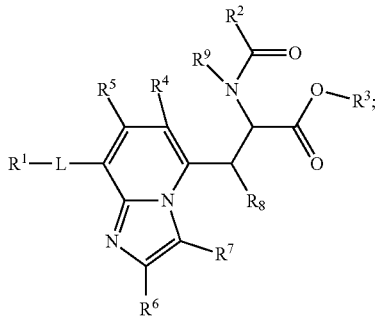
[0005] There is a need to for improved α4β7 integrin antagonist molecules for the treatment of autoimmune and inflammatory diseases, including inflammatory bowel disease.

SUMMARY

[0006] The present disclosure provides compounds that are inhibitors for α4β7 integrin. The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using (or administering) and making the compounds. The compounds provided herein are useful in treating diseases, disorders, or conditions that are mediated by α4β7 integrin. The disclosure also provides compounds for use in therapy. The disclosure further provides compounds for use in a method of treating a disease, disorder, or condition that is mediated by α4β7 integrin. Moreover, the disclosure provides uses of the compounds in the manufacture of a medicament for the treatment of a disease, disorder or condition that is mediated by α4β7 integrin.

[0007] In one aspect, provided is a compound having the structure of Formula I, or a pharmaceutically acceptable salt thereof:

(I)



[0008] L is selected from a bond, —O—C(O)—*, —NH—, —C(O)—N(H)—*, and —N(H)—C(O)—*; and * indicates the point of attachment of L to R^1;

[0009] R^1 is selected from A^1, A^2, A^3, and A^4;

[0010] A^1 is 5-10 membered heteroaryl containing one to five heteroatoms or groups independently selected from S, N, and O; wherein A^1 optionally comprises one to three C(O); and wherein A^1 is optionally substituted with one to six R^{A1};

[0011] A^2 is C_{6-10}aryl, optionally substituted with one to six R^{A1};

[0012] A^3 is $—NR^{1a}R^{1b}$; and

[0013] A^4 is C_{5-10}cycloalkyl or 5-14 membered heterocyclyl; wherein A^4 is optionally substituted with one to four R^{A1};

[0014] each R^{A1} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, $—S(O)_m—C_{1-4}$alkyl, C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$alkylene-C_{3-8}cycloalkyl, and —O-phenyl;

[0015] each C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$ alkylene-C_{3-8}cycloalkyl, and —O-phenyl of R^{A1} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, and C_{1-6}haloalkoxyl;

[0016] each C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl of R^{A1} is optionally substituted with one to three R^{1c}; wherein each R^{1c} is independently selected from C_{1-4}alkoxyl, hydroxyl, cyano, $—NR^{1a}R^{1b}$, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl; wherein each C_{3-8}cycloalkyl and 3-6 membered heterocyclyl of R^{1c} is independently optionally substituted with one to three R^{1d}; and

[0017] each R^{1d} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, C_{1-6}haloalkoxyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl;

[0018] R^2 is selected from C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl; wherein R^2 is optionally substituted with one to six R^{B1}; and wherein each R^{B1} is independently selected from halo, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-8}haloalkyl,

C_{1-8}haloalkoxyl, —$NR^{2a}R^{2b}$, —R^{2e}—$NR^{2a}R^{2b}$, —$NR^{2a}S(O)_nR^{2c}$, —$S(O)_m$—R^{2c}, —R^{2e}—$S(O)_m$—R^{2c}, —$S(O)_nNR^{2a}R^{2b}$, —$CONR^{2a}R^{2b}$, $COOR^{2b}$, —$NR^{2a}COOR^{2b}$, —$NR^{2a}COR^{2c}$, C_{3-12}cycloalkyl, 3-12 membered heterocyclyl, and C_{6-10}aryl; and

[0019] each C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-8}haloalkyl, and C_{1-8}haloalkoxyl of R^{B1} is independently optionally substituted with one to two R^{2d};

[0020] each C_{6-10}aryl, and 5-6 membered heteroaryl of R^{B1} is independently optionally substituted with one to four R^{2f};

[0021] each C_{3-12}cycloalkyl, and 3-12 membered heterocyclyl of R^{B1} is independently optionally substituted with one to four groups independently selected from one to six groups independently selected from $=CR^{2a}R^{2b}$, and R^{2f};

[0022] each R^{2a} and R^{2b} is independently selected from H, C_{1-6}alkyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-8 membered heterocyclyl;

[0023] each C_{1-6}alkyl and C_{1-8}haloalkyl of R^{2a} and R^{2b} is optionally substituted with one to three R^{aa}, wherein each R^{aa} is independently selected from hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{3-6}cycloalkyl, C_{3-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{aa} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl; and

[0024] each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-8 membered heterocyclyl of R^{2a} and R^{2b} is optionally substituted with one to three R^{bb}; wherein each R^{bb} is independently selected from halo, hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{1-6}alkoxyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{bb} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl;

[0025] R^{2c} is selected from C_{1-6}alkyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{2c} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl;

[0026] each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{2c} is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}haloalkyl, and 5-6 membered heteroaryl; and the 5-6 membered heteroaryl is optionally substituted with one to three groups independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl;

[0027] each R^{2d} is independently selected from cyano, azido, oxo, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{2d} is optionally substituted with one to three groups independently selected with halo, hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, and C_{3-6}cycloalky;

[0028] R^{2e} is C_{1-4}alkylene;

[0029] each R^{2f} is independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4} alkoxyl, C_{1-6}haloalkoxyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl; wherein each C_{3-6}cycloalkyl, C_{6-10}aryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl of R^{2f} is independently optionally substituted with one to three groups independently selected with halo, hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, C_{3-6}cycloalky, and 4-6 membered heterocyclyl, and

[0030] R^3 is selected from H, C_{1-6}alkyl, —C_{1-4}alkylene-$NR^{a1}R^{a2}$, —C_{1-4}alkylene-$C(O)NR^{a1}R^{a2}$, —C_{1-4} alkylene-O—C(O)—C_{1-4}alkyl, —C_{1-4}alkylene-O—C(O)—O—C_{1-4}alkyl, —C_{1-4}alkylene-O—C(O)—C_{1-4}alkylene-$NR^{a1}R^{a2}$, —C_{1-4}alkylene-O—C_{1-4}alkxyl, C_{3-8}cycloalkyl, —C_{1-4}alkylene-C_{3-8}cycloalkyl, 4-6 membered heterocyclyl, and —C_{1-4}alkylene-4-6 membered heterocyclyl; and

[0031] each C_{3-8}cycloalkyl, —C_{1-4}alkylene-C_{3-8}cycloalkyl, 4-6 membered heterocyclyl, and —C_{1-4}alkylene-(4-6 membered heterocyclyl) of R^3 is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, and C_{1-4}haloalkyl; or

[0032] R^3 together with the N that attaches to R^9 forms a 5 membered heterocyclyl; wherein the 5 membered heterocyclyl is optionally substituted with one to two groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, and C_{6-10}aryl; wherein the C_{6-10}aryl is optionally substituted with one to three groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl;

[0033] each R^4, R^5, R^6, R^7, and R^8 is independently selected from H, halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}haloalkyl, C_{1-4}haloalkoxyl, and C_{3-6}cycyloalky;

[0034] R^9 is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl;

[0035] each R^{1a} and R^{1b} is independently selected from H, C_{1-6}alkyl, and C_{1-6}haloalkyl;

[0036] m is selected from 0, 1, and 2; and

[0037] n is 1 or 2.

DETAILED DESCRIPTION

Definitions and General Parameters

[0038] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0039] As used in the present specification, the following words, phrases and symbols are generally intended to have

the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0040] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, —$CONH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

[0041] A squiggly line on a chemical group as shown below, for example,



indicates a point of attachment, i.e., it shows the broken bond by which the group is connected to another described group.

[0042] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-8} alkyl" indicates that the alkyl group has from 1 to 8 carbon atoms.

[0043] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ±10%. In other embodiments, the term "about" includes the indicated amount ±5%. In certain other embodiments, the term "about" includes the indicated amount ±1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0044] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl), or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., —$(CH_2)_3CH_3$), sec-butyl (i.e., —$CH(CH_3)CH_2CH_3$), isobutyl (i.e., —$CH_2CH(CH_3)_2$) and tert-butyl (i.e., —$C(CH_3)_3$); and "propyl" includes n-propyl (i.e., —$(CH_2)_2CH_3$) and isopropyl (i.e., —$CH(CH_3)_2$).

[0045] "Alkylene" (including those which are part of other groups) refers to branched and unbranched divalent "alkyl" groups. As used herein, alkylene has 1 to 20 carbon atoms (i.e., C_{1-20}alkylene), 1 to 8 carbon atoms (i.e., C_{1-8} alkylene), 1 to 6 carbon atoms (i.e., C_{1-6} alkylene), or 1 to 4 carbon atoms (i.e., C_{1-4} alkylene). Examples include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene or 1,2-dimethylethylene. Unless stated otherwise, the definitions propylene and butylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propylene also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, and 1,2-dimethylethylene.

[0046] "Alkenyl" refers to an aliphatic group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0047] "Alkynyl" refers to an aliphatic group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-20} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0048] "Alkoxy" refers to the group "alkyl-O—". Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more hydrogen atoms are replaced by a halogen.

[0049] "Acyl" refers to a group —C(═O)R, wherein R is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include formyl, acetyl, cylcohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0050] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl ring, the resulting ring system is heteroaryl.

[0051] "Azido" refers to the group —N_3.

[0052] "Cyano" or "carbonitrile" refers to the group —CN.

[0053] "Cycloalkyl" refers to a saturated or partially saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl groups also include partially unsaturated ring systems containing one or more double bonds, including fused ring systems with one aromatic ring and one non-aromatic ring, but not fully aromatic ring systems.

[0054] "Bridged" refers to a ring fusion wherein non-adjacent atoms on a ring are joined by a divalent substituent, such as an alkylenyl or heteroalkylenyl group or a single heteroatom. Quinuclidinyl and admantanyl are examples of bridged ring systems.

[0055] The term "fused" refers to a ring which is bound to an adjacent ring.

[0056] "Spiro" refers to a ring substituent which is joined by two bonds at the same carbon atom. Examples of spiro groups include 1,1-diethylcyclopentane, dimethyl-dioxolane, and 4-benzyl-4-methylpiperidine, wherein the cyclopentane and piperidine, respectively, are the spiro substituents.

[0057] "Halogen" or "halo" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include difluoromethyl (—CHF_2) and trifluoromethyl (—CF_3).

[0058] The term "heterocyclyl" or "heterocycle" as used herein refers to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic multiple ring system that has at least one heteroatom in the ring (i.e., at least one annular heteroatom selected from O, N, S, S(O), $S(O)_2$, and N-oxide groups). Unless otherwise specified, a heterocyclyl group has from 3 to about 20 annular atoms, for example from 3 to 12 annular atoms, for example from 3 to 10 annular atoms, for example from 5 to 10 annular atoms or for example from 5 to 6 annular atoms. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The rings of the multiple condensed ring (e.g., bicyclic heterocyclyl) system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Heterocycles include, but are not limited to, groups derived from azetidine, aziridine, imidazolidine, morpholine, oxirane (epoxide), oxetane, piperazine, piperidine, pyrazolidine, piperidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, tetrahydro-2H-thiopyran 1,1-dioxide, quinuclidine, N-bromopyrrolidine, N-chloropiperidine, and the like. Heterocycles include spirocycles, such as, for example, aza or oxo-spiroheptanes. Heterocyclyl groups also include partially unsaturated ring systems containing one or more double bonds, including fused ring systems with one aromatic ring and one non-aromatic ring, but not fully aromatic ring systems. Examples include dihydroquinolines, e.g., 3,4-dihydroquinoline, dihydroisoquinolines, e.g., 1,2-dihydroisoquinoline, dihydroimidazole, tetrahydroimidazole, etc., indoline, isoindoline, isoindolones (e.g., isoindolin-1-one), isatin, dihydrophthalazine, quinolinone, spiro[cyclopropane-1,1'-isoindolin]-3'-one, and the like. Additional examples of heterocycles include 3,8-diazabicyclo[3.2.1] octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo [3.1.1]heptanyl, 3-oxa-7,9-diazabicyclo [3.3.1]nonanyl, and hexahydropyrazino[2,1-c][1,4]oxazinyl, for example.

[0059] "Hydroxyl" and "hydroxy" are used interchangeably and refer to —OH. "Oxo" refers to the group (=O) or (O). Where tautomeric forms of the compound exist, hydroxyl and oxo groups are interchangeable.

[0060] "Heteroaryl" refers to an aromatic group, including groups having an aromatic tautomer or resonance structure, having a single ring, multiple rings, or multiple fused rings, with at least one heteroatom in the ring, i.e., one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the nitrogen or sulfur may be oxidized. Thus, the term includes rings having one or more annular O, N, S, S(O), $S(O)_2$, and N-oxide groups. The term includes rings having one or more annular C(O) groups. As used herein, heteroaryl include 5 to 20 ring atoms (i.e., 5- to 20-membered heteroaryl), 5 to 12 ring atoms (i.e., 5- to 12-membered heteroaryl), or 5 to 10 ring atoms (i.e., 5- to 10-membered heteroaryl), and 1 to 5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and oxidized forms of the heteroatoms. Examples of heteroaryl groups include pyridin-2(1H)-one, pyridazin-3(2H)-one, pyrimidin-4(3H)-one, quinolin-2(1H)-one, pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Heteroaryl does not encompass or overlap with aryl as defined above.

[0061] "Sulfonyl" refers to the group —$S(O)_2R$, where R is alkyl, haloalkyl, heterocyclyl, cycloalkyl, heteroaryl, or aryl. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0062] Whenever the graphical representation of a group terminates in a singly bonded nitrogen atom, that group represents an —NH group unless otherwise indicated. Similarly, unless otherwise expressed, hydrogen atom(s) are implied and deemed present where necessary in view of the knowledge of one of skill in the art to complete valency or provide stability.

[0063] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or an "arylenyl" group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0064] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0065] The term "substituted" means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom's normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof. Polymers or similar indefinite structures arrived at by defining substituents with further sub-

stituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein. For example, the term "substituted aryl" includes, but is not limited to, "alkylaryl." Unless specified otherwise, where a group is described as optionally substituted, any substituents of the group are themselves unsubstituted.

[0066] In some embodiments, the term "substituted alkyl" refers to an alkyl group having one or more substituents including hydroxyl, halo, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl. In additional embodiments, "substituted cycloalkyl" refers to a cycloalkyl group having one or more substituents including alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, halo, oxo, and hydroxyl; "substituted heterocyclyl" refers to a heterocyclyl group having one or more substituents including alkyl, haloalkyl, heterocyclyl, cycloalkyl, aryl, heteroaryl, alkoxy, halo, oxo, and hydroxyl; "substituted aryl" refers to an aryl group having one or more substituents including halo, alkyl, haloalkyl, cycloalkyl, heterocyclyl, heteroaryl, alkoxy, and cyano; "substituted heteroaryl" refers to an heteroaryl group having one or more substituents including halo, alkyl, haloalkyl, heterocyclyl, heteroaryl, alkoxy, and cyano and "substituted sulfonyl" refers to a group —$S(O)_2R$, in which R is substituted with one or more substituents including alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl. In other embodiments, the one or more substituents may be further substituted with halo, alkyl, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted. In other embodiments, the substituents may be further substituted with halo, alkyl, haloalkyl, alkoxy, hydroxyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is unsubstituted.

[0067] Some of the compounds exist as tautomeric isomers. Tautomeric isomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0068] Any formula or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0069] The disclosure also includes compounds of the present disclosure, in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound of the present disclosure, when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0070] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of the present disclosure.

[0071] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0072] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0073] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound, and which are not biologically or otherwise undesirable. Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inor-

ganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, mono, di or tri cycloalkyl amines, mono, di or tri arylamines or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0074] Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

[0075] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0076] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival).

[0077] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0078] "Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In one embodiment, the subject is a human.

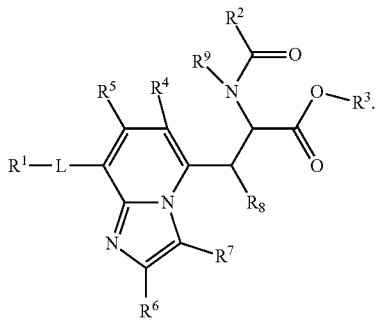
[0079] The term "therapeutically effective amount" or "effective amount" of a compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition responsive to inhibition of α4β7 integrin activity. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one or ordinary skill in the art.

[0080] The term "inhibition" indicates a decrease in the baseline activity of a biological activity or process. "Inhibition of activity of α4β7 integrin" or variants thereof refers to a decrease in activity of α4β7 integrin as a direct or indirect response to the presence of a compound of the present application relative to the activity of α4β7 integrin in the absence of the compound of the present application. "Inhibition of α4β7" refers to a decrease in α4β7 integrin activity as a direct or indirect response to the presence of a compound described herein relative to the activity of α4β7 integrin in the absence of the compound described herein. In some embodiments, the inhibition of α4β7 integrin activity may be compared in the same subject prior to treatment, or other subjects not receiving the treatment.

Compounds

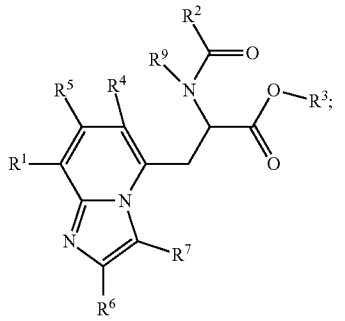
[0081] Provided herein are compounds that function as inhibitors of α4β7 integrin. In one aspect, provided is a compound having structure of Formula (I), or a pharmaceutically acceptable salt thereof:

(I)



R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and L are defined as above.

[0082] In another aspect, provided are compounds of formula (II):



(II)

[0083] wherein R^1 is selected from A^1, A^2, and A^3;

[0084] A^1 is 5-10 membered heteroaryl containing one to five heteroatoms or groups independently selected from S, N, and O; wherein A^1 optionally comprises one to three C(O); and wherein A^1 is optionally substituted with one to six R^{A1};

[0085] A^2 is C_{6-10}aryl, optionally substituted with one to six R^{A1}; and

[0086] A^3 is $—NR^{1a}R^{1b}$;

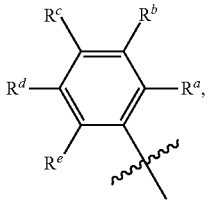
[0087] wherein each R^{A1} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6} haloalkoxyl, $—S(O)_m—C_{1-4}$alkyl, C_{3-6}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$alkylene-C_{3-8}cycloalkyl, and —O-phenyl;

[0088] wherein each C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$alkylene-C_{3-8}cycloalkyl, and —O-phenyl of R^{A1} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, and C_{1-6}haloalkoxyl; and

[0089] wherein each C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl of R^{A1} is optionally substituted with one to three R^{1c}; wherein each R^{1c} is independently selected from C_{1-4}alkoxyl, hydroxyl, cyano, $—NR^{1a}R^{1b}$, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl; wherein each C_{3-8}cycloalkyl and 3-6 membered heterocyclyl of R^{1c} is independently optionally substituted with one to three R^{1d}; and

[0090] wherein each R^{1d} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}-alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, C_{1-6}haloalkoxyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl;

[0091] R^2 is selected from



and C_{3-8}cycloalkyl;

[0092] wherein each R^a, R^b, R^c, R^d, and R^e is independently selected from H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{1-8}haloalkyl, C_{1-6}alkoxyl, C_{1-8}haloalkoxyl, $—NR^{2a}R^{2b}$, $—NR^{2a}S(O)_nR^{2c}$, $—S(O)_m—R^{2c}$, $—S(O)_nNR^{2a}R^{2b}$, $—CONR^{2a}R^{2b}$, $—NR^{2a}COOR^{2b}$, $—NR^{2a}COR^{2c}$, C_{3-6}cycloalkyl, C_{6-10}aryl, 3-8 membered heterocyclyl, and 5-6 membered heteroaryl;

[0093] wherein each C_{1-6}alkyl, C_{1-8}haloalkyl, C_{1-6}alkoxyl, and C_{1-8}haloalkoxyl of R^a, R^b, R^c, R^d, and R^e is independently optionally substituted with one to two R^{2d}; and

[0094] wherein each C_{6-10}aryl, and 5-6 membered heteroaryl of R^a, R^b, R^c, R^d, and R^e is optionally substituted with one to four R^{2f};

[0095] wherein each C_{3-6}cycloalkyl, and 3-8 membered heterocyclyl of R^a, R^b, R^c, R^d, and R^e is optionally substituted with one to six groups with one to six groups independently selected from $=CR^{2a}R^{2b}$ and R^{2f};

[0096] wherein each R^{2a} and R^{2b} is independently selected from H, C_{1-6}alkyl, and C_{1-8}haloalkyl; each C_{1-6}alkyl and C_{1-8}haloalkyl of R^{2a} and R^{2b} is optionally substituted with one group selected from cyano, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, phenyl, and 4-6 membered heterocyclyl; wherein each C_{3-6}cycloalkyl, phenyl, and 4-6 membered heterocyclyl is optionally substituted with one to three groups independently selected from halo, cyano, $—NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl; and

[0097] wherein R^{2c} is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, and phenyl; wherein phenyl of R^{2c} is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}haloalkyl, and 6 membered heteroaryl; and wherein the 6 membered heteroaryl is optionally substituted with one to three groups independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl;

[0098] wherein each R^{2d} is independently selected from cyano, hydroxyl, C_{1-4}alkoxyl, and $—NR^{1a}R^{1b}$;

[0099] wherein each R^{2f} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl; and

[0100] the C_{3-8}cycloalkyl of R^2 is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-8}haloalkoxyl, and C_{1-8}haloalkyl;

[0101] R^3 is selected from H, C_{1-6}alkyl, $—C_{1-4}$alkylene-$NR^{a1}R^{a2}$, $—C_{1-4}$alkylene-$C(O)NR^{1a}R^{1b}$, $—C_{1-4}$ alkylene-$O—C(O)—C_{1-4}$alkyl, $—C_{1-4}$alkylene-$O—C(O)—O—C_{1-4}$alkyl, $—C_{1-4}$alkylene-$O—C(O)—C_{1-4}$alkylene-$NR^{1a}R^{1b}$, $—C_{1-4}$alkylene-$O—C_{1-}$

4alkxyl, C_{3-8}cycloalkyl, 4-6 membered heterocyclyl, and —C_{1-4} alkylene-(4-6 membered heterocyclyl);

[0102] wherein each C_{3-8}cycloalkyl, 4-6 membered heterocyclyl, and —C_{1-4}alkylene-(4-6 membered heterocyclyl) of R^3 is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, and C_{1-4}haloalkyl; or

[0103] R^3 together with the N that attaches to R^9 forms a 5 membered heterocyclyl; wherein the 5 membered heterocyclyl is optionally substituted with one to two groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, and C_{6-10}aryl; wherein the C_{6-10}aryl is optionally substituted with one to three groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl;

[0104] each R^4, R^5, R^6, and R^7 is independently selected from H, halo, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4} alkoxyl, C_{1-4}haloalkyl, and C_{3-6}cycyloalky;

[0105] R^9 is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl;

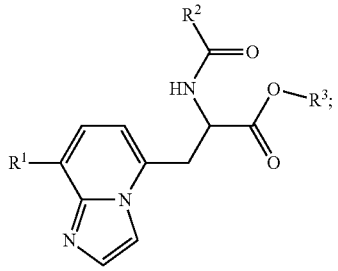
[0106] each R^{1a} and R^{1b} is independently selected from H, C_{1-6}alkyl, and C_{1-6}haloalkyl;

[0107] m is selected from 0, 1, and 2; and

[0108] n is 1 or 2.

[0109] In another aspect, provided are compounds of formula (IIa):

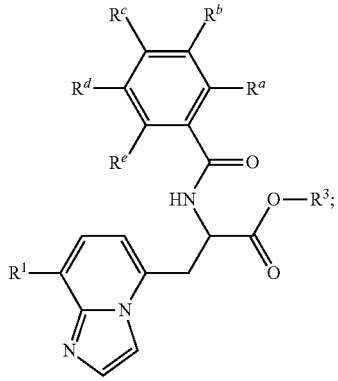
(IIa)



R^1, R^2, and R^3 are as defined above in formula (I), (II), or elsewhere in this disclosure.

[0110] In another aspect, provided are compounds of formula (IIb), or pharmaceutically acceptable salts thereof:

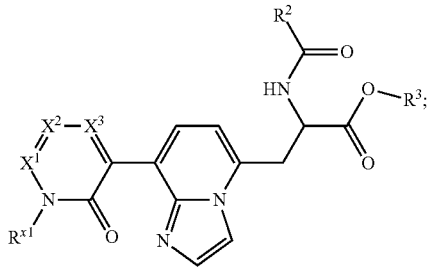
(IIb)



wherein R^1, R^3, R^a, R^b, R^c, R^d, and R^e are as defined above in formula (I), (II), or elsewhere in this disclosure.

[0111] In another aspect, provided are compounds of formula (IIc), or pharmaceutically acceptable salts thereof:

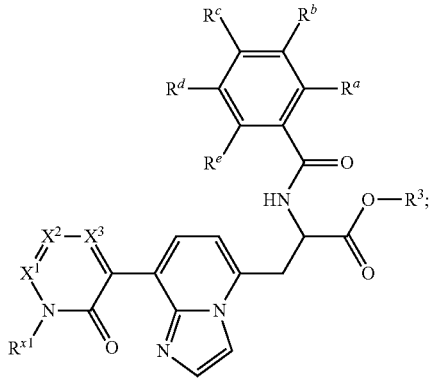
(IIc)



wherein R^2, and R^3 are as defined above in formula (I), (II), or elsewhere in this disclosure. Each X^1, X^2, and X^3 is independently selected from CR^{x1}, and N; and each R^{x1} is independently selected from H, and R^{A1}.

[0112] In another aspect, provided are compounds of formula (IId), or pharmaceutically acceptable salts thereof:

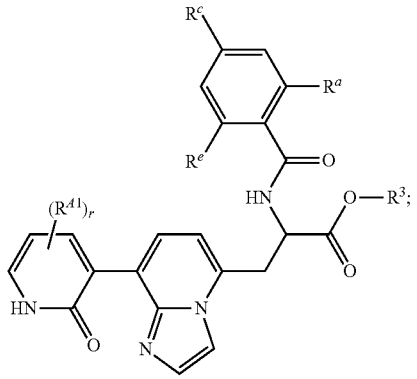
(IId)



R^3 is as defined above in formula (I) or (II). R^a, R^b, R^c, R^d, and R^e are as defined above in formula (II), or elsewhere in this disclosure. X^1, X^2, X^3, and R^{x1} are as defined above in formula (IIc), or elsewhere in this disclosure.

[0113] In another aspect, provided are compounds of formula (IIe), or pharmaceutically acceptable salts thereof:

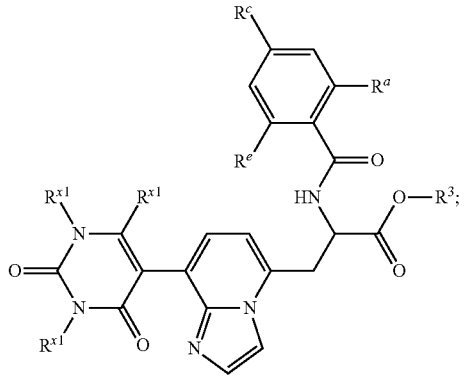
(IIe)



wherein R^3, and R^{A1} are as defined above in formula (I), (II), or elsewhere in this disclosure. R^a, R^c, and R^e are as defined above in formula (II), or elsewhere in this disclosure. r is an integer selected from 0, 1, 2, 3, and 4.

[0114] In another aspect, provided are compounds of Formula (IIf), or pharmaceutically acceptable salts thereof:

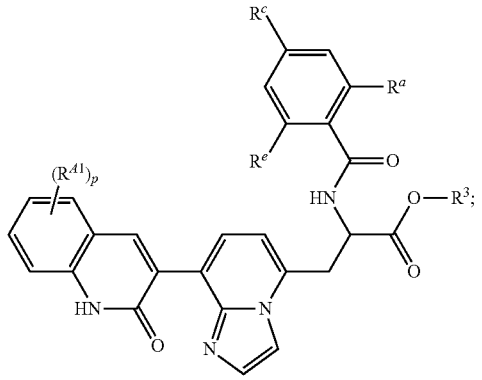
(IIf)



wherein R^3 is as defined above in formula (I), (II), or elsewhere in this disclosure. R^a, R^c, and R^e are as defined above in formula (II). R^{x1} is as defined above in formula (IIc), or elsewhere in this disclosure.

[0115] In another aspect, provided are compounds of formula (IIg), or pharmaceutically acceptable salts thereof:

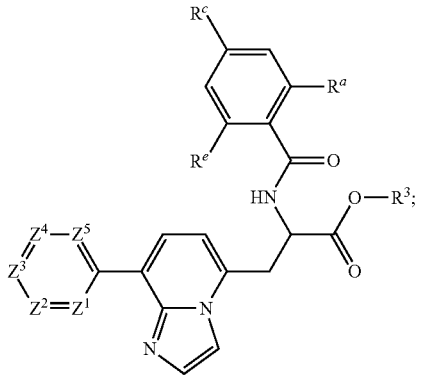
(IIg)



wherein R^3, and R^{A1} are as defined above in formula (I), (II), or elsewhere in this disclosure. R^a, R^c, and R^e are as defined above in formula (II), or elsewhere in this disclosure. p is an integer selected from 0, 1, 2, 3, 4, 5, and 6.

[0116] In another aspect, provided are compounds of formula (IIh), or pharmaceutically acceptable salts thereof:

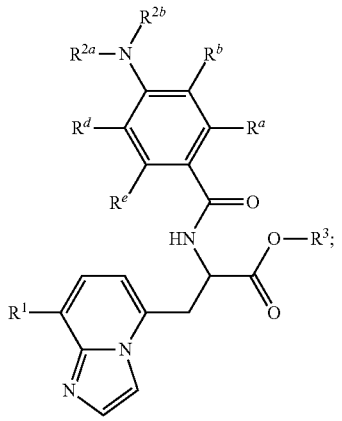
(IIh)



wherein R^3 is as defined above in formula (I), (II) or elsewhere in this disclosure. R^a, R^c, and R^e are as defined above in formula (II), or elsewhere in this disclosure. Each Z^1, Z^2, Z^3, Z^4, and Z^5 is independently selected from CR^{x1}, and N; and each R^{x1} is independently selected from H, and R^{A1}.

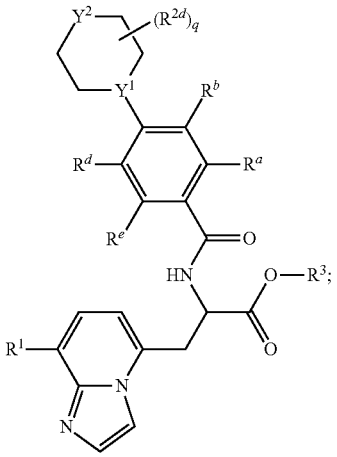
[0117] In another aspect, provided are compounds of formula (IIi), or pharmaceutically acceptable salts thereof:

(IIi)



wherein R^1, R^3, R^{2a}, and R^{2b} are as defined above in formula (I) or (II). R^a, R^b, R^d, and R^e are as defined above in formula (II).

[0118] In another aspect, provided are compounds of formula (IIj), or pharmaceutically acceptable salts thereof:



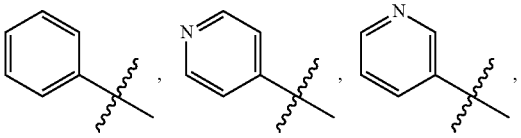
(IIj)

wherein R^1, R^3, and R^{2d} are as defined above in formula (I), (II), or elsewhere in this disclosure. R^a, R^b, R^d, and R^e are as defined above in formula (II), or elsewhere in this disclosure. Y^1 is selected from CR^{y1}, and N. Y^2 is selected from $CR^{y1}R^{y1}$, NR^{y2}, O, and $S(O)_2$. Each R^{y1} is independently selected from H, and R^{2d}. R^{y2} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. q is an integer selected from 0, 1, 2, and 3.

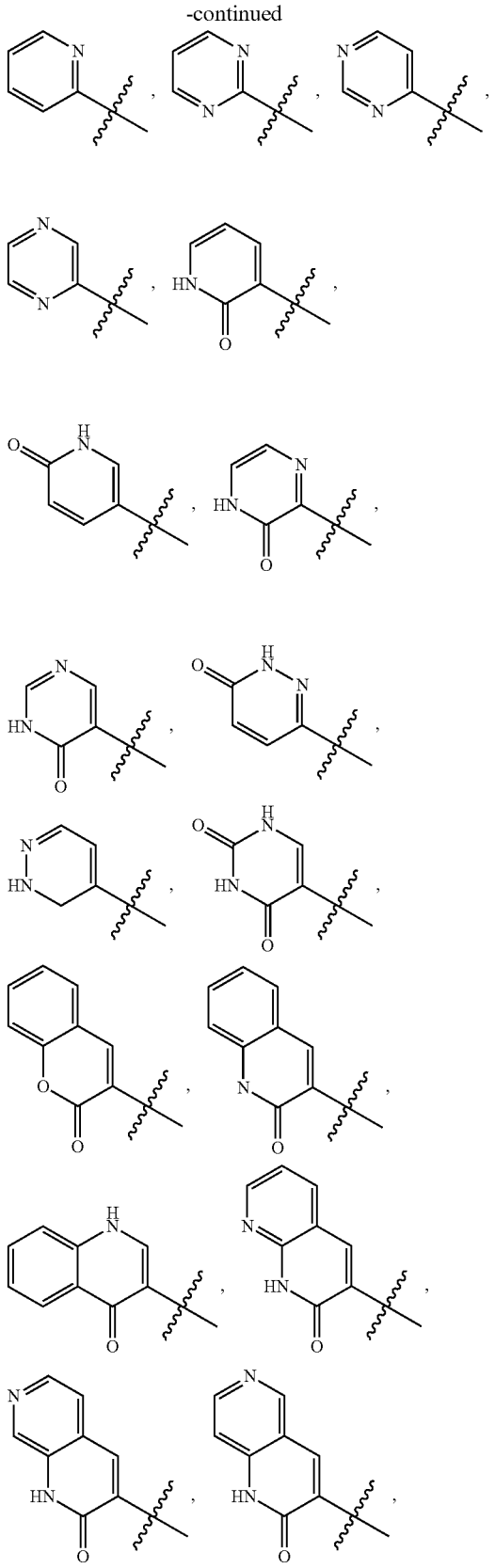
[0119] In some embodiments of formula (I), L is a bond. In some embodiments, L is —N(H)—C(O)—*, * indicates the point of attachment of L to R^1.

[0120] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is selected from phenyl, naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoxazolyl, pyridinonyl, quinolinonyl, pyrazinonyl, pyrimidinonyl, pyridazinonyl, quinazolinonyl, quinazolindionyl, pyridopyrimidine-dionyl, and imidazopyridinonyl; and each R^1 is independently optionally substituted with one to four R^{A1}. In some embodiments, each R^{A1} is independently selected from halo, CN, OH, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, C_{1-4}haloalkoxyl, and —$S(O)_2$—C_{1-6}alkyl. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, —NH_2, —$N(CH_3)_2$, —CH_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —$CH_2OCH_2CH_3$, —$CH_2OCH(CH_3)_2$, —CH_2F, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —OCH_2F, —$OCHF_2$, —OCF_3, —OCH_2CH_2F, —OCH_2CHF_2, and —OCH_2CF_3. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, —CH_3, —CF_3, —OCH_3, —$CH_2OCH_2CH_3$, and NH_2.

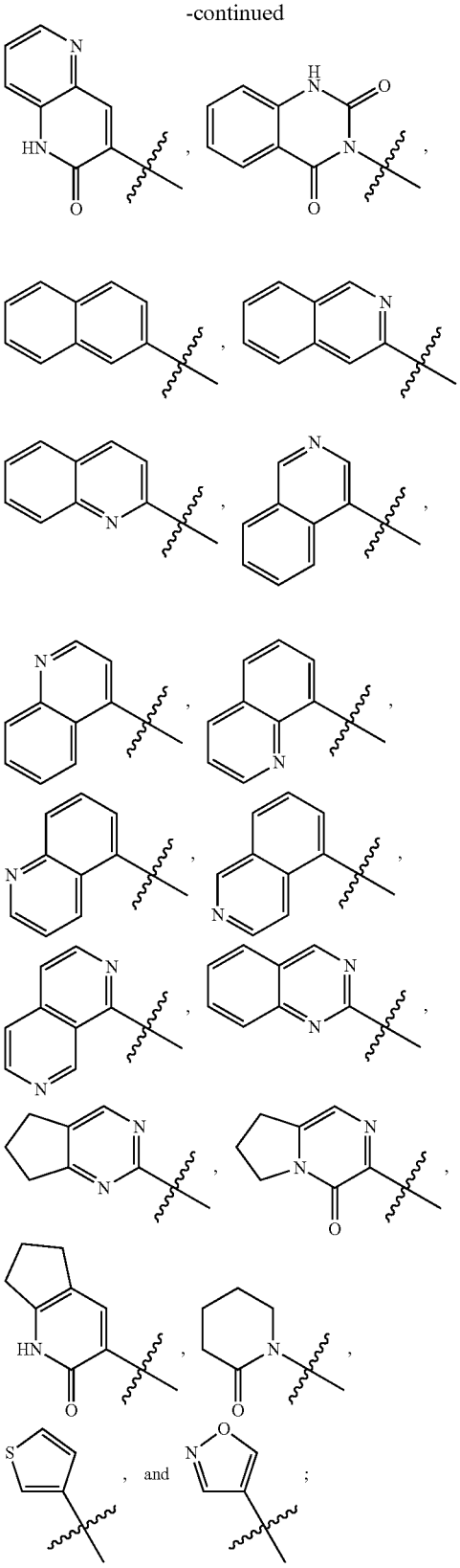
[0121] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is selected from



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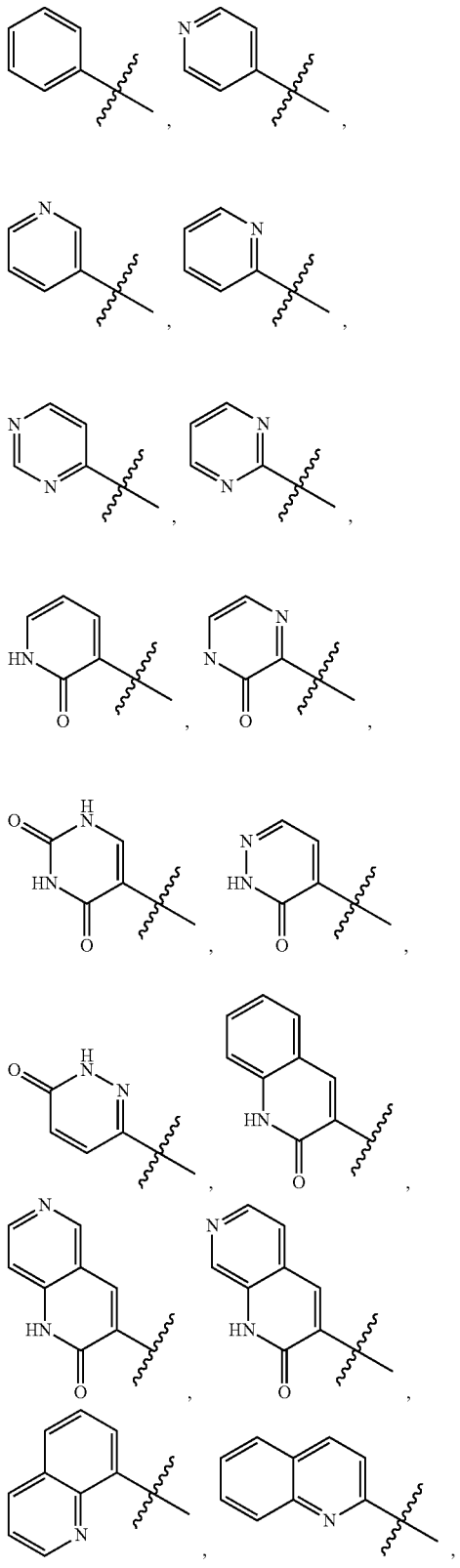


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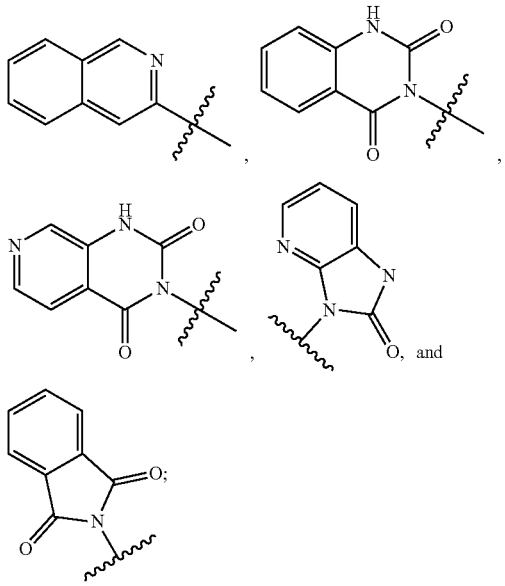


each R^1 is optionally substituted with one to three R^{41}.

[0122] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is selected from

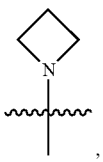


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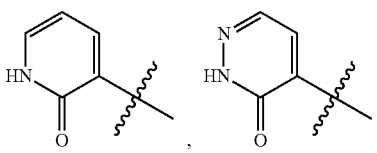
and each R^1 is optionally substituted with one to three R^{A1}.

[0123] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is A^1 or A^2, each A^1 or A^2 is substituted with one to four R^{A1}, and each R^{A1} is independently selected from halo, CN, OH, $—NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, C_{1-4}haloalkoxyl, —O—C_{3-6}cycloalkyl,

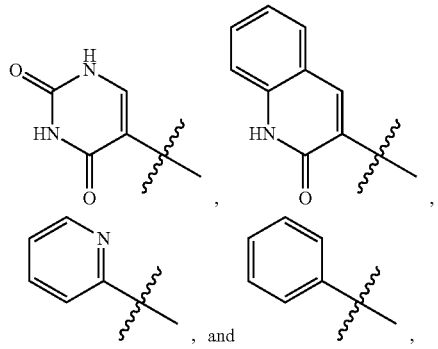


and $—S(O)_2—C_{1-6}$alkyl. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, OH, $—NH_2$, $—N(CH_3)_2$, $—CH_3$, $—CH_2CH_3$, $—CH(CH_3)_2$, $—C(CH_3)_3$, $—OCH_3$, $—OCH_2CH_3$, $—OCH(CH_3)_2$, $—OC(CH_3)_3$, $—CH_2OCH_3$, $—CH_2OCH_2CH_3$, $—CH_2OCH(CH_3)_2$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—OCH_2F$, $—OCHF_2$, $—OCF_3$, $—OCH_2CH_2F$, $—OCH_2CHF_2$, $—OCH_2CF_3$, $—SO_2CH_3$, and $—SO_2CH_2CH_3$. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, NH_2, $—N(CH_3)_2$, $—CH_3$, $—CF_3$, $—OCH_3$, and $—CH_2OCH_2CH_3$.

[0124] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is selected from

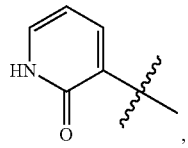


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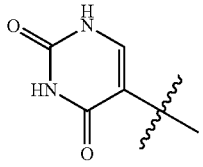
each R^1 is optionally substituted with one to three R^{A1}. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, $—NH_2$, $—N(CH_3)_2$, $—CH_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—CH_2OCH_2CH_3$, $—CH_2OCH(CH_3)_2$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—OCH_2F$, $—OCHF_2$, $—OCF_3$, $—OCH_2CH_2F$, $—OCH_2CHF_2$, and $—OCH_2CF_3$. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, NH_2, $—CH_3$, $—CF_3$, $—OCH_3$, and $—CH_2OCH_2CH_3$.

[0125] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is



which is optionally substituted with one to three R^{A1}. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, $—NH_2$, $—N(CH_3)_2$, $—CH_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—CH_2OCH_2CH_3$, $—CH_2OCH(CH_3)_2$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—OCH_2F$, $—OCHF_2$, $—OCF_3$, $—OCH_2CH_2F$, $—OCH_2CHF_2$, and $—OCH_2CF_3$. In some embodiments, each R^{A1} is independently selected from $—CH_3$, $—OCH_3$, and $—CF_3$.

[0126] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is

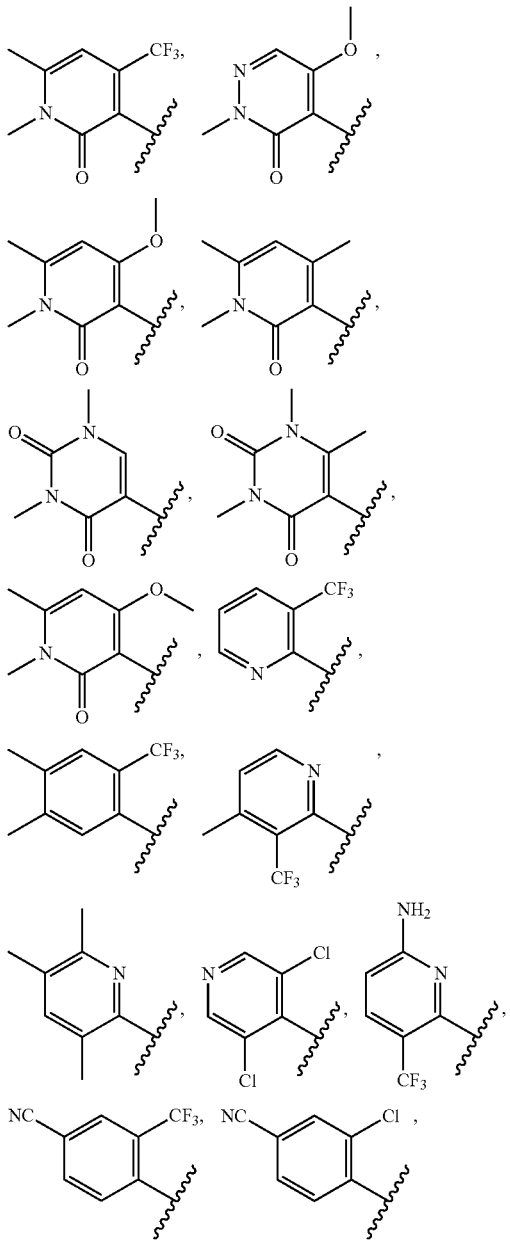


optionally substituted with one to three R^{A1}. In some embodiments, each R^{A1} is independently selected from F, Cl, CN, $—NH_2$, $—N(CH_3)_2$, $—CH_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—CH_2OCH_2CH_3$, $—CH_2OCH(CH_3)_2$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—OCH_2F$, $—OCHF_2$, $—OCF_3$, $—OCH_2CH_2F$,

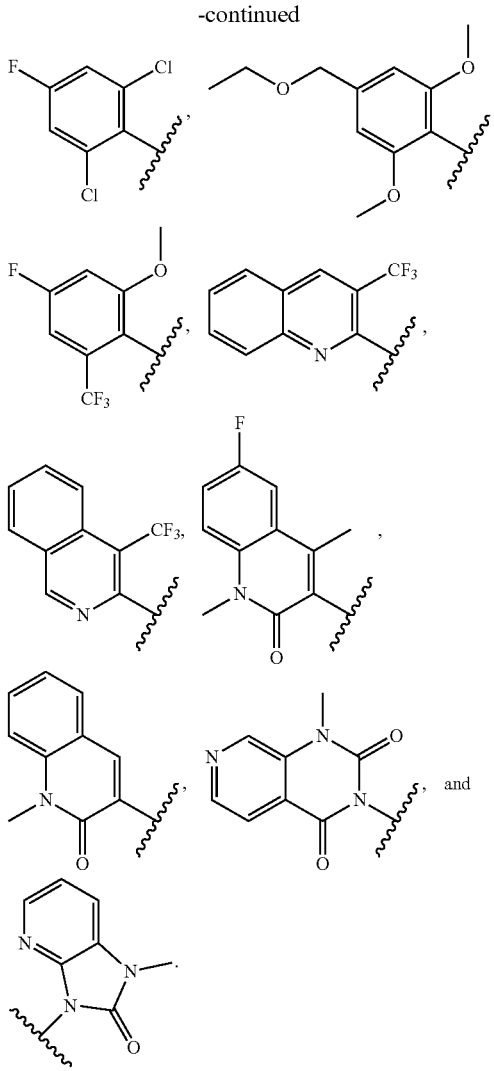
—OCH_2CHF_2, and —OCH_2CF_3. In some embodiments, each R^{A1} is independently selected from —CH_3, —OCH_3, and —CF_3.

[0127] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is phenyl optionally substituted with one to three R^{A1}; and each R^{A1} is independently selected from F, Cl, CN, —NH_2, —$N(CH_3)_2$, —CH_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —$CH_2OCH_2CH_3$, —$CH_2OCH(CH_3)_2$, —CH_2F, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —OCH_2F, —$OCHF_2$, —OCF_3, —OCH_2CH_2F, —OCH_2CHF_2, and —OCH_2CF_3.

[0128] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is selected from

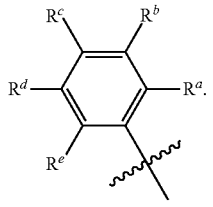


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[0129] In some embodiments of formula (I), (II), (IIa), (IIb), (IIi), or (IIj), R^1 is —$N(R^{1a})(R^{1b})$. In some embodiments, R^1 is —NH_2. In some embodiments, R^1 is —$NH(CH_3)$. In some embodiments, R^1 is —$N(CH_3)_2$.

[0130] In some embodiments of formula (I), (II), (IIa), or (IIc), R^2 is

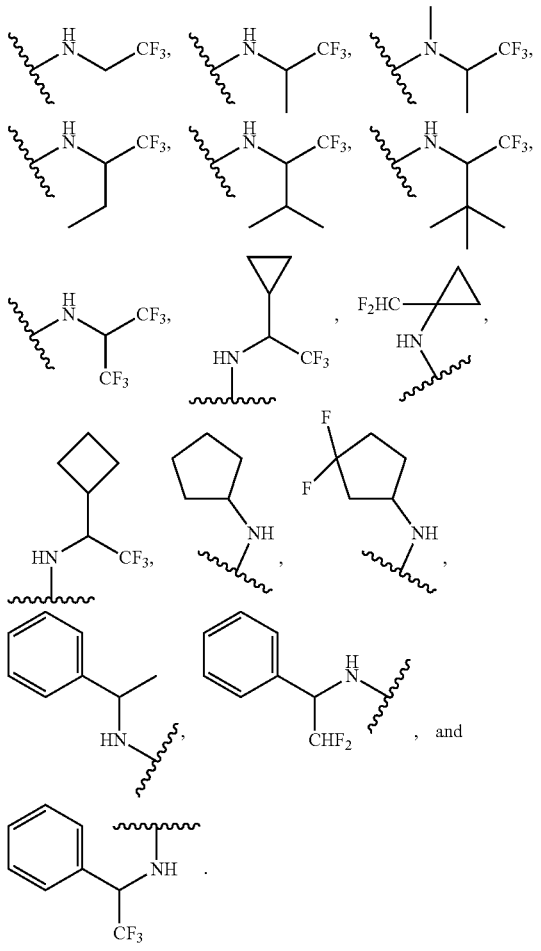


In some embodiments of formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), each R^a and R^e is independently selected from H, F, Cl, CN, CH_3, —OCH_3, and —CF_3. In some embodiments, both R^a and R^e are F. In some embodiments of formula (I), (II), (IIa), (IIb), (IIc),

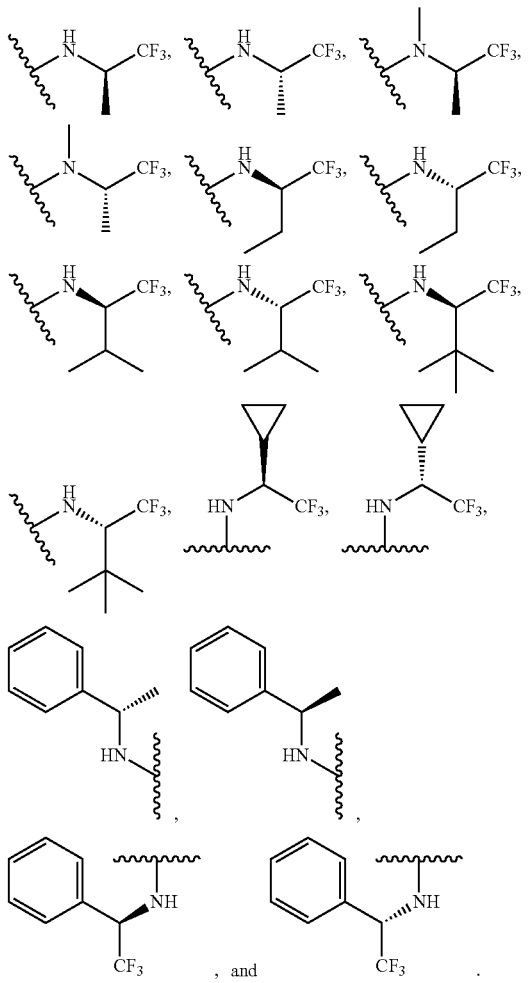
(IId), (IIi), or (IIj), each R^b and R^d is independently selected from H, F, Cl, CN, CH_3, —OCH_3, and —CF_3. In some embodiments, both R^b and R^d are H.

[0131] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from H, halo, C_{1-6}alkyl, C_{1-8}haloalkyl, —$NR^{2a}R^{2b}$, —$S(O)_nNR^{2a}R^{2b}$, C_{3-6}cycloalkyl, and 3-8 membered heterocyclyl. In some embodiments, R^c is selected from —$NR^{2a}R^{2b}$, —$S(O)_nNR^{2a}R^{2b}$, and 3-6 membered heterocyclyl. In some embodiments, R^c is —$NR^{2a}R^{2b}$. In some embodiments, R^{2a} is selected from H, and C_{1-4}alkyl. In some embodiments, R^c is —NHR^{2b}. In some embodiments, R^{2b} is selected from C_{1-4}alkyl, and C_{1-6}haloalkyl. In some embodiments, R^{2b} is C_{1-6}haloalkyl. In some embodiments, R^{2b} is —C_{1-5}alkylene-CF_3. In some embodiments, R^{2b} is selected from -methylene-CF_3, -ethylene-CF_3, -propylene-CF_3, -butylene-CF_3, and -pentylene-CF_3. In some embodiments, R^{2b} is —C_{1-5}alkylene-CF_3 substituted with phenyl. In some embodiments, phenyl is substituted with one or three groups independently selected from halo, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl. In some embodiments, phenyl is substituted with one group selected from F, Cl, —CH_3, —CH_2F, —CHF_2, and —CF_3.

[0132] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is H, —CHF_2,

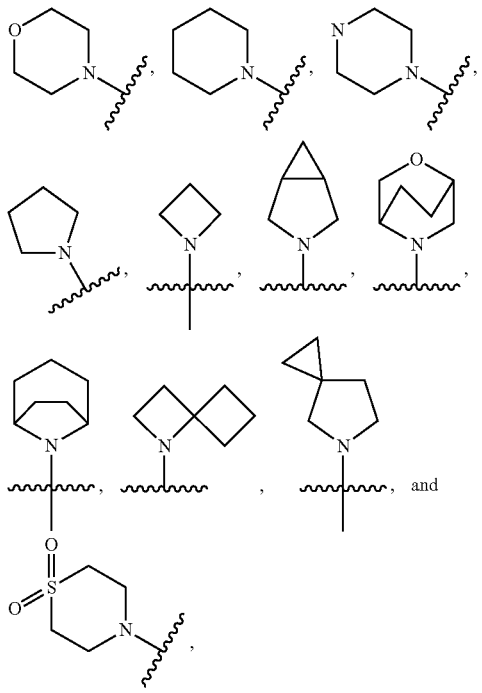


[0133] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from



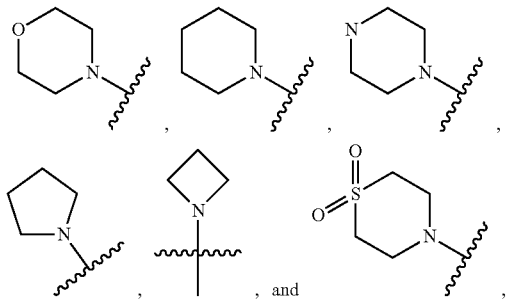
[0134] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is 3-8 membered heterocyclyl optionally substituted with one to three R^{2f}. In some embodiments, R^c is 3-8 membered spiro, fused or bridged heterocyclyl. In some embodiments, R^c is selected from azetidinyl, aziridinyl, imidazolidinyl, morpholinyl, oxetanyl, piperazinyl, piperidinyl, pyrazolidinyl, piperidinyl, pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, tetrahydrothiophenyl, dihydropyridinyl, tetrahydropyridinyl, 1,1-dioxide-thiomorpholinyl, and quinuclidinyl; each R^c is optionally substituted with one to three R^{2f}. In some embodiments, R^c is selected from morpholinyl, piperidinyl, tetrahydropyranyl, and pyrrolidinyl; each of which is optionally substituted with one to three R^{2f}. Each R^{2f} is independently selected from halo, hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl. In some embodiments, each R^{2f} is independently selected from F, Cl, CN, —OH, —CH_3, —$CH(CH_3)_2$, and —CF_3.

[0135] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from



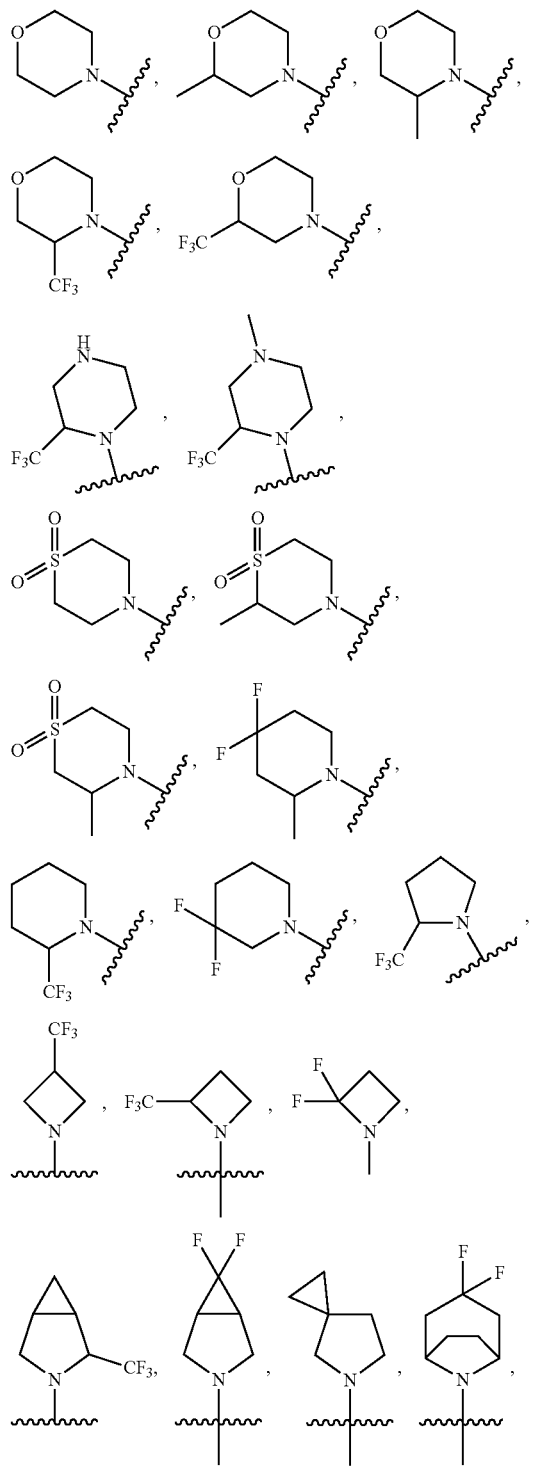
and each R^c is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-6}cycloalkyl, and —CH_2C_{3-6}cycloalkyl. In some embodiments, each R^c is optionally substituted with one to three groups independently selected from F, Cl, OH, CN, NH_2, —CH_3, —$CH(CH_3)_2$, —CH_2F, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, and cyclopropyl. In some embodiments, each R^c is optionally substituted with one to three groups independently selected from F, Cl, —CH_3, —CH_2F, —CHF_2, and —CF_3.

[0136] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from

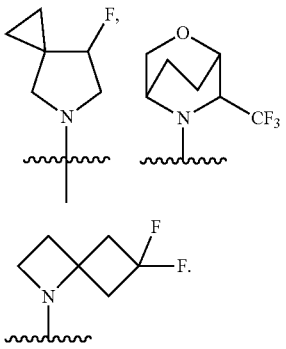


and each R^c is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, and C_{1-4}haloalkyl. In some embodiments, each R^c is optionally substituted with one to three groups independently selected from F, Cl, OH, CN, NH_2, —CH_3, —$CH(CH_3)_2$, —CH_2F, —CHF_2, —CF_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, C_{3-6}cycloalkyl, and —CH_2C_{3-6}cycloalkyl. In some embodiments, each R^c is optionally substituted with one to three groups independently selected from F, Cl, —CH_3, —CH_2F, —CHF_2, and —CF_3.

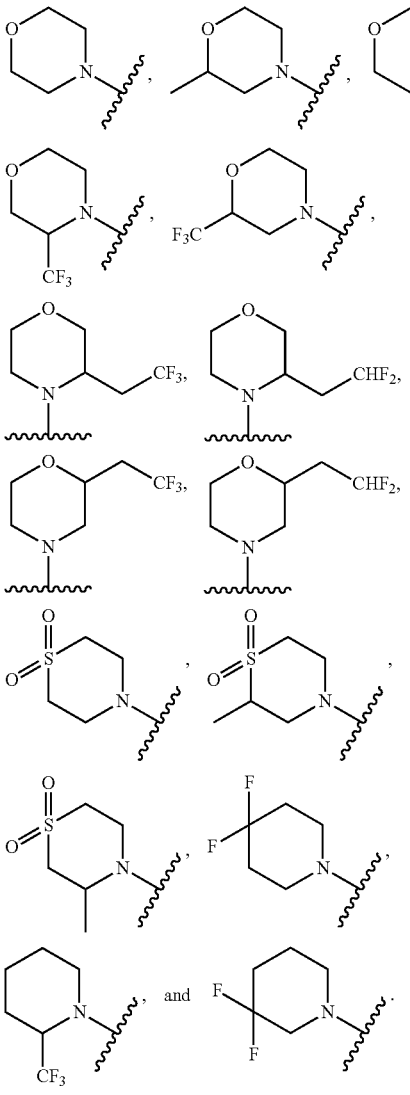
[0137] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from



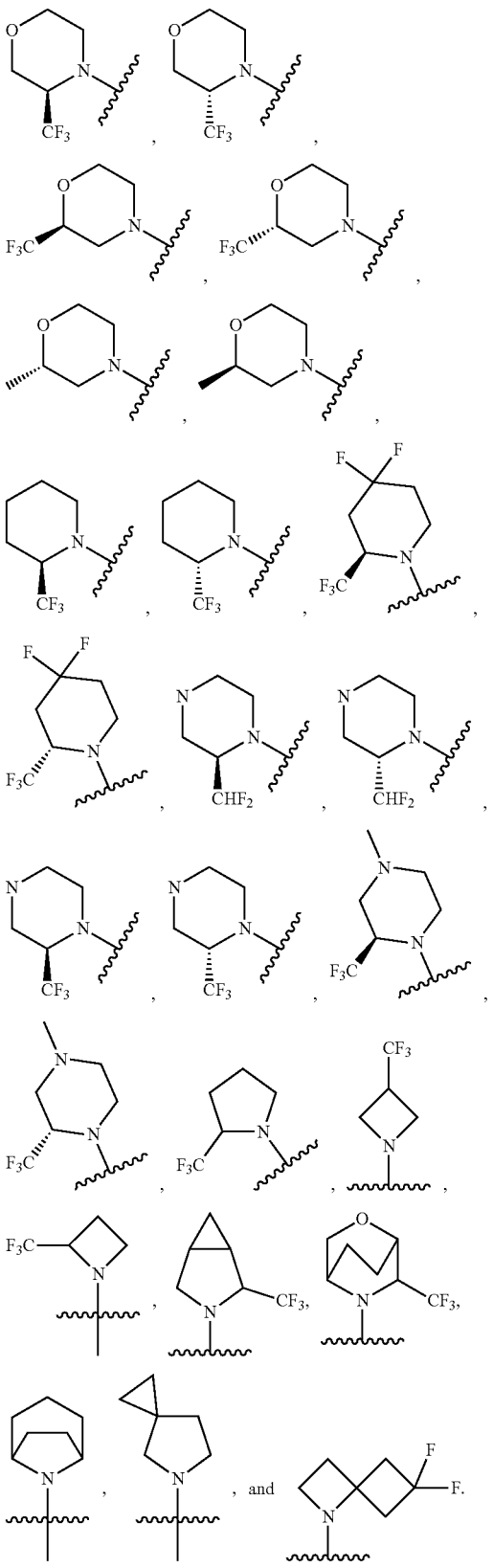
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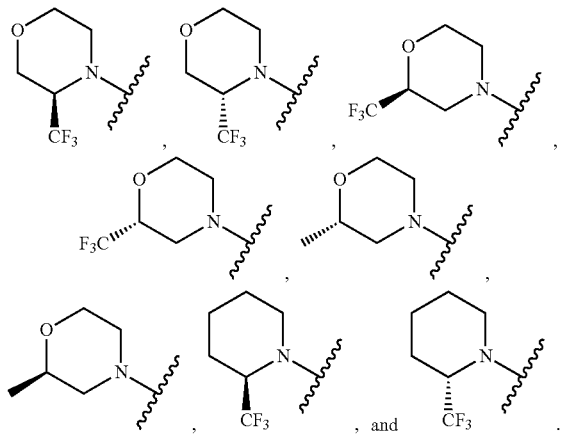
In some embodiments, R^c is selected from selected from



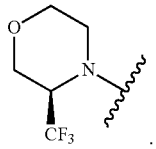
[0138] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId) (IIe), (IIf), (IIg), or (IIh), R^c is selected from



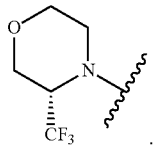
In some embodiments, R^c is selected from



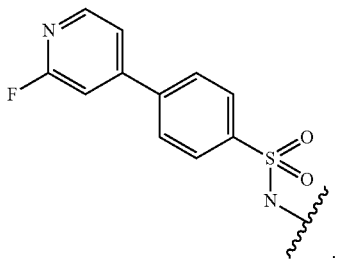
[0139] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is



In some embodiments, R^c is CF_3

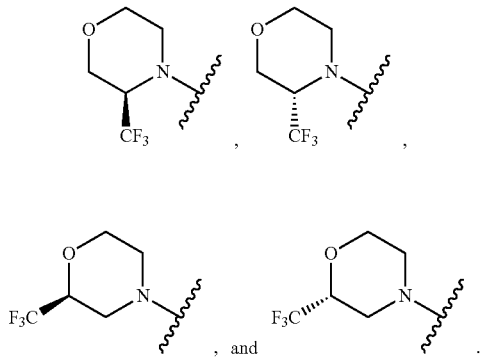


[0140] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is $—NHS(O)_2R^{2c}$, R^{2c} is selected from C_{1-4}alkyl, phenyl, and C_{1-4}haloalkyl. In some embodiments, R^{2c} is selected from $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, and $—CF_3$. In some embodiments, R^{2c} is phenyl optionally substituted with pyridinyl, and the pyridinyl is optionally substituted with halo. In some embodiments, the pyridinyl is optionally substituted with F. In some embodiments, R^c is

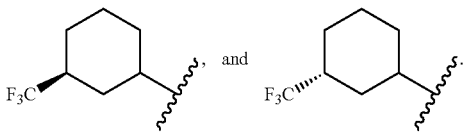


[0141] In some embodiments of formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^c is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. In some embodiments, R^c is selected from H, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, CH_2CH_2F, $—CH_2CHF_2$, and $—CH_2CF_3$. In some embodiments, R^c is selected from H, and $—CF_3$.

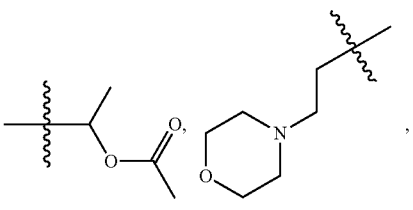
[0142] In some embodiments of formula (I), (II), (IIa), or (IIc), R^2 is cyclohexyl optionally substituted with one or two groups independently selected from with C_{1-4}alkyl and C_{1-4}haloalkyl. In some embodiments, R^2 is cyclohexyl optionally substituted with one group selected from $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, and $—CF_3$. In some embodiments, R^2 is cyclohexyl substituted with $—CF_3$. In some embodiments, R^2 is selected from



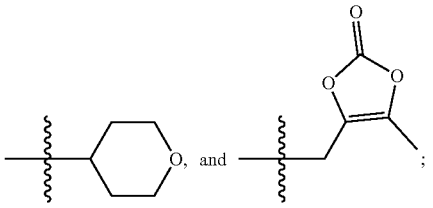
In some embodiments, R^2 is selected from



[0143] In some embodiments of formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), R^3 is selected from H, methyl, ethyl, propyl, butyl, $—CH_2C(O)N(CH_3)_2$, $—(CH_2)_2N(CH_2CH_3)_2$, $—CH_2—O—C(O)CH_3$, $—(CH_2)_2—O—C(O)CH_3$, $—CH_2—O—C(O)C(CH)_3$, $—(CH_2)_2—O—C(O)C(CH)_3$, $—CH_2—O—C(O)—O—CH_3$, $—CH_2—O—C(O)—O—CH_2CH_3$, $—CH_2—O—C(O)—O—CH(CH_3)_2$, $—CH_2—O—C(O)—O—C(OH_3)_3$, $—(CH_2)_2C(O)CH_3$,



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In some embodiments, R^3 is H.

[0144] In some embodiments of formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), R^3 is methyl. In some embodiments, R^3 is ethyl. In some embodiments, R^3 is propyl.

[0145] In some embodiments of formula (I) or (II), each R^4, R^5, R^6, R^7, and R^8 is independently selected from H, F, Cl, CN, —NH_2, —$N(CH_3)_2$, —CH_3, —CH_2F, —CHF_2, —CF_3, and —OCH_3. In some embodiments, each R^4, R^5, R^6, R^7, and R^8 is independently selected from H, F, —CH_3, and —CF_3. In some embodiments, each R^4, R^5, R^6, R^7, and R^8 is H.

[0146] In some embodiments of formula (I), R^9 is selected from H, —CH_3, and CF_3. In some embodiments, R^9 is H. In some embodiments, each R^4, R^5, R^6, R^7, R^8, and R^9 is H.

[0147] In some embodiments of formula (IIc), or (IId), X^1, X^2, and X^3 are CR^{x1}. In some embodiments, X^1 is N; and X^2 and X^3 are CR^{x1}. In some embodiments, X^1 and X^2 are CR^{x1}; and X^3 is N. In some embodiments (IIc), (IId), (IIf), or (IIh), each R^{x1} is independently selected from H, F, Cl, CN, —NH_2, —$N(CH_3)_2$, —CH_3, —CH_2F, —CHF_2, —CF_3, and —OCH_3. In some embodiments, each R^{x1} is independently selected from H, F, Cl, —NH_2, —$N(CH_3)_2$, —CH_3, —CF_3, —OCH_3, and —OCF_3.

[0148] In some embodiments of formula (IIe), r is selected from 1, 2, 3, and 4. In some embodiments, r is selected from 1, 2, and 3.

[0149] In some embodiments of formula (IIg), p is selected from 1, 2, 3, and 4. In some embodiments, p is selected from 1, 2, and 3.

[0150] In some embodiments of formula (IIh), Z^1 is N, and Z^2, Z^3, Z^4, and Z^5 are CR^{x1}. In some embodiments, Z^2 is N, and Z^1, Z^3, Z^4, and Z^5 are CR^{x1}. In some embodiments, Z^3 is N, and Z^1, Z^2, Z^4, and Z^5 are CR^{x1}.

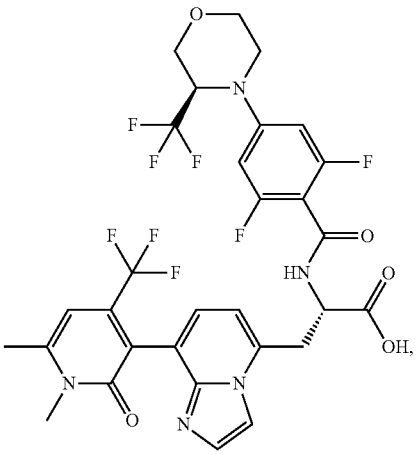
[0151] In some embodiments of formula (IIj), Y^1 is CH or N. In some embodiments, Y^1 is N. In some embodiments, Y^2 is selected from CH_2, NR^{y2}, O, and $S(O)_2$. In some embodiments, Y^1 is N, and Y^2 is O. In some embodiments, Y^1 is N, and Y^2 is CH_2. In some embodiments, Y^1 is N, and Y^2 is $S(O)_2$. In some embodiments, each R^{2d} is independently selected from F, OH, —CH_3, —$CH(CH_3)_2$, —CH_2F, —CHF_2, and —CF_3. In some embodiments, R^{2d} is —CF_3.

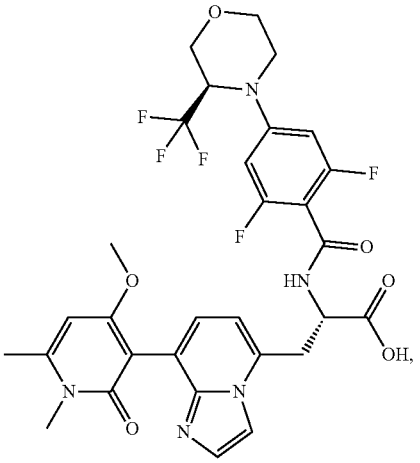
[0152] In some embodiments of formula (IIj), q is selected from 0 and 1. In some embodiments, q is 1.

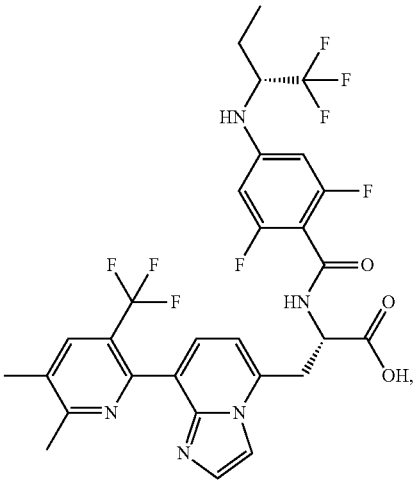
[0153] In one embodiment, the compound of the present disclosure is selected from examples 1-96.

[0154] In one embodiment, the compound of the present disclosure is selected from examples 97-121.

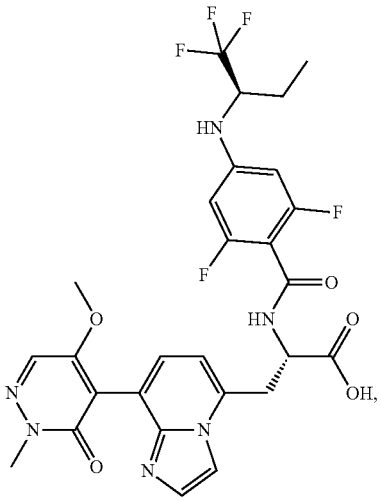
[0155] In one embodiment, the compound of the present disclosure is selected from:

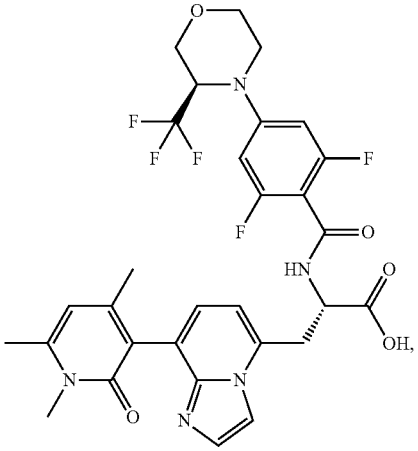


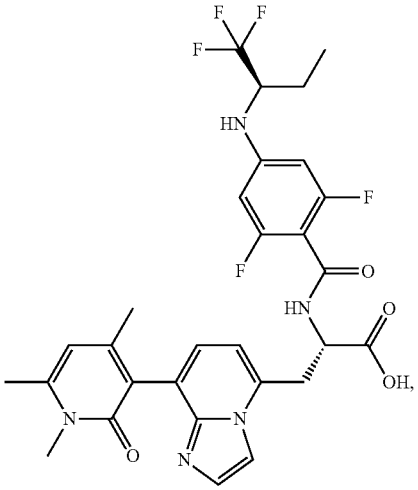




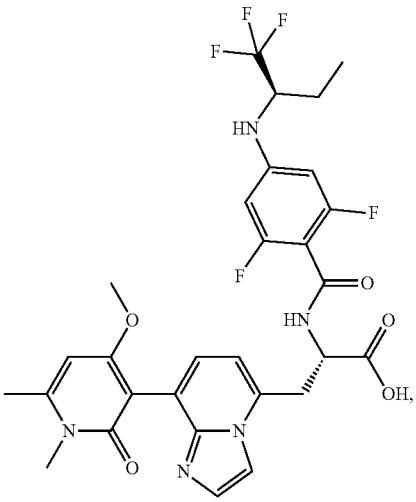
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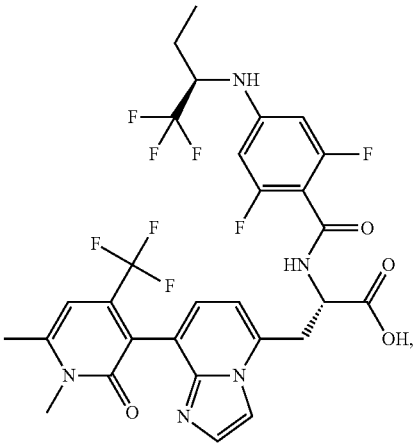


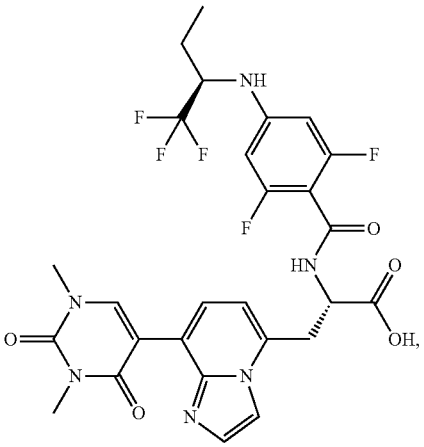




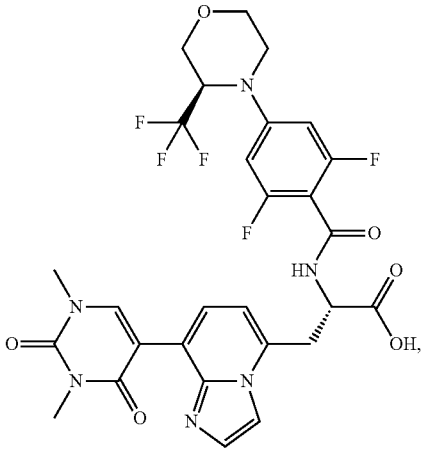
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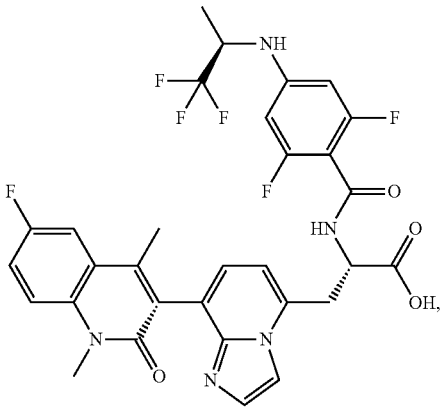


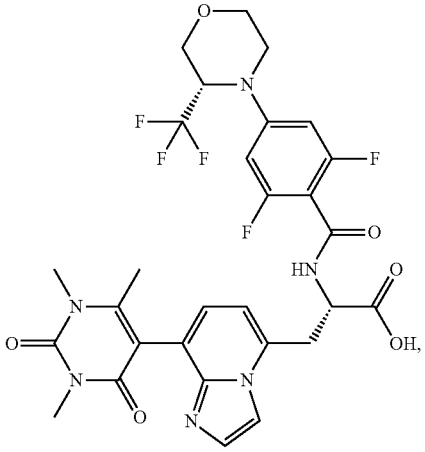




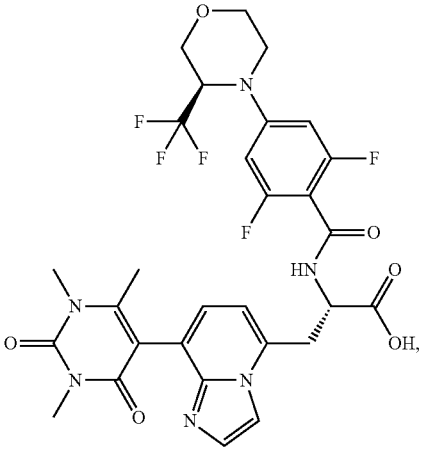
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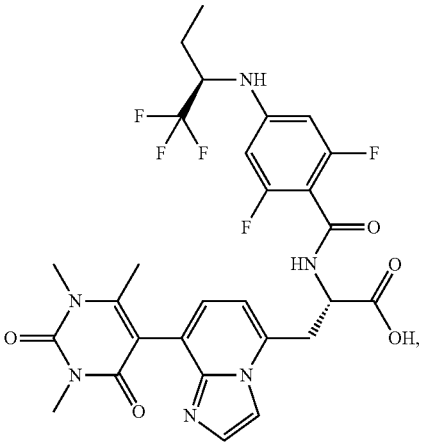


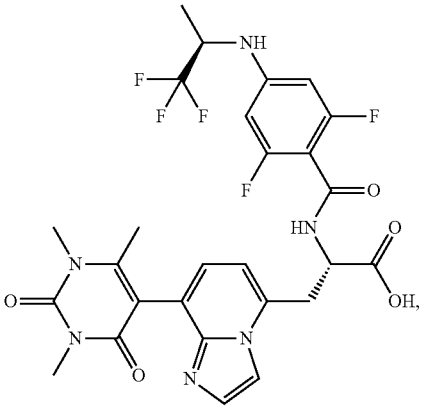




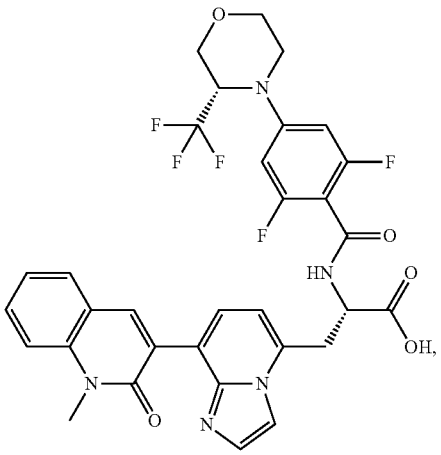
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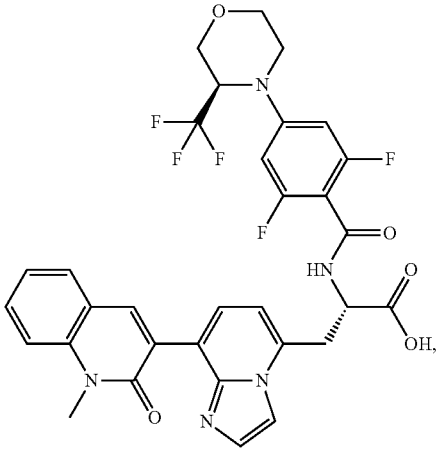


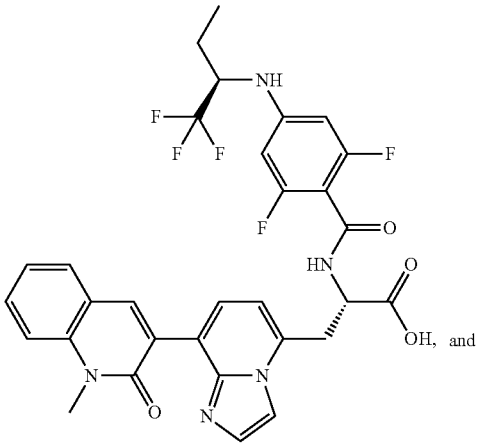




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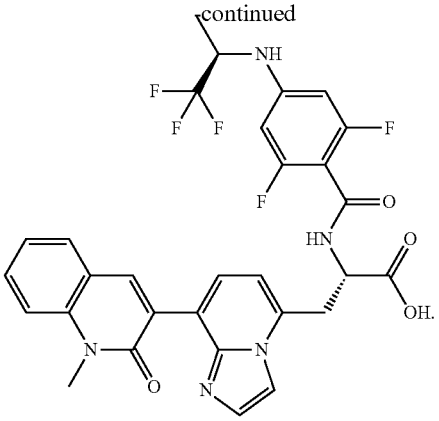






and

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[0156] Provided are also compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof, in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0157] In some embodiments, the compound of the present disclosure contains one to six deuterium (^{2}H, or D). In some embodiments, one of R^a, R^b, R^c, R^d, and R^e contains one to six D. In some embodiments, R^e contains one to six D. In some embodiments, R^e is CD_3.

[0158] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts.

[0159] A "solvate" is formed by the interaction of a solvent and a compound. Solvates of salts of the compounds

described herein are also provided. Hydrates of the compounds described herein are also provided.

[0160] A "prodrug" is a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

[0161] In certain embodiments, provided are optical isomers, racemates, or other mixtures thereof of the compounds described herein or pharmaceutically acceptable salts or a mixture thereof. In those situations, the single enantiomer or diastereomer, i.e., optically active form, can be obtained by asymmetric synthesis or by resolution of the racemate. Resolution of racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high pressure liquid chromatography (HPLC) column. In addition, provided are also Z- and E-forms (or cis- and trans- forms) of the hydroxyamidine compounds described herein. Specifically, Z- and E- forms are included even if only one designation is named for both carbon-carbon double bonds as well as the hydroxyamidine bond.

[0162] Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound (s).

[0163] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. A mixture of enantiomers at a ratio other than 1:1 is a "scalemic" mixture.

[0164] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0165] "Atropisomers" are stereoisomers arising due to hindered rotation about a single bond, where the barrier to rotation about the bond is high enough to allow for isolation of individual stereoisomers.

[0166] Compositions provided herein that include a compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof may include racemic mixtures, or mixtures containing an enantiomeric excess of one enantiomer or single diastereomers or diastereomeric mixtures. All such isomeric forms of these compounds are expressly included herein the same as if each and every isomeric form were specifically and individually listed.

[0167] In certain embodiments, provided are also chelates, non-covalent complexes, and mixtures thereof, of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof. A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding).

Therapeutic Uses of the Compounds

[0168] The methods described herein may be applied to cell populations in vivo or ex vivo. "In vivo" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "Ex vivo" means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. Exemplary tissue samples include tumors and biopsies thereof. In this context, the invention may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the invention may be used ex vivo to determine the optimal schedule and/or dosing of administration of an $\alpha4\beta7$ integrin inhibitor for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for in vivo treatment. Other ex vivo uses for which the invention may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0169] In some embodiments, compounds described herein, for example, compounds of formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analog thereof, may be used to treat subjects who have or are suspected of having disease states, disorders, and conditions (also collectively referred to as "indications") responsive or believed to be responsive to the inhibition of $\alpha4\beta7$ integrin activity. In some embodiments, the compounds described herein may be used to inhibit the activity of $\alpha4\beta7$ integrin. In some embodiments, the compounds described herein may be used to inhibit excessive or destructive immune reactions or growth or a proliferation of a cell, such as a cancer cell, or inhibit immunosuppression.

Methods

[0170] In some embodiments, the present disclosure provides a compound described herein useful as an inhibitor of $\alpha4\beta7$ integrin. In some embodiments, the present disclosure provides a method of treating an inflammatory disease or condition comprising administering a compound described herein.

[0171] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

[0172] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and at least one additional therapeutic agent and at least one pharmaceutically acceptable excipient.

[0173] The present disclosure provides a compound described herein for use in therapy.

[0174] In another embodiment, the present disclosure provides a compound described herein for use in the manufacture of a medicament for treating a disease or condition provided herein.

[0175] In some embodiments, provided is a compound described herein useful for the treatment of a disease or condition in a patient that is amenable to treatment by inhibiting $\alpha4\beta7$ integrin. Diseases or conditions that may be treated with the compounds described herein include a solid tumor, diabetes, an inflammatory disease, graft versus host

disease, primary sclerosing cholangitis, HIV, an autoimmune disease, inflammatory bowel disease (IBD), alcoholic hepatitis, systemic lupus erythematosus (SLE), and lupus nephritis.

[0176] In some embodiments, provided is a compound described herein useful for the treatment of an inflammatory disease or condition in a patient that is mediated, at least in part, by $\alpha 4\beta 7$ integrin.

[0177] "Administering" or "administration" refers to the delivery of one or more therapeutic agents to a patient. In some embodiments, the administration is a monotherapy wherein a compound described herein is the only active ingredient administered to the patient in need of therapy. In another embodiment, the administration is co-administration such that two or more therapeutic agents are delivered together during the course of the treatment. In some embodiments, two or more therapeutic agents may be co-formulated into a single dosage form or "combined dosage unit", or formulated separately and subsequently combined into a combined dosage unit, as is typically for intravenous administration or oral administration as a mono or bilayer tablet or capsule.

[0178] In some embodiments, the compound described herein is administered to a human patient in need thereof in an effective amount, such as, from about 0.1 mg to about 1000 mg per dose of said compound. In some embodiments, the effective amount is from about 0.1 mg to about 400 mg per dose. In some embodiments, the effective amount is from about 0.1 mg to about 300 mg per dose. In some embodiments, the effective amount is from about 0.1 mg to about 200 mg per dose. In some embodiments, the effective amount is from about 1 mg to about 100 mg per dose. In other embodiments, the effective amount is about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 18 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 200 mg, or about 300 mg per dose.

[0179] In some embodiments, the compound described herein and at least one additional therapeutic agent is administered to a human patient in need thereof in an effective amount of each agent, independently from about 0.1 mg to about 1000 mg per dose of a compound or formulation per dose per compound. In some embodiments, the effective amount of the combination treatment of a compound described herein and an additional compound is independently from about 0.1 mg to about 200 mg per compound per dose. In some embodiments, the effective amount of the combination treatment of a compound described herein and an additional compound is independently from about 1 mg to about 100 mg per compound per dose. In other embodiments, the effective amount of the combination treatment of a compound described herein and an additional compound is for each component, about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 18 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 200 mg, or about 500 mg each per dose.

[0180] In some embodiments, the dose of a compound described herein and/or a combination of the dose of the compound described herein and/or the dose of an additional therapeutic agent is administered once per day, twice per day, or thrice per day. In yet another embodiment, the dose of a compound described herein and/or the dose of an additional therapeutic agent is administered as a loading dose of from about 0.1 mg to about 1000 mg per compound on the first day and each day or on alternate days or weekly for up to a month followed by a regular regimen of a compound described herein and/or one or more additional therapeutic agents or therapies. The maintenance dose may be about 0.1 mg to about 1000 mg once per day, twice per day, thrice per day, or weekly, for each component of a multi component drug regimen. A qualified care giver or treating physician is aware of what dose regimen is best for a particular patient or particular presenting conditions and will make appropriate treating regimen decisions for that patient. Thus, in another embodiment, the qualified caregiver is able to tailor a dose regimen of the compound described herein and/or an additional therapeutic agent(s) as disclosed herein to fit with the particular needs of the patient. Thus, it will be understood that the amount of the dose of a compound described herein and the amount of the dose of an additional therapeutic agent actually administered will usually be determined by a physician, in light of the relevant circumstances, including the condition(s) to be treated, the chosen route of administration, the actual compound (e.g., salt or free base) administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0181] Co-administration may also include administering component drugs, e.g., one on more compounds described herein and one or more additional (e.g., a second, third, fourth or fifth) therapeutic agent(s). Such combination of one on more compounds described herein and one or more additional therapeutic agent(s) may be administered simultaneously or in sequence (one after the other) within a reasonable period of time of each administration (e.g., about 1 minute to 24 hours) depending on the pharmacokinetic and/or pharmacodynamics properties of each agent or the combination. Co-administration may also involve treatment with a fixed combination wherein agents of the treatment regimen are combinable in a fixed dosage or combined dosage medium, e.g., solid, liquid or aerosol. In some embodiments, a kit may be used to administer the drug or drug components.

[0182] Thus, some embodiments of the present disclosure is a method of treating a disease or condition mediated, at least in part, by $\alpha 4\beta 7$ integrin, comprising administering therapeutically effective amounts of formulations of one on more compounds described herein and one or more additional therapeutic agents, including for example, via a kit to a patient in need thereof. It will be understood that a qualified care giver will administer or direct the administration of a therapeutically effective amount of any of the compound(s) or combinations of compounds of the present disclosure.

[0183] "Intravenous administration" is the administration of substances directly into a vein, or "intravenously." Compared with other routes of administration, the intravenous (IV) route is a faster way to deliver fluids and medications throughout the body. An infusion pump can allow precise control over the flow rate and total amount of medication delivered. However, in cases where a change in the flow rate would not have serious consequences, or if pumps are not available, the drip is often left to flow simply by placing the bag above the level of the patient and using the clamp to regulate the rate. Alternatively, a rapid infuser can be used if the patient requires a high flow rate and the IV access device is of a large enough diameter to accommodate it. This

is either an inflatable cuff placed around the fluid bag to force the fluid into the patient or a similar electrical device that may also heat the fluid being infused. When a patient requires medications only at certain times, intermittent infusion is used which does not require additional fluid. It can use the same techniques as an intravenous drip (pump or gravity drip), but after the complete dose of medication has been given, the tubing is disconnected from the IV access device. Some medications are also given by IV push or bolus, meaning that a syringe is connected to the IV access device and the medication is injected directly (slowly, if it might irritate the vein or cause a too-rapid effect). Once a medicine has been injected into the fluid stream of the IV tubing there must be some means of ensuring that it gets from the tubing to the patient. Usually this is accomplished by allowing the fluid stream to flow normally and thereby carry the medicine into the bloodstream; however, a second fluid injection is sometimes used, as a "flush", following the injection to push the medicine into the bloodstream more quickly. Thus, in some embodiments, compound(s) or combination of compounds described herein may be administered by IV administration alone or in combination with administration of certain components of the treatment regimen by oral or parenteral routes.

[0184] "Oral administration" is a route of administration where a substance is taken through the mouth, and includes buccal, sub labial, and sublingual administration, as well as enteral administration and that through the respiratory tract, unless made through, e.g., tubing so the medication is not in direct contact with any of the oral mucosa. Typical form for the oral administration of therapeutic agents includes the use of tablets or capsules. Thus, in some embodiments, compound(s) or combination of compounds described herein may be administered by oral route alone or in combination with administration of certain components of the treatment regimen by IV or parenteral routes.

Pharmaceutical Formulations

[0185] The compounds described herein may be administered in a pharmaceutical formulation. Pharmaceutical formulations/compositions contemplated by the present disclosure comprise, in addition to a carrier, the compound described herein or a combination of compounds described herein optionally in combination with an additional therapeutic agent.

[0186] Pharmaceutical formulations/compositions contemplated by the present disclosure may also be intended for administration by injection and include aqueous solutions, oil suspensions, emulsions (with sesame oil, corn oil, cottonseed oil, or peanut oil) as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[0187] Sterile injectable solutions are prepared by incorporating the component compound(s) in the required amount in the appropriate solvent with various other ingredients as enumerated above or as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0188] In making pharmaceutical compositions that comprise compound described herein optionally in combination with an additional agent/therapy useful for the purpose or pharmaceutically acceptable salt thereof, the active ingredient is usually diluted by an excipient or carrier and/or enclosed or mixed with such a carrier that may be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 20% by weight of the active compounds, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0189] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0190] The compositions of the disclosure may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. In some embodiments, sustained release formulations are used. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations.

[0191] Certain compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" or "combined dosage unit" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of one or more of the active materials (e.g., a compound described herein, optionally in combination with an additional therapeutic agent calculated to produce the desired effect, in association with a suitable pharmaceutical excipient in for example, a tablet, capsule, ampoule or vial for injection). It will be understood, however, that the amount of each active agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compounds administered and their

relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0192] For preparing solid compositions such as tablets, the principal active ingredient(s) is/are mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present disclosure. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient(s) are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0193] The tablets or pills comprising compound described herein of the present disclosure optionally in combination with the second agent may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acidic conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage element, the latter being in the form of an envelope over the former. In some embodiments, the inner dosage element may comprise the compound described herein and the outer dosage element may comprise the second or additional therapeutic agent or vice versa. Alternatively, the combined dosage unit may be side by side configuration as in a capsule or tablet where one portion or half of the tablet or capsule is filled with a formulation of the compound described herein while the other portion or half of the table or capsule comprises the additional therapeutic agent.

[0194] A variety of materials may be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate. One of ordinary skill in the art is aware of techniques and materials used in the manufacture of dosages of formulations disclosed herein.

[0195] A "sustained release formulation" or "extended release formulation" is a formulation which is designed to slowly release a therapeutic agent into the body over an extended period of time, whereas an "immediate release formulation" is a formulation which is designed to quickly release a therapeutic agent into the body over a shortened period of time. In some cases the immediate release formulation may be coated such that the therapeutic agent is only released once it reaches the desired target in the body (e.g., the stomach). One of ordinary skill in the art is able to develop sustained release formulations of the presently disclosed compounds without undue experimentation. Thus in some embodiments, compound(s) or combination of compounds described herein may be delivered via sustained released formulations alone or in combination with administration of certain components of the treatment regimen by oral, IV or parenteral routes.

[0196] A lyophilized formulation may also be used to administer a compound described herein singly or in combination with an additional therapeutic agent. One of skill in the art is aware of how to make and use lyophilized formulations of drug substances amenable to lyophilization.

[0197] Spray-dried formulation may also be used to administer a compound described herein singly or in combination with an additional therapeutic agent. One of skill in the art is aware of how to make and use spray-dried formulations of drug substances amenable to spray-drying. Other known formulation techniques may also be employed to formulate a compound or combination of compounds disclosed herein.

[0198] The compounds disclosed herein are useful for the treatment of diseases or conditions mediated, at least in part, by $\alpha4\beta7$ integrin. Non-limiting examples of diseases or conditions mediated, at least in part, by $\alpha4\beta7$ integrin include, without limitation, acne, acid-induced lung injury, Addison's disease, adrenal hyperplasia, adrenocortical insufficiency, adult-onset Still's disease, adult respiratory distress syndrome (ARDS), age-related macular degeneration, aging, alcoholic hepatitis, alcoholic liver disease, allergen-induced asthma, allergic bronchopulmonary, allergic conjunctivitis, allergic contact dermatitis, allergies, allergic encephalomyelitis, allergic neuritis, allograft rejection, alopecia, alopecia areata, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, angina pectoris, angioedema, angiofibroma, anhidrotic ectodermal dysplasia-ill, antiglomerular basement membrane disease, antigen-antibody complex mediated diseases, ankylosing spondylitis, antiphospholipid syndrome, aphthous stomatitis, appendicitis, arthritis, ascites, aspergillosis, asthma, atherosclerosis, atherosclerotic plaques, atopic dermatitis, atrophic thyroiditis, autoimmune diseases, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune polyendocrinopathies, autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), autoimmune hepatitis, autoimmune thyroid disorders, autoinflammatory diseases, back pain, Bacillus anthracis infection, Bechet's disease, bee sting-induced inflammation, Behçet's syndrome, Bell's palsy, berylliosis, Blau syndrome, bone pain, bronchiolitis, bullous pemphigoid (BP) asthma, burns, bursitis, cardiac hypertrophy, carpal tunnel syndrome, Castleman's disease, catabolic disorders, cataracts, Celiac disease, cerebral aneurysm, chemical irritant-induced inflammation, chorioretinitis, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, chronic heart failure, chronic lung disease of prematurity, chronic obstructive pulmonary disease (COPD), chronic pancreatitis, chronic prostatitis, chronic recurrent multifocal osteomyelitis, cicatricial alopecia, colitis, complex regional pain syndrome, complications of organ transplantation, conjunctivitis, connective tissue disease, contact dermatitis, corneal graft neovascularization, corneal ulcer, Crohn's disease, cryopyrin-associated periodic syndromes, cutaneous lupus erythematosus (CLE), cryptococcosis, cystic fibrosis, deficiency of the interleukin-1 receptor antagonist (DIRA), dermatitis, dermatitis endotoxemia, dermatomyositis, diabetic macular edema, diverticulitis, eczema, encephalitis, endometriosis, endotoxemia, eosinophilic pneumonias, epicondylitis, epidermolysis bullosa, erythema multiforme, erythroblastopenia, esophagitis, familial amyloidotic polyneuropathy, familial cold urticarial, familial Mediterranean fever, fetal growth retardation, fibromyalgia, fistulizing Crohn's disease, food allergies, giant cell arteritis, glaucoma, glioblastoma, glomerular disease, glomerular nephritis, glomerulonephritis, gluten-sensitive enteropathy, gout, gouty arthritis, graft-versus-host disease (GVHD), granulomatous hepatitis, Graves' disease, growth plate injuries, Guillain-Barre syndrome, gut diseases, hair loss, Hashimoto's thyroiditis, head injury, headache, hearing loss, heart disease, hemangioma, hemolytic anemia, hemophilic joints, Henoch-Scholein purpura, hepatitis, hereditary peri-

odic fever syndrome, heritable disorders of connective tissue, herpes zoster and simplex, hidradenitis suppurativa (HS), hip replacement, Hodgkin's disease, Huntington's disease, hyaline membrane disease, hyperactive inflammatory response, hyperammonemia, hypercalcemia, hypercholesterolemia, hypereosinophilic syndrome (HES), hyperimmunoglobulinemia D with recurrent fever (HIDS), hypersensitivity pneumonitis, hypertropic bone formation, hypoplastic and other anemias, hypoplastic anemia, ichthyosis, idiopathic demyelinating polyneuropathy, Idiopathic inflammatory myopathies (dermatomyositis, polymyositis), idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, immunoglobulin nephropathies, immune complex nephritis, immune thrombocytopenic purpura (ITP), incontinentia pigmenti (IP, Bloch-Siemens syndrome), infectious mononucleosis, infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes; inflammation, inflammation of the CNS, inflammatory bowel disease (IBD), inflammatory disease of the lower respiratory tract including bronchitis or chronic obstructive pulmonary diseases, inflammatory disease of the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis, inflammatory diseases of the respiratory tract, inflammatory ischemic event such as stroke or cardiac arrest, inflammatory lung disease, inflammatory myopathy such as myocarditis, inflammatory liver disease, inflammatory neuropathy, inflammatory pain, insect bite-induced inflammation, interstitial cystitis, interstitial lung disease, iritis, irritant-induced inflammation, ischemia/reperfusion, joint replacement, juvenile arthritis, juvenile rheumatoid arthritis, keratitis, kidney injury caused by parasitic infections, kidney transplant rejection, leptospirosis, leukocyte adhesion deficiency, lichen sclerosus (LS), Lambert-Eaton myasthenic syndrome, Loeffler's syndrome, lupus, lupus nephritis, Lyme disease, Marfan syndrome (MFS), mast cell activation syndrome, mastocytosis, meningitis, meningioma, mesothelioma, mixed connective tissue disease, Muckle-Wells syndrome (urticaria deafness amyloidosis), mucositis, multiple organ injury syndrome, multiple sclerosis, muscle wasting, muscular dystrophy, myasthenia gravis (MG), myelodysplastic syndrome, myocarditis, myositis, nasal sinusitis, necrotizing enterocolitis, neonatal onset multisystem inflammatory disease (NOMID), neovascular glaucoma, nephrotic syndrome, neuritis, neuropathological diseases, non-allergen induced asthma, obesity, ocular allergy, optic neuritis, organ transplant rejection, Osier-Weber syndrome, osteoarthritis, osteogenesis imperfecta, osteonecrosis, osteoporosis, osterarthritis, otitis, pachyonychia congenita, Paget's disease, Paget's disease of bone, pancreatitis, Parkinson's disease, pediatric rheumatology, pelvic inflammatory disease, pemphigus, pemphigus vulgaris (PV), bullous pemphigoid (BP), pericarditis, periodic fever, periodontitis, peritoneal endometriosis, pernicious anemia (Addison's disease), pertussis, PFAPA (periodic fever aphthous pharyngitis and cervical adenopathy), pharyngitis and adenitis (PFAPA syndrome), plant irritant-induced inflammation, pneumocystis infection, pneumonia, pneumonitis, poison ivy/urushiol oil-induced inflammation, polyarthritis nodosa, polychondritis, polycystic kidney disease, polymyalgia rheumatic, giant cell arteritis, polymyositis, pouchitis, reperfusion injury and transplant rejection, primary biliary cirrhosis, primary pulmonary hypertension, primary sclerosing cholangitis (PSC), proctitis, psoriasis, psoriasis vulgaris, psoriatic arthritis, psoriatic epidermis, psychosocial stress diseases, pulmonary disease, pulmonary fibrosis, pulmonary hypertension, pyoderma gangrenosum, pyogenic granuloma retrolental fibroplasias, pyogenic sterile arthritis, Raynaud's syndrome, Reiter's disease, reactive arthritis, renal disease, renal graft rejection, reperfusion injury, respiratory distress syndrome, retinal disease, retrolental fibroplasia, Reynaud's syndrome, rheumatic carditis, rheumatic diseases, rheumatic fever, rheumatoid arthritis, rhinitis, rhinitis psoriasis, rosacea, sarcoidosis, Schnitzler syndrome, scleritis, sclerosis, scleroderma, scoliosis, seborrhea, sepsis, septic shock, severe pain, Sezary syndrome, sickle cell anemia, silica-induced disease (Silicosis), Sjogren's syndrome, skin diseases, skin irritation, skin rash, skin sensitization (contact dermatitis or allergic contact dermatitis), sleep apnea, spinal cord injury, spinal stenosis, spondyloarthropathies, sports injuries, sprains and strains, Stevens-Johnson syndrome (SJS), stroke, subarachnoid hemorrhage, sunburn, synovial inflammation, systemic inflammatory response syndrome (SIRS), systemic lupus erythematosus, systemic mast cell disease (SMCD), systemic vasculitis, systemic-onset juvenile idiopathic arthritis, temporal arteritis, tendinitis, tenosynovitis, thrombocytopenia, thyroditis, thyroiditis, tissue transplant, toxoplasmosis, trachoma, transplantation rejection, traumatic brain injury, tuberculosis, tubulointerstitial nephritis, tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS), type 1 diabetes, type 2 diabetes, complications from type 1 or type 2 diabetes, ulcerative colitis, urticaria, uterine fibroids, uveitis, uveoretinitis, vascular restenosis, vasculitis, vasculitis (NHLBI), vitiligo, Wegener's granulomatosis, and Whipple's disease.

[0199] In further embodiments, the methods are provided for alleviating a symptom of a disease or disorder mediated, at least in part, by $\alpha4\beta7$ integrin. In some embodiments, the methods include identifying a mammal having a symptom of a disease or disorder mediated, at least in part, by $\alpha4\beta7$ integrin, and providing to the mammal an amount of a compound as described herein effective to ameliorate (i.e., lessen the severity of) the symptom.

[0200] In some embodiments, the disease or condition mediated, at least in part, by $\alpha4\beta7$ integrin is an inflammatory disease or LPS induced endotoxin shock. In some embodiments, the disease is an autoimmune disease. In particular embodiments, the autoimmune disease is systemic lupus erythematosus (SLE), myestenia gravis, rheumatoid arthritis (RA), acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis (MS), inflammatory bowel disease (IBD), sepsis, psoriasis, Sjoegren's syndrome, autoimmune hemolytic anemia, asthma, or chronic obstructive pulmonary disease (COPD), ankylosing spondylitis, acute gout and ankylosing spondylitis, reactive arthritis, monoarticular arthritis, osteoarthritis, gouty arthritis, juvenile arthritis, juvenile onset rheumatoid arthritis, juvenile rheumatoid arthritis or psoriatic arthritis. In other embodiments, the disease is inflammation. In yet other embodiments, the disease is excessive or destructive immune reactions, such as asthma, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), and lupus.

[0201] In some embodiments, the disease or condition mediated, at least in part, by $\alpha4\beta7$ integrin is inflammatory bowel disease (IBD). The term "inflammatory bowel disease" or "IBD" as used herein is a collective term describing inflammatory disorders of the gastrointestinal tract, the most

common forms of which are ulcerative colitis and Crohn's disease. Other forms of IBD that can be treated with the presently disclosed compounds, compositions and methods include diversion colitis, ischemic colitis, infectious colitis, chemical colitis, microscopic colitis (including collagenous colitis and lymphocytic colitis), atypical colitis, pseudomembranous colitis, fulminant colitis, autistic enterocolitis, indeterminate colitis, Behçet's disease, gastroduodenal CD, jejunoileitis, ileitis, ileocolitis, Crohn's (granulomatous) colitis, irritable bowel syndrome, mucositis, radiation induced enteritis, short bowel syndrome, celiac disease, stomach ulcers, diverticulitis, pouchitis, proctitis, and chronic diarrhea.

[0202] Treating or preventing IBD also includes ameliorating or reducing one or more symptoms of IBD. As used herein, the term "symptoms of IBD" refers to detected symptoms such as abdominal pain, diarrhea, rectal bleeding, weight loss, fever, loss of appetite, and other more serious complications, such as dehydration, anemia and malnutrition. A number of such symptoms are subject to quantitative analysis (e.g., weight loss, fever, anemia, etc.). Some symptoms are readily determined from a blood test (e.g., anemia) or a test that detects the presence of blood (e.g., rectal bleeding). The term "wherein said symptoms are reduced" refers to a qualitative or quantitative reduction in detectable symptoms, including but not limited to a detectable impact on the rate of recovery from disease (e.g., rate of weight gain). The diagnosis is typically determined by way of an endoscopic observation of the mucosa, and pathologic examination of endoscopic biopsy specimens.

[0203] The course of IBD varies, and is often associated with intermittent periods of disease remission and disease exacerbation. Various methods have been described for characterizing disease activity and severity of IBD as well as response to treatment in subjects having IBD. Treatment according to the present methods is generally applicable to a subject having IBD of any level or degree of disease activity.

[0204] In some embodiments, the disease or condition treated by the administration of a compound of composition described herein includes acute gout and ankylosing spondylitis, allergic disorders, Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Amyotrophic lateral sclerosis and multiple sclerosis, atherosclerosis, bacterial infections, bone cancer pain and pain due to endometriosis, BRAF resistant melanoma, brain stem glioma or pituitary adenomas, burns, bursitis, cancer of the anal region, cancer of the endocrine system, cancer of the kidney or ureter (e.g., renal cell carcinoma, and carcinoma of the renal pelvis), cancer of the penis, cancer of the small intestine, cancer of the thyroid, cancer of the urethra, cancers of the blood such as acute myeloid leukemia, cancers of the tongue, carcinoma of the cervix, carcinoma of the endometrium, carcinoma of the fallopian tubes, carcinoma of the renal pelvis, carcinoma of the vagina or carcinoma of the vulva, chronic myeloid leukemia, chronic or acute leukemia, chronic pain, classic Bartter syndrome, common cold conjunctivitis, coronary heart disease, cutaneous or intraocular melanoma, dermatitis, dysmenorrhea, eczema, endometriosis, familial adenomatous polyposis, fibromyalgia, fungal infections, gout, gynecologic tumors, uterine sarcomas, carcinoma of the fallopian tubes, headache, hemophilic arthropathy, Parkinson's disease, AIDS, herpes zoster, Hodgkin's disease, Huntington's, hyperprostaglandin E syndrome, influenza, iritis, juvenile arthritis, juvenile onset rheumatoid arthritis, juvenile rheumatoid arthritis, low back and neck pain, lymphocytic lymphomas, myofascial disorders, myositis, neuralgia, neurodegenerative disorders such as Alzheimer's disease, neuroinflammatory disorders, neuropathic pain, carcinoma of the vulva, Parkinson's disease, pediatric malignancy, pulmonary fibrosis rectal cancer, rhinitis, sarcoidosis, sarcomas of soft tissues, scleritis, skin cancer, solid tumors of childhood, spinal axis tumors, sprains and strains, stomach cancer, stroke, subacute and chronic musculoskeletal pain syndromes such as bursitis, surgical or dental procedures, symptoms associated with influenza or other viral infections, synovitis, toothache, ulcers, uterine cancer, uterine sarcomas, uveitis, vasculitis, viral infections, viral infections (e.g., influenza) and wound healing.

[0205] Criteria useful for assessment of disease activity in subjects with ulcerative colitis can be found in, e.g., Truelove et al. (1955) Br Med J 2:1041-1048.) Using these criteria, disease activity can be characterized in a subject having IBD as mild disease activity or severe disease activity. Subjects who do not meet all the criteria for severe disease activity, and who exceed the criteria for mild disease activity are classified as having moderate disease activity.

[0206] The presently disclosed treatment methods can also be applied at any point in the course of the disease. In some embodiments, the methods are applied to a subject having IBD during a time period of remission (i.e., inactive disease). In such embodiments, the present methods provide benefit by extending the time period of remission (e.g., extending the period of inactive disease) or by preventing, reducing, or delaying the onset of active disease. In other embodiments, methods may be applied to a subject having IBD during a period of active disease. Such methods provide benefit by reducing the duration of the period of active disease, reducing or ameliorating one or more symptoms of IBD, or treating IBD.

[0207] Measures for determining efficacy of treatment of IBD in clinical practice have been described and include, for example, the following: symptom control; fistula closure; extent of corticosteroid therapy required; and, improvement in quality of life. Heath-related quality of life (HRQL) can be assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), which is extensively used in clinical practice to assess quality of life in a subject with IBD. (See Guyatt et al. (1989) Gastroenterology 96:804-810.) In some embodiments, the disease or condition is immune-mediated liver injury, disease or condition.

[0208] In some embodiments, the disease or condition mediated, at least in part, by $\alpha 4\beta 7$ integrin is alcoholic hepatitis. Alcoholic hepatitis is a clinical syndrome characterized by jaundice and liver failure that develops in subjects with chronic and active alcohol abuse. (See Akriviadis E. et. al, Ann Gastroenterol. 2016 April-June; 29(2): 236-237). Alcoholic hepatitis can cause cirrhosis and fibrosis of the liver cells. Glucocorticoids, (e.g., prednisolone) and phosophodiesterase inhibitors (e.g., pentoxifylline) can be used to treat alcoholic hepatitis. The compounds herein can be used as stand-alone treatments or in combination with the current treatments for alcoholic hepatitis.

[0209] In one aspect, the present disclosure provides methods of treating or preventing a human immunodeficiency virus (HIV) infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition provided herein.

[0210] In some embodiments, the disease or condition mediated, at least in part, by α4β7 integrin is systemic lupus erythematosus (SLE), lupus nephritis, lupus-related, or other autoimmune disorders or a symptom of SLE. Symptoms of systemic lupus erythematosus include joint pain, joint swelling, arthritis, fatigue, hair loss, mouth sores, swollen lymph nodes, sensitivity to sunlight, skin rash, headaches, numbness, tingling, seizures, vision problems, personality changes, abdominal pain, nausea, vomiting, abnormal heart rhythms, coughing up blood and difficulty breathing, patchy skin color and Raynaud's phenomenon.

Combination Therapy

[0211] Also provided are methods of treatment in which a compound described herein is given to a patient in combination with one or more additional active agents or therapy.

[0212] Thus in some embodiments, a method of treating diseases or conditions mediated, at least in part, by α4β7 integrin and/or diseases or symptoms that co-present or are exacerbated or triggered by the diseases or conditions mediated, at least in part, by α4β7 integrin, e.g., an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, comprises administering to a patient in need thereof an effective amount of a compound described herein optionally in combination with an additional agent (e.g., a second, third, fourth or fifth active agent) which can be useful for treating diseases or conditions mediated, at least in part, by α4β7, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction incident to or co-presenting with diseases or conditions mediated, at least in part, by α4β7 integrin. Treatment with the second, third, fourth or fifth active agent may be prior to, concomitant with, or following treatment with a compound described herein. In some embodiments, a compound described herein is combined with another active agent in a single dosage form. Suitable therapeutics that may be used in combination with a compound described herein include, but are not limited to, therapeutic agents provided herein, or a combination comprising at least one therapeutic agent provided herein.

[0213] Included herein are methods of treatment in which a compound described herein is administered in combination with an agent for treatment of an inflammatory disease or condition. Examples of agents for treatment of an inflammatory disease or condition that can be used in combination with compounds described herein, include alpha-fetoprotein modulators; adenosine A3 receptor antagonist; adrenomedullin ligands; AKT1 gene inhibitors; antibiotics; antifungals; ASK1 inhibitors; ATPase inhibitors; beta adrenoceptor antagonists; BTK inhibitors; calcineurin inhibitors; carbohydrate metabolism modulators; cathepsin S inhibitors; CCR9 chemokine antagonists; CD233 modulators; CD29 modulators; CD3 antagonists; CD40 ligand inhibitors; CD40 ligand receptor antagonists; chemokine CXC ligand inhibitors; CHST15 gene inhibitors; collagen modulators; CSF-1 antagonists; CX3CR1 chemokine modulators; ecobiotics; eotaxin ligand inhibitors; EP4 prostanoid receptor agonists; F1F0 ATP synthase modulators; farnesoid X receptor (FXR and NR1H4) agonists or modulators; fecal microbiota transplantation (FMT); fractalkine ligand inhibitors; free fatty acid receptor 2 antagonists; GATA 3 transcription factor inhibitors; glucagon-like peptide 2 agonists; glucocorticoid agonists; Glucocorticoid receptor modulators; guanylate cyclase receptor agonists; HIF prolyl hydroxylase inhibitors; histone deacetylase inhibitors; HLA class II antigen modulators; hypoxia inducible factor-1 stimulator; ICAM1 gene inhibitors; IL-1 beta ligand modulators; IL-12 antagonists; IL-13 antagonists; IL-18 antagonists; IL-22 agonists; IL-23 antagonists; IL-23A inhibitors; IL-6 antagonists; IL-7 receptor antagonists; IL-8 receptor antagonists; integrin alpha-4/beta-1 antagonists; integrin alpha-4/beta-7 antagonists; integrin antagonists; interleukin ligand inhibitors; interleukin receptor 17A antagonists; interleukin-1 beta ligands; interleukin 1 like receptor 2 inhibitors; IL-6 receptor modulators; JAK tyrosine kinase inhibitors; Jak1 tyrosine kinase inhibitors; Jak3 tyrosine kinase inhibitors; lactoferrin stimulators; LanC like protein 2 modulators; leukocyte elastate inhibitors; leukocyte proteinase-3 inhibitors; MAdCAM inhibitors; melanin concentrating hormone (MCH-1) antagonist; melanocortin agonists; metalloprotease-9 inhibitors; microbiome-targeting therapeutics; natriuretic peptide receptor C agonists; neuregulin-4 ligands; NLPR3 inhibitors; NKG2 D activating NK receptor antagonists; nuclear factor kappa B inhibitors; opioid receptor antagonists; OX40 ligand inhibitors; oxidoreductase inhibitors; P2X7 purinoceptor modulators; PDE 4 inhibitors; Pellino homolog 1 inhibitors; PPAR alpha/delta agonists; PPAR gamma agonists; protein fimH inhibitors; P-selectin glycoprotein ligand-1 inhibitors; Ret tyrosine kinase receptor inhibitors; RIP-1 kinase inhibitors; RIP-2 kinase inhibitors; RNA polymerase inhibitors; sphingosine 1 phosphate phosphatase 1 stimulators; sphingosine-1-phosphate receptor-1 agonists; sphingosine-1-phosphate receptor-5 agonists; sphingosine-1-phosphate receptor-1 antagonists; sphingosine-1-phosphate receptor-1 modulators; stem cell antigen-1 inhibitors; superoxide dismutase modulators; SYK inhibitors; tissue transglutaminase inhibitor; TLR-3 antagonists; TLR-4 antagonists; Toll-like receptor 8 (TLR8) inhibitors; TLR-9 agonists; TNF alpha ligand inhibitors; TNF ligand inhibitors; TNF alpha ligand modulators; TNF antagonists; TPL-2 inhibitors; tumor necrosis factor 14 ligand modulators; tumor necrosis factor 15 ligand inhibitors; Tyk2 tyrosine kinase inhibitors; type I IL-1 receptor antagonists; vanilloid VR1 agonists; and zonulin inhibitors, and combinations thereof.

[0214] Adenosine A3 receptor antagonists include PBF-677.

[0215] Adrenomedullin ligands include adrenomedullin.

[0216] Antibiotics include ciprofloxacin, clarithromycin, metronidazole, vancomycin, rifamycin, rifaximin, and tosufloxacin.

[0217] ASK1 inhibitors include GS-4997.

[0218] Alpha-fetoprotein modulators include ACT-101.

[0219] Anti-CD28 inhibitors include JNJ-3133 and abatacept.

[0220] Beta adrenoceptor antagonists include NM-001.

[0221] BTK inhibitors include GS-4059.

[0222] Calcineurin inhibitors: include tacrolimus, and ciclosporin.

[0223] Carbohydrate metabolism modulators include ASD-003.

[0224] Cathepsin S inhibitors include VBY-129.

[0225] CCR9 chemokine antagonists include CCX-507.

[0226] CD233 modulators include GSK-2831781.

[0227] CD29 modulators include PF-06687234.

[0228] CD3 antagonists include NI-0401.

[0229] CD4 antagonists include IT-1208.

[0230] CD40 ligand inhibitors include SAR-441344, and letolizumab.

[0231] CD40 gene inhibitors include NJA-730.

[0232] CD40 ligand receptor antagonists include FFP-104, BI-655064.

[0233] Chaperonin binding immunoglobulin protein includes IRL-201805.

[0234] Chemokine CXC ligand inhibitors include LY-3041658.

[0235] CHST15 gene inhibitors include STNM-01.

[0236] Collagen modulators include ECCS-50 (DCCT-10).

[0237] COT protein kinase inhibitors include GS-4875.

[0238] CSF-1 antagonists include JNJ-40346527 (PRV-6527), and SNDX-6352.

[0239] CX3CR1 chemokine modulators include E-6130.

[0240] Ecobiotics include SER-287.

[0241] Eotaxin ligand inhibitors include bertilimumab.

[0242] EP4 prostanoid receptor agonists include KAG-308.

[0243] F1F0 ATP synthase modulators include LYC-30937 EC.

[0244] Fractalkine ligand inhibitors include quetmolimab (E-6011).

[0245] Free fatty acid receptor 2 antagonists include GLPG-0974.

[0246] GATA 3 transcription factor inhibitors include SB-012.

[0247] Glucagon-like peptide 2 agonists include teduglutide, and apraglutide.

[0248] Glucocorticoid receptor agonists include budesonide, beclomethasone dipropionate, and dexamethasone sodium phosphate.

[0249] Glucocorticoid receptor modulators/TNF ligand inhibitors include ABBV-3373.

[0250] Guanylate cyclase receptor agonists include dolcanatide.

[0251] HIF prolyl hydroxylase inhibitors include DS-1093, and AKB-4924.

[0252] HIF prolyl hydroxylase-2 inhibitors/hypoxia inducible factor-1 stimulators include GB-004.

[0253] Histone deacetylase inhibitors include givinostat.

[0254] Histone deacetylase-6 inhibitors include CKD-506.

[0255] HLA class II antigen modulators include HLA class II protein modulators.

[0256] ICAM1 gene inhibitors include alicaforsen.

[0257] IL-12 antagonists include ustekinumab (IL12/IL23).

[0258] IL-13 antagonists include tralokinumab.

[0259] IL-18 antagonists include GSK-1070806.

[0260] IL-22 agonists include RG-7880.

[0261] IL-23 antagonists include tildrakizumab, risankizumab (BI-655066), mirikizumab (LY-3074828), brazikumab (AMG-139), and PTG-200.

[0262] IL-23A inhibitors include guselkumab.

[0263] IL-6 antagonists include olokizumab.

[0264] IL-7 receptor antagonists include OSE-127.

[0265] IL-8 receptor antagonists include clotrimazole.

[0266] Integrin alpha-4/beta-1 antagonists include natalizumab.

[0267] Integrin alpha-4/beta-7 antagonists include etrolizumab (a4b7/aEb7), vedolizumab, carotegast methyl, TRK-170 (a4b7/a4b1), PN-10943, and PTG-100.

[0268] Integrin antagonists include E-6007.

[0269] Interleukin ligand inhibitors include bimekizumab (IL-17A/IL-17F).

[0270] Interleukin receptor 17A antagonists include brodalumab.

[0271] Interleukin-1 beta ligands include K(D)PT.

[0272] Interleukin 1 like receptor 2 inhibitors include BI-655130.

[0273] IL-6 receptor modulators include olamkicept.

[0274] JAK tyrosine kinase inhibitors include tofacitinib (1/3), peficitinib (1/3), TD-3504, an TD-1473. Jak1 tyrosine kinase inhibitors include a compound disclosed in WO2008/109943. Examples of other JAK inhibitors include, but are not limited to, AT9283, AZD1480, baricitinib, BMS-911543, fedratinib, filgotinib (GLPG0634), gandotinib (LY2784544), INCB039110, lestaurtinib, momelotinib (CYT0387), NS-018, pacritinib (SB1518), peficitinib (ASP015K), ruxolitinib, tofacitinib (formerly tasocitinib), XL019, upadacitinib (ABT-494), filgotinib, GLPG-0555, SHR-0302, and brepocitinib (PF-06700841) (JAK1/Tyk2).

[0275] Jak3 tyrosine kinase inhibitors include PF-06651600.

[0276] Lactoferrin stimulators include recombinant human lactoferrin (VEN-100).

[0277] LanC like protein 2 modulators include BT-11.

[0278] Leukocyte elastase inhibitors/Leukocyte proteinase-3 inhibitors include tiprelestat.

[0279] MAdCAM inhibitors include SHP-647 (PF-547659).

[0280] Melanin concentrating hormone (MCH-1) antagonists include CSTI-100.

[0281] Melanocortin MC1 receptor agonists include ASP-3291, and PL-8177.

[0282] Metalloprotease-9 inhibitors include GS-5745.

[0283] Microbiome modulator include ABI-M201.

[0284] Natriuretic peptide receptor C agonists include plecanatide.

[0285] Neuregulin-4 ligands include NRG-4.

[0286] NKG2 D activating NK receptor antagonists include JNJ-4500.

[0287] NLPR3 inhibitors include dapansutrile, BMS-986299, SB-414, MCC-950, IFM-514, JT-194, PELA-167, and NBC-6.

[0288] Farnesoid X receptor (FXR and NR1H4) agonists or modulators include AGN-242266, cilofexor tromethamine (GS-9674), EDP-305, EYP-001, GNF-5120, MET-409, nidufexor (LMB-763), obeticholic acid, TERN-101, and tropifexor.

[0289] Nuclear factor kappa B inhibitors include Thetanix.

[0290] Opioid receptor antagonists include naltrexone, and IRT-103.

[0291] OX40 ligand inhibitors include KHK-4083.

[0292] Oxidoreductase inhibitors include olsalazine.

[0293] Pellino homolog 1 inhibitors include BBT-401.

[0294] P2X7 purinoceptor modulators include SGM-1019.

[0295] PDE 4 inhibitors include apremilast.

[0296] PPAR alpha/delta agonists include elafibranor (GFT-1007).

[0297] PPAR gamma agonists include GED-0507-34-Levo.

[0298] Protein fimH inhibitors include sibofimloc (EB-8018).

[0299] P-selectin glycoprotein ligand-1 inhibitors include SEL-K2, AbGn-168H, and neihulizumab.

[0300] Ret tyrosine kinase receptor inhibitors include GSK-3179106.

[0301] RIP-1 kinase inhibitors include GSK-2982772.

[0302] RIP-2 kinase inhibitors include GSK-2983559.

[0303] Sphingosine 1 phosphate phosphatase 1 stimulators include etrasimod.

[0304] Sphingosine-1-phosphate receptor-1 agonists include ozanimod. mocravimod (KRP-203), and BMS-986166.

[0305] Sphingosine-1-phosphate receptor-1 agonists/Sphingosine-1-phosphate receptor-5 agonists include ozanimod.

[0306] Sphingosine-1-phosphate receptor-1 antagonists include amiselimod (MT-1303).

[0307] Sphingosine-1-phosphate receptor-1 modulators include OPL-002.

[0308] Stem cell antigen-1 inhibitors include Ampion (DMI-9523).

[0309] Superoxide dismutase modulators include midismase.

[0310] Syk inhibitors include GS-9876.

[0311] Tissue transglutaminase inhibitor includes zampilimab.

[0312] TLR-3 antagonists include PRV-300.

[0313] TLR-4 antagonists include JKB-122.

[0314] Toll-like receptor 8 (TLR8) inhibitors include E-6887, IMO-4200, IMO-8400, IMO-9200, MCT-465, MEDI-9197, motolimod, resiquimod, VTX-1463, and VTX-763.

[0315] TLR-9 agonists include cobitolimod, IMO-2055, IMO-2125, lefitolimod, litenimod, MGN-1601, and PUL-042.

[0316] TNF alpha ligand inhibitors include adalimumab, certolizumab pegol, infliximab, golimumab, DLX-105, Debio-0512, HMPL-004, CYT-020-TNFQb, Hemay-007, and V-565.

[0317] TNF antagonists include AVX-470, tulinercept, and etanercept.

[0318] TPL-2 inhibitors include GS-4875.

[0319] Tumor necrosis factor 14 ligand modulators include AEVI-002.

[0320] Tumor necrosis factor 15 ligand inhibitors include PF-06480605.

[0321] Tyk2 tyrosine kinase inhibitors include PF-06826647, and BMS-986165.

[0322] TrkA receptor antagonist includes SNA-125.

[0323] Type I IL-1 receptor antagonists include anakinra.

[0324] Zonulin inhibitors include larazotide acetate.

[0325] Included herein are methods of treatment in which a compound described herein is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

[0326] Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC_{50} that is at least 50-fold lower than the IC_{50} for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

[0327] In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

[0328] The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be chosen from cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

[0329] In some embodiments, the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

[0330] In some embodiments, the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

[0331] In some embodiments, the anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

[0332] Included herein are methods of treatment in which a compound described herein, is administered in combination with an immunosuppressant. In some embodiments, the immunosuppressant is methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

[0333] Included herein are methods of treatment in which a compound described herein, is administered in combination with a class of agent for treatment of IBD. Examples of classes of agents for treatment of IBD that can be used in combination with a compound described herein include ASK1 inhibitors, beta adrenoceptor antagonists, BTK inhibitors, beta-glucuronidase inhibitors, bradykinin receptor modulators, calcineurin inhibitors, calcium channel inhibitors, cathepsin S inhibitors, CCR3 chemokine antagonists, CD40 ligand receptor antagonists, chemokine CXC ligand inhibitors, CHST15 gene inhibitors, collagen modulators, CSF-1 antagonists, cyclooxygenase inhibitors, cytochrome P450 3A4 inhibitors, eotaxin ligand inhibitors, EP4 prostanoid receptor agonists, erythropoietin receptor agonists, fractalkine ligand inhibitors, free fatty acid receptor 2 antagonists, GATA 3 transcription factor inhibitors, glucagon-like peptide 2 agonists, glucocorticoid agonists, guanylate cyclase receptor agonists, histone deacetylase inhibitors, HLA class II antigen modulators, IL-12 antagonists, IL-13 antagonists, IL-23 antagonists, IL-6 antagonists, IL-6 receptor modulators, interleukin-7 receptor modulators, IL-7 antagonists, IL-8 antagonists, integrin alpha-4/beta-1 antagonists, integrin alpha-4/beta-7 antagonists, integrin alpha-E antagonists, integrin antagonists, integrin beta-7 antagonists, interleukin ligand inhibitors, interleukin-2 ligand, interleukin receptor 17A antagonists, interleukin-1 beta ligands, interleukin-1 beta ligand modulators, IRAK4 inhibitors, JAK tyrosine kinase inhibitors, Jak1 tyrosine kinase inhibitors, Jak3 tyrosine kinase inhibitors, LanC like protein 2 modulators, lipoxygenase modulators, MAdCAM inhibitors, matrix metalloprotease inhibitors, melanocortin

agonists, metalloprotease-9 inhibitors, natriuretic peptide receptor C agonists, neuregulin-4 ligands, NKG2 D activating NK receptor antagonists, opioid receptor antagonists, opioid receptor delta antagonists, oxidoreductase inhibitors, P2X7 purinoceptor agonists, PDE 4 inhibitors, phagocytosis stimulating peptide modulators, potassium channel inhibitors, PPAR alpha agonists, PPAR delta agonists, PPAR gamma agonists, protein fimH inhibitors, P-selectin glycoprotein ligand-1 inhibitors, RNA polymerase inhibitors, sphingosine 1 phosphate phosphatase 1 stimulators, sphingosine 1 phosphate phosphatase modulators, sphingosine-1-phosphate receptor-1 agonists, sphingosine-1-phosphate receptor-1 antagonists, sphingosine-1-phosphate receptor-1 modulators, sphingosine-1-phosphate receptor-5 modulators, STAT3 gene inhibitors, stem cell antigen-1 inhibitors, superoxide dismutase modulators, superoxide dismutase stimulators, SYK inhibitors, TGF beta 1 ligand inhibitors, thymulin agonists, TLR antagonists, TLR agonists, TNF alpha ligand inhibitors, TNF antagonists, tumor necrosis factor 14 ligand modulators, type II TNF receptor modulators, Tpl 2 inhibitors, and Zonulin inhibitors.

[0334] Included herein are methods of treatment in which a compound described herein is administered in combination with an agent for treatment of IBD. Examples of agents for treatment of IBD that can be used in combination with a compound described herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analog thereof, include those provided herein for the treatment of an inflammatory disease or condition, and ABX-464, adalimumab; alicaforsen, ALLO-ASC-CD, AMG-966, anakinra, apremilast; Alequel; AMG-139; amiselimod, ASD-003, ASP-3291, AX-1505, BBT-401, balsalazide; beclomethasone dipropionate; BI-655130, BMS-986184; budesonide; CEQ-508; certolizumab; ChAdOx2-HAV, dexamethasone sodium phosphate, DNVX-078, etanercept; cibinetide; Clostridium butyricum; ETX-201, golimumab; GS-4997, GS-9876, GS-4875, GS-4059, infliximab; mesalazine, HLD-400, LYC-30937 EC; IONIS-JB11-2.5Rx, JNJ-64304500, JNJ-4447, naltrexone; natalizumab; neihulizumab, olsalazine; PH-46-A, propionyl-L-carnitine; PTG-100; remestemcel-L; tacrolimus; teduglutide; tofacitinib; ASP-1002; ustekinumab; vedolizumab; AVX-470; INN-108; SGM-1019; PF-06480605; PF-06651600; PF-06687234; RBX-8225, SER-287; Thetanix; TOP-1288; VBY-129; 99mTc-annexin V-128; bertilimumab; DLX-105; dolcanatide; FFP-104; filgotinib; foralumab; GED-0507-34-Levo; givinostat; GLPG-0974; iberogast; JNJ-40346527; K(D)PT; KAG-308; KHK-4083; KRP-203; larazotide acetate; LY-3074828, midismase; olokizumab; OvaSave; P-28-GST; PF-547659; prednisolone; QBECO; RBX-2660, RG-7835; JKB-122; SB-012; STNM-01; Debio-0512; TRK-170; zucapsaicin; ABT-494; Ampion; BI-655066; carotegast methyl; cobitolimod; elafibranor; etrolizumab; GS-5745; HMPL-004; LP-02, ozanimod; peficitinib; quetmolimab (E-6011); RHB-104; rifaximin; tildrakizumab; tralokinumab; brodalumab; laquinimod; plecanatide; vidofludimus; and AZD-058.

[0335] Included herein are methods of treatment in which a compound described herein is administered in combination with an agent for treatment of graft versus host disease. Examples of agents for treatment of graft versus host disease that can be used in combination with a compound described herein include those provided herein for the treatment of an inflammatory disease or condition, and [18F]F-AraG, AM-01, Alpha 1 antitrypsin stimulator: AAT-IV and CSL-964; Allocetra, efavaleukin alfa (AMG-592), arsenic trioxide, ATIR-101, belatacept, belimumab, beta lactamase modulator: ribaxamase, bortezomib, brentuximab vedotin, brimonidine, brimonidine tartrate, cannabidiol, ciclosporin, CYP-001, um, dilanubicel, dornase alfa, DSM-9843, eculizumab, EDP-1066, everolimus, Furestem, GL-101, ibrutinib, IMSUT-CORD, IRX-4204, itolizumab, KD-025, MaaT-013, milatuzumab, mizoribine, mycophenolate mofetil, MSCTC-0010, nalotimagene carmaleucel, MET-2, nilotinib, narsoplimab (OMS-721), pacritinib, PF-05285401, ProTmune, QPI-1002, remestemcel-L, RGI-2001, saratin, SCM-CGH, sirolimus, T-allo10, telmisartan, TOP-1288, TZ-101, voclosporin; CCR5 chemokine antagonist: leronlimab (PRO-140); CD40 ligand receptor antagonist: iscalimab; Complement C1s subcomponent inhibitor: CE-1145, sutimlimab, Cinryze, BIVV-009; B-lymphocyte antigen CD20 inhibitor: obinutuzumab, rituximab; CASP9 gene stimulator: rivogenlecleucel; CD3 antagonist or CD7 inhibitor: T-Guard; Complement C5a factor inhibitor: olendalizumab; Dipeptidyl peptidase IV inhibitor: begelomab; JAK1/2 tyrosine kinase inhibitor: ruxolitinib; Jak1 tyrosine kinase inhibitor: itacitinib; Interleukin-2 ligand: aldesleukin; Interleukin 22 ligand: F-652; IL-2 receptor alpha subunit inhibitor: basiliximab and inolimomab; IL-6 receptor agonist: PLX-1; IL-6 receptor antagonist: clazakizumab; OX40 ligand inhibitor: KY-1005; An example of such OX40 inhibitor is a compound disclosed in U.S. Pat. No. 8,450,460, the entire contents of which are incorporated herein by reference; Signal transducer CD24 modulator: CD24-IgFc; Somatostatin receptor agonist: Thymoglobulin; and sphingosine-1-phosphate receptor-1 agonist: ponesimod.

[0336] Included herein are methods of treatment in which a compound described herein is administered in combination with an agent for treatment of primary sclerosing cholangitis. Examples of agents for treatment of primary sclerosing cholangitis that can be used in combination with compounds described herein include those provided herein for the treatment of an inflammatory disease or condition, and BTT-1023, CM-101, Doconexent, GRI-0124, HTD-1801, HTD-2802, hymecromone, IDN-7314, NGM-282, norursodeoxycholic acid, ORBCEL-C, integrin alpha-V/beta-1 and beta-6 antagonist: PLN-74809; PPAR delta agonist: seladelpar lysine; SCT-5-27, PTGS2 gene and TGF beta 1 gene inhibitor: SCT-5-27, and STP-705; Farnesoid X receptor (FXR, NR1H4) agonists or modulators: AGN-242266, cilofexor tromethamine (GS-9674), EDP-305, EYP-001, GNF-5120, MET-409, nidufexor (LMB-763), obeticholic acid, TERN-101, tropifexor; liver X receptor antagonist: DUR-928; and CCR5/CCR2 chemokine antagonist: cenicriviroc.

[0337] In some embodiments, the one or more additional therapeutic agents is selected from the group consisting of: combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-

trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or a pharmaceutically acceptable salt of any of the foregoing, or any combinations thereof.

[0338] In some embodiments, the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or a pharmaceutically acceptable salt of any of the foregoing, or any combinations thereof.

[0339] In some embodiments, the one or more additional therapeutic agent is an immune modulating agent, e.g., an immunostimulant or an immunosuppressant. In certain other embodiments, an immune modulating agent is an agent capable of altering the function of immune checkpoints, including the CTLA-4, LAG-3, B7-H3, B7-H4, Tim3, BTLA, KIR, A2aR, CD200 and/or PD-1 pathways. In other embodiments, the immune modulating agent is immune checkpoint modulating agents. Exemplary immune checkpoint modulating agents include anti-CTLA-4 antibody (e.g., ipilimumab), anti-LAG-3 antibody, anti-B7-H3 antibody, anti-B7-H4 antibody, anti-Tim3 antibody, anti-BTLA antibody, anti-KIR antibody, anti-A2aR antibody, anti CD200 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-CD28 antibody, anti-CD80 or -CD86 antibody, anti-B7RP1 antibody, anti-B7-H3 antibody, anti-HVEM antibody, anti-CD137 or -CD137L antibody, anti-OX40 or -OX40L antibody, anti-CD40 or -CD40L antibody, anti-GAL9 antibody, anti-IL-10 antibody and A2aR drug. For certain such immune pathway gene products, the use of either antagonists or agonists of such gene products is contemplated, as are small molecule modulators of such gene products. In some embodiments, immune modulating agents include those agents capable of altering the function of mediators in cytokine mediated signaling pathways.

[0340] In some embodiments, a compound as disclosed herein may be combined with one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents in any dosage amount of the compound described herein (e.g., from 10 mg to 1000 mg of compound).

[0341] A compound described herein may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0342] In some embodiments, provided are kits comprising a pharmaceutical composition comprising a compound described herein or a compound described herein and at least one additional therapeutic agent, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier. In some embodiments, kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analog thereof, in combination with one or more (e.g., one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents are provided. Any pharmaceutical composition provided in the present disclosure may be used in the kits, the same as if each and every composition were specifically and individually listed for use in a kit. In some embodiments, the kit comprises instructions for use in the treatment of an inflammatory disease or condition. In some embodiments, the instructions in the kit are directed to use of the pharmaceutical composition for the treatment of IBD.

List of Abbreviations and Acronyms

[0343]

Abbreviation	Meaning
%	Percent
° C.	Degree Celsius
Ac	Acetyl
AcOH	Acetic acid
ACN/CH_3CN/ MeCN	Acetonitrile
ADME	Absorption, distribution, metabolism and excretion
AIBN	2,2'-Azobis(2-methylpropionitrile)
Aq.	Aqueous
ASK	Apoptosis signal-regulating kinase
Bicarb	Bicarbonate
Bn	Benzyl
BOC/Boc	Tert-butyloxycarbonyl
Bpin	Pinacolborane
br	Broad
CAS	Chemical Abstract Service
cataCXium A	Di(1-adamantyl)-n-butylphospine
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CREST	Calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly and telangiectasia
CVP	Cyclophosphamide, vincristine, prednisone
d	Doublet
D/d	Deuterium
DAST	Diethylaminosulfur trifluoride
DABCO ®	1,4-Diazabicyclo[2.2.2]octane
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane/methylene chloride
dd	Doublet of doublets
DIEA	N,N-Diisopropylethylamine
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxy ethane
DMF	Dimethylformamide
DMPK	Drug metabolism and pharmacokinetics
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphinc)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane

-continued

Abbreviation	Meaning
EC_{50}	The half maximal effective concentration
equiv/eq	Equivalents
EA	Ethyl acetate
Et	Ethyl
Et_2O	Diethyl ether
EtOAc/AcOEt	Ethyl acetate
EtOH	Ethanol
F	Fahrenheit
FBS	Fetal bovine serum
g	Grams
Gp	Glycoprotein
h/hr	Hours
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
hex	Hexanes
HPLC	High pressure liquid chromatography
Hz	Hertz
IL	Interleukin
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant (MHz)
JAK	Janus kinase
Kg/kg	Kilogram
KOAc	Potassium acetate
L	Liter
LCMS/LC-MS	Liquid chromatography-mass spectrometry
LHMDS	Lithium hexamethyl disilazide
LiMg-TMP	2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex
M	Molar
m	multiplet
M+	Mass peak
M + H	Mass peak plus hydrogen
m-CPBA	Meta-Chloroperbenzoic acid
Me	Methyl
Me_2N	Dimethylamine
MeI	Methyl Iodide
MeOH	Methanol
MeOTs	Methyl Tosylate
mg	Milligram
MHz	Megahertz
min/m	Minute
ml/mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Mass spectroscopy
MS	Multiple sclerosis
MsCl	Methanesulfonyl chloride
MTBE	Methyl tert-Butyl ether
M/Z	Mass/Charge
N	Normal
NADH	Nicotinamide adenine dinucleotide in reduced form
NaOH	Sodium hydroxide
NBS	N-Bromosuccinimide
ng	Nanograms
NIS	N-Iodosuccinimide
nM	Nanomolar
NMR	Nuclear magnetic resonance
ON	Overnight
PEG	Polyethylene glycol
PET	Positron emission tomography
Ph	Phenyl
PhMe	Toluene
$PhNO_2$	Nitrobenzene
$PhNTf_2$	N-Phenyl triflamide
pH	Expressing the acidity or alkalinity of a solution
prep	Preparative
RA	Rheumatoid arthritis
Rf	Retention factor
RPM	Revolutions per minute
RT/r	Room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s	Second
s	Singlet

-continued

Abbreviation	Meaning
sat.	Saturated
SFC	Super-critical fluid chromatography
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
SPhos Pd G3	(2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
SYK	Spleen tyrosine kinase
t	Triplet
TBACl	Tetrabutylammonium chloride
TBS/TBDMS	Tert-butyldimethylsilyl
tBuOH	Tert-Butanol
tBuBrettPhos Pd G3	[(2-Di-tert-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
TCA	Trichloroacetic acid
TEA/NEt_3	Triethylamine
temp.	Temperature
TES	Triethylsilane
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMP	Tetramethyl piperidine
TMS	Trimethylsilyl
Tol	Toluene
TPL2	Tumor Progression Locus 2 Kinase
Trityl	Triphenylmethyl
Vac	Vacuum
w/v	Weight/volume
w/w	Weight/weight
XPhos Pd G3	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
δ	Chemical shift (ppm)
μg	Microgram
μL/μl	Microliter
μM	Micromolar
μm	Micrometer
μmol	Micromole

Synthesis

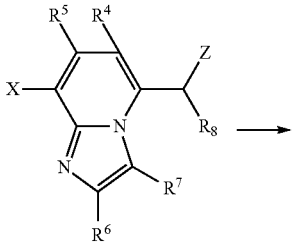
[0344] The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds of formula (I), e.g., compounds having structures described by one or more of formula (I), or other formulas or compounds disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analog thereof, may be accomplished as described in the following examples.

General Schemes

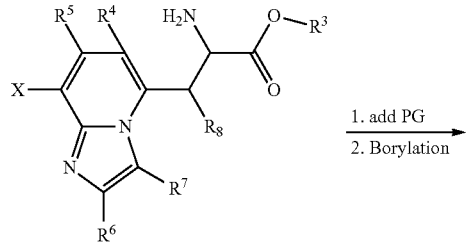
[0345] Typical embodiments of compounds in accordance with the present disclosure may be synthesized using the general reaction schemes and/or examples described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Starting materials are typically obtained from commercial sources or synthesized using

published methods for synthesizing compounds which are embodiments of the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein.

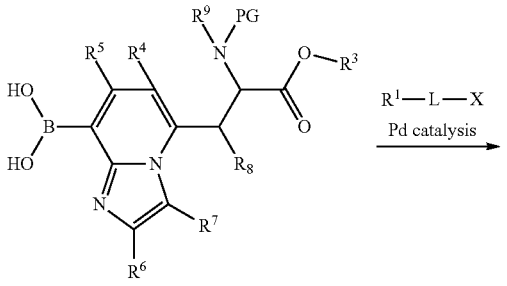
General Scheme 1



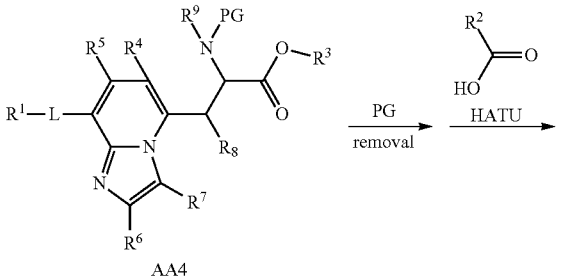
Intermediate AA1



AA2

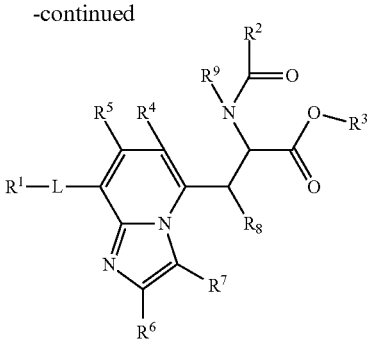


AA3



AA4

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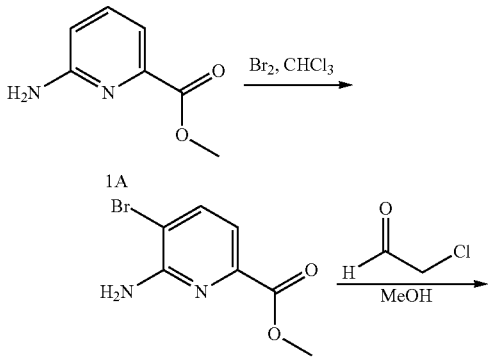
AA5

[0346] Scheme 1 describes a general route that was used to prepare compounds of Formula I. From Intermediate AA1 that has an alcohol or halogen as Z, and halogen group as X, amino acid esters (AA2) can be prepared under a variety of conditions (eg. Schollkopf, Maruoka, etc). After appropriate protection of the free amine with protecting groups (PG), eg. Trityl, Boc, etc., AA2 was converted to a boronic acid or boronic ester (AA3) under standard conditions (eg. Miyaura). R^1 was introduced under a variety of cross coupling conditions to give AA4. After removal of the amine protecting group (PG) under appropriate conditions, the amine was coupled with acids to provide heterocyclic compounds AA5.

EXAMPLES

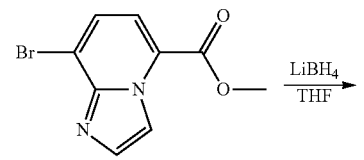
Example 1

[0347]

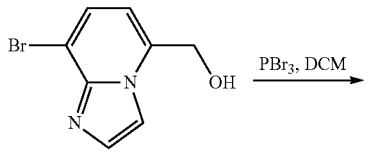


1A

1B

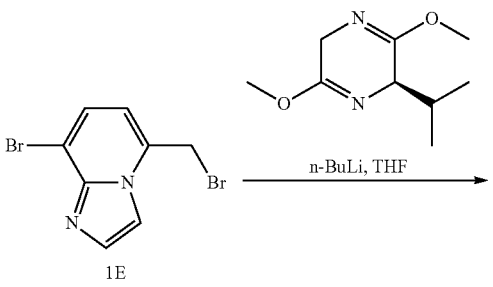


1C

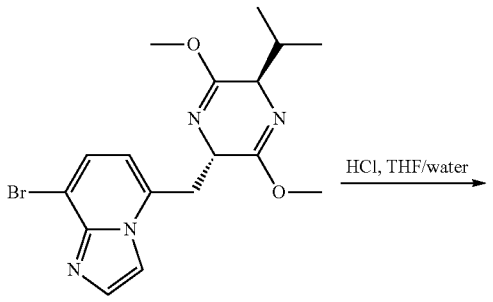


1D

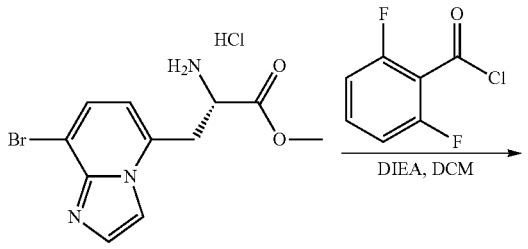
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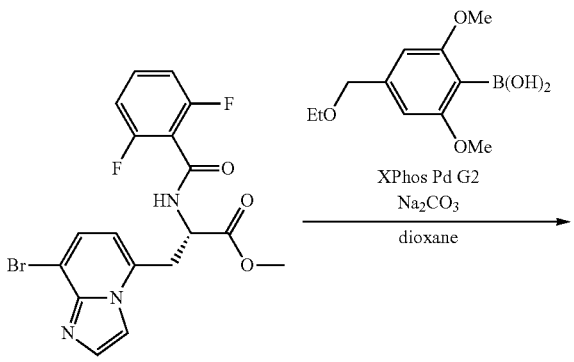
1E



1F

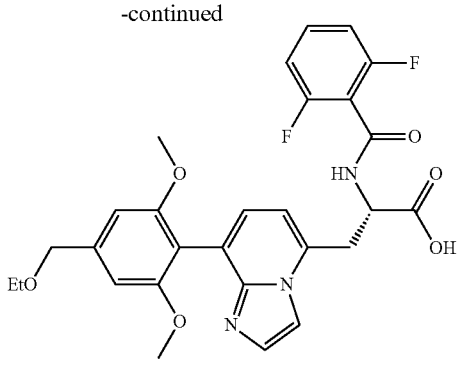


1G



1H

-continued



1

[0348] Synthesis of methyl 6-amino-5-bromopicolinate (1B): To a stirred solution of methyl 6-aminopicolinate (200 g, 1.21 mol) in $CHCl_3$ (2 L) was added a solution of bromine (418 g, 2.63 mol) in $CHCl_3$ (4 L) at −10° C. The reaction mixture was allowed to warm to room temperature and was stirred for 18 h. Next, the reaction mixture was cooled to 0° C. and quenched with an aqueous saturated sodium thiosulfate solution. It was extracted with dichloromethane (3×3 L), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated. To the crude residue, methanol was added and it was stirred for 30 min, then filtered. This material was treated with acetonitrile and stirred for 30 min, then filtered and concentrated under reduced pressure to obtain compound 1B.

[0349] Synthesis of methyl 8-bromoimidazo[1,2-a]pyridine-5-carboxylate (1C): To a stirred solution of compound 1B (75 g, 0.324 mol) in methanol (750 mL) was added 2-chloro acetaldehyde in water (55%, 450 mL) at RT. The resulting reaction mixture was heated to 65° C. and stirred for 18 h. After completion of the reaction, reaction mixture cooled to room temperature and concentrated. The crude compound was basified with a saturated aqueous solution of sodium bicarbonate (pH 8-9) an extracted with EtOAc (1000 mL×2). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to obtain 1C.

[0350] Synthesis of (8-bromoimidazo[1,2-a]pyridin-5-yl) methanol (1D): To a stirred solution of 1C (75 g, 294 mmol) in THF (750 mL) was slowly added 2M $LiBH_4$ in THF (441 mL, 882 mmol) at 0° C., the resulting reaction mixture was heated to 40° C. for 2 h. Next, the reaction mixture was cooled to 0° C., then quenched with ice water and stirred for 30 min. The mixture was acidified with 2N hydrochloric acid to a pH of about 4 and heated to 40° C. for 2 h. The reaction mixture was cooled to room temperature and basified with a saturated aqueous solution of sodium bicarbonate (pH 8) and extracted with DCM (1000 mL×2). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum to obtain 1D.

[0351] Synthesis of 8-bromo-5-(bromomethyl)imidazo[1,2-a]pyridine (1E): To a stirred solution of 1D (40 g, 176 mmol) in DCM (800 mL) was slowly added PBr_3 (95.1 g, 352 mmol) in DCM (180 mL) at 0° C., the resulting reaction mixture was allowed to warm to room temperature and stir for 18 h. The reaction mixture was concentrated, cooled to 0° C. and basified with a saturated aqueous solution of sodium bicarbonate (pH 8). The resulting solids were collected by filtration and dried under vacuum to obtain 1E.

[0352] Synthesis of 8-bromo-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridine (1F): n-Butyllithium (2.5 M in hexane, 72.4 mL, 181 mmol) was added dropwise to a stirred solution of (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (33.35 g, 181 mmol) in THF (1.05 L) at −78° C. and the resulting reaction mixture was stirred for 30 minutes. Next, 1E (35 g, 120 mmol) in THF (700 mL) was added dropwise over 30 min. The reaction mixture was stirred for 1 h, and then it was allowed to warm to room temperature over 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with water and saturated sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash chromatography on silica gel (eluent 30% EtOAc/petether) to obtain pure compound, which was further purified by normal phase SFC to obtain 1F.

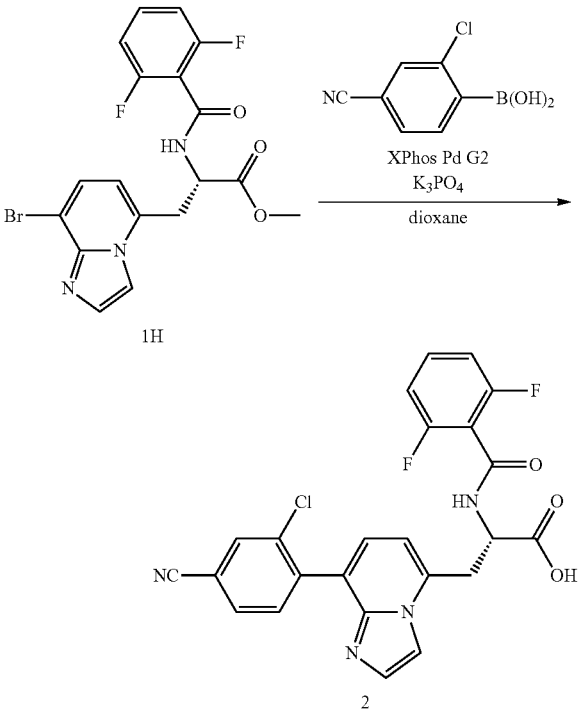
[0353] Synthesis of methyl (S)-2-amino-3-(8-bromoimidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (1G): To a stirred solution of 1F (65 mg, 0.17 mmol) in THF (4.2 mL) was added 2M hydrochloric acid (0.33 mL, 0.66 mmol), and the reaction was allowed to stir for 30 min at room temperature. It was concentrated to yield 1G, which was used without further purification.

[0354] Synthesis of methyl (S)-3-(8-bromoimidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro benzamido)propanoate (1H): To a stirred solution of crude 1G (15 mg, 0.05 mmol) and DIEA (0.044 mL, 0.25 mmol) in dichloromethane (2 ml) was added 2,6-difluorobenzoyl chloride (0.008 mL, 0.06 mmol), and the reaction was allowed to stir at room temperature for 1 hour. It was directly purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes) to yield 1H.

[0355] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (1): A microwave vial was charged with 1H (20 mg, 0.05 mmol), (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid (11 mg, 0.05 mmol), and XPhos Pd G2 (2 mg, 0.002 mmol). Next, dioxane (0.5 mL) and 2M aqueous sodium carbonate (0.08 mL, 0.16 mmol) were added, and the reaction was degassed with argon and sealed. It was heated to 120° C. for 30 minutes by microwave irradiation, and then was cooled to room temperature. It was diluted with DMSO, acidified with trifluoroacetic acid, and purified by preparatory HPLC to yield 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J=8.3 Hz, 1H), 8.55 (d, J=2.3 Hz, 1H), 8.23 (d, J=2.1 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H), 7.61-7.44 (m, 1H), 7.39 (d, J=7.6 Hz, 1H), 7.11 (dd, J=8.5, 7.6 Hz, 2H), 6.81 (s, 2H), 5.08 (ddd, J=10.7, 8.2, 4.4 Hz, 1H), 4.54 (s, 2H), 3.78 (dd, J=15.8, 4.4 Hz, 1H), 3.67 (d, J=2.1 Hz, 6H), 3.61-3.54 (m, 2H), 1.20 (t, J=7.0 Hz, 3H). ES/MS 540.2 ($M+H^+$).

Example 2

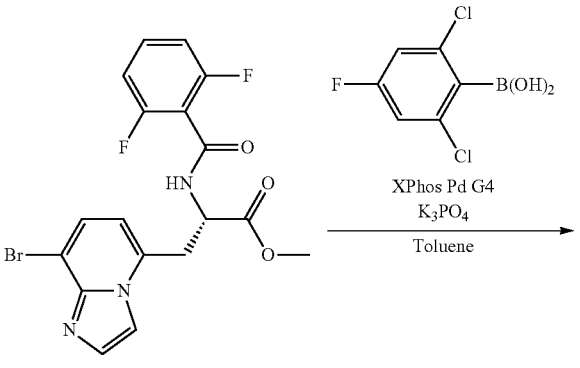
[0356]



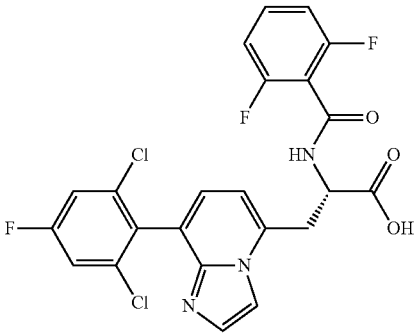
[0357] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl) imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (2): The title compound was prepared according to the method presented for the synthesis of compound 1 of Example 1 starting with (2-chloro-4-cyanophenyl)boronic acid and 1H. MS (m/z) 481.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.29 (d, J=8.2 Hz, 1H), 8.30 (s, 1H), 8.05-7.91 (m, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 7.11 (dd, J=8.5, 7.6 Hz, 2H), 5.05 (s, 1H), 1.22 (s, 2H).

Example 3

[0358]



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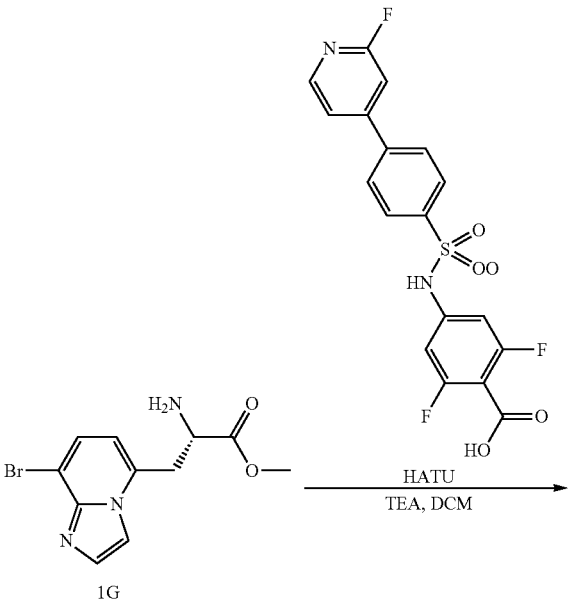
3

[0359] Synthesis of (S)-3-(8-(2,6-dichloro-4-fluorophenyl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluorobenzamido) propanoic acid (3): The title compound was prepared according to the method presented for the synthesis of compound 1 of Example 1 starting with (2,6-dichloro-4-fluorophenyl)boronic acid and 1H. MS (m/z) 508.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.25 (s, 1H), 9.28 (d, J=8.3 Hz, 1H), 7.79 (d, J=8.6 Hz, 2H), 7.63-7.33 (m, 1H), 7.27-6.95 (m, 2H), 5.09 (s, 1H), 3.78 (m, 2H), 3.55 (m, 1H).

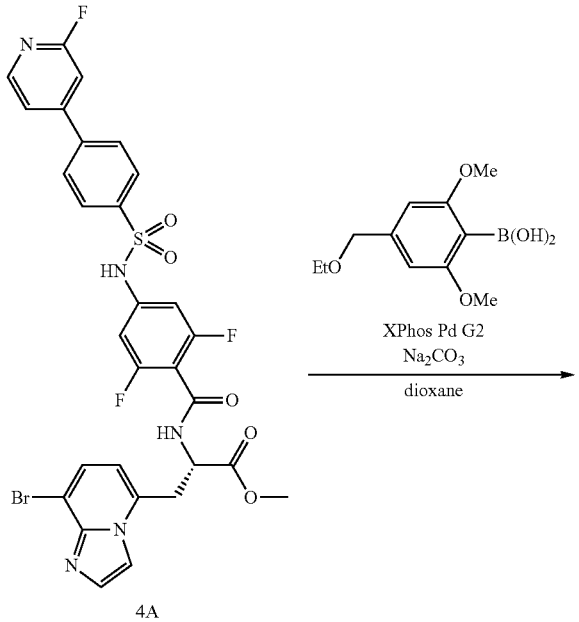
Example 4

[0360] Synthesis of methyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(3-(difluoro methoxy)-2,6-difluorobenzamido)propanoate (4A): To a stirred solution of 1G (110 mg, 0.37 mmol) in DCM was added 2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl) sulfonamido)benzoic acid (181 mg, 0.44 mmol), HATU (210 mg, 0.55 mmol) and TEA (0.322 mL, 1.8 mmol). The reaction mixture was allowed to stir for 2 hr at RT. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography using EA/hexanes as eluent give the title compound.

[0361] Synthesis of (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido) benzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (4): The title compound was prepared according to the method presented for the synthesis of compound 1 of Example 1 starting with (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid and 4A. MS (m/z) 790.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 11.23 (s, 1H), 9.13 (d, J=8.1 Hz, 1H), 8.51 (s, 1H), 8.34 (d, J=5.3 Hz, 1H), 8.21 (s, 1H), 8.11-8.02 (m, 2H), 8.02-7.89 (m, 2H), 7.82-7.67 (m, 2H), 7.59 (d, J=1.7 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 6.79 (d, J=8.3 Hz, 5H), 5.08-4.93 (m, 1H), 4.53 (s, 2H), 3.73 (dd, J=15.9, 4.6 Hz, 1H), 3.63 (d, J=15.0 Hz, 7H), 3.57 (q, J=7.0 Hz, 2H), 1.20 (t, J=7.0 Hz, 3H).

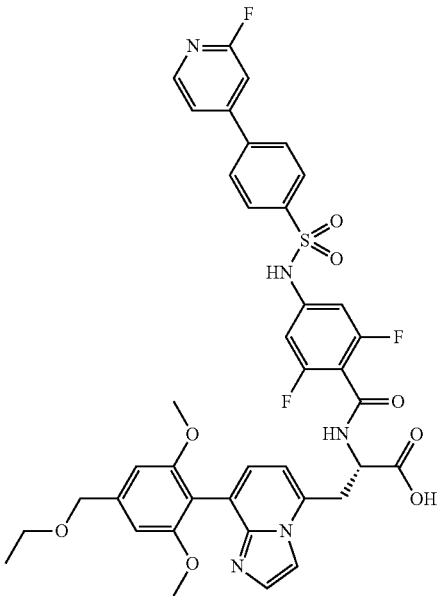


1G



4A

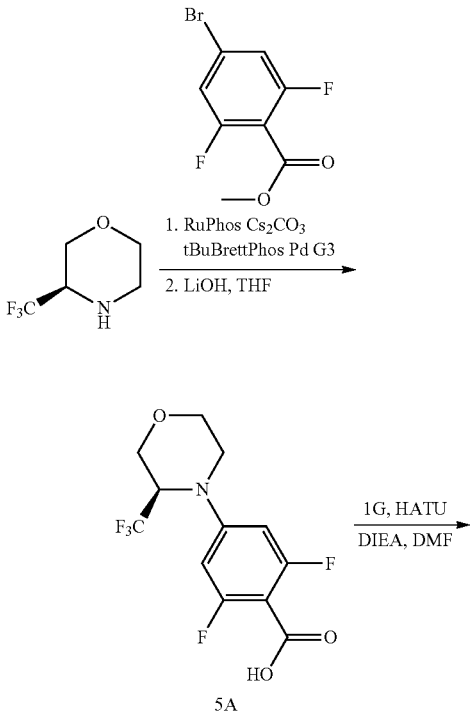
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4

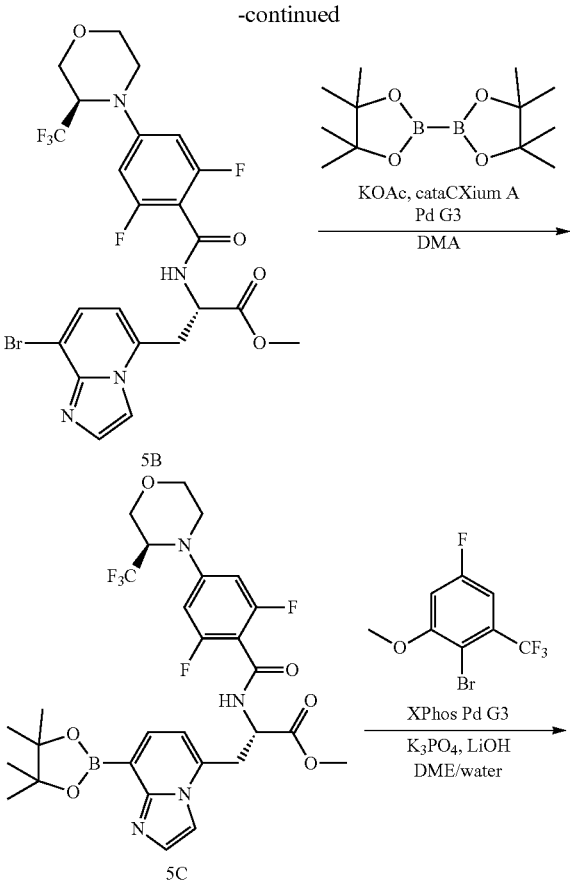
Example 5

[0362]



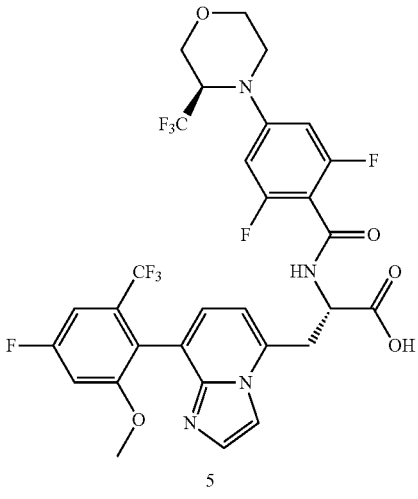
5A

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5B

5C



5

[0363] Synthesis of (R)-2,6-difluoro-4-(3-(trifluoromethyl)morpholino)benzoic acid (5A): To a 150 mL pressure vessel containing a stir bar was added methyl 4-bromo-2,6-difluorobenzoate (200 mg, 0.52 mmol), RuPhos (48 mg, 0.10 mmol), tBuBrettPhos Pd G3 (44 mg, 0.052 mmol), Cs_2CO_3 (844 mg, 2.6 mmol), (R)-3-(trifluoromethyl)morpholine (198 mg, 1.0 mmol) and toluene (6 mL). The reaction vessel was then sealed and heated at 90° C. overnight. The reaction mixture was cooled to RT and filtered over a pad of Celite, rinsed with EtOAc and the filtrate was evaporated to dryness under reduced pressure. The material

was purified by silica gel chromatography using EtOAc in Hexane as eluent. To this material was added THF (2.6 mL) and aqueous LiOH (0.78 mL, 1.0 M). The reaction mixture was stirred at 40° C. for 20 hrs and 50° C. for an additional 4 hours. The reaction mixture was cooled to RT and acidified with 1.0 M HCl before extracting with EtOAc. Organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford 5A.

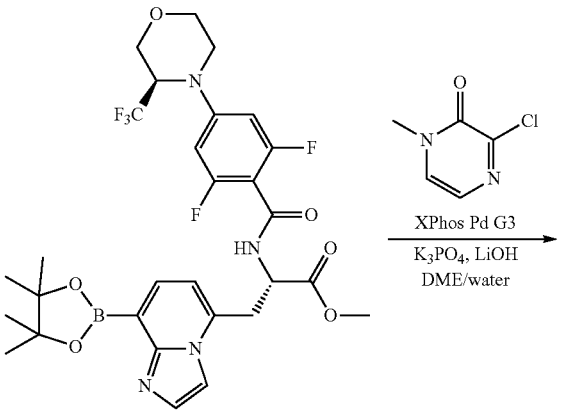
[0364] Synthesis of methyl (S)-3-(8-bromoimidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoate (5B): To a stirred solution of compound 1G (250 mg, 0.75 mmol), compound 5A (233 mg, 0.75 mmol), and N,N-diisopropylethylamine (0.781 mL, 4.5 mmol) in DMF (2 mL) was added HATU (341 mg, 0.897 mmol), and the reaction was allowed to stir at room temperature for 2 hours. It was diluted with ethyl acetate, washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified by silica gel chromatography eluting with hexanes/ethyl acetate/methanol gradients to yield 5B.

[0365] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (5C): To a solution of 5B (473 mg, 0.80 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (406 mg, 1.6 mmol), and potassium acetate (236 mg, 2.4 mmol) in dimethylacetamide (4 mL) degassed with nitrogen was added cataCXium A Pd G3 (29 mg, 0.04 mmol). The reaction was sealed and heated to 100° C. for 1 hour. It was cooled to room temperature, water was added to precipitate the product, and the solids were collected via filtration. The solids were further portioned between water and ethyl acetate. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, and concentrated to yield 5C.

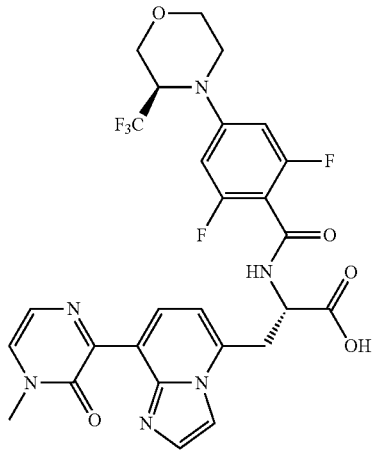
[0366] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-fluoro-2-methoxy-6-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (5): To a solution of 5C (50 mg, 0.078 mmol), and 2-bromo-5-fluoro-1-methoxy-3-(trifluoromethyl) benzene (43 mg, 0.16 mmol) in 1,2-dimethoxyethane (2 mL) was added 1M potassium phosphate in water (0.274 mL, 0.274 mmol), and the reaction was degassed with nitrogen. To this, XPhos Pd G3 (6 mg, 0.008 mmol) was added, and the reaction was sealed heated to 90° C. for 20 minutes. It was cooled to room temp, and 1M lithium hydroxide (0.235 mL, 0.24 mmol) was added, and it was stirred for 10 minutes. It was diluted with dimethylsulfoxide, acidified with TFA, and purified by preparatory HPLC to yield 5. MS (m/z) 691.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.17 (s, 1H), 9.07-8.84 (m, 1H), 8.57 (s, 1H), 8.25 (s, 1H), 7.78 (d, J=25.1 Hz, 1H), 7.54 (d, J=10.4 Hz, 1H), 7.43 (d, J=8.4 Hz, 1H), 6.72 (d, J=11.8 Hz, 2H), 5.03 (s, 1H), 4.89 (s, 1H), 4.14 (d, J=12.7 Hz, 1H), 3.93 (d, J=8.8 Hz, 1H), 3.77-3.61 (m, 4H), 3.60-3.34 (m, 7H), 3.22 (d, J=12.5 Hz, 1H).

Example 6

[0367] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (6): The title compound was prepared according to the method presented for the synthesis of compound 5 starting with 5C and 3-chloro-1-methylpyrazin-2(1H)-one. MS (m/z) 607.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 9.36 (d, J=7.9 Hz, 1H), 8.94 (d, J=8.2 Hz, 1H), 8.68 (d, J=2.3 Hz, 1H), 8.32 (d, J=2.2 Hz, 1H), 7.99 (d, J=4.0 Hz, 1H), 7.66 (dt, J=4.0, 0.7 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 6.72 (d, J=12.1 Hz, 2H), 5.08-4.96 (m, 1H), 4.87 (d, J=9.4 Hz, 1H), 4.13 (d, J=12.8 Hz, 1H), 3.92 (dd, J=11.4, 3.8 Hz, 1H), 3.80-3.68 (m, 2H), 3.61 (s, 3H), 3.59-3.46 (m, 2H), 3.39 (d, J=12.8 Hz, 1H), 3.19 (t, J=12.3 Hz, 1H).



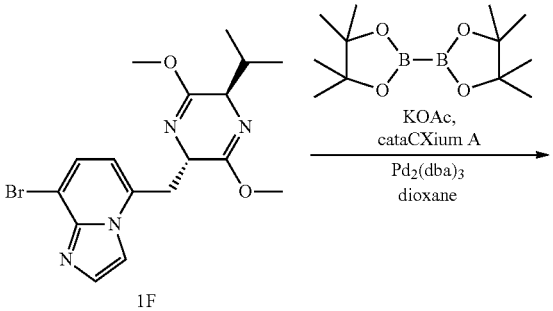
5C



6

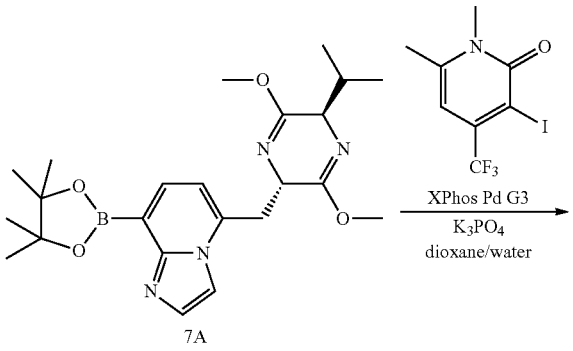
Example 7

[0368]

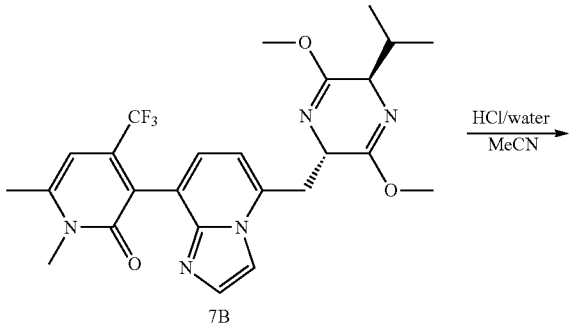


1F

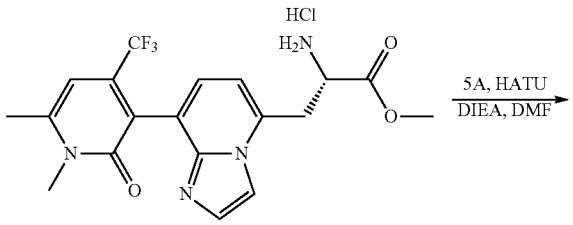
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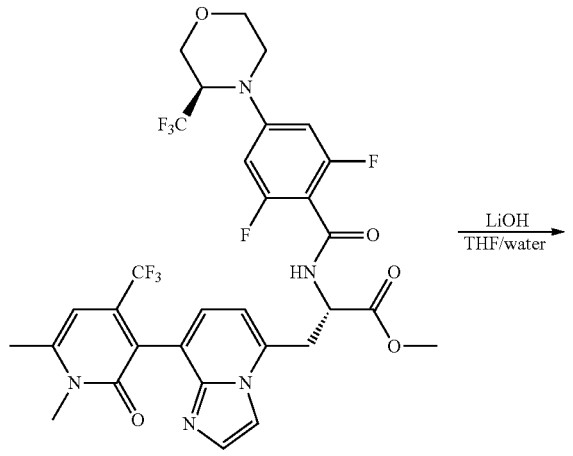
7A



7B

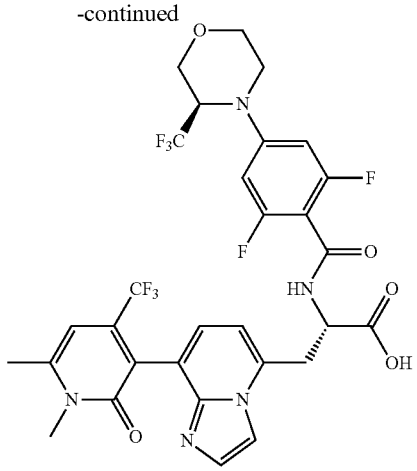


7C



7D

-continued



7

[0369] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine (7A): To a suspension of 1F (500 mg, 1.27 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (743 mg, 2.9 mmol) in dioxane (8 mL) was added potassium acetate (374 mg, 3.8 mmol), tris(dibenzylideneacetone)dipalladium (0) (47 mg, 0.05 mmol), and cataCXium A (68 mg, 0.15 mmol), and the reaction was degassed with nitrogen, sealed, and heated to 90° C. for 16 hours. It was cooled to room temperature, diluted with ethyl acetate, filtered over celite, and concentrated to yield 7A.

[0370] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one (7B): To a solution of 7A (150 mg, 0.34 mmol) and 3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one (130 mg, 0.41 mmol) in dioxane (5 ml) was added XPhos Pd G3 (87 mg, 0.1 mmol) and 1M aqueous tribasic potassium phosphate (1.2 mL, 1.2 mmol), and the reaction was degassed with nitrogen, sealed, and heated to 90° C. for 1 hour. The reaction was cooled to room temperature, concentrated, and purified by silica gel chromatography (eluent ethyl acetate/methanol) to yield 7B.

[0371] Synthesis of methyl (S)-2-amino-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl) imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (7C): To a stirred solution of 7B (320 mg, 0.636 mmol) in acetonitrile (2 mL) was added 2M hydrochloric acid (1.6 mL), and the reaction was allowed to stir at room temperature for 2 hours. The reaction was concentrated and purified by silica gel chromatography (eluent: 0-40% methanol/dichloromethane) to yield 7C.

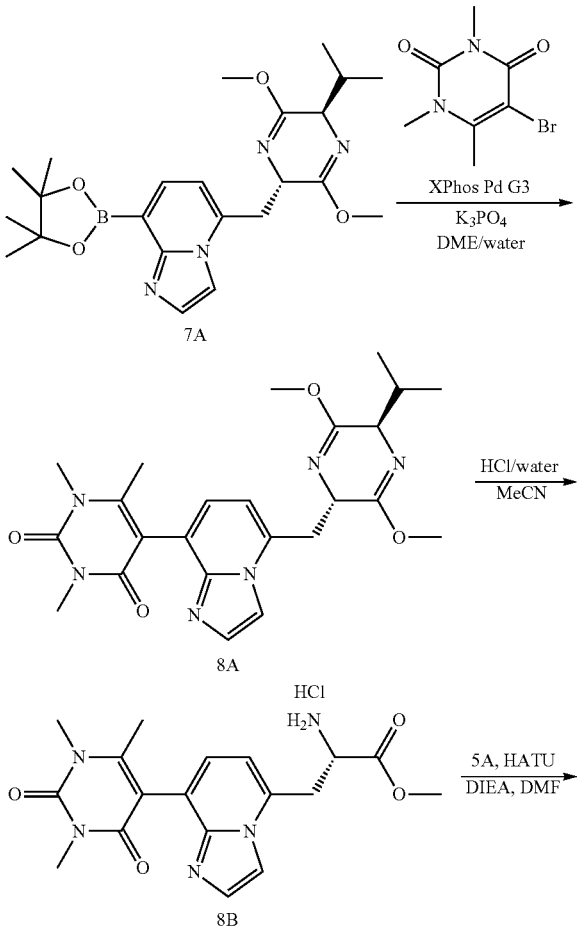
[0372] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl) imidazo[1,2-a]pyridin-5-yl)propanoate (7D): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 7C. MS (m/z) 701.7 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.07 (dd, J=22.2, 8.0 Hz, 1H), 8.60 (d, J=21.1 Hz, 1H), 8.32 (d, J=7.5 Hz, 1H), 7.74 (t, J=10.0 Hz, 1H), 7.39 (dd, J=22.7, 7.5 Hz, 1H), 6.75 (d, J=3.2 Hz, 1H), 6.72 (t, J=3.0

Hz, 2H), 5.21-5.01 (m, 1H), 4.90 (dd, J=8.6, 3.5 Hz, 1H), 4.14 (d, J=12.8 Hz, 1H), 3.93 (dd, J=11.6, 3.8 Hz, 1H), 3.81-3.71 (m, 1H), 3.68 (d, J=9.4 Hz, 3H), 3.52 (d, J=2.7 Hz, 3H), 3.40 (d, J=13.0 Hz, 1H), 3.20 (t, J=12.3 Hz, 1H), 2.57 (d, J=1.7 Hz, 3H).

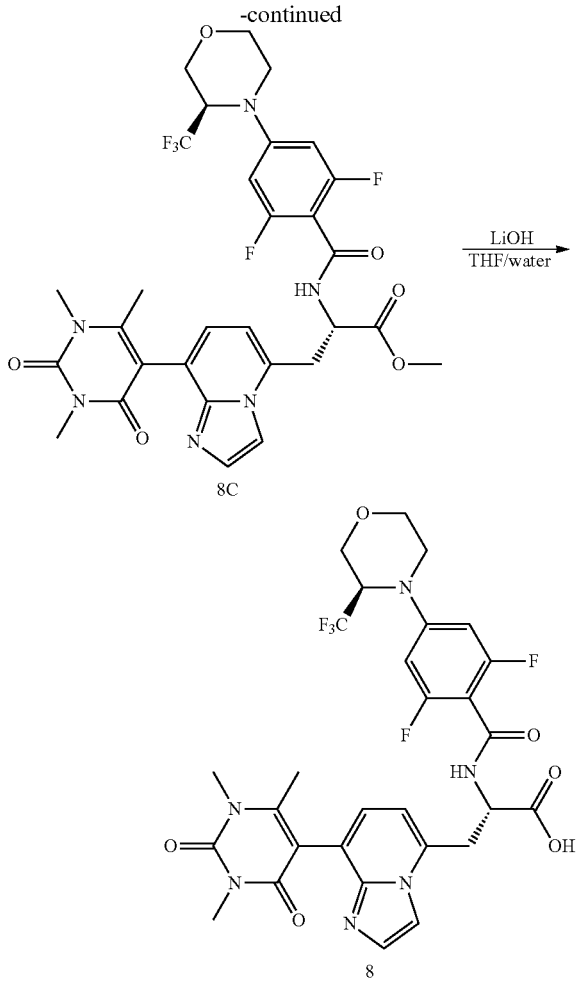
[0373] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (7): To a solution of 7D (223 mg, 0.32 mmol) in tetrahydrofuran (2 mL) was added 1M aqueous lithium hydroxide (1.6 mL, 1.6 mmol), and the reaction was allowed to stir at room temperature for 1 hour. It was concentrated and purified by preparatory HPLC to yield 8. MS (m/z) 687.6 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.02-8.91 (m, 1H), 8.65-8.51 (m, 1H), 8.32 (dd, J=7.9, 2.1 Hz, 1H), 7.75 (dd, J=12.3, 7.5 Hz, 1H), 7.46-7.32 (m, 1H), 6.72 (d, J=11.9 Hz, 3H), 5.07-4.96 (m, 1H), 4.94-4.83 (m, 1H), 4.14 (d, J=12.7 Hz, 1H), 3.93 (dd, J=11.4, 3.8 Hz, 1H), 3.75 (td, J=14.7, 13.4, 7.0 Hz, 2H), 3.66-3.54 (m, 1H), 3.51 (d, J=2.6 Hz, 4H), 3.44-3.33 (m, 1H), 3.20 (t, J=12.4 Hz, 1H), 2.57 (s, 3H).

Example 8

[0374]



-continued



[0375] Synthesis of 5-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-1,3,6-trimethylpyrimidine-2,4(1H,3H)-dione (8A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 5-bromo-1,3,6-trimethylpyrimidine-2,4(1H,3H)-dione and substituting 1,2-dimethoxyethane for dioxane.

[0376] Synthesis of methyl (S)-2-amino-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (8B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 8A.

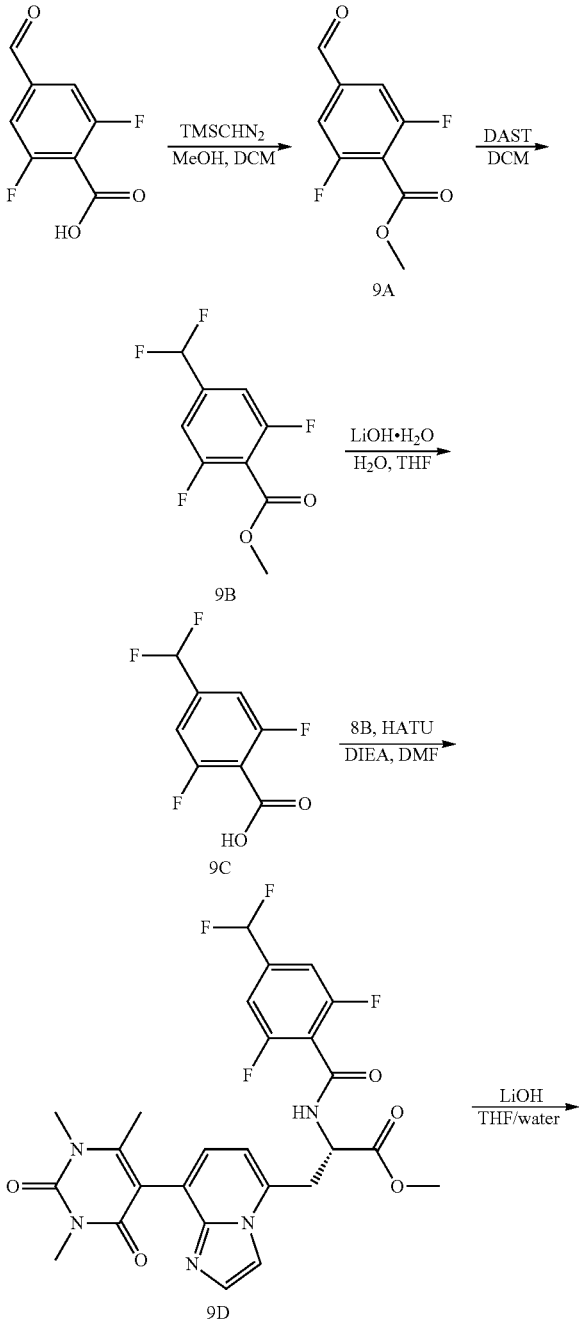
[0377] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (8C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 8B.

[0378] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (8): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 8C. MS (m/z) 651.3 [M+H]+.

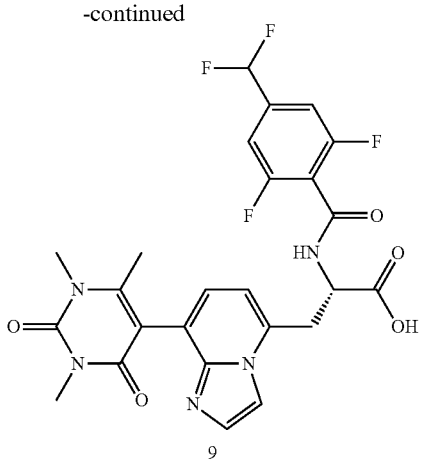
^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 8.96 (t, J=8.9 Hz, 1H), 8.58 (d, J=27.9 Hz, 1H), 8.33 (d, J=13.5 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.38 (dd, J=40.1, 7.4 Hz, 1H), 6.72 (d, J=12.0 Hz, 2H), 5.05-4.82 (m, 2H), 4.14 (d, J=12.7 Hz, 1H), 3.99-3.86 (m, 1H), 3.79-3.48 (m, 4H), 3.46 (d, J=1.6 Hz, 3H), 3.39 (d, J=12.7 Hz, 1H), 3.23 (s, 3H), 3.19 (d, J=13.5 Hz, 1H), 2.12-1.99 (m, 3H).

Example 9

[0379]



-continued



9

[0380] Synthesis of methyl 2,6-difluoro-4-formylbenzoate (9A): To a stirred solution of 2,6-difluoro-4-formylbenzoic acid (431 mg, 2.3 mmol) in dichloromethane (11.6 mL) and methanol (4.6 mL) was carefully added a solution of (trimethylsilyl)diazomethane (3.5 mL, 2M in diethyl ether) at room temperature. The reaction mixture was allowed to stir for 10 minutes and then concentrated under reduced pressure to give 9A.

[0381] Synthesis methyl 4-(difluoromethyl)-2,6-difluorobenzoate (9B): To a stirred solution of 9A (202 mg, 1.0 mmol) in dichloromethane (10 mL) was added diethylaminosulfur trifluoride (0.27 mL, 2.0 mmol) at RT. The reaction mixture was allowed to stir for 4 h. Dichloromethane and water were added to the reaction mixture. The aqueous layer was separated and extracted twice with dichloromethane. The combined organics were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The material was purified on silica gel eluting with ethyl acetate/hexanes to give 9B.

[0382] Synthesis of 4-(difluoromethyl)-2,6-difluorobenzoic acid (9C): To a stirred solution of 9B (153 mg, 0.69 mmol) in tetrahydrofuran (3.8 mL) and water (3.8 mL) was added lithium hydroxide hydrate (145 mg, 3.4 mmol) at room temperature. The reaction mixture was allowed to stir for 16 h. The mixture was acidified with 1M hydrochloric acid and extracted four times with ethyl acetate. The combined organics were dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 9C.

[0383] Synthesis of methyl (S)-2-(4-(difluoromethyl)-2,6-difluorobenzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (9D): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 9C and 8B.

[0384] Synthesis of (S)-2-(4-(difluoromethyl)-2,6-difluorobenzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (9): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 9D. MS (m/z) 548.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.30 (s, 1H), 13.38 (s, 1H), 9.43 (dd, J=8.2, 2.9 Hz, 1H), 8.60 (d, J=31.8 Hz, 1H), 8.34 (d, J=13.6 Hz, 1H), 7.76 (s, 1H), 7.40 (d, J=7.4 Hz, 3H), 7.05 (t, J=55.2 Hz,

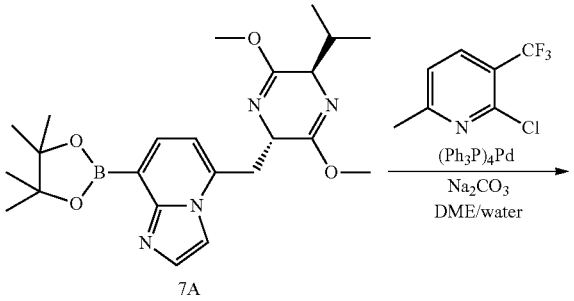
1H), 5.10 (ddd, J=11.5, 7.6, 4.1 Hz, 1H), 3.87-3.73 (m, 1H), 3.66-3.43 (m, 4H), 3.25 (s, 3H), 2.08 (d, J=6.9 Hz, 3H).

Example 10

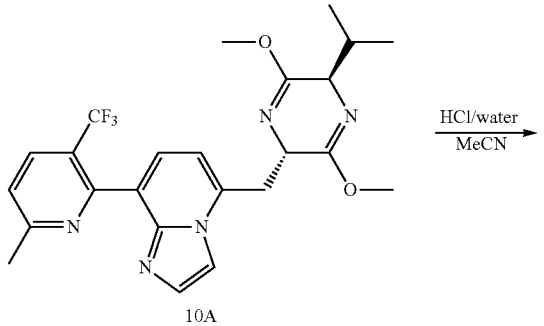
[0385] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridine (10A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 2-chloro-6-methyl-3-(trifluoromethyl)pyridine and substituting 1,2-dimethoxyethane for dioxane, tetrakis(triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0386] Synthesis of methyl (S)-2-amino-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl) imidazo[1,2-a]pyridin-5-yl) propanoate hydrochloride (10B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 10A.

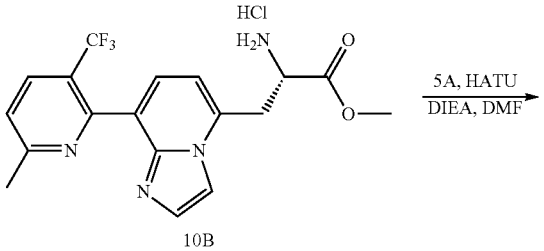
[0387] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (10C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 10B.



7A

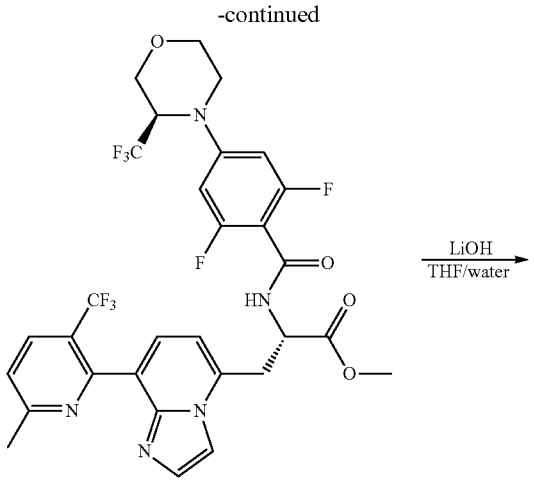


10A

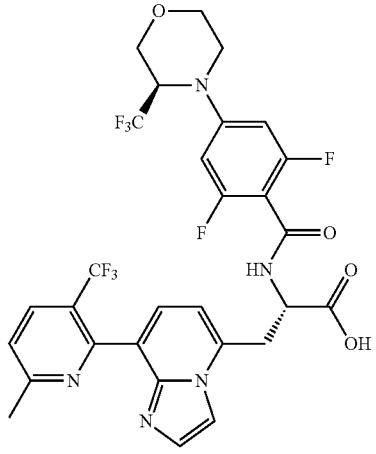


10B

-continued



10C

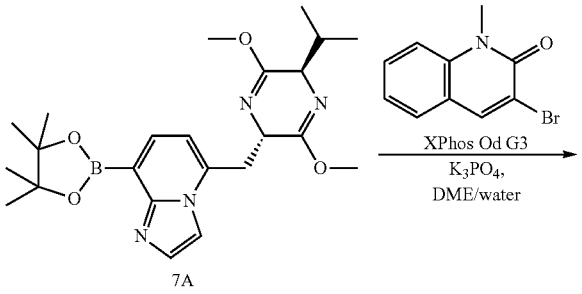


10

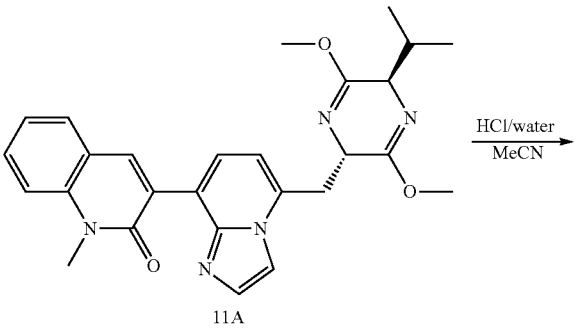
[0388] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (8): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 10C. MS (m/z) 658.8 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.27-13.10 (m, 1H), 8.98 (d, J=8.1 Hz, 1H), 8.61 (s, 1H), 8.33 (d, J=8.3 Hz, 1H), 8.26 (s, 1H), 7.85 (s, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.39 (s, 1H), 6.75 (d, J=11.9 Hz, 2H), 5.02 (ddt, J=13.2, 7.4, 3.3 Hz, 1H), 4.91 (tt, J=11.4, 5.5 Hz, 1H), 4.16 (d, J=12.7 Hz, 2H), 3.95 (dd, J=11.5, 3.8 Hz, 1H), 3.80-3.69 (m, 1H), 3.65-3.49 (m, 2H), 3.42 (d, J=13.4 Hz, 1H), 3.28-3.15 (m, 1H), 2.62 (s, 3H).

Example 11

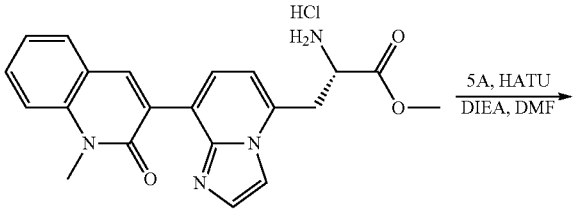
[0389] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-1-methylquinolin-2(1H)-one (11A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 3-bromo-1-methylquinolin-2(1H)-one and substituting 1,2-dimethoxyethane for dioxane.



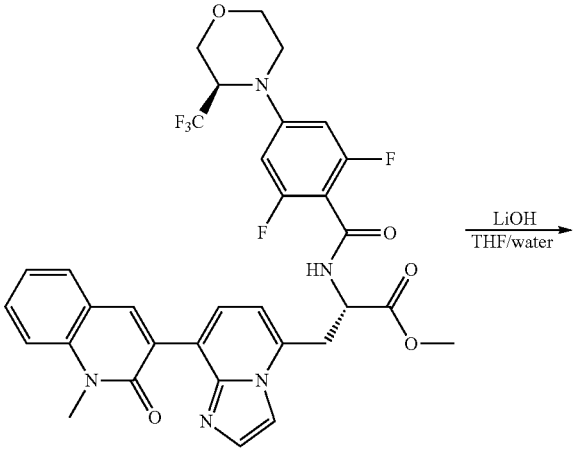
7A



11A

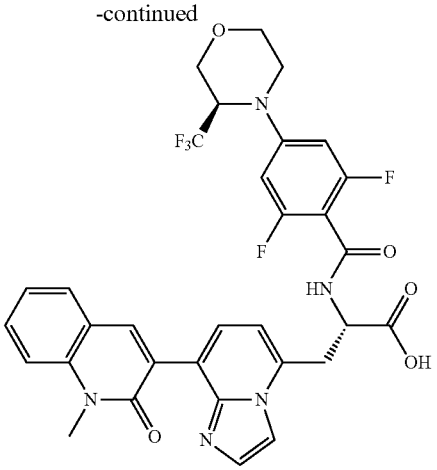


11B



11C

-continued



11

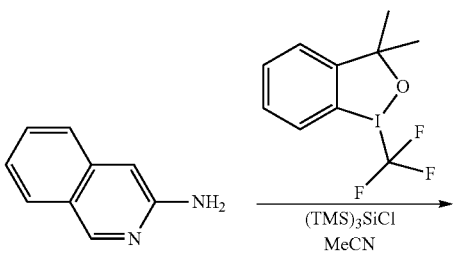
[0390] Synthesis of methyl (S)-2-amino-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl) imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (11B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 11A.

[0391] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (11C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 11B.

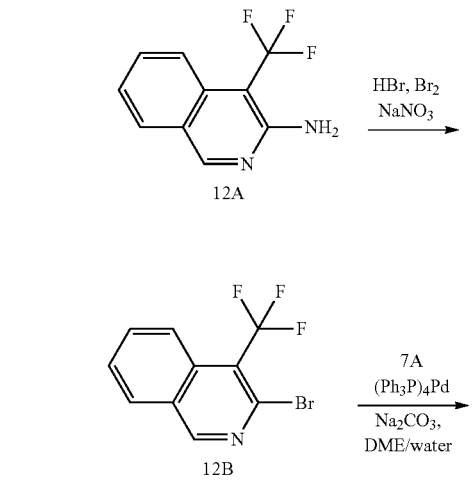
[0392] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (8): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 11C. MS (m/z) 655.7 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (d, J=8.1 Hz, 1H), 8.60 (d, J=2.2 Hz, 1H), 8.34 (d, J=2.1 Hz, 1H), 8.25 (s, 1H), 8.04-7.95 (m, 1H), 7.86 (dt, J=8.0, 1.5 Hz, 1H), 7.75 (ddd, J=8.7, 7.1, 1.6 Hz, 1H), 7.67 (d, J=8.6 Hz, 1H), 7.45-7.31 (m, 2H), 6.76 (d, J=11.8 Hz, 2H), 4.99 (dd, J=12.1, 6.5 Hz, 1H), 4.89 (d, J=9.2 Hz, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.94 (dd, J=11.5, 3.8 Hz, 1H), 3.72 (s, 4H), 3.70 (s, 19H), 3.63-3.57 (m, OH), 3.53 (dd, J=12.0, 8.6 Hz, 1H), 3.41 (d, J=12.8 Hz, 1H), 3.21 (t, J=12.2 Hz, 1H).

Example 12

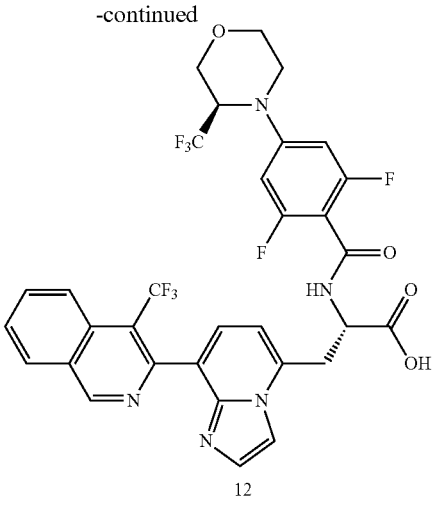
[0393]

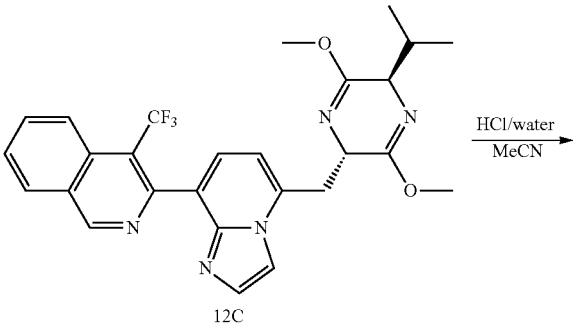


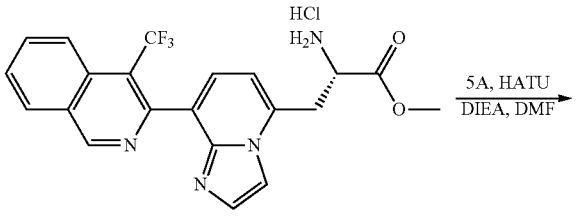
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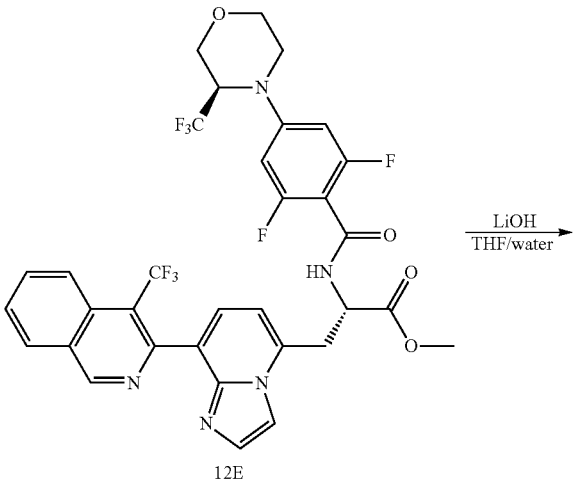


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[0394] Synthesis of 4-(trifluoromethyl)isoquinolin-3-amine (12A): To a stirred solution of 3-amino isoquinoline (150 mg, 1.04 mmol) in MeCN was added 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (412.1 mg, 1.25 mmol) and tris(trimethylsilyl)silyl chloride (0.35 ml, 1.25 mmol). This mixture was heated to 80° C. for 1 hour. The reaction mixture was filtered through celite, rinsed with EtOAc and purified by silica gel chromatography using EtOAc in hexanes as eluent to give the title compound.

[0395] Synthesis of 3-bromo-4-(trifluoromethyl)isoquinoline (12B): To a stirred solution of 12A (91 mg, 0.43 mmol) in HBr (6.9 mL) was added Br_2 (0.13 ml, 2.57 mmol). The reaction mixture was kept at 0° C. for 10 minutes at which time $NaNO_2$ (147.96 mg, 2.14 mmol) was added as a premade solution in water (5 mL). The reaction mixture was allowed to stir at 0° C. for 30 min then allowed to warm to RT for 60 min. The reaction was quenched with sodium bicarbonate, extracted with DCM, concentrated and purified by silica gel chromatography eluting Hex/EtOAc to give the title compound.

[0396] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-4-(trifluoromethyl)isoquinoline (12C): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 12B and substituting 1,2-dimethoxyethane for dioxane, tetrakis (triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0397] Synthesis of methyl (S)-2-amino-3-(8-(4-(trifluoromethyl)isoquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (12D): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 12C.

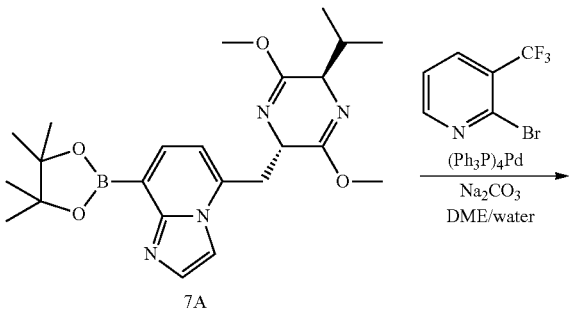
[0398] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4-(trifluoromethyl)isoquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (12E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 12D.

[0399] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-(trifluoromethyl) isoquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (12): The title compound was prepared according to the

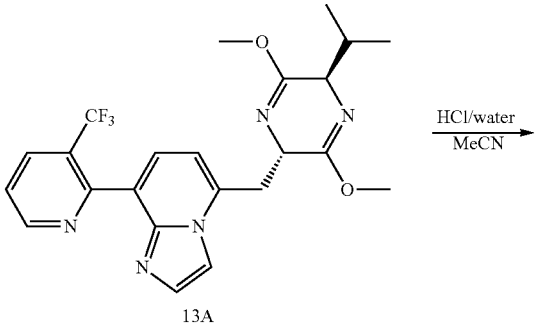
method presented for the synthesis of compound 7 starting with 12E. MS (m/z) 694.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 9.71 (s, 1H), 9.01 (d, J=8.2 Hz, 1H), 8.65 (s, 1H), 8.49 (d, J=8.2 Hz, 1H), 8.27 (d, J=9.0 Hz, 2H), 8.14 (t, J=7.8 Hz, 1H), 8.01 (t, J=7.6 Hz, 1H), 7.94 (s, 1H), 7.44 (s, 1H), 6.76 (d, J=11.9 Hz, 2H), 5.05 (s, 1H), 4.91 (d, J=8.1 Hz, 1H), 4.16 (d, J=12.7 Hz, 1H), 3.95 (dd, J=11.5, 3.8 Hz, 1H), 3.76 (dd, J=27.2, 14.0 Hz, 2H), 3.68-3.49 (m, 2H), 3.42 (d, J=12.7 Hz, 1H), 3.22 (t, J=12.3 Hz, 1H).

Example 13

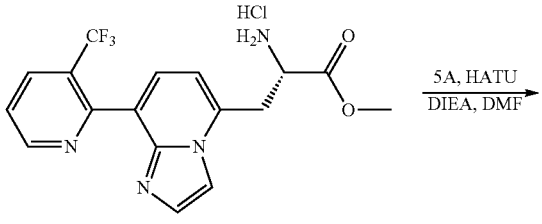
[0400] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridine (13A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 2-bromo-3-(trifluoromethyl)pyridine and substituting 1,2-dimethoxyethane for dioxane, tetrakis(triphenylphosphine) palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.



7A

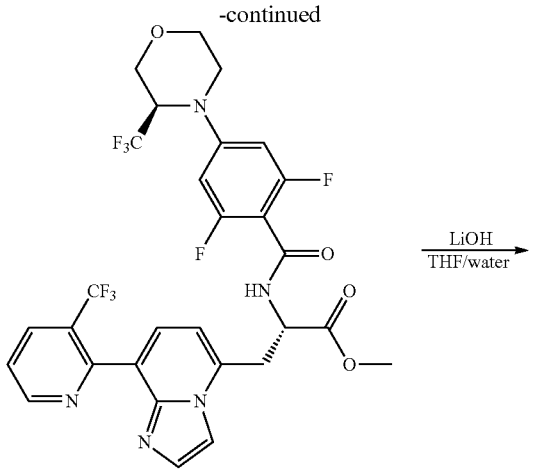


13A

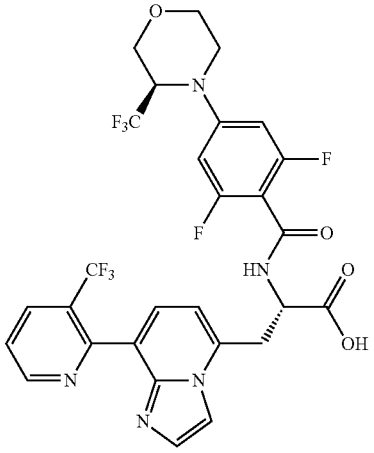


13B

-continued



13C



13

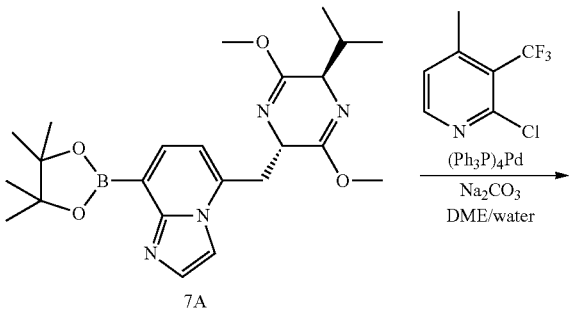
[0401] Synthesis of methyl (S)-2-amino-3-(8-(3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (13B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 13A.

[0402] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (13C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 13B.

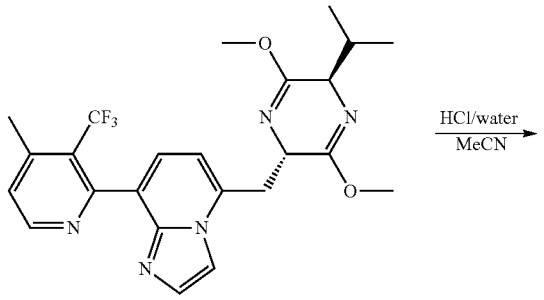
[0403] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (13): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 13C. MS (m/z) 644.6 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.04-8.95 (m, 2H), 8.66 (s, 1H), 8.47 (dd, J=8.2, 1.5 Hz, 1H), 8.31 (s, 1H), 7.92 (d, J=7.5 Hz, 1H), 7.86 (dd, J=8.2, 4.9 Hz, 1H), 7.43 (d, J=7.5 Hz, 1H), 6.74 (d, J=11.8 Hz, 2H), 5.10-4.99 (m, 1H), 4.97-4.84 (m, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.95 (dd, J=11.5, 3.8 Hz, 1H), 3.85-3.68 (m, 2H), 3.68-3.48 (m, 2H), 3.41 (d, J=12.6 Hz, 1H), 3.22 (t, J=12.5 Hz, 1H).

Example 14

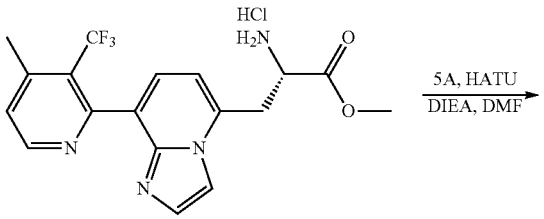
[0404]



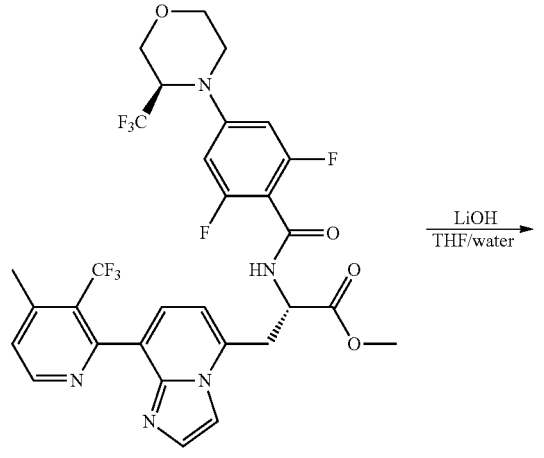
7A



14A

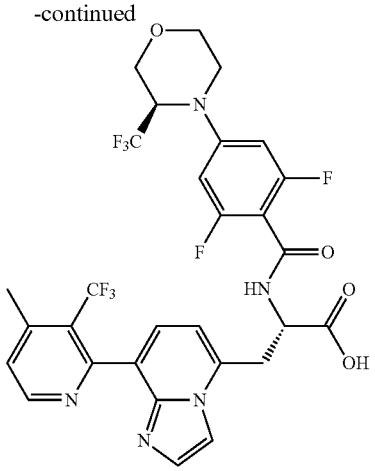


14B



14C

-continued



14

[0405] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(4-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridine (14A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 2-chloro-4-methyl-3-(trifluoromethyl)pyridine and substituting 1,2-dimethoxyethane for dioxane, tetrakis(triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0406] Synthesis of methyl (S)-2-amino-3-(8-(4-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate hydrochloride (14B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 14A.

[0407] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (14C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 14B.

[0408] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (14): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 14C. MS (m/z) 658.7 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.21 (s, 1H), 8.98 (d, J=8.1 Hz, 1H), 8.80 (d, J=5.0 Hz, 1H), 8.61 (s, 1H), 8.27 (s, 1H), 7.80 (d, J=7.4 Hz, 1H), 7.72 (d, J=5.1 Hz, 1H), 7.38 (d, J=7.5 Hz, 1H), 6.74 (d, J=11.8 Hz, 2H), 5.08-4.97 (m, 1H), 4.97-4.85 (m, 1H), 4.16 (d, J=12.7 Hz, 1H), 3.95 (dd, J=11.6, 3.8 Hz, 1H), 3.82-3.68 (m, 2H), 3.65-3.48 (m, 2H), 3.46-3.37 (m, 1H), 3.22 (t, J=12.5 Hz, 1H), 2.62 (q, J=2.6 Hz, 3H).

Example 15

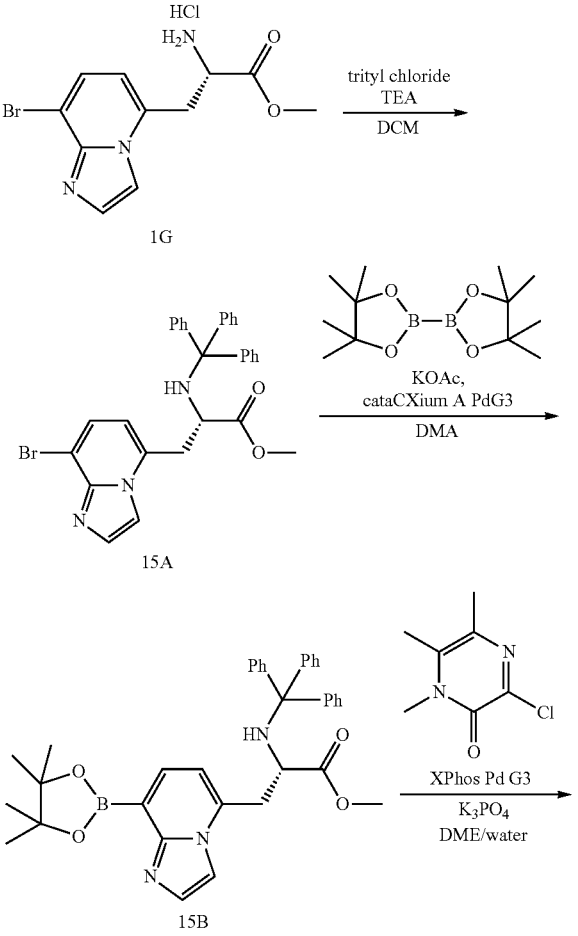
[0409] Synthesis of methyl (S)-3-(8-bromoimidazo[1,2-a]pyridin-5-yl)-2-(tritylamino) propanoate (15A): To a stirred suspension of 1G (684 mg, 2.05 mmol) in dichloromethane (60 mL) was added triethylamine (0.693 mL, 5 mmol) and trityl chloride (570 mg, 2.05 mmol), and the reaction was stirred at room temperature for 12 hours. It was portioned between dichloromethane and water, separated, and the organics were dried over anhydrous sodium sulfate, filtered,

and concentrated. It was purified by silica gel chromatography (eluent: ethyl acetate/hexanes) to yield 15A.

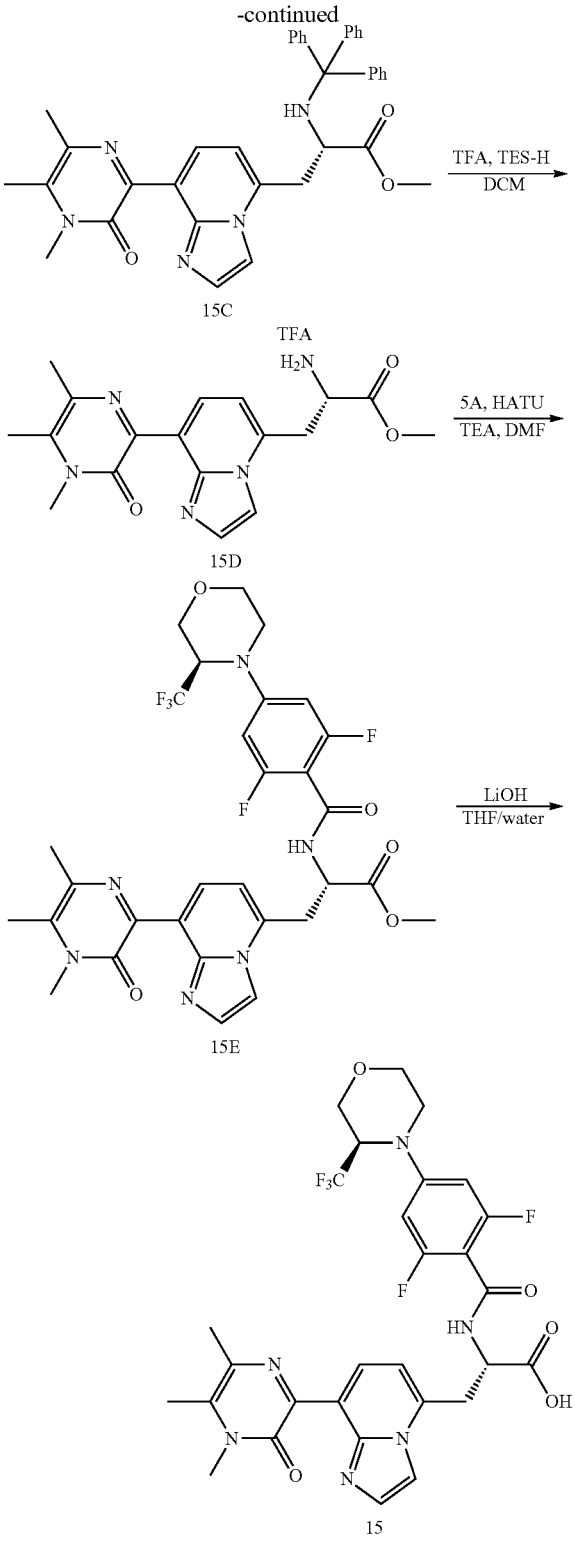
[0410] Synthesis of methyl (S)-3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo [1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (15B): The title compound was prepared according to the method presented for the synthesis of compound 5C starting with 15A.

[0411] Synthesis of methyl (S)-3-(8-(4,5,6-trimethyl-3-oxo-3,4-dihydropyrazin-2-yl) imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (15C): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 15B and 3-chloro-1,5,6-trimethylpyrazin-2(1H)-one and substituting 1,2-dimethoxyethane for dioxane.

[0412] Synthesis of methyl (S)-2-amino-3-(8-(4,5,6-trimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (15D): To a stirred solution of 15C (393 mg, 0.66 mmol) in dichloromethane (3 mL) was added triethylsilane (92 mg, 0.79 mmol) and trifluoroacetic acid (0.25 mL, 3 mmol), and the reaction was stirred for 30 minutes. It was concentrated to yield crude 15C, which was taken to the next reaction without further purification.



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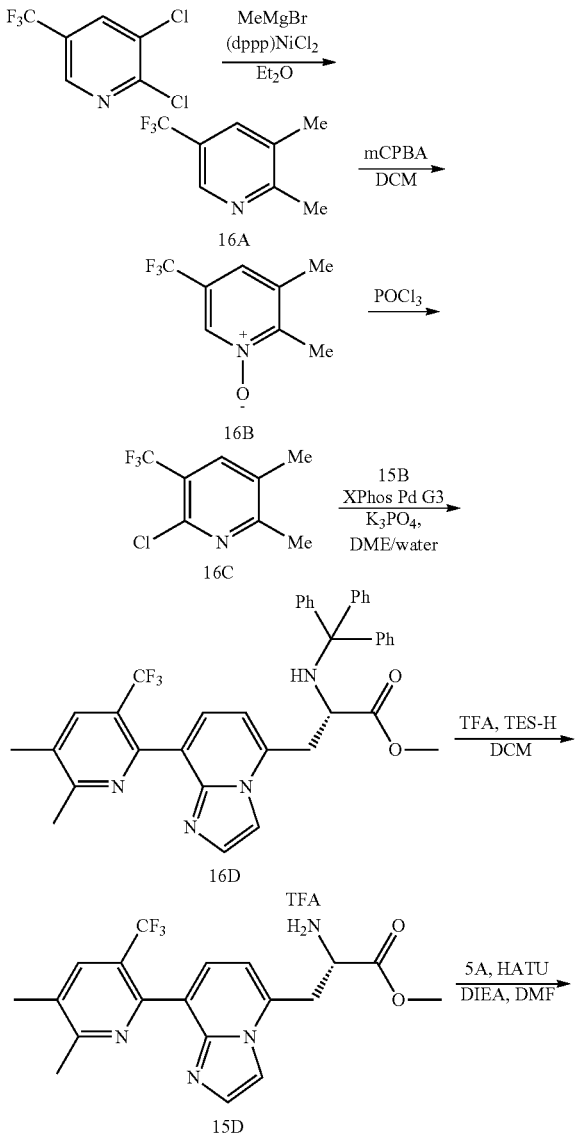
[0413] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4,5,6-trimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (15E): The title compound was prepared according to the method presented for the synthesis

of compound 5B starting with 5A and 15D and substituting triethylamine for diisopropylethylamine.

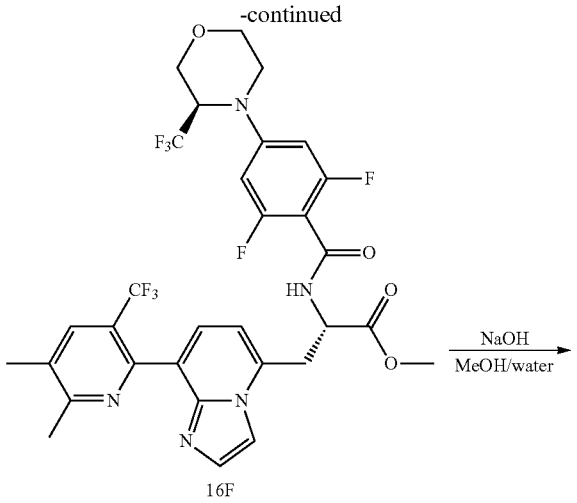
[0414] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4,5,6-trimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (15): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 15E. MS (m/z) 635.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.47 (s, 1H), 13.20 (s, 1H), 9.27 (d, J=8.0 Hz, 1H), 8.95 (d, J=8.2 Hz, 1H), 8.66 (s, 1H), 8.30 (s, 1H), 7.48 (d, J=8.0 Hz, 1H), 6.74 (d, J=12.0 Hz, 2H), 5.06-4.95 (m, 1H), 4.95-4.82 (m, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.99-3.90 (m, 1H), 3.84-3.75 (m, 1H), 3.72 (s, 1H), 3.65 (s, 3H), 3.60-3.50 (m, 2H), 3.40 (d, J=12.7 Hz, 1H), 3.27-3.15 (m, 1H), 2.54 (s, 3H), 2.50 (s, 3H).

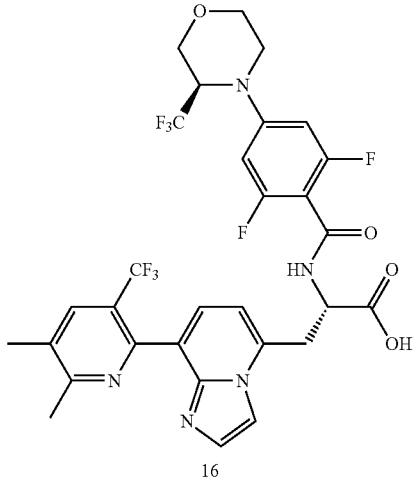
Example 16

[0415]



-continued





[0416] Synthesis of 2,3-dimethyl-5-(trifluoromethyl)pyridine (16A): To a solution of 2,3-dichloro-5-(trifluoromethyl) pyridine (2.16 g, 10 mmol) in ether (50 mL) degassed with nitrogen was added the (1,3-bis(diphenylphosphanyl)propane)nickel(II) chloride (271 mg, 0.5 mmol), then methylmagnesium bromide in ether (3M, 8.3 mL, 25 mmol), and the reaction was sealed and heated to 40° C. for 16 hours. It was cooled to room temperature and water was added to quench the excess organometallic reagent. The aqueous layer was extracted twice with ether and once with dichloromethane. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated. It was purified by silica gel chromatography (eluent dichloromethane) to yield 16A.

[0417] Synthesis of 2,3-dimethyl-5-(trifluoromethyl)pyridine 1-oxide (16B): To a solution of 16A (400 mg, 2.3 mmol) in dichloromethane (10 mL) was added m-chloroperbenzoic acid (77%, 768 mg, 3.4 mmol), and the reaction was stirred overnight at room temperature. It was directly purified by silica gel chromatography, eluting with a methanol/dichloromethane gradient to yield 16B.

[0418] Synthesis of 2-chloro-5,6-dimethyl-3-(trifluoromethyl)pyridine (16C): To solid 16B (280 mg, 1.46 mmol) was added neat phosphoryl trichloride (4.5 g, 29 mmol), and the reaction was heated to 60° C. overnight. It was cooled to

RT and concentrated. It was purified by silica gel chromatography (eluent: dichloromethane/hexanes) to yield 16C.

[0419] Synthesis of methyl (S)-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl)imidazo [1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (16D): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 15B and 16C and substituting 1,2-dimethoxyethane for dioxane.

[0420] Synthesis of methyl (S)-2-amino-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl) imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (16E): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 16D.

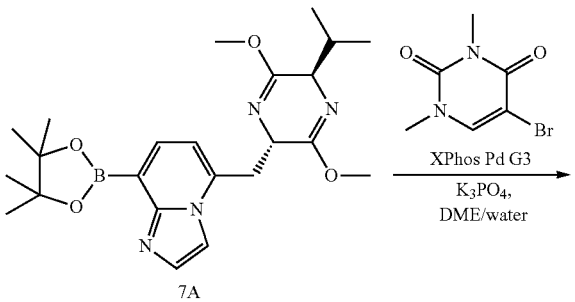
[0421] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (16F): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 16E.

[0422] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (16): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 16F and substituting sodium hydroxide for lithium hydroxide and methanol for tetrahydrofuran. MS (m/z) 672.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.97 (d, J=8.1 Hz, 1H), 8.58 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.80 (s, 1H), 7.37 (s, 1H), 6.72 (d, J=11.8 Hz, 2H), 4.98 (d, J=11.8 Hz, 1H), 4.88 (d, J=8.6 Hz, 1H), 4.14 (d, J=12.8 Hz, 1H), 3.93 (dd, J=11.4, 3.8 Hz, 1H), 3.80-3.66 (m, 2H), 3.63-3.16 (m, 4H), 2.53 (s, 3H), 2.44 (s, 3H).

Example 17

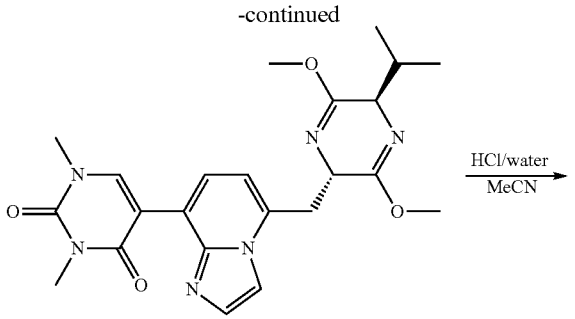
[0423] Synthesis of 5-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (17A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 5-bromo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione and substituting 1,2-dimethoxyethane for dioxane.

[0424] Synthesis of methyl (S)-2-amino-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)imidazo [1,2-a]pyridin-5-yl)propanoate hydrochloride (17B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 17A.

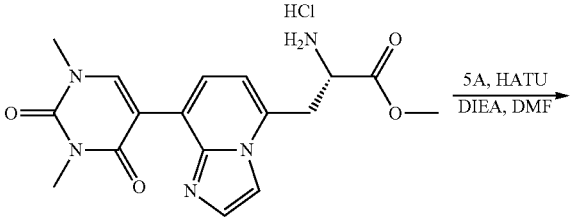


7A

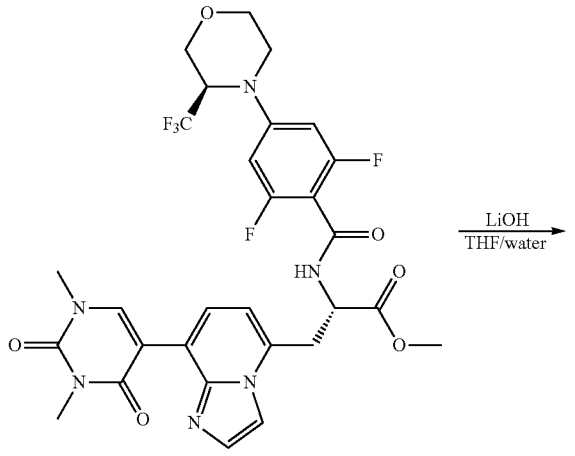
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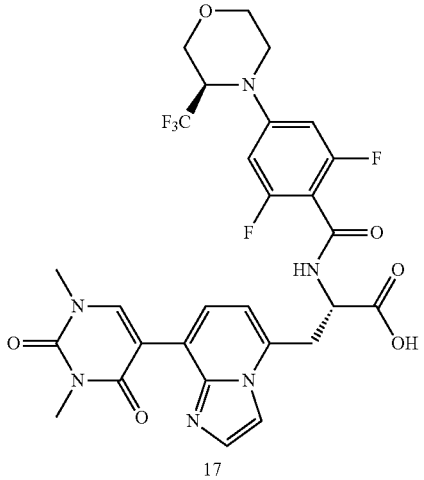
17A



17B



17C



17

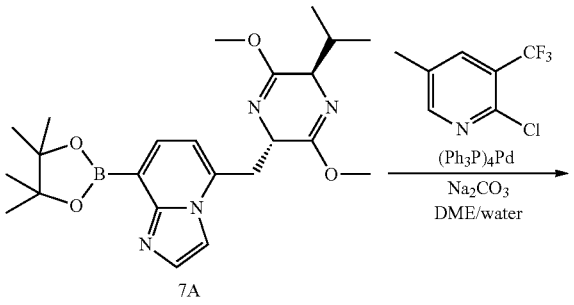
[0425] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo [1,2-a]pyridin-5-yl)propanoate (17C): The title compound

was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 17B.

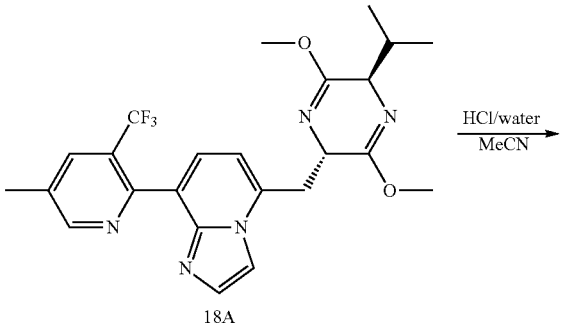
[0426] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (17): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 17C. MS (m/z) 636.7 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J=8.0 Hz, 1H), 8.56 (d, J=2.2 Hz, 1H), 8.34 (d, J=2.1 Hz, 1H), 8.20 (s, 1H), 7.85 (dd, J=7.5, 1.1 Hz, 1H), 7.36 (d, J=7.6 Hz, 1H), 6.74 (d, J=11.8 Hz, 2H), 5.03-4.81 (m, 2H), 4.14 (d, J=12.7 Hz, 1H), 3.94 (dd, J=11.5, 3.8 Hz, 1H), 3.75-3.68 (m, 3H), 3.60-3.49 (m, 1H), 3.41 (s, 4H), 3.26 (s, 4H).

Example 18

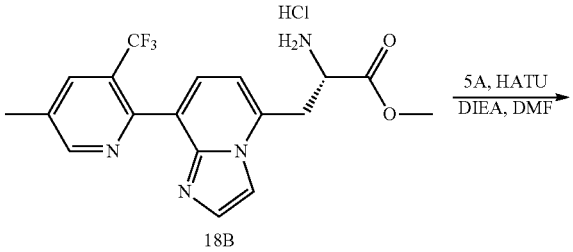
[0427]



7A

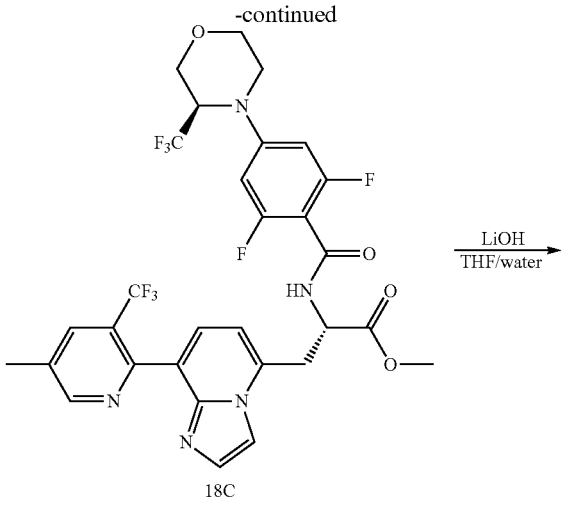


18A

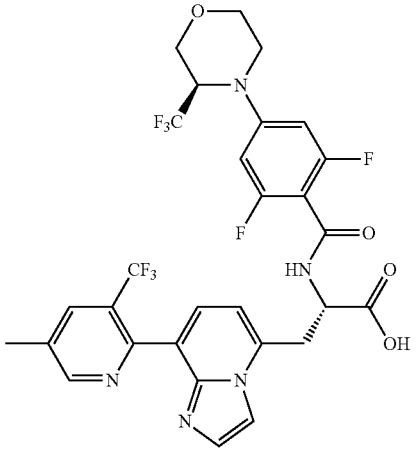


18B

-continued



18C



18

[0428] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(5-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridine (18A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 2-chloro-5-methyl-3-(trifluoromethyl)pyridine and substituting 1,2-dimethoxyethane for dioxane, tetrakis(triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0429] Synthesis of methyl (S)-2-amino-3-(8-(5-methyl-3-(trifluoromethyl)pyridin-2-yl) imidazo[1,2-a]pyridin-5-yl) propanoate hydrochloride (18B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 18A.

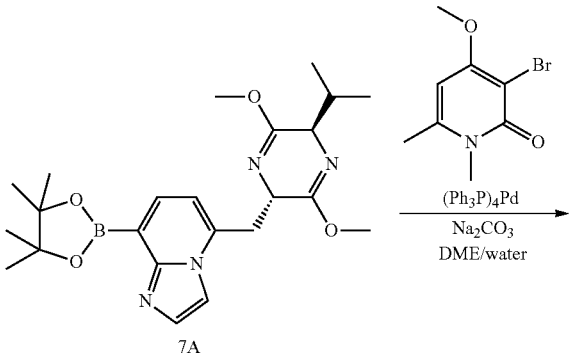
[0430] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(5-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (18C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 18B.

[0431] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(5-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (18): The title compound was prepared according to the method presented for the synthesis of

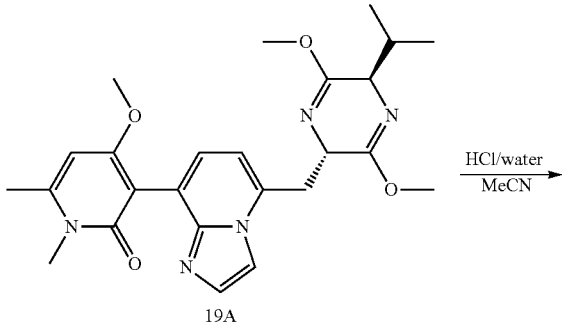
compound 7 starting with 18C. MS (m/z) 658.4 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 8.98 (d, J=8.1 Hz, 1H), 8.85 (d, J=1.9 Hz, 1H), 8.62 (s, 1H), 8.31 (d, J=1.9 Hz, 1H), 8.27 (s, 1H), 7.85 (s, 1H), 7.40 (s, 1H), 6.74 (d, J=11.8 Hz, 2H), 5.02 (d, J=10.9 Hz, 1H), 4.91 (d, J=9.1 Hz, 1H), 4.16 (d, J=12.7 Hz, 1H), 3.95 (dd, J=11.5, 3.8 Hz, 1H), 3.75 (t, J=16.1 Hz, 2H), 3.64-3.49 (m, 2H), 3.41 (d, J=12.7 Hz, 1H), 3.22 (t, J=12.5 Hz, 1H), 2.53 (s, 3H).

Example 19

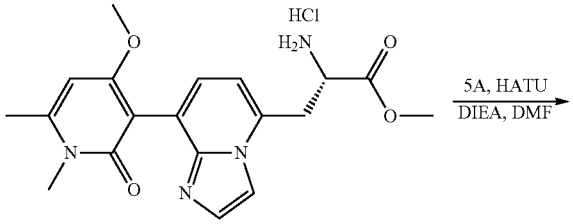
[0432]



7A

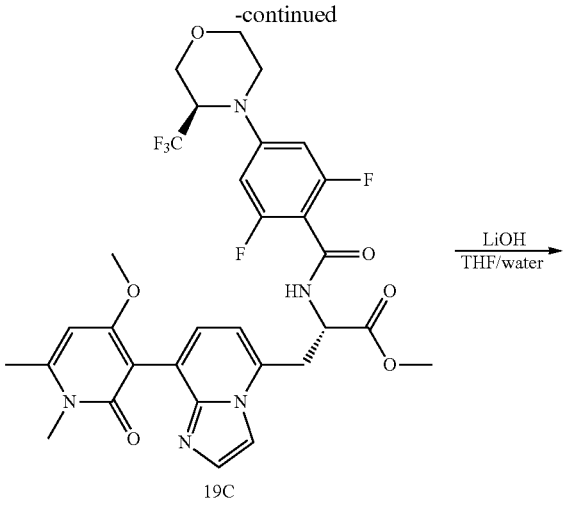


19A

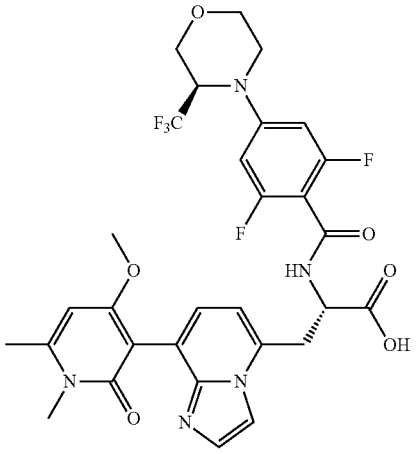


19B

-continued



19C



19

[0433] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-4-methoxy-1,6-dimethylpyridin-2(1H)-one (19A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 3-bromo-4-methoxy-1,6-dimethylpyridin-2(1H)-one and substituting 1,2-dimethoxyethane for dioxane, tetrakis (triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0434] Synthesis of methyl (S)-2-amino-3-(8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate hydrochloride (19B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 19A.

[0435] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (19C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 19B.

[0436] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (19): The title compound was prepared according to the method presented for the synthesis

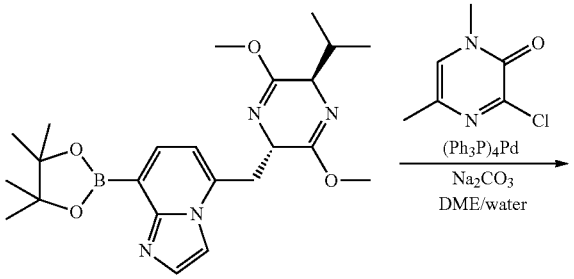
of compound 7 starting with 19C. MS (m/z) 650.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.87 (s, 1H), 13.19 (s, 1H), 9.01 (d, J=8.0 Hz, 1H), 8.53 (d, J=2.2 Hz, 1H), 8.28 (d, J=2.2 Hz, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 6.76 (d, J=11.8 Hz, 2H), 6.50 (s, 1H), 4.96 (td, J=17.0, 15.0, 7.1 Hz, 2H), 4.16 (d, J=12.7 Hz, 1H), 3.96 (dd, J=11.4, 3.7 Hz, 1H), 3.76 (s, 5H), 3.62-3.50 (m, 2H), 3.47 (s, 4H), 3.23 (t, J=12.4 Hz, 1H).

Example 20

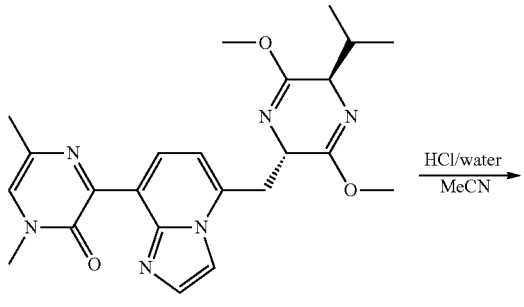
[0437] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-1,5-dimethylpyrazin-2(1H)-one (20A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 3-chloro-1,5-dimethylpyrazin-2(1H)-one and substituting 1,2-dimethoxyethane for dioxane.

[0438] Synthesis of methyl (S)-2-amino-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (20B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 20A.

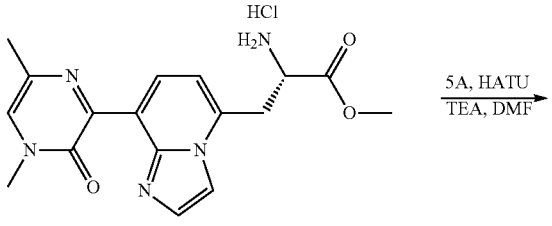
[0439] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (20C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 20B and substituting triethylamine for diisopropylethylamine.



7A

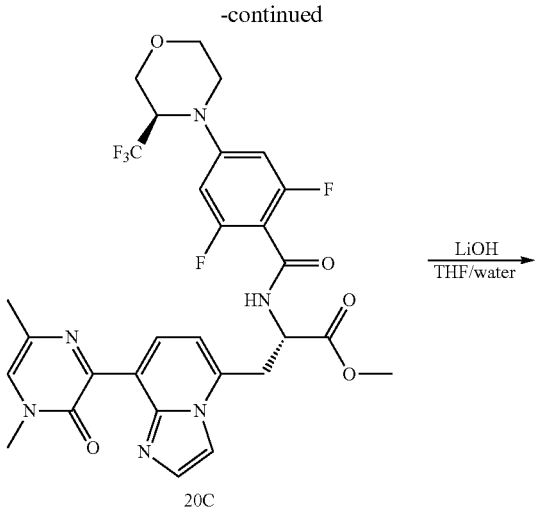


20A

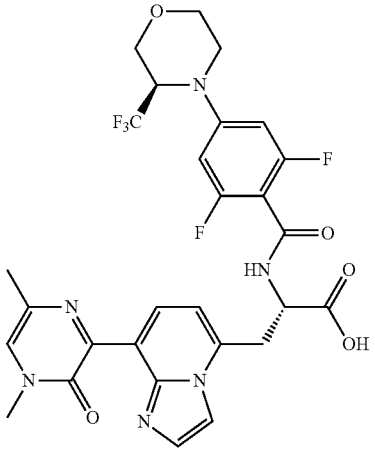


20B

-continued



20C

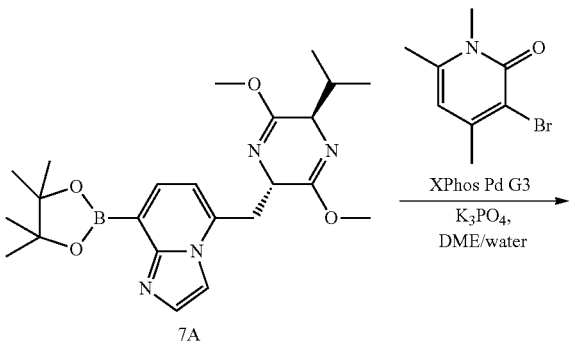


20

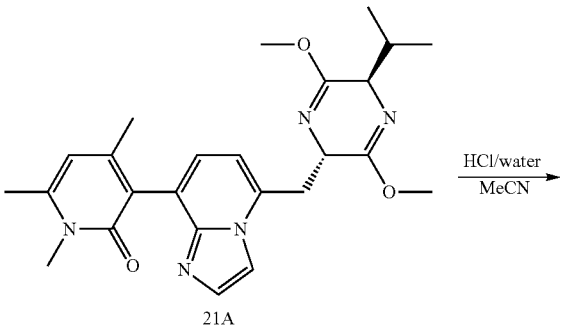
[0440] Synthesis (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (20): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 20C. MS (m/z) 621.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.28-9.20 (m, 1H), 8.95 (d, J=8.1 Hz, 1H), 8.69-8.64 (m, 1H), 8.33-8.28 (m, 1H), 7.86 (s, 1H), 7.47 (d, J=8.0 Hz, 1H), 6.72 (d, J=12.0 Hz, 2H), 5.05-4.94 (m, 1H), 4.94-4.81 (m, 1H), 4.18-4.09 (m, 1H), 3.93 (dd, J=11.4, 3.8 Hz, 1H), 3.77 (dd, J=15.4, 4.6 Hz, 1H), 3.74-3.66 (m, 1H), 3.62-3.34 (m, 6H), 3.25-3.13 (m, 1H), 2.43-2.38 (m, 3H).

Example 21

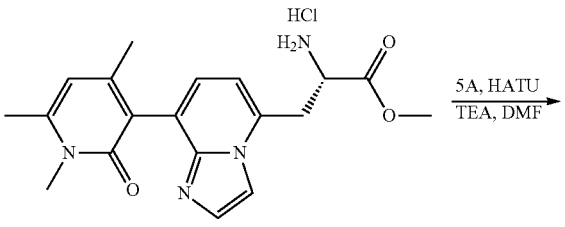
[0441] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-1,4,6-trimethylpyridin-2(1H)-one (21A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 3-bromo-1,4,6-trimethylpyridin-2(1H)-one and substituting 1,2-dimethoxyethane for dioxane.



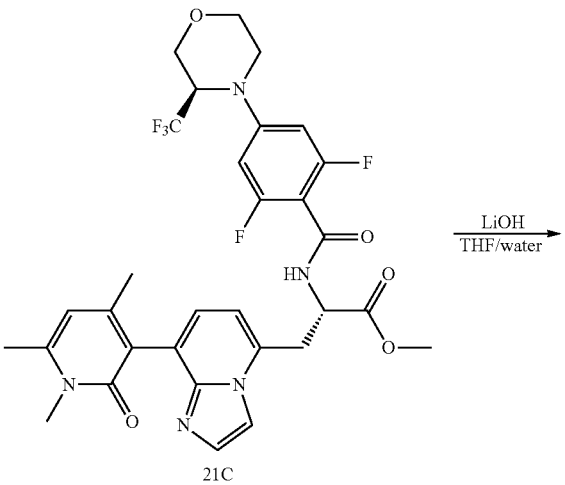
7A



21A

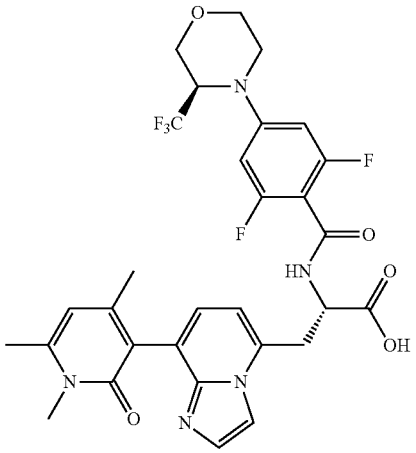


21B



21C

-continued



21

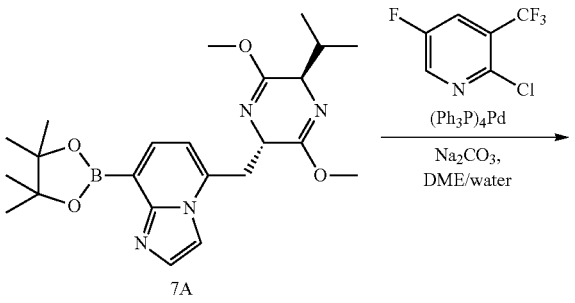
[0442] Synthesis of methyl (S)-2-amino-3-(8-(1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl) imidazo[1,2-a]pyridin-5-yl)propanoate hydrochloride (21B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 20B.

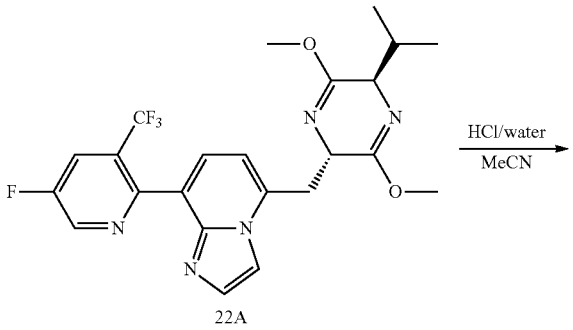
[0443] Synthesis methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (21C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 21B and substituting triethylamine for diisopropylethylamine. MS (m/z) 648.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.12 (dd, J=16.3, 7.7 Hz, 1H), 8.00 (s, 1H), 7.59 (s, 1H), 7.00 (d, J=24.0 Hz, 1H), 6.76 (dd, J=11.7, 6.7 Hz, 3H), 6.15 (s, 1H), 4.90 (d, J=10.0 Hz, 2H), 4.14 (d, J=12.8 Hz, 1H), 3.93 (d, J=11.5 Hz, 1H), 3.72 (d, J=6.9 Hz, 1H), 3.71-3.65 (m, 3H), 3.65-3.44 (m, 2H), 3.40 (s, 4H), 3.31 (s, 2H), 3.27-3.07 (m, 1H), 2.37 (s, 3H), 1.79 (s, 3H), 1.24 (t, J=6.2 Hz, 3H).

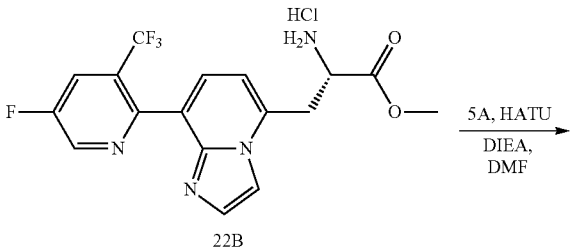
[0444] Synthesis (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (21): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 21C. MS (m/z) 634.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.02-8.93 (m, 1H), 8.61-8.49 (m, 1H), 8.32-8.24 (m, 1H), 7.75 (m, 1H), 7.44-7.29 (m, 1H), 6.72 (d, J=11.9 Hz, 2H), 6.27 (s, 1H), 5.07-4.83 (m, 2H), 4.14 (d, J=12.7 Hz, 1H), 3.93 (dd, J=11.5, 3.7 Hz, 1H), 3.81-3.67 (m, 2H), 3.60-3.29 (m, 6H), 3.24-3.13 (m, 1H), 2.42 (s, 3H), 1.95-1.87 (m, 3H).

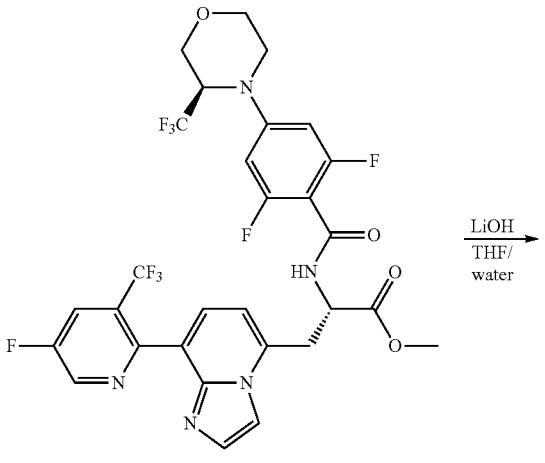
Example 22

[0445]

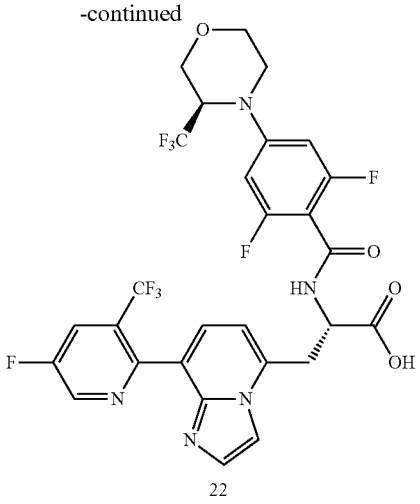








-continued



[0446] Synthesis of 8-(5-fluoro-3-(trifluoromethyl)pyridin-2-yl)-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridine (22A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 2-chloro-5-fluoro-3-(trifluoromethyl)pyridine and substituting 1,2-dimethoxyethane for dioxane, tetrakis(triphenylphosphine)palladium(0) for XPhos Pd G3 and 2M aqueous sodium carbonate for 1M potassium phosphate.

[0447] Synthesis of methyl (S)-2-amino-3-(8-(5-fluoro-3-(trifluoromethyl)pyridin-2-yl)imidazo [1,2-a]pyridin-5-yl) propanoate hydrochloride (22B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 22A.

[0448] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(5-fluoro-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (22C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 22B.

[0449] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(5-fluoro-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (22): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 22C. MS (m/z) 662.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 9.08 (s, 1H), 8.98 (d, J=8.1 Hz, 1H), 8.57 (d, J=8.8 Hz, 2H), 8.21 (s, 1H), 7.81 (s, 1H), 7.34 (s, 1H), 6.74 (d, J=11.8 Hz, 2H), 5.02 (s, 1H), 4.91 (d, J=9.9 Hz, 1H), 4.16 (d, J=12.8 Hz, 1H), 3.95 (dd, J=11.5, 3.8 Hz, 1H), 3.72 (d, J=11.0 Hz, 2H), 3.56 (q, J=13.0, 11.0 Hz, 2H), 3.41 (d, J=12.8 Hz, 1H), 3.22 (t, J=12.3 Hz, 1H).

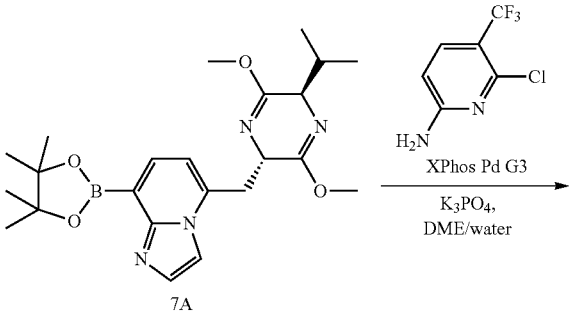
Example 23

[0450] Synthesis of 6-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-5-(trifluoromethyl)pyridin-2-amine (23A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 6-chloro-5-(trifluoromethyl)pyridin-2-amine and substituting 1,2-dimethoxyethane for dioxane.

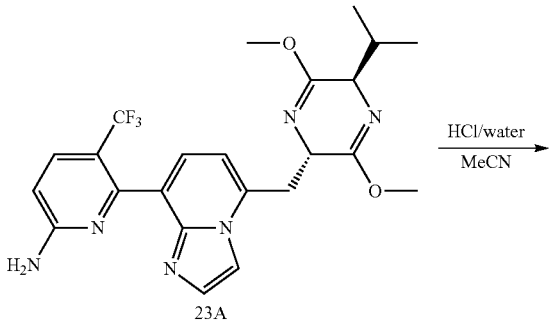
[0451] Synthesis methyl (S)-2-amino-3-(8-(6-amino-3-(trifluoromethyl)pyridin-2-yl)imidazo [1,2-a]pyridin-5-yl) propanoate hydrochloride (23B): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 23A.

[0452] Synthesis of methyl (S)-3-(8-(6-amino-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido) propanoate (23C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 23B.

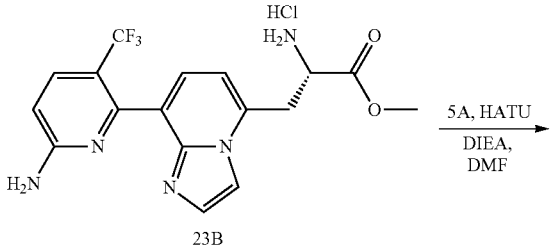
[0453] Synthesis of (S)-3-(8-(6-amino-3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid (23): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 23C. MS (m/z) 659.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.97 (dd, J=8.3, 1.7 Hz, 1H), 8.65 (d, J=2.3 Hz, 1H), 8.34 (d, J=2.2 Hz, 1H), 7.86 (dd, J=8.3, 4.6 Hz, 2H), 7.41 (d, J=7.5 Hz, 1H), 7.02 (s, 2H), 6.70 (dd, J=19.4, 10.3 Hz, 3H), 5.00 (ddd, J=10.8, 8.2, 4.5 Hz, 1H), 4.89 (dd, J=8.7, 3.6 Hz, 1H), 4.14 (d, J=12.7 Hz, 1H), 3.93 (dd, J=11.5, 3.8 Hz, 1H), 3.83-3.65 (m, 2H), 3.65-3.46 (m, 2H), 3.40 (d, J=13.0 Hz, 1H), 3.20 (t, J=12.8 Hz, 1H).



7A

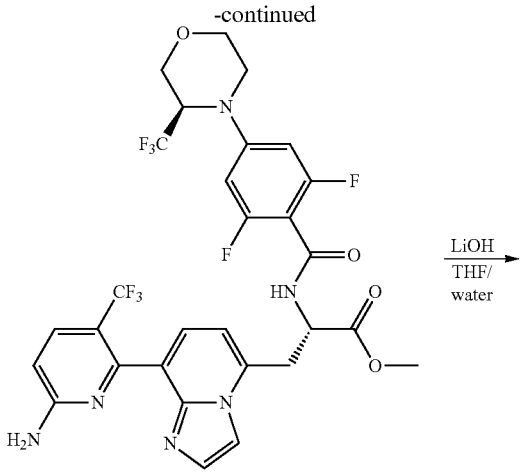


23A

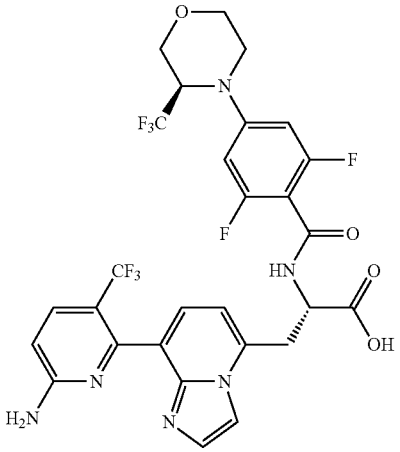


23B

-continued



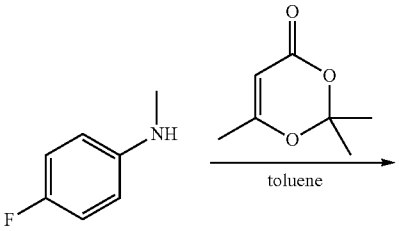
23C



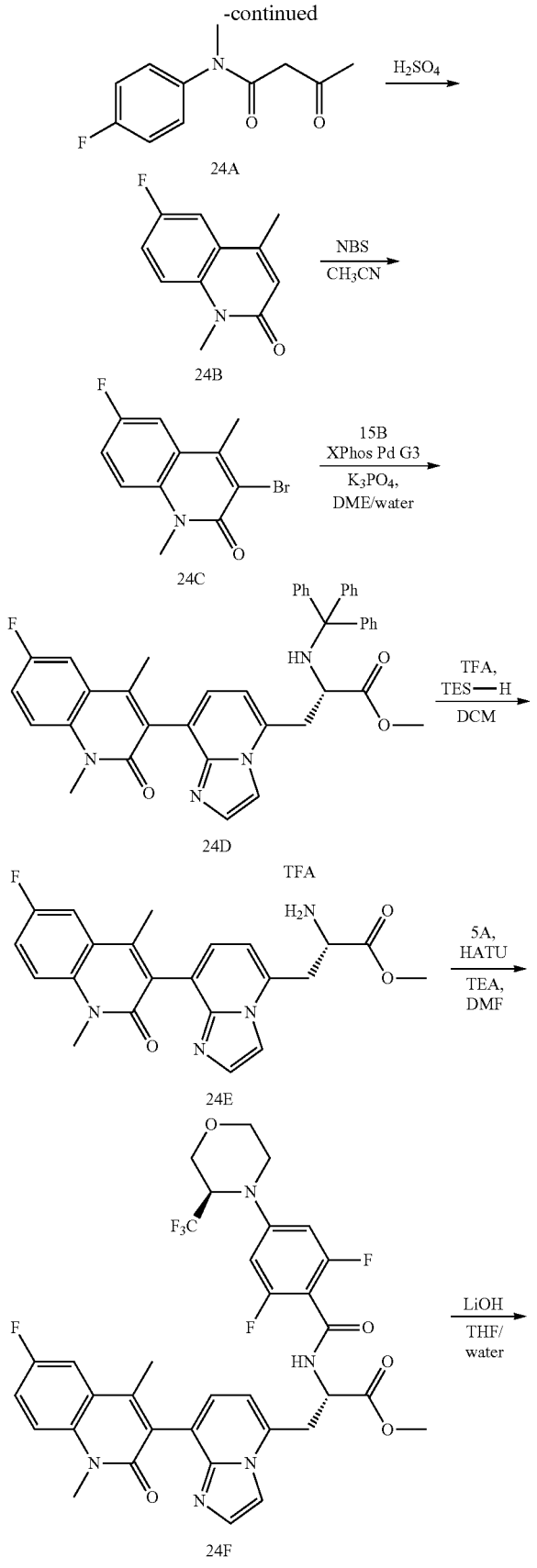
23

Example 24

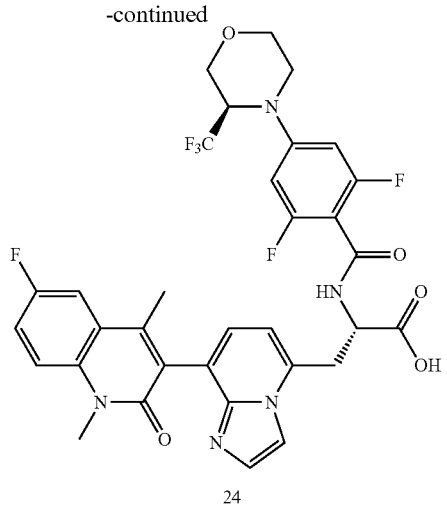
[0454] Synthesis of N-(4-fluorophenyl)-N-methyl-3-oxobutanamide (24A): To a solution of 4-fluoro-N-methyl-aniline (0.500 g, 4.00 mmol) in toluene (4.0 mL) at 110° C. in an open vial (to evaporate off acetone-byproduct) was added 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.568 g, 4.00 mmol) and the mixture was heated at 110° C. for 3 h. Upon completion, the solvent was evaporated off under reduced pressure. The material was purified by flash chromatography using EA in hexanes to afford the product (mixture of keto and enol form).



-continued



-continued



[0455] Synthesis of 6-fluoro-1,4-dimethylquinolin-2(1H)-one (24B): A mixture of 24A (0.250 g, 1.20 mmol) and concentrated H_2SO_4 (5.53 g, 56.4 mmol) was heated at 95° C. for 2 h. Upon completion, the reaction mixture was poured over ice. The precipitate was filtered off to afford the product that was used without further purification.

[0456] Synthesis of 6-fluoro-1,4-dimethylquinolin-2(1H)-one (24C): To a microwave vial was added 24B (0.210 g, 1.10 mmol), NBS (0.489 g, 2.75 mmol) and CH_3CN (11 mL), and the mixture was heated at 100° C. for 1 h. The precipitate was filtered off to afford the title compound and used without further purification.

[0457] Synthesis of methyl (S)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl) imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (24D): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 24C.

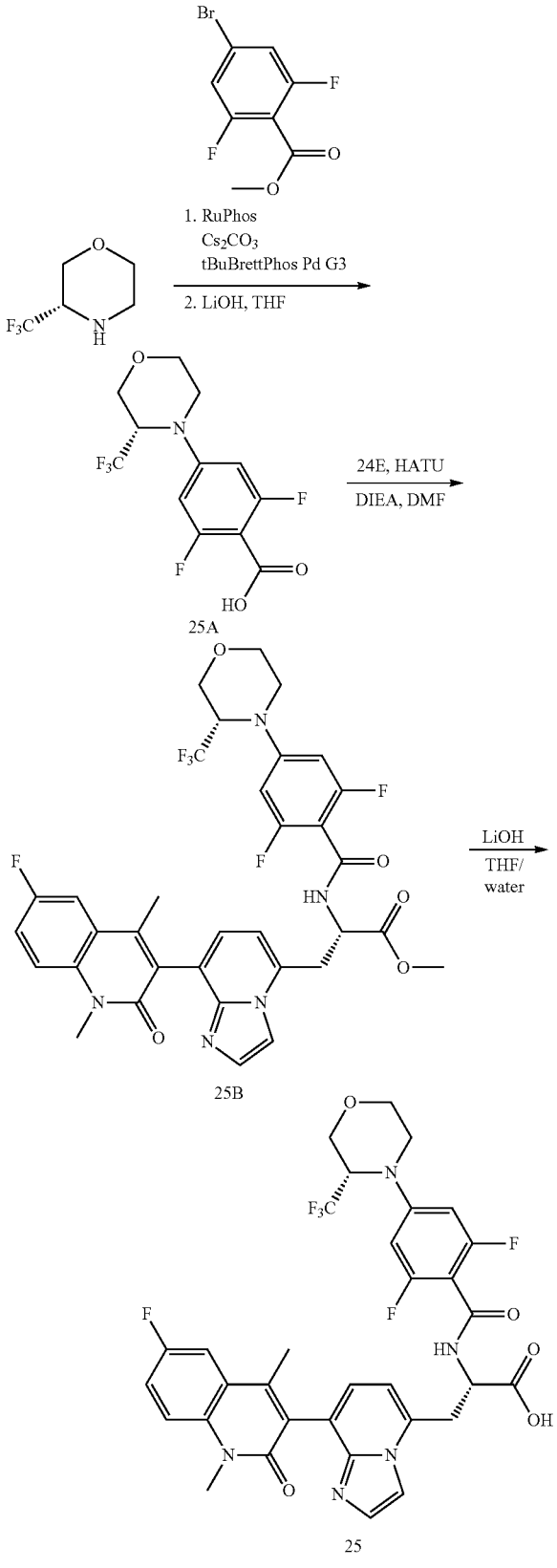
[0458] Synthesis of methyl (S)-2-amino-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydro quinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate trifluoroacetate (24E): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 24D.

[0459] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (24F): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 24E.

[0460] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (24): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 24F. MS (m/z) 688.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (t, J=7.7 Hz, 1H), 8.61 (d, J=27.1 Hz, 1H), 8.32 (s, 1H), 7.82 (m, 2H), 7.77-7.64 (m, 2H), 7.45 (d, J=43.0 Hz, 1H), 6.75 (d, J=11.8 Hz, 2H), 5.07-5.00 (m, 1H), 4.95-4.82 (m, 1H), 4.16 (d, J=12.6 Hz, 1H), 3.95 (d, J=10.0 Hz, 1H), 3.73 (d, J=13.3 Hz, 1H), 3.69 (s, 3H), 3.55 (t, J=12.2 Hz, 2H), 3.42 (m, 2H), 3.24 (d, J=12.5 Hz, 1H), 2.24 (d, J=6.2 Hz, 3H).

Example 25

[0461]



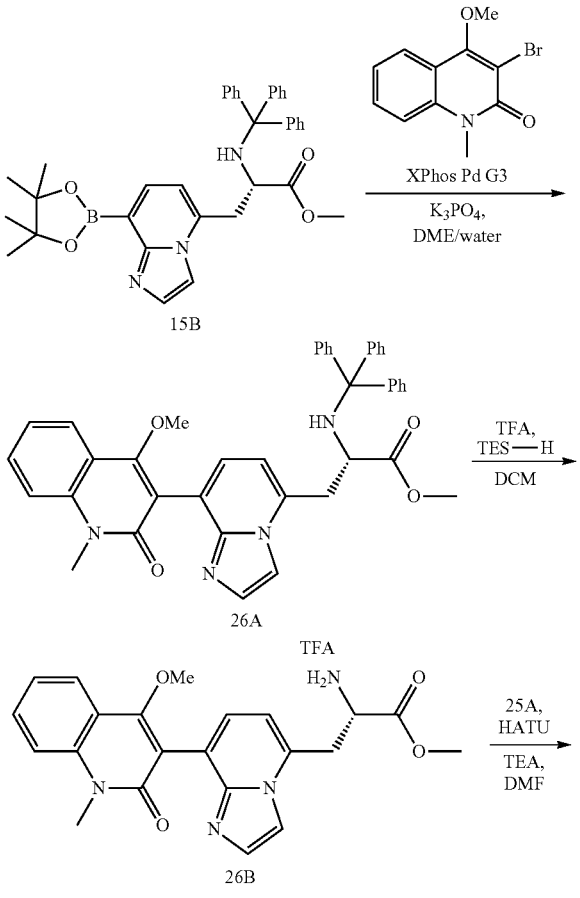
[0462] Synthesis of (S)-2,6-difluoro-4-(3-(trifluoromethyl)morpholino)benzoic acid (25A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with (S)-3-(trifluoromethyl)morpholine.

[0463] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (25B): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 25A and 24E.

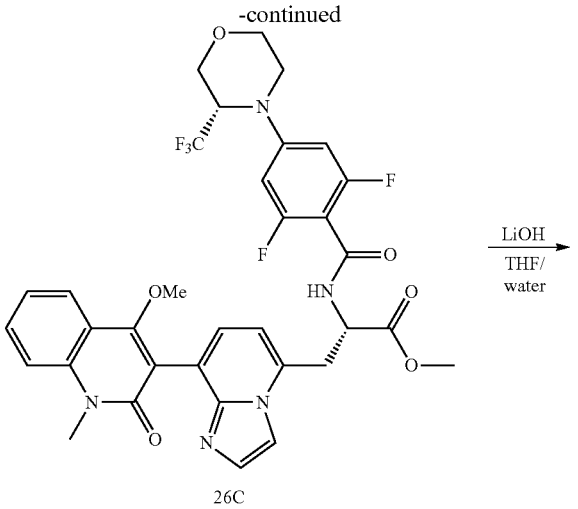
[0464] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (25): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 25B. MS (m/z) 688.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (t, J=7.2 Hz, 1H), 8.67-8.57 (m, 1H), 8.36-8.24 (m, 1H), 7.87-7.78 (m, 2H), 7.74-7.62 (m, 2H), 7.54-7.34 (m, 1H), 6.75 (d, J=11.4 Hz, 2H), 5.10-4.98 (m, 1H), 4.95-4.84 (m, 1H), 4.16 (d, J=12.8 Hz, 1H), 3.95 (d, J=8.6 Hz, 1H), 3.84-3.71 (m, 3H), 3.69 (s, 3H), 3.56 (d, J=3.3 Hz, 3H), 3.41 (d, J=2.6 Hz, 2H), 3.25 (d, J=20.0 Hz, 1H), 2.24 (d, J=8.3 Hz, 3H).

Example 26

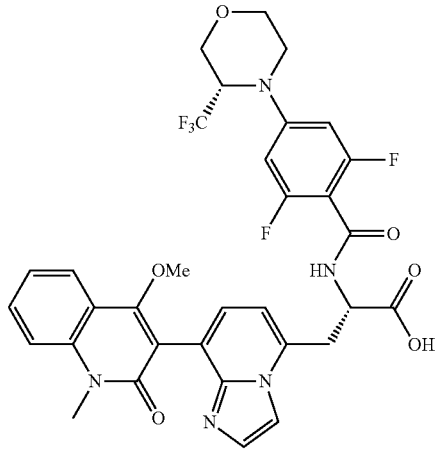
[0465]



-continued



26C



26

[0466] Synthesis of methyl (S)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (26A): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 3-bromo-4-methoxy-1-methylquinolin-2(1H)-one.

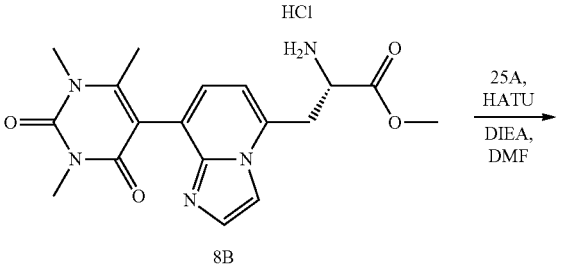
[0467] Synthesis of methyl (S)-2-amino-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate trifluoroacetate (26B): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 26A.

[0468] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (26C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 25A and 26B.

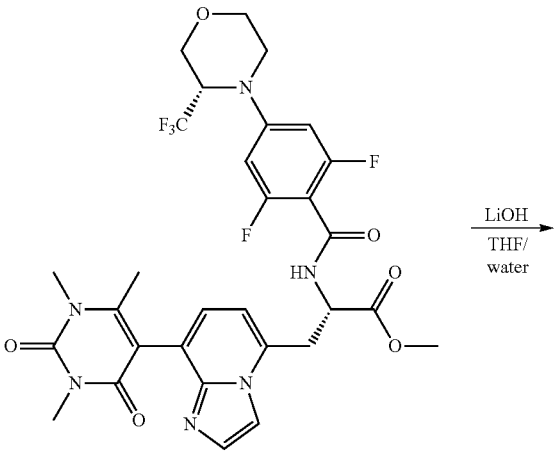
[0469] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (26): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 26C. MS (m/z) 686.8 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (d, J=8.1 Hz, 1H), 8.64 (s, 1H), 8.35 (s, 1H), 8.05-7.88 (m, 2H), 7.80 (t, J=7.8 Hz, 1H), 7.69 (d, J=8.6 Hz, 1H), 7.55-7.31 (m, 2H), 6.76 (d, J=11.9 Hz, 2H), 5.04 (td, J=9.3, 7.8, 4.3 Hz, 1H), 4.91 (dt, J=11.7, 7.9 Hz, 1H), 4.16 (d, J=12.7 Hz, 1H), 3.96 (dd, J=11.6, 3.7 Hz, 1H), 3.82 (d, J=16.2 Hz, 0H), 3.73 (d, J=12.7 Hz, 1H), 3.67 (s, 3H), 3.55 (td, J=13.5, 12.0, 4.5 Hz, 1H), 3.42 (d, J=11.5 Hz, 3H), 3.29-3.17 (m, 1H).

Example 27

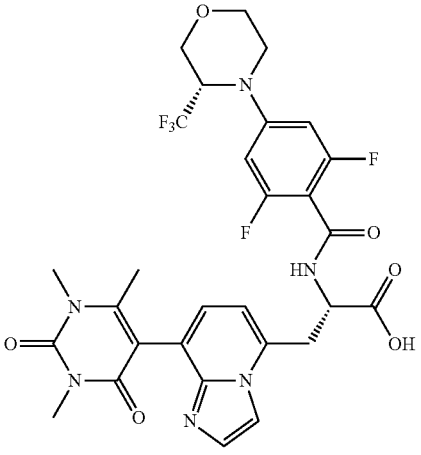
[0470]



8B



27A



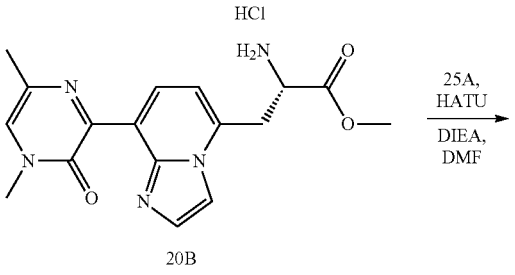
27

[0471] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo [1,2-a]pyridin-5-yl)propanoate (27A): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 25A and 8B.

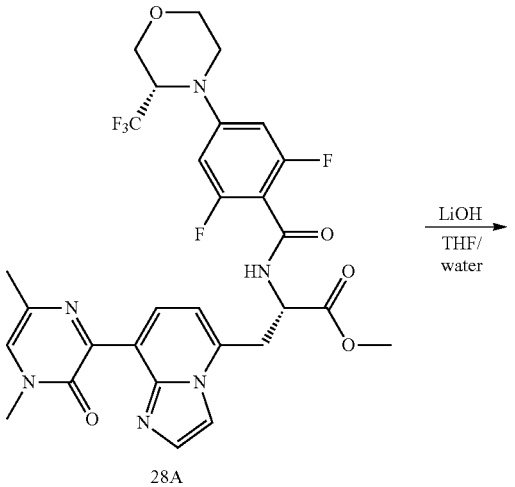
[0472] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a] pyridin-5-yl) propanoic acid (27): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 27A. MS (m/z) 651.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 8.96 (t, J=8.9 Hz, 1H), 8.58 (d, J=26.6 Hz, 1H), 8.33 (d, J=13.2 Hz, 1H), 7.74 (t, J=9.1 Hz, 1H), 7.39 (dd, J=35.3, 7.6 Hz, 1H), 6.78-6.66 (m, 2H), 6.57 (s, 1H), 5.07-4.81 (m, 2H), 4.14 (d, J=12.7 Hz, 1H), 3.98-3.86 (m, 1H), 3.80-3.47 (m, 6H), 3.46 (d, J=2.0 Hz, 3H), 3.40 (d, J=12.9 Hz, 1H), 3.23 (s, 4H), 2.13-1.98 (m, 3H).

Example 28

[0473]

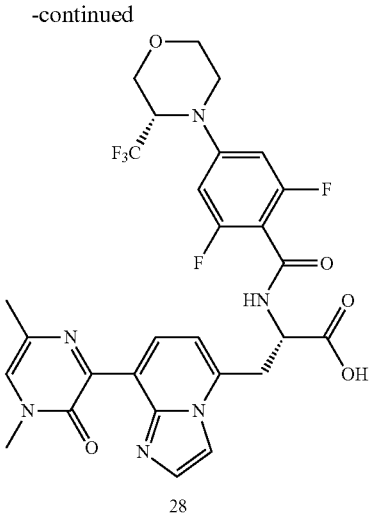


20B



28A

-continued



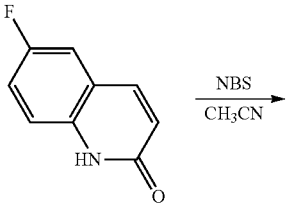
28

[0474] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate (28A): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 25A and 20B. MS (m/z) 635.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (d, J=7.9 Hz, 1H), 9.03 (d, J=7.9 Hz, 1H), 8.73-8.65 (m, 1H), 8.33 (s, 1H), 7.88 (s, 1H), 7.50 (d, J=8.0 Hz, 1H), 5.14-5.02 (m, 1H), 4.95-4.81 (m, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.99-3.89 (m, 1H), 3.84-3.48 (m, 10H), 3.41 (d, J=12.5 Hz, 1H), 3.21 (t, J=12.5 Hz, 1H), 2.43 (s, 3H).

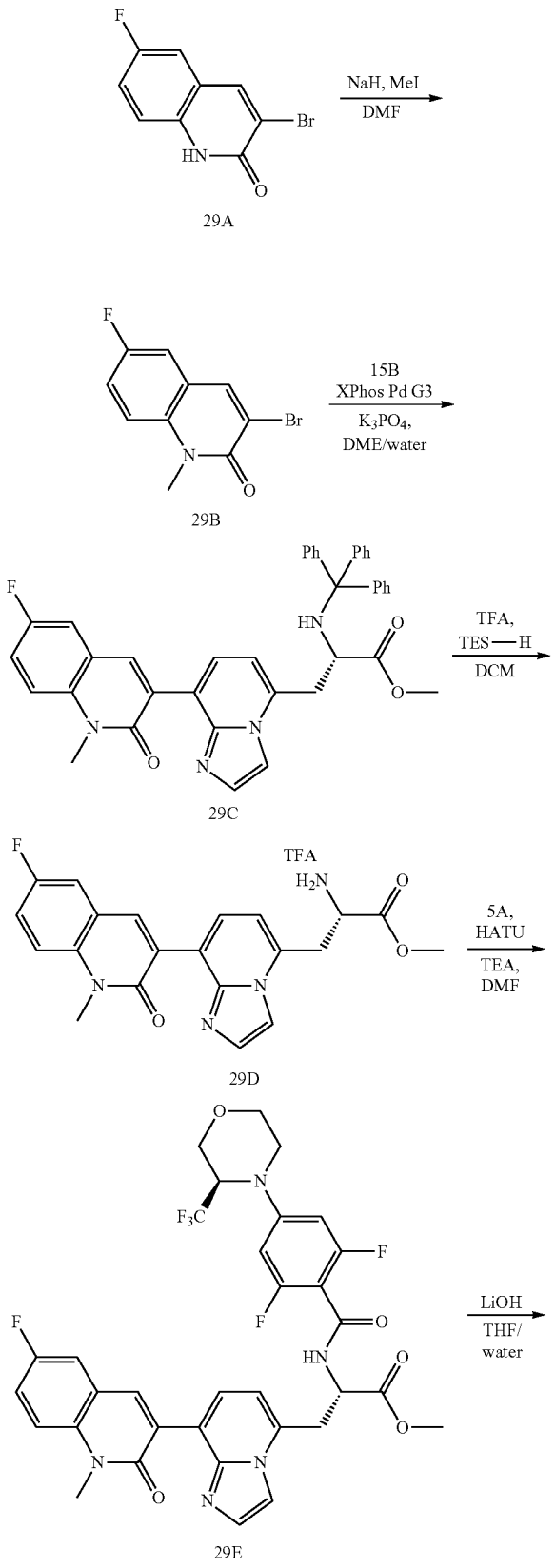
[0475] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (28): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 28A. MS (m/z) 621.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (d, J=7.9 Hz, 1H), 8.95 (d, J=8.1 Hz, 1H), 8.70-8.65 (m, 1H), 8.34-8.29 (m, 1H), 7.88 (s, 1H), 7.49 (d, J=7.9 Hz, 1H), 6.74 (d, J=12.0 Hz, 2H), 5.07-4.95 (m, 1H), 4.95-4.82 (m, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.98-3.89 (m, 1H), 3.79 (dd, J=15.5, 4.7 Hz, 1H), 3.72 (d, J=12.9 Hz, 1H), 3.66-3.45 (m, 5H), 3.41 (d, J=13.1 Hz, 1H), 3.21 (t, J=12.5 Hz, 1H), 2.43 (s, 3H).

Example 29

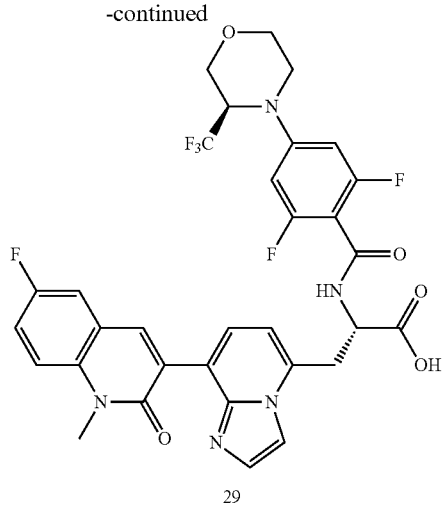
[0476]



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[0477] Synthesis of 3-bromo-6-fluoroquinolin-2(1H)-one (29A): To a microwave vial was added 6-fluoroquinolin-2 (1H)-one (0.252 g, 1.55 mmol), NBS (0.562 g, 3.16 mmol) and CH_3CN (3.8 mL), and the mixture was heated at 100° C. for 90 min. The precipitate was filtered off to afford the title compound. The filtrate was concentrated under reduced pressure and the material was purified by silica gel chromatography using MeOH in DCM (0-25%) to afford the title compound.

[0478] Synthesis of 3-bromo-6-fluoro-1-methylquinolin-2 (1H)-one (29B): To a solution of 29A (0.418 g, 1.73 mmol) in DMF (17 mL) at 0° C. was added NaH (83.0 mg, 2.10 mmol). The mixture was stirred for 5 min at 0° C., followed by the addition of iodomethane (0.270 g, 1.90 mmol). The cold bath was removed, and the mixture was stirred for 12 h at rt. Upon completion, the reaction was quenched with aq NaOH, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The material was purified by silica gel chromatography using MeOH in DCM (0-25%) to afford the title compound.

[0479] Synthesis of methyl (S)-3-(8-(6-fluoro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl) imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (29C): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 29B.

[0480] Synthesis of methyl (S)-2-amino-3-(8-(6-fluoro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (29D): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 29C.

[0481] Synthesis of methyl (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(6-fluoro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (29E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 29D.

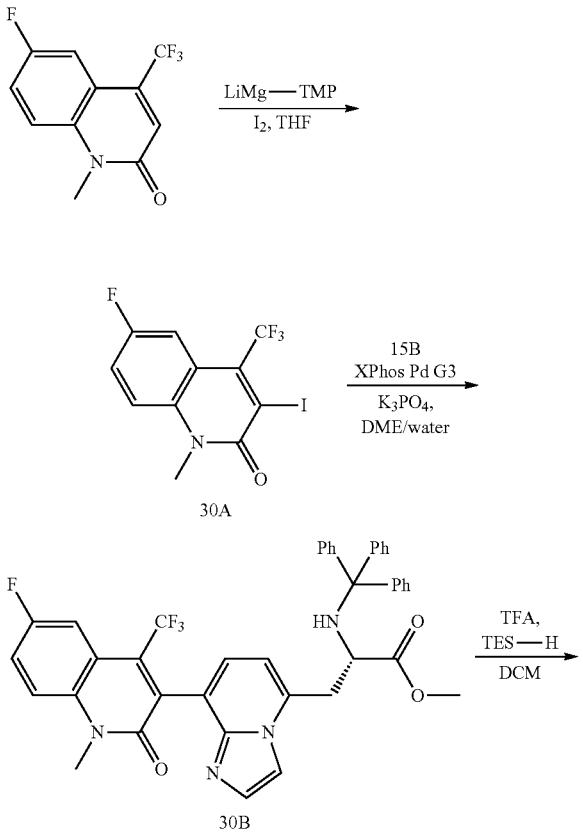
[0482] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-fluoro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (29): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 29E. MS (m/z) 674.2 [M+H]+. ^1H

NMR (400 MHz, DMSO-d6) δ 9.00 (d, J=8.1 Hz, 1H), 8.58 (s, 1H), 8.29 (d, J=21.6 Hz, 2H), 7.99 (d, J=7.5 Hz, 1H), 7.80-7.61 (m, 3H), 7.40 (d, J=9.2 Hz, 1H), 6.77 (d, J=11.7 Hz, 2H), 5.04-4.96 (m, 1H), 4.95-4.87 (m, 1H), 4.16 (d, J=12.6 Hz, 1H), 3.96 (dd, J=11.5, 2.0 Hz, 1H), 3.74 (s, 3H), 3.72 (m, 1H), 3.64-3.51 (m, 4H), 3.21 (t, 3.21 (t, J=15.5 Hz, 1H).

Example 30

[0483] Synthesis of 6-fluoro-3-iodo-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one (30A): To a stirred solution of 6-fluoro-1-methyl-4-(trifluoromethyl)quinolin-2(1F)-one (417 mg, 1.7 mmol) in THF (1.3 mL) was added LiMg-TMP (3.06 mL, 1M) dropwise at −78° C. The reaction mixture was allowed to stir for 30 min, then a solution of iodine (863 mg, 3.4 mmol) in THF was then added at −78° C. The reaction mixture was allowed to warm to RT then was concentrated under reduced pressure, and purified by silica gel chromatography using ethyl acetate/hexanes as the eluent to afford the title compound.

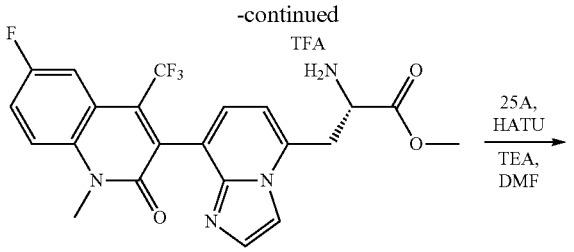
[0484] Synthesis methyl (S)-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro quinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (30B): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 30A.



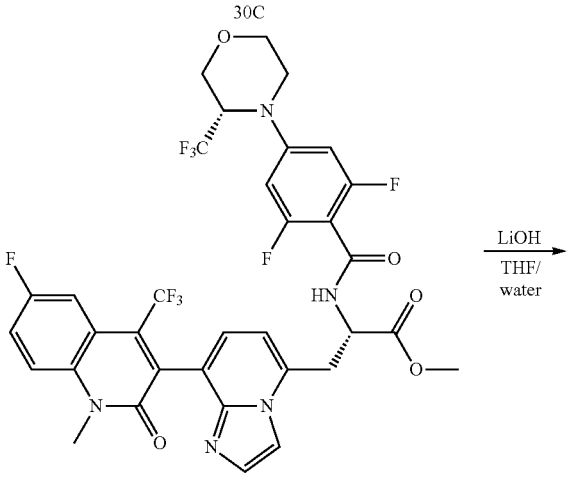
30A

30B

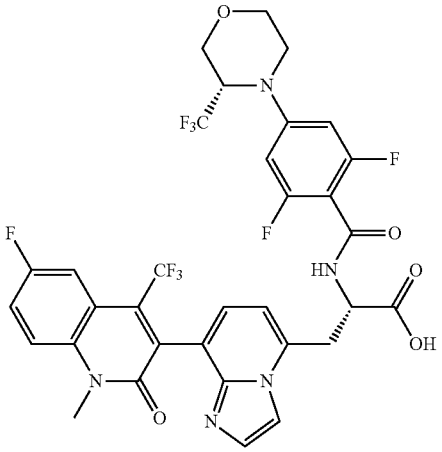
-continued



30C



30D



30

[0485] Synthesis of methyl (S)-2-amino-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (30C): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 30B.

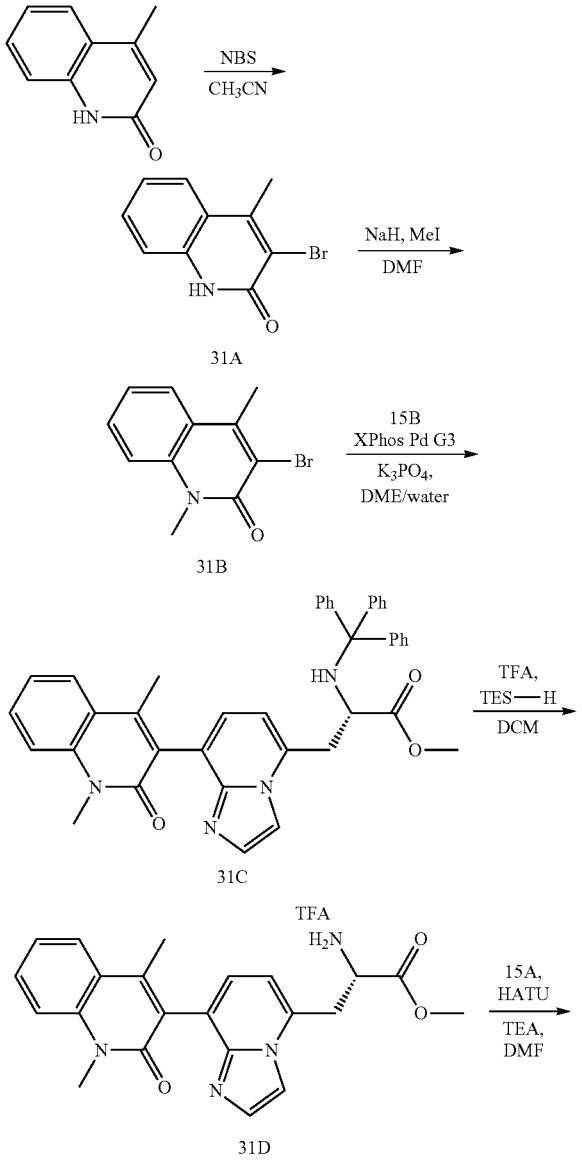
[0486] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (30D): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 25A and 30C.

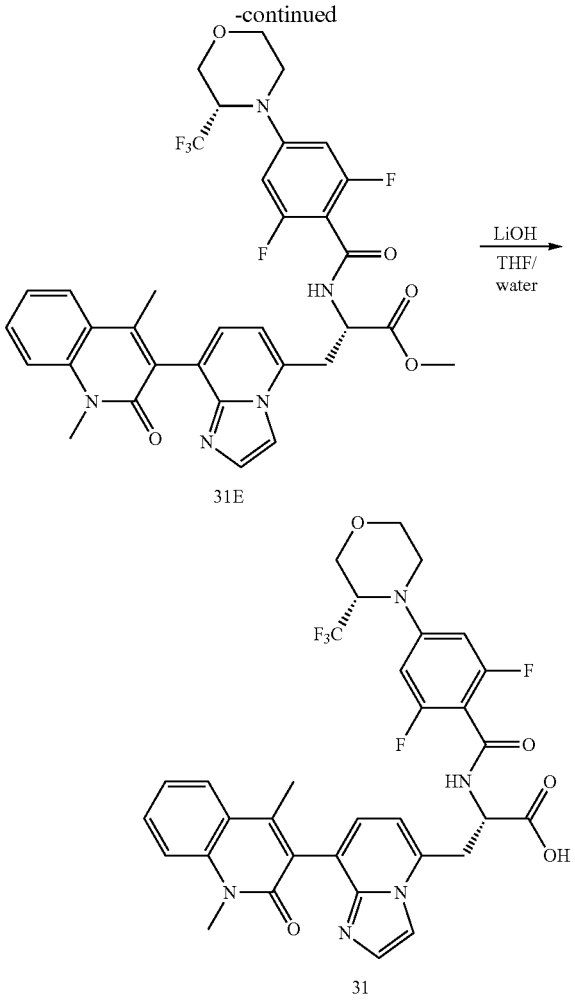
[0487] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-fluoro-1-methyl-

2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (30): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 30D. MS (m/z) 742.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 13.14 (s, 1H), 8.94 (t, J=8.9 Hz, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 7.91-7.70 (m, 2H), 7.70-7.54 (m, 1H), 7.31 (s, 1H), 6.69 (d, J=11.7 Hz, 2H), 4.96 (d, J=9.6 Hz, 1H), 4.85 (d, J=9.2 Hz, 1H), 4.09 (d, J=12.7 Hz, 1H), 3.89 (dd, J=11.7, 3.7 Hz, 1H), 3.67 (d, J=2.1 Hz, 3H), 3.49 (d, J=11.2 Hz, 1H), 3.16 (t, J=12.6 Hz, 1H).

Example 31

[0488]





[0489] Synthesis of 3-bromo-4-methylquinolin-2(1H)-one (31A): The title compound was prepared according to the method presented for the synthesis of compound 29A starting with 4-methylquinolin-2(1H)-one.

[0490] Synthesis of 3-bromo-1,4-dimethylquinolin-2(1H)-one (31B): The title compound was prepared according to the method presented for the synthesis of compound 29D starting with 31A.

[0491] Synthesis of methyl (S)-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo [1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (31C): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 31B.

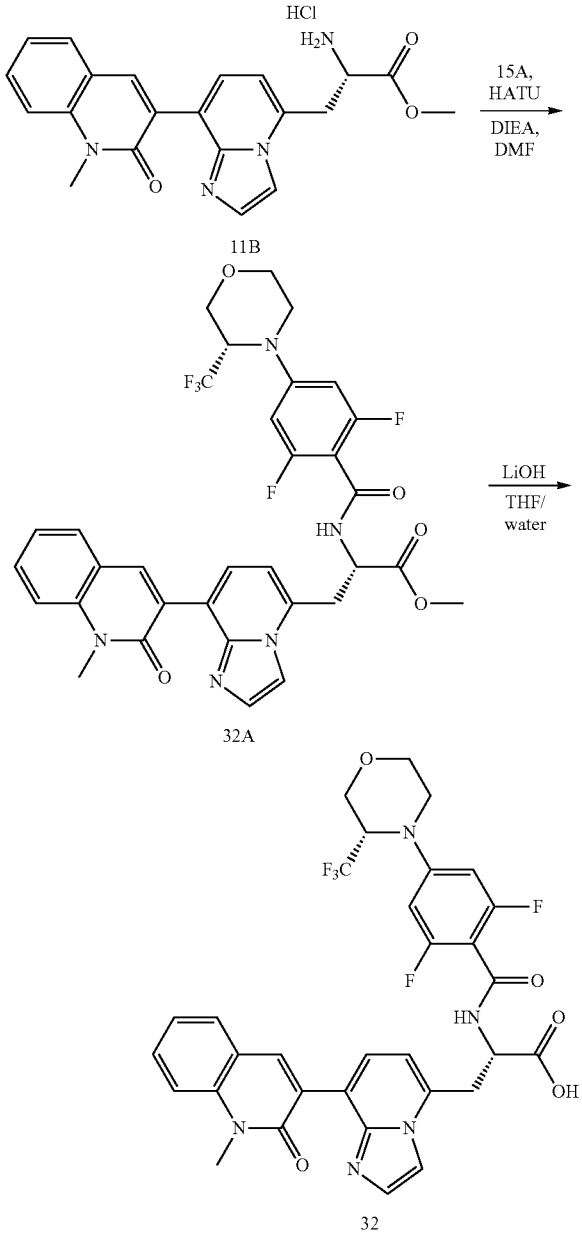
[0492] Synthesis of methyl (S)-2-amino-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoatetrifluoroacetate (31D): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 31C.

[0493] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (31E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 15A and 31D.

[0494] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (31): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 30E. MS (m/z) 670.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (t, J=7.6 Hz, 1H), 8.60 (d, J=26.0 Hz, 1H), 8.32 (s, 1H), 7.99 (dd, J=8.2, 4.8 Hz, 1H), 7.77 (t, J=7.8 Hz, 2H), 7.68 (d, J=8.6 Hz, 1H), 7.52-7.34 (m, 2H), 6.75 (d, J=12.0 Hz, 2H), 5.08-4.98 (m, 1H), 4.91 (dt, J=9.9, 5.2 Hz, 1H), 4.16 (d, J=12.7 Hz, 1H), 3.95 (d, J=11.7 Hz, 1H), 3.86-3.50 (m, 7H), 3.42 (d, J=12.8 Hz, 1H), 3.23 (t, J=12.3 Hz, 1H), 2.27 (d, J=7.7 Hz, 3H).

Example 32

[0495]

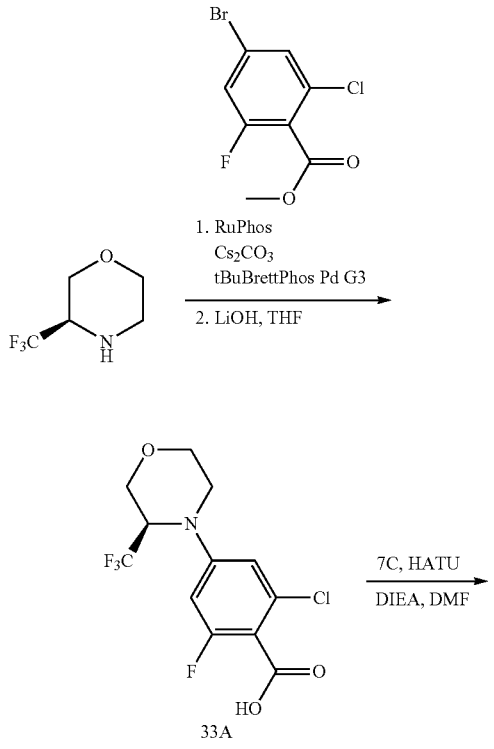


[0496] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (32A): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 15A and 11B.

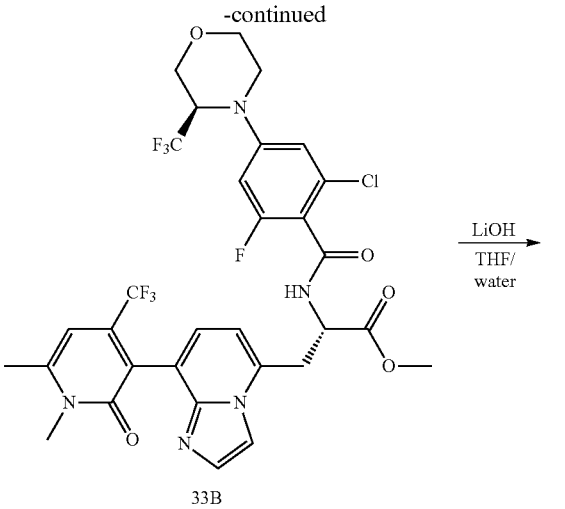
[0497] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (32): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 32A. MS (m/z) 655.8 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.21 (s, 1H), 9.00 (d, J=8.0 Hz, 1H), 8.59 (d, J=1.9 Hz, 1H), 8.33 (d, J=2.0 Hz, 1H), 8.25 (s, 1H), 7.99 (dd, J=7.5, 1.0 Hz, 1H), 7.86 (dt, J=7.8, 1.6 Hz, 1H), 7.75 (ddd, J=8.6, 7.1, 1.5 Hz, 1H), 7.66 (d, J=8.6 Hz, 1H), 7.48-7.31 (m, 2H), 6.76 (d, J=11.8 Hz, 2H), 4.99 (ddd, J=13.1, 8.2, 4.1 Hz, 1H), 4.89 (d, J=9.1 Hz, 1H), 4.15 (d, J=12.7 Hz, 1H), 3.94 (dd, J=11.4, 3.8 Hz, 1H), 3.80-3.73 (m, 1H), 3.72 (s, 4H), 3.70 (s, 1H), 3.64-3.48 (m, 2H), 3.41 (d, J=12.9 Hz, 1H), 3.21 (t, J=12.4 Hz, 1H).

Example 33

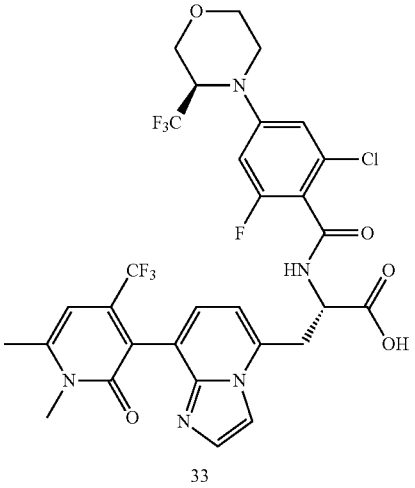
[0498]



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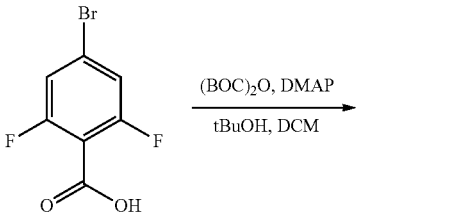
33B

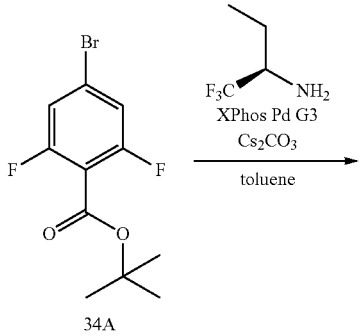


33

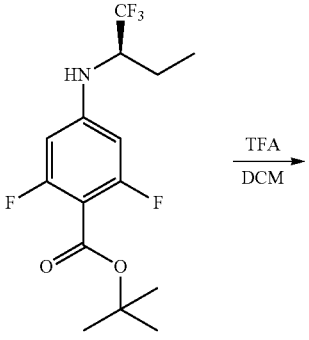
Example 34

[0502]

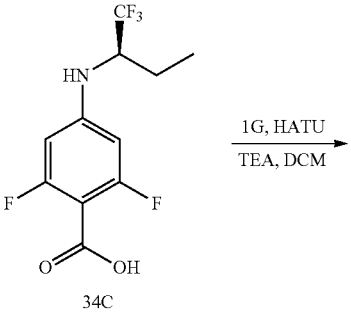




34A



34B



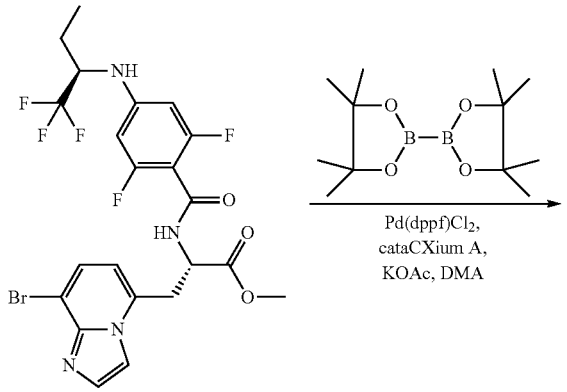
34C

[0499] Synthesis of (R)-2-chloro-6-fluoro-4-(3-(trifluoromethyl)morpholino)benzoic acid acid (33A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with methyl 4-bromo-2-chloro-6-fluorobenzoate.

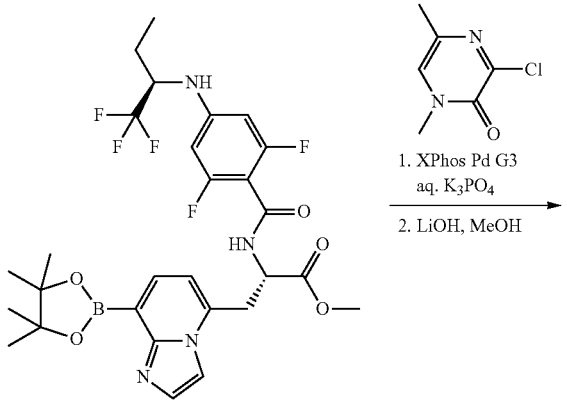
[0500] Synthesis of methyl (S)-2-(2-chloro-6-fluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (33B): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 33A and 7C.

[0501] Synthesis of (S)-2-(2-chloro-6-fluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (33): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 33B. MS (m/z) 704.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 9.11 (dd, J=8.4, 4.9 Hz, 1H), 8.63-8.53 (m, 1H), 8.39-8.26 (m, 1H), 7.85-7.68 (m, 1H), 7.51-7.38 (m, 1H), 6.94-6.84 (m, 2H), 6.73 (s, 1H), 5.16-4.99 (m, 1H), 4.99-4.85 (m, 1H), 4.15 (d, J=12.8 Hz, 1H), 3.99-3.90 (m, 1H), 3.86-3.46 (m, 7H), 3.42-3.33 (m, 1H), 3.29-3.16 (m, 1H), 2.59 (s, 3H).

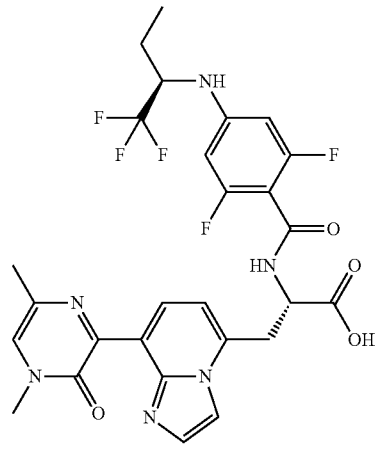
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34D



34E



34

[0503] Synthesis of tert-butyl 4-bromo-2,6-difluorobenzoate (34A): To a stirred solution of 4-bromo-2,6-difluorobenzoic acid (5 g, 21.1 mmol) in dichloromethane (50 mL) and tert-butyl alcohol (50 mL) was added di-tert-butyl dicarbonate (9.2 g, 42.2 mol) followed by 4-dimethylaminopyridine (0.8 g, 6.3 mmol). The reaction mixture was allowed to stir at RT for 12 h. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate (100 mL) and washed with a 10% aqueous solution of citric acid (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude material. This material was suspended in hexanes, the solid was filtered off and the filtrate was evaporated under reduced pressure to afford compound 34A. MS (m/z) 236.6 $[M+H—C_4H_8]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.69-7.56 (m, 2H), 1.50 (s, 9H).

[0504] Synthesis of tert-butyl (R)-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoate (34B): To a stirred suspension of tert-butyl 4-bromo-2,6-difluorobenzoate (34A) (250 mg, 0.55 mmol), (R)-1,1,1-trifluorobutan-2-amine (85 mg, 0.67 mmol), and cesium carbonate (904 mg, 2.8 mmol) in toluene (5 mL) was added XPhos Pd G3 (42 mg, 0.06 mmol). The reaction mixture was sparged with nitrogen and then heated to 90° C. for 12 h. The mixture was cooled to RT and diluted with ethyl acetate (50 mL). The resultant suspension was filtered through a pad of celite, and the filtrate was evaporated under reduced pressure to afford compound 34B. MS (m/z) 284.1 $[M+H—C_4H_8]^+$.

[0505] Synthesis of (R)-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid (34C): To a stirred solution of tert-butyl (R)-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl) amino)benzoate (34B) (188 mg, 0.55 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was allowed to stir at RT for 20 mins. The reaction mixture was concentrated under reduced pressure to afford crude material. This material was purified by silica gel column chromatography and eluted ethyl acetate in hexane to afford compound 34C. MS (m/z) 338.1 $[M+H]^+$.

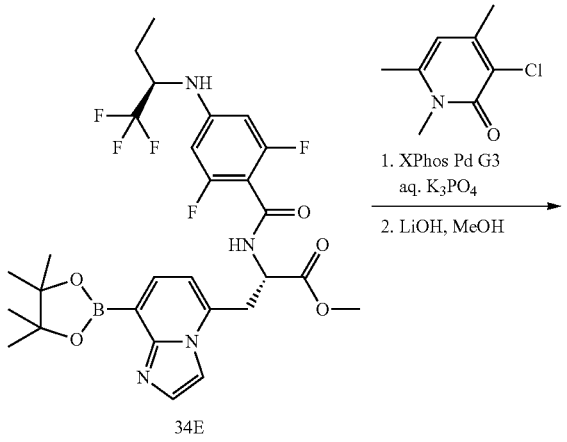
[0506] Synthesis of methyl (S)-3-(8-bromoimidazo[1,2-a] pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoate (34D): The title compound was prepared according to the method presented for the synthesis of compound 4A starting with 34C and 1G.

[0507] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1, 1,1-trifluorobutan-2-yl)amino) benzamido)-3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (34E): The title compound was prepared according to the method presented for the synthesis of compound 5C starting with 34D.

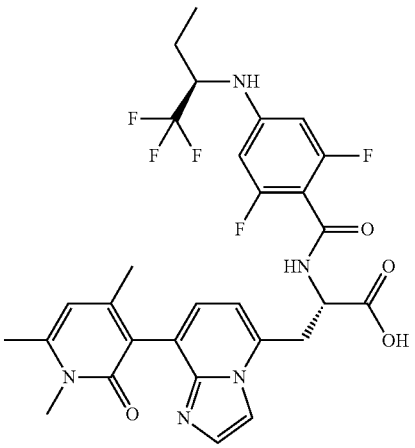
[0508] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4,6-dimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (34): The title compound was prepared according to the method presented for the synthesis of compound 5 starting with 3-chloro-1,5-dimethylpyrazin-2(1H)-one and 34E. MS (m/z) 539.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 9.21 (d, J=7.7 Hz, 1H), 8.79 (d, J=8.2 Hz, 1H), 8.65 (d, J=2.3 Hz, 1H), 8.30 (d, J=2.2 Hz, 1H), 7.86 (s, 1H), 7.46 (d, J=8.0 Hz, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.7 Hz, 2H), 4.96 (s, 1H), 4.27 (s, 1H), 3.80-3.74 (m, 1H), 3.57 (s, 4H), 2.41 (d, J=0.8 Hz, 3H), 1.73 (td, J=6.8, 3.1 Hz, 1H), 1.56-1.48 (m, 1H), 0.89 (t, J=7.3 Hz, 3H).

Example 35

[0509]



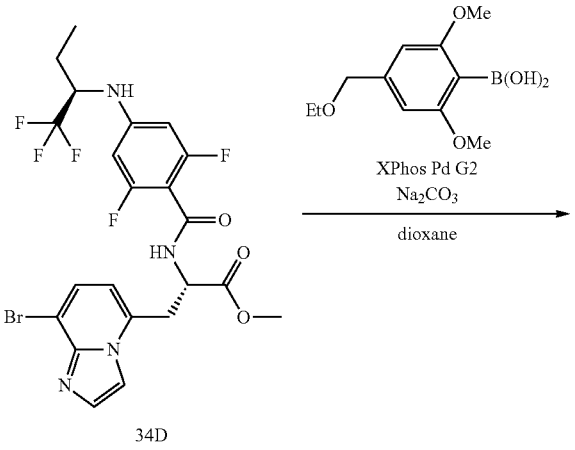
34E



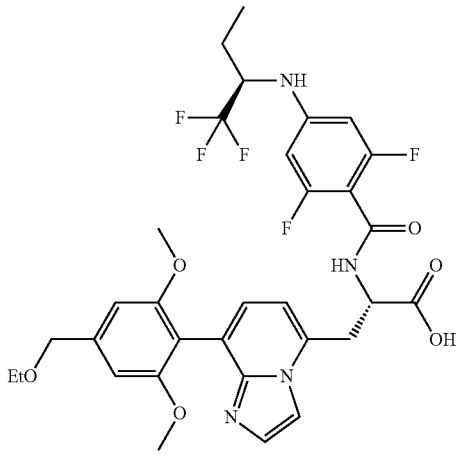
35

Example 36

[0511]



34D



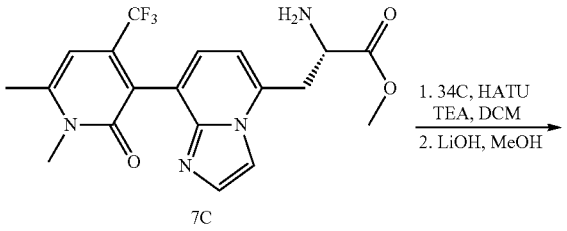
36

[0510] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (35): The title compound was prepared according to the method presented for the synthesis of compound 5 starting with 3-chloro-1,4,6-trimethylpyridin-2(1H)-one and 34E. MS (m/z) 606.2 $[M+H]^+$. 1 H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 8.82 (t, J=9.4 Hz, 1H), 8.54 (d, J=24.5 Hz, 1H), 8.27 (s, 1H), 7.73 (s, 1H), 7.41-7.28 (m, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.7 Hz, 2H), 6.27 (s, 1H), 4.97 (s, 1H), 4.29 (s, 1H), 3.78-3.66 (m, 2H), 3.52 (d, J=13.6 Hz, 2H), 3.44 (s, 3H), 2.42 (s, 3H), 1.91 (d, J=6.2 Hz, 3H), 1.74 (d, J=8.5 Hz, 1H), 1.57-1.45 (m, 1H), 0.89 (t, J=7.2 Hz, 3H).

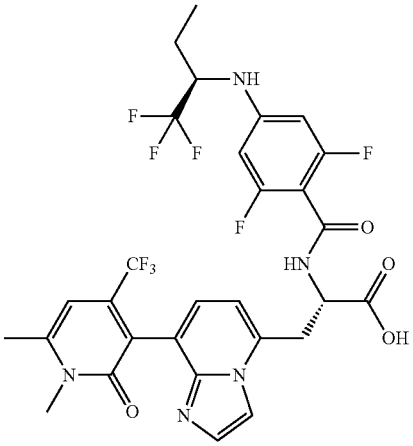
[0512] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (36): The title compound was prepared according to the method presented for the synthesis of compound 1 of Example 1 starting with 34D. MS (m/z) 665.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.18 (s, 1H), 8.84 (d, J=8.3 Hz, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 7.79 (d, J=7.0 Hz, 1H), 7.38 (d, J=9.5 Hz, 1H), 6.82 (d, J=9.7 Hz, 3H), 6.45 (d, J=11.6 Hz, 2H), 5.03-4.95 (m, 1H), 4.55 (s, 2H), 4.37-4.26 (m, 1H), 3.75 (dd, J=15.8, 4.5 Hz, 2H), 3.68 (d, J=2.5 Hz, 5H), 3.62-3.55 (m, 3H), 1.83-1.72 (m, 1H), 1.58-1.46 (m, 1H), 1.22 (t, J=7.0 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H).

Example 37

[0513]



7C

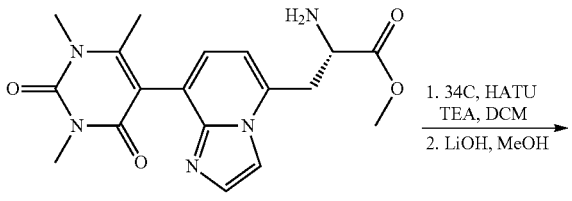


37

[0514] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (37): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 34C. MS (m/z) 665.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.18 (s, 1H), 8.84 (d, J=8.3 Hz, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 7.79 (d, J=7.0 Hz, 1H), 7.38 (d, J=9.5 Hz, 1H), 6.82 (d, J=9.7 Hz, 3H), 6.45 (d, J=11.6 Hz, 2H), 5.03-4.95 (m, 1H), 4.55 (s, 2H), 4.37-4.26 (m, 1H), 3.75 (dd, J=15.8, 4.5 Hz, 2H), 3.68 (d, J=2.5 Hz, 5H), 3.62-3.55 (m, 3H), 1.83-1.72 (m, 1H), 1.58-1.46 (m, 1H), 1.22 (t, J=7.0 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H).

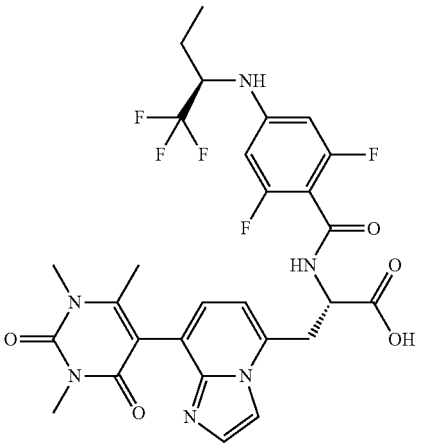
Example 38

[0515]



8B

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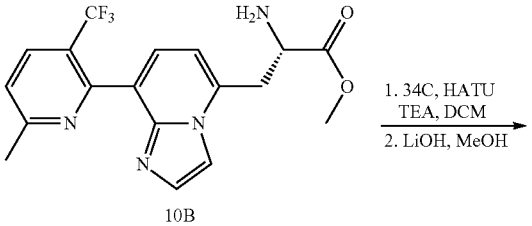


38

[0516] (S)-2-(2,6-Difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (38): The title compound was prepared according to the method presented for the synthesis of compound 8 starting with 34C. MS (m/z) 623.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.81 (t, J=8.1 Hz, 1H), 8.57 (d, J=27.4 Hz, 1H), 8.33 (d, J=12.7 Hz, 1H), 7.78-7.69 (m, 1H), 7.38 (dd, J=41.5, 7.6 Hz, 1H), 6.80 (d, J=9.4 Hz, 1H), 6.41 (dd, J=11.6, 2.5 Hz, 2H), 5.04-4.82 (m, 1H), 4.28 (d, J=9.7 Hz, 1H), 3.73 (td, J=15.8, 4.6 Hz, 1H), 3.62-3.47 (m, 1H), 3.46 (d, J=1.4 Hz, 3H), 3.23 (s, 3H), 2.06 (d, J=4.9 Hz, 3H), 1.75 (dd, J=10.6, 7.3 Hz, 0H), 1.61-1.40 (m, 1H), 1.05 (s, 1H), 0.90 (t, J=7.3 Hz, 3H).

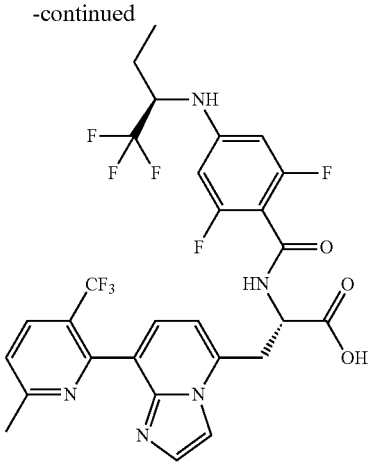
Example 39

[0517]



10B

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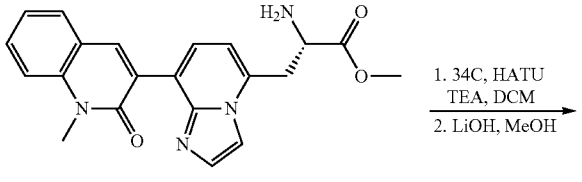


39

[0518] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(6-methyl-3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (39): The title compound was prepared according to the method presented for the synthesis of compound 10 starting with 34C. MS (m/z) 630.8 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.38-12.92 (m, 1H), 8.82 (dd, J=8.0, 2.0 Hz, 1H), 8.69-8.49 (m, 1H), 8.32 (d, J=8.3 Hz, 1H), 8.24 (s, 1H), 7.96-7.74 (m, 1H), 7.69 (d, J=8.3 Hz, 1H), 7.44-7.28 (m, 1H), 6.80 (d, J=9.3 Hz, 1H), 6.43 (d, J=11.8 Hz, 2H), 5.06-4.94 (m, 1H), 4.30 (tqd, J=10.9, 7.6, 7.1, 3.7 Hz, 1H), 3.80-3.69 (m, 1H), 3.64-3.52 (m, 1H), 2.62 (s, 3H), 1.77 (dqd, J=14.6, 7.3, 3.1 Hz, 1H), 1.52 (ddq, J=14.3, 10.4, 7.2 Hz1, 1H), 0.92 (t, J=7.3 Hz, 3H).

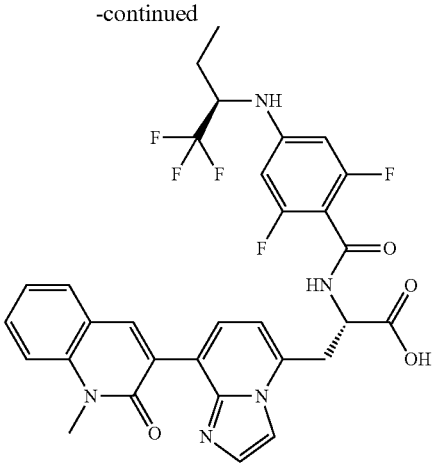
Example 40

[0519] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (40): The title compound was prepared according to the method presented for the synthesis of compound 11 starting with 34C. MS (m/z) 627.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.85 (dd, J=8.2, 1.9 Hz, 1H), 8.60 (d, J=2.3 Hz, 1H), 8.35 (d, J=2.2 Hz, 1H), 8.24 (s, 1H), 8.00 (d, J=7.5 Hz, 1H), 7.86 (dd, J=7.9, 1.5 Hz, 1H), 7.75 (ddd, J=8.7, 7.1, 1.6 Hz, 1H), 7.67 (d, J=8.5 Hz, 1H), 7.46-7.32 (m, 2H), 6.82 (d, J=9.3 Hz, 1H), 6.50-6.38 (m, 2H), 4.97 (ddd, J=10.7, 8.2, 4.6 Hz, 1H), 4.29 (q, J=8.5 Hz, 2H), 3.72 (s, 4H), 3.58 (dd, J=15.6, 10.4 Hz, 1H), 1.75 (ddq, J=14.9, 7.5, 4.2 Hz, 1H), 1.51 (ddq, J=14.3, 10.2, 7.2 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).



11B

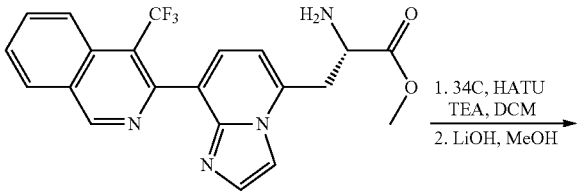
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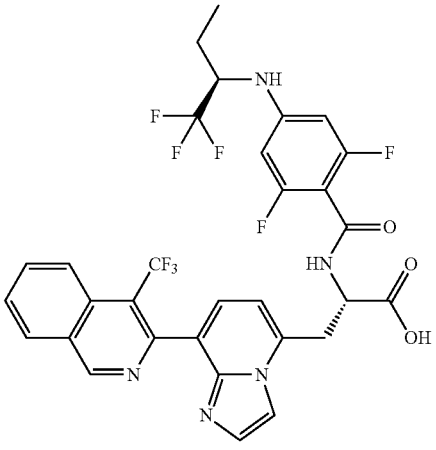
40

Example 41

[0520]



12B



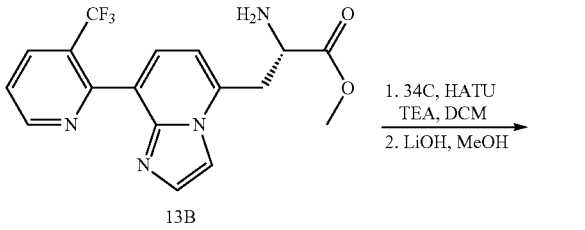
41

[0521] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-(trifluoromethyl)isoquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (41): The title compound was prepared according to the method presented for the synthesis of compound 12 starting with 34C. MS (m/z) 666.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.17 (s, 1H), 9.71 (s, 1H), 8.85 (d, J=8.3 Hz, 1H), 8.62 (s, 1H), 8.48 (d, J=8.1 Hz, 1H), 8.27 (d, J=8.5 Hz, 2H), 8.14 (t, J=7.8 Hz, 1H), 8.01 (t, J=7.6 Hz, 1H), 7.92 (s, 1H), 7.42 (s, 1H), 6.81 (d, J=9.3 Hz, 1H), 6.44 (d, J=11.7 Hz, 2H), 5.02

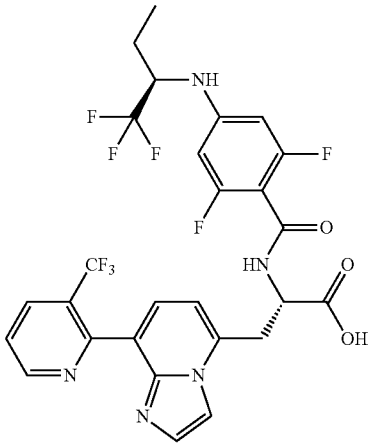
(s, 1H), 4.31 (s, 1H), 3.78 (d, J=15.3 Hz, 1H), 3.66-3.53 (m, 1H), 1.77 (ddd, J=13.8, 7.2, 3.2 Hz, 1H), 1.53 (ddd, J=17.6, 14.1, 7.3 Hz, 1H), 0.92 (t, J=7.3 Hz, 3H).

Example 42

[0522] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (42): The title compound was prepared according to the method presented for the synthesis of compound 13 starting with 34C. MS (m/z) 616.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.05-8.98 (m, 1H), 8.83 (dd, J=8.2, 2.0 Hz, 1H), 8.67 (d, J=2.2 Hz, 1H), 8.48 (dd, J=8.3, 1.5 Hz, 1H), 8.34 (d, J=2.1 Hz, 1H), 7.95 (d, J=7.5 Hz, 1H), 7.86 (dd, J=8.1, 4.9 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 6.85-6.76 (m, 1H), 6.43 (d, J=11.6 Hz, 2H), 5.03 (ddd, J=10.9, 8.2, 4.6 Hz, 1H), 4.30 (q, J=8.7, 7.8 Hz, 1H), 3.79 (dd, J=15.5, 4.5 Hz, 1H), 3.61 (dd, J=15.5, 10.7 Hz, 1H), 1.76 (dqd, J=14.6, 7.2, 3.1 Hz, 1H), 1.52 (ddd, J=13.8, 10.4, 7.1 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).



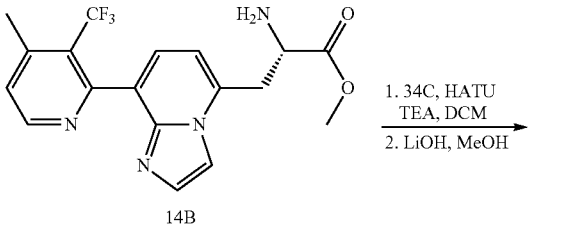
13B



42

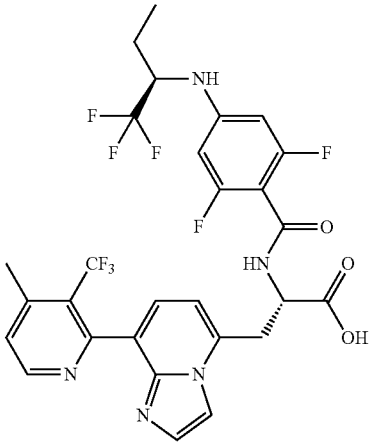
Example 43

[0523]



14B

-continued

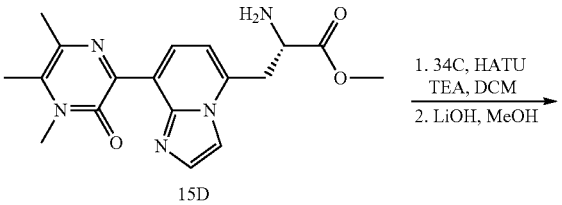


43

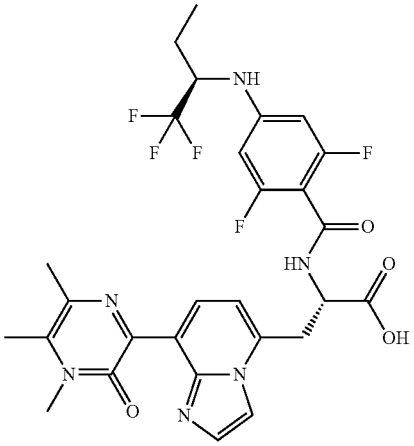
[0524] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-methyl-3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (43): The title compound was prepared according to the method presented for the synthesis of compound 14 starting with 34C. MS (m/z) 630.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.86-8.77 (m, 2H), 8.67-8.61 (m, 1H), 8.31 (d, J=1.7 Hz, 1H), 7.84 (d, J=7.4 Hz, 1H), 7.73 (d, J=5.0 Hz, 1H), 7.41 (d, J=7.5 Hz, 1H), 6.81 (d, J=9.4 Hz, 1H), 6.43 (d, J=11.6 Hz, 2H), 5.00 (td, J=9.3, 8.4, 4.4 Hz, 1H), 4.31 (d, J=8.1 Hz, 1H), 3.83-3.69 (m, 1H), 3.59 (dd, J=15.5, 10.7 Hz, 1H), 2.62 (d, J=2.6 Hz, 3H), 1.76 (ddq, J=11.5, 7.4, 4.2, 3.8 Hz, 1H), 1.52 (ddt, J=17.7, 14.4, 7.3 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).

Example 44

[0525]



15D

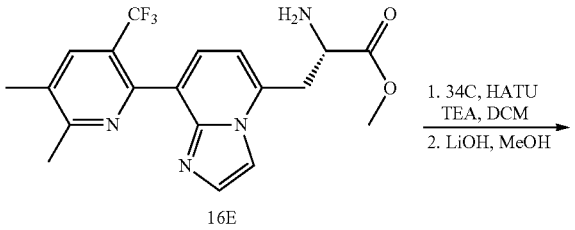


44

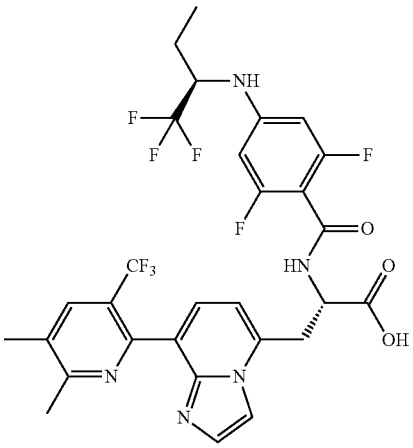
[0526] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4,5,6-trimethyl-3-oxo-3,4-dihydropyrazin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (44): The title compound was prepared according to the method presented for the synthesis of compound 15 starting with 34C. MS (m/z) 607.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.47 (s, 1H), 13.17 (s, 1H), 9.25 (d, J=7.9 Hz, 1H), 8.80 (d, J=8.2 Hz, 1H), 8.65 (s, 1H), 8.30 (s, 1H), 7.47 (d, J=8.0 Hz, 1H), 6.80 (d, J=9.3 Hz, 1H), 6.42 (d, J=11.9 Hz, 2H), 5.04-4.92 (m, 1H), 4.34-4.22 (m, 1H), 3.77 (dd, J=15.4, 4.6 Hz, 1H), 3.65 (s, 3H), 3.57 (dd, J=15.5, 10.5 Hz, 1H), 2.54 (s, 3H), 2.50 (s, 3H), 1.83-1.69 (m, 1H), 1.59-1.44 (m, OH), 0.91 (t, J=7.3 Hz, 3H).

Example 45

[0527]



16E

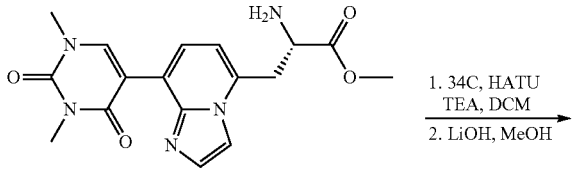


45

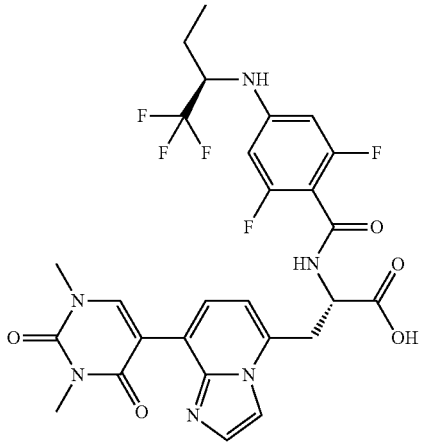
[0528] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (45): The title compound was prepared according to the method presented for the synthesis of compound 16 starting with 34C. MS (m/z) 644.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.80 (dd, J=8.2, 1.9 Hz, 1H), 8.62 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.85 (d, J=7.4 Hz, 1H), 7.39 (d, J=7.5 Hz, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.7 Hz, 2H), 4.98 (ddd, J=10.8, 8.1, 4.6 Hz, 1H), 4.29 (q, J=9.6, 8.9 Hz, 1H), 3.75 (dd, J=15.6, 4.6 Hz, 1H), 3.58 (m, 1H), 2.54 (s, 3H), 2.45 (s, 3H), 1.74 (dtd, J=14.6, 7.4, 3.2 Hz, 1H), 1.50 (ddt, J=17.8, 14.5, 7.3 Hz, 1H), 0.89 (t, J=7.3 Hz, 3H).

Example 46

[0529]



17B

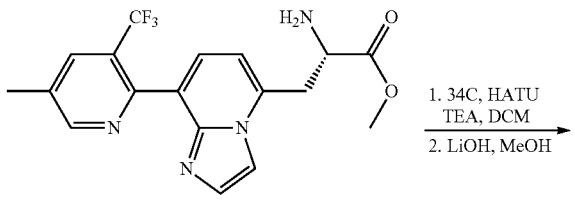


46

[0530] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (46): The title compound was prepared according to the method presented for the synthesis of compound 17 starting with 34C. MS (m/z) 608.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.82 (dd, J=8.1, 1.9 Hz, 1H), 8.55 (d, J=2.2 Hz, 1H), 8.34 (d, J=2.1 Hz, 1H), 8.20 (s, 1H), 7.84 (d, J=7.5 Hz, 1H), 7.35 (d, J=7.6 Hz, 1H), 6.81 (d, J=9.4 Hz, 1H), 6.48-6.34 (m, 2H), 4.93 (ddt, J=12.6, 6.5, 3.3 Hz, 1H), 4.28 (d, J=8.4 Hz, 1H), 3.70 (dd, J=15.7, 4.6 Hz, 1H), 3.41 (s, 3H), 3.26 (s, 3H), 1.75 (ddd, J=13.8, 7.2, 3.3 Hz, 1H), 1.50 (ddt, J=17.7, 14.4, 7.3 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).

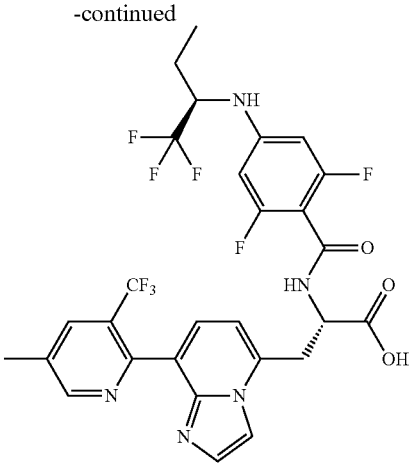
Example 47

[0531]



18B

-continued

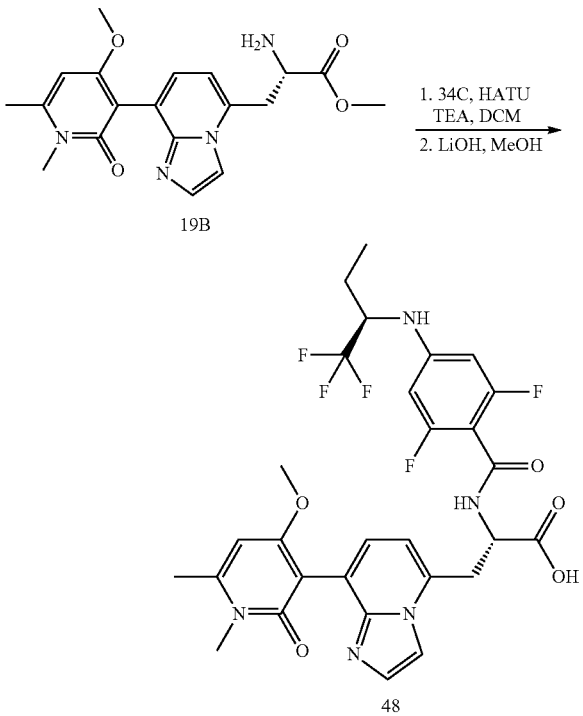


47

[0532] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(5-methyl-3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (47): The title compound was prepared according to the method presented for the synthesis of compound 18 starting with 34C. MS (m/z) 630.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 8.83 (d, J=10.3 Hz, 2H), 8.58 (s, 1H), 8.31 (s, 1H), 8.23 (s, 1H), 7.81 (s, 1H), 7.36 (s, 1H), 6.80 (d, J=9.4 Hz, 1H), 6.43 (d, J=11.6 Hz, 2H), 5.00 (s, 1H), 4.31 (d, J=10.2 Hz, 1H), 3.74 (d, J=15.6 Hz, 1H), 3.63-3.51 (m, 1H), 2.53 (s, 3H), 1.76 (ddd, J=13.7, 7.2, 3.2 Hz, 1H), 1.52 (ddd, J=14.0, 10.5, 7.2 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).

Example 48

[0533]



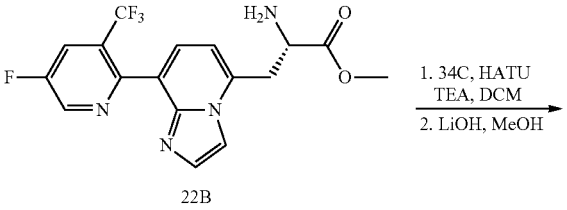
19B

48

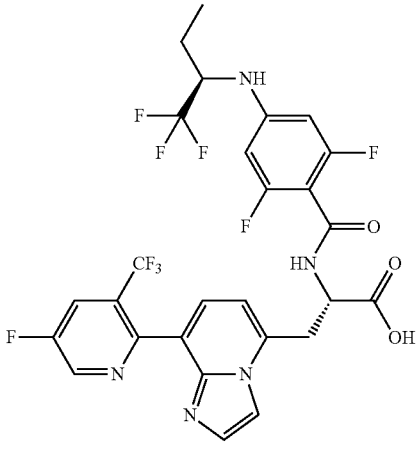
[0534] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (48): The title compound was prepared according to the method presented for the synthesis of compound 19 starting with 34C. MS (m/z) 622.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.85 (s, 1H), 13.14 (s, 1H), 8.85 (d, J=8.0 Hz, 1H), 8.52 (d, J=2.3 Hz, 1H), 8.28 (s, 1H), 7.79 (d, J=7.5 Hz, 1H), 7.36 (d, J=7.7 Hz, 1H), 6.82 (d, J=9.3 Hz, 1H), 6.57-6.33 (m, 3H), 4.93 (d, J=11.1 Hz, 1H), 4.31 (d, J=9.7 Hz, 1H), 3.76 (s, 4H), 3.56 (dd, J=15.9, 10.3 Hz, 1H), 3.47 (s, 3H), 1.85-1.69 (m, 1H), 1.62-1.43 (m, 1H), 0.92 (t, J=7.3 Hz, 3H).

Example 49

[0535]



22B

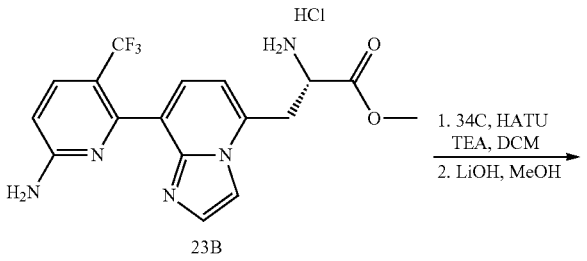


49

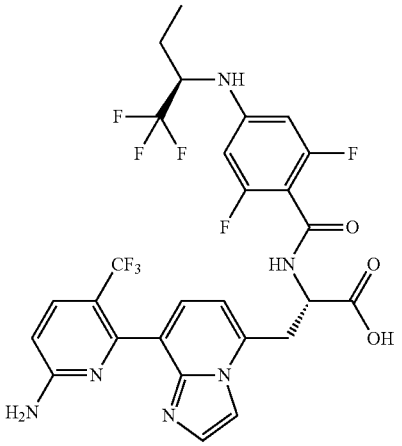
[0536] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(5-fluoro-3-(trifluoromethyl) pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (49): The title compound was prepared according to the method presented for the synthesis of compound 22 starting with 34C. MS (m/z) 634.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 9.09 (s, 1H), 8.83 (d, J=8.2 Hz, 1H), 8.57 (d, J=8.7 Hz, 2H), 8.21 (s, 1H), 7.81 (s, 1H), 7.34 (s, 1H), 6.80 (d, J=9.4 Hz, 1H), 6.43 (d, J=11.8 Hz, 2H), 5.00 (s, 1H), 4.31 (s, 1H), 3.74 (d, J=15.5 Hz, 1H), 3.57 (t, J=13.4 Hz, 1H), 1.84-1.69 (m, 1H), 1.52 (ddd, J=13.6, 10.3, 7.0 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).

Example 50

[0537]



23B

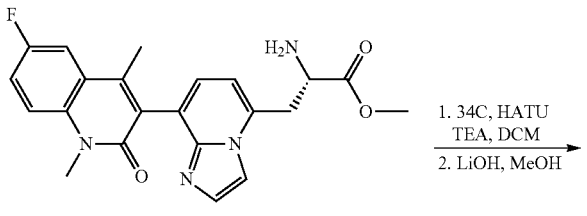


50

[0538] (S)-3-(8-(6-amino-3-(trifluoromethyl)pyridin-2-yl) imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid (50): The title compound was prepared according to the method presented for the synthesis of compound 23 starting with 34C. MS (m/z) 630.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.81 (dd, J=8.1, 1.6 Hz, 1H), 8.64 (d, J=2.3 Hz, 1H), 8.34 (d, J=2.2 Hz, 1H), 7.86 (dd, J=8.2, 5.3 Hz, 2H), 7.40 (d, J=7.6 Hz, 1H), 7.03 (s, 2H), 6.80 (d, J=9.4 Hz, 1H), 6.73-6.63 (m, 1H), 6.41 (d, J=11.6 Hz, 2H), 5.06-4.91 (m, 1H), 4.29 (d, J=10.3 Hz, 1H), 3.75 (dd, J=15.5, 4.5 Hz, 1H), 3.57 (dd, J=15.5, 10.7 Hz, 1H), 1.74 (ddt, J=15.0, 7.6, 3.8 Hz, 1H), 1.50 (ddt, J=17.6, 14.3, 7.2 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).

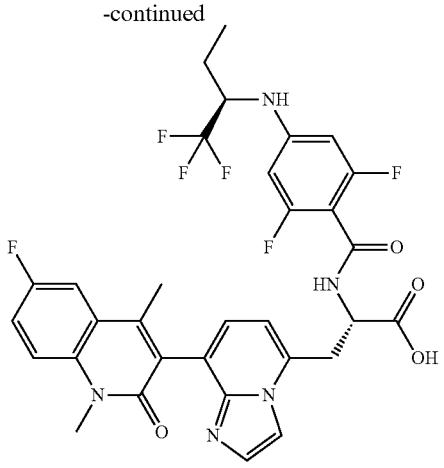
Example 51

[0539]



24E

-continued

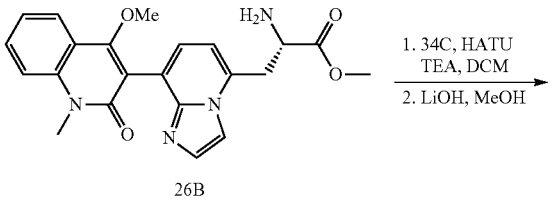


51

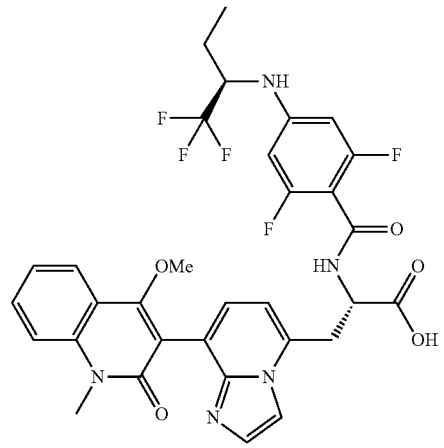
[0540] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (51): The title compound was prepared according to the method presented for the synthesis of compound 24 starting with 34C. MS (m/z) 660.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J=6.9 Hz, 1H), 8.60 (d, J=27.0 Hz, 2H), 8.31 (d, J=15.4 Hz, 1H), 7.88-7.79 (m, 2H), 7.75-7.64 (m, 2H), 7.52-7.36 (m, 2H), 6.80 (s, 1H), 6.44 (d, J=11.8 Hz, 2H), 5.06-4.94 (m, 2H), 4.36-4.25 (m, 2H), 3.83-3.72 (m, 2H), 3.69 (s, 3H), 3.61-3.48 (m, 3H), 1.82-1.70 (m, 2H), 1.58-1.47 (m, 2H), 0.92 (t, J=7.2 Hz, 3H).

Example 52

[0541]



26B



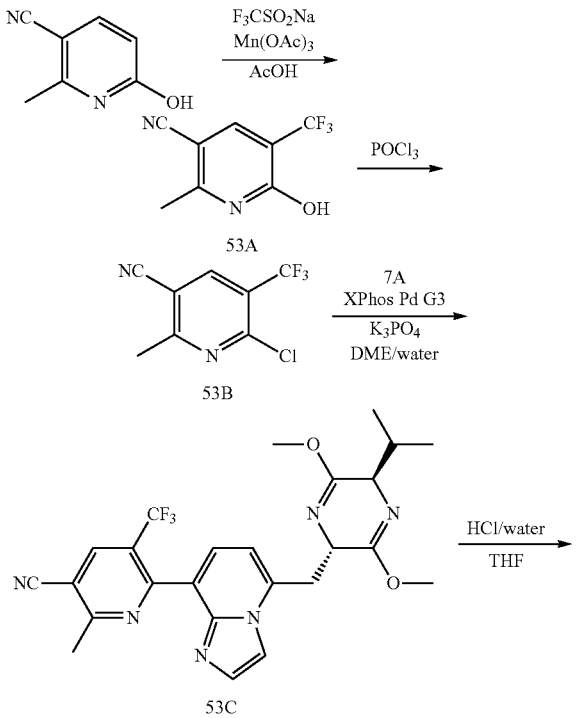
52

[0542] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (52): The title compound was prepared according to the method presented for the synthesis of compound 26 starting with 34C. MS (m/z) 658.9 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 8.84 (d, J=8.1 Hz, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 8.04-7.88 (m, 2H), 7.80 (t, J=7.9 Hz, 1H), 7.69 (d, J=8.5 Hz, 1H), 7.55-7.35 (m, 2H), 6.82 (d, J=9.4 Hz, 1H), 6.45 (d, J=12.0 Hz, 2H), 5.07-4.94 (m, 1H), 4.38-4.23 (m, 1H), 3.88-3.72 (m, 1H), 3.67 (s, 3H), 3.44 (s, 3H), 1.84-1.70 (m, 1H), 1.61-1.44 (m, 1H), 0.92 (t, J=7.3 Hz, 3H).

Example 53

[0543] Synthesis of 6-hydroxy-2-methyl-5-(trifluoromethyl)nicotinonitrile (53A): To a suspension of 6-hydroxy-2-methylnicotinonitrile (500 mg, 3.7 mmol) and sodium triflinate (1.75 g, 11 mmol) in glacial acetic acid (70 mL) was added Mn(III) acetate hydrate (3.00 g, 11 mmol) portionwise, and the reaction was stirred in an open vessel overnight. Water was added, and it was extracted twice with ethyl acetate. The organics were dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified by silica gel chromatography (eluent 1-10% MeOH/DCM) to yield 53A.

[0544] Synthesis of 6-chloro-2-methyl-5-(trifluoromethyl) nicotinonitrile (53B): A suspension of 53A (425 mg, 2.1 mmol) in phosphoyl trichloride (3.2 g, 21 mmol) was heated to 80° C. for 16 hours. It was concentrated, and saturated sodium bicarbonate was added until a pH of ~6 was reached. It was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified by silica gel chromatography (eluent: 5-100% EtOAc/hexanes) to yield 53B.

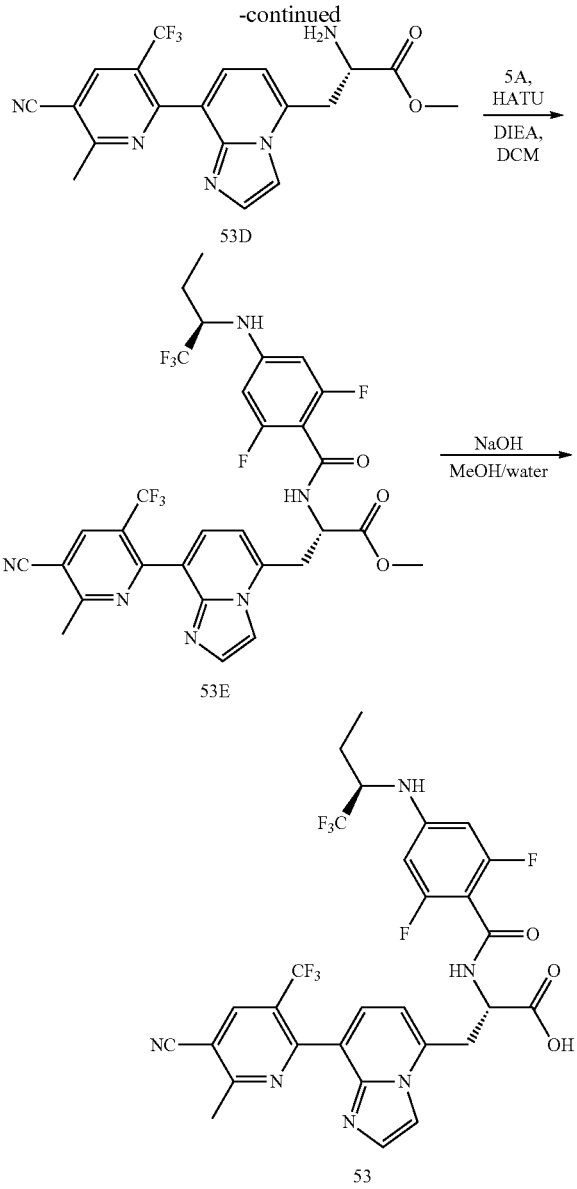


53A

53B

53C

-continued



53D

53E

53

[0545] Synthesis of 6-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-2-methyl-5-(trifluoromethyl)nicotinonitrile (53C): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 53B and substituting 1,2-dimethoxyethane for dioxane.

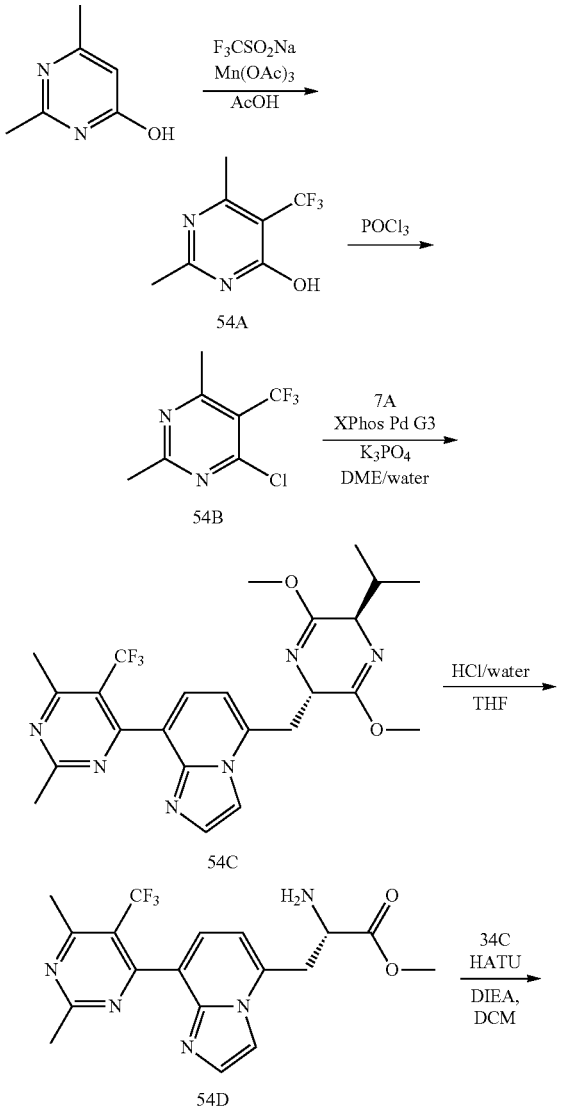
[0546] Synthesis of methyl (S)-2-amino-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl) propanoate hydrochloride (53D): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 53C.

[0547] Synthesis of methyl (S)-3-(8-(5-cyano-6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino) benzamido)propanoate (53E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 5A and 53D.

[0548] Synthesis of (S)-3-(8-(5-cyano-6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid (53): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 53E. MS (m/z) 655.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.81 (d, J=8.0 Hz, 1H), 8.58 (s, 1H), 8.24 (s, 1H), 7.92-7.82 (m, 1H), 7.36 (d, J=7.5 Hz, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.6 Hz, 2H), 5.04-4.90 (m, 1H), 4.36-4.21 (m, 1H), 3.73 (dd, J=15.7, 4.6 Hz, 1H), 3.57 (dd, J=15.6, 10.5 Hz, 1H), 2.80 (s, 3H), 1.84-1.66 (m, 1H), 1.60-1.38 (m, 1H), 0.89 (t, J=7.3 Hz, 3H).

Example 54

[0549]



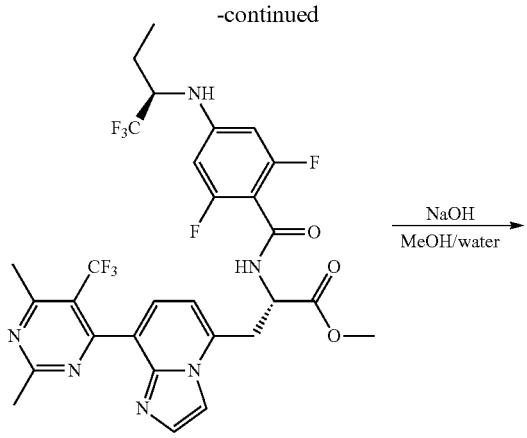
54A

54B

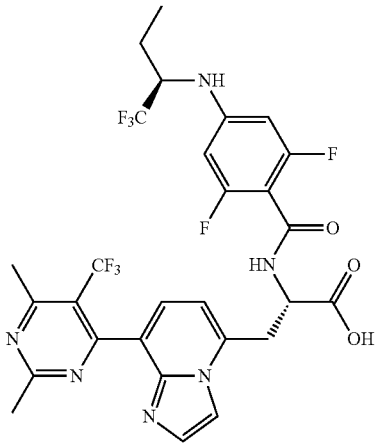
54C

54D

-continued



54E



54

[0550] Synthesis of 2,6-dimethyl-5-(trifluoromethyl)pyrimidin-4-ol (54A): The title compound was prepared according to the method presented for the synthesis of compound 53A starting with 2,6-dimethylpyrimidin-4-ol.

[0551] Synthesis of 4-chloro-2,6-dimethyl-5-(trifluoromethyl)pyrimidine (54B): The title compound was prepared according to the method presented for the synthesis of compound 53A starting with 54A.

[0552] Synthesis of 8-(2,6-dimethyl-5-(trifluoromethyl) pyrimidin-4-yl)-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridine (54C): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 54B.

[0553] Synthesis of methyl (S)-2-amino-3-(8-(2,6-dimethyl-5-(trifluoromethyl)pyrimidin-4-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (54D): The title compound was prepared according to the method presented for the synthesis of compound 53D starting with 54C.

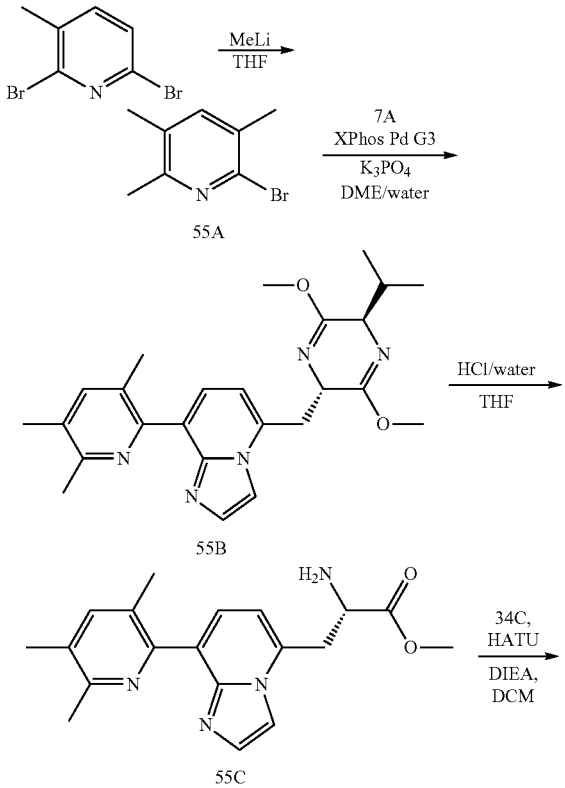
[0554] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(2,6-dimethyl-5-(trifluoromethyl)pyrimidin-4-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (54E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 34C and 54D.

[0555] Synthesis of (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (54): The title compound was prepared according to the method presented for the synthesis of compound 53 starting with 54E. MS (m/z) 645.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.80 (dd, J=8.1, 2.2 Hz, 1H), 8.57 (d, J=2.1 Hz, 1H), 8.24 (s, 1H), 7.83 (d, J=7.4 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H), 6.79 (d, J=9.3 Hz, 1H), 6.42 (d, J=11.6 Hz, 2H), 4.96 (ddt, J=9.7, 6.0, 2.9 Hz, 1H), 4.29 (d, J=9.4 Hz, 1H), 3.72 (dd, J=15.5, 4.5 Hz, 1H), 3.56 (dd, J=15.5, 10.6 Hz, 1H), 2.73 (q, J=2.2 Hz, 3H), 2.69 (s, 3H), 1.75 (dqd, J=14.6, 7.3, 3.1 Hz, 1H), 1.50 (ddt, J=17.7, 14.4, 7.2 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).

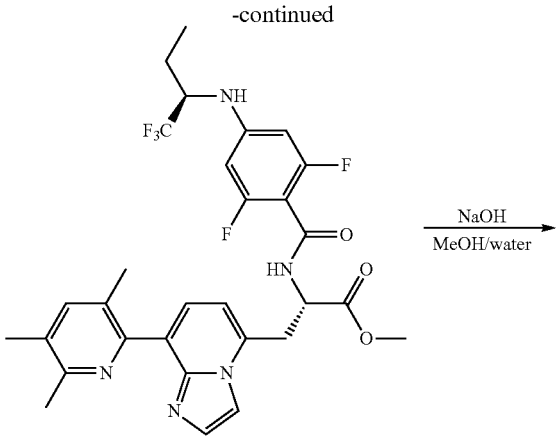
Example 55

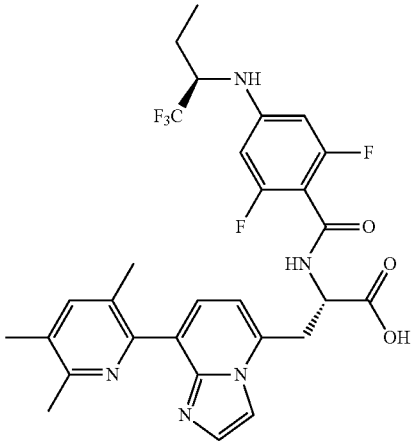
[0556] Synthesis of 2-bromo-3,5,6-trimethylpyridine (55A): To a solution of the 2,6-dibromo-3,5-dimethylpyridine (300 mg, 1.13 mmol) in THF (5 mL) at −78° C. was added methyllithium in diethyl ether (1.6M, 0.85 mL, 1.36 mmol) dropwise, then the reaction was allowed to stir at this temperature for 1 h, then was warmed to RT and stirred for 16 additional hours. It was quenched by the addition of saturated ammonium chloride in water and extracted three times with DCM. The combined organics were dried over anhydrous sodium sulfatre, filtered, and concentrated. It was purified by silica gel chromatography (eluent: 5-30% EA/hexanes) to yield 55A.

[0557] Synthesis of 5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(3,5,6-trimethylpyridin-2-yl)imidazo[1,2-a]pyridine (55B): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 55A.



-continued





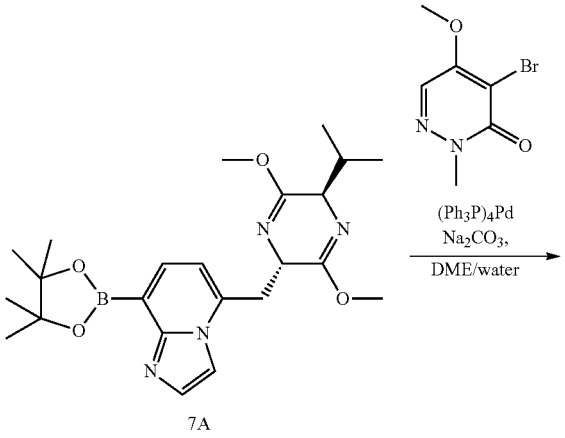
[0558] Synthesis of methyl (S)-2-amino-3-(8-(3,5,6-trimethylpyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (55C): The title compound was prepared according to the method presented for the synthesis of compound 53D starting with 55B.

[0559] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(3,5,6-trimethylpyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (55D): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 34C and 55C.

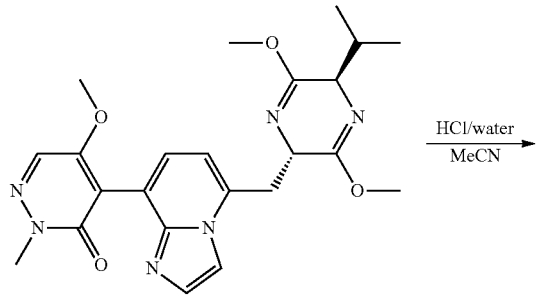
[0560] Synthesis of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(3,5,6-trimethylpyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (55): The title compound was prepared according to the method presented for the synthesis of compound 53 starting with 55D. MS (m/z) 590.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.80 (dd, J=8.2, 2.3 Hz, 1H), 8.58 (d, J=2.2 Hz, 1H), 8.21 (d, J=2.1 Hz, 1H), 7.93 (d, J=7.5 Hz, 1H), 7.73 (s, 1H), 7.35 (d, J=7.5 Hz, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.6 Hz, 2H), 5.05-4.87 (m, 1H), 4.28 (d, J=10.0 Hz, 1H), 3.73 (dd, J=15.4, 4.5 Hz, 1H), 3.55 (dd, J=15.4, 10.6 Hz, 1H), 2.48 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H), 1.75 (ddt, J=13.7, 7.4, 3.7 Hz, 1H), 1.50 (ddt, J=17.5, 14.2, 7.2 Hz, 1H), 0.89 (t, J=7.3 Hz, 3H).

Example 56

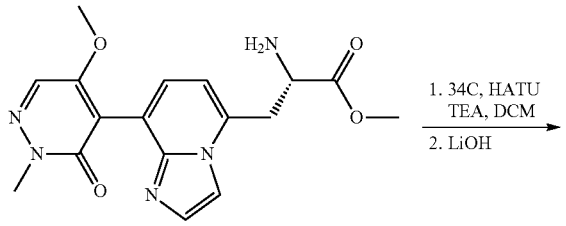
[0561]



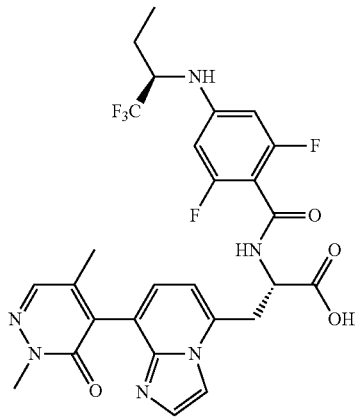
7A



56A



56B



56

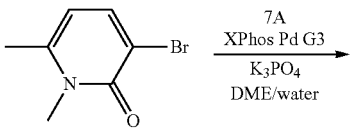
[0562] Synthesis of 4-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl) methyl)imidazo[1,2-a]pyridin-8-yl)-5-methoxy-2-methylpyridazin-3(2H)-one (55A): The title compound was prepared according to the method presented for the synthesis of compound 7B starting with 7A and 4-bromo-5-methoxy-2-methylpyridazin-3(2H)-one.

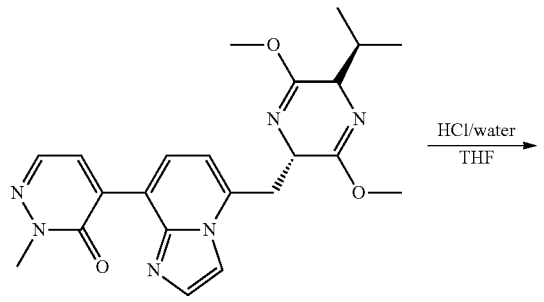
[0563] Synthesis of methyl (S)-2-amino-3-(8-(5-methoxy-2-methyl-3-oxo-2,3-dihydro pyridazin-4-yl)imidazo[1,2-a] pyridin-5-yl)propanoate (56B3): The title compound was prepared according to the method presented for the synthesis of compound 7C starting with 56A.

[0564] Synthesis (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(2,5-dimethyl-3-oxo-2,3-dihydropyridazin-4-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (56): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 56B. MS (m/z) 610.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 14.12 (s, 1H), 13.17 (s, 1H), 8.85 (d, J=8.1 Hz, 1H), 8.57 (s, 1H), 8.36 (d, J=22.4 Hz, 2H), 7.91 (s, 1H), 7.40 (d, J=7.7 Hz, 1H), 6.82 (d, J=9.4 Hz, 1H), 6.44 (d, J=11.7 Hz, 2H), 4.95 (d, J=11.0 Hz, 1H), 4.31 (s, 1H), 3.77-3.69 (m, 4H), 3.73 (s, 4H), 3.57 (dd, J=15.7, 10.3 Hz, 1H), 1.86-1.67 (m, OH), 1.52 (ddd, J=13.7, 10.3, 7.1 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).

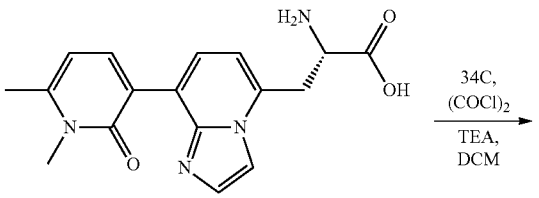
Example 57

[0565]



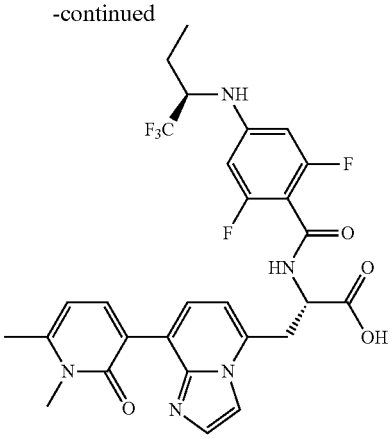


57A



57B

-continued



57

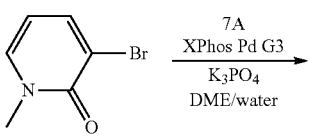
[0566] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-1,6-dimethylpyridin-2(1H)-one (57A): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 3-bromo-1,6-dimethylpyridin-2(1H)-one.

[0567] Synthesis of (S)-2-amino-3-(8-(1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (57B): To a solution of 57A (114 mg, 0.26 mmol) in tetrahydrofuran (5 mL) was added 1M hydrochloric acid (1.3 mL, 1.3 mmol), and the reaction was allowed to stir at room temperature for 3 days. It was concentrated and purified by silica gel chromatography (eluent methanol/DCM) to yield 57B.

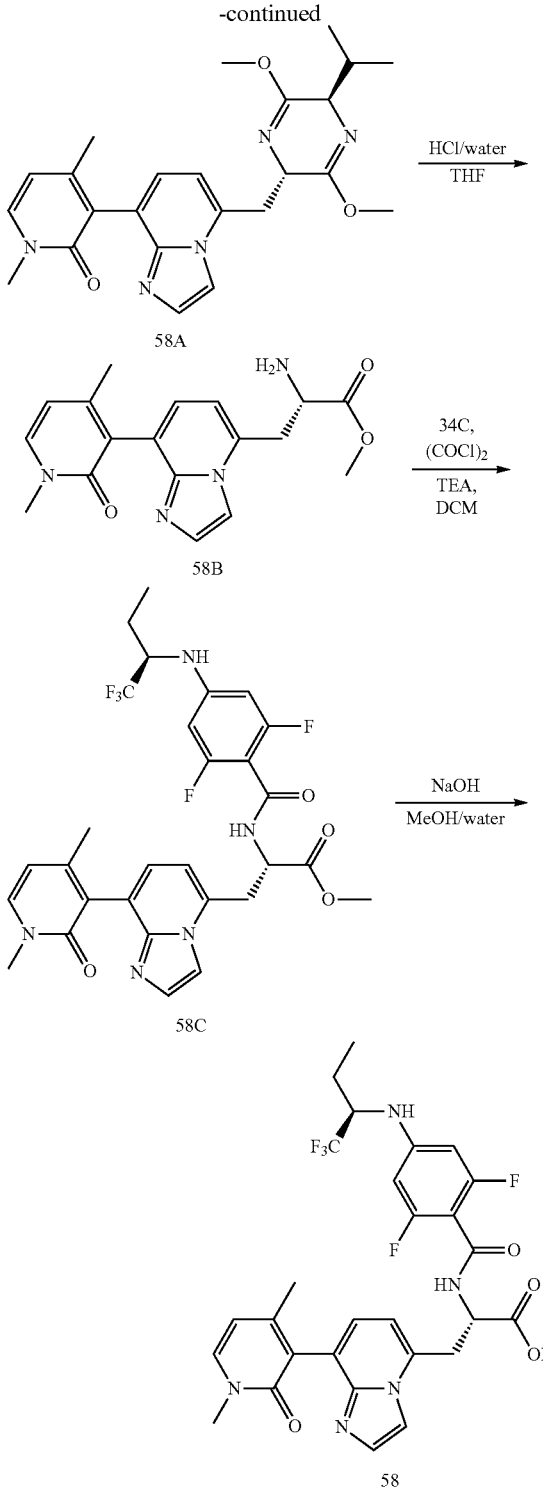
[0568] Synthesis of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (57): To a solution of 34C (50 mg, 0.2 mmol) in dichloromethane (1 mL) was added oxalyl chloride (31 mg, 0.22 mmol) and DMF (1 drop), and the reaction was allowed to stir for 1 hour. To this, 57B (53 mg, 0.08 mmol) and triethylamine (114 mg, 1.1 mmol) were added, and the reaction was stirred at room temperature for 1 hour. It was concentrated, diluted with DMSO, acidified with trifluoroacetic acid, and purified by preparatory HPLC to yield 57. MS (m/z) 592.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.14 (s, 1H), 8.82 (d, J=8.1 Hz, 1H), 8.54 (s, 1H), 8.28 (s, 1H), 7.87 (d, J=7.5 Hz, 1H), 7.64 (s, 1H), 7.32 (d, J=7.8 Hz, 1H), 6.80 (d, J=9.4 Hz, 1H), 6.53-6.32 (m, 3H), 4.93 (t, J=11.5 Hz, 1H), 4.29 (d, J=9.7 Hz, 1H), 3.71 (dd, J=15.6, 4.6 Hz, 1H), 3.54 (m, 4H), 1.83-1.68 (m, 1H), 2.49 (s, 3H), 1.75 (m, 1H), 1.50 (ddd, J=14.0, 10.5, 7.2 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).

Example 58

[0569]



-continued



58

[0570] Synthesis of 3-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-1,4-dimethylpyridin-2(1H)-one (58A): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 3-bromo-1,4-dimethylpyridin-2(1H)-one.

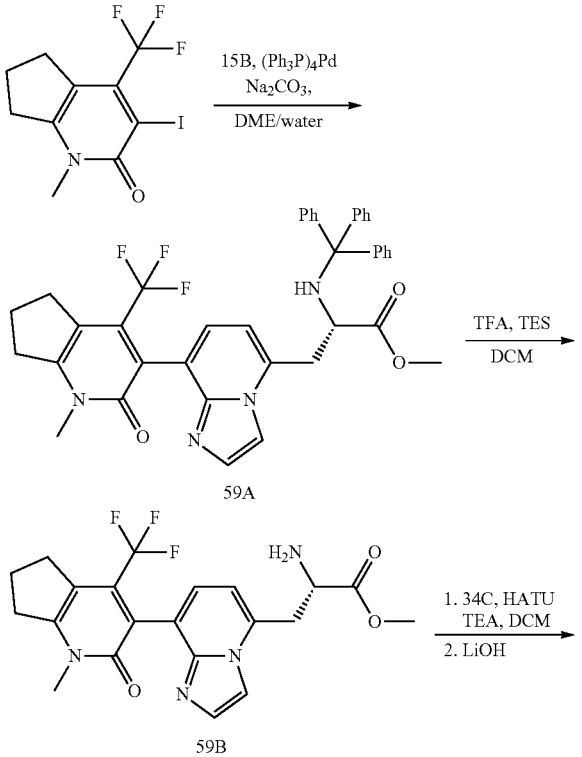
[0571] Synthesis of methyl (S)-2-amino-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (58B): The title compound was prepared according to the method presented for the synthesis of compound 53C starting with 58A.

[0572] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (58C): To a solution of 34C (50 mg, 0.2 mmol) in dichloromethane (1 mL) was added oxalyl chloride (31 mg, 0.22 mmol) and DMF (1 drop), and the reaction was allowed to stir for 1 hour. To this, 58B (53 mg, 0.08 mmol) and triethylamine (63 mg, 0.62 mmol) were added, and the reaction was stirred at room temperature for 1 hour. It was purified by silica gel chromatography (eluent: methanol/DCM) to yield 58C.

[0573] Synthesis of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,4-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (58): The title compound was prepared according to the method presented for the synthesis of compound 53 starting with 58C. MS (m/z) 592.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.82 (t, J=9.2 Hz, 1H), 8.54 (d, J=24.3 Hz, 1H), 8.28 (s, 1H), 7.81 (d, J=7.0 Hz, 1H), 6.79 (d, J=9.4 Hz, 1H), 6.41 (d, J=11.8 Hz, 2H), 6.32 (d, J=7.0 Hz, 1H), 4.97 (s, 1H), 4.29 (s, 1H), 3.6 (m, 1H), 3.72 (s, 1H), 3.45 (s, 3H), 1.95 (d, J=6.5 Hz, 3H), 1.75 (s, 1H), 1.59-1.40 (m, 1H), 0.89 (t, J=7.3 Hz, 3H).

Example 59

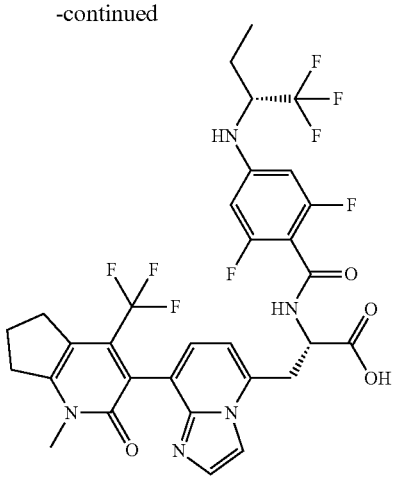
[0574]



59A

59B

-continued



59

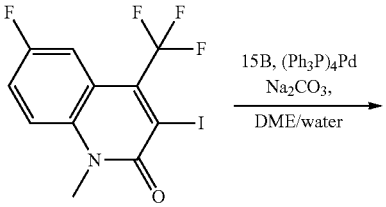
[0575] Synthesis of methyl (S)-3-(8-(1-methyl-2-oxo-4-(trifluoromethyl)-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (59A): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 3-iodo-1-methyl-4-(trifluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridin-2-one.

[0576] Synthesis of methyl (S)-2-amino-3-(8-(1-methyl-2-oxo-4-(trifluoromethyl)-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (59B): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 59A.

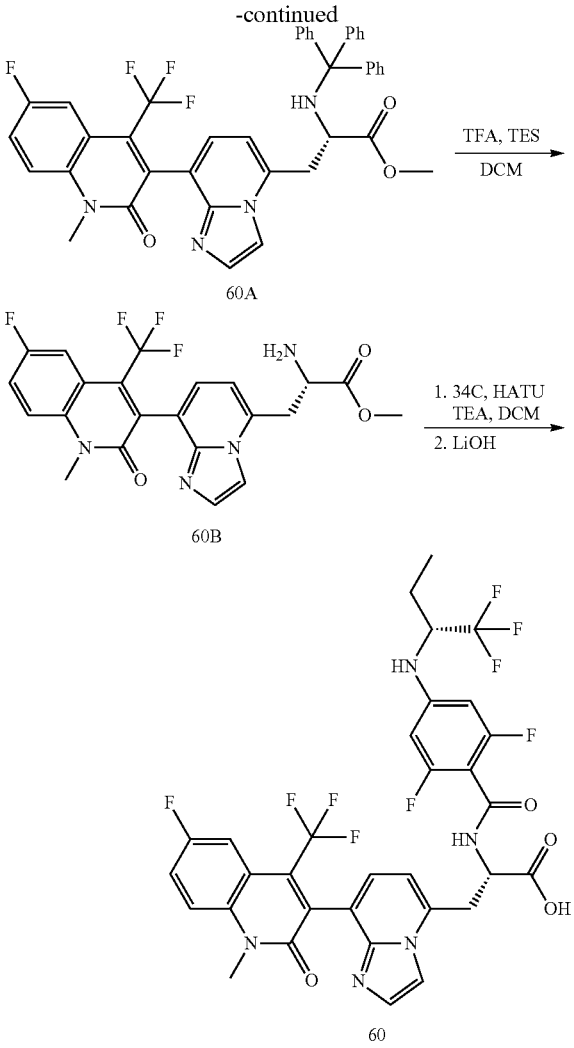
[0577] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-4-(trifluoromethyl)-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl) imidazo[1,2-a]pyridin-5-yl)propanoic acid (59): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 59B and 34C. MS (m/z) 674.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.13 (s, 1H), 8.83 (dd, J=12.7, 8.1 Hz, 1H), 8.53 (s, 1H), 8.21-8.39 (m, 1H), 7.70 (s, 1H), 7.38 (s, 1H), 6.79 (d, J=9.3 Hz, 1H), 6.43 (d, J=11.8 Hz, 2H), 4.93-5.03 (M, 1H) 4.30 (d, J=10.0 Hz, 1H), 3.72 (d, J=15.4 Hz, 1H), 3.51 (s, 2H), 3.15 (t, J=7.9 Hz, 2H), 2.96 (d, J=11.3 Hz, 2H), 2.17 (s, 2H), 1.86-1.65 (m, OH), 1.65-1.38 (m, 1H), 0.92 (t, J=7.3 Hz, 3H).

Example 60

[0578]



-continued



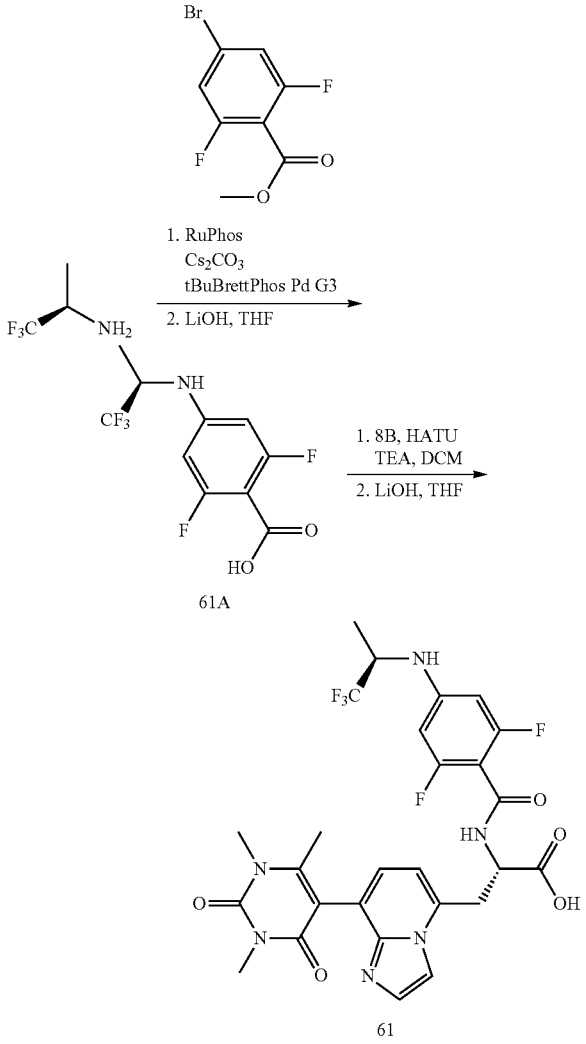
[0579] Synthesis of methyl (S)-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (60A): The title compound was prepared according to the method presented for the synthesis of compound 15C starting with 15B and 6-fluoro-3-iodo-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one.

[0580] Synthesis of methyl (S)-2-amino-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (60B): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 60A.

[0581] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(6-fluoro-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (60): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 60B and 34C. MS (m/z) 714.2 [M+H]+. 1H NMR (400 MHz, D6-DMSO) δ 13.39-12.87 (m, 1H), 8.78 (dd, J=10.3, 8.1 Hz, 1H), 8.58-8.37 (d, 1H), 8.31-8.10 (m, 1H), 7.84 (dd, J=9.6, 5.0 Hz, 1H), 7.78 (ddd, J=9.6, 7.6, 2.8 Hz, 1H), 7.60 (dq, J=10.1, 2.5 Hz, 1H), 7.33 (dd, J=26.7, 7.3 Hz, 1H), 6.73 (d, J=9.4 Hz, 1H), 6.37 (d, J=11.8 Hz, 2H), 5.01-4.86 (m, 1H), 4.34-4.15 (m, 1H), 3.67 (d, J=2.1 Hz, 3H), 3.60-3.55 (m, 1H), 3.49 (dd, J=15.8, 11.3 Hz, 1H), 1.70 (dtd, J=14.4, 7.2, 6.7, 2.9 Hz, 1H), 1.54-1.37 (m, 1H), 0.94-0.75 (t, 3H).

Example 61

[0582]



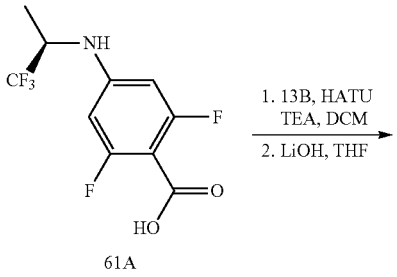
[0583] Synthesis of (R)-2,6-difluoro-4-((1,1,1-trifluoropropan-2-yl)amino)benzoic acid (61A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with (R)-1,1,1-trifluoropropan-2-amine.

[0584] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (61): The title compound was prepared according to the method presented for the synthesis of compound 8 starting with 8B and 61A. MS (m/z) 609.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.80 (t, J=8.2 Hz, 1H), 8.57 (d, J=29.0 Hz, 1H), 8.32 (d, J=14.1 Hz, 1H), 7.73 (s, 1H), 7.50-7.27 (m, 1H), 6.87 (d,

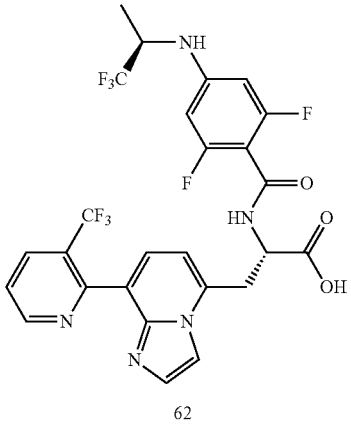
J=9.2 Hz, 1H), 6.45-6.32 (m, 2H), 5.03-4.88 (m, 1H), 4.49 (d, J=7.9 Hz, 1H), 3.78-3.64 (m, 1H), 3.46 (d, J=1.3 Hz, 3H), 3.23 (s, 3H), 2.06 (d, J=5.1 Hz, 3H), 1.25 (d, J=6.7 Hz, 3H), 1.05 (s, 3H).

Example 62

[0585] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(3-(trifluoromethyl)pyridin-2-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (62): The title compound was prepared according to the method presented for the synthesis of compound 13 starting with 13B and 61A. MS (m/z) 602.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J=4.8 Hz, 1H), 8.82 (d, J=8.2 Hz, 1H), 8.50 (m, 1H), 8.43 (d, J=8.1 Hz, 1H), 7.91-7.73 (m, 1H), 7.30 (m, 1H), 6.86 (d, J=9.2 Hz, 1H), 6.39 (d, J=11.5 Hz, 2H), 4.98 (s, 1H), 4.63-4.37 (m, 1H), 3.69 (m, 1H), 3.54 (m, 1H), 1.25 (d, J=6.7 Hz, 3H).



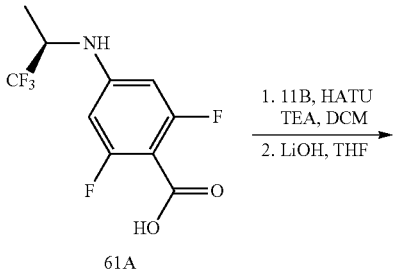
61A



62

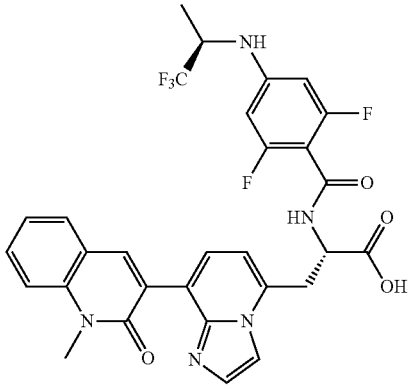
Example 63

[0586]



61A

-continued

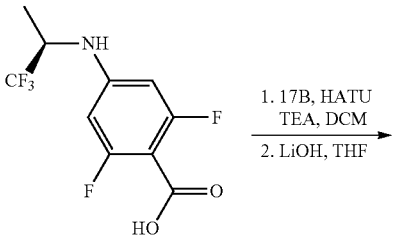


63

[0587] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (63): The title compound was prepared according to the method presented for the synthesis of compound 11 starting with 11B and 61A. MS (m/z) 613.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J=8.0 Hz, 1H), 8.58 (d, J=2.2 Hz, 1H), 8.33 (d, J=2.1 Hz, 1H), 8.25 (s, 1H), 7.99 (d, J=7.5 Hz, 1H), 7.86 (dd, J=7.9, 1.5 Hz, 1H), 7.75 (ddd, J=8.6, 7.1, 1.5 Hz, 1H), 7.66 (d, J=8.5 Hz, 1H), 7.45-7.33 (m, 2H), 6.89 (d, J=9.2 Hz, 1H), 6.42 (d, J=11.5 Hz, 2H), 4.97 (ddd, J=10.4, 8.0, 4.4 Hz, 1H), 4.50 (q, J=7.4 Hz, 1H), 3.72 (s, 4H), 3.57 (dd, J=15.8, 10.4 Hz, 1H), 1.26 (d, J=6.7 Hz, 3H).

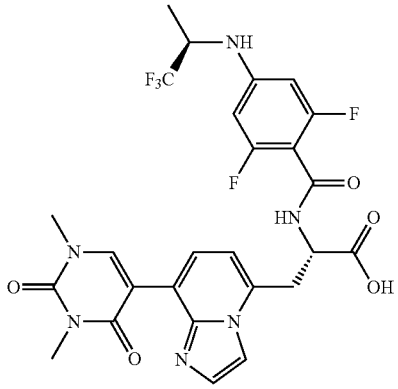
Example 64

[0588] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (64): The title compound was prepared according to the method presented for the synthesis of compound 17 starting with 17B and 61A. MS (m/z) 595.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J=8.0 Hz, 1H), 8.54 (d, J=2.2 Hz, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.85 (dd, J=7.5, 1.1 Hz, 1H), 7.34 (d, J=7.6 Hz, 1H), 6.89 (d, J=9.2 Hz, 1H), 6.41 (d, J=11.5 Hz, 2H), 4.93 (ddd, J=9.6, 7.6, 4.2 Hz, 1H), 4.49 (dq, J=14.6, 7.0 Hz, 1H), 3.70 (dd, J=15.6, 4.5 Hz, 1H), 3.60-3.48 (m, 1H), 3.41 (s, 3H), 3.26 (s, 3H), 1.25 (d, J=6.7 Hz, 3H).



61A

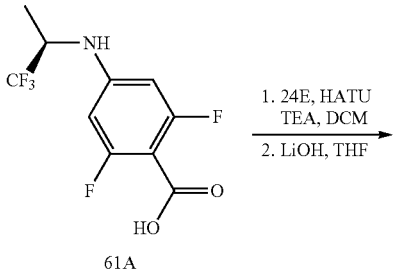
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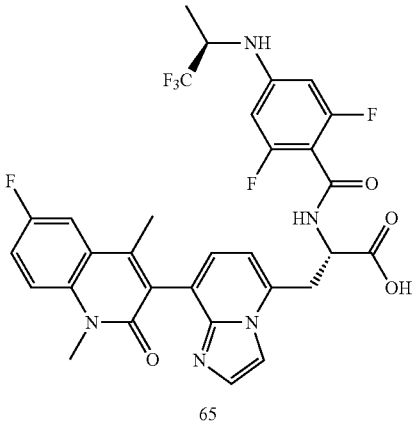
64

Example 65

[0589]



61A

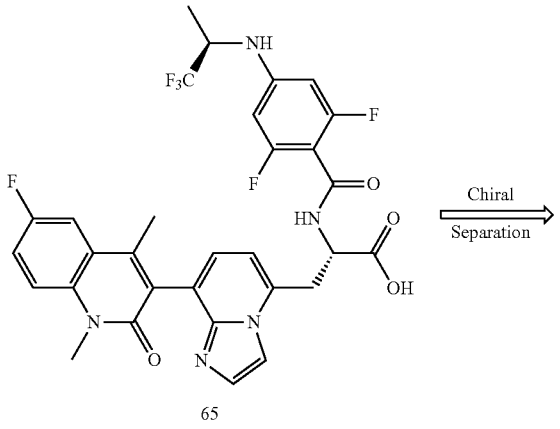


65

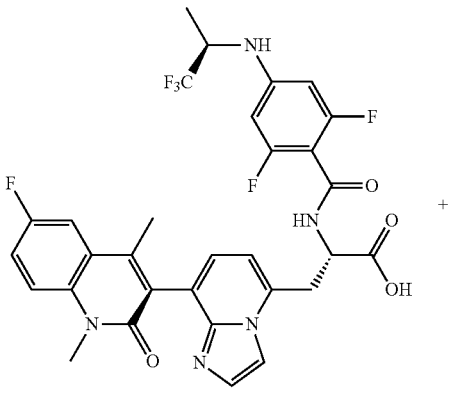
[0590] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (65): The title compound was prepared according to the method presented for the synthesis of compound 17 starting with 24E and 61A. MS (m/z) 645.6 $[M+H]^+$. 1 H NMR (400 MHz, DMSO-d6) δ 8.84 (dd, J=8.1, 4.9 Hz, 1H), 8.59 (dd, J=28.6, 2.2 Hz, 1H), 8.30 (dd, J=14.3, 2.2 Hz, 1H), 7.87-7.76 (m, 2H), 7.71 (dd, J=9.4, 4.9 Hz, 1H), 7.65 (ddd, J=9.3, 7.9, 2.8 Hz, 1H), 7.54-7.29 (m, 1H), 6.89 (d, J=9.2 Hz, 1H), 6.40 (dd, J=11.5, 2.1 Hz, 2H), 5.16-4.82 (m, 1H), 4.49 (h, J=7.0 Hz, 1H), 3.77 (td, J=15.9, 4.5 Hz, 1H), 3.67 (d, J=1.1 Hz, 3H), 3.58-3.44 (m, 1H), 2.28-2.14 (m, 3H), 1.26 (dd, J=6.8, 1.4 Hz, 3H).

Examples 66 and 67

[0591] Preparation of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino) benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoic acid (66): 65 was separated into its 2 diastereomeric atropisomers by supercritical fluid chromatography using 60% MeOH/TEA co-solvent, at a flow rate of 50 mL/min, using an Chiralpak IE 5 μm 21×250 mm column. The title compound was identified as the second eluting peak. MS (m/z) 646.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.18 (s, 1H), 8.84 (dd, J=8.3, 3.8 Hz, 1H), 8.58 (d, J=28.3 Hz, 1H), 8.29 (d, J=14.7 Hz, 1H), 7.81 (ddd, J=9.4, 5.5, 2.8 Hz, 1H), 7.76-7.59 (m, 2H), 7.43 (dd, J=44.0, 7.4 Hz, 1H), 6.88 (d, J=9.1 Hz, 1H), 6.44-6.31 (m, 2H), 5.07-4.90 (m, 1H), 4.49 (q, J=7.2 Hz, 1H), 3.84-3.70 (m, 1H), 3.67 (d, J=1.1 Hz, 3H), 3.65-3.45 (m, 1H), 2.22 (d, J=7.5 Hz, 3H), 1.26 (d, J=6.6 Hz, 3H).

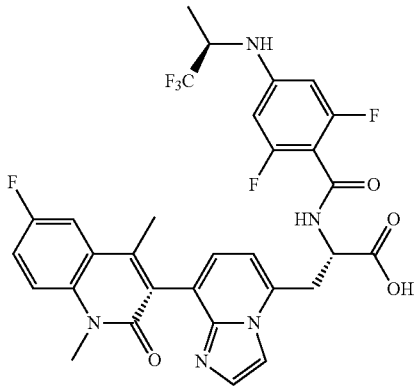


65



66

-continued

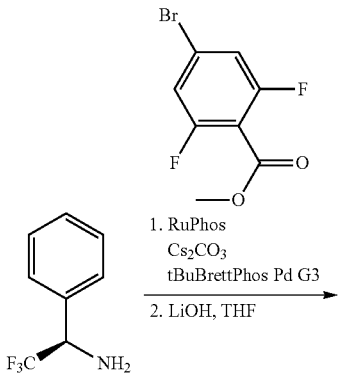


67

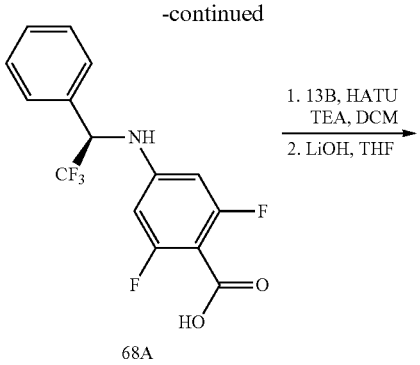
[0592] Preparation of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino) benzamido)-3-(8-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)imidazo[1,2-a] pyridin-5-yl)propanoic acid (67): 65 was separated into its 2 diastereomeric atropisomers by supercritical fluid chromatography using 60% MeOH/TEA co-solvent, at a flow rate of 50 mL/min, using an Chiralpak IE 5 μm 21×250 mm column. The title compound was identified as the first eluting peak. MS (m/z) 646.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (dd, J=8.2, 4.2 Hz, 1H), 8.59 (dd, J=29.0, 2.2 Hz, 1H), 8.36-8.21 (m, 1H), 7.87-7.77 (m, 2H), 7.75-7.60 (m, 2H), 7.43 (dd, J=47.2, 7.5 Hz, 1H), 6.88 (d, J=9.2 Hz, 1H), 6.40 (dd, J=11.5, 1.8 Hz, 2H), 4.99 (dtt, J=15.0, 9.9, 4.6 Hz, 1H), 4.50 (dq, J=14.5, 7.2 Hz, 1H), 3.76 (td, J=16.0, 4.5 Hz, 1H), 3.67 (d, J=1.3 Hz, 3H), 3.64-3.46 (m, 1H), 2.23 (d, J=5.8 Hz, 3H), 1.34-1.18 (m, 3H).

Example 68

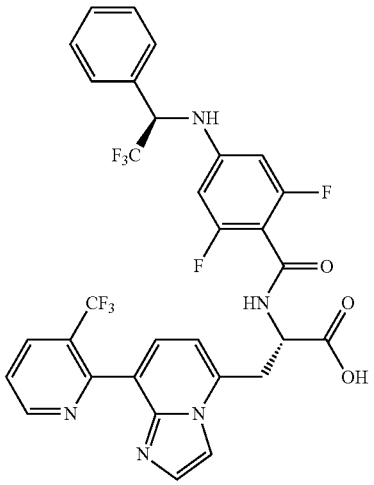
[0593]



-continued



68A



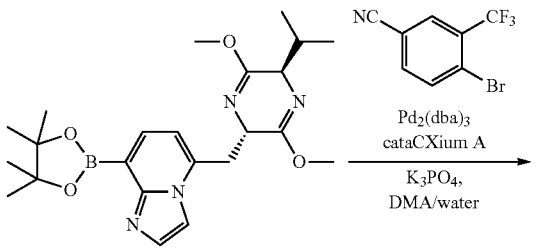
68

[0594] Synthesis of (R)-2,6-difluoro-4-((2,2,2-trifluoro-1-phenylethyl)amino)benzoic acid (68A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with (R)-2,2,2-trifluoro-1-phenylethan-1-amine.

[0595] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (68): The title compound was prepared according to the method presented for the synthesis of compound 13 starting with 13B and 68A. MS (m/z) 664.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.99 (d, J=4.8 Hz, 1H), 8.83 (d, J=8.2 Hz, 1H), 8.55 (s, 1H), 8.45 (d, J=8.1 Hz, 1H), 7.91-7.76 (m, 1H), 7.55 (d, J=7.0 Hz, 4H), 7.46-7.19 (m, 3H), 6.52 (d, J=11.4 Hz, 2H), 5.69 (t, J=8.9 Hz, 1H), 4.98 (d, J=12.4 Hz, 1H), 3.72 (m, 1H), 3.62-3.44 (m, 1H).

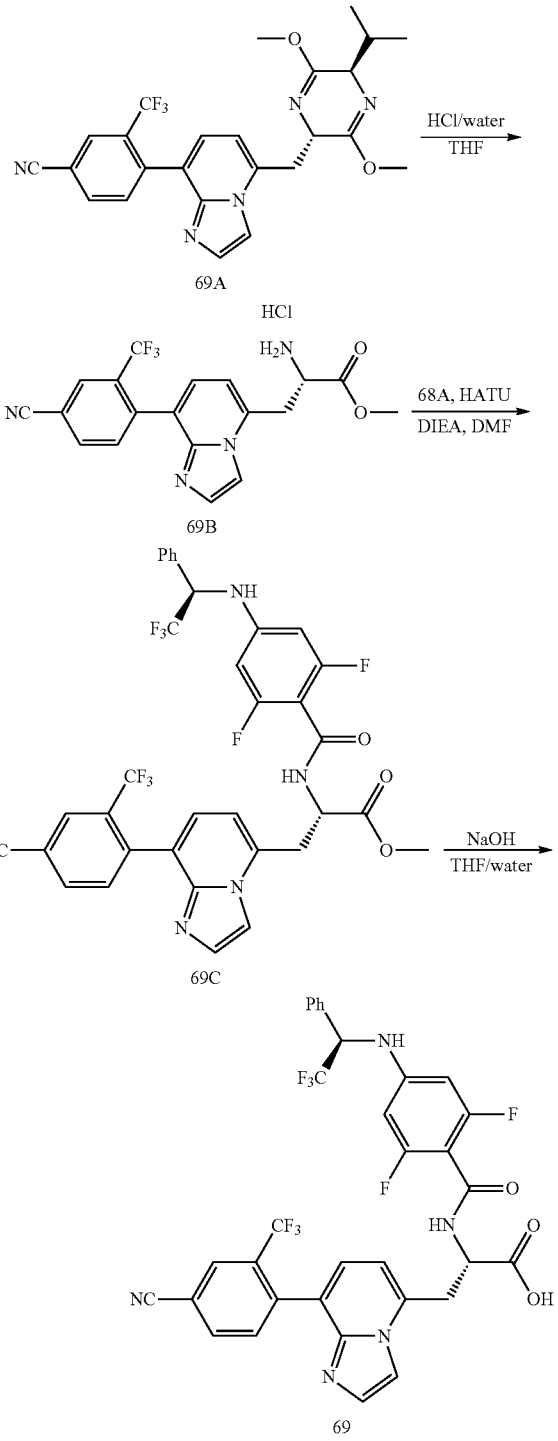
Example 69

[0596]



7A

-continued



[0597] Synthesis of 4-(5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridin-8-yl)-3-(trifluoromethyl)benzonitrile (69A): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 4-bromo-3-(trifluoromethyl)benzonitrile and substituting 2:1 cataCXium A/$Pd_2(dba)_3$ for XPhos Pd G3.

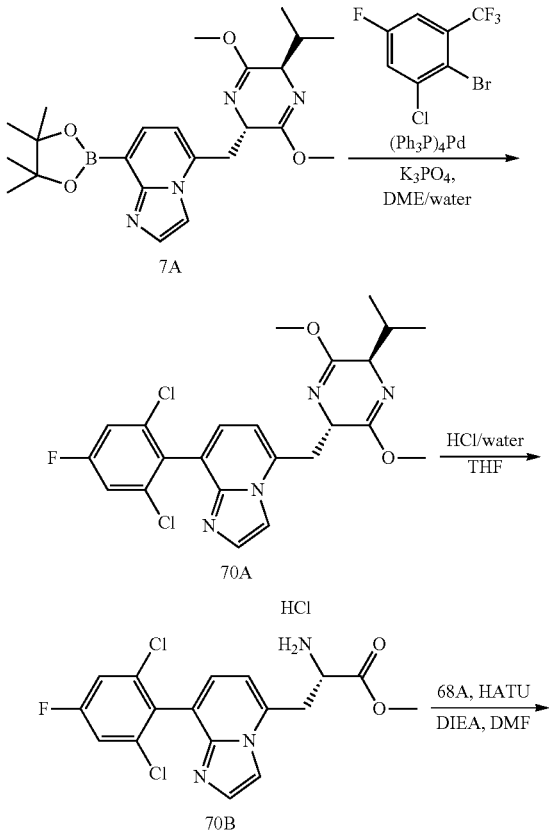
[0598] Synthesis of methyl (S)-2-amino-3-(8-(4-cyano-2-(trifluoromethyl)phenyl) imidazo[1,2-a]pyridin-5-yl)propanoate (69B): The title compound was prepared according to the method presented for the synthesis of compound 53C starting with 69A.

[0599] Synthesis of methyl (S)-3-(8-(4-cyano-2-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)propanoate (69C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 68A and 69B.

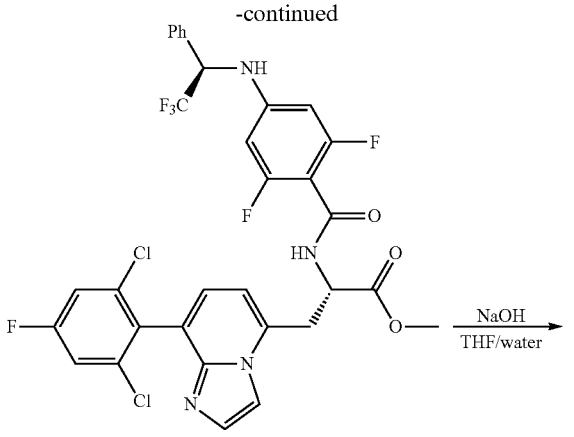
[0600] (S)-3-(8-(4-Cyano-2-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)propanoic acid (69): The title compound was prepared according to the method presented for the synthesis of compound 53 starting with 69C. MS (m/z) 688.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J=8.3 Hz, 1H), 8.55 (d, J=1.5 Hz, 1H), 8.49 (s, 1H), 8.33 (d, J=8.1 Hz, 1H), 8.14 (s, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.68 (s, 1H), 7.54 (t, J=6.7 Hz, 3H), 7.48-7.32 (m, 3H), 7.27 (s, 1H), 6.52 (d, J=11.4 Hz, 2H), 5.78-5.60 (m, 1H), 5.06-4.90 (m, 1H), 3.75-3.63 (m, 1H).

Example 70

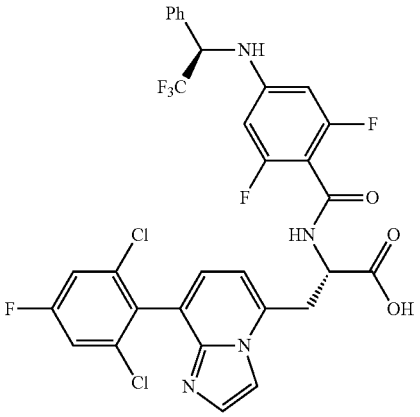
[0601]



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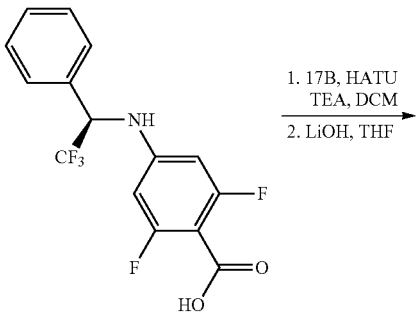
70C



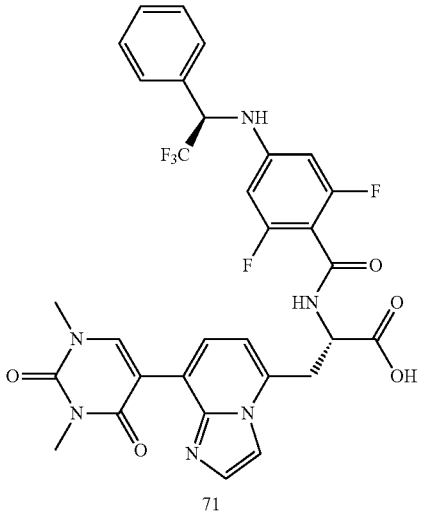
70

Example 71

[0606]



68A



71

[0602] Synthesis of 8-(2,6-dichloro-4-fluorophenyl)-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)imidazo[1,2-a]pyridine (70A): The title compound was prepared according to the method presented for the synthesis of compound 53B starting with 7A and 4-2-bromo-1,3-dichloro-5-fluorobenzene and substituting tetrakis(triphenylphosphine)palladium(0) for XPhos Pd G3.

[0603] Synthesis of methyl (S)-2-amino-3-(8-(2,6-dichloro-4-fluorophenyl)imidazo[1,2-a]pyridin-5-yl)propanoate (70B): The title compound was prepared according to the method presented for the synthesis of compound 53C starting with 70A.

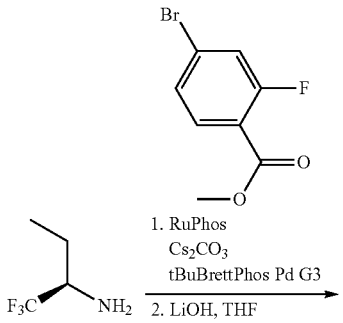
[0604] Synthesis of methyl (S)-3-(8-(2,6-dichloro-4-fluorophenyl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)propanoate (70C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 68A and 70B.

[0605] (S)-3-(8-(2,6-dichloro-4-fluorophenyl)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)propanoic acid (70): The title compound was prepared according to the method presented for the synthesis of compound 53 starting with 70C. MS (m/z) 681.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J=8.3 Hz, 1H), 8.60 (s, 1H), 8.29 (s, 1H), 7.96-7.68 (m, 3H), 7.60-7.47 (m, 3H), 7.47-7.26 (m, 3H), 6.50 (d, J=11.4 Hz, 2H), 5.67 (q, J=8.5 Hz, 1H), 5.16-4.86 (m, 1H), 3.74 (dd, J=15.6, 4.6 Hz, 1H), 3.64-3.47 (m, 1H).

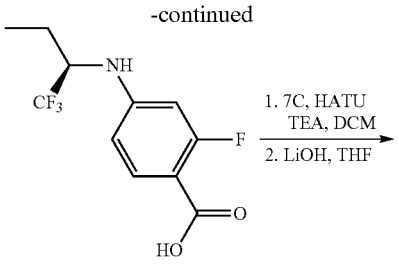
[0607] (S)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)-3-(8-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (71): The title compound was prepared according to the method presented for the synthesis of compound 17 starting with 17B and 68A. MS (m/z) 657.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J=8.0 Hz, 1H), 8.52 (s, 1H), 8.30 (s, 1H), 7.83 (d, J=7.5 Hz, 1H), 7.64-7.47 (m, 3H), 7.48-7.18 (m, 4H), 6.53 (d, J=11.6 Hz, 2H), 5.68 (p, J=8.6 Hz, 1H), 4.91 (ddd, J=10.5, 8.1, 4.5 Hz, 1H), 3.68 (dd, J=15.9, 4.5 Hz, 1H), 3.55 (m, 1H), 3.41 (s, 3H), 3.26 (s, 3H).

Example 72

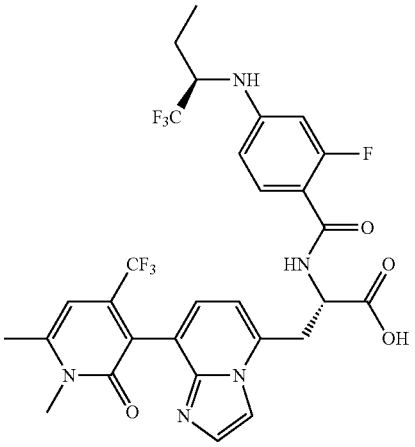
[0608]



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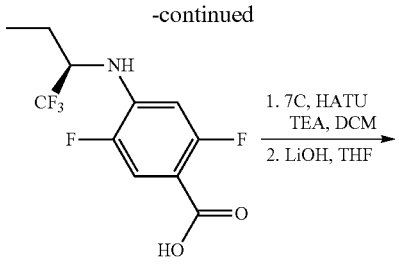


72A

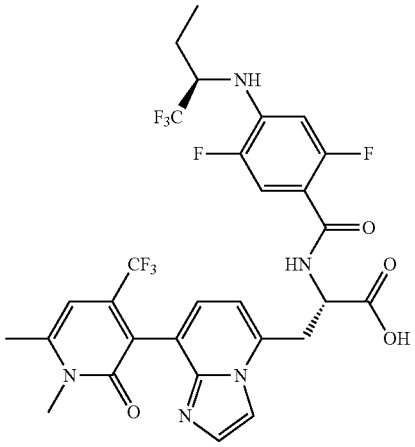


72

-continued



73A



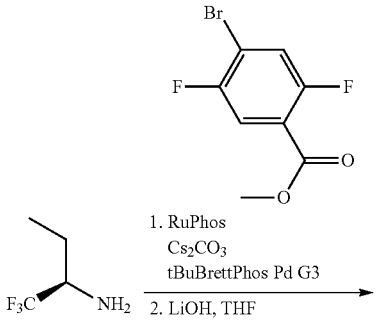
73

[0609] Synthesis of (R)-2-fluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid (72A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with methyl 4-bromo-2-fluorobenzoate and (R)-1,1,1-trifluorobutan-2-amine.

[0610] (S)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(2-fluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido) propanoic acid (72): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 7C and 72A. MS (m/z) 648.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 8.61 (dd, J=12.2, 2.1 Hz, 1H), 8.37-8.27 (m, 1H), 8.13 (dt, J=17.4, 6.9 Hz, 1H), 7.69 (dd, J=17.0, 7.4 Hz, 1H), 7.44-7.22 (m, 2H), 6.76 (d, J=8.7 Hz, 1H), 6.61-6.52 (m, 2H), 5.05-4.86 (m, 1H), 4.27 (d, J=8.9 Hz, 1H), 3.82-3.54 (m, 2H), 3.44 (t, J=1.5 Hz, 2H), 3.25-3.15 (m, 3H), 2.08-1.97 (m, 3H), 1.76 (ddd, J=13.7, 7.2, 3.2 Hz, 1H), 1.54 (ddt, J=17.6, 14.4, 7.3 Hz, 1H), 0.91 (t, J=7.3 Hz, 3H).

Example 73

[0611]

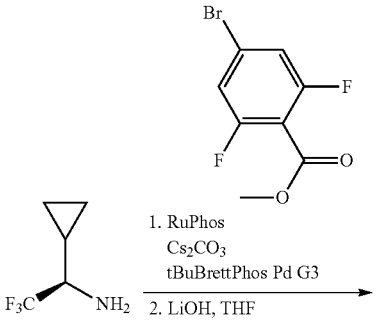


[0612] Synthesis of (R)-2,5-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid (73A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with methyl 4-bromo-2,5-difluorobenzoate and (R)-1,1,1-trifluorobutan-2-amine.

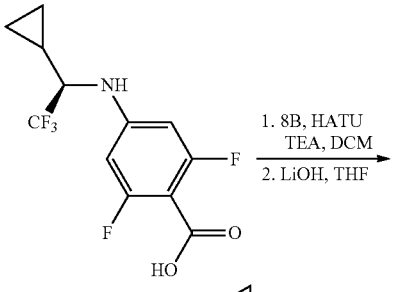
[0613] (S)-2-(2,5-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (73): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 7C and 73A. MS (m/z) 623.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.65-8.59 (m, 1H), 8.37-8.24 (m, 2H), 7.75-7.68 (m, 1H), 7.43-7.32 (m, 1H), 7.27-7.12 (m, 1H), 6.98-6.89 (m, 1H), 6.68-6.60 (m, 1H), 5.04-4.94 (m, 1H), 4.45-4.32 (m, 1H), 3.84-3.58 (m, 2H), 3.49-3.42 (m, 3H), 3.27-3.19 (m, 3H), 2.10-2.01 (m, 3H), 1.86-1.67 (m, 2H), 0.91 (t, J=7.3 Hz, 3H).

Example 74

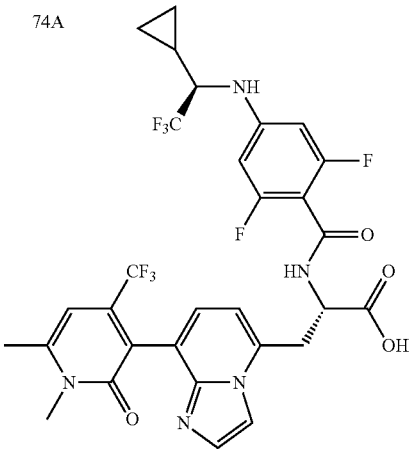
[0614]



-continued



74A



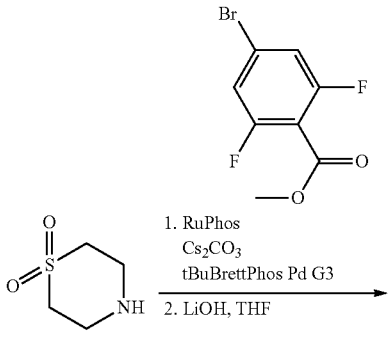
74

[0615] Synthesis of (R)-4-((1-cyclopropyl-2,2,2-trifluoroethyl)amino)-2,6-difluorobenzoic acid (74A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with (R)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine.

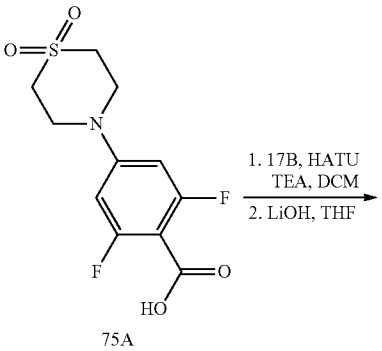
[0616] (S)-2-(4-(((R)-1-cyclopropyl-2,2,2-trifluoroethyl)amino)-2,6-difluorobenzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (74): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 7B and 74A. MS (m/z) 672.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.18-13.10 (m, 1H), 8.82 (dd, J=14.0, 8.1 Hz, 1H), 8.67-8.48 (m, 1H), 8.42-8.25 (m, 1H), 7.82-7.64 (m, 1H), 7.49-7.28 (m, 1H), 6.95 (d, J=9.5 Hz, 1H), 6.72 (s, 1H), 6.40 (d, J=11.7 Hz, 2H), 5.06-4.94 (m, 1H), 3.99-3.87 (m, 1H), 3.79-3.69 (m, 1H), 3.66-3.56 (m, 1H), 3.56-3.51 (m, 3H), 2.59 (s, 3H), 1.12-0.98 (m, 1H), 0.67-0.56 (m, 1H), 0.56-0.43 (m, 2H), 0.34-0.23 (m, 1H).

Example 75

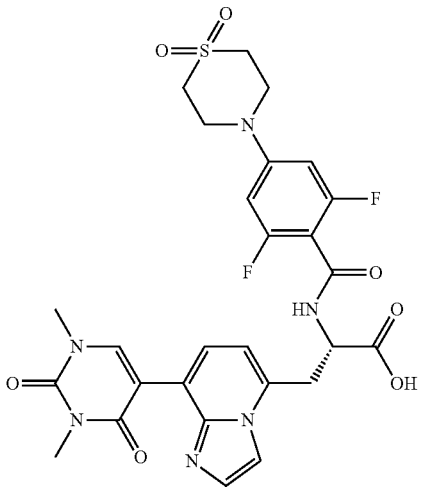
[0617]



-continued



75A



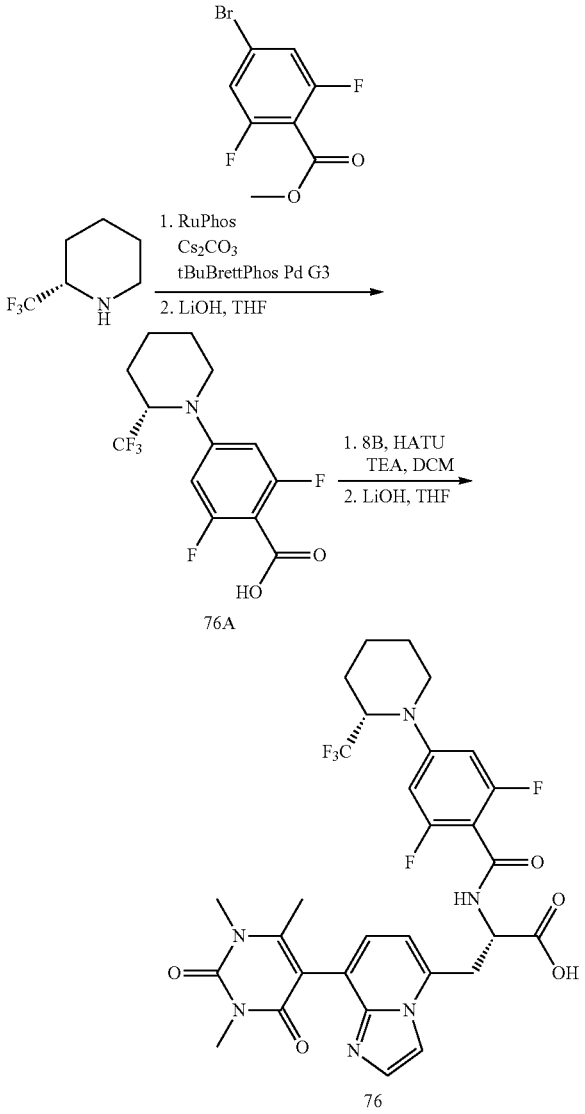
75

[0618] Synthesis of 4-(1,1-dioxidothiomorpholino)-2,6-difluorobenzoic acid (75A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting with thiomorpholine 1,1-dioxide.

[0619] (S)-3-(8-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl)-2-(4-(1,1-dioxidothiomorpholino)-2,6-difluorobenzamido)propanoic acid (75): The title compound was prepared according to the method presented for the synthesis of compound 17 starting with 17B and 75A. MS (m/z) 617.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.92 (d, J=8.0 Hz, 1H), 8.54 (s, 1H), 8.27 (d, J=35.0 Hz, 2H), 7.84 (d, J=7.5 Hz, 1H), 7.34 (d, J=7.7 Hz, 1H), 6.75 (d, J=11.8 Hz, 2H), 5.01-4.88 (m, 1H), 3.84 (d, J=5.8 Hz, 4H), 3.71 (dd, J=15.7, 4.4 Hz, 1H), 3.42 (s, 3H), 3.26 (s, 3H), 3.06 (t, J=4.9 Hz, 4H).

Example 76

[0620]

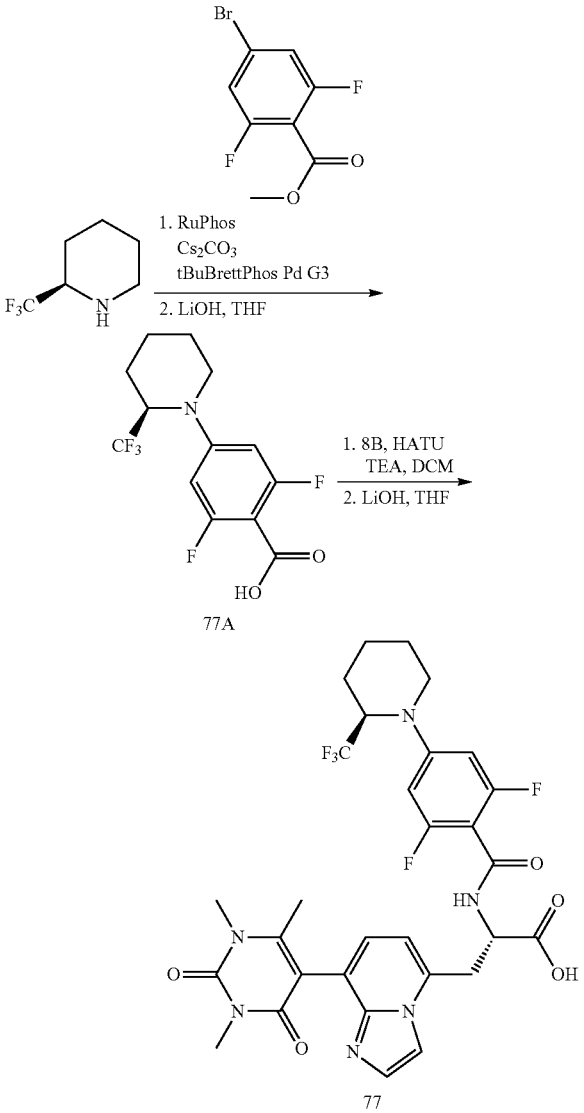


[0621] Synthesis of (S)-2,6-difluoro-4-(2-(trifluoromethyl)piperidin-1-yl)benzoic acid (76A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting (S)-2-(trifluoromethyl) piperidine.

[0622] (S)-2-(2,6-difluoro-4-((S)-2-(trifluoromethyl)piperidin-1-yl)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (76): The title compound was prepared according to the method presented for the synthesis of compound 8 starting with 8B and 76A. MS (m/z) 648.7 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 14.34 (s, 1H), 13.21 (s, 1H), 8.93 (t, J=8.9 Hz, 1H), 8.60 (dd, 1H), 8.36 (dd, J=13.0, 2.2 Hz, 1H), 7.81-7.72 (m, 1H), 7.49-7.31 (m, 1H), 6.72 (dd, J=12.1, 2.6 Hz, 2H), 5.06-4.86 (m, 2H), 3.75 (td, J=15.4, 4.5 Hz, 1H), 3.66-3.50 (m, 2H), 3.47 (d, J=1.8 Hz, 3H), 3.24 (s, 3H), 3.00 (t, J=12.3 Hz, 1H), 2.11-2.04 (m, 3H), 1.96 (d, J=14.7 Hz, 1H), 1.85-1.41 (m, 5H).

Example 77

[0623]



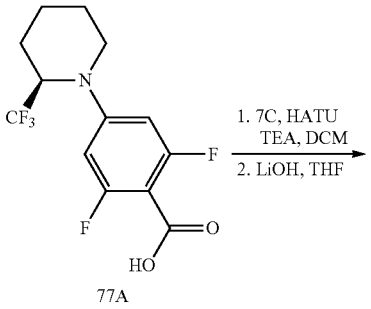
[0624] Synthesis of (R)-2,6-difluoro-4-(2-(trifluoromethyl)piperidin-1-yl)benzoic acid (77A): The title compound was prepared according to the method presented for the synthesis of compound 5A starting (R)-2-(trifluoromethyl) piperidine.

[0625] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imidazo[1,2-a]pyridin-5-yl) propanoic acid (77): The title compound was prepared according to the method presented for the synthesis of compound 8 starting with 8B and 77A. MS (m/z) 650.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 14.40 (s, 1H), 13.22 (s, 1H), 8.93 (t, J=9.8, 8.2 Hz, 1H), 8.60 (dd, 1H), 8.35

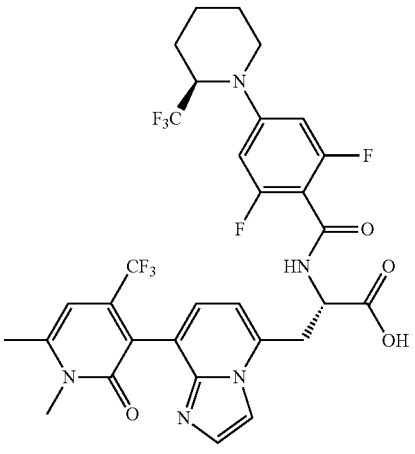
(dd, J=13.7, 2.1 Hz, 1H), 7.82-7.70 (m, 1H), 7.50-7.31 (m, 1H), 6.72 (dd, J=12.1, 2.6 Hz, 2H), 5.07-4.84 (m, 1H), 3.75 (td, J=15.2, 4.6 Hz, 1H), 3.68-3.49 (m, 2H), 3.47 (s, 3H), 3.24 (s, 3H), 3.00 (t, J=12.2 Hz, 1H), 2.12-2.03 (m, 3H), 1.96 (d, J=14.5 Hz, 1H), 1.86-1.40 (m, 5H).

Example 78

[0626] (S)-2-(2,6-difluoro-4-((R)-2-(trifluoromethyl)piperidin-1-yl)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (78): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 7C and 77A. MS (m/z) 686.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.93 (dd, J=14.6, 8.1 Hz, 1H), 8.65-8.47 (m, 1H), 8.39-8.18 (m, 1H), 7.81-7.62 (m, 1H), 7.47-7.26 (m, 1H), 6.77-6.66 (m, 3H), 5.08-4.87 (m, 2H), 3.82-3.68 (m, 1H), 3.66-3.56 (m, 2H), 3.55-3.45 (m, 3H), 3.01 (t, J=12.3 Hz, 1H), 2.59 (s, 3H), 2.02-1.90 (m, 1H), 1.85-1.66 (m, 2H), 1.66-1.42 (m, 3H).



77A



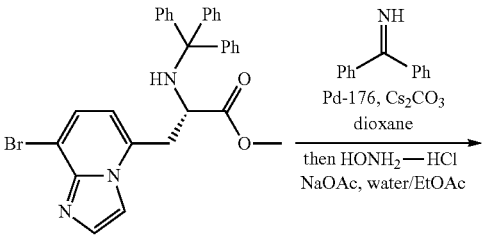
78

Example 79

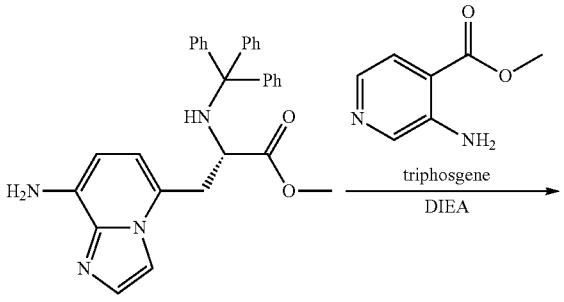
[0627] Synthesis of methyl (S)-3-(8-aminoimidazo[1,2-a]pyridin-5-yl)-2-(tritylamino) propanoate (79A): To a stirred solution of 15A (3.461 g, 6.4 mmol), benzophenone imine (1.29 mL, 1.393 g, 7.69 mmol), and cesium carbonate (4.137 g, 13 mmol) in dioxane (24 mL) was added allyl[(R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene]palladium(II) chloride (195 mg, 0.324 mmol) and it was alternatively evacuated and purged with nitrogen three times. The mixture was heated at 90° C. for 3 h, diluted with ethyl acetate (25 mL) and water (25 mL) and hydroxylamine hydrochloride (0.89 g, 13 mmol) and sodium acetate trihydrate (2.6 g, 19 mmol) were added and left to stir for an additional 4 h. The organic layer was decanted and solvents were evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with methanol in dichloromethane to afford 79A.

[0628] Synthesis of methyl (S)-3-(3-(5-(3-methoxy-3-oxo-2-(tritylamino)propyl)imidazo[1,2-a]pyridin-8-yl) ureido)isonicotinate (79B): To a stirred solution of methyl 3-aminoisonicotinate (205 mg, 0.43 mmol), diisopropyl ethylamine (0.18 mL, 1 mmol), in THF (5 mL) was added triphosgene (52 mg, 0.172 mmol) and let stir for 2 h. 79A (110 mg, 0.721 mmol) was added and the mixture was stirred an additional 1 h. Volatile components were removed on a rotary evaporator and the residue was chromatographed on silica gel eluting with methanol in dichloromethane to afford 79B.

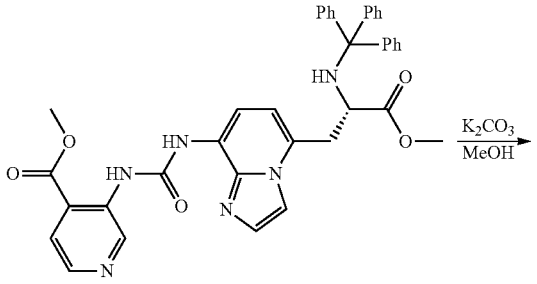
[0629] Synthesis methyl (S)-3-(8-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (79C): A solution of 79B (200 mg, 0.30 mmol), potassium carbonate (0.21 g, 1.52 mmol) in DMF (1 mL) and methanol (1 mL) was stirred for 20 minutes. Volatile components were removed on a rotary evaporator and the residue was chromatographed on silica gel eluting with methanol in dichloromethane to afford 79C.



15A

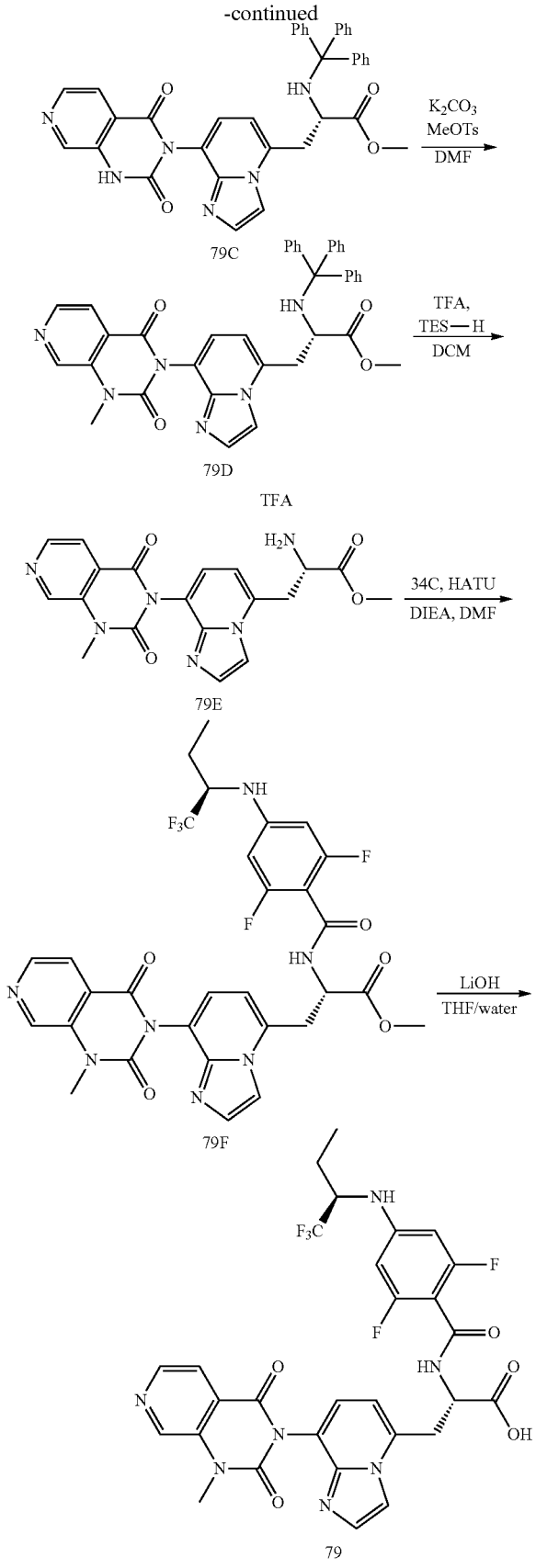


79A



79B

-continued



[0630] Synthesis of methyl (S)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (79D): To a stirred solution of 79C (129 mg, 0.207 mmol) in DMF (1.5 mL) was added potassium carbonate (143 mg, 1.0 mmol) and methyl tosylate (39 mg, 2.07 mmol), and the reaction was stirred overnight at room temperature. It was concentrated and purified by silica gel chromatography (methanol/dichloromethane) to yield 79D.

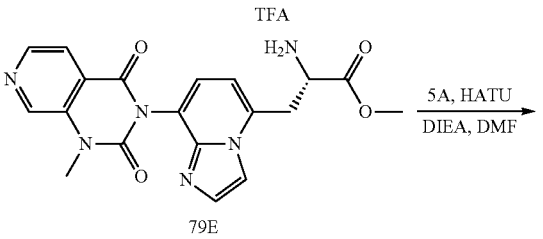
[0631] Synthesis of methyl (S)-2-amino-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (79E): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 79C.

[0632] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl) imidazo[1,2-a]pyridin-5-yl)propanoate (79F): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 34C and 79E. MS (m/z) 660.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.09 (s, 1H), 8.99 (d, J=7.7 Hz, 1H), 8.64 (d, J=5.0 Hz, 1H), 8.56 (s, 1H), 8.26 (s, 1H), 7.96 (q, J=4.4 Hz, 2H), 7.41 (d, J=7.8 Hz, 1H), 6.84 (d, J=9.4 Hz, 1H), 6.47 (d, J=11.9 Hz, 2H), 5.06 (dt, J=12.6, 6.3 Hz, 1H), 4.39-4.17 (m, 1H), 3.77 (d, J=5.1 Hz, 1H), 3.73 (d, J=4.9 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 1.77 (ddt, J=16.7, 9.3, 4.7 Hz, 1H), 1.53 (ddd, J=13.7, 10.2, 6.9 Hz, 1H), 0.92 (t, J=7.3 Hz, 3H).

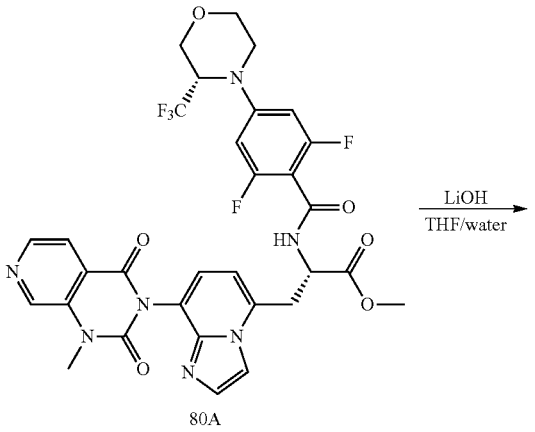
[0633] Synthesis of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo [1,2-a]pyridin-5-yl)propanoic acid (79): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 79F. MS (m/z) 646.2 [M+H]+. ^1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 9.08 (s, 1H), 8.88 (d, J=7.9 Hz, 1H), 8.63 (dd, J=4.9, 0.9 Hz, 1H), 8.53 (s, 1H), 8.23 (s, 1H), 7.94 (t, J=4.8 Hz, 1H), 7.38 (s, 1H), 6.81 (d, J=9.4 Hz, 1H), 6.44 (d, J=11.6 Hz, 2H), 4.95 (d, J=6.9 Hz, 1H), 4.30 (s, 1H), 3.77-3.69 (m, 1H), 3.65 (d, J=1.9 Hz, 3H), 3.60 (d, J=10.9 Hz, 1H), 1.75 (dq, J=10.5, 3.7, 3.2 Hz, 1H), 1.51 (ddd, J=13.8, 10.3, 7.1 Hz, 1H), 0.90 (t, J=7.3 Hz, 3H).

Example 80

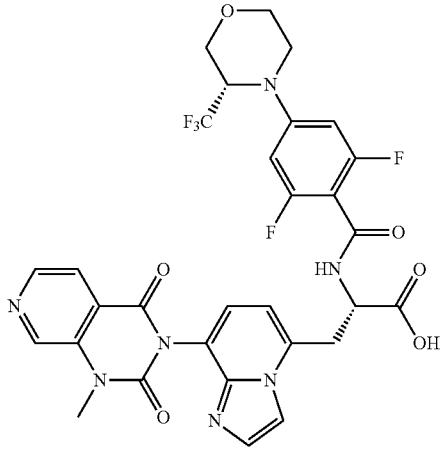
[0634]



-continued



80A



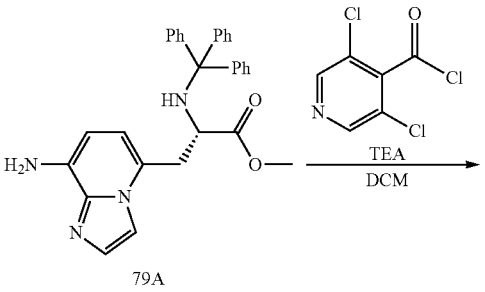
80

[0635] Synthesis of methyl (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (80A): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 15A and 79E.

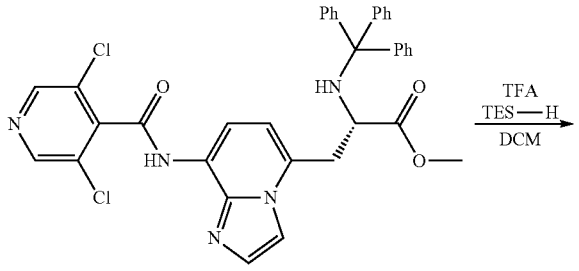
[0636] Synthesis of (S)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (80): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 80A. MS (m/z) 674.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.34-8.96 (m, 2H), 8.75-8.49 (m, 2H), 8.33 (s, 1H), 8.16-7.85 (m, 2H), 7.48 (d, J=7.8 Hz, 1H), 6.77 (d, J=12.1 Hz, 2H), 5.21-4.76 (m, 3H), 4.16 (d, J=12.7 Hz, 1H), 3.95 (d, J=11.6 Hz, 2H), 3.76 (s, 1H), 3.66 (s, 3H), 3.57 (d, J=11.7 Hz, 1H), 3.43 (d, J=12.8 Hz, 1H), 3.25 (d, J=12.7 Hz, 1H), 2.50 (s, 3H).

Example 81

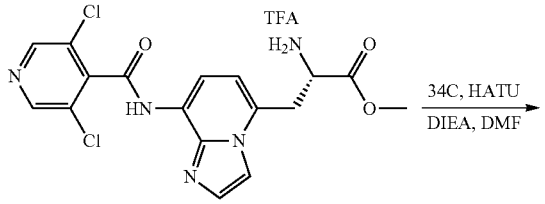
[0637]



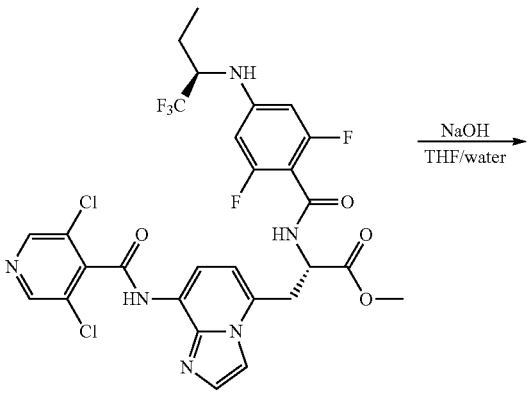
79A



81A

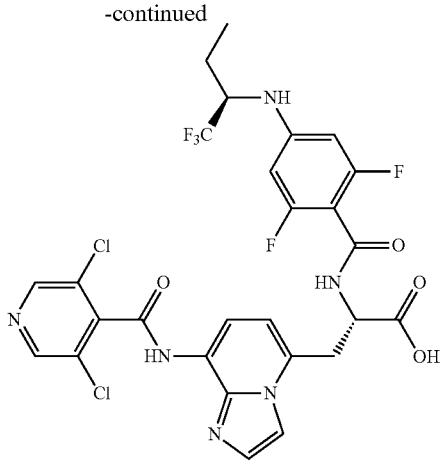


81B



81C

-continued



81

[0638] Synthesis of methyl (S)-3-(8-(3,5-dichloroisonicotinamido)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (81A): To a stirred solution of 79A (100 mg, 0.21 mmol) and triethylamine (106 mg, 1.1 mmol) in dichloromethane (5 mL) was added 3,5-dichloro isonicotinoyl chloride (44 mg, 0.21 mmol), and the reaction was stirred for 1 hour at room temperature. It was concentrated and purified by silica gel chromatography (eluent: methanol/DCM) to yield 81A.

[0639] Synthesis of methyl (S)-2-amino-3-(8-(3,5-dichloroisonicotinamido)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (81B): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 81A.

[0640] Synthesis of methyl (S)-3-(8-(3,5-dichloroisonicotinamido)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoate (81C): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 34C and 81B.

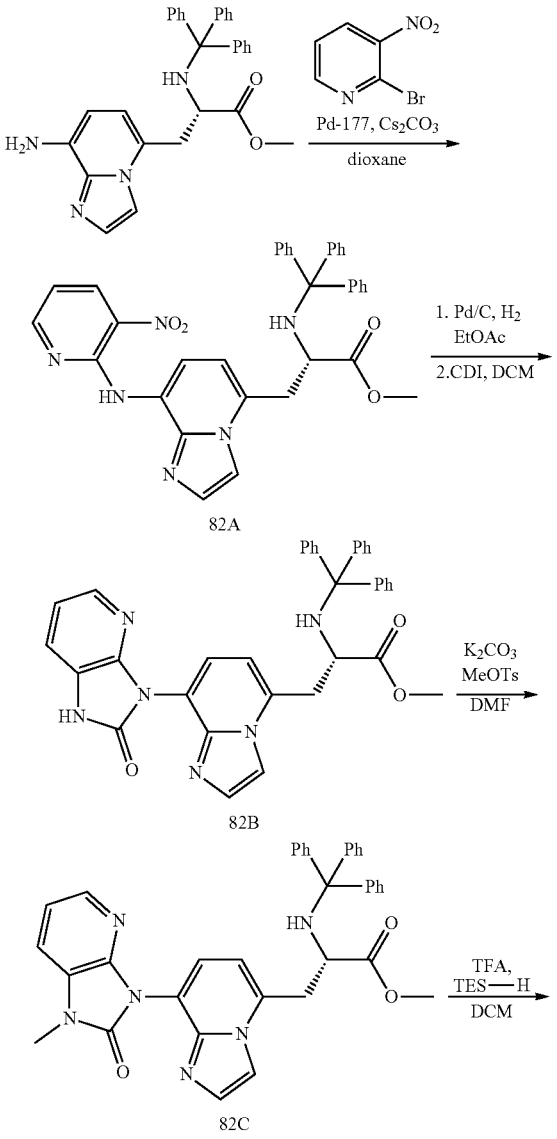
[0641] Synthesis of (S)-3-(8-(3,5-dichloroisonicotinamido)imidazo[1,2-a]pyridin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid (81): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 81A. MS (m/z) 659.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 8.80 (d, J=8.0 Hz, 1H), 8.76 (s, 2H), 8.20 (s, 1H), 8.14 (d, J=7.9 Hz, 1H), 7.85 (s, 1H), 6.95 (d, J=7.9 Hz, 1H), 6.80 (d, J=9.4 Hz, 1H), 6.44 (d, J=11.7 Hz, 2H), 4.82 (td, J=9.2, 8.3, 4.5 Hz, 1H), 4.29 (d, J=9.8 Hz, 1H), 3.53 (dd, J=15.3, 4.4 Hz, 1H), 3.49-3.30 (m, 1H), 1.74 (d, J=7.2 Hz, 1H), 1.65-1.35 (m, 1H), 0.90 (t, J=7.3 Hz, 3H).

Example 82

[0642] Synthesis of methyl (S)-3-(8-((3-nitropyridin-2-yl)amino)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (82A): (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)allyl) palladium(II) chloride (12 mg, 0.016 mmol), cesium carbonate (308 mg, 0.944 mmol), methyl (S)-3-(8-aminoimidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (150 mg, 0.315 mmol), 2-bromo-3-nitropyridine (76.67 mg, 0.38 mmol) and dioxane (1.6 mL) were added to a vial which was sparged with nitrogen. The mixture was heated to 90° C. for 2 hours. It was added to silica gel and chromatographed eluting with ethyl acetate in hexanes to yield 82A.

[0643] Synthesis of methyl (S)-3-(8-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (82B): 82A (172 mg, 0.287 mmol), ethyl acetate (5 mL) and 10% palladium on carbon (50 mg) were added to a parr shaker and shaken under 1 atm of hydrogen for 16 hours. It was filtered and concentrated under reduced pressure. Dichloromethane (5 mL) and carbonyl dimidazole (84 mg, 0.52 mmol) were added sequentially, and it was allowed to stir for 4 hours. The crude mixture was added to silica gel and chromatographed eluting with hexanes and ethyl acetate to afford 82B.

[0644] Synthesis of methyl (S)-3-(8-(1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)-2-(tritylamino)propanoate (82C): The title compound was prepared according to the method presented for the synthesis of compound 79D starting with 82B.

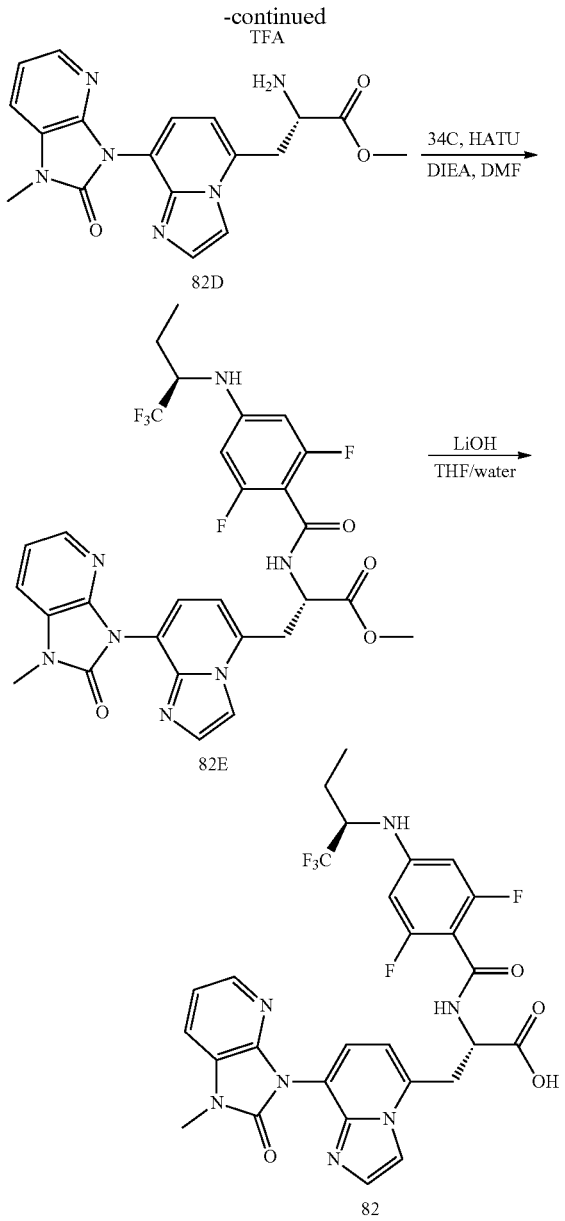


82A

82B

82C

-continued



[0645] Synthesis of methyl (S)-2-amino-3-(8-(1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate trifluoroacetate (82D): The title compound was prepared according to the method presented for the synthesis of compound 15D starting with 82C.

[0646] Synthesis of methyl (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoate (82E): The title compound was prepared according to the method presented for the synthesis of compound 5B starting with 34C and 81B.

[0647] Synthesis of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)imidazo[1,2-a]pyridin-5-yl)propanoic acid (82): The title compound was prepared according to the method presented for the synthesis of compound 7 starting with 82E. MS (m/z) 618.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J=7.9 Hz, 1H), 8.56 (s, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.90 (dd, J=5.0, 1.3 Hz, 1H), 7.69 (dd, J=7.7, 1.3 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.22 (dd, J=7.8, 5.2 Hz, 1H), 6.81 (d, J=9.4 Hz, 1H), 6.44 (d, J=11.7 Hz, 2H), 5.02-4.88 (m, 1H), 4.29 (s, 1H), 3.72 (dd, J=15.8, 4.8 Hz, 1H), 3.66-3.54 (m, 1H), 3.46 (s, 3H), 1.75 (td, J=7.3, 4.2 Hz, 1H), 1.62-1.45 (m, 1H), 0.90 (t, J=7.3 Hz, 3H).

α4β7 Integrin Cell Capture Assay

[0648] The potency of inhibitors in preventing α4β7 integrin interaction with MadCAM-1 was measured by monitoring the capture of α4β7 integrin expressing cells on a recombinant MadCAM-1 extracellular domain-coated plate.

[0649] 384-well plates (Corning 3702) were coated with MadCAM-1 extracellular domain by dispensing 20 μL of MAdCAM-1 at 1.0 μg/mL per well and incubating overnight at 4° C. The plates were then washed with PBS and blocked with 3% BSA for 2 hours before being washed again.

[0650] RPM18866 cells were spun down and re-suspended in assay medium (DMEM+0.5% FBS+0.5 mM $MnCl_2$) at a density of 0.5×10^6 cells/mL. The cells were then dispensed (60 μL/well) to a 384-well plate (Greiner 781280) that was previously spotted with 60 nL of test compound per well. The plates were incubated at 37° C. for 1 hour. 50 μL of cells were transferred to the blocked, MadCAM-1-coated plates and incubated for 30 minutes at 37° C. 10 μL of 12% glutaraldehyde containing Hoechst 33342 (0.06 mg/mL) was added to the cells (2% glutaraldehyde and 0.01 mg/mL final concentrations). The plates were incubated for 90 minutes at room temperature. The plates were then washed 3 times with 70 μL of PBS per well and imaged on a Cellomics ArrayScan instrument. The cells that were bound to the plate were counted and plotted against the compound concentration to determine the EC_{50} of the test compounds. Results are presented in Table 1.

TABLE 1

Example	α4β7 EC_{50} (nM)
1	7.8
2	74.0
3	252.7
4	0.2
5	0.5
6	3.8
7	0.2
8	0.3
9	3.8
10	3.2
11	0.4
12	1.1
13	6.3
14	1.5
15	0.5
16	0.8
17	1.8
18	2.2
19	0.3
20	2.4
21	0.4
22	3.9
23	1.9
24	0.2
25	1.6
26	1.6
27	1.5
28	48.9
29	0.5
30	1.1
31	1.8
32	3.5
33	0.1
34	5.9
35	0.8

TABLE 1-continued

Example	α4β7 EC_{50} (nM)
36	1.7
37	0.5
38	0.4
39	6.7
40	0.6
41	3.8
42	8.3
43	1.8
44	2.0
45	1.9
46	2.8
47	6.8
48	0.7
49	21.3
50	4.6
51	0.6
52	0.3
53	2.5
54	14.7
55	21.5
56	1.3
57	4.8
58	2.7
59	0.2
60	0.4
61	1.1
62	8.9
63	0.9
64	6.2
65	0.2
66	3.8
67	0.3
68	2.8
69	5.4
70	32.3
71	0.9
72	11.0
73	17.7
74	0.2
75	7.2
76	8.7
77	1.6
78	0.3
79	0.4
80	3.0

TABLE 1-continued

Example	α4β7 EC_{50} (nM)
81	0.4
82	1.2
83	NA
84	NA
85	NA
86	NA
87	NA
88	NA
89	NA
90	NA
91	NA
92	NA
93	NA
94	NA
95	NA
96	NA
97	NA
98	0.173
99	0.167
100	NA
101	NA
102	0.734
103	NA
104	5.754
105	NA
106	8.487
107	NA
108	0.085
109	0.414
110	NA
111	NA
112	NA
113	5.797
114	0.14
115	0.475
116	NA
117	NA
118	0.194
119	NA
120	0.131
121	NA

[0651] Examples 83-121 in Table 2 were prepared by processes described herein.

TABLE 2

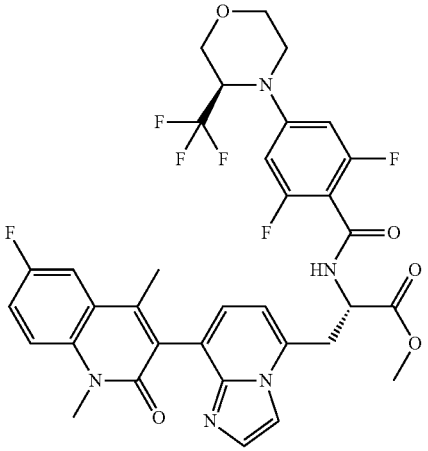
Example	Structure	1H-NMR	M/Z $[M + H]^+$
83		1H NMR (400 MHz, DMSO-d6) δ 9.10 (dd, J = 11.7, 8.2 Hz, 1H), 8.62 (d, J = 32.9 Hz, 1H), 8.32 (dd, J = 13.7, 2.1 Hz, 1H), 7.89-7.77 (m, 2H), 7.75-7.70 (m, 1H), 7.70-7.63 (m, 1H), 7.46 (dd, J = 40.9, 7.5 Hz, 1H), 6.76 (d, J = 11.8 Hz, 2H), 5.18-5.06 (m, 1H), 4.96-4.86 (m, 1H), 4.17 (d, J = 12.7 Hz, 1H), 3.96 (d, J = 8.4 Hz, 1H), 3.87-3.77 (m, 1H), 3.74 (d, J = 6.8 Hz, 3H), 3.69 (s, 3H), 3.65-3.49 (m, 2H), 3.43 (d, J = 12.4 Hz, 1H), 3.28-3.18 (m, 1H), 2.24 (d, J = 8.8 Hz, 3H).	702.2

TABLE 2-continued

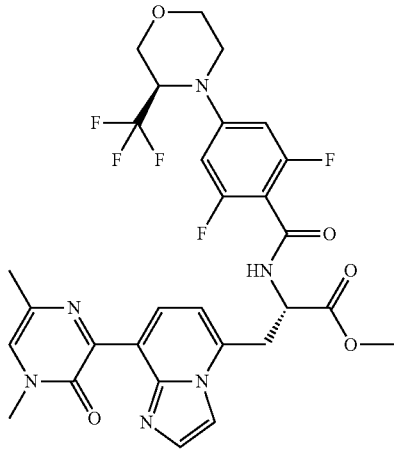
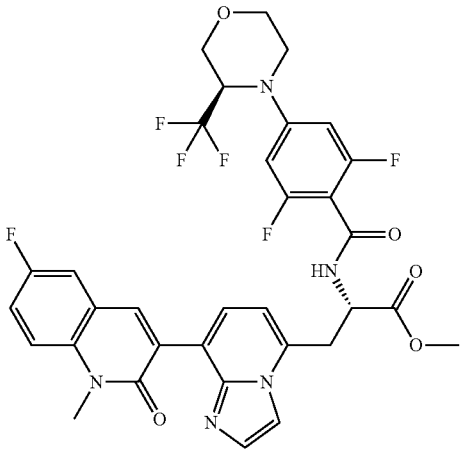
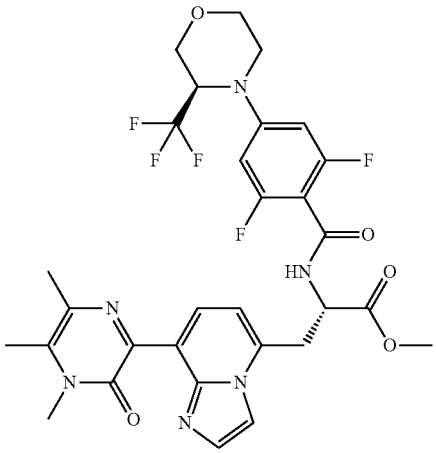
Example	Structure	1H-NMR	M/Z [M + H]+
84		1H NMR (400 MHz, DMSO-d6) δ 9.25 (d, J = 7.9 Hz, 1H), 9.04 (d, J = 8.0 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.37-8.30 (m, 1H), 7.88 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 11.9 Hz, 2H), 5.14-5.04 (m, 1H), 4.95-4.83 (m, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.95 (dd, J = 11.6, 3.8 Hz, 1H), 3.86-3.48 (m, 10H), 3.41 (d, J = 12.5 Hz, 1H), 3.21 (t, J = 12.5 Hz, 1H), 2.44 (s, 3H).	635.2
85		1H NMR (400 MHz, DMSO-d6) δ 9.09 (d, J = 7.9 Hz, 1H), 8.59 (s, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 7.98 (d, J = 7.1 Hz, 1H), 7.78-7.74 (m, 1H), 7.74-7.70 (m, 1H), 7.66 (td, J = 9.2, 8.8, 2.8 Hz, 1H), 7.42-7.38 (m, 1H), 6.78 (d, J = 11.8 Hz, 2H), 5.13-5.05 (m, 1H), 4.95-4.86 (m, 1H), 4.17 (d, J = 12.7 Hz, 1H), 3.96 (dd, J = 11.6, 3.6 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 2H), 3.69 (d, J = 12.0 Hz, 1H), 3.64 (d, J = 10.5 Hz, 1H), 3.60-3.50 (m, 2H), 3.45-3.40 (m, 1H), 3.27-3.19 (m, 1H).	688.2
86		1H NMR (400 MHz, DMSO-d6) δ 13.49 (s, 1H), 9.26 (d, J = 7.9 Hz, 1H), 9.03 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.31 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 12.0 Hz, 2H), 5.15-5.03 (m, 1H), 4.95-4.83 (m, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.94 (dd, J = 11.5, 3.7 Hz, 1H), 3.84-3.58 (m, 9H), 3.57-3.46 (m, 1H), 3.41 (d, J = 12.7 Hz, 1H), 3.27-3.14 (m, 1H), 2.54 (s, 3H), 2.49 (s, 3H).	649.2

TABLE 2-continued

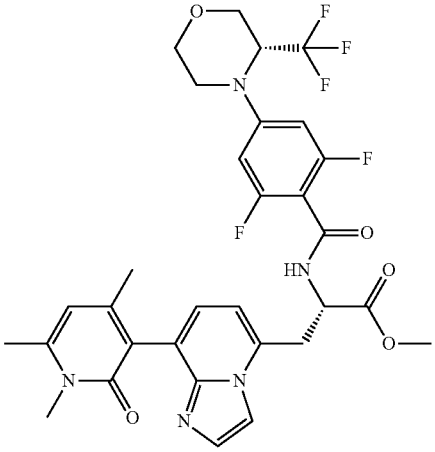
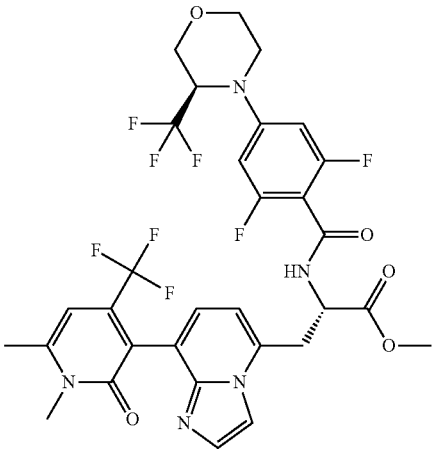
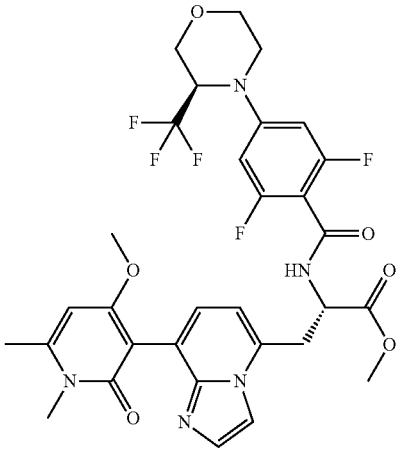
Example	Structure	1H-NMR	M/Z [M + H]+
87		1H NMR (400 MHz, DMSO-d6) δ 9.12 (dd, J = 16.3, 7.7 Hz, 1H), 8.00 (s, 1H), 7.59 (s, 1H), 7.00 (d, J = 24.0 Hz, 1H), 6.76 (dd, J = 11.7, 6.7 Hz, 3H), 6.15 (s, 1H), 4.90 (d, J = 10.0 Hz, 2H), 4.14 (d, J = 12.8 Hz, 1H), 3.93 (d, J = 11.5 Hz, 1H), 3.72 (d, J = 6.9 Hz, 1H), 3.71-3.65 (m, 3H), 3.65-3.44 (m, 2H), 3.40 (s, 4H), 3.31 (s, 2H), 3.27-3.07 (m, 1H), 2.37 (s, 3H), 1.79 (s, 3H), 1.24 (t, J = 6.2 Hz, 3H).	648.3
88		1H NMR (400 MHz, DMSO-d6) δ 9.07 (dd, J = 22.2, 8.0 Hz, 1H), 8.60 (d, J = 21.1 Hz, 1H), 8.32 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 10.0 Hz, 1H), 7.39 (dd, J = 22.7, 7.5 Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H), 6.72 (t, J = 3.0 Hz, 2H), 5.21-5.01 (m, 1H), 4.90 (dd, J = 8.6, 3.5 Hz, 1H), 4.14 (d, J = 12.8 Hz, 1H), 3.93 (dd, J = 11.6, 3.8 Hz, 1H), 3.81-3.71 (m, 1H), 3.68 (d, J = 9.4 Hz, 3H), 3.52 (d, J = 2.7 Hz, 3H), 3.40 (d, J = 13.0 Hz, 1H), 3.20 (t, J = 12.3 Hz, 1H), 2.57 (d, J = 1.7 Hz, 3H).	701.681
89		1H NMR (400 MHz, Chloroform-d) δ 7.82 (d, J = 14.9 Hz, 1H), 7.60 (s, 1H), 7.07 (d, J = 7.0 Hz, 1H), 6.67 (d, J = 7.1 Hz, 1H), 6.38 (d, J = 12.1 Hz, 2H), 6.05 (s, 1H), 5.19 (s, 1H), 4.30 (d, J = 12.5 Hz, 1H), 4.07 (td, J = 11.6, 10.0, 3.8 Hz, 2H), 3.79 (ddt, J = 12.7, 4.3, 2.2 Hz, 1H), 3.74-3.40 (m, 11H), 3.29 (d, J = 12.3 Hz, 1H), 2.40 (s, 3H), 1.87 (s, 2H).	664.0

TABLE 2-continued

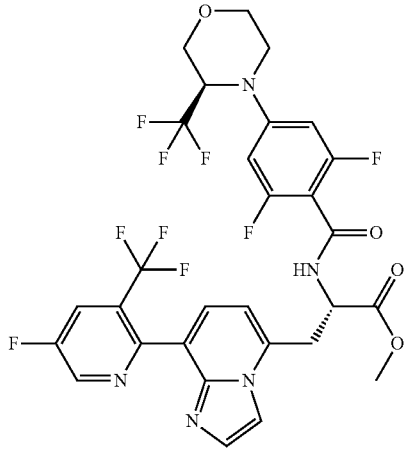
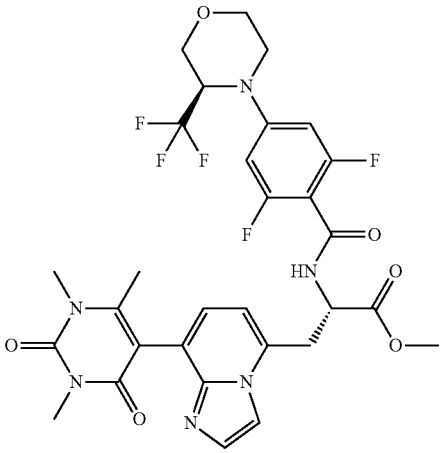
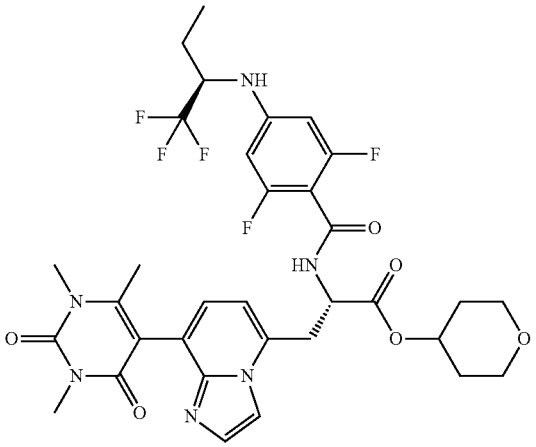
Example	Structure	1H-NMR	M/Z [M + H]+
90		1H NMR (400 MHz, DMSO-d6) δ 9.13 (d, J = 7.7 Hz, 1H), 8.99 (d, J = 2.7 Hz, 1H), 8.43 (dd, J = 8.9, 2.8 Hz, 1H), 8.08 (s, 1H), 7.60 (s, 1H), 7.20 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.1 Hz, 1H), 6.78 (d, J = 11.7 Hz, 2H), 5.05-4.86 (m, 2H), 4.16 (d, J = 12.8 Hz, 1H), 3.95 (dd, J = 11.6, 3.8 Hz, 1H), 3.78-3.70 (m, 1H), 3.69 (s, 3H), 3.61-3.39 (m, 4H), 3.23 (t, J = 12.0 Hz, 1H).	676.2
91		1H NMR (400 MHz, DMSO-d6) δ 9.06 (dd, J = 13.4, 8.0 Hz, 1H), 8.58 (d, J = 31.4 Hz, 1H), 8.33 (d, J = 13.3 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.46-7.31 (m, 1H), 6.74 (dd, J = 11.8, 3.6 Hz, 2H), 5.06 (d, J = 4.8 Hz, 1H), 4.89 (s, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.94 (dd, J = 11.5, 3.8 Hz, 1H), 3.81-3.33 (m, 11H), 3.23 (s, 4H), 2.06 (d, J = 7.1 Hz, 3H).	665.2
92		1H NMR (400 MHz, DMSO-d6) δ 8.93 (dd, J = 17.0, 7.8 Hz, 1H), 8.59 (dd, J = 31.7, 2.2 Hz, 1H), 8.35 (dd, J = 10.9, 2.2 Hz, 1H), 7.81-7.69 (m, 1H), 7.40 (dd, J = 35.3, 7.5 Hz, 1H), 6.83 (d, J = 9.3 Hz, 1H), 6.43 (dd, J = 11.5, 3.4 Hz, 2H), 4.99 (dtt, J = 22.5, 9.4, 5.1 Hz, 2H), 4.28 (d, J = 9.1 Hz, 2H), 3.83-3.69 (m, 5H), 3.56 (dd, J = 15.3, 10.9 Hz, 1H), 3.49 (dq, J = 7.5, 4.0, 3.5 Hz, 1H), 3.45 (s, 3H), 3.23 (s, 3H), 2.96 (t, J = 6.3 Hz, 2H), 2.07 (d, J = 3.8 Hz, 3H), 1.84 (q, J = 6.6, 5.1 Hz, 2H), 1.74 (dtd, J = 14.7, 7.3, 3.2 Hz, 1H), 1.53 (ddt, J = 15.8, 10.4, 5.5 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H).	707.473

TABLE 2-continued

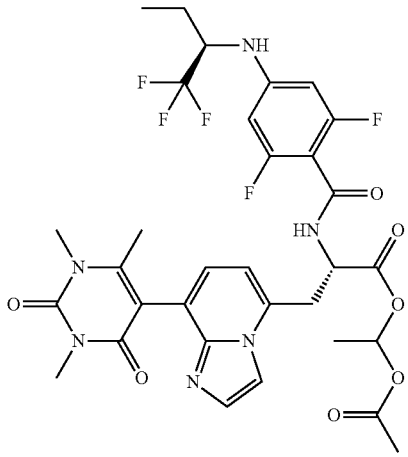
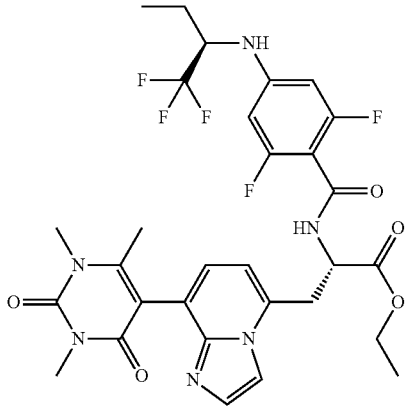
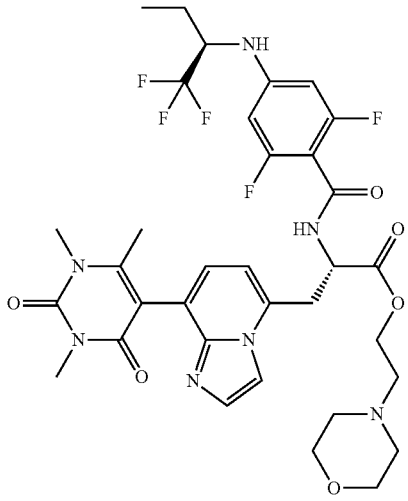
Example	Structure	1H-NMR	M/Z [M + H]+
93		1H NMR (400 MHz, DMSO-d6) δ 9.00-8.86 (m, 1H), 8.58 (ddd, J = 31.1, 7.9, 2.2 Hz, 1H), 8.34 (ddd, J = 12.0, 4.5, 2.2 Hz, 1H), 7.79-7.69 (m, 1H), 7.49-7.31 (m, 1H), 6.83 (ddt, J = 10.6, 7.5, 3.9 Hz, 2H), 6.42 (dt, J = 11.6, 2.8 Hz, 2H), 5.04 (dddd, J = 33.2, 24.8, 11.6, 6.0 Hz, 1H), 4.29 (s, 1H), 3.72 (dd, J = 15.2, 11.0 Hz, 1H), 3.45 (s, 3H), 3.23 (s, 3H), 2.12-2.00 (m, 6H), 1.84-1.67 (m, 1H), 1.50 (td, J = 13.4, 7.2 Hz, 1H), 1.42 (dt, J = 9.8, 5.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H).	708.688
94		1H NMR (400 MHz, DMSO-d6) δ 8.91 (dd, J = 12.1, 8.0 Hz, 1H), 8.58 (dd, J = 32.9, 2.2 Hz, 1H), 8.34 (dd, J = 11.6, 2.1 Hz, 1H), 7.74 (t, J = 8.5 Hz, 1H), 7.39 (dd, J = 37.3, 7.5 Hz, 1H), 6.82 (d, J = 9.4 Hz, 1H), 6.42 (dd, J = 11.4, 3.2 Hz, 2H), 5.08-4.89 (m, 1H), 4.29 (d, J = 10.0 Hz, 1H), 4.21-4.06 (m, 2H), 3.75 (d, J = 4.5 Hz, 1H), 3.72-3.60 (m, 1H), 3.53 (dd, J = 15.4, 11.0 Hz, 1H), 3.46 (s, 3H), 3.23 (s, 3H), 2.07 (d, J = 5.4 Hz, 3H), 1.75 (ddd, J = 13.7, 7.3, 3.2 Hz, 1H), 1.50 (ddd, J = 13.7, 10.4, 7.0 Hz, 1H), 1.19 (q, J = 7.2 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H).	651.159
95		1H NMR (400 MHz, DMSO-d6) δ 10.11 (s, 1H), 8.95 (dd, J = 13.6, 7.8 Hz, 1H), 8.53 (d, J = 30.5 Hz, 1H), 8.35 (s, 1H), 7.72 (s, 1H), 7.37 (d, J = 30.0 Hz, 1H), 6.86 (d, J = 9.4 Hz, 1H), 6.44 (d, J = 12.6 Hz, 2H), 5.09 (s, 1H), 4.47 (d, J = 17.6 Hz, 2H), 4.30 (s, 1H), 4.09-3.49 (m, 4H), 3.46 (d, J = 1.6 Hz, 3H), 3.23 (s, 3H), 3.15 (s, 2H), 2.79 (d, J = 63.9 Hz, 1H), 2.06 (d, J = 7.7 Hz, 3H), 1.74 (d, J = 8.0 Hz, 1H), 1.60-1.40 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H).	736.266

TABLE 2-continued

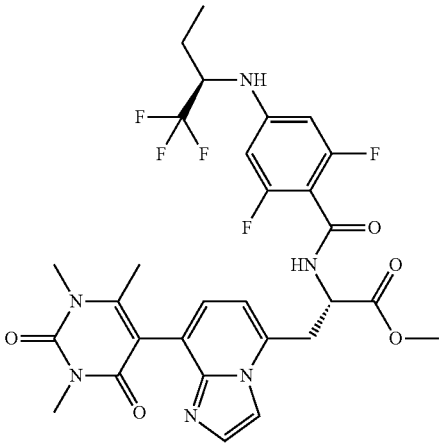
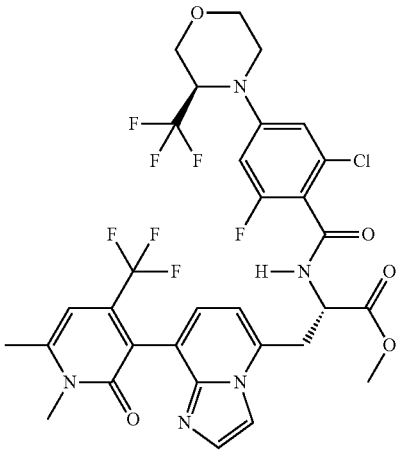
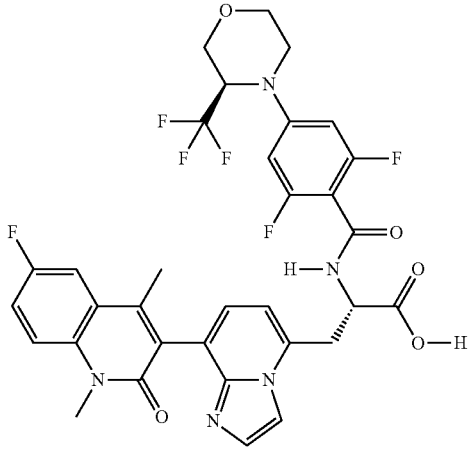
Example	Structure	1H-NMR	M/Z [M + H]+
96		1H NMR (400 MHz, DMSO-d6) δ 8.91 (dd, J = 12.1, 8.0 Hz, 1H), 8.58 (dd, J = 31.6, 2.2 Hz, 1H), 8.39-8.31 (m, 1H), 7.74 (dd, J = 9.8, 7.4 Hz, 1H), 7.38 (dd, J = 36.8, 7.5 Hz, 1H), 6.83 (d, J = 9.4 Hz, 1H), 6.42 (dd, J = 11.5, 3.4 Hz, 2H), 5.15-4.93 (m, 1H), 4.28 (s, 1H), 3.79-3.72 (m, 1H), 3.70 (d, J = 6.9 Hz, 3H), 3.65-3.53 (m, 1H), 3.23 (s, 3H), 2.06 (d, J = 7.3 Hz, 3H), 1.75 (ddd, J = 13.9, 7.4, 3.2 Hz, 1H), 1.50 (ddd, J = 13.8, 10.4, 7.2 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H).	636.848
97		1H NMR (400 MHz, DMSO-d6) δ 9.21 (d, J = 8.2 Hz, 1H), 8.64-8.52 (m, 1H), 8.38-8.24 (m, 1H), 7.82-7.68 (m, 1H), 7.49-7.35 (m, 1H), 6.95-6.85 (m, 2H), 6.72 (s, 1H), 5.23-5.09 (m, 1H), 4.99-4.86 (m, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.98-3.92 (m, 1H), 3.83-3.65 (m, 4H), 3.65-3.43 (m, 6H), 3.40 (d, J = 13.1 Hz, 1H), 3.23 (t, J = 12.4 Hz, 1H), 2.59 (s, 3H).	718.2
98		1H NMR (400 MHz, DMSO-d6) δ 9.00 (t, J = 7.7 Hz, 1H), 8.61 (d, J = 27.1 Hz, 1H), 8.32 (s, 1H), 7.82 (m, 2H), 7.77-7.64 (m, 2H), 7.45 (d, J = 43.0 Hz, 1H), 6.75 (d, J = 11.8 Hz, 2H), 5.07-5.00 (m, 1H), 4.95-4.82 (m, 1H), 4.16 (d, J = 12.6 Hz, 1H), 3.95 (d, J = 10.0 Hz, 1H), 3.73 (d, J = 13.3 Hz, 1H), 3.69 (s, 3H), 3.55 (t, J = 12.2 Hz, 2H), 3.42 (m, 2H), 3.24 (d, J = 12.5 Hz, 1H), 2.24 (d, J = 6.2 Hz, 3H).	688.2

TABLE 2-continued

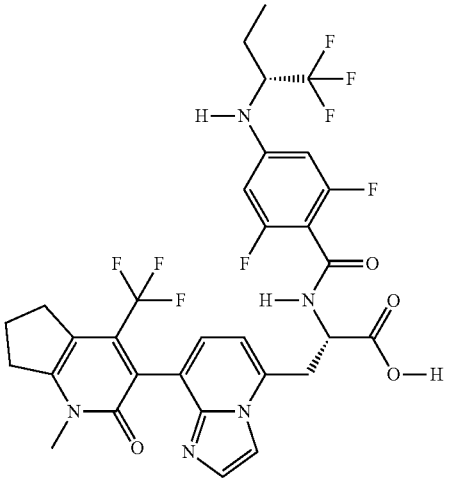
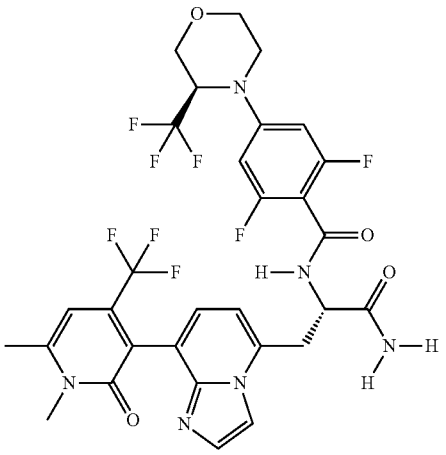
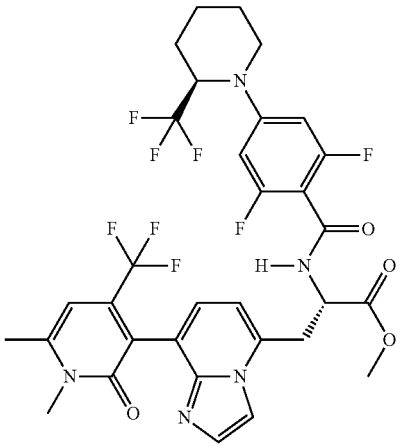
Example	Structure	1H-NMR	M/Z [M + H]+
99		1H NMR (400 MHz, DMSO-d6) δ 8.92 (dd, J = 7.9, 4.3 Hz, 1H), 8.84 (dd, J = 4.3, 1.4 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 7.66 (dt, J = 8.7, 4.4 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.46 (dd, J = 7.3, 2.1 Hz, 1H), 6.63 (dd, J = 12.0, 4.7 Hz, 2H), 6.56 (d, J = 1.8 Hz, 1H), 4.69 (ddd, J = 13.2, 8.8, 4.9 Hz, 2H), 3.80-3.63 (m, 1H), 3.49 (d, J = 2.2 Hz, 3H), 3.48-3.34 (m, 1H), 3.34-3.21 (m, 1H), 3.21-3.07 (m, 1H), 2.54 (s, 3H), 1.90 (ddd, J = 14.2, 10.5, 7.1 Hz, 1H), 1.76 (ddt, J = 11.2, 7.3, 4.0 Hz, 1H), 1.61-1.34 (m, 2H), 0.86 (dt, J = 10.9, 7.3 Hz, 6H).	713.5
100		1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 8.3 Hz, 1H), 8.08 (dd, J = 2.6, 1.4 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 1.2 Hz, 1H), 7.31 (s, 1H), 7.02-6.92 (m, 1H), 6.86-6.79 (m, 1H), 6.75 (d, J = 11.6 Hz, 2H), 6.54 (d, J = 0.9 Hz, 1H), 5.02-4.84 (m, 2H), 4.15 (d, J = 12.7 Hz, 1H), 3.95 (dd, J = 11.5, 3.8 Hz, 1H), 3.74 (d, J = 12.7 Hz, 1H), 3.55 (t, J = 11.4 Hz, 1H), 3.49 (s, 3H), 3.41 (dd, J = 15.7, 4.8 Hz, 1H), 3.30-3.17 (m, 1H), 2.52 (s, 4H).	687.2
101		1H NMR (400 MHz, DMSO-d6) δ 9.04 (dd, J = 21.3, 7.9 Hz, 1H), 8.60 (d, J = 20.7 Hz, 1H), 8.33 (s, 1H), 7.74 (s, 1H), 7.51-7.31 (m, 1H), 6.74 (d, J = 10.2 Hz, 3H), 5.10 (d, J = 9.0 Hz, 1H), 5.02-4.88 (m, 1H), 4.13-3.64 (m, 4H), 3.54 (t, J = 1.9 Hz, 4H), 3.01 (t, J = 12.2 Hz, 1H), 2.59 (s, 3H), 2.5 (m, 3H), 1.97 (d, J = 14.5 Hz, 1H), 1.74 (d, J = 11.8 Hz, 1H), 1.69-1.26 (m, 3H).	700.2

TABLE 2-continued

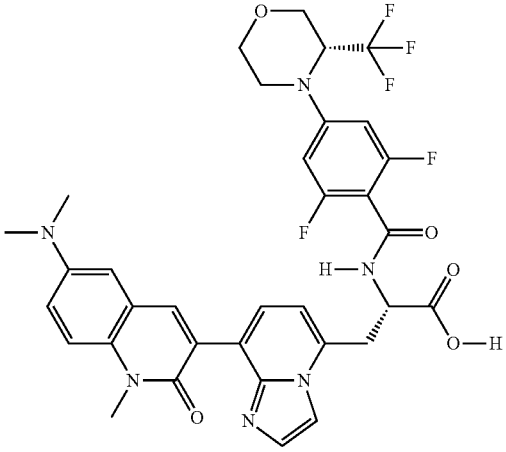
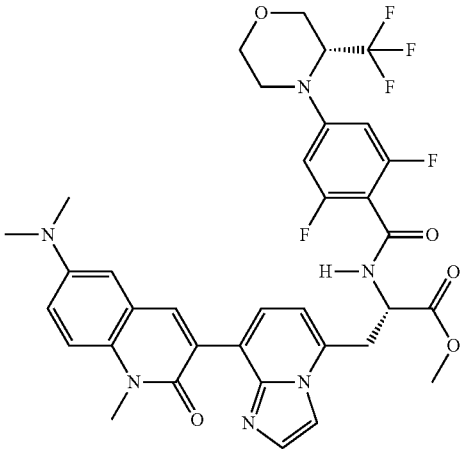
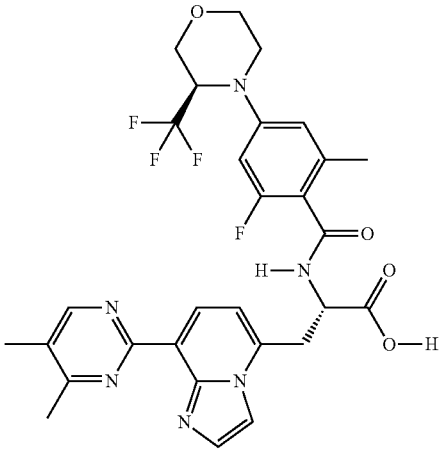
Example	Structure	1H-NMR	M/Z [M + H]+
102		1H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 9.00 (d, J = 8.1 Hz, 1H), 8.61 (s, 1H), 8.34 (s, 1H), 8.15 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.35-7.27 (m, 1H), 7.13 (s, 1H), 6.77 (d, J = 12.0 Hz, 2H), 5.01 (s, 1H), 4.91 (d, J = 9.3 Hz, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.96 (d, J = 11.5 Hz, 1H), 3.77 (d, J = 16.0 Hz, 2H), 3.70 (s, 3H), 3.65-3.56 (m, 1H), 3.56-3.50 (m, 1H), 3.42 (d, J = 12.9 Hz, 1H), 3.23 (t, J = 12.4 Hz, 1H), 2.96 (s, 6H).	699.3
103		1H NMR (400 MHz, DMSO-d6) δ 9.10 (d, J = 7.9 Hz, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 6.78 (d, J = 12.2 Hz, 2H), 5.09 (s, 1H), 4.91 (d, J = 9.4 Hz, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.96 (d, J = 11.6 Hz, 1H), 3.80 (s, 1H), 3.77 (s, 1H), 3.73 (d, J = 1.8 Hz, 3H), 3.70 (d, J = 1.8 Hz, 3H), 3.68-3.59 (m, 1H), 3.55 (t, J = 11.3 Hz, 1H), 3.43 (d, J = 12.7 Hz, 1H), 3.23 (t, J = 12.2 Hz, 1H), 2.96 (d, J = 1.8 Hz, 6H).	713.3
104		1H NMR (400 MHz, DMSO-d6) δ 13.83 (s, 1H), 8.91 (d, J = 7.8 Hz, 1H), 8.80 (d, J = 8.3 Hz, 1H), 8.76 (s, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 6.66-6.60 (m, 2H), 5.11-5.02 (m, 1H), 4.86-4.75 (m, 1H), 4.13 (d, J = 12.6 Hz, 1H), 3.93 (dd, J = 11.3, 3.7 Hz, 1H), 3.82 (dd, J = 15.5, 4.5 Hz, 1H), 3.75-3.67 (m, 1H), 3.63 (dd, J = 15.6, 10.8 Hz, 1H), 3.51 (ddd, 1H), 3.31 (d, J = 12.1 Hz, 1H), 3.26-3.16 (m, 1H), 2.67 (s, 3H), 2.37 (s, 3H), 2.06 (s, 3H).	601.3

TABLE 2-continued

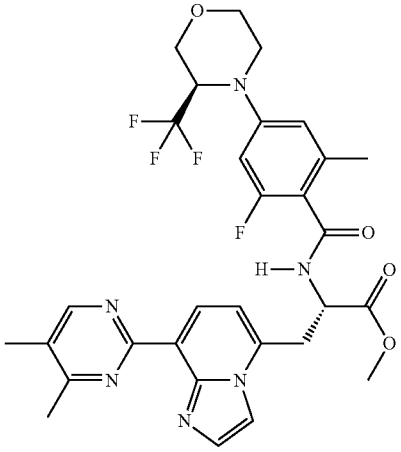
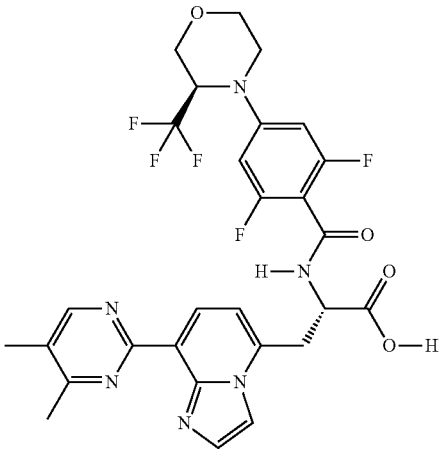
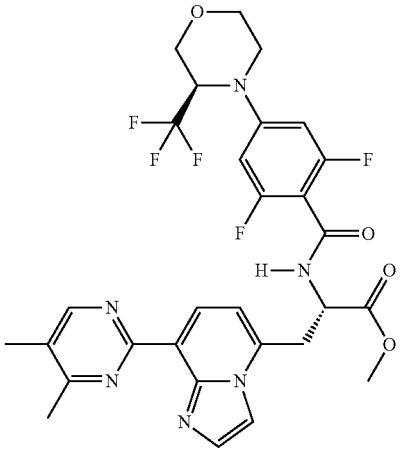
Example	Structure	1H-NMR	M/Z [M + H]+
105		1H NMR (400 MHz, DMSO-d6) δ 13.84 (s, 1H), 8.94-8.86 (m, 2H), 8.76 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.38 (d, J = 2.3 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 6.68-6.60 (m, 2H), 5.17-5.09 (m, 1H), 4.87-4.75 (m, 1H), 4.13 (d, J = 12.6 Hz, 1H), 3.93 (dd, J = 11.4, 3.7 Hz, 2H), 3.84 (dd, J = 15.4, 4.7 Hz, 1H), 3.74 (s, 3H), 3.73-3.62 (m, 1H), 3.51 (ddd, 1H), 3.32 (d, J = 12.5 Hz, 1H), 3.27-3.16 (m, 1H), 2.67 (s, 3H), 2.37 (s, 3H), 2.07 (s, 3H).	615.3
106		1H NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 8.3 Hz, 1H), 8.90 (d, J = 7.8 Hz, 1H), 8.76 (d, J = 0.9 Hz, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 11.9 Hz, 2H), 5.07-5.00 (m, 1H), 4.92-4.82 (m, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.94 (dd, J = 11.5, 3.8 Hz, 1H), 3.83 (dd, J = 15.3, 4.6 Hz, 1H), 3.76-3.68 (m, 1H), 3.62 (dd, J = 15.4, 10.7 Hz, 1H), 3.38 (s, 2H), 3.26-3.17 (m, 1H), 2.67 (s, 3H), 2.37 (s, 3H).	605.6
107		1H NMR (400 MHz, DMSO-d6) δ 13.83 (s, 1H), 9.02 (d, J = 8.1 Hz, 1H), 8.90 (d, J = 7.8 Hz, 1H), 8.76 (d, J = 0.9 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 12.0 Hz, 2H), 5.17-5.07 (m, 1H), 4.93-4.82 (m, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.94 (dd, J = 11.6, 3.8 Hz, 1H), 3.85 (dd, J = 15.3, 4.8 Hz, 1H), 3.75 (s, 3H), 3.71-3.61 (m, 2H), 3.51 (dd, J = 11.8, 3.2 Hz, 1H), 3.40 (d, J = 12.8 Hz, 1H), 3.26-3.18 (m, 1H), 2.67 (s, 3H), 2.37 (s, 3H).	619.6

TABLE 2-continued

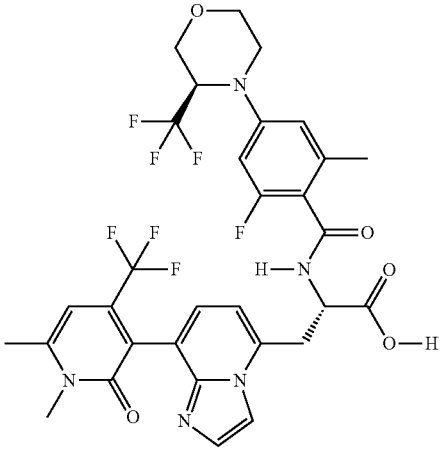
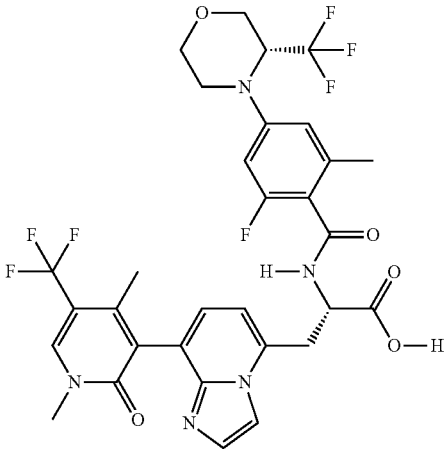
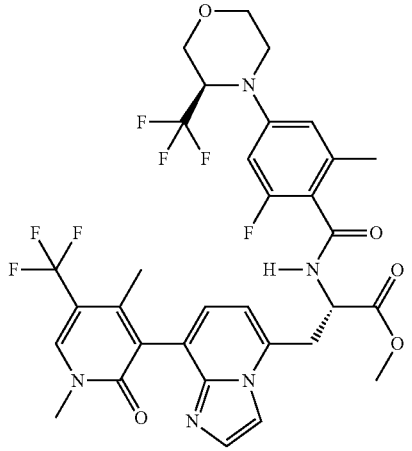
Example	Structure	1H-NMR	M/Z [M + H]+
108		1H NMR (400 MHz, DMSO-d6) δ 8.85 (dd, J = 8.3, 3.8 Hz, 1H), 8.57 (s, 1H), 7.76 (s, 1H), 7.40 (s, 1H), 6.73 (s, 1H), 6.70-6.62 (m, 2H), 5.06 (dd, J = 8.3, 4.1 Hz, 1H), 4.84 (d, J = 9.7 Hz, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.94 (d, J = 10.8 Hz, 1H), 3.72 (d, J = 12.9 Hz, 2H), 3.56 (s, 5H), 3.34 (d, J = 12.8 Hz, 1H), 3.25 (d, J = 12.4 Hz, 1H), 2.59 (s, 3H), 2.06 (d, J = 10.5 Hz, 3H).	684.2
109		1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.85 (d, J = 8.3 Hz, 1H), 8.58 (d, J = 24.5 Hz, 2H), 8.32 (s, 1H), 7.85 (s, 1H), 7.44 (dd, J = 25.8, 7.5 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 5.06 (ddd, J = 11.5, 8.1, 4.3 Hz, 1H), 4.83 (d, J = 9.5 Hz, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.98-3.91 (m, 1H), 3.74 (t, J = 16.1 Hz, 2H), 3.65-3.56 (m, 1H), 3.51 (d, J = 10.4 Hz, 2H), 3.34 (d, J = 12.5 Hz, 1H), 3.23 (t, J = 12.4 Hz, 1H), 2.15-2.00 (m, 6H).	684.2
110		1H NMR (400 MHz, DMSO-d6) δ 8.94 (t, J = 7.3 Hz, 1H), 8.61 (d, J = 17.2 Hz, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 7.86 (s, 1H), 7.44 (dd, J = 23.9, 7.5 Hz, 1H), 6.66 (d, J = 10.7 Hz, 2H), 5.14 (d, J = 10.5 Hz, 1H), 4.83 (d, J = 9.7 Hz, 1H), 4.15 (d, J = 12.6 Hz, 1H), 3.95 (d, J = 11.5 Hz, 1H), 3.77 (d, J = 15.9 Hz, 1H), 3.74 (d, J = 3.6 Hz, 3H), 3.71 (s, 1H), 3.66-3.58 (m, 1H), 3.54 (s, 3H), 3.50 (s, 1H), 3.34 (d, J = 12.5 Hz, 1H), 3.23 (t, J = 12.5 Hz, 1H), 2.12-2.02 (m, 6H).	698.2

TABLE 2-continued

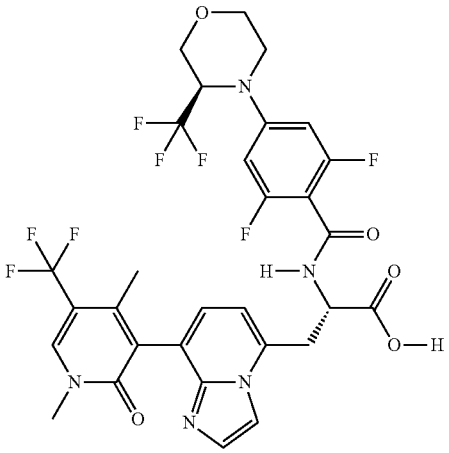
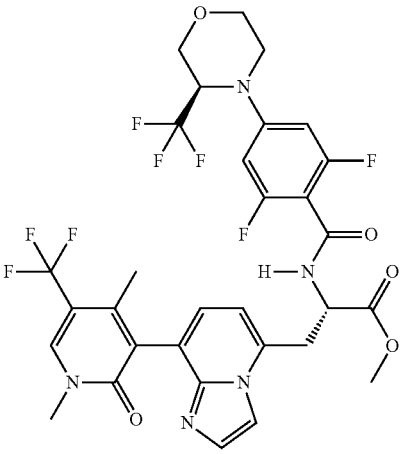
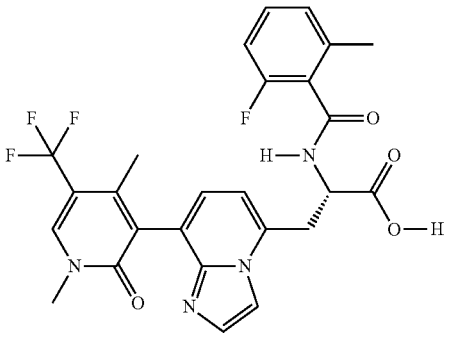
Example	Structure	1H-NMR	M/Z [M + H]+
111		1H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 8.97 (dd, J = 14.6, 8.2 Hz, 1H), 8.62 (s, 1H), 8.54 (s, 1H), 8.32 (s, 1H), 7.82 (s, 1H), 7.40 (d, J = 39.0 Hz, 1H), 6.74 (d, J = 11.9 Hz, 2H), 5.02 (d, J = 10.4 Hz, 1H), 4.91 (d, J = 7.8 Hz, 1H), 4.16 (d, J = 12.8 Hz, 1H), 3.97-3.90 (m, 1H), 3.80 (s, 1H), 3.72 (d, J = 11.7 Hz, 1H), 3.57 (s, 1H), 3.54 (s, 3H), 3.42 (d, J = 13.3 Hz, 2H), 3.22 (t, J = 12.6 Hz, 1H), 2.02 (d, J = 9.5 Hz, 3H).	688.2
112		1H NMR (400 MHz, DMSO-d6) δ 9.07 (dd, J = 19.8, 8.0 Hz, 1H), 8.65 (s, 1H), 8.55 (s, 1H), 8.32 (d, J = 12.7 Hz, 1H), 7.83 (s, 1H), 7.50-7.33 (m, 1H), 6.75 (d, J = 11.9 Hz, 2H), 5.18-5.03 (m, 1H), 4.91 (d, J = 9.3 Hz, 1H), 4.16 (d, J = 12.6 Hz, 1H), 3.99-3.91 (m, 1H), 3.83-3.76 (m, 1H), 3.74 (s, 3H), 3.72 (s, 2H), 3.68-3.56 (m, 1H), 3.54 (s, 3H), 3.42 (d, J = 12.8 Hz, 1H), 3.22 (t, J = 12.2 Hz, 1H), 2.02 (d, J = 12.8 Hz, 3H).	702.2
113		1H NMR (400 MHz, DMSO-d6) δ 13.22 (s, 1H), 9.07 (dd, J = 8.3, 2.4 Hz, 1H), 8.60 (s, 1H), 8.54 (s, 1H), 8.30 (s, 1H), 7.85 (s, 1H), 7.44 (d, J = 24.3 Hz, 1H), 7.33-7.25 (m, 1H), 7.04 (dd, J = 7.9, 3.3 Hz, 1H), 7.02-6.96 (m, 1H), 5.10 (s, 1H), 3.78 (d, J = 16.1 Hz, 1H), 3.65-3.57 (m, 1H), 3.54 (d, J = 1.4 Hz, 3H), 2.14 (d, J = 14.1 Hz, 3H), 2.04 (d, J = 4.4 Hz, 3H).	531.1

TABLE 2-continued

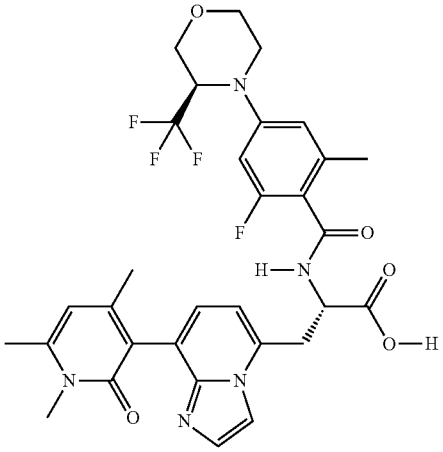
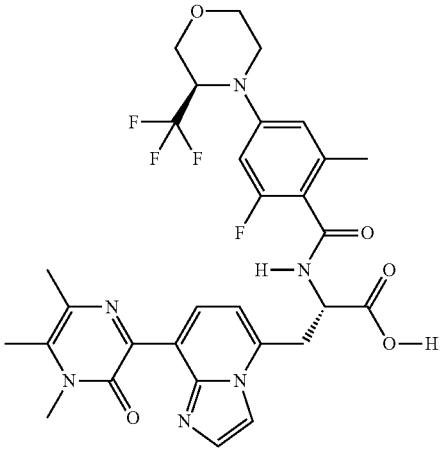
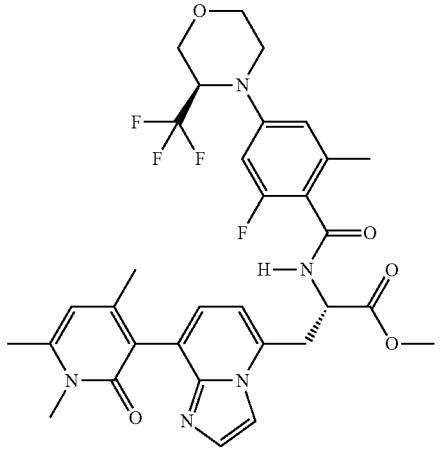
Example	Structure	1H-NMR	M/Z [M + H]+
114		1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 8.3 Hz, 1H), 8.58 (d, 1H), 8.29 (d, J = 6.5, 2.1 Hz, 1H), 7.82-7.68 (m, 1H), 7.42 (dd, J = 27.6, 7.5 Hz, 1H), 6.68-6.55 (m, 2H), 6.29 (s, 1H), 5.08-4.96 (m, 1H), 4.89-4.72 (m, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.98-3.84 (m, 1H), 3.81-3.63 (m, 2H), 3.62-3.48 (m, 2H), 3.46 (s, 3H), 3.37-3.28 (m, 1H), 3.28-3.17 (m, 1H), 2.44 (s, 3H), 2.12-2.02 (m, 3H), 1.95 (s, 3H).	630.2
115		1H NMR (400 MHz, DMSO-d6) δ 13.48 (s, 1H), 13.14 (s, 1H), 9.26 (d, J = 7.9 Hz, 1H), 8.81 (d, J = 8.2 Hz, 1H), 8.72-8.56 (m, 1H), 8.34-8.22 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 6.69-6.52 (m, 2H), 5.10-4.92 (m, 1H), 4.89-4.69 (m, 1H), 4.13 (d, J = 12.6 Hz, 1H), 3.98-3.88 (m, 1H), 3.78 (dd, J = 15.5, 4.5 Hz, 1H), 3.71 (d, J = 12.6 Hz, 1H), 3.67-3.58 (m, 4H), 3.56-3.48 (m, 1H), 3.32 (d, J = 12.5 Hz, 1H), 3.27-3.16 (m, 1H), 2.54 (s, 3H), 2.46 (s, 3H), 2.07 (s, 3H).	631.2
116		1H NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 7.7 Hz, 1H), 8.58 (d, J = 14.0 Hz, 1H), 8.32-8.27 (m, 1H), 7.79 (t, J = 6.9 Hz, 1H), 7.41 (dd, J = 24.9, 7.5 Hz, 1H), 6.70-6.60 (m, 2H), 6.30 (s, 1H), 5.18-5.06 (m, 1H), 4.90-4.77 (m, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.99-3.90 (m, 1H), 3.82-3.67 (m, 5H), 3.67-3.49 (m, 2H), 3.46 (s, 3H), 3.38-3.29 (m, 1H), 3.29-3.17 (m, 1H), 2.44 (s, 3H), 2.11-2.04 (m, 3H), 1.95 (s, 3H).	644.3

TABLE 2-continued

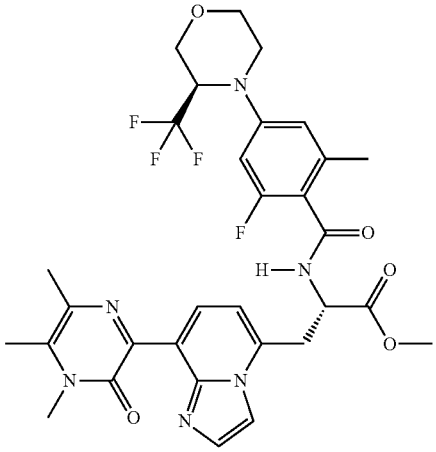
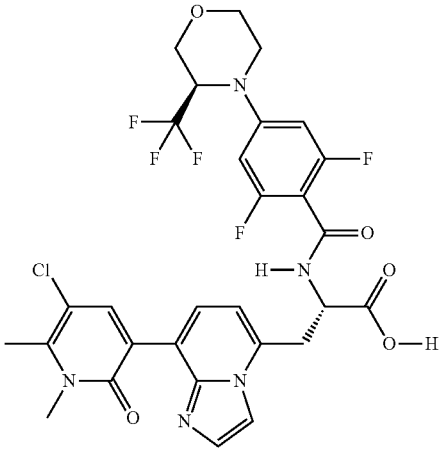
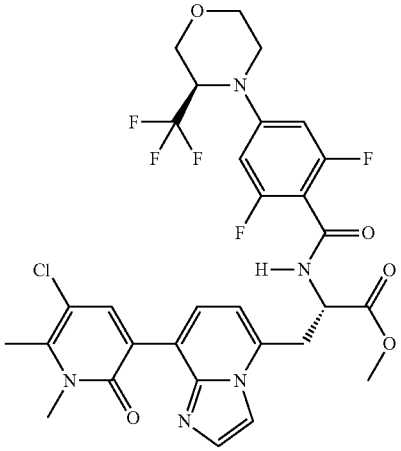
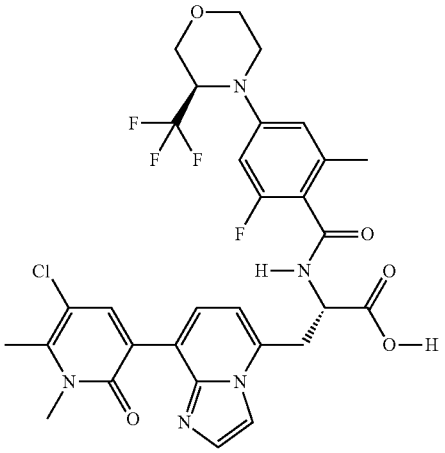
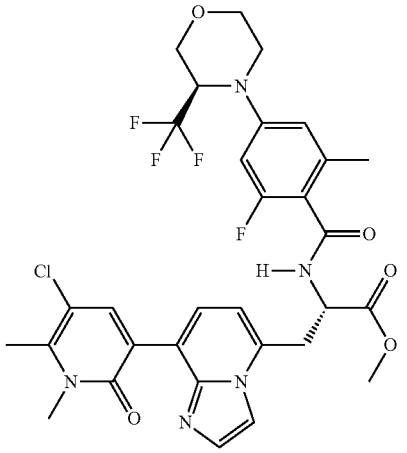
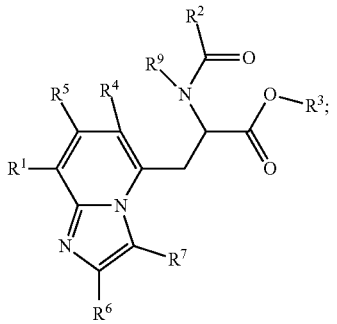
Example	Structure	1H-NMR	M/Z [M + H]+
117		1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 9.26 (d, J = 7.9 Hz, 1H), 8.89 (d, J = 8.0 Hz, 1H), 8.72-8.65 (m, 1H), 8.34-8.29 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 6.70-6.61 (m, 2H), 5.16-5.03 (m, 1H), 4.88-4.75 (m, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.94 (dd, J = 11.2, 3.7 Hz, 1H), 3.80 (dd, J = 15.6, 4.7 Hz, 1H), 3.75-3.58 (m, 8H), 3.57-3.46 (m, 1H), 3.37-3.29 (m, 1H), 3.28-3.16 (m, 1H), 2.54 (s, 3H), 2.50 (s, 3H), 2.07 (s, 3H).	645.3
118		1H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J = 8.1 Hz, 1H), 8.53 (s, 1H), 8.28 (s, 1H), 8.02-7.86 (m, 2H), 7.33 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 11.8 Hz, 2H), 5.03-4.83 (m, 2H), 4.16 (d, J = 12.7 Hz, 1H), 3.95 (dd, J = 11.5, 3.8 Hz, 1H), 3.78-3.68 (m, 2H), 3.64-3.48 (m, 6H), 3.28-3.17 (m, 1H), 2.60 (s, 3H).	654.1
119		1H NMR (400 MHz, DMSO-d6) δ 9.08 (d, J = 7.8 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.84 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 11.9 Hz, 2H), 5.11-5.02 (m, 1H), 4.96-4.85 (m, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.95 (dd, J = 11.5, 3.8 Hz, 1H), 3.80-3.68 (m, 5H), 3.67-3.49 (m, 5H), 3.42 (d, 1H), 3.28-3.18 (m, 1H), 2.61 (s, 3H).	668.1

TABLE 2-continued

Example	Structure	1H-NMR	M/Z [M + H]+
120		1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 8.2 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.31 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.89 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 6.71-6.61 (m, 2H), 5.08-4.97 (m, 1H), 4.89-4.77 (m, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.94 (dd, J = 11.4, 3.7 Hz, 1H), 3.78-3.69 (m, 1H), 3.61 (s, 3H), 3.57-3.53 (m, 3H), 3.34 (d, J = 12.3 Hz, 1H), 3.29-3.18 (m, 1H), 2.61 (s, 3H), 2.07 (s, 3H).	650.1
121		1H NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 8.0 Hz, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.32 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.89 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 6.73-6.61 (m, 2H), 5.15-5.04 (m, 1H), 4.90-4.77 (m, 1H), 4.14 (d, J = 12.6 Hz, 1H), 3.95 (dd, J = 11.3, 3.7 Hz, 1H), 3.80-3.68 (m, 4H), 3.65-3.48 (m, 6H), 3.34 (d, J = 12.4 Hz, 1H), 3.23 (t, J = 12.1 Hz, 1H), 2.61 (s, 3H), 2.08 (s, 3H).	664.1

1-47. (canceled)

48. A method for treating an inflammatory disease or condition associated with α4β7 integrin, comprising administrating to a subject in need thereof an effective amount of a pharmaceutical composition comprising a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

wherein R^1 is selected from A^1, A^2, and A^3;

A^1 is 5-10 membered heteroaryl containing one to five heteroatoms or groups independently selected from S, N, and O; wherein A^1 optionally comprises one to three C(O); and wherein A^1 is optionally substituted with one to six R^{A1}:

A^2 is C_{5-10}aryl, optionally substituted with one to six R^{A1}; and

A^3 is $—NR^{1a}R^{1b}$;

wherein each R^{A1} is independently selected from halo, cyano, hydroxyl, $—NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, $—S(O)_m—C_{1-4}$alkyl, C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$alkylene-C_{3-8} cycloalkyl, and —O-phenyl;

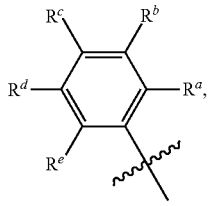
wherein each C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, $—O—C_{3-8}$cycloalkyl, —O-(3-6 membered heterocyclyl), $—O—C_{1-4}$alkylene-C_{3-8}cycloalkyl, and —O-phenyl of R^{A1} is

optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, and C_{1-6}haloalkoxyl; and

wherein each C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl of R^{41} is optionally substituted with one to three R^{1c} wherein each R^{1c} is independently selected from C_{1-4}alkoxyl, hydroxyl, cyano, —$NR^{1a}R^{1b}$, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl; wherein each C_{3-8}cycloalkyl and 3-6 membered heterocyclyl of R^{1c} is independently optionally substituted with one to three R^{1d}; and

wherein each R^{1d} is independently selected from halo cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, C_{1-6}haloalkoxyl, C_{3-8} cycloalkyl, and 3-6 membered heterocyclyl;

R^2 is selected from



and C_{3-8}cycloalkyl;

wherein each R^a, R^b, R^c, R^d, and R^e is independently selected from H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{1-8}haloalkyl, C_{1-6}alkoxyl, C_{1-8}haloalkoxyl, —$NR^{2a}R^{2b}$, —$NR^{2a}S(O)_nR^{2c}$, —$S(O)_m$—R^{2c}, —$S(O)_nNR^{2a}R^{2b}$, —$CONR^{2a}R^{2b}$, —$NR^{2a}COOR^{2b}$, —$NR^{2a}COR^{2c}$, C_{3-6}cycloalkyl, C_{6-10}aryl, 3-8 membered heterocyclyl, and 5-6 membered heteroaryl;

wherein each C_{1-6}alkyl, C_{1-8}haloalkyl, C_{1-6}alkoxyl, and C_{1-8}haloalkoxyl of R^a, R^b, R^c, R^d, and R^e is independently optionally substituted with one to two R^{2d}; and

wherein each C_{6-10}aryl, and 5-6 membered heteroaryl of R^a, R^b, R^c, R^d, and R^e is optionally substituted with one to four R^{2f};

wherein each C_{3-6}cycloalkyl, and 3-8 membered heterocyclyl of R^a, R^b, R^c, R^d, and R^e is optionally substituted with one to six groups with one to six groups independently selected from =$CR^{2a}R^{2b}$ and R^{2f};

wherein each R^{2a} and R^{2b} is independently selected from H, C_{1-6}alkyl, and C_{1-8}haloalkyl; each C_{1-6}alkyl and C_{1-8}haloalkyl of R^{2a} and R^{2b} is optionally substituted with one group selected from cyano, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, phenyl, and 4-6 membered heterocyclyl; wherein each C_{3-6}cycloalkyl, phenyl, and 4-6 membered heterocyclyl is optionally substituted with one to three groups independently selected from halo, cyano, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl;

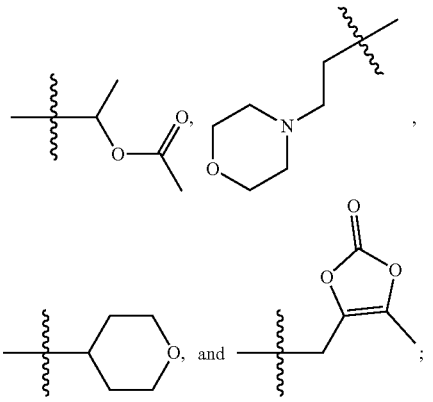
wherein R^{2c} is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, and phenyl; wherein phenyl of R^{2c} is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}haloalkyl, and 6 membered heteroaryl; and wherein the 6 membered heteroaryl is optionally substituted with one to three groups independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl;

wherein each R^{2d} is independently selected from cyano, hydroxyl, C_{1-4}alkoxyl, and —$NR^{1a}R^{1b}$;

wherein each R^{2f} is independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl; and

the C_{3-8}cycloalkyl of R^2 is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, —$NR^{1a}R^{1b}$, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-8}haloalkoxyl, and C_{1-8}haloalkyl;

R^3 is selected from selected from H, methyl, ethyl, propyl, butyl, —$CH_2C(O)N(CH_3)_2$, —$(CH_2)_2N(CH_2CH_3)_2$, —CH_2—O—$C(O)CH_3$, —$(CH_2)_2$—O—$C(O)CH_3$, —CH_2—O—$C(O)C(CH)_3$, —$(CH_2)_2$—O—$C(O)C(CH)_3$, —CH_2—O—C(O)—O—CH_3, —$CH(CH_3)$—O—C(O)—O—CH_3, —CH_2—O—C(O)—O—CH_2CH_3, —CH_2—O—C(O)—O—$CH(CH_3)_2$, —CH_2—O—C(O)—O—$C(CH_3)_3$, —$(CH_2)_2C(O)CH_3$,



or

R^3 together with the N that attaches to R^9 forms a 5 membered heterocyclyl; wherein the 5 membered heterocyclyl is optionally substituted with one to two groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, and C_{6-10}aryl; wherein the C_{6-10}aryl is optionally substituted with one to three groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl;

each R^4, R^5, R^6, and R^7 is independently selected from H, halo, —$NR^{1a}R^{1b}$, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}haloalkyl, and C_{3-6}cycyloalky;

R^9 is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl;

each R^{1a} and R^{1b} is independently selected from H, C_{1-6}alkyl, and C_{1-6}haloalkyl;

m is selected from 0, 1, and 2;

n is 1 or 2; and

at least one pharmaceutically acceptable carrier.

49. The method of claim **48**, wherein the disease or condition is an inflammatory disease.

50. The method of claim **49** wherein the inflammatory disease of condition is selected from inflammatory bowel disease (IBD), Ulcerative colitis (UC), Crohn's disease, graft-versus-host disease (GVHD), and primary sclerosing cholangitis (PSC).

51. The method of claim **48**, further comprising at least one or more additional therapeutic agent.

52. The method of claim **51**, wherein the at least one or more additional therapeutic agent is a JAK tyrosine kinase inhibitor, Tumor Progression Locus 2 (TPL2) inhibitors, Toll-like receptor 8 (TLR8) inhibitors, and IRAK4 inhibitors.

53. The method of claim **52**, wherein the as least one or more additional therapeutic agent is a JAK tyrosine kinase inhibitor and wherein the JAK tyrosine kinase inhibitor is fligotinib.

* * * * *