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(73) Patenthaver: **GILEAD SCIENCES, INC., 333 Lakeside Drive Foster City, California 94404, USA**

(72) Opfinder: **BLOMGREN, Peter A., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA**
CAMPBELL, Taryn, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
CHANDRASEKHAR, Jayaraman, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
CLARK, Christopher T., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
CODELLI, Julian A., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
CURRIE, Kevin S., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
KROPF, Jeffrey E., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
MOAZAMI, Yasamin, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
NAVA, Nicole, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
PATEL, Leena, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
PERREAULT, Stephane, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
PERRY, Jason K., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
SEDILLO, Kassandra F., 12 Lawrence Drive Apt. 308, Princeton, New Jersey 08540, USA
SEEGER, Natalie, 21 W. Hartwell Avenue, Salt Lake City, Utah 84115, USA
STEVENS, Kirk L., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
TREIBERG, Jennifer Anne, c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
YEUNG, Suet C., c/o Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, California 94404, USA
ZHAO, Zhongdong, c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404, USA

Fortsættes ...

(74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**

(54) Benævnelse: **3-(QUINOLIN-8-YL)-1,4-DIHYDROPYRIDO[3,4-D]PYRIMIDIN-2,4-DION-DERIVATER SOM ALPHA4BETA7-INTEGRINHÆMMERE TIL BEHANDLING AF INFLAMMATORISKE SYGDOMME**

(56) Fremdragne publikationer:
WO-A1-01/21584
WO-A1-2006/131200
WO-A1-99/36393
SIRCAR ILA ET AL: "Synthesis and SAR of N-Benzoyl-L-Biphenylalanine Derivatives: Discovery of TR-14035, A Dual alpha4beta7/alpha4beta1 Integrin Antagonist", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 10, no. 6, 2002, pages 2051 - 2066, XP002250477, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(02)00021-4

DESCRIPTION

Description

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/752,805, filed October 30, 2018, and U.S. Provisional Application No. 62/823,987, filed March 26, 2019.

FIELD

[0002] The present disclosure relates generally to novel compounds that have α4β7 integrin inhibitory action. These compounds can be used in therapy as an inhibitor of α4β7 integrin.

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] WO 99/36393 A discloses inhibitors of α4β7 mediated adhesion and their use in therapy. Sircar et al., Bioorg. Med. Chem 10 (2002): 2051-2066, discloses the synthesis and structure-activity relationship (SAR) of novel compounds derived from N-benzoyl-L-biphenylalanine, which showed integrin antagonist activity. WO 01/21584 A discloses tyrosine-derived compounds that are said to be inhibitors of alpha4 containing integrin-mediated

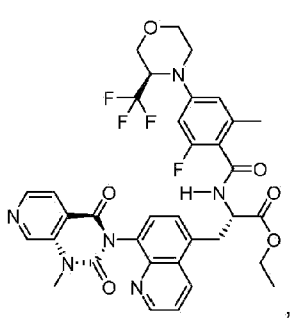
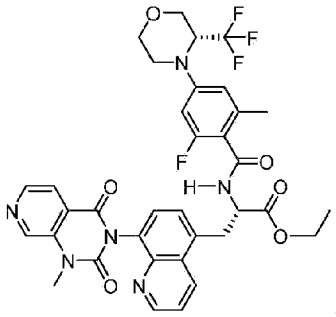
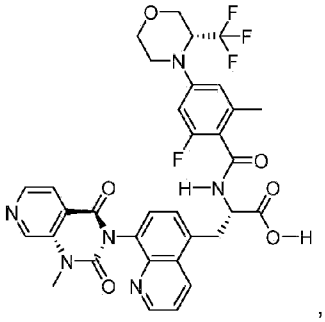
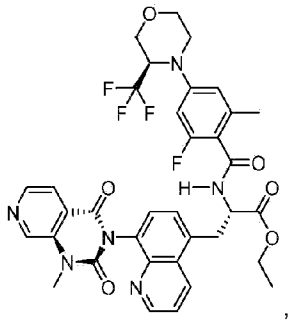
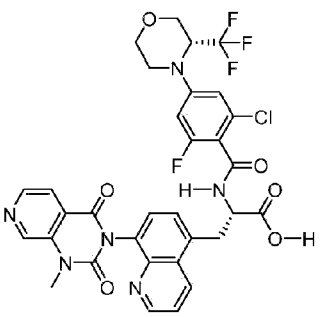
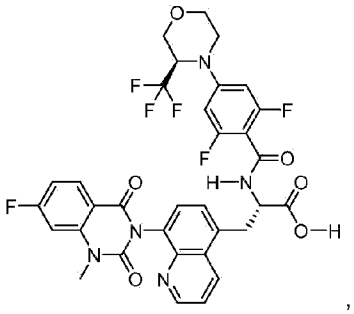
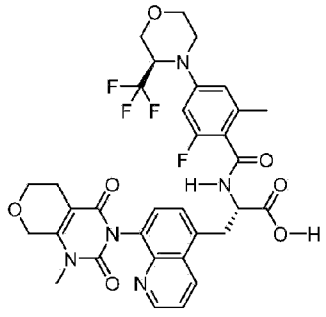
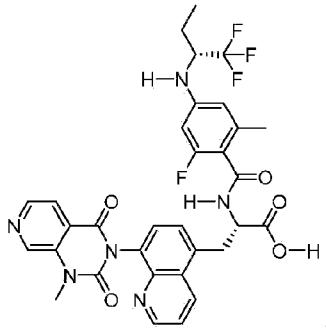
binding to ligands such as VCAM-1 and MAdCAM. WO 2006/131200 A discloses 2,6-quinolinyl derivatives, which are said to be useful in the treatment of α4β1 and/or α4β7 dependent medical conditions.

[0006] There is a need to for improved α4β7 integrin antagonist molecules for the treatment of autoimmune and inflammatory diseases, including inflammatory bowel disease.

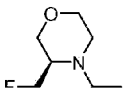
SUMMARY

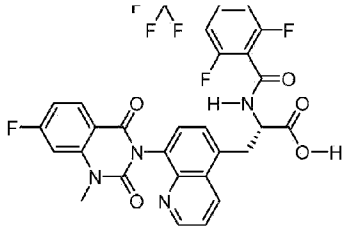
[0007] The present invention is defined by the appended claims.

[0008] In one aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, which is


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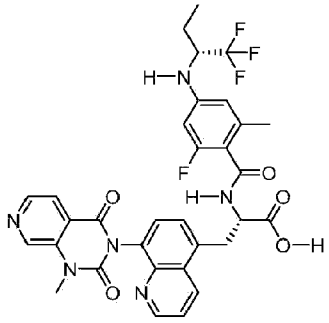
[0009] In one embodiment of the present invention, the compound is





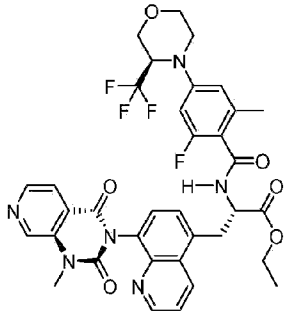
or a pharmaceutically acceptable salt thereof.

[0010] In one embodiment of the present invention, the compound is



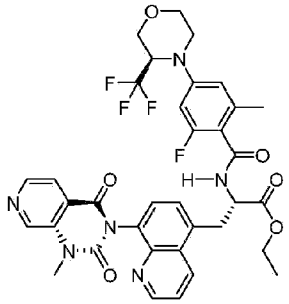
or a pharmaceutically acceptable salt thereof.

[0011] In one embodiment of the present invention, the compound is



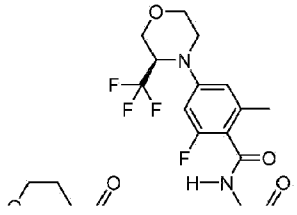
or a pharmaceutically acceptable salt thereof.

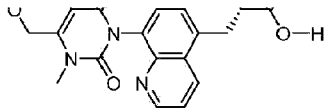
[0012] In one embodiment of the present invention, the compound is



or a pharmaceutically acceptable salt thereof.

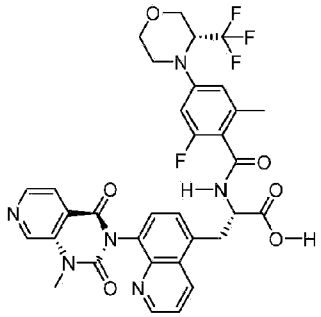
[0013] In one embodiment of the present invention, the compound is





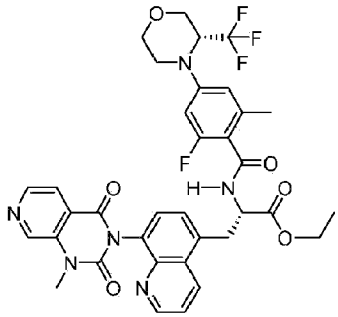
or a pharmaceutically acceptable salt thereof.

[0014] In one embodiment of the present invention, the compound is



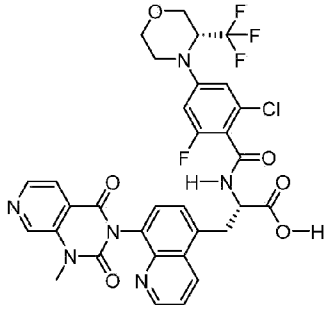
or a pharmaceutically acceptable salt thereof.

[0015] In one embodiment of the present invention, the compound is



or a pharmaceutically acceptable salt thereof.

[0016] In one embodiment of the present invention, the compound is



or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

Definitions and General Parameters

[0017] The following description sets forth exemplary methods, parameters and the like.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] "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. $-CH(CH_3)_2$).

[0024] "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.

[0025] "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).

[0026] "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_{2-6} 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.

[0027] "Alkoxy" and "alkoxyl" are used interchangeably and refer to the group "alkyl-O-". Examples of alkoxyl and alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. "Haloalkoxyl" refers to an alkoxyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen.

[0028] "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.

[0029] "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.

[0030] "Azido" refers to the group $-N_3$.

[0031] "Cyano" or "carbonitrile" refers to the group -CN.

[0032] "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.

[0033] "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.

[0034] The term "fused" refers to a ring which is bound to an adjacent ring.

[0035] "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.

[0036] "Spiro" also refers to a bicyclic portion, wherein the two rings are connected through a single common atom. Spiro compounds may be fully carbocyclic or heterocyclic. Examples of spiro groups include 5-oxa-8-azaspiro[3.5]nonane, 7-oxa-4-azaspiro[2.5]octane, and $5A^2$-azaspiro[2.4]heptane.

[0037] "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 ($-CF_3$).

[0038] 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 O, N, S, S(O), $S(O)_2$,

and N-oxide 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.

[0039] "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.

[0040] "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.

[0041] "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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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 substituents 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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 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.

[0051] 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.

[0052] 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.

[0053] 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 inorganic 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.

[0054] 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.

[0055] Salts, such as TFA salts, can be converted to the free-bases/acids or other pharmaceutically acceptable salts.

[0056] 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.

[0057] "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.

[0058] "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 be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0059] "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. The subject can be a mammal, e.g., a human.

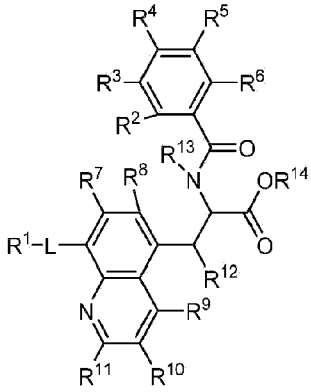
[0060] The term "therapeutically effective amount" or "effective amount" of a compound described herein or pharmaceutically acceptable salts, stereoisomer, or a mixture thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration 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.

[0061] 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. The inhibition of α4β7 integrin activity may be compared in the same subject prior to treatment, or other subjects not receiving the treatment.

COMPOUNDS

[0062] Provided herein are compounds that function as inhibitors of α4β7 integrin. The present disclosure provides a compound having structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I);

wherein:

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

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

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

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

A^3 is C_{5-10}cycloalkyl or 5-14 membered heterocyclyl; wherein A^3 is optionally substituted with one to four groups independently selected from oxo and R^a; and

A^4 is $-NR^{a1}R^{a2}$;

wherein each R^a is independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, $-S(O)_m-C_{1-6}$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^a is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, 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_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, and -$S(O)_m$-C_{1-6}alkyl of R^a is optionally substituted with one to three R^{a3}, wherein each R^{a3} is independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-6}alkoxyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl;

wherein each C_{3-8}cycloalkyl and 3-6 membered heterocyclyl of R^{a3} is optionally substituted with one to three R^{a4}; and each R^{a4} is independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, 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;

each R^2, R^3, R^4, R^5, and R^6 is independently selected from H, 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, -$NR^{b1}R^{b2}$, -$R^{b3}S(O)_mR^{b4}$, -$S(O)_mR^{b4}$, -$NR^{b1}S(O)_nR^{b4}$, -$COOR^{b1}$, -$CONR^{b1}R^{b2}$, -$NR^{b1}COOR^{b2}$, -$NR^{b1}COR^{b4}$, -$R^{b3}NR^{b1}R^{b2}$, -$S(O)_nNR^{b1}R^{b2}$, C_{3-12}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-12 membered heterocyclyl;

wherein 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^2, R^3, R^4, R^5, and R^6 is optionally substituted with one to two R^c; wherein each R^c is independently selected from azido, oxo, cyano, halo, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-4}alkoxyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^c is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-6}haloalkyl, C_{1-4}alkoxyl, and C_{3-6}cycloalkyl;

wherein each C_{6-10}aryl, and 5-6 membered heteroaryl of R^2, R^3, R^4, R^5, and R^6 is independently optionally substituted with one to five R^b; and

wherein each C_{3-12}cycloalkyl, and 3-12 membered heterocyclyl of R^2, R^3, R^4, R^5, and R^6 is independently optionally substituted with one to six groups independently selected from $=CR^{b1}R^{b2}$ and R^b;

wherein each R^b is independently selected from azido, cyano, halo, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-6}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^b is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl;

wherein each R^{b1} and R^{b2} is independently selected from H, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-3}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-8 membered heterocyclyl;

wherein each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{b1} and R^{b2} is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, 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; and

wherein each C_{1-8}alkyl and C_{1-8}haloalkyl of R^{b1} and R^{b2} is optionally substituted with one to two R^{b5};

wherein R^{b3} is C_{1-4}alkylene;

wherein R^{b4} is selected from C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and the 4-6 membered heterocyclyl of R^{b4} is optionally substituted with one to three R^{b6};

wherein each R^{b5} is independently selected from cyano, hydroxyl, C_{1-4}alkoxyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; and each C_{1-4}alkoxyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{b5} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, and phenyl; and

wherein each R^{b6} is independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, phenyl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl; wherein each C_{3-6}cycloalkyl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl of R^{b6} is independently optionally substituted with one to three groups independently selected from halo, cyano, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl; or

R^2 and R^3, R^3 and R^4, or R^5 and R^6 together with the atoms to which they are attached form a C_{6-10}aryl, 5-6 membered heteroaryl, C_{3-6}cycloalkyl, or 5-6 membered heterocyclyl; wherein each C_{6-10}aryl, 5-6 membered heteroaryl, C_{3-6}cycloalkyl, and 5-6 membered heterocyclyl is independently optionally substituted with one to three groups independently selected from halo, cyano, $-NR^{a1}R^{a2}$, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, C_{1-4}alkylene-C_{3-8}cycloalkyl, C_{1-4}alkylene-C_{6-10}aryl, and C_{1-4}alkylene-(5-6 membered heteroaryl);

each R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, hydroxyl, cyano, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, and $-NR^{a1}R^{a2}$;

R^{13} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl; and

R^{14} 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}alkyl, 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);

wherein 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^{14} is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl; or

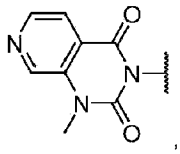
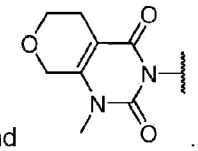
R^{14} together with the N that attaches to R^{13} forms a 5 membered heterocyclyl; wherein the 5 membered heterocyclyl is optionally substituted with one to two groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, and C_{6-10}aryl; wherein the C_{6-10}aryl is optionally substituted with one to three groups independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxyl, and C_{1-6}haloalkyl;

each R^{a1} and R^{a2} is independently selected from H, C_{1-6}alkyl, and C_{1-6}haloalkyl;

m is selected from 0, 1, and 2; and

n is selected from 1, and 2.

[0063] In some embodiments of the present invention, R^1 of formula (I) is selected from:

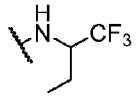

, and

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[0064] In formula (I), , each R^2, R^3, R^4, R^5, and R^6 can be independently selected from H, halo, CN, OH, $-NR^{b1}R^{b2}$, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, and C_{1-6}haloalkoxyl. For example, each R^2, R^3, R^4, R^5, and R^6 can be independently selected from H, F, Cl, CN, OH, $-NH_2$, $-N(CH_3)_2$, $-CH_3$, CD_3, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, and $-OCF_3$.In some embodiments of the present invention, both R^2 and R^6 of formula (I) are F.

[0065] In some embodiments of the present invention R^2 of formula (I) is F, and R^6 of formula (I) is $-CH_3$.

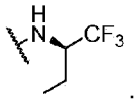
[0066] In formula (I), R^4 can be selected from H, $-NR^{b1}R^{b2}$, $-NR^{b1}S(O)_nR^{b4}$, and 3-8 membered heterocyclyl. For example, the 3-8 membered heterocyclyl of R^4 contains one to two heteroatoms or groups independently selected from S, N, O, and $S(O)_2$.

[0067] In some embodiments of the present invention, R^4 of formula (I) is



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[0068] In some embodiments of the present invention, R^4 of formula (I) is



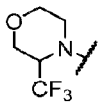
.

[0069] In formula (I), R^4 can be a 3-8 membered heterocyclyl optionally substituted with one to three R^b; and each R^b is independently selected from halo, hydroxyl, cyano, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-4}haloalkyl. In some embodiments, each R^4 is optionally substituted with one to two groups independently selected from F, Cl, CN, -OH, $-CH_3$, $-CH(CH_3)_2$, and $-CF_3$.

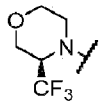
[0070] For example, in formula (I), R^4 can be a 3-8 membered spiro, fused or bridged heterocyclyl. For example, R^4 can be selected from azetidinyl, aziridinyl, imidazolidinyl, morpholinyl, oxetanyl, piperazinyl, piperidinyl, pyrazolidinyl, piperidinyl, pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, tetrahydrothiophenyl, dihydropyridinyl, tetrahydropyridinyl, 1,1-dioxide-thiomorpholinyl, and quinuclidinyl; and each R^4 is optionally substituted with one to three R^b. For example, R^4 can be selected from morpholinyl, piperidinyl, tetrahydropyranyl, and pyrrolidinyl; each R^4 is optionally substituted with one to three R^b. Each R^b can be independently selected from halo, hydroxyl, cyano, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}alkoxyl, and C_{1-}

$_4$haloalkyl. For example, each R^b can be independently selected from F, Cl, CN, -OH, -CH_3, -$CH(CH_3)_2$, and -CF_3.

[0071] In some embodiments of the present invention, R^4 of formula (I) is



[0072] In some embodiments of the present invention, R^4 of formula (I) is



[0073] In formula (I), each R^7, R^8, R^9, R^{10}, and R^{11} can be independently selected from H, F, Cl, CN, -NH_2, -$N(CH_3)_2$, -CH_3, -CH_2F, -CHF_2, -CF_3, -OCH_3, and -OCF_3. For example, each R^7, R^8, R^9, R^{10}, and R^{11} can be selected from H, F, CN, -$N(CH_3)_2$, -CH_3, and -CF_3.

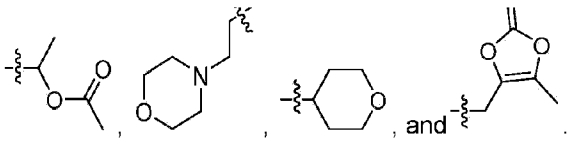
[0074] In formula (I), R^{12} can be H or -CH_3.

[0075] In formula (I), R^{13} can be H or -CH_3.

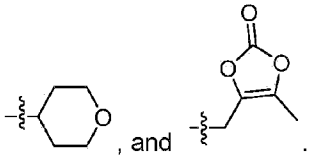
[0076] In formula (I), each R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} can be H.

[0077] In formula (I), R^{14} can be selected from C_{1-6}alkyl, C_{3-8}cycloalkyl, and 4-6 membered heterocyclyl. For example, each C_{3-8}cycloalkyl and 4-6 membered heterocyclyl of R^{14} can be optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, and C_{1-4}haloalkyl. For example, R^{14} can be selected from -C_{1-4}alkylene-$NR^{a1}R^{a2}$, -C_{1-4}alkylene-C(O)N $R^{a1}R^{a2}$, -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-$NR^{a1}R^{a2}$, and -C_{1-4}alkylene-O-C_{1-4}alkyl. When administered to a biological system, provided esters can generate active ingredients where R^{14} is hydrogen, as a result of chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s).

[0078] In formula (I), R^{14} can be 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-$C(CH_3)_3$, -$(CH_2)_2C(O)CH_3$,



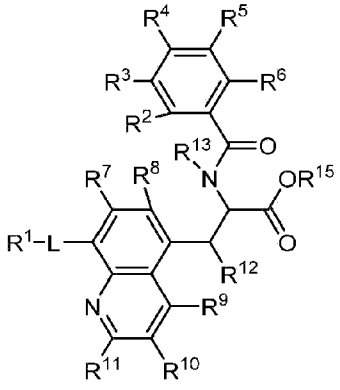
For example, R^{14} can be selected from H, $-CH_2-O-C(O)C(CH)_3$, $-CH(CH_3)-O-C(O)-O-CH_3$,



[0079] In some embodiments of the present invention, R^{14} is H.

[0080] In some embodiments of the present invention, R^{14} is CH_2CH_3.

[0081] The present disclosure also provides compounds of Formula (J):



(J);

or a pharmaceutically acceptable salt thereof, wherein:

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

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

A^1 is 5-10 membered heteroaryl containing one to five heteroatoms 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^a;

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

A^3 is C_{5-10}cycloalkyl or 5-14 membered heterocyclyl; wherein A^3 is optionally substituted with one to four groups independently selected from oxo and R^a; and

A^4 is $-NR^{a1}R^{a2}$;

wherein each R^a is independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, 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_{1-6}alkyl, C_{3-8}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, -O-C_{3-3}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_{3-3}cycloalkyl, -O-(3-6 membered heterocyclyl), -O-C_{1-4}alkylene-C_{3-8}cycloalkyl, and -O-phenyl of R^a is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, 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_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, and -$S(O)_m$-C_{1-6}alkyl of R^a is optionally substituted with one to three R^{a3}, wherein each R^{a3} is independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-6}alkoxyl, C_{3-3}cycloalkyl, and 3-6 membered heterocyclyl;

wherein each C_{3-8}cycloalkyl and 3-6 membered heterocyclyl of R^{a3} is optionally substituted with one to three R^{a4}; and each R^{a4} is independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, C_{1-6}haloalkoxyl, C_{3-3}cycloalkyl, and 3-6 membered heterocyclyl;

each R^2, R^3, R^4, R^5, and R^6 is independently selected from H, 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, -$NR^{b1}R^{b2}$, - $R^{b3}S(O)_mR^{b4}$, -$S(O)_mR^{b4}$, -$NR^{b1}S(O)_nR^{b4}$, -$COOR^{b1}$, -$CONR^{b1}R^{b2}$, -$NR^{b1}COOR^{b2}$, -$NR^{b1}COR^{b4}$, -$R^{b3}NR^{b1}R^{b2}$, -$S(O)_nNR^{b1}R^{b2}$, C_{3-12}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-12 membered heterocyclyl;

wherein 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^2, R^3, R^4, R^5, and R^6 is optionally substituted with one to two R^c; wherein each R^c is independently selected from azido, oxo, cyano, halo, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-4}alkoxyl, C_{3-3}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^c is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, -$NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-6}haloalkyl, C_{1-4}alkoxyl, and C_{3-6}cycloalkyl;

wherein each C_{6-10}aryl, and 5-6 membered heteroaryl of R^2, R^3, R^4, R^5, and R^6 is independently optionally substituted with one to five R^b; and

wherein each C_{3-12}cycloalkyl, and 3-12 membered heterocyclyl of R^2, R^3, R^4, R^5, and R^6 is independently optionally substituted with one to six groups independently selected from

$=CR^{b1}R^{b2}$ and R^b;

wherein each R^b is independently selected from azido, cyano, halo, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-6}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^b is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl;

wherein each R^{b1} and R^{b2} is independently selected from H, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 3-8 membered heterocyclyl;

wherein each C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{b1} and R^{b2} is independently optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, 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; and

wherein each C_{1-8}alkyl and C_{1-8}haloalkyl of R^{b1} and R^{b2} is optionally substituted with one to two R^{b5};

wherein R^{b3} is C_{1-4}alkylene;

wherein R^{b4} is selected from C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-6}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; wherein each C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and the 4-6 membered heterocyclyl of R^{b4} is optionally substituted with one to three R^{b6};

wherein each R^{b5} is independently selected from cyano, hydroxyl, C_{1-4}alkoxyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl; and each C_{1-4}alkoxyl, C_{3-8}cycloalkyl, C_{6-10}aryl, 5-6 membered heteroaryl, and 4-6 membered heterocyclyl of R^{b5} is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, and phenyl; and

wherein each R^{b6} is independently selected from halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, C_{3-6}cycloalkyl, phenyl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl; wherein each C_{3-6}cycloalkyl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl of R^{b6} is independently optionally substituted with one to three groups independently selected from halo, cyano, $-NR^{a1}R^{a2}$, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxyl; or

R^2 and R^3, R^3 and R^4, or R^5 and R^6 together with the atoms to which they are attached form a C_{6-10}aryl, 5-6 membered heteroaryl, C_{3-6}cycloalkyl, or 5-6 membered heterocyclyl; wherein each C_{6-10}aryl, 5-6 membered heteroaryl, C_{3-6}cycloalkyl, and 5-6 membered heterocyclyl is independently optionally substituted with one to three groups independently selected from halo, cyano, -$NR^{a1}R^{a2}$, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{3-3}cycloalkyl, 3-6 membered heterocyclyl, C_{6-10}aryl, 5-6 membered heteroaryl, C_{1-4}alkylene-C_{3-8}cycloalkyl, C_{1-4}alkylene-C_{6-10}aryl, and C_{1-4}alkylene-(5-6 membered heteroaryl);

each R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, hydroxyl, cyano, C_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxyl, and -$NR^{a1}R^{a2}$;

R^{13} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl;

R^{15} is selected from H, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{3-10}cycloalkyl, 3-14 membered heterocyclyl, C_{6-10}aryl, 5-10 membered heteroaryl, -C_{1-4}alkylene-$NR^{a1}R^{a2}$, -C_{1-4}alkylene-$C(O)NR^{a1}R^{a2}$, and -L^1-R^{16};

wherein L^1 is selected from -C_{1-4}alkylene-, -C_{1-4}alkylene-O-, -C_{1-4}alkylene-C(O)-, -C_{1-4}alkylene-O-C(O)-, -C_{1-4}alkylene-O-C(O)-C_{1-4}alkylene-, -C_{1-4}alkylene-C(O)-O-, -C_{1-4}alkylene-C(O)-O-C_{1-4}alkylene, -C_{1-4}alkylene-O-C(O)-O-, -C_{1-4}alkylene-O-C(O)-O-C_{1-4}alkylene-, -C_{1-4}alkylene-NR^{a1}C(O)-O-, and -C_{1-4}alkylene-O-C(O)-NR^{a1}-; and

wherein R^{16} is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-14 membered heterocyclyl, C_{6-10}aryl, and 5-10 membered heteroaryl;

wherein each C_{3-10}cycloalkyl, 3-14 membered heterocyclyl, C_{6-10}aryl, and 5-10 membered heteroaryl of R^{15} and R^{16} is optionally substituted with one to four groups independently selected from halo, hydroxyl, -$COOR^{b7}$, -$NR^{a1}R^{a2}$, -$S(O)_2R^{a5}$, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}haloalkyl, C_{1-4}haloalkoxyl, and -C_{1-4}alkylene-$NR^{a1}R^{a2}$;

each R^{a1} and R^{a2} is independently selected from H, C_{1-6}alkyl, and C_{1-6}haloalkyl;

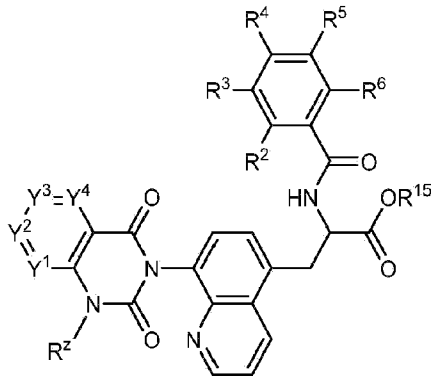
R^{a5} is C_{1-6}alkyl;

R^{b7} is independently selected from H and C_{1-6}alkyl;

m is selected from 0, 1, and 2; and

n is selected from 1, and 2.

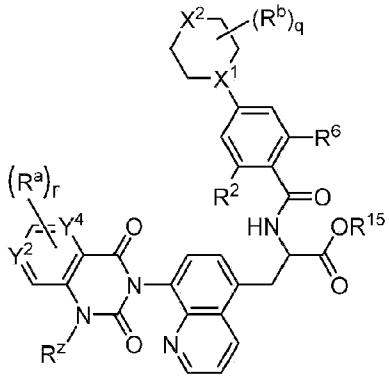
[0082] The present disclosure also provides a compound of formula (J), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Ja):



(Ja);

wherein each Y^1, Y^2, Y^3, and Y^4 is independently selected from CR^y, and N; wherein each R^y is independently selected from H and R^a; and wherein R^z is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl.

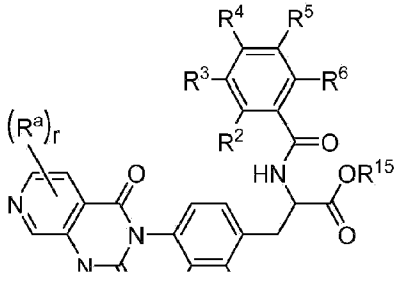
[0083] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Jb):

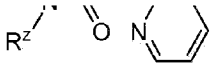


(Jb);

wherein each Y^2 and Y^4 is independently selected from CR^y, and N. Each R^y is independently selected from H and R^a. R^z is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-3}cycloalkyl, and 3-6 membered heterocyclyl. X^1 is selected from CR^{x1}, and N. X^2 is selected from $CR^{x1}R^{x2}$, NR^{x2}, O, and $S(O)_2$. R^{x1} is selected from H, and R^b; and R^{x2} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. q is selected from 0, 1, 2, and 3; and r is selected from 0, 1, and 2.

[0084] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Jc):

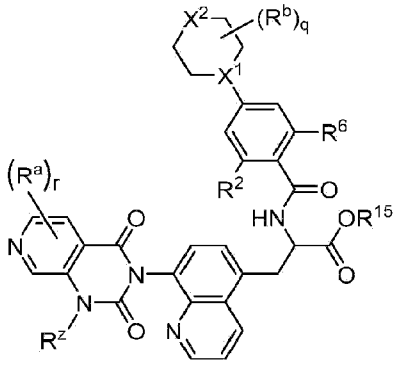




(Jc);

wherein R^z is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl; and wherein r is selected from 0, 1, 2, and 3.

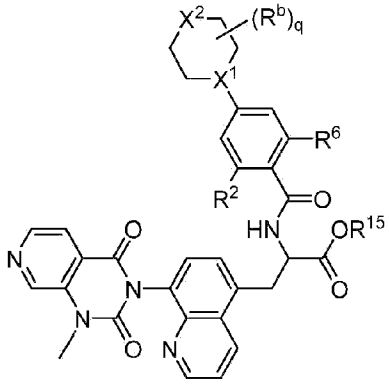
[0085] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Jd):



(Jd);

wherein R^z is selected from H, $-CH_3$, $-CD_3$-CH_2F, $-CHF_2$, $-CF_3$, and $-CH_2CH_3$; X^1 is selected from CR^{x1}, and N. X^2 is selected from $CR^{x1}R^{x2}$, NR^{x2}, O, and $S(O)_2$. R^{x1} is selected from H, and R^b; and R^{x2} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. q is selected from 0, 1, 2, and 3; and r is selected from 0, 1, 2, and 3.

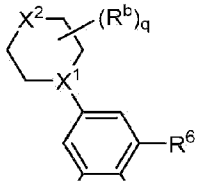
[0086] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Je):

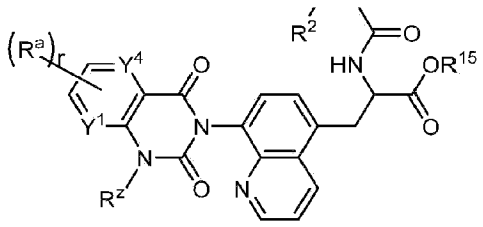


(Je);

wherein X^1 is selected from CR^{x1}, and N. X^2 is selected from $CR^{x1}R^{x2}$, NR^{x2}, O, and $S(O)_2$. R^{x1} is selected from H, and R^b; and R^{x2} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. q is selected from 0, 1, 2, and 3.

[0087] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Jf):

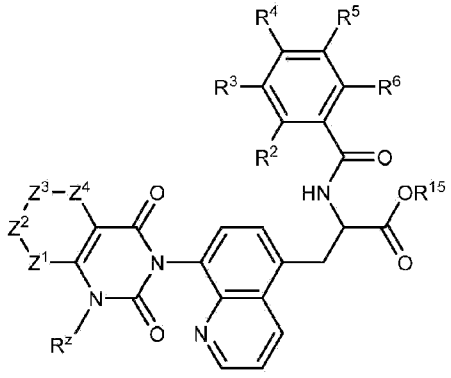




(Jf);

wherein each Y^1 and Y^4 is independently selected from CR^y, and N. Each R^y is independently selected from H and R^a. R^z is selected from H, $-CH_3$, $-CD_3$-CH_2F, $-CHF_2$, $-CF_3$, and $-CH_2CH_3$. X^1 is selected from CR^{x1}, and N. X^2 is selected from $CR^{x1}R^{x2}$, NR^{x2}, O, and $S(O)_2$. R^{x1} is selected from H, and R^b; and R^{x2} is selected from H, C_{1-4}alkyl, and C_{1-4}haloalkyl. q is selected from 0, 1, 2, and 3; and r is selected from 0, 1, and 2.

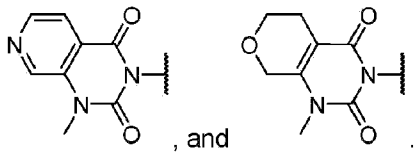
[0088] The present disclosure also provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (Jg):



(Jg);

wherein each Z^1, Z^2, Z^3, and Z^4 is independently selected from $CR^{y1}R^{y2}$, NR^{z1}, and O; wherein each R^{y1} and R^{y2} is independently selected from H and R^a; and wherein each R^z and R^{z1} is independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, and 3-6 membered heterocyclyl.

[0089] In some embodiments of the present invention, R^1 of formula (I), or (J) is selected from:



, and

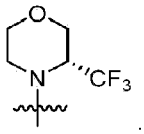
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[0090] In formula (J), (Ja), or (Jc), or a pharmaceutically acceptable salt thereof, R^3 and R^5 can be H.

[0091] In formula (J), (Ja), (Jb), (Jc), (Jd), (Je), or (Jf), or a pharmaceutically acceptable salt thereof, each R^2 and R^6 can be independently selected from H, halo, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}haloalkyl, C_{1-4}haloalkoxyl, C_{3-6}cycloalkyl, and 3-7 membered heterocyclyl. For example, each R^2 and R^6 is independently selected from F, Cl, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, -

CH_2F, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-NH_2$, and $-N(CH_3)_2$. For example, each R^2 and R^6 is independently selected from F, Cl, and $-CH_3$. In some embodiments of the present invention, R^2 is F, and R^6 is $-CH_3$. In some embodiments of the present invention, each R^2 and R^6 is independently selected from F, and Cl. In some embodiments of the present invention, R^2 and R^6 are F.

[0092] In some embodiments of the present invention, R^4 of formula (J), (Ja), (Jb), (Jc), (Jd), (Je), or (Jf), or a pharmaceutically acceptable salt thereof R^4 is



[0093] In formula (J), (Ja), (Jb), (Jc), (Jd), (Je), or (Jf), or a pharmaceutically acceptable salt thereof, R^{15} can be selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-3}cycloalkyl, 4-10 membered heterocyclyl, and C_{6-10}aryl. For example, R^{15} can be selected from H, C_{1-6}alkyl, and phenyl; and phenyl is optionally substituted with one to three groups independently selected from halo, C_{1-4}alkyl, C_{1-4}alkoxyl, C_{1-4}haloalkyl, and C_{1-4}haloalkoxyl. For example, R^{15} can be selected from H, 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, and phenyl.

[0094] In formula (J), (Ja), (Jb), (Jc), (Jd), (Je), or (Jf), or a pharmaceutically acceptable salt thereof, R^{15} can be $-L^1-R^{16}$. For example, L^1 can be selected from $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2-O-C(O)-C_{1-4}$alkyl, and $-CH_2-O-C(O)-O-C_{1-4}$alkyl. For example, R^{16} can be selected from $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_2CH_3$, phenyl, pyridinyl, imidazolyl, tetrahydrofuranyl, morpholinyl, and tetrahydropyranyl. Each phenyl, pyridinyl, imidazolyl, tetrahydrofuranyl, morpholinyl, and tetrahydropyranyl of R^{16} can be optionally substituted with one to two groups independently selected from F, $-CH_3$, $-CH_2CH_3$, hydroxyl, and -COOH.

[0095] Provided are also compounds described herein or pharmaceutically acceptable salts, stereoisomer, 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, stereoisomer, 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.

[0096] The compound of the present disclosure can contain one to six deuterium (^{2}H, or D). For example, one of R^2, R^3, R^4, R^5, and R^6 contains one to six D, or R^6 contains one to six D. For example, R^6 is CD_3.

[0097] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, and polymorphs 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.

[0098] 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.

[0099] 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.

[0100] 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.

[0101] 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).

[0102] "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.

[0103] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0104] "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.

[0105] In certain embodiments, provided are atropisomers thereof of the compounds described herein or pharmaceutically acceptable salts.

[0106] Compositions provided herein that include a compound described herein or pharmaceutically acceptable salts, stereoisomer, 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.

[0107] In certain embodiments, provided are also chelates, non-covalent complexes, and mixtures thereof, of the compounds described herein or pharmaceutically acceptable salts, stereoisomer, 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

[0108] 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 compounds or pharmaceutically acceptable salts of the present invention may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds or pharmaceutically acceptable salts of the present invention may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of an α4β7 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 compounds or pharmaceutically acceptable salts of the present 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.

[0109] In some embodiments, compounds described herein, for example, compounds of formula (I), , 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 α4β7 integrin activity. The compounds described herein may be used to inhibit the activity of α4β7 integrin. 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.

[0110] In some embodiments, compounds described herein, for example, compounds of formula (J), (Ja), (Jb), (Jc), (Jd), (Je), or (Jf), 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 α4β7 integrin activity. In some embodiments, the compounds described herein may be used to inhibit the activity of α4β7 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

[0111] The present disclosure provides a compound described herein, e.g., the compounds as claimed herein, useful as an inhibitor of α4β7 integrin. For example, the present disclosure provides a method of treating an inflammatory disease or condition comprising administering a compound described herein.

[0112] The present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

[0113] 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.

[0114] The present disclosure provides a compound described herein for use in therapy.

[0115] The present disclosure provides a compound described herein for use in the

manufacture of a medicament for treating a disease or condition provided herein.

[0116] For example, 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 α4β7 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.

[0117] The present disclosure also provides 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 α4β7 integrin.

[0118] "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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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. A kit may be used to administer the drug or drug components.

[0123] Thus, the present disclosure, for example, provides a method of treating a disease or condition mediated, at least in part, by α4β7 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.

[0124] "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.

[0125] "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

[0126] The compounds described herein, e.g., the compounds as claimed 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] The compounds disclosed herein are useful for the treatment of diseases or conditions mediated, at least in part, by α4β7 integrin. Non-limiting examples of diseases or conditions mediated, at least in part, by α4β7 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, anti-glomerular 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 periodic 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, Sézary 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.

[0140] For example, the methods are provided for alleviating a symptom of a disease or disorder mediated, at least in part, by α4β7 integrin. The methods can include identifying a mammal having a symptom of a disease or disorder mediated, at least in part, by α4β7 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.

[0141] In some embodiments, the disease or condition mediated, at least in part, by α4β7 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.

[0142] In some embodiments, the disease or condition mediated, at least in part, by α4β7 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] The treatment methods described herein 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.

[0148] 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.

[0149] In some embodiments, the disease or condition mediated, at least in part, by α4β7 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 Apr-Jun; 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 disclosed herein, e.g., the compounds as claimed herein, can be used as stand-alone treatments or in combination with the current treatments for alcoholic hepatitis.

[0150] The present disclosure also 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.

[0151] 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

[0152] The present disclosure also provides methods of treatment in which a compound described herein, e.g., the compounds as claimed herein, is given to a patient in combination with one or more additional active agents or therapy.

[0153] Thus in some examples, 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.

[0154] The present disclosure describes 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.

[0155] Adenosine A3 receptor antagonists include PBF-677.

[0156] Adrenomedullin ligands include adrenomedullin.

[0157] Antibiotics include ciprofloxacin, clarithromycin, metronidazole, vancomycin, rifamycin, rifaximin, and tosufloxacin.

[0158] ASK1 inhibitors include GS-4997.

[0159] Alpha-fetoprotein modulators include ACT-101.

[0160] Anti-CD28 inhibitors include JNJ-3133 and abatacept.

[0161] Beta adrenoceptor antagonists include NM-001.

[0162] BTK inhibitors include GS-4059.

[0163] Calcineurin inhibitors: include tacrolimus, and ciclosporin.

[0164] Carbohydrate metabolism modulators include ASD-003.

[0165] Cathepsin S inhibitors include VBY-129.

[0166] CCR9 chemokine antagonists include CCX-507.

[0167] CD233 modulators include GSK-2831781.

[0168] CD29 modulators include PF-06687234.

[0169] CD3 antagonists include NI-0401.

[0170] CD4 antagonists include IT-1208.

[0171] CD40 ligand inhibitors include SAR-441344, and letolizumab.

[0172] CD40 gene inhibitors include NJA-730.

[0173] CD40 ligand receptor antagonists include FFP-104, BI-655064.

[0174] Chaperonin binding immunoglobulin protein includes IRL-201805.

[0175] Chemokine CXC ligand inhibitors include LY-3041658.

[0176] CHST15 gene inhibitors include STNM-01.

[0177] Collagen modulators include ECCS-50 (DCCT-10).

[0178] COT protein kinase inhibitors include GS-4875.

[0179] CSF-1 antagonists include JNJ-40346527 (PRV-6527), and SNDX-6352.

[0180] CX3CR1 chemokine modulators include E-6130.

[0181] Ecobiotics include SER-287.

[0182] Eotaxin ligand inhibitors include bertilimumab.

[0183] EP4 prostanoid receptor agonists include KAG-308.

[0184] F1F0 ATP synthase modulators include LYC-30937 EC.

[0185] Fractalkine ligand inhibitors include quetmolimab (E-6011).

[0186] Free fatty acid receptor 2 antagonists include GLPG-0974.

[0187] GATA 3 transcription factor inhibitors include SB-012.

[0188] Glucagon-like peptide 2 agonists include teduglutide, and apraglutide.

[0189] Glucocorticoid receptor agonists include budesonide, beclomethasone dipropionate, and dexamethasone sodium phosphate.

[0190] Glucocorticoid receptor modulators /TNF ligand inhibitors include ABBV-3373.

[0191] Guanylate cyclase receptor agonists include dolcanatide.

[0192] HIF prolyl hydroxylase inhibitors include DS-1093, and AKB-4924.

[0193] HIF prolyl hydroxylase-2 inhibitors /hypoxia inducible factor-1 stimulators include GB-004.

[0194] Histone deacetylase inhibitors include givinostat.

[0195] Histone deacetylase-6 inhibitors include CKD-506.

[0196] HLA class II antigen modulators include HLA class II protein modulators.

[0197] ICAM1 gene inhibitors include alicaforsen.

[0198] IL-12 antagonists include ustekinumab (IL12/IL23).

[0199] IL-13 antagonists include tralokinumab.

[0200] IL-18 antagonists include GSK-1070806

[0201] IL-22 agonists include RG-7880.

[0202] IL-23 antagonists include tildrakizumab, risankizumab (BI-655066), mirikizumab (LY-3074828), brazikumab (AMG-139), and PTG-200.

[0203] IL-23A inhibitors include guselkumab.

[0204] IL-6 antagonists include olokizumab.

[0205] IL-7 receptor antagonists include OSE-127.

[0206] IL-8 receptor antagonists include clotrimazole.

[0207] Integrin alpha-4/beta-1 antagonists include natalizumab.

[0208] Integrin alpha-4/beta-7 antagonists include etrolizumab (a4b7/aEb7), vedolizumab, carotegast methyl, TRK-170 (a4b7/a4b1), PN-10943, and PTG-100.

[0209] Integrin antagonists include E-6007.

[0210] Interleukin ligand inhibitors include bimekizumab (IL-17A/IL-17F).

[0211] Interleukin receptor 17A antagonists include brodalumab.

[0212] Interleukin-1 beta ligands include K(D)PT.

[0213] Interleukin 1 like receptor 2 inhibitors include BI-655130.

[0214] IL-6 receptor modulators include olamkicept.

[0215] 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).

[0216] Jak3 tyrosine kinase inhibitors include PF-06651600.

[0217] Lactoferrin stimulators include recombinant human lactoferrin (VEN-100).

[0218] LanC like protein 2 modulators include BT-11.

[0219] Leukocyte elastase inhibitors/Leukocyte proteinase-3 inhibitors include tiprelestat.

[0220] MAdCAM inhibitors include SHP-647 (PF-547659).

[0221] Melanin concentrating hormone (MCH-1) antagonists include CSTI-100.

[0222] Melanocortin MC1 receptor agonists include ASP-3291, and PL-8177.

[0223] Metalloprotease-9 inhibitors include GS-5745.

[0224] Microbiome modulator include ABI-M201.

[0225] Natriuretic peptide receptor C agonists include plecanatide.

[0226] Neuregulin-4 ligands include NRG-4.

[0227] NKG2 D activating NK receptor antagonists include JNJ-4500.

[0228] NLPR3 inhibitors include dapansutrile, BMS-986299, SB-414, MCC-950, IFM-514, JT-194, PELA-167, and NBC-6.

[0229] 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.

[0230] Nuclear factor kappa B inhibitors include Thetanix.

[0231] Opioid receptor antagonists include naltrexone, and IRT-103.

[0232] OX40 ligand inhibitors include KHK-4083.

[0233] Oxidoreductase inhibitors include olsalazine.

[0234] Pellino homolog 1 inhibitors include BBT-401.

[0235] P2X7 purinoceptor modulators include SGM-1019.

[0236] PDE 4 inhibitors include apremilast.

[0237] PPAR alpha/delta agonists include elafibranor (GFT-1007).

[0238] PPAR gamma agonists include GED-0507-34-Levo.

[0239] Protein fimH inhibitors include sibofimloc (EB-8018).

[0240] P-selectin glycoprotein ligand-1 inhibitors include SEL-K2, AbGn-168H, and neihulizumab.

[0241] Ret tyrosine kinase receptor inhibitors include GSK-3179106.

[0242] RIP-1 kinase inhibitors include GSK-2982772.

[0243] RIP-2 kinase inhibitors include GSK-2983559.

[0244] Sphingosine 1 phosphate phosphatase 1 stimulators include etrasimod.

[0245] Sphingosine-1-phosphate receptor-1 agonists include ozanimod. mocravimod (KRP-203), and BMS-986166.

[0246] Sphingosine-1-phosphate receptor-1 agonists/Sphingosine-1-phosphate receptor-5 agonists include ozanimod.

[0247] Sphingosine-1-phosphate receptor-1 antagonists include amiselimod (MT-1303).

[0248] Sphingosine-1-phosphate receptor-1 modulators include OPL-002.

[0249] Stem cell antigen-1 inhibitors include Ampion (DMI-9523).

[0250] Superoxide dismutase modulators include midismase.

[0251] Syk inhibitors include GS-9876.

[0252] Tissue transglutaminase inhibitor includes zampilimab.

[0253] TLR-3 antagonists include PRV-300.

[0254] TLR-4 antagonists include JKB-122.

[0255] 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.

[0256] TLR-9 agonists include cobitolimod, IMO-2055, IMO-2125, lefitolimod, litenimod, MGN-1601, and PUL-042.

[0257] TNF alpha ligand inhibitors include adalimumab, certolizumab pegol, infliximab, golimumab, DLX-105, Debio-0512, HMPL-004, CYT-020-TNFQb, Hemay-007. and V-565.

[0258] TNF antagonists include AVX-470, tulinercept, and etanercept.

[0259] TPL-2 inhibitors include GS-4875.

[0260] Tumor necrosis factor 14 ligand modulators include AEVI-002.

[0261] Tumor necrosis factor 15 ligand inhibitors include PF-06480605.

[0262] Tyk2 tyrosine kinase inhibitors include PF-06826647, and BMS-986165.

[0263] TrkA receptor antagonist includes SNA-125.

[0264] Type I IL-1 receptor antagonists include anakinra.

[0265] Zonulin inhibitors include larazotide acetate.

[0266] The present disclosure also describes 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.

[0267] 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.

[0268] 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.

[0269] 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.

[0270] In some embodiments, the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

[0271] 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.

[0272] 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.

[0273] The present disclosure also describes 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.

[0274] The present disclosure also describes 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.

[0275] The present disclosure also describes 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-JBI1-2.5Rx, 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.

[0276] The present disclosure also describes 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. 8,450,460; Signal transducer CD24 modulator: CD24-IgFc; Somatostatin receptor agonist: Thymoglobulin; and sphingosine-1-phosphate receptor-1 agonist: ponesimod.

[0277] The present disclosure also describes 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.

[0278] 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.

[0279] 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.

[0280] 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.

[0281] In some embodiments, a compound as disclosed herein (e.g., a compound described 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).

[0282] 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.

[0283] Also 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

[0284]

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*-butylphosphine
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

DPPA
: Diphenylphosphoryl azide

dppf
: 1,1'-Bis(diphenylphosphino)ferrocene

dppp

1,3-Bis(diphenylphosphino)propane

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

minim
: 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

PhNOz
: 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

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 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium

TBTU
: tetrafluoroborate

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

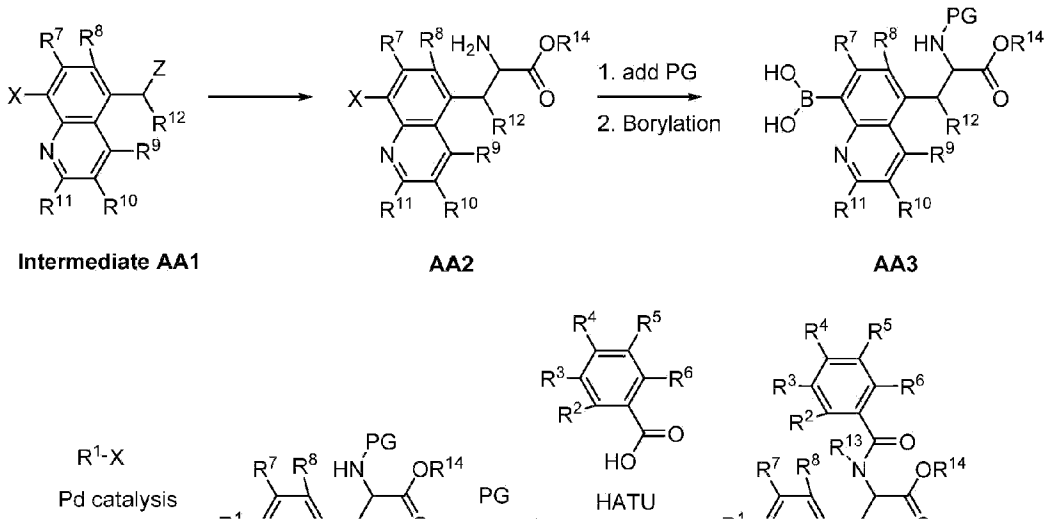
[0285] The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. 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.

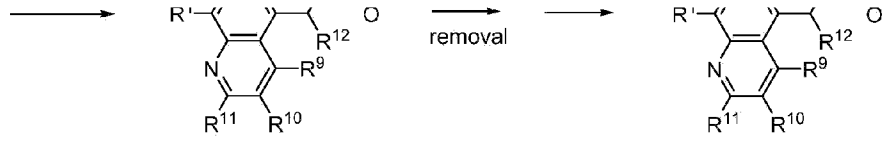
[0286] Salts, such as TFA salts, can be converted to the free-bases/acids or other pharmaceutically acceptable salts.

General Schemes

[0287] 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

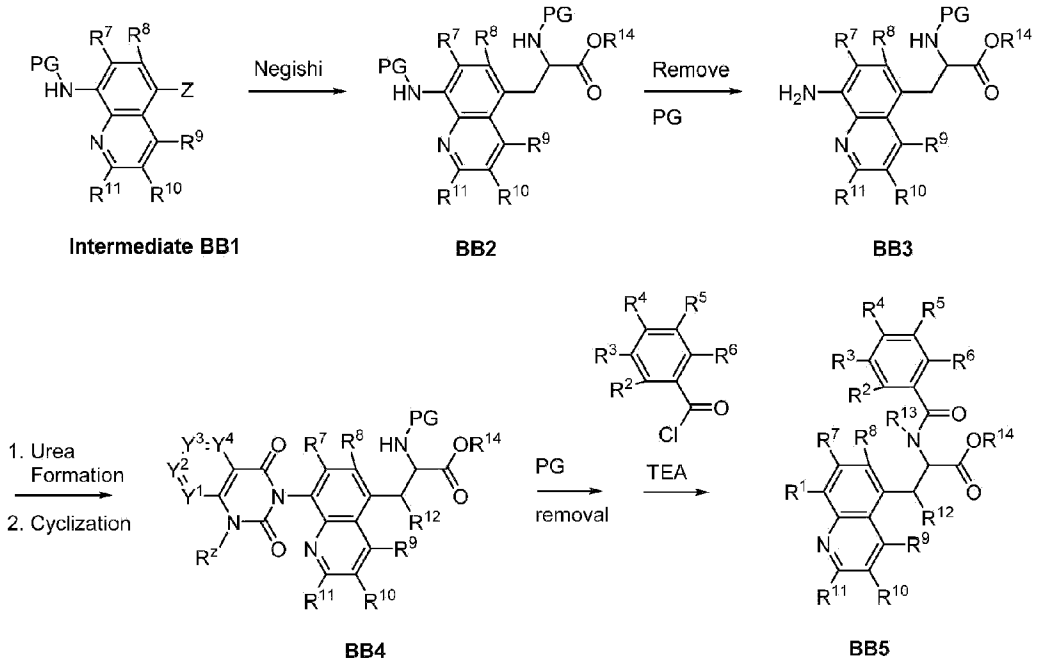




AA4 AA5

[0288] Scheme 1 describes a general route that was used to prepare some compounds of Formula (I). From Intermediate **AA1** that has hydroxyl or halogen group as Z, and halogen group as X, amino acid esters (**AA2**) can be prepared under a variety of conditions (e.g., Schollkopf, Maruoka, etc). After appropriate protection of the free amine with protecting groups (PG), e.g., 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.**

General Scheme 2



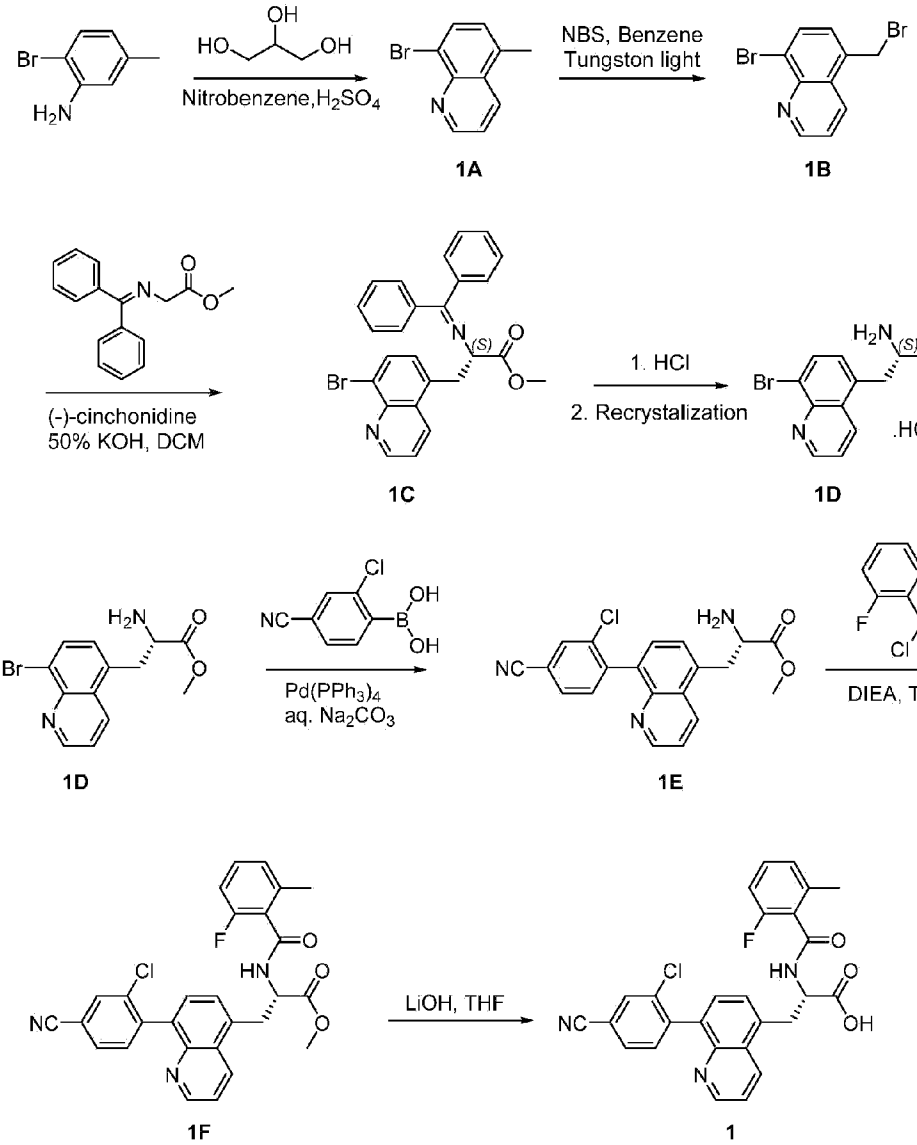
Intermediate BB1 BB2 BB3 BB4 BB5

[0289] Scheme 2 describes a general route that was used to prepare some compounds of Formula (I). From Intermediate **BB1** that has a halogen group as Z, amino acid esters (**BB2**) can be prepared under a variety of conditions (primarily by Negishi). After appropriate removal of the protecting group (e.g., benzyloxycarbonyl, CBZ), **BB2** was converted to the free amine (**BB3**) under standard conditions (e.g., Pd/H_2). R^1 was introduced under a variety of urea forming conditions with appropriate carboxylic acid or amines to give **BB4.** After removal of the amine protecting group (PG) under appropriate conditions, the amine was coupled with carboxylic acids or acid chlorides to provide heterocyclic compounds **BB5.**

EXAMPLES

Example 1 (for illustrative purposes)

[0290] Synthesis of 8-bromo-5-methylquinoline (**1A**): To a stirred solution of 2-bromo-5-methyl aniline (1200 g, 6.45 mol) in nitrobenzene (660 mL) and 75% H_2SO_4 (3.6 L) was added glycerol (1180 g, 6.45 mol) at RT and then slowly heated to 150 °C for 3 h. The mixture was cooled to RT and poured into ice-water while maintaining the temperature below 10 °C. The pH was adjusted ~10 with aqueous 10N NaOH and the product was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford material that was dissolved in DCM/hexanes (5:1) and stirred for 30 minutes. The solid was filtered off and the filtrate was evaporated under reduced pressure to afford 1A.



[0291] Synthesis of 8-bromo-5-(bromomethyl)quinoline (**1B**): To a stirred solution of compound

1A (500 g, 2.25 mol) in benzene (7.5 L) was added NBS (481 g, 2.7 mol) at RT. The reaction mixture was heated to 80 °C under tungsten light for 12 h. The reaction was cooled to RT, water added and extracted with ethyl acetate. The organic layer was separated, washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This material was triturated with 20% ethyl acetate in hexane at RT. The material was filtered, washed with hexane and dried under reduced pressure to afford **1B.**

[0292] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-((diphenylmethylene)amino) propanoate (**1C**): To a stirred solution of **1B** (392 g, 1.3 mol) in DCM (9 L) was added (-)-cinchonidine (35 g, 0.12 mol) at RT. The reaction mixture was cooled to 10 °C, KOH (2.4 L, 50% aq) was added followed by methyl 2-((diphenylmethylene)amino) acetate (300 g, 1.2 mol). The reaction mixture was allowed to stir at RT for 6 h. The reaction mixture was diluted with water and stirred for 15 minutes. DCM was added and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. This material was purified by 100-200 mesh silica gel column chromatography and eluted with 10-15% ethyl acetate in hexane afforded compound **1C.**

[0293] Synthesis of methyl (S)-2-amino-3-(8-bromoquinolin-5-yl)propanoate (**1D**): To a stirred solution of **1C** (400 g, 845 mmol) in methanol (2 L) was added HCl in 1,4-dioxane (2.8 L, 4N) keeping the temperature below 5 °C. The reaction mixture was allowed to stir at RT for 48 h. The reaction mixture was concentrated under reduced pressure, dissolved in water, and washed with ethyl acetate. The aqueous layer was adjusted to -pH 8 using sat. $NaHCO_3$ and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a 70:30 mixture of racemic **1D.** A suspension of this material in MTBE was heated to reflux for 1 h. The reaction mixture was cooled to RT, the solid was filtered off and the filtrate was evaporated under reduced pressure to obtain a solid, which was again stirred with MTBE at RT. The solid was filtered off and the filtrate was evaporated under reduced pressure to afford **1D.** This material was dissolved in ethyl acetate, cooled to 0 °C, followed by addition of 4N HCl and allowed to stir at RT for 1 h. The reaction mixture was concentrated under reduced pressure and triturated with MTBE to afford **1D.**

[0294] Synthesis of methyl (S)-2-amino-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl) propanoate (**1E**): To a microwave vial was added **1D** (50 mg, 0.145 mmol), (2-chloro-4-cyanophenyl)boronic acid (45 mg, 0.246 mmol), $Pd(PPh_3)_4$ (8 mg, 0.007 mmol), and aq Na_2CO_3 (0.217 mL, 2M) in DME (2 mL). The reaction mixture was allowed to stir at 120 °C for 20 min. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-30% MeOH in EA to afford the title compound.

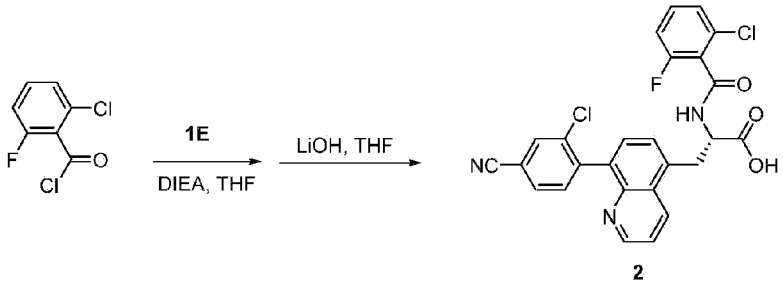
[0295] Synthesis of methyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2-fluoro-6-methylbenzamido)propanoate (**1F**): To a stirred solution of **1E** (29 mg, 0.08 mmol) in THF (2

mL) was added 2-fluoro-6-methylbenzoyl chloride (21 mg, 0.12 mmol) and DIEA (0.07 mL, 0.4 mmol). The reaction mixture was allowed to stir for 1h, then diluted with DCM and concentrated. The material was purified on silica gel eluting with MeOH in DCM (0-30%) to give the title compound.

[0296] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2-fluoro-6-methylbenzamido)propanoic acid (**1**): To a stirred solution of **1F** (35 mg, 0.07 mmol) in THF (3 mL) was added aqueous LiOH (0.35 mL, 0.035 mmol). The reaction mixture was allowed to stir for 1 h then concentrated under reduced pressure. The material was purified via reverse phase HPLC to afford the title compound. MS (m/z) 488.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.03 (d, J = 8.4 Hz, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.68 - 7.60 (m, 3H), 7.55 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 6.1 Hz, 1H), 6.99 (d, J = 6.7 Hz, 2H), 4.82 (t, J = 9.9 Hz, 1H), 3.39 (d, J = 12.9 Hz, 1H), 2.65 (s, 1H), 2.31 (s, 1H), 2.07 (s, 1H), 1.96 (s, 3H).

Example 2 (for illustrative purposes)

[0297]



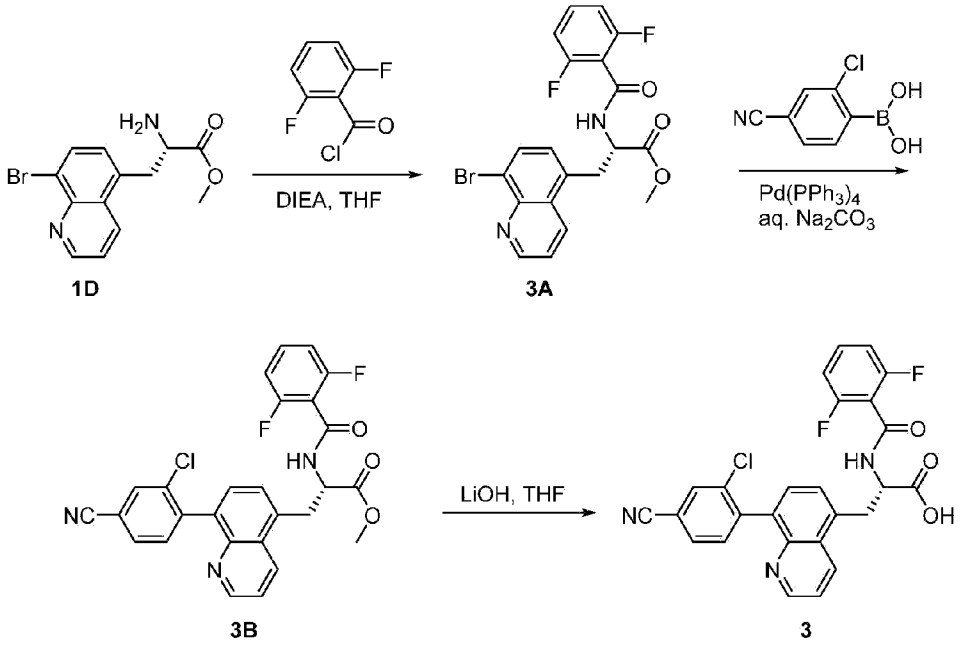
2

[0298] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2-chloro-6-fluoro benzamido)propanoic acid (**2**): The title compound was prepared according to the method presented for the synthesis of compound **1F** and **1** starting with 2-chloro-6-fluorobenzoyl chloride and **1E.** MS (m/z) 508.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.27 (d, J = 8.3 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.65 (dd, J = 8.6, 1.7 Hz, 1H), 8.16 (dd, J = 1.7, 0.4 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.68 - 7.60 (m, 3H), 7.54 (d, J = 7.9 Hz, 1H), 7.42 (td, J = 8.3, 6.1 Hz, 1H), 7.30 - 7.19 (m, 2H), 4.82 (s, 1H), 3.77 (d, J = 14.7 Hz, 1H), 3.38 (dd, J = 14.6, 10.6 Hz, 1H).

Example 3 (for illustrative purposes)

[0299] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(2,6-difluorobenzamido) propanoate (**3A**): The title compound was prepared according to the method presented for the synthesis of compound **1F** starting with 2,6-difluorobenzoyl chloride and **1D.**

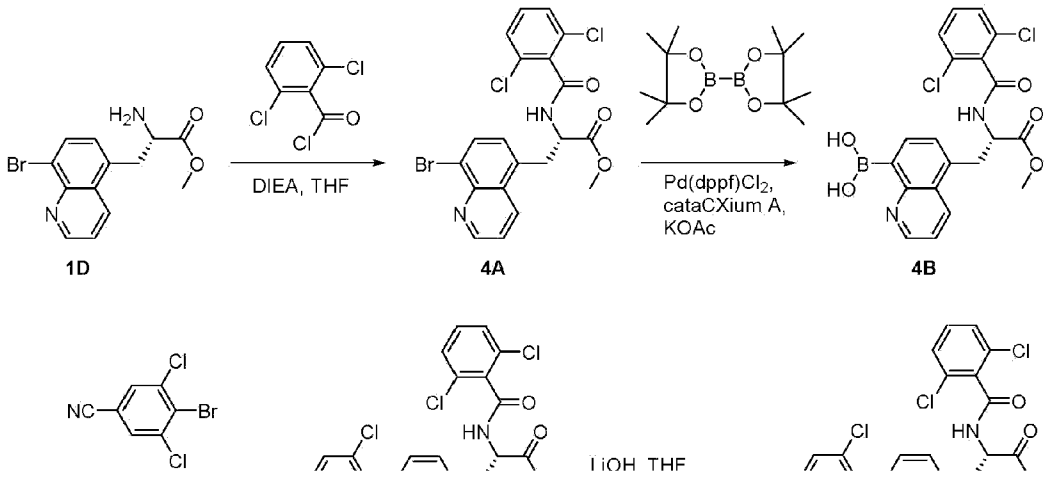
[0300] Synthesis of methyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro benzamido)propanoate (**3B**): The title compound was prepared according to the method presented for the synthesis of compound **1E** starting with **3A.**

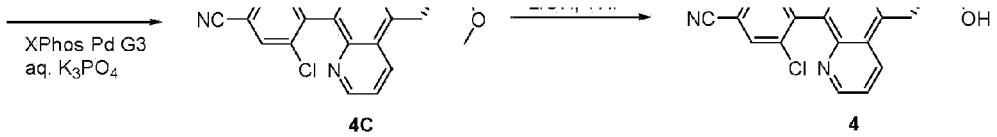


[0301] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro benzamido)propanoic acid (**3**): The title compound was prepared according to the method presented for the synthesis of compound **1F** starting with **3B.** MS (m/z) 492.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.25 (d, J = 8.1 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.8, 1.7 Hz, 1H), 8.15 (d, J = 1.7 Hz, 1H), 7.90 (dd, J = 8.0, 1.7 Hz, 1H), 7.66 - 7.61 (m, 3H), 7.57 (d, J = 7.9 Hz, 1H), 7.53 - 7.41 (m, 1H), 7.10 (t, J = 8.0 Hz, 2H), 4.77 (s, 1H), 3.76 (s, 1H), 3.41 (s, 1H).

Example 4 (for illustrative purposes)

[0302]





4C 4

[0303] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(2,6-dichlorobenzamido) propanoate (**4A**): The title compound was prepared according to the method presented for the synthesis of compound **3A** starting with 2,6-dichlorobenzoyl chloride and **1D.**

[0304] Synthesis of (S)-(5-(2-(2,6-dichlorobenzamido)-3-methoxy-3-oxopropyl)quinolin-8-yl)boronic acid (**4B**): To a stirred solution of **4A** (0.61 g, 1.4 mmol) in dioxane was added bis(pinacolato)diboron (0.42 g, 1.6 mmol), followed by KOAc (0.4 g, 4.1 mmol), Pd(dppf)Cl_2 (0.03 g, 0.03 mmol), and cataCXium A (0.04 g, 0.08 mmol). The reaction vessel was flushed with nitrogen then heated to 100 °C for 4 hrs. EA was added then filtered through Celite and concentrated under reduced pressure to afford the title compound that was used without further purification.

[0305] Synthesis of methyl (S)-3-(8-(2,6-dichloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichlorobenzamido)propanoate (**4C**): To a stirred solution **4B** (0.08 g, 0.017 mmol) in DME was added 4-bromo-3,5-dichlorobenzonitrile (0.08 g, 0.034 mmol), XPhos Pd G3 (0.014 g, 0.0017 mmol) and aq. K_3PO_4 (0.6 mL, 1 M). The reaction was degassed with nitrogen and heated at 90 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give the title compound that was used without further purification.

[0306] Synthesis of (S)-3-(8-(2,6-dichloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichloro benzamido)propanoic acid (**4**): The title compound was prepared according to the method presented for the synthesis of compound 1 starting with **4C.** MS (m/z) 558.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.28 (d, J = 8.4 Hz, 1H), 8.82 (dd, J = 4.2, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.6 Hz, 1H), 8.25 - 8.15 (m, 2H), 7.74 - 7.62 (m, 2H), 7.60 (d, J = 7.3 Hz, 1H), 7.45 - 7.32 (m, 3H), 4.83 (ddd, J = 11.8, 8.6, 3.7 Hz, 1H), 3.78 (dd, J = 14.5, 3.8 Hz, 1H), 3.38 (dd, J = 14.5, 11.0 Hz, 1H).

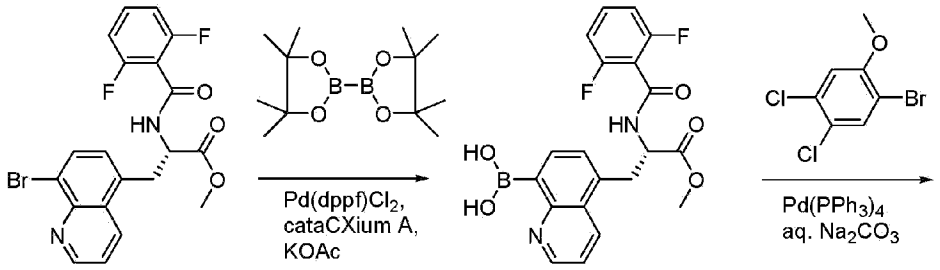
Example 5 (for illustrative purposes)

[0307] Synthesis of (S)-(5-(2-(2,6-difluorobenzamido)-3-methoxy-3-oxopropyl)quinolin-8-yl)boronic acid (**5A**): The title compound was prepared according to the method presented for the synthesis of compound **4B** of Example 4 starting with **3A.**

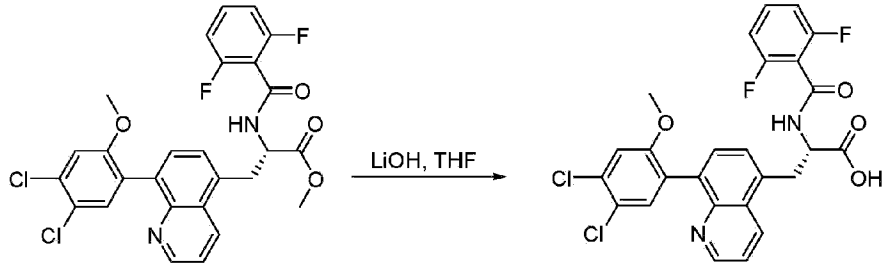
[0308] Synthesis of methyl (S)-3-(8-(4,5-dichloro-2-methoxyphenyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoate (**5B**): To a microwave vial was added **5A** (145 mg, 0.234 mmol), 1-bromo-4,5-dichloro-2-methoxybenzene (50 mg, 0.195 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol), and aq Na_2CO_3 (0.293 mL, 2M) in DME (2 mL). The reaction mixture was allowed

to stir at 120 °C for 30 min. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the title compound.

[0309] Synthesis of (S)-3-(8-(4,5-dichloro-2-methoxyphenyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (**5**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **5B.** MS (m/z) 530.7 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.27 (d, J = 8.1 Hz, 1H), 8.86 (dd, J = 4.3, 1.6 Hz, 1H), 8.73 - 8.61 (m, 1H), 7.66 (dd, J = 8.6, 4.3 Hz, 1H), 7.60 (q, J = 7.4 Hz, 2H), 7.52 - 7.43 (m, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.16 - 7.05 (m, 2H), 4.78 - 4.70 (m, 1H), 3.74 (dd, J = 14.5, 4.4 Hz, 1H), 3.64 (s, 3H), 3.39 (dd, J = 14.6, 10.1 Hz, 1H), 1.05 (s, 1H).



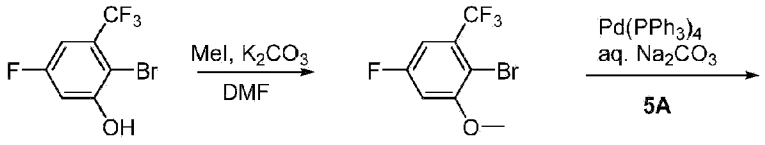
3A 5A



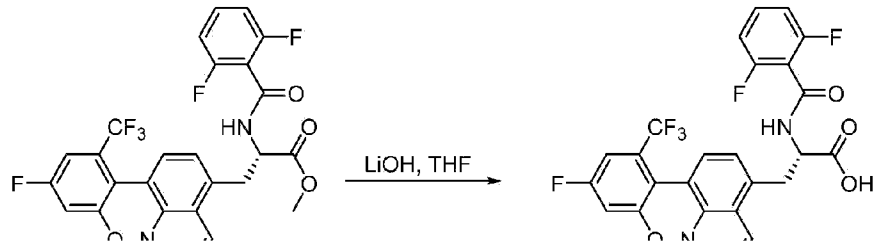
5B 5

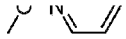
Example 6 (for illustrative purposes)

[0310]

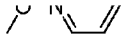


6A





6B



6

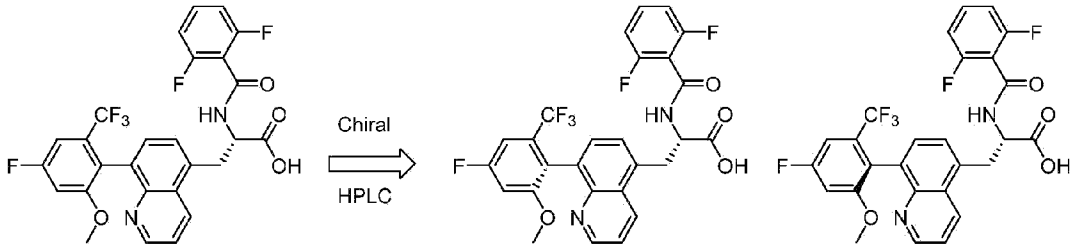
[0311] Synthesis of 2-bromo-5-fluoro-1-methoxy-3-(trifluoromethyl)benzene (**6A**): To a stirred solution of 2-bromo-5-fluoro-3-(trifluoromethyl)phenol (0.21 g, 0.64 mmol) in DMF was added K_2CO_3 (133 mg, 0.96 mmol) and iodomethane (0.105 g, 0.74 mmol). The reaction mixture was allowed to stir at RT. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure and purified by silica gel chromatography using hexanes/EA as gradient.

[0312] Synthesis of methyl (2S)-2-(2,6-difluorobenzamido)-3-(8-(4-fluoro-2-methoxy-6-(trifluoromethyl)phenyl)quinolin-5-yl)propanoate (**6B**): The title compound was prepared according to the method presented for the synthesis of compound **5B** starting with **5A** and **6A.**

[0313] Synthesis of (2S)-2-(2,6-difluorobenzamido)-3-(8-(4-fluoro-2-methoxy-6-(trifluoromethyl)phenyl)quinolin-5-yl)propanoic acid (**6**): The title compound was prepared according to the method presented for the synthesis of compound 1 starting with **6B.** MS (m/z) 549.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.28 (dd, J = 12.4, 8.1 Hz, 1H), 8.81 (dd, J = 4.2, 1.6 Hz, 1H), 8.67 (d, J = 8.7 Hz, 1H), 7.67 - 7.56 (m, 2H), 7.49 (dqd, J = 8.2, 6.6, 1.6 Hz, 2H), 7.41 - 7.34 (m, 1H), 7.29 (dd, J = 9.1, 2.5 Hz, 1H), 7.11 (ddd, J = 8.3, 7.4, 3.8 Hz, 2H), 4.84 - 4.75 (m, 1H), 3.76 (dd, J = 31.6, 4.3 Hz, 1H), 3.59 (d, J = 5.7 Hz, 3H), 3.42 (ddd, J = 21.3, 14.6, 10.4 Hz, 1H).

Examples 7 and 8 (for illustrative purposes)

[0314]



6 7 8

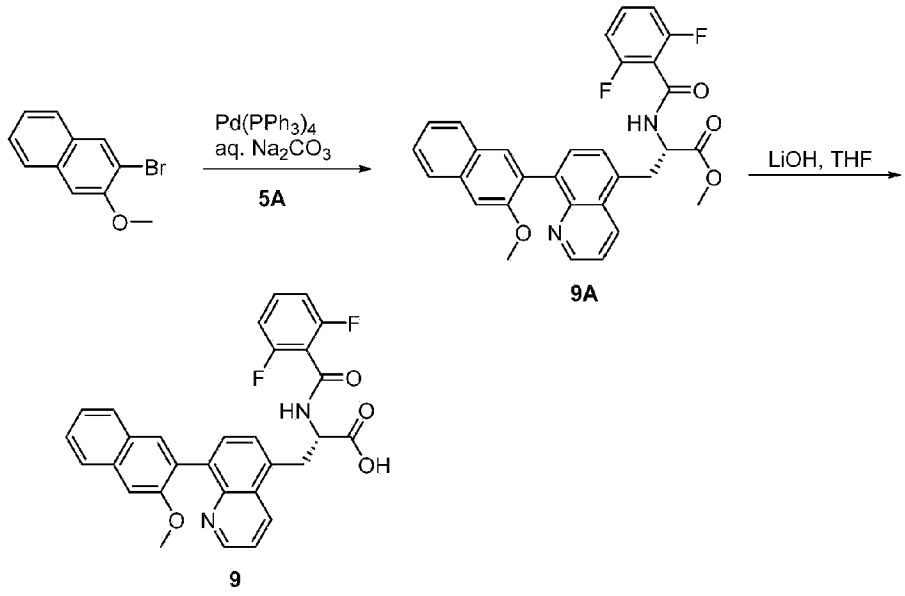
[0315] Preparation of (S)-2-(2,6-difluorobenzamido)-3-((R)-8-(4-fluoro-2-methoxy-6-(trifluoromethyl)phenyl)quinolin-5-yl)propanoic acid (**7**): **6** was separated into its 2 diastereomeric atropisomers by supercritical fluid chromatography using 25% EtOH/TFA co-solvent, at a flow rate of 50 mL/min, using an AD-H 5 µm 21x250 mm column. The title compound was identified as the first eluting peak. MS (m/z) 549.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol-d4) δ 9.36 (dd, J = 8.7, 1.6 Hz, 1H), 8.95 (dd, J = 5.0, 1.5 Hz, 1H), 8.00 (dd, J = 8.7,

5.0 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.78 (dd, J = 7.4, 0.9 Hz, 1H), 7.45 (tt, J = 8.4, 6.4 Hz, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.02 - 6.95 (m, 2H), 5.12 (dd, J = 9.8, 5.2 Hz, 1H), 4.03 (dd, J = 14.4, 5.2 Hz, 1H), 3.71 - 3.63 (m, 4H).

[0316] Preparation of (S)-2-(2,6-difluorobenzamido)-3-((S)-8-(4-fluoro-2-methoxy-6-(trifluoromethyl)phenyl)quinolin-5-yl)propanoic acid (**8**): **6** was separated into its 2 diastereomeric atropisomers by supercritical fluid chromatography using 25% EtOH/TFA cosolvent, at a flow rate of 50 mL/min, using an AD-H 5 µm 21x250 mm column. The title compound was identified as the second eluting peak. MS (m/z) 549.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol-d4) δ 9.35 (dd, J = 8.7, 1.5 Hz, 1H), 8.95 (dd, J = 5.0, 1.5 Hz, 1H), 7.99 (dd, J = 8.6, 5.0 Hz, 1H), 7.86 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.45 (tt, J = 8.6, 6.4 Hz, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 7.03 - 6.96 (m, 2H), 5.14 (dd, J = 9.9, 5.0 Hz, 1H), 4.04 (dd, J = 14.6, 5.1 Hz, 1H), 3.69 - 3.61 (m, 4H).

Example 9 (for illustrative purposes)

[0317]



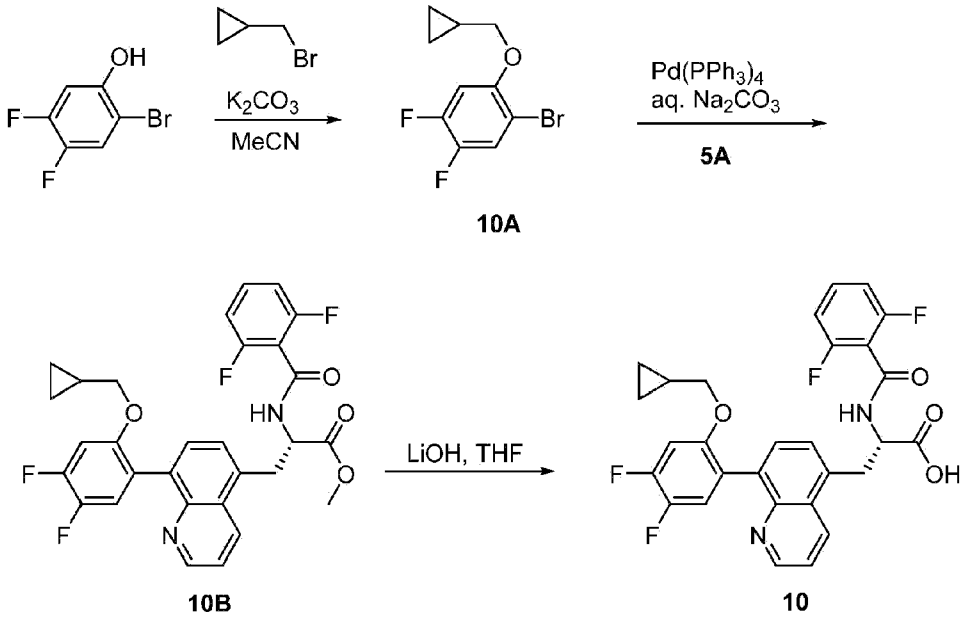
[0318] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(8-(3-methoxynaphthalen-2-yl)quinolin-5-yl)propanoate (**9A**): The title compound was prepared according to the method presented for the synthesis of compound **5B** starting with 2-bromo-3-methoxynaphthalene and **5A.**

[0319] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(3-methoxynaphthalen-2-yl)quinolin-5-yl)propanoic acid (**9**): The title compound was prepared according to the method presented for the synthesis of compound 1 starting with **9A.** MS (m/z) 513.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.2 Hz, 1H), 8.86 (d, J = 4.8 Hz, 2H), 7.95 - 7.83 (m, 2H), 7.81 - 7.64

(m, 3H), 7.55 - 7.43 (m, 3H), 7.38 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.17 - 7.08 (m, 2H), 4.80 (ddd, J = 10.1, 8.1, 4.4 Hz, 1H), 3.80 (dd, J = 14.6, 4.5 Hz, 1H), 3.71 (s, 3H), 3.45 (dd, J = 14.6, 10.1 Hz, 1H).

Example 10 (for illustrative purposes)

[0320]



10B 10

[0321] Synthesis of 1-bromo-2-(cyclopropylmethoxy)-4,5-difluorobenzene (**10A**): To a stirred solution of 2-bromo-4,5-difluorophenol (1.2 g, 5.5 mmol) in MeCN was added K_2CO_3 (2.3 g, 16.4 mmol) and (bromomethyl)cyclopropane (0.82 g, 6.0 mmol). The reaction mixture was allowed to stir for 2 hr at 70 °C. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel chromatography using hexanes/EA as gradient.

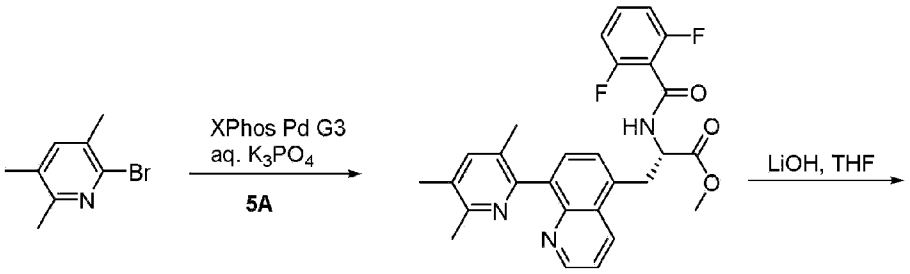
[0322] Synthesis of methyl (S)-3-(8-(2-(cyclopropylmethoxy)-4,5-difluorophenyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoate (**10B**): The title compound was prepared according to the method presented for the synthesis of compound **5B** starting with **10A** and **5A.**

[0323] Synthesis of (S)-3-(8-(2-(cyclopropylmethoxy)-4,5-difluorophenyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (**10**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **10B.** MS (m/z) 538.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 12.81(s, 1H), 9.28 (d, J = 8.1 Hz, 1H), 8.89 (d, J = 4.1 Hz, 1H), 8.69 (s, 2H), 7.66 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.37 - 7.21 (m, 2H), 7.16 - 7.08 (m, 2H), 4.76 (td, J = 10.3, 9.2, 4.2 Hz, 1H), 3.78 - 3.74 (m, 2H), 3.41 (dd, J = 14.6, 10.0 Hz, 1H), 3.10 (p, J = 4.8 Hz, 2H), 0.81 (d, J = 4.8 Hz, 1H), 0.24 (dt, J = 9.0,

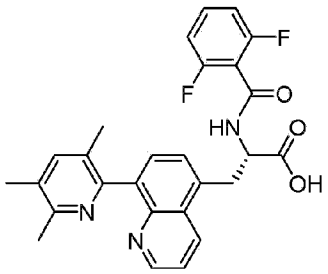
2.9 Hz, 2H), -0.01 - -0.05 (m, 2H).

Example 11 (for illustrative purposes)

[0324] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(8-(3,5,6-trimethylpyridin-2-yl)quinolin-5-yl)propanoate (**11A**): The title compound was prepared according to the method presented for the synthesis of compound **4C** of Example 4 starting with 2-bromo-3,5,6-trimethyl pyridine and **5A.**



11A

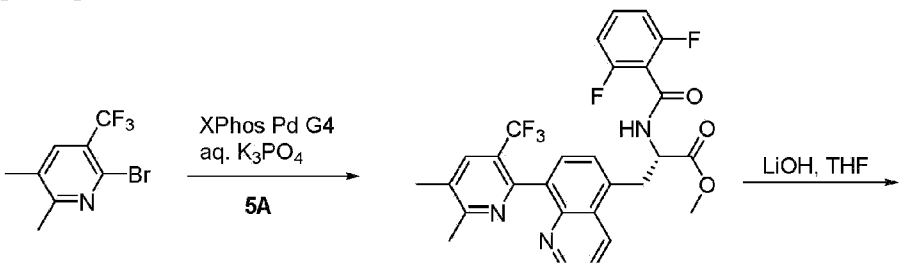


11

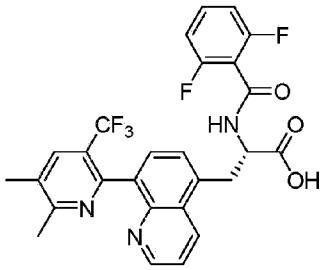
[0325] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(3,5,6-trimethylpyridin-2-yl)quinolin-5-yl)propanoic acid (**11**): The title compound was prepared according to the method presented for the synthesis of compound 1 starting with **11A.** MS (m/z) 476.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.33 (d, J = 8.3 Hz, 1H), 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.78 - 8.72 (m, 1H), 8.36 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.78 - 7.69 (m, 2H), 7.49 (tt, J = 8.5, 6.6 Hz, 1H), 7.11 (dd, J = 8.4, 7.6 Hz, 2H), 4.84 - 4.74 (m, 1H), 3.85 (dd, J = 14.3, 4.2 Hz, 1H), 3.43 (dd, J = 14.4, 10.4 Hz, 1H), 2.64 (s, 3H), 2.46 (s, 3H), 2.05 (s, 3H).

Example 12 (for illustrative purposes)

[0326]



12A



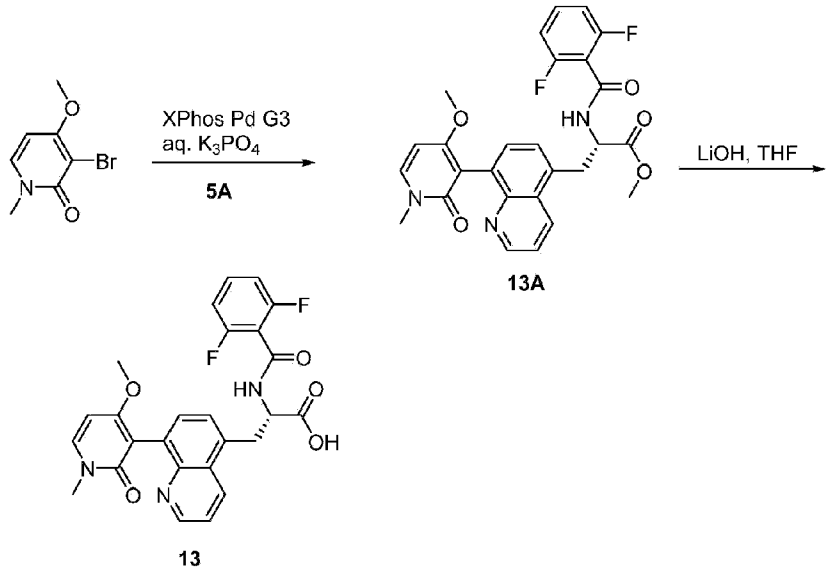
12

[0327] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(8-(5,6-dimethyl-3-(trifluoro methyl)pyridin-2-yl)quinolin-5-yl)propanoate (**12A**): The title compound was prepared according to the method presented for the synthesis of compound **4C** of Example 4 starting with 2-bromo-5,6-dimethyl-3-(trifluoromethyl)pyridine and **5A** with Pd XPhos G4.

[0328] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(5,6-dimethyl-3-(trifluoromethyl) pyridin-2-yl)quinolin-5-yl)propanoic acid (**12**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **12A.** MS (m/z) 530.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.28 (d, J = 8.1 Hz, 1H), 8.77 (dd, J = 4.1, 1.6 Hz, 1H), 8.62 (dd, J = 8.7, 1.6 Hz, 1H), 8.02 (s, 1H), 7.62 - 7.54 (m, 3H), 7.52 - 7.43 (m, 1H), 7.11 (dd, J = 8.5, 7.5 Hz, 2H), 4.74 (td, J = 9.0, 4.3 Hz, 1H), 3.75 (m, 1H), 3.40 (m, 1H), 2.50 (s, 3H), 2.41 (s, 3H).

Example 13 (for illustrative purposes)

[0329]



13A

13

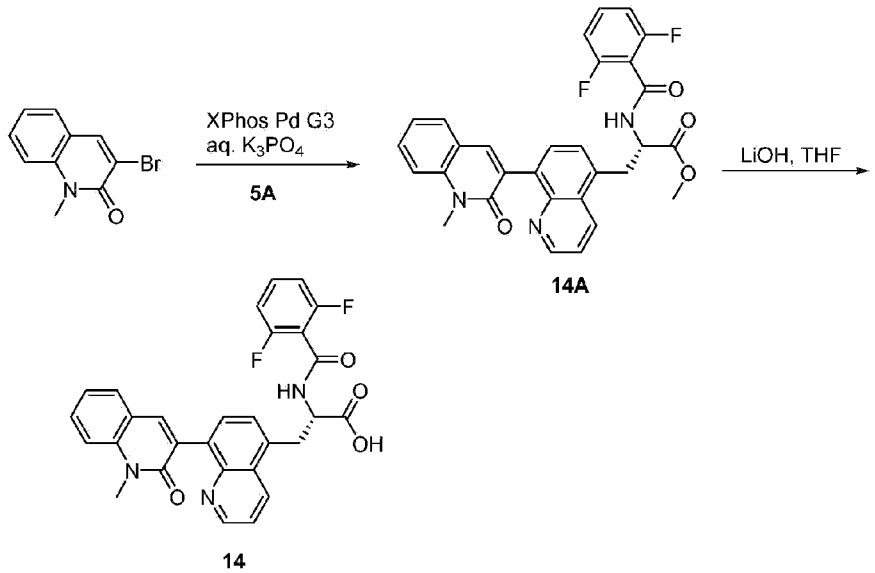
[0330] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-

dihydropyridin-3-yl)quinolin-5-yl)propanoate (**13A**): The title compound was prepared according to the method presented for the synthesis of compound **4C** of Example 4 starting with 3-bromo-4-methoxy-1-methylpyridin-2(1H)-one and **5A.**

[0331] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid (**13**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **13A.** MS (m/z) 464.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.32 (d, J = 7.9 Hz, 1H), 9.08 - 8.98 (m, 1H), 8.96 (d, J = 4.6 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.91 - 7.83 (m, 1H), 7.75 - 7.65 (m, 2H), 7.50 (tt, J = 8.4, 6.5 Hz, 1H), 7.16 - 7.08 (m, 2H), 6.49 (dd, J = 7.7, 3.5 Hz, 1H), 4.84 - 4.72 (m, 1H), 3.85 - 3.75 (m, 1H), 3.68 (d, J = 7.5 Hz, 3H), 3.55 - 3.40 (m, 4H).

Example 14 (for illustrative purposes)

[0332]



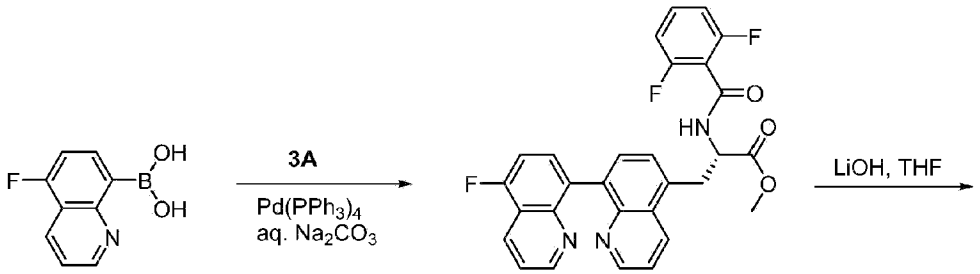
[0333] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoate (**14A**): The title compound was prepared according to the method presented for the synthesis of compound **4C** of Example 4 starting with 3-bromo-1-methylquinolin-2(1H)-one and **5A.**

[0334] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid (**14**): The title compound was prepared according to the method presented for the synthesis of compound **1**starting with **14A.** MS (m/z) 514.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.1 Hz, 1H), 8.88 (d, J = 4.3 Hz, 1H), 8.77 (s, 1H), 7.98 (s, 1H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.70 - 7.56 (m, 3H), 7.49 (tt, J = 8.4, 6.5 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.18 - 7.08 (m, 2H), 4.75 (td, J = 9.5, 4.5 Hz, 1H), 3.77 (dd, J = 14.5, 4.5 Hz, 1H), 3.68 (s, 3H), 3.44 (dd, J = 14.5, 9.9 Hz, 1H).

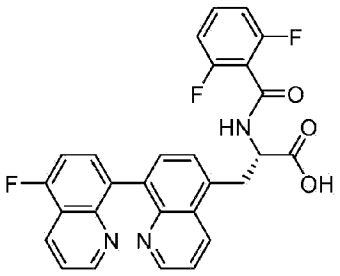
Example 15 (for illustrative purposes)

[0335] Synthesis of methyl (S)-2-(2,6-difluorobenzamido)-3-(5'-fluoro-[8,8'-biquinolin]-5-yl)propanoate (**15A**): The title compound was prepared according to the method presented for the synthesis of compound **3B** starting with (5-fluoroquinolin-8-yl)boronic acid and **3A.**

[0336] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(5'-fluoro-[8,8'-biquinolin]-5-yl)propanoic acid (**15**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **15A.** MS (m/z) 502.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.32 (d, J = 8.1 Hz, 1H), 8.74 (dd, J = 4.2, 1.8 Hz, 1H), 8.70 (s, 1H), 8.56 (d, J = 8.7 Hz, 1H), 7.77 - 7.43 (m, 8H), 7.19 - 7.05 (m, 2H), 4.79 (m, 1H), 3.77 - 3.65 (m, J = 1H), 3.56 - 3.40 (m, 1H).



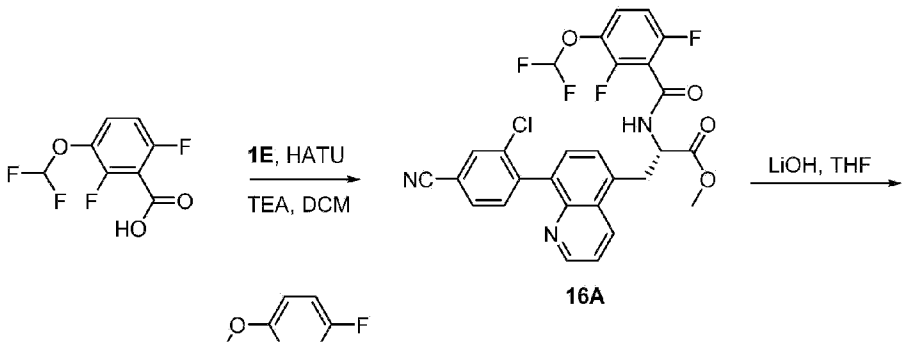
15A



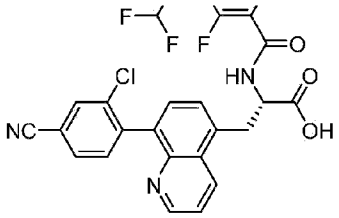
15

Example 16 (for illustrative purposes)

[0337]



16A



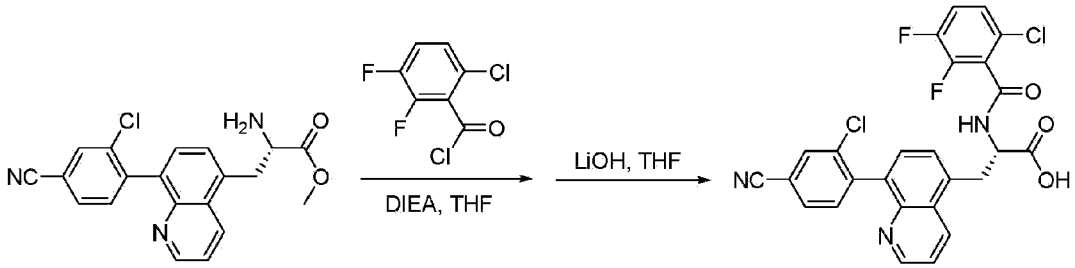
16

[0338] Synthesis of methyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(3-(difluoro methoxy)-2,6-difluorobenzamido)propanoate (**16A**): To a stirred solution of **1E** (0.15 g, 0.41 mmol) in DCM was added 3-(difluoromethoxy)-2,6-difluorobenzoic acid (0.11 g, 0.49 mmol), HATU (0.187 g, 0.49 mmol) and TEA (0.36 mL, 2.1 mmol). The reaction mixture was allowed to stir for 2 hr at RT. The reaction mixture was concentrated under reduced pressure and used without further purification.

[0339] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(3-(difluoromethoxy)-2,6-difluorobenzamido)propanoic acid (**16**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **16A.** MS (m/z) 559.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.16 (m, J = 8.4 Hz, 3H), 7.67 (d, J = 8.5 Hz, 2H), 7.56 - 7.21 (m, 6H), 4.75 (ddd, J = 11.7, 8.4, 3.7 Hz, 1H), 3.10 (m, 2H) 2.99 (dd, J = 14.3, 11.3 Hz, 1H).

Example 17 (for illustrative purposes)

[0340]

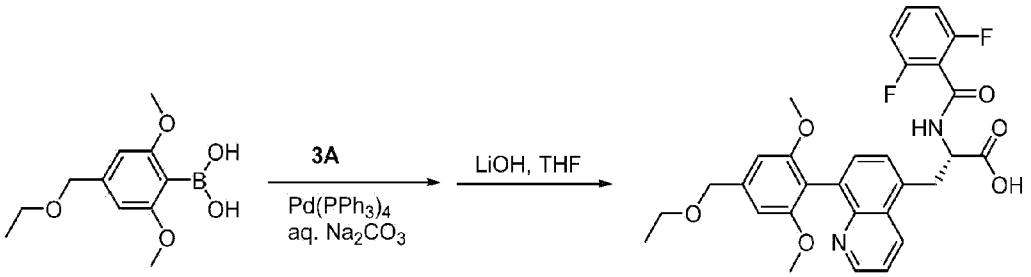


1E 17

[0341] Synthesis of (S)-2-(6-chloro-2,3-difluorobenzamido)-3-(8-(2-chloro-4-cyanophenyl) quinolin-5-yl)propanoic acid (**17**): The title compound was prepared according to the method presented for the synthesis of compound **1F** and **1** starting with 6-chloro-2,3-difluorobenzoyl chloride and **1E.** MS (m/z) 559.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.37 (d, J = 8.4 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.6, 1.6 Hz, 1H), 8.16 (dd, J = 1.6, 0.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.67 - 7.64 (m, 1H), 7.63 (s, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.33 (td, J = 8.7, 3.8 Hz, 1H), 4.83 (s, 1H), 3.84 - 3.74 (m, 1H), 3.38 (dd, J = 14.6, 10.6 Hz, 1H).

Example 18 (for illustrative purposes)

[0342]

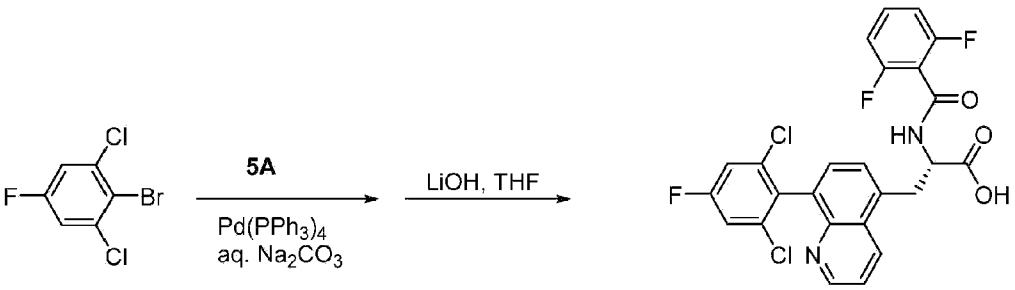


18

[0343] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)quinolin-5-yl)propanoic acid (**18**): The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid and **3A.** MS (m/z) 551.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.09 (s, 1H), 9.30 (d, J = 8.1 Hz, 1H), 9.10 - 8.69 (m, 2H), 7.96 - 7.30 (m, 4H), 7.11 (t, J = 8.0 Hz, 2H), 6.75 (d, J = 3.4 Hz, 2H), 4.85 - 4.74 (m, 1H), 4.53 (s, 2H), 3.86 - 3.66 (m, 1H), 3.64 - 3.53 (m, 8H), 3.45 (dd, J = 14.7, 10.1 Hz, 1H), 1.21 (t, J = 7.0 Hz, 3H).

Example 19 (for illustrative purposes)

[0344]

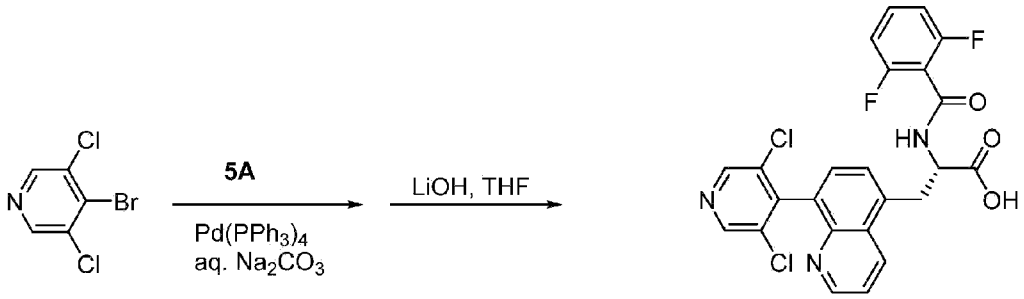


19

[0345] Synthesis of (S)-3-(8-(2,6-dichloro-4-fluorophenyl)quinolin-5-yl)-2-(2,6-difluoro benzamido)propanoic acid (**19**): The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with 2-bromo-1,3-dichloro-5-fluorobenzene and **5A.** MS (m/z) 518.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 9.26 (d, J = 8.1 Hz, 1H), 8.82 (dd, J = 4.1, 1.6 Hz, 1H), 8.68 - 8.58 (m, 1H), 7.70 - 7.59 (m, 3H), 7.57 (d, J = 7.3 Hz, 1H), 7.47 (tt, J = 8.5, 6.5 Hz, 1H), 7.15 - 7.03 (m, 2H), 4.78 (ddd, J = 10.2, 8.1, 4.4 Hz, 1H), 3.76 (dd, J = 14.5, 4.4 Hz, 1H), 3.41 (dd, J = 14.6, 10.3 Hz, 1H).

Example 20 (for illustrative purposes)

[0346]

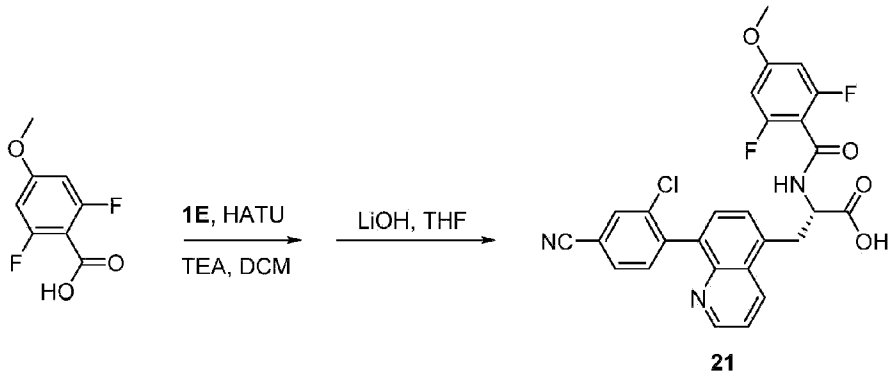


20

[0347] Synthesis of (S)-3-(8-(3,5-dichloropyridin-4-yl)quinolin-5-yl)-2-(2,6-difluoro benzamido)propanoic acid (**20**): The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with 4-bromo-3,5-dichloropyridine and **5A.** MS (m/z) 501.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.27 (d, J = 8.2 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.75 (d, J = 2.4 Hz, 2H), 8.66 (dd, J = 8.7, 1.7 Hz, 1H), 7.69 - 7.60 (m, 3H), 7.47 (tt, J = 8.5, 6.5 Hz, 1H), 7.09 (dd, J = 8.4, 7.5 Hz, 2H), 4.80 (ddd, J = 10.4, 8.2, 4.4 Hz, 1H), 3.78 (dd, J = 14.5, 4.4 Hz, 1H), 3.43 (dd, J = 14.6, 10.4 Hz, 1H).

Example 21 (for illustrative purposes)

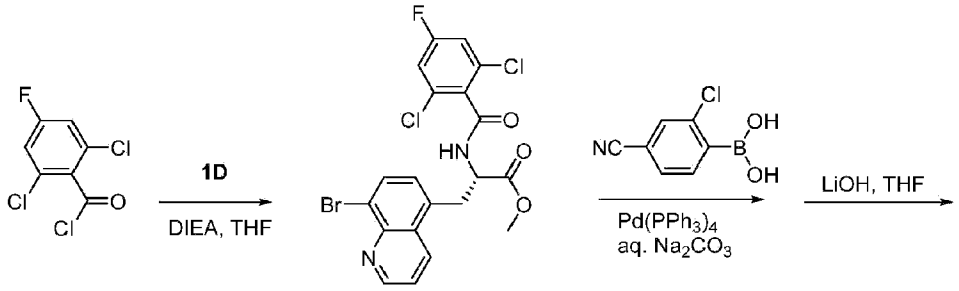
[0348] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-methoxybenzamido)propanoic acid (**21**): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with 2,6-difluoro-4-methoxybenzoic acid and **1E.** MS (m/z) 523.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.41 (s, 1H), 8.62 (s, 1H), 8.30 (s, 1H), 8.15 - 7.98 (m, 4H), 7.11 (d, J = 6.7 Hz, 3H), 6.82 (d, J = 9.1 Hz, 2H), 6.67 (s, 2H), 4.47 (s, 2H), 3.62 (s, 6H), 3.53 (q, J = 7.0 Hz, 2H), 3.18 (dd, J = 124.4, 13.3 Hz, 2H), 1.28 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H).



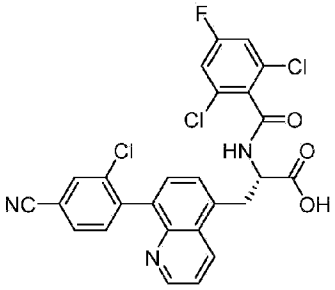
21

Example 22 (for illustrative purposes)

[0349] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichloro-4-fluorobenzamido)propanoic acid (**22**): The title compound was prepared according to the method presented for the synthesis of compound **3A, 3B,** and **3** starting with 2,6-dichloro-4-fluorobenzoyl chloride and **1D.** MS (m/z) 541.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.26 (d, J = 8.5 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (dd, J = 1.6, 0.4 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.69 - 7.58 (m, 3H), 7.50 (d, J = 8.6 Hz, 3H), 4.84 (s, 1H), 3.76 (dd, J = 14.5, 4.1 Hz, 1H), 3.37 (s, 1H).



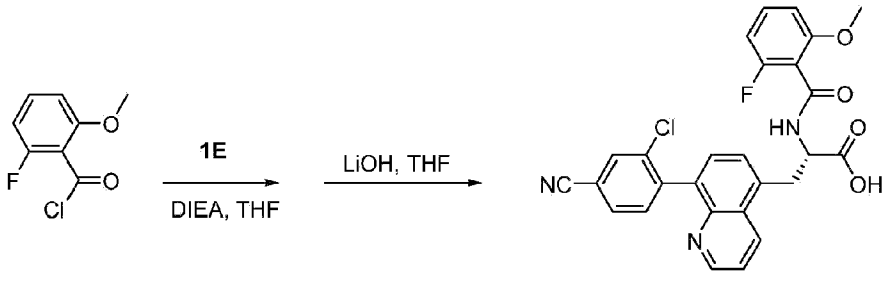
22A



22

Example 23 (for illustrative purposes)

[0350]



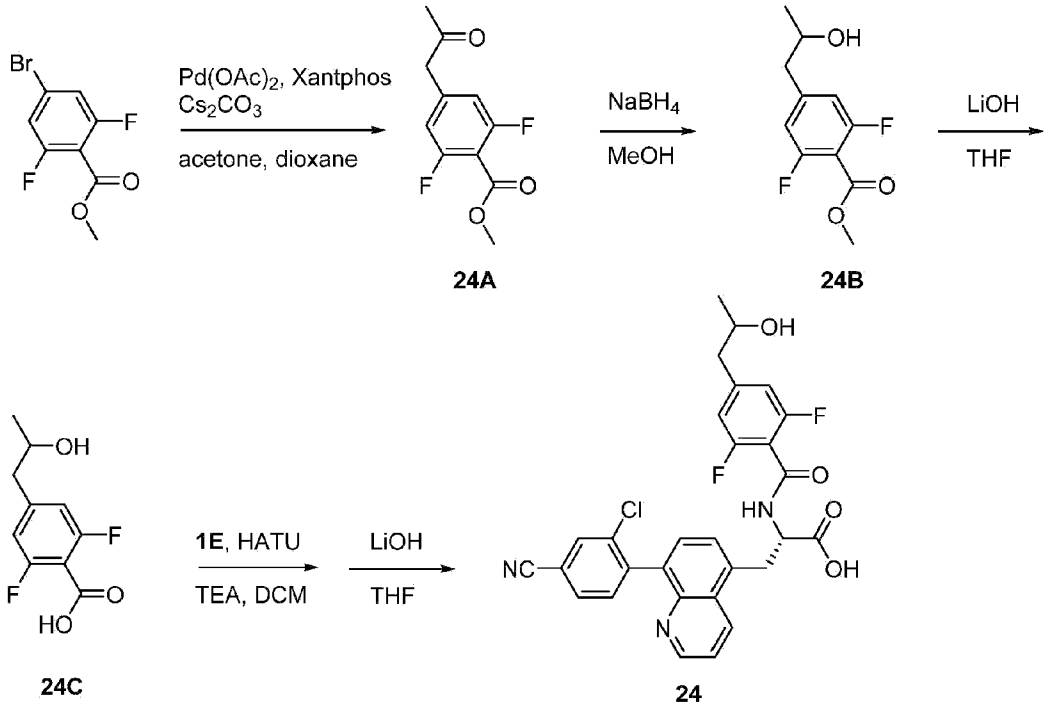
23

[0351] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2-fluoro-6-methoxy benzamido)propanoic acid (**23**): The title compound was prepared according to the method presented for the synthesis of compound **1F** and **1** starting with 2-fluoro-6-methoxy benzoyl

chloride and **1E.** MS (m/z) 504.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.92 (d, J = 8.1 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (dd, J = 1.6, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.68 - 7.64 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.35 (td, J = 8.4, 6.8 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.78 (t, J = 8.6 Hz, 1H), 4.80 - 4.68 (m, 1H), 3.69 - 3.65 (m, 1H), 3.63 (s, 3H), 3.50 - 3.40 (m, 1H).

Example 24 (for illustrative purposes)

[0352]



[0353] Synthesis of methyl 2,6-difluoro-4-(2-oxopropyl)benzoate (**24A**): To a stirred solution of methyl 4-bromo-2,6-difluorobenzoate (0.15 g, 0.41 mmol) in 1,4-dioxane was added acetone (1.8 mL), $Pd(OAc)_2$ (18 mg, 0.081 mmol), Cs_2CO_3 (1.05 g, 3.2 mmol), and 4,5-bis(diphenyl phosphino)-9,9-dimethylxanthene (93.98 mg, 0.16 mmol). This mixture was flushed with N_2 for 5 min, then heated to 100 °C for 2.5 hours. The reaction mixture was filtered through celite, rinsed with EA and purified by silica gel chromatography using EA in hexanes as eluent to give the title compound.

[0354] Synthesis of methyl 2,6-difluoro-4-(2-hydroxypropyl)benzoate (**24B**): To a stirred solution of **24A** (306.4 mg, 1.34 mmol) in MeOH was added ammonium acetate (1.04 g, 13.43 mmol). $NaBH_4$ (83.81 mg, 2.22 mmol) was then slowly added to prevent major exotherm. The reaction mixture was stirred for 2 hours at RT followed by addition of NaOH (1M) and DCM. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The material was purified by silica gel chromatography using EA and hexanes as eluent to

afford the title compound.

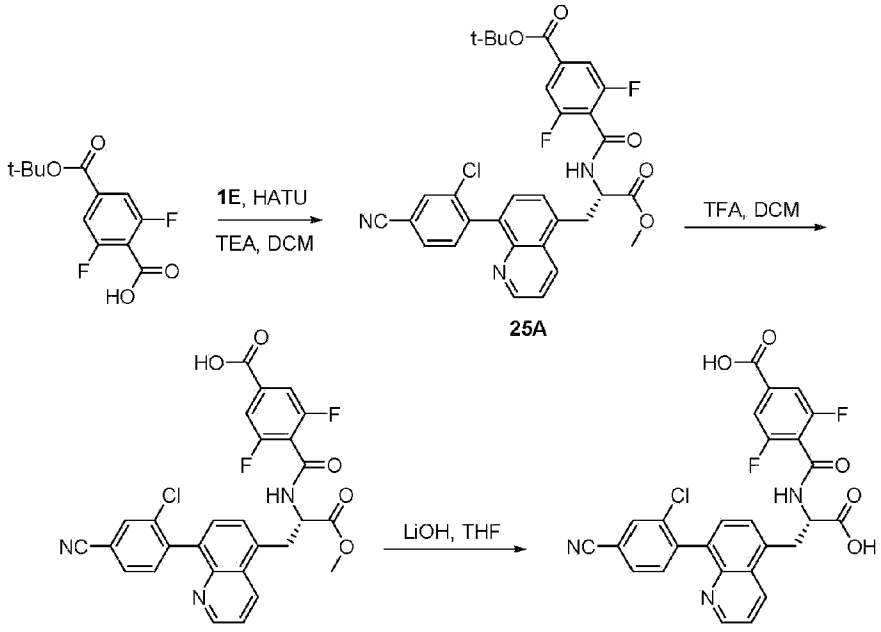
[0355] Synthesis of 2,6-difluoro-4-(2-hydroxypropyl)benzoic acid (**24C**): To a stirred solution of **24B** (87.3 mg, 0.38 mmol) in THF was added LiOH (79.56 mg, 1.9 mmol). The reaction mixture was stirred at RT for 3 hours then HCl (1M) and EA was added. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give the title compound which was used without further purification.

[0356] (2S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(2-hydroxypropyl) benzamido)propanoic acid (**24**): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **1E** and **24C.** MS (m/z) 550.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.18 (d, J = 8.1 Hz, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.64 (dd, J = 8.6, 1.6 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.68 - 7.59 (m, 3H), 7.57 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 4.80 - 4.69 (m, 1H), 3.80 (pd, J = 8.9, 7.6, 3.0 Hz, 2H), 3.40 (s, 1H), 2.62 (d, J = 6.2 Hz, 2H), 1.02 (d, J = 6.1 Hz, 3H).

Example 25 (for illustrative purposes)

[0357] Synthesis of tert-butyl (S)-4-((3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-1-methoxy -1-oxopropan-2-yl)carbamoyl)-3,5-difluorobenzoate (**25A**): The title compound was prepared according to the method presented for the synthesis of compound **16A** starting with 4-(tert-butoxycarbonyl)-2,6-difluorobenzoic acid and **1E.**

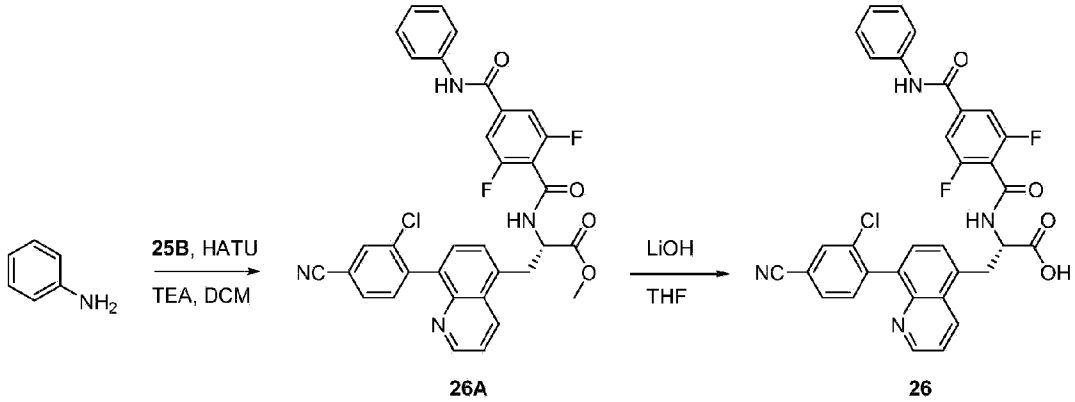
[0358] Synthesis of (S)-4-((3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-3,5-difluorobenzoic acid (**25B**): To a stirred solution of **25A** (150 mg, 0.25 mmol) in DCM was added TFA (1.5 mL). The reaction mixture was stirred for 2 hours at RT, concentrated under reduced pressure, and then purified by silica gel chromatography using DCM and MeOH as the eluent to afford the title compound.



[0359] (S)-4-((1-carboxy-2-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)ethyl)carbamoyl)-3,5-difluorobenzoic acid (**25**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **25B.** MS (m/z) 535.8 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.40 (d, J = 8.2 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.95 - 7.86 (m, 1H), 7.64 (t, J = 4.3 Hz, 1H), 7.61 (d, J = 5.1 Hz, 1H), 7.57 (dd, J = 7.7, 6.0 Hz, 2H), 4.80 (t, J = 11.5 Hz, 1H), 3.79 (s, 1H), 3.41 (s, 1H).

Example 26 (for illustrative purposes)

[0360]

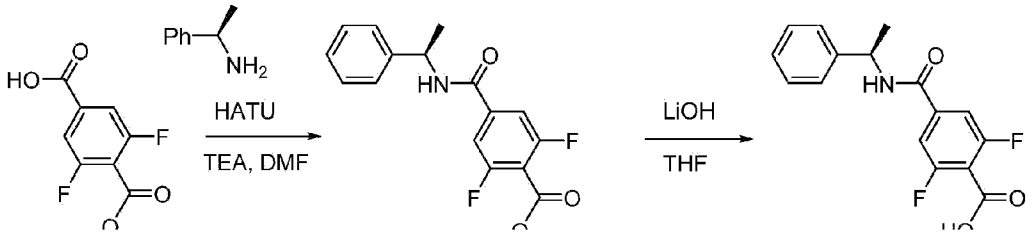


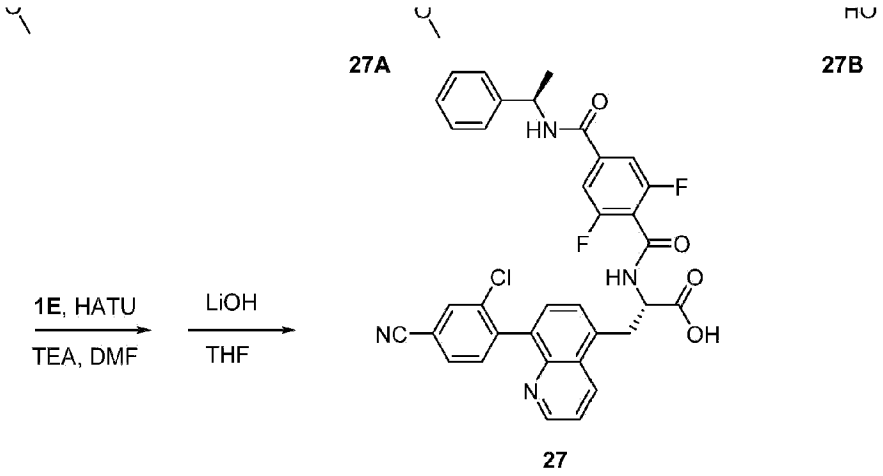
26A **26**

[0361] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(phenylcarbamoyl) benzamido)propanoic acid (**26**): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **25B** and aniline. MS (m/z) 611.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.41 (d, J = 8.3 Hz, 1H), 8.88 - 8.80 (m, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.76 - 7.61 (m, 7H), 7.57 (d, J = 7.9 Hz, 1H), 7.42 - 7.29 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 4.81 (s, 1H), 3.76 (s, 1H), 3.25 - 3.17 (m, 1H).

Example 27 (for illustrative purposes)

[0362]





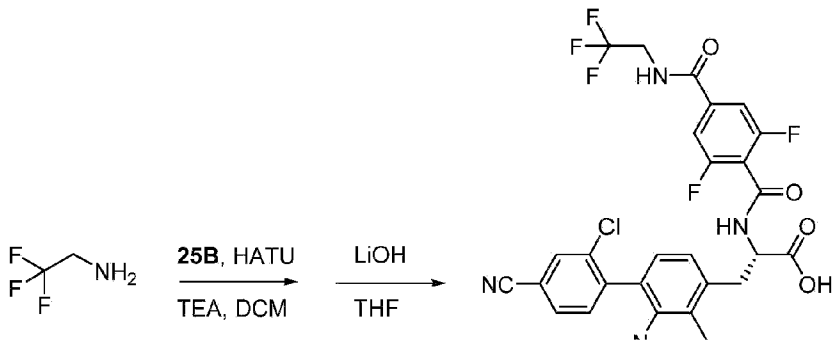
[0363] Synthesis of methyl (R)-2,6-difluoro-4-((1-phenylethyl)carbamoyl)benzoate (**27A**): To a stirred solution of 3,5-difluoro-4-(methoxycarbonyl)benzoic acid (20 mg, 0.093 mmol) in DMF was added (R)-1-phenylethan-1-amine (13.46 mg, 0.11 mmol), HATU (42 mg, 0.11 mmol), and TEA (0.06 mL, 0.463 mmol). The reaction was stirred for 1 h at RT, concentrated under reduced pressure, and then purified by silica gel chromatography using DCM/MeOH as eluent.

[0364] Synthesis of (R)-2,6-difluoro-4-((1-phenylethyl)carbamoyl)benzoic acid (**27B**): To a stirred solution of **27A** (29.5 mg, 0.09 mmol) in THF was added aqueous LiOH (0.46 mL, 1 M). The mixture was allowed to stir at RT for 3 hours, concentrated under reduced pressure, and then purified by silica gel chromatography using DCM/MeOH as eluent

[0365] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(((R)-1-phenylethyl) carbamoyl)benzamido)propanoic acid (**27**): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **27B.** MS (m/z) 639.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.35 (d, J = 8.3 Hz, 1H), 8.98 (d, J = 7.9 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.66 - 7.53 (m, 6H), 7.32 (dt, J = 15.1, 7.5 Hz, 4H), 7.21 (t, J = 7.1 Hz, 1H), 5.11 (t, J = 7.3 Hz, 1H), 4.80 (s, 1H), 3.50-3.40 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H).

Example 28 (for illustrative purposes)

[0366]





28

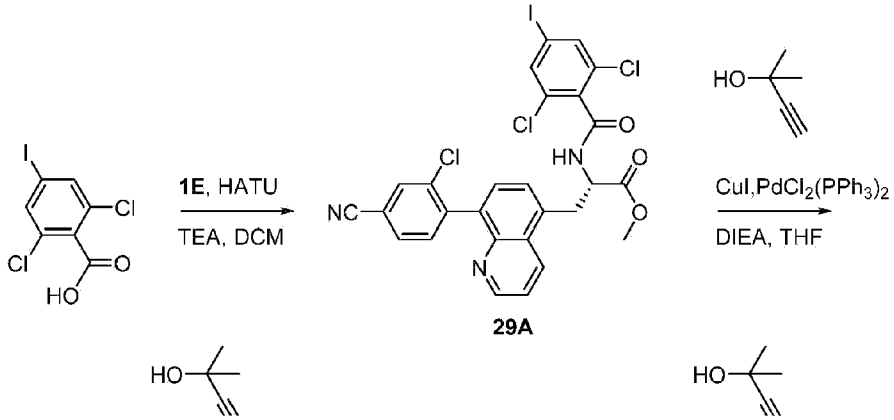
[0367] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((2,2,2-trifluoro ethyl)carbamoyl)benzamido)propanoic acid (**28**): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **25B.** MS (m/z) 616.9 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.38 (d, J = 8.3 Hz, 1H), 9.29 (t, J = 6.4 Hz, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 - 8.60 (m, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 4.6 Hz, 1H), 7.62 - 7.58 (m, 3H), 7.57 (d, J = 7.9 Hz, 1H), 4.80 (s, 1H), 4.09 (dd, J = 9.8, 6.4 Hz, 1H), 3.75-3.60 (m, 1H).

Example 29 (for illustrative purposes)

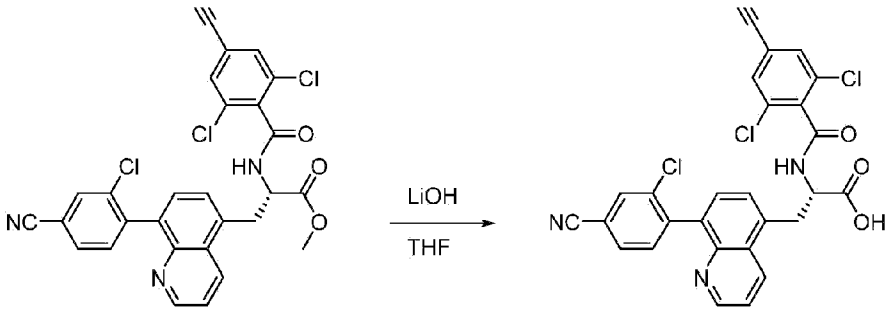
[0368] Synthesis of ethyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichloro-4-iodobenzamido)propanoate (**29A**): The title compound was prepared according to the method presented for the synthesis of compound **16A** starting with 2,6-dichloro-4-iodobenzoic acid and **1E.**

[0369] Synthesis of methyl (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichloro-4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzamido)propanoate (29B): To a stirred solution of **29A** (60 mg, 0.09 mmol) in THF was added 2-methylbut-3-yn-2-ol (0.02 ml, 0.27 mmol), CuI (3.44 mg, 0.02 mmol), $PdCl_2(PPh_3)_2$ (12.71 mg, 0.02 mmol), and DIEA (0.08 ml, 0.45 mmol). The reaction mixture was allowed to stir for 1 h at 60 °C then concentrated under reduced pressure and used without further purification.

[0370] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-dichloro-4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzamido)propanoic acid (**29**): The title compound was prepared according to the method presented for the synthesis of compound **1** starting with **29B.** MS (m/z) 606.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 9.30 (d, J = 7.9 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.6, 1.7 Hz, 1H), 8.18 - 8.13 (m, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.68 - 7.57 (m, 2H), 7.61 - 7.48 (m, 1H), 7.43 (s, 1H), 7.41 - 7.30 (m, 3H), 4.85 (s, 1H), 3.76 (dd, J = 14.4, 4.2 Hz, 1H), 3.39 (t, J = 12.4 Hz, 1H), 1.43 (d, J = 3.7 Hz, 6H).



29A

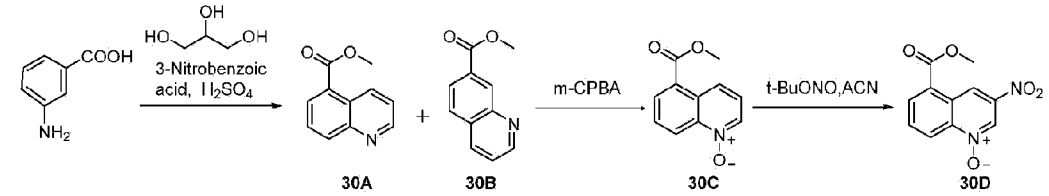


29B 29

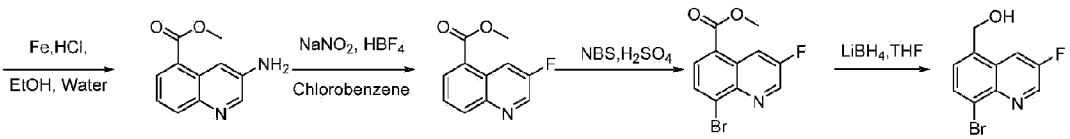
Example 30 (for illustrative purposes)

[0371] Synthesis of methyl quinoline-5-carboxylate (**30A**): To a stirred solution of 3-nitrobenzoic acid (244.0 g, 1.46 mol) in conc. H_2SO_4 (750 mL) was added glycerol (1.17 L, 15.33 mol) and 3-aminobenzoic acid (500.0 g, 3.65 mol). The resulting reaction mixture was heated to 150 °C for 7h. Then the reaction mixture was cooled to 0 °C and treated with methanol (5.0 L) and the resulting reaction mixture was heated to reflux for 12 h. The reaction mixture was cooled to 0 °C and quenched with ice water and neutralized with solid Na_2CO_3. The aqueous was extracted with EA (4 L x 2), the organic layer was separated dried over Na_2SO_4 and concentrated under reduced pressure. The material was purified by column chromatography using EA/ petroleum ether to obtain **30A.**

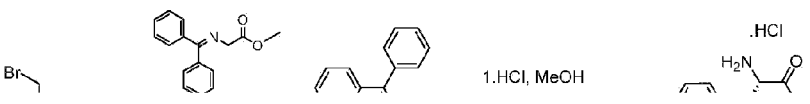
[0372] Synthesis of 5-(methoxycarbonyl)quinoline 1-oxide (**30C**): m-CPBA (604.8 g, 2.19 mol) was added to a solution of compound **30A** (205.0 g, 1.095 mol) in chloroform (4.1 L) at 0 °C. The resulting reaction mixture was allowed to warm RT and stirred for 6 h. The reaction mixture was cooled to 0 °C and quenched with sat $NaHCO_3$ solution and extracted with DCM. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 5% MeOH/DCM as eluent to obtain **30C.**

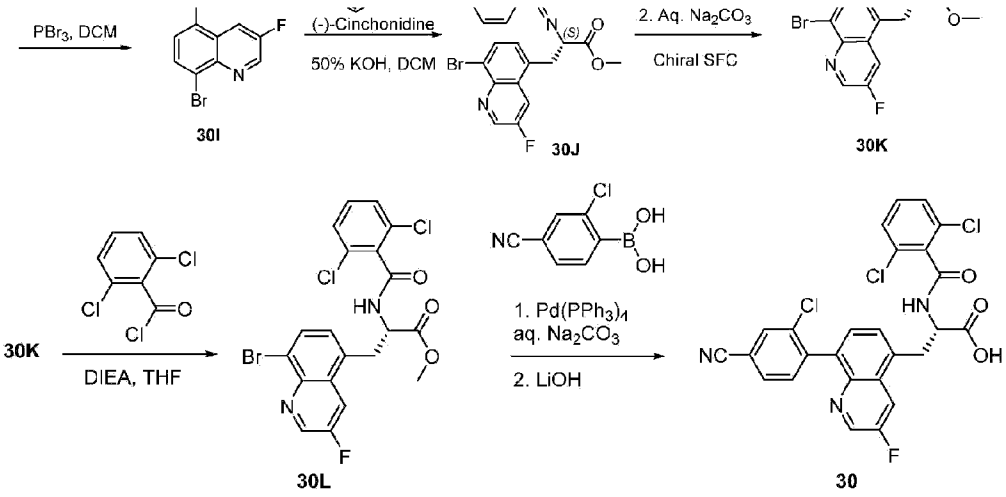


30A 30B 30C 30D



30E 30F 30G 30H





[0373] Synthesis of 5-(methoxycarbonyl)-3-nitroquinoline 1-oxide **(30D):** *t*-BuONO (708.1 mL, 5.9 mol) was added to a solution of compound **30C** (120.0 g, 0.59 mol) in acetonitrile (6.0 L) at RT and the resulting reaction mixture was heated to 100 °C in an autoclave for 8 h. The reaction mixture was cooled to RT and concentrated under reduced pressure. The compound was washed with EA to afford compound **30D.**

[0374] Synthesis of methyl 3-aminoquinoline-5-carboxylate **(30E):** Fe Powder (39.38 g, 0.705 mol) and conc. HCl (50.0 mL) were added to a solution of compound **30D** (25.0 g, 0.1 mol) in a mixture of ethanol (500 mL) and water (500 mL) at 70 °C and the resulting reaction mixture was stirred for 18 h. The reaction mixture was cooled to RT, filtered through celite, concentrated under reduced pressure and extracted with DCM. The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The compound was purified by column chromatography using 50% EA in pet ether as eluent to obtain **30E.**

[0375] Synthesis of methyl 3-fluoroquinoline-5-carboxylate **(30F):** A solution of sodium nitrite (13.64 g, 0.197 mol) in water (60.0 mL) was added to a solution of compound **30E** (20.0 g, 0.0989 mol) in 50% HBF_4 (200 mL) at 0 °C. The reaction mixture was allowed warm to RT and stirred for 2 h, then filtered under vacuum. The filtered compound was added to chlorobenzene, and the reaction mixture was refluxed at 125 °C for 2 h. The chlorobenzene was removed by distillation resulting in a material which was dissolved in DCM and water. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The compound was purified by column chromatography using 4-5% EA in **petroleum** ether as eluent to obtain **30F.**

[0376] Synthesis of methyl 8-bromo-3-fluoroquinoline-5-carboxylate **(30G):** NBS (41.89 g, 0.243 mol) was added to a stirred solution of **30F** (25.0 g, 0.121 mol) in H_2SO_4 (500.0 mL) at 0 °C and the resulting reaction mixture was allowed warm to RT and allowed to stir for 24 h. The reaction mixture was poured onto crushed ice and the solid obtained was filtered and dried under reduced pressure to afford compound **30G.**

[0377] Synthesis of (8-bromo-3-fluoroquinolin-5-yl)methanol **(31H):** To a stirred solution of **30G (**26.0 g, 0.091 mol) in THF (260 mL) was slowly added 2M $LiBH_4$ in THF (137 mL, 0.274 mol) at 0 °C. The reaction mixture was heated to 40 °C for 2 h then cooled to 0 °C, quenched with ice water and stirred for 30 minutes. The reaction mixture was acidified with aq. 2N HCl (pH 4-5) and heated to 40 °C for 2 h. The reaction mixture was cooled to RT and basified with sat. NaHCOs solution (pH 8-9), extracted with DCM (250 mL x 2). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The compound was washed with pentane to afford **31H.**

[0378] Synthesis of 8-bromo-5-(bromomethyl)-3-fluoroquinoline **(30I):** PBr_3 (48.5 g, 0.179 mol) was added to a stirred solution of **31H** (23.0 g, 0.0897 mol) in DCM (230 mL) at 0 °C, the mixture was allowed warm to RT and allowed to stir for 18 h. The reaction mixture was concentrated, cooled to 0 °C and basified with sat. Na_2CO_3 solution (PH 8-9) to obtain a solid that was collected by filtration and dried under vacuum to obtain **30I.**

[0379] Synthesis of methyl (S)-3-(8-bromo-3-fluoroquinolin-5-yl)-2-((diphenylmethylene) amino)propanoate **(30J):** To a stirred solution of methyl 2-((diphenylmethylene)amino)acetate (16.6 g, 0.0655 mol) in DCM (500 mL) was added (-)-cinchonidine (1.93 g, 0.0065 mol) at RT. The reaction mixture was cooled to 0 °C. KOH solution (50%) (133 mL) and **30I** (23.0 g, 0.0721) were added and the reaction mixture was allowed to stir at RT for 6 h. The reaction mixture was diluted with water (200 mL) and stirred for 15 minutes. After washing with water and EA, the combined organic layer was dried over anhydrous Na_2SO_4, filtered through Celite, washed with EA, and concentrated under reduced pressure to obtain **30J.**

[0380] Synthesis of free base methyl (S)-2-amino-3-(8-bromo-3-fluoroquinolin-5-yl) propanoate **(30K):** 4M HCl in 1,4-dioxane (720 mL) was added to a stirred solution of **30J** (60 g, 0.1221 mol) in methanol (420 mL) at 0 °C. The reaction mixture was allowed to stir at RT for 36 h. The reaction mixture was concentrated under reduced pressure, dissolved in water (100 mL) and washed with EA (100 mL x 2 L). The aqueous layer was separated and basified (pH~8) using Sat.Na_2CO_3 and extracted with DCM (500 mL X 5). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **30K.**

[0381] Chiral purification of methyl (S)-2-amino-3-(8-bromo-3-fluoroquinolin-5-yl) propanoate hydrochloride **(30K): 30K** was enriched in the desired enantiomer by supercritical fluid chromatography using 50% (0.5% TEA in IPA) co-solvent, at a flow rate of 100 mL/min, using an Chiralpak IC (30x250 mm), 5 µm column.

[0382] Synthesis of methyl (S)-2-amino-3-(8-bromo-3-fluoroquinolin-5-yl)propanoate hydrochloride **(30K):** The free amine was dissolved in DCM (300 mL) and treated with 4M HCl in 1,4-dioxane (100 mL) at 0 °C and the reaction mixture was allowed to stir at RT for 30 min then concentrated under reduced pressure to afford **30K** as the HCl salt.

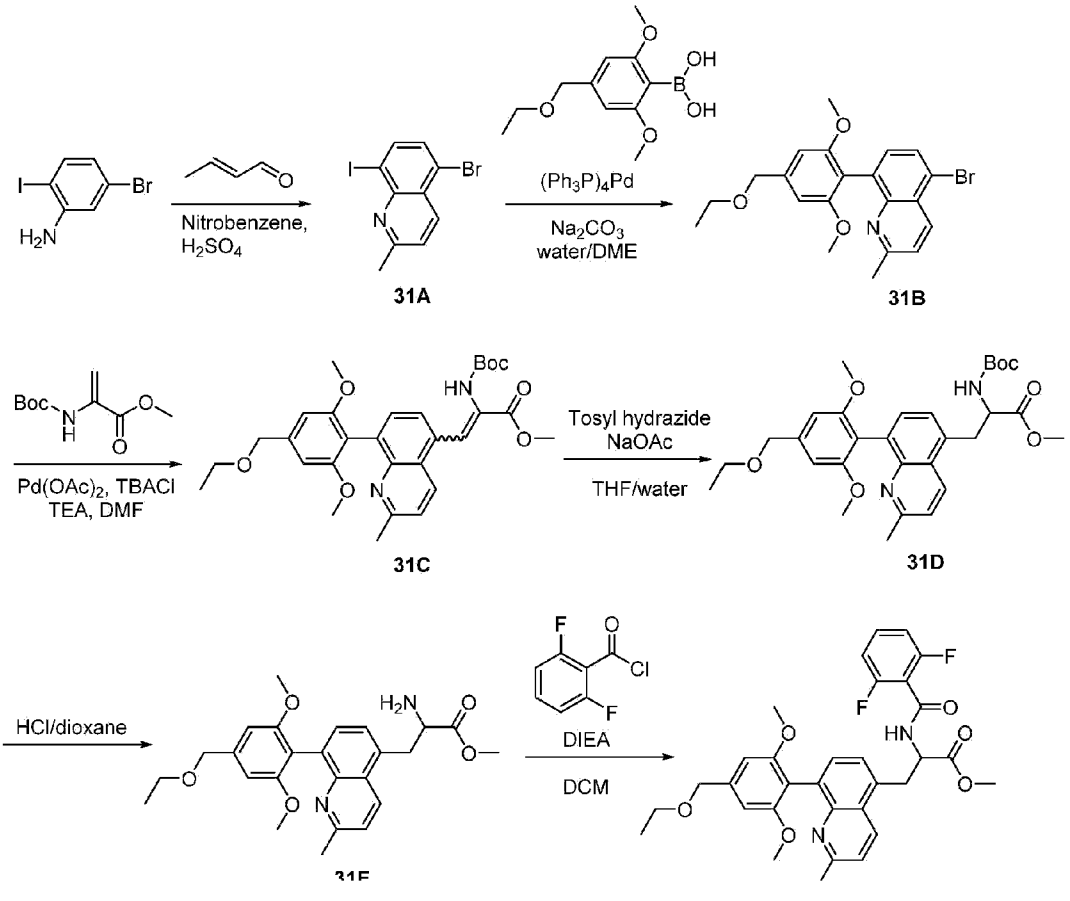
[0383] Synthesis of methyl (S)-3-(8-bromo-3-fluoroquinolin-5-yl)-2-(2,6-dichloro

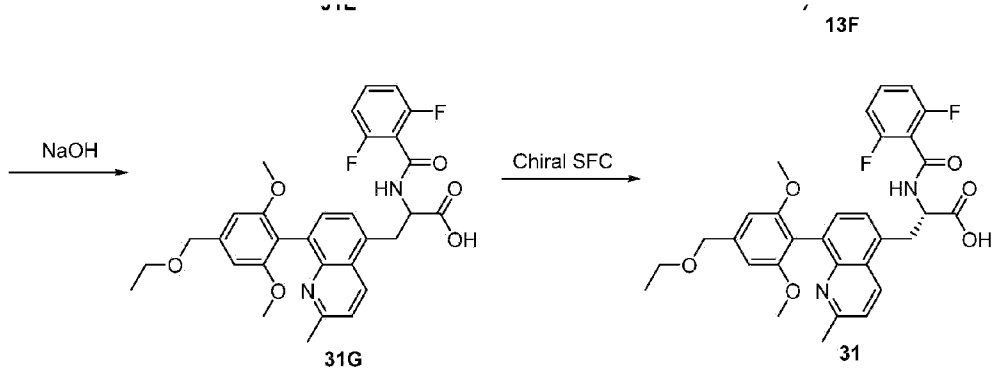
benzamido)propanoate (**30L**): The title compound was prepared according to the method presented for the synthesis of compound **1F** starting with **30K** and 2,6-dichlorobenzoyl chloride.

[0384] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)-3-fluoroquinolin-5-yl)-2-(2,6-dichlorobenzamido)propanoic acid (**30**): The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **30L.** MS (m/z) 542.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.24 (d, J = 8.4 Hz, 1H), 8.90 (d, J = 2.7 Hz, 1H), 8.46 (d, J = 10.3 Hz, 1H), 8.16 (dd, J = 1.6, 0.4 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.43 - 7.24 (m, 3H), 4.87 (s, 1H), 3.69 (dd, J = 14.6, 4.2 Hz, 1H), 3.45 - 3.35 (m, 1H).

Example 31 (for illustrative purposes)

[0385] Synthesis of 5-bromo-8-iodo-2-methylquinoline (**31A**): To a stirred solution of 2-iodo-5-bromoaniline (5 g, 17 mmol) in nitrobenzene (1.7 mL) and 75% H_2SO_4 (15 mL) was added but-2-enal (2.35 g, 34 mmol) at RT and then slowly heated to 150 °C for 3 h. Caution: highly exothermic reaction. The mixture was cooled to RT and poured into ice-water while maintaining the temperature below 10 °C. The pH was adjusted to ~12 with solid KOH, and the resulting material was collected. The material was washed three times with water, then were taken up in ethyl acetate and filtered. The organic solution was concentrated, then purified via flash chromatography, eluting with a linear gradient of 5-100% DCM/hexanes, to yield **31A**.





[0386] Synthesis of 5-bromo-8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-2-methylquinoline (**31B**): To a stirred solution of compound **31A** (850 mg, 2.44 mmol) and (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid (586 mg, 2.44 mmol) in 1,2-dimethoxyethane (12 mL) was added 2M sodium carbonate in water (2.44 mL, 4.9 mmol), and the reaction was degassed with dry nitrogen. To this, tetrakis(triphenylphosphine)palladium(0) (141 mg, 0.12 mmol) was added, the reaction was sealed, and it was heated to 80 °C for 16 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate, and washed with water and brine. It was then dried over anhydrous sodium sulfate, filtered, concentrated and purified via flash chromatography, eluting with a linear gradient of 5-50% ethyl acetate/hexanes, to yield **31B**.

[0387] Synthesis of methyl 2-((*tert*-butoxycarbonyl)amino)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-2-methylquinolin-5-yl)acrylate (**31C**): To a stirred solution of **31B** (190 mg, 0.46 mmol) in DMF (4.7 mL) was added palladium(II) acetate, and the reaction was degassed with nitrogen for 30 minutes. To this, methyl 2-((*tert*-butoxycarbonyl)amino)acrylate (230 mg, 1.1 mmol), tetrabutylammonium chloride (152 mg, 0.55 mmol), and trimethylamine (0.074 mL, 0.53 mmol) were added, and the reaction was sealed and heated to 90 °C for 3 hours. It was cooled to RT, diluted with ethyl acetate, and washed with 10% citric acid, saturated sodium bicarbonate, and saturated sodium chloride. It was dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified via flash chromatography, eluting with a linear gradient of 5-100% ethyl acetate/hexanes, to yield compound **31C.**

[0388] Synthesis of methyl 2-((*tert*-butoxycarbonyl)amino)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-2-methylquinolin-5-yl)propanoate (**31D**): To a stirred solution of **31C** (150 mg, 0.28 mmol) and tosyl hydrazide (781 mg, 4 mmol) in THF (3 mL) at 60 °C was added sodium acetate (609 mg, 4 mmol) in water (3 mL) dropwise, then the reaction was heated to reflux overnight. It was partitioned between ethyl acetate and water, and then the aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was twice more subjected to these conditions to yield **31D.**

[0389] Synthesis of methyl 2-amino-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-2-methyl quinolin-5-yl)propanoate dihydrochloride (**31E**): To a stirred solution of compound **31D** (150 mg, 0.28 mmol) in ethyl acetate (2 mL) was added 4M hydrogen chloride in dioxane (0.7 mL,

1.8 mmol), and the reaction was allowed to stir overnight at RT. It was diluted with EA, and the resulting solids were collected by trituration to yield **31E**.

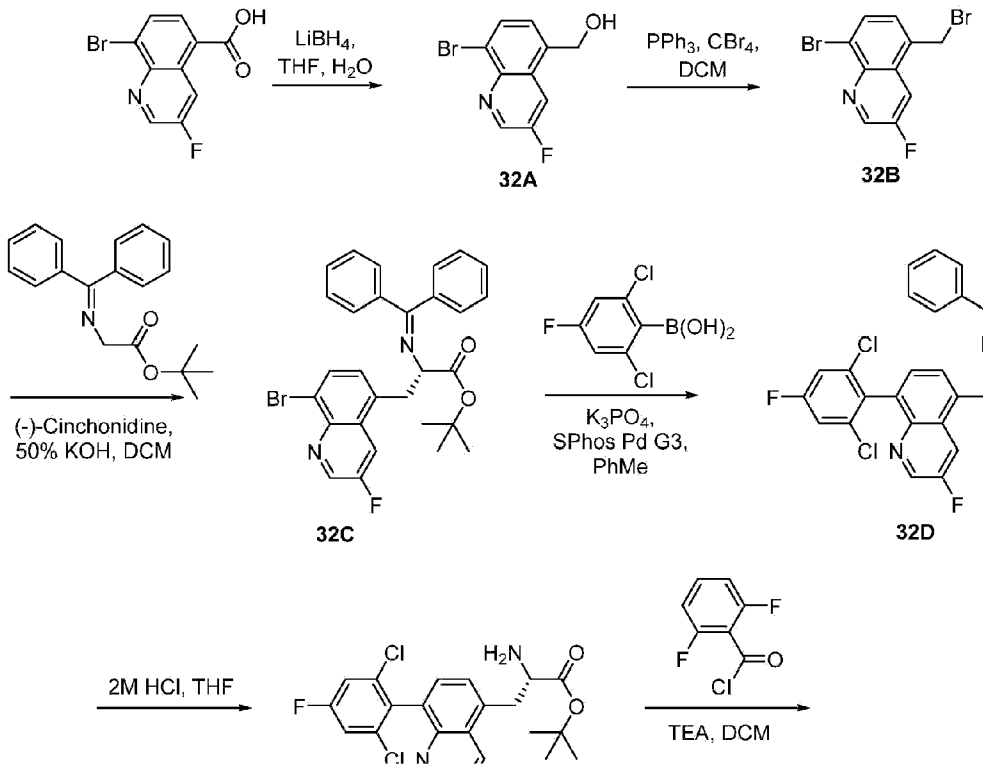
[0390] Synthesis of methyl 2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)-2-methylquinolin-5-yl)propanoate (**31F**): The title compound was prepared according to the method presented for the synthesis of compound **1F** starting with **31E** and 2,6-difluorobenzoyl chloride.

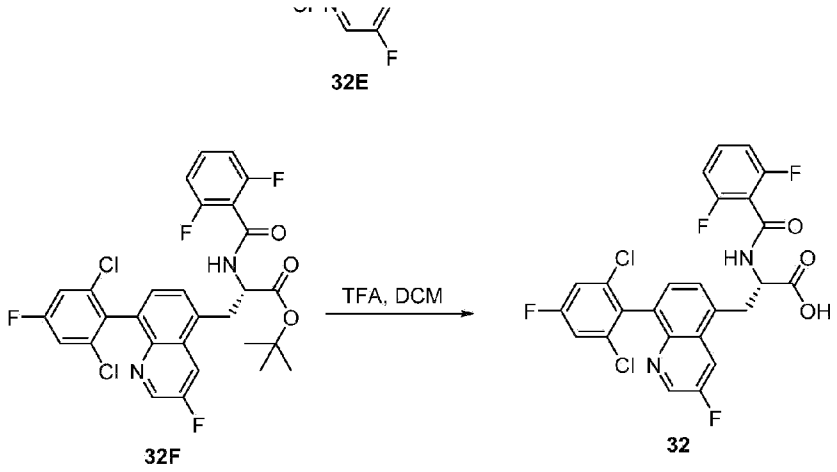
[0391] Synthesis of 2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl) -2-methylquinolin-5-yl)propanoic acid (**31G**): Synthesized via sodium hydroxide method to yield **31G.**

[0392] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)-2-methylquinolin-5-yl)propanoic acid (**31**): 2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxy methyl)-2,6-dimethoxyphenyl)-2-methylquinolin-5-yl)propanoic acid (**31G**) was separated into its two enantiomers by supercritical fluid chromatography using 20% MeOH/DEA co-solvent on an IC SFC column to yield the desired enantiomer **31H** as the second eluting peak. MS (m/z) 565.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.56 (d, J = 8.7 Hz, 1H), 7.51 - 7.41 (m, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 7.15 - 7.05 (m, 2H), 6.68 (s, 2H), 4.50 (s, 2H), 4.40 (s, 1H), 3.68 - 3.49 (m, 9H), 3.42 - 3.34 (m, 1H), 2.45 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H).

Example 32 (for illustrative purposes)

[0393]





[0394] Synthesis of (8-bromo-3-fluoroquinolin-5-yl)methanol (**32A**): A flask containing methyl 8-bromo-3-fluoroquinoline-5-carboxylate (1.06 g, 3.73 mmol) in THF (19 mL) was flushed with N_2, and then $LiBH_4$ (813 mg, 37.3 mmol) was added in one portion. After stirring at RT for 1 h, the reaction mixture was cooled to 0 °C and water (6 mL) was added, followed by the dropwise addition of 1M HCl (84 mL). The reaction mixture was heated to 40 °C for 2.5 hours and then cooled to RT before diluting with water and EA. Aqueous was extracted and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-100% EA in hexanes to afford the title compound.

[0395] Synthesis of 8-bromo-5-(bromomethyl)-3-fluoroquinoline (**32B**): Triphenylphosphine (1.12 g, 4.27 mmol) and CBr_4 (1.42 g, 4.27 mmol) were added to a stirred solution of **32A** (729 mg, 2.85 mmol) in DCM (5.7 mL) and this was stirred at RT for 20 min. The reaction mixture was then subjected to silica gel chromatography using 0-40% EA in hexanes to give the title compound.

[0396] Synthesis of tert-butyl (S)-3-(8-bromo-3-fluoroquinolin-5-yl)-2-((diphenylmethylene) amino)propanoate (**32C**): To a stirred solution of tert-butyl 2-((diphenylmethylene)amino)acetate (270 mg, 0.914 mmol) in DCM (7 mL) was added (-)-cinchonidine (27 mg, 0.091 mmol). The mixture was cooled to 0 °C with an ice bath before adding 50% aq KOH solution (1.8 mL), followed by **32B** (321 mg, 1.01 mmol). The reaction stirred in the ice bath as it slowly warmed to RT. After 3.5 hours, the reaction was diluted with water and DCM, and aqueous was extracted. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-30% EA in hexanes to afford the title compound.

[0397] Synthesis of tert-butyl (S)-3-(8-(2,6-dichloro-4-fluorophenyl)-3-fluoroquinolin-5-yl)-2-((diphenylmethylene)amino)propanoate (**32D**): **32C** (65 mg, 0.122 mmol), (2,6-dichloro-4-fluorophenyl)boronic acid (51 mg, 0.244 mmol), K_3PO_4 (91 mg, 0.426 mmol), SPhos Pd G3 (95 mg, 0.122 mmol) were dissolved in toluene (2.4 mL) and heated to 100 °C for 3 hours. After

cooling to RT, the reaction mixture was diluted with EA and filtered through celite. The filtrate was concentrate under reduced pressure and the resulting residue was purified by silica gel chromatography using 0-50% EA in hexanes to give the title compound.

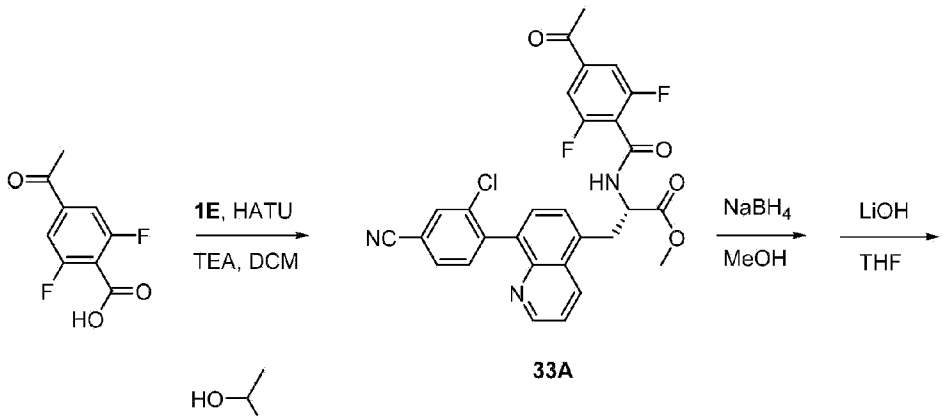
[0398] Synthesis of tert-butyl (S)-2-amino-3-(8-(2,6-dichloro-4-fluorophenyl)-3-fluoro quinolin-5-yl)propanoate (**32E**): 2M HCl (0.43 mmol, 0.21 mL) was added to a stirred solution of **32D** (88.2 mg, 0.14 mmol) in THF (0.84 mL). After stirring at RT for 2 hours, sat. NaHCOs and EA were added. Aqueous was extracted and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-90% EA in hexanes with 1% TEA to afford the title compound.

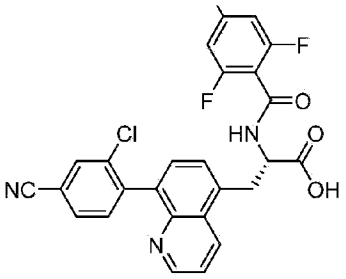
[0399] Synthesis of tert-butyl (S)-3-(8-(2,6-dichloro-4-fluorophenyl)-3-fluoroquinolin-5-yl)-2-(2,6-difluorobenzamido)propanoate (**32F**): To a stirred solution of **32E** (36.6 mg, 0.081 mmol) in DCM (0.54 mL) was added TEA (23 µL, 0.161 mmol). The reaction was cooled to 0 °C before adding 2,6-difluorobenzoyl chloride (15 µL, 0.121 mmol) dropwise. After stirring at RT for 1.25 hours, water and DCM were added. Aqueous layer was extracted and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-40% EA in hexanes to give the title compound.

[0400] Synthesis of (S)-3-(8-(2,6-dichloro-4-fluorophenyl)-3-fluoroquinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (**32**): TFA (0.12 mL, 1.61 mmol) was added to a stirred solution of **32F** (47.9 mg, 0.081 mmol) in DCM (0.40 mL). After stirring at RT for 3 hours, more TFA (0.06 mL, 0.81 mmol) was added. The reaction was stirred for another hour at RT, and then concentrated under reduced pressured. The material was purified by prep HPLC using 0-100% MeCN in water with 1% TFA to afford the title compound. MS (m/z) 537.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 9.27 (d, J = 8.2 Hz, 1H), 8.90 (d, J = 2.7 Hz, 1H), 8.45 (dd, J = 10.5, 2.8 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 7.3 Hz, 1H), 7.48 (ddd, J = 8.5, 6.5, 1.9 Hz, 1H), 7.15 - 7.05 (m, 2H), 4.82 (ddd, J = 10.2, 8.1, 4.5 Hz, 1H), 3.78-3.55 (m, 1H), 3.43 (dd, J = 14.7, 10.3 Hz, 1H).

Example 33 (for illustrative purposes)

[0401]





33

[0402] Synthesis of methyl (S)-2-(4-acetyl-2,6-difluorobenzamido)-3-(8-(2-chloro-4-cyano phenyl)quinolin-5-yl)propanoate (**33A**): The title compound was prepared according to the method presented for the synthesis of compound **16A** starting with **1E** and 4-acetyl-2,6-difluorobenzoic acid.

[0403] (2S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(1-hydroxyethyl) benzamido)propanoic acid (**33**): The title compound was prepared according to the method presented for the synthesis of compound **24B** and **16** starting with **33A.** MS (m/z) 563.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.19 (d, J = 8.2 Hz, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.63 (dd, J = 8.7, 1.6 Hz, 1H), 8.16 (dd, J = 1.6, 0.4 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.73 - 7.50 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 4.71 (d, J = 6.5 Hz, 1H), 1.27 (d, J = 6.5 Hz, 3H).

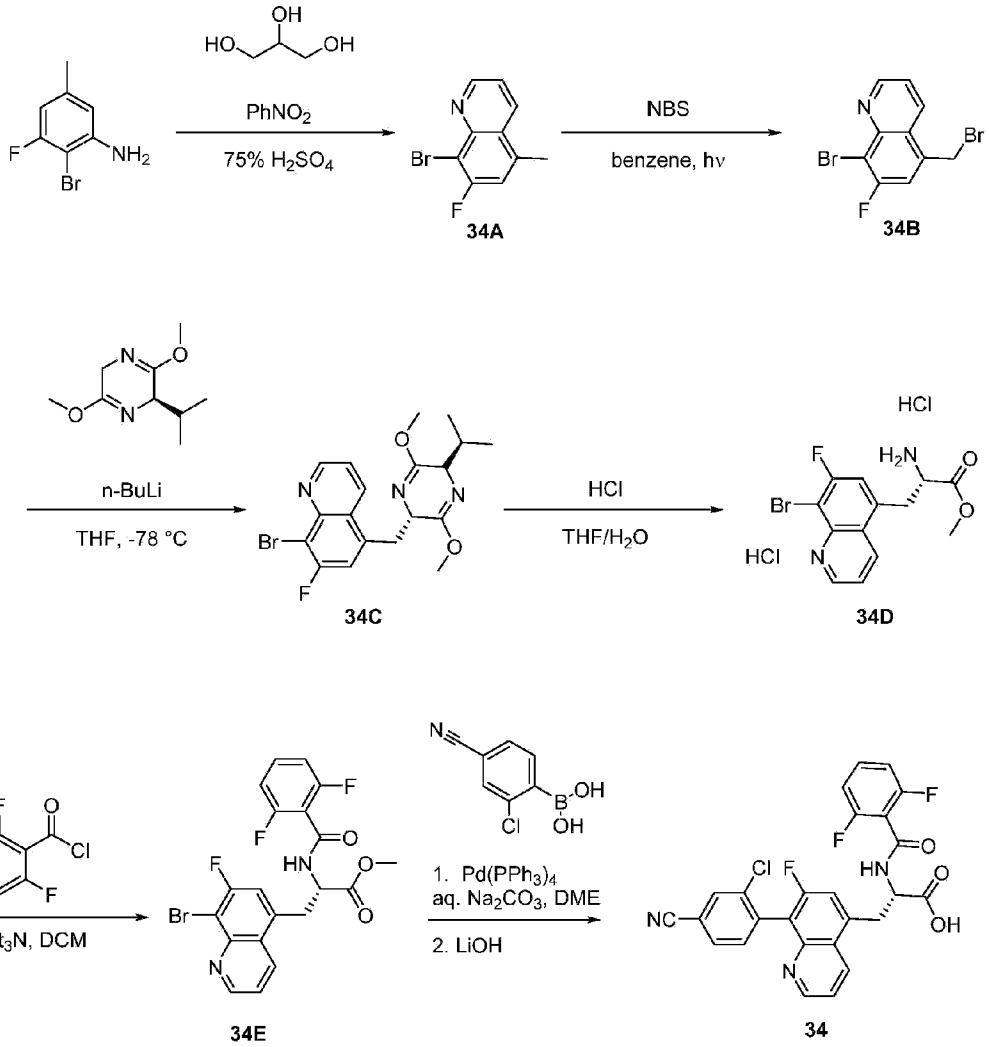
Example 34 (for illustrative purposes)

[0404] Synthesis of 8-bromo-7-fluoro-5-methylquinoline (**34A**): the title compound was prepared according to the method presented for the synthesis of compound **1A** in Example 1 starting with 2-bromo-3-fluoro-5-methylaniline. MS (m/z) 240.0 $[M+H]^+$.

[0405] Synthesis of 8-bromo-5-(bromomethyl)-7-fluoroquinoline **34B:** the title compound was prepared according to the method presented for the synthesis of compound **1B** in Example 1 starting with **34A.** MS (m/z) 317.9 $[M+H]^+$.

[0406] Synthesis of 8-bromo-7-fluoro-5-(((2S,5S)-5-isopropyl-3,6-dimethoxy-2,5-dihydro pyrazin-2-yl)methyl)quinoline (**34C**): A solution of (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (0.365 mL, 2.04 mmol) in THF (10 mL) was cooled to -78 °C with stirring and under positive nitrogen pressure. The mixture was treated dropwise with n-BuLi (0.98 mL, 1.6 M, 1.57 mmol). A solution of **34B** (497 mg, 1.57 mmol) is then added as a THF solution (1.0 M). After 30 minutes, the reaction mixture was removed from the cooling bath, quenched with a saturated aqueous solution of NH_4Cl, and allowed to warm to RT with vigorous stirring. The resulting mixture was extracted twice with EA, and the combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel chromatography using 0-20% EA in hexanes to afford the title compound. MS (m/z) 422.1 $[M+H]^+$.

[0407] Synthesis of methyl (S)-2-amino-3-(8-bromo-7-fluoroquinolin-5-yl)propanoate dihydrochloride (**34D**): To a stirred solution of **34C** (380 mg, 0.9 mmol) in THF (3.6 mL) was added 2M aqueous hydrochloric acid (2.7 mL, 5.4 mmol). After 3 h, the reaction mixture was concentrated under reduced pressure to afford the title compound (as a mixture with valine methyl ester hydrochloride), which was advanced without further purification. MS (m/z) 327.0 $[M+H]^+$.



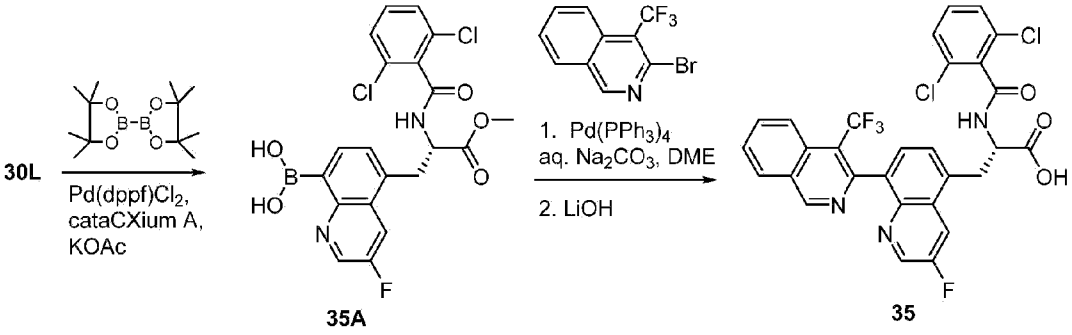
[0408] Synthesis of Methyl (S)-3-(8-bromo-7-fluoroquinolin-5-yl)-2-(2,6-difluorobenzamido) propanoate (**34E**): the title compound was prepared according to the method presented for the synthesis of compound **1F** in Example 1 starting with **34.** MS (m/z) 467.0 $[M+H]^+$.

[0409] Synthesis of (2S)-3-(8-(2-chloro-4-cyanophenyl)-7-fluoroquinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (**34**): the title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **34E.** MS (m/z) 510.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.27 (dd, J = 8.3, 1.3 Hz, 1H), 8.87 (dt, J = 3.9, 1.8 Hz, 1H), 8.67 (dd, J = 8.6, 1.6 Hz, 1H), 8.24 (t, J = 1.9 Hz, 1H), 7.95 (ddd, J = 7.9, 4.2, 1.7 Hz, 1H), 7.67 - 7.57 (m, 3H), 7.49 (ttd, J = 8.7, 6.6, 2.3 Hz, 1H), 7.16 - 7.08 (m, 2H), 4.82 (dddd, J

= 10.8, 8.4, 4.2, 2.2 Hz, 1H), 3.85 (ddd, J = 18.1, 14.5, 4.1 Hz, 1H), 3.42 (ddd, J = 19.5, 14.6, 10.8 Hz, 1H).

Example 35 (for illustrative purposes)

[0410]



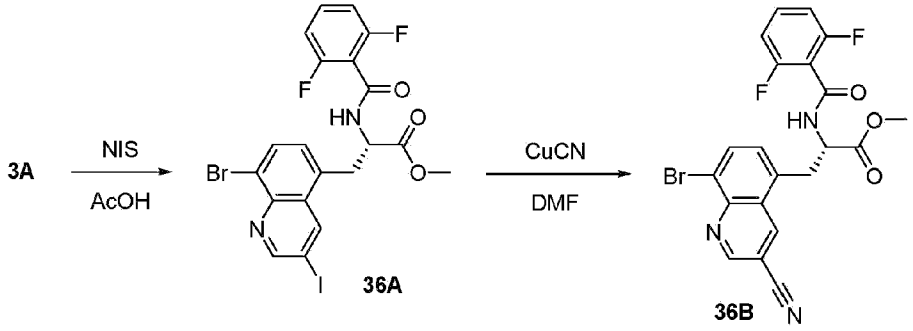
[0411] Synthesis of (S)-(5-(2-(2,6-dichlorobenzamido)-3-methoxy-3-oxopropyl)-3-fluoroquinolin-8-yl)boronic acid (**35A**): the title compound was prepared according to the method presented for the synthesis of compound **5A** starting with **30L.**

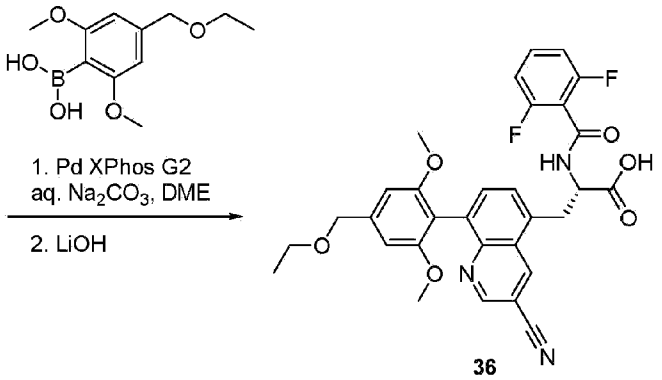
[0412] Synthesis of (S)-2-(2,6-dichlorobenzamido)-3-(3-fluoro-8-(4-(trifluoromethyl) isoquinolin-3-yl)quinolin-5-yl)propanoic acid (**35**): the title compound was prepared according to the method presented for the synthesis of compound **4C** and **4** starting with **35A** and 3-bromo-4-(trifluoromethyl)isoquinoline (**71B**). MS (m/z) 601.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 9.60 (d, J = 3.4 Hz, 1H), 9.29 (dd, J = 14.2, 8.4 Hz, 1H), 8.81 (dd, J = 3.4, 2.8 Hz, 1H), 8.46 (ddd, J = 10.1, 6.9, 2.8 Hz, 1H), 8.38 (dd, J = 8.2, 1.1 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.10 - 8.01 (m, 1H), 7.94 - 7.85 (m, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.69 (dd, J = 7.3, 1.9 Hz, 1H), 7.45 - 7.35 (m, 3H), 4.85 (dtd, J = 23.5, 9.2, 4.5 Hz, 1H), 3.69 (dt, J = 14.4, 4.4 Hz, 1H), 3.44 (dd, J = 14.6, 10.1 Hz, 1H).

Example 36 (for illustrative purposes)

[0413] Synthesis of methyl (S)-3-(8-bromo-3-iodoquinolin-5-yl)-2-(2,6-difluorobenzamido) propanoate (**36A**): A solution of **3A** (300 mg, 0.67 mmol) in AcOH (2.5 mL) was treated with N-iodosuccinimide (300 mg, 1.34 mmol) and stirred at 70 °C for 24 h. A second quantity of N-iodosuccinimide (300 mg, 1.34 mmol) was added, and stirring continued at 70 °C for an additional 24 h. The mixture was cooled to RT and concentrated under reduced pressure. The resulting residue was dissolved in DCM, and washed with saturated aqueous $NaHCO_3$, back-extracting the aqueous twice with DCM. The combined organic layers were adsorbed onto silica gel for purification by silica gel chromatography using 0-100% EA in hexanes to afford the title compound. MS (m/z) 575.0 [M+H]+.

[0414] Synthesis of methyl (S)-3-(8-bromo-3-cyanoquinolin-5-yl)-2-(2,6-difluorobenzamido) propanoate (**36B**): A suspension of **36A** (50 mg, 0.087 mmol) and cuprous cyanide (12 mg, 0.130 mmol) in DMF (1.5 mL) was stirred at 135 °C under microwave irradiation for 30 min. The reaction mixture was then cooled to RT, diluted with EA and saturated aqueous NaCl, and filtered through celite. The phases were separated, and the aqueous layer was further extracted twice with EA. The combined organic layers were concentrated under reduced pressure and the resulting residue purified by silica gel chromatography using 0-40% EA in hexanes to afford the title compound. MS (m/z) 474.0 [M+H]+.



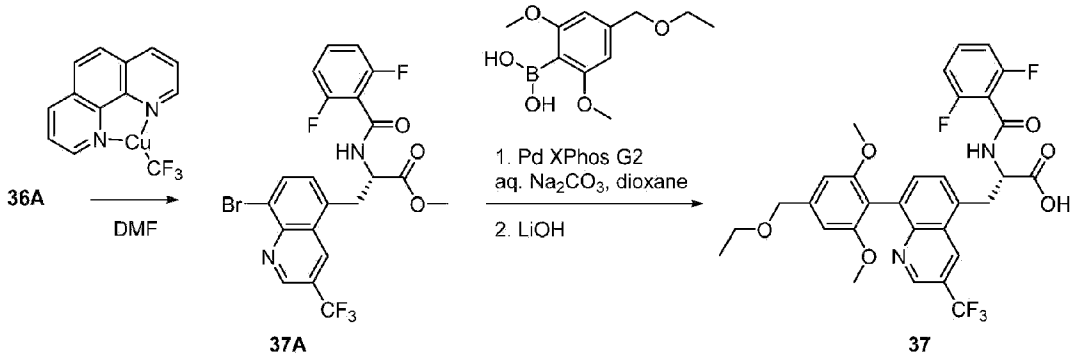


[0415] Synthesis of (S)-3-(3-cyano-8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid (**36**): the title compound was prepared according to the method presented for the synthesis of compound **18** starting with **36B.** MS (m/z) 576.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.27 (d, J = 8.1 Hz, 1H), 9.21 (d, J = 2.1 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.49 (tt, J = 8.4, 6.6 Hz, 1H), 7.15 - 7.08 (m, 2H), 6.71 (q, J = 1.3 Hz, 2H), 4.82 (ddd, J = 10.0, 8.2, 4.5 Hz, 1H), 4.52 (s, 2H), 3.77 - 3.70 (m, 1H), 3.61 - 3.45 (m, 9H), 1.21 (t, J = 7.0 Hz, 3H).

Example 37 (for illustrative purposes)

[0416] Synthesis of methyl (S)-3-(8-bromo-3-(trifluoromethyl)quinolin-5-yl)-2-(2,6-difluoro benzamido)propanoate (**37A**): A vial was charged with **36A** (50 mg, 0.087 mmol) and (1,10-phenanthroline)(trifluoromethyl)copper(I) (98 mg, 0.313 mmol), sealed with a septum cap, and purged with nitrogen for 15 min. DMF (1 mL, previously degassed by sparging with nitrogen for

15 min) was added, and the mixture stirred vigorously at 50 °C for 1 h. The reaction mixture was cooled to RT, diluted with EA, and filtered through celite. The resulting filtrate was washed with saturated aqueous $NaHCO_3$, and the aqueous layer back-extracted twice with EA. The combined organic layers were adsorbed onto silica gel for silica gel chromatography using 0-50% EA in hexanes to afford the title compound. MS (m/z) 517.1 [M+H]+.



[0417] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)-3-(trifluoromethyl)quinolin-5-yl)propanoic acid (**37**): the title compound was prepared according to the method presented for the synthesis of compound **18** starting with **37A.** MS (m/z) 619.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.31 (d, J = 8.0 Hz, 1H), 9.08 - 9.06 (m, 1H), 8.97 (dd, J = 2.3, 1.1 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.50 (tt, J = 8.5, 6.6 Hz, 1H), 7.15 - 7.08 (m, 2H), 6.72 (q, J = 1.3 Hz, 2H), 4.78 (ddd, J = 9.7, 8.0, 4.6 Hz, 1H), 4.53 (s, 2H), 3.77 (dd, J = 14.8, 4.6 Hz, 1H), 3.61 - 3.43 (m, 9H), 1.22 (t, J = 7.0 Hz, 3H).

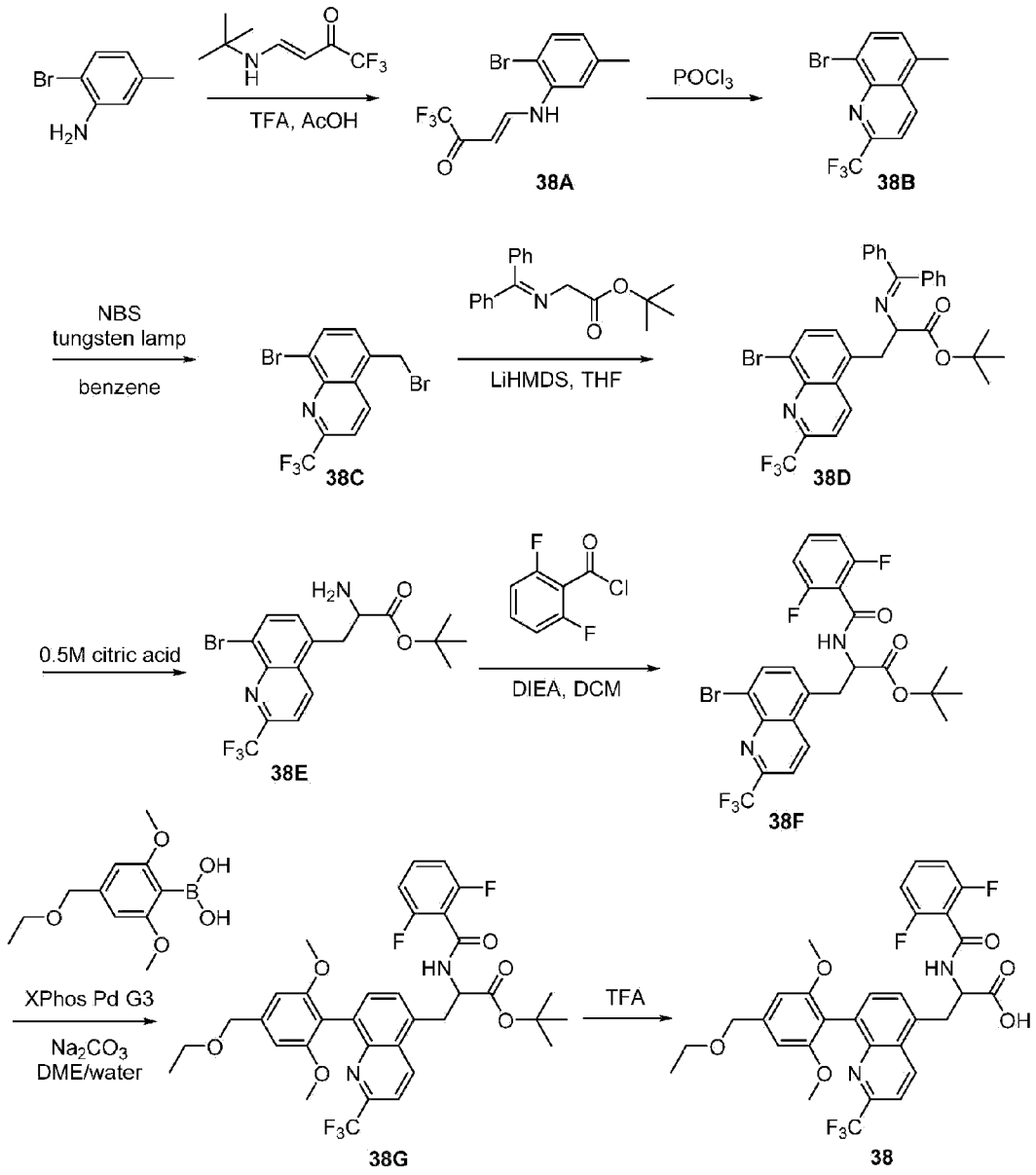
Example 38 (for illustrative purposes)

[0418] Synthesis of 4-((2-bromo-5-methylphenyl)amino)-1,1,1-trifluorobut-3-en-2-one (38A): To a stirred solution of 2-bromo-5-methylaniline (2.149 g, 12 mmol) and 4-(*tert*-butylamino)-1,1,1-trifluorobut-3-en-2-one (2.05 g, 10.5 mmol) in glacial acetic acid (4 mL) was added TFA (4 mL), and the reaction was heated to 75 °C for 16 hours. It was cooled to RT, poured onto water, and the solids were collected via filtration to yield **38A.**

[0419] Synthesis of 8-bromo-5-methyl-2-(trifluoromethyl)quinoline (**38B**): To a stirred suspension of compound **38A** (2.81 g, 9.1 mmol) in heptane (9 mL) was added $POCl_3$ (0.855 mL, 9.12 mmol), and the reaction was heated to 100 °C overnight. It was poured onto a solution of 2M sodium carbonate in water. It was extracted twice with ethyl acetate, and the combined organics were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified via flash chromatography, eluting with a linear gradient of 1-20% ethyl acetate/hexanes, to yield **38B.**

[0420] Synthesis of 8-bromo-5-(bromomethyl)-2-(trifluoromethyl)quinoline (**38C**): To a stirred solution of **38B** (1.32 g, 4.6 mmol) in benzene (10 mL) was added N-bromosuccinimide (0.97 g, 5.5 mmol), and the reaction was heated to reflux under a tungsten work lamp for 16 hours. It

was cooled to RT, filtered and concentrated. The residue was dissolved in ethyl acetate and washed twice with water and once with saturated sodium chloride solution. It was purified via flash chromatography, eluting with a linear gradient of 5-70% DCM/hexanes, to yield compound **38C.**



[0421] Synthesis of *tert*-butyl 3-(8-bromo-2-(trifluoromethyl)quinolin-5-yl)-2-((diphenyl methylene)amino)propanoate (**38D**): A stirred solution of *tert*-butyl 2-((diphenylmethylene) amino)acetate (260 mg, 0.88 mmol) in tetrahydrofuran (3 mL) under dry nitrogen was cooled to -78 °C. 1M Lithium hexamethyldisilazide in THF (0.968 mL, 0.968 mmol) was added dropwise, then the reaction was stirred at this temperature for 15 minutes. To this, a solution of **38C** (357 mg, 0.97 mmol) in THF (2 mL) was added, and the reaction was allowed to warm to RT and stir for 16 hours. It was quenched by the addition of saturated ammonium chloride, and it was partitioned between water and ethyl acetate. The aqueous was extracted with ethyl acetate, and the combined organics were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated. It was purified via flash chromatography,

eluting with a linear gradient of 5-50% ethyl acetate/hexanes, to yield compound **38D.**

[0422] Synthesis of *tert*-butyl 2-amino-3-(8-bromo-2-(trifluoromethyl)quinolin-5-yl)propanoate (**38E**): To a stirred solution of compound **38D** (335 mg, 0.57 mmol) in tetrahydrofuran (6 mL) was added 0.5M citric acid in water (5.7 mL, 2.87 mmol), and the reaction was allowed to stir for 1 h at RT. It was diluted with water, and washed once with diethyl ether. The aqueous was treated with 1M sodium hydroxide in water until a pH of ~8 was reached, and it was extracted twice with diethyl ether. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to yield **38E.**

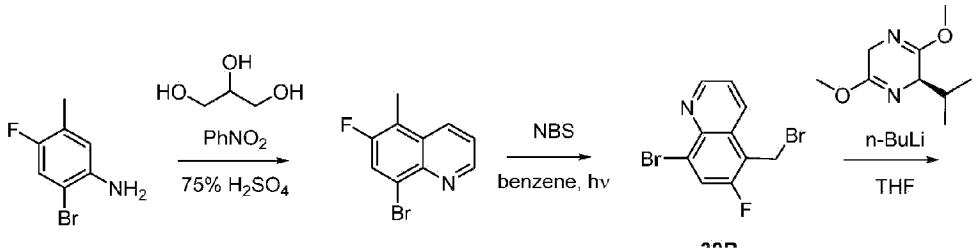
[0423] Synthesis of *tert*-butyl 3-(8-bromo-2-(trifluoromethyl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoate (**38F**): The title compound was prepared according to the method presented for the synthesis of compound **1F** starting with **38E** and 2,6-difluorobenzoyl chloride.

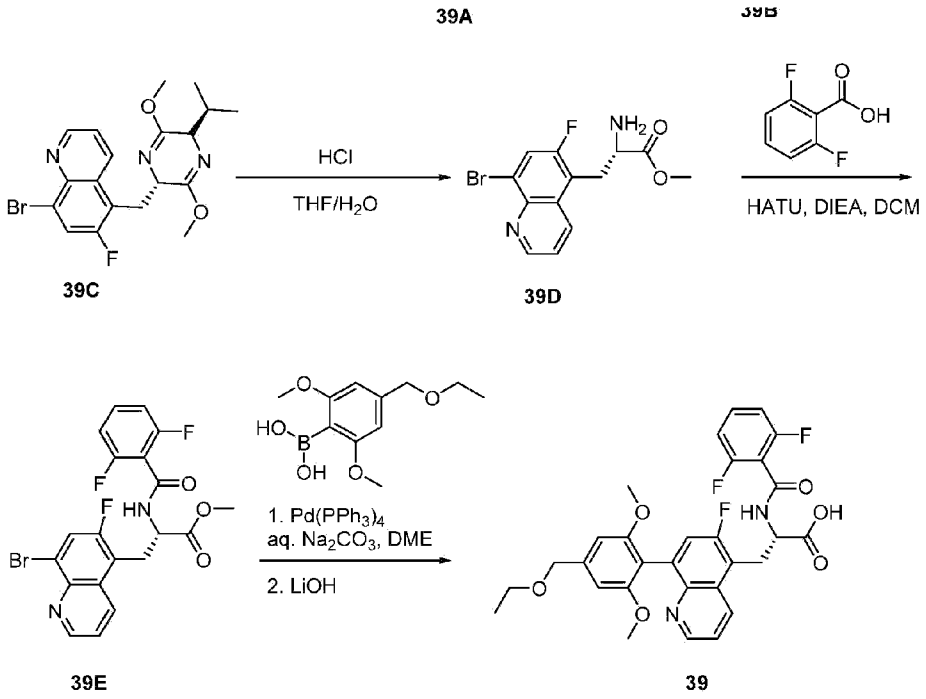
[0424] Synthesis of *tert*-butyl 2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-2-(trifluoromethyl)quinolin-5-yl)propanoate (**38G**): To a solution of **38F** (187 mg, 0.33 mmol) and (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid (104 mg, 0.44 mmol) in 1,2-dimethoxyethane (3 mL) was added 2M sodium carbonate in water (0.5 mL, 0.67 mmol), and the reaction was degassed with nitrogen. To this, XPhos Pd G3 (14 mg, 0.017 mmol) was added, the reaction was sealed, and it was heated to 85 °C for 1 h. It was cooled to RT and purified by flash chromatography, eluting with a linear gradient of 1-10% MeOH/DCM, to yield 38G.

[0425] Synthesis of 2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)-2-(trifluoromethyl)quinolin-5-yl)propanoic acid (**38**): To a solution of **38G** (214 mg, 0.32 mmol) in DCM (1 mL) was added TFA (723 mg, 6 mmol), and the reaction was allowed to stir at RT for 4 hours. It was concentrated and purified via preparatory HPLC to yield **38.** MS (m/z) 619.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.1 Hz, 1H), 8.85 (dd, J = 8.9, 0.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.48 (tt, J = 8.4, 6.5 Hz, 1H), 7.11 (dd, J = 8.5, 7.5 Hz, 2H), 6.72 (q, J = 1.3 Hz, 2H), 4.77 (ddd, J = 10.1, 8.0, 4.5 Hz, 1H), 4.52 (d, J = 0.7 Hz, 2H), 3.76 (dd, J = 14.7, 4.5 Hz, 1H), 3.64 - 3.50 (m, 8H), 3.44 (dd, J = 14.8, 10.1 Hz, 1H), 1.20 (t, J = 7.0 Hz, 3H).

Example 39 (for illustrative purposes)

[0426]





[0427] Synthesis of 8-bromo-6-fluoro-5-methylquinoline (**39A**) the title compound was prepared according to the method presented for the synthesis of compound 1A in Example 1 using 2-bromo-4-fluoro-5-methylaniline. MS (m/z) 240.0 [M+H]+.

[0428] Synthesis of 8-bromo-5-(bromomethyl)-6-fluoroquinoline (**39B**): the title compound was prepared according to the method presented for the synthesis of compound **1B** in Example 1 using **39A.** MS (m/z) 317.9 [M+H]+.

[0429] Synthesis of 8-bromo-6-fluoro-5-(((2S,5S)-5-isopropyl-3,6-dimethoxy-2,5-dihydro pyrazin-2-yl)methyl)quinoline (**39C**): the title compound was prepared according to the method presented for the synthesis of compound **34C**4 using **39B.** MS (m/z) 422.1 [M+H]+.

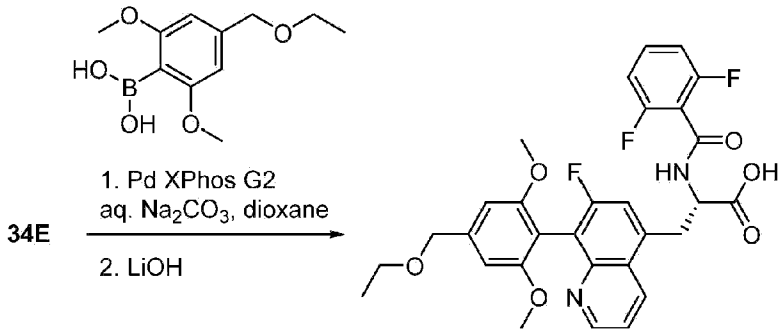
[0430] Synthesis of Methyl (S)-2-amino-3-(8-bromo-6-fluoroquinolin-5-yl)propanoate (**39D**): the title compound was prepared according to the method presented for the synthesis of compound **34** using **39C.** MS (m/z) 327.0 [M+H]+.

[0431] Synthesis of Methyl (S)-3-(8-bromo-6-fluoroquinolin-5-yl)-2-(2,6-difluorobenzamido) propanoate **(39E):** the title compound was prepared according to the method presented for the synthesis of compound **16A** in Example 16 using **39D.** MS (m/z) 467.0 [M+H]+.

[0432] Synthesis of (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)-6-fluoroquinolin-5-yl)propanoic acid (39): the title compound was prepared according to the method presented for the synthesis of compound **18** using **39E.** MS (m/z) 569.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.3 Hz, 1H), 8.83 - 8.70 (m, 2H), 7.68 (dd, J = 8.8, 4.3 Hz, 1H), 7.55 - 7.44 (m, 2H), 7.11 (dd, J = 8.5, 7.6 Hz, 2H), 6.75 (s, 2H), 4.77 (td, J = 8.5, 6.2 Hz, 1H), 4.54 (s, 2H), 3.70 - 3.50 (m, 11 H), 1.22 (t, J = 7.0 Hz, 3H).

Example 40 (for illustrative purposes)

[0433]



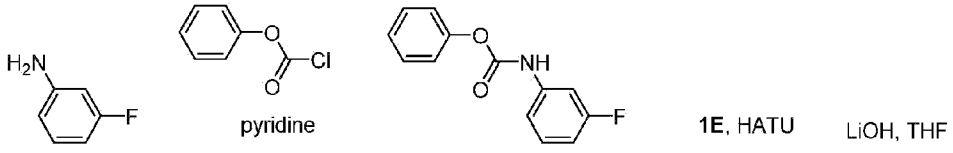
40

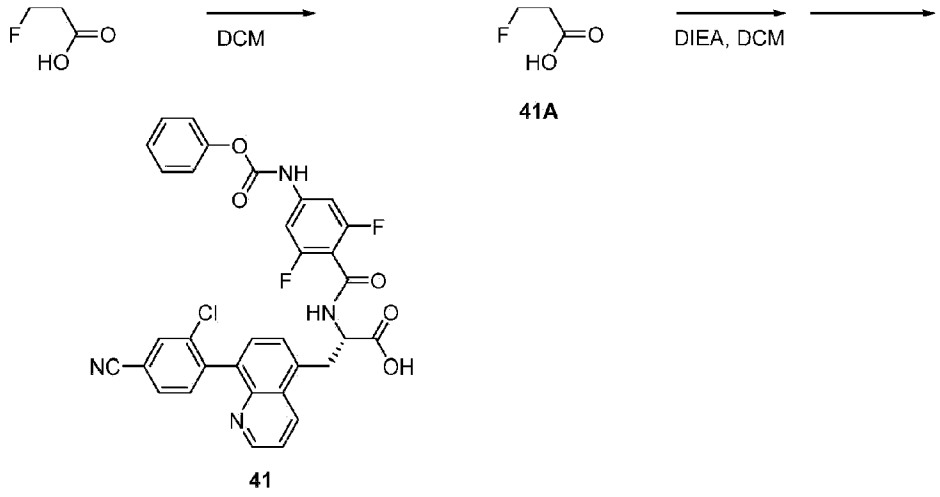
[0434] (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)-7-fluoroquinolin-5-yl)propanoic acid **(40):** the title compound was prepared according to the method presented for the synthesis of compound **18** using **34E.** MS (m/z) 569.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.32 (d, J = 8.1 Hz, 1H), 8.83 (dd, J = 4.3, 1.5 Hz, 1H), 8.70 (d, J = 5.0 Hz, 1H), 7.64 (dd, J = 8.0, 3.9 Hz, 1H), 7.56 - 7.46 (m, 2H), 7.18 - 7.10 (m, 2H), 6.75 (d, J = 1.7 Hz, 2H), 4.80 (ddd, J = 10.6, 8.1, 4.1 Hz, 1H), 4.54 (s, 2H), 3.80 (dd, J = 14.6, 4.1 Hz, 1H), 3.62 - 3.55 (m, 8H), 3.43 (dd, J = 14.8, 10.5 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H).

Example 41 (for illustrative purposes)

[0435] Synthesis of 2,6-difluoro-4-((phenoxycarbonyl)amino)benzoic acid **(41A):** To a stirred solution of 4-amino-2,6-difluorobenzoic acid (504 mg, 2.16 mmol) in DCM was added phenyl chloroformate (0.41 ml, 3.24 mmol) and pyridine (0.87 ml, 10.81 mmol). The reaction mixture was allowed to stir for 3 hr at RT. The reaction mixture was concentrated under reduced pressure and purified by reverse phase preparative chromatography using aqueous 0.1% TFA/MeCN as the eluent.

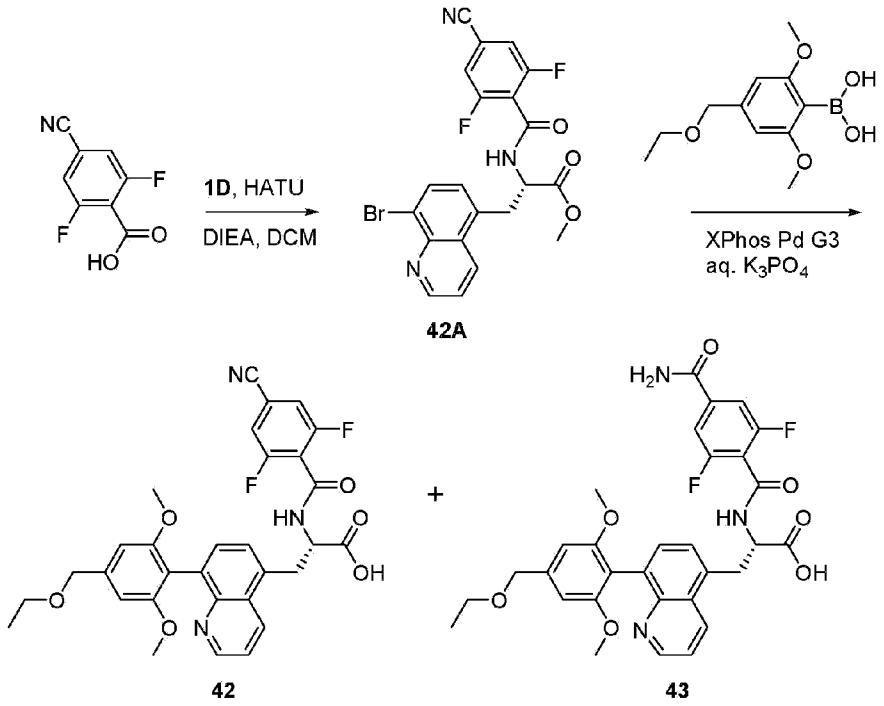
[0436] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((phenoxycarbonyl)amino)benzamido)propanoic acid **(41):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **41A** and 1E. MS (m/z) 686.5 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 10.76 (s, 1H), 9.18 (d, J = 8.0 Hz, 1H), 8.81 (s, 1H), 7.85 - 7.37 (m, 6H), 7.32 - 7.13 (m, 5H), 6.72 (s, 2H), 4.74 (s, 1H), 4.52 (s, 2H), 3.85-3.75 (m, 1H), 3.60 - 3.51 (m, 8H), 1.20 (t, J = 7.0 Hz, 3H).





Example 42 and Example 43 (for illustrative purposes)

[0437]



[0438] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(4-cyano-2,6-difluoro benzamido) propanoate **(42A):** To a stirred solution of 4-cyano-2,6-difluorobenzoic acid (0.12 g, 0.65 mmol) in DCM was added **1D** (0.2 g, 0.65 mmol), HATU (0.25 g, 0.65 mmol) and TEA (1 mL). The reaction mixture was allowed to stir ON at RT. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography using EA in hexanes as the eluent.

[0439] (S)-2-(4-cyano-2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy

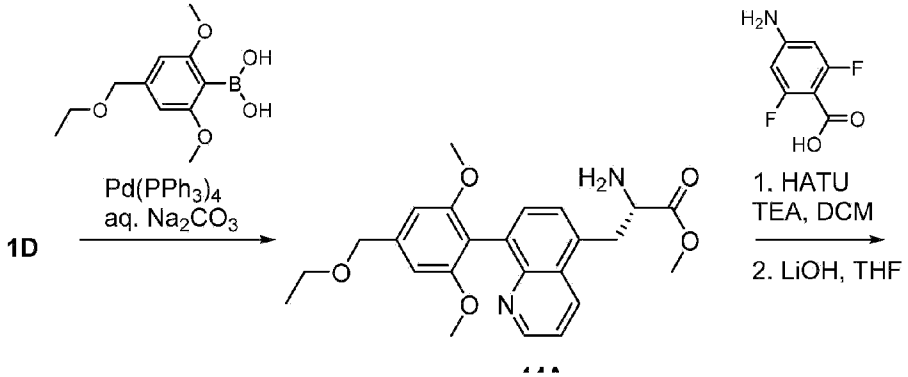
phenyl)quinolin-5-yl)propanoic acid **(42):** To a microwave vial was added **42A** (0.24 g, 0.5 mmol), (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid (200 mg, 0.5 mmol), XPhos Pd G3 (0.043 g, 0.05 mmol), and K_3PO_4 (0.21 g, 0.15 mmol) in dioxane (2 mL). The reaction mixture was allowed to stir at 120°C for 30 min. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The mixture was purified by silica gel chromatography using MeOH and DCM as eluent to afford both **42** and **43.** MS (m/z) 576.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.72 (dd, J = 4.1, 1.6 Hz, 1H), 8.60 (s, 1H), 8.15 (s, 1H), 7.72 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.53 - 7.46 (m, 2H), 7.36 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 2.3 Hz, 2H), 4.61 (s, 1H), 4.50 (s, 2H), 3.68 (dd, J = 14.0, 4.7 Hz, 1H), 3.56 (d, J = 7.0 Hz, 1H), 3.52 (d, J = 7.1 Hz, 6H), 3.44 - 3.33 (m, 1H),1.20 (t, J = 7.0 Hz, 3H).

[0440] (S)-2-(4-carbamoyl-2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxy phenyl)quinolin-5-yl)propanoic acid **(43).** MS (m/z) 595.5 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 9.48 (d, J = 8.0 Hz, 1H), 8.74 (dd, J = 4.1, 1.7 Hz, 1H), 8.53 (dd, J = 8.7, 1.7 Hz, 1H), 8.01 - 7.73 (m, 2H), 7.53 (dd, J = 8.6, 4.1 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 7.3 Hz, 1H), 6.76 - 6.63 (m, 2H), 4.75 (td, J = 8.8, 4.4 Hz, 1H), 4.50 (s, 2H), 3.91 - 3.61 (m, 1H), 3.55 (t, J = 7.0 Hz, 2H), 3.53 (s, 3H), 3.46 - 3.22 (m, 4H), 1.20 (t, J = 7.0 Hz, 3H).

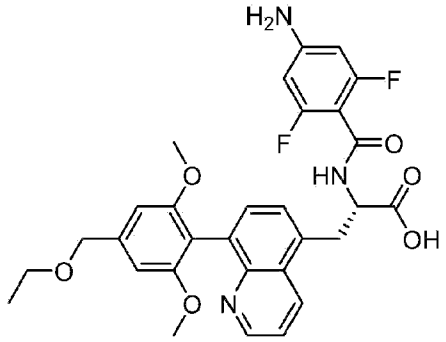
Example 44 (for illustrative purposes)

[0441] Synthesis of methyl (S)-2-amino-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl) quinolin-5-yl)propanoate **(44A):** The title compound was prepared according to the method presented for the synthesis of compound **1E** starting with (4-(ethoxymethyl)-2,6-dimethoxy phenyl)boronic acid.

[0442] (S)-2-(4-amino-2,6-difluorobenzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl) quinolin-5-yl)propanoic acid **(44):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **44A** and 4-amino-2,6-difluorobenzoic acid. MS (m/z) 567.6 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 2H), 8.67 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 37.5 Hz, 3H), 6.74 (d, J = 2.2 Hz, 2H), 6.11 (d, J = 10.7 Hz, 2H), 4.75 - 4.62 (m, 1H), 4.53 (s, 2H), 3.81 - 3.65 (m, 1H), 3.58 (d, J = 7.0 Hz, 2H), 3.55 (d, J = 6.1 Hz, 7H), 1.20 (t, J = 7.0 Hz, 3H).



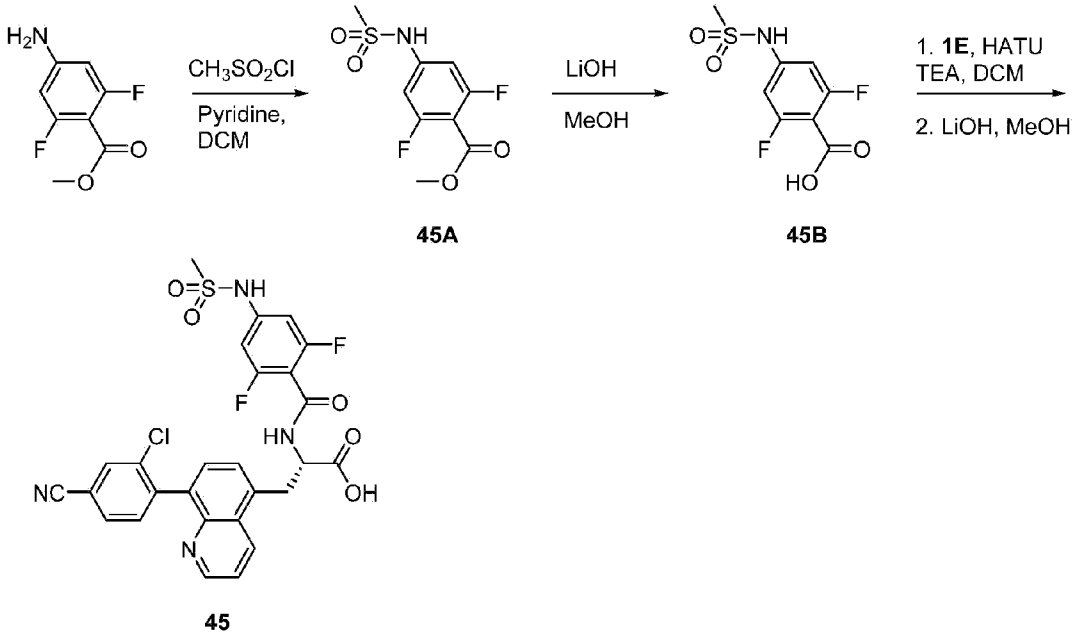
44A



44

Example 45 (for illustrative purposes)

[0443]



45A

45B

45

[0444] Synthesis of methyl 2,6-difluoro-4-(methylsulfonamido)benzoate **(45A):** To a stirred solution of methyl 4-amino-2,6-difluorobenzoate (500 mg, 0.3 mmol) in DCM was added methyl sulfonyl chloride (0.31 ml, 0.4 mmol), and pyridine (1.08 mL, 1.3 mmol). The reaction was stirred for at RT ON. The reaction mixture was diluted with EA, washed with 1M HCl, bicarbonate, brine, and dried, filtered, and concentrated. The material was recrystallized from EA/hexanes to yield the title compound.

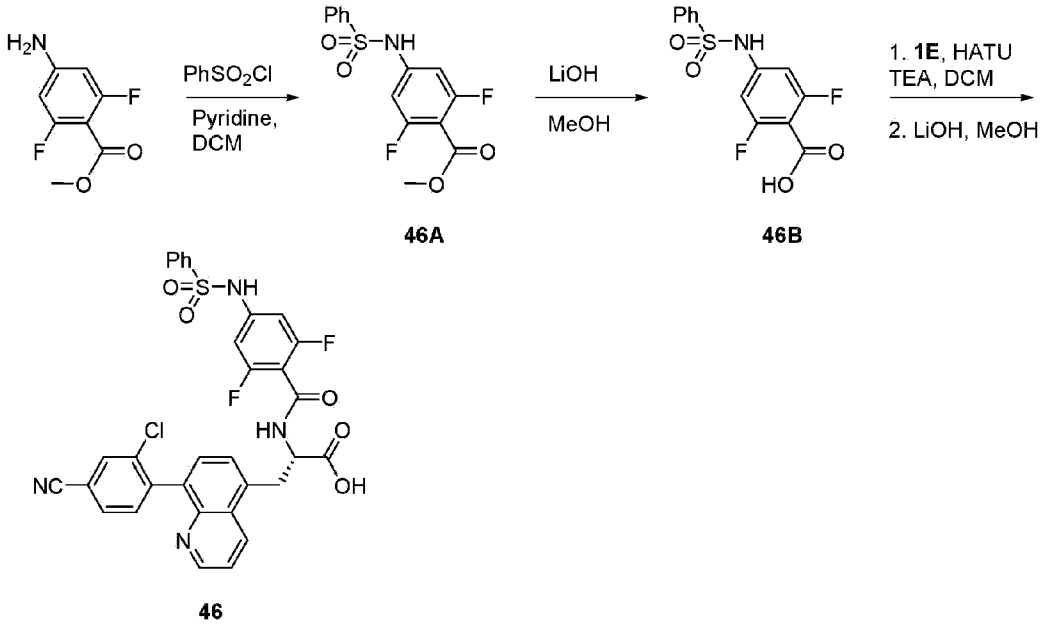
[0445] Synthesis of 2,6-difluoro-4-(methylsulfonamido)benzoic acid **(45B):** To a stirred solution of **45A** (534 mg, 0.2 mmol) in THF was added aqueous LiOH (5 mL, 2 M). The mixture was allowed to stir at RT for 2 days, diluted with water and acidified with 1 M HCl. The material was extracted with DCM, dried, filtered, and concentrated under reduced pressure. The material

purified by silica gel chromatography using EA/hexanes as eluent to afford the title compound.

[0446] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(methyl sulfonamido)benzamido)propanoic acid **(45):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **45B.** MS (m/z) 585.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.15 (d, J = 8.1 Hz, 1H), 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.7 Hz, 1H), 8.17 (dd, J = 1.6, 0.4 Hz, 1H), 7.92 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 - 7.55 (m, 4H), 6.83 (d, J = 9.3 Hz, 2H), 4.83 - 4.68 (m, 1H), 3.87 - 3.66 (m, 1H), 3.51 - 3.33 (m, 1H), 3.14 (s, 3H).

Example 46 (for illustrative purposes)

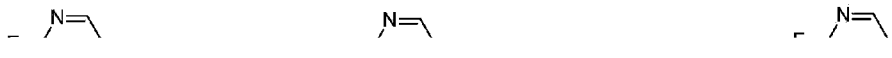
[0447]

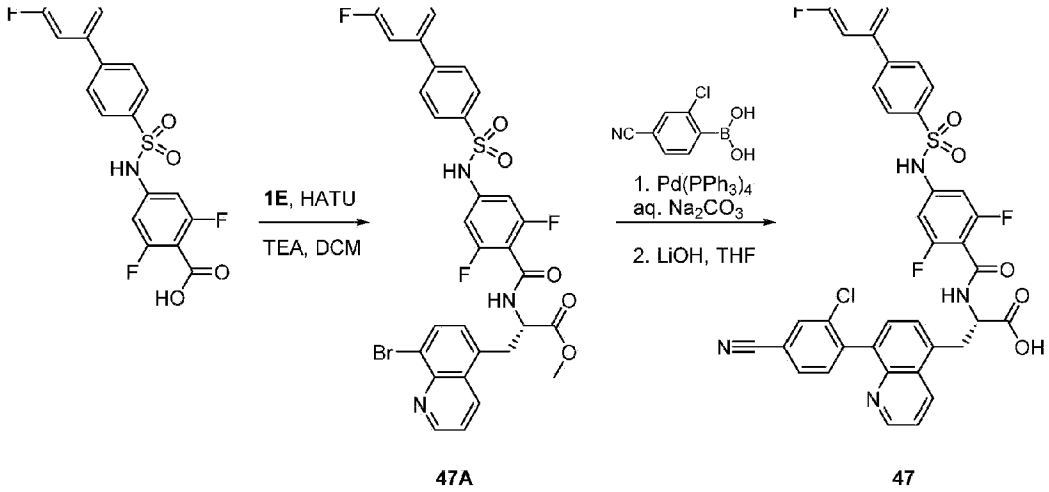


[0448] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(phenyl sulfonamido)benzamido)propanoic acid **(46):** The title compound was prepared according to the method presented for the synthesis of compounds **45A, 45B,** and **45** starting with phenyl sulfonyl chloride. MS (m/z) 647.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.12 (d, J = 8.1 Hz, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.63 - 8.60 (m, 1H), 8.17 (d, J = 1.7 Hz, 1H), 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.89 - 7.82 (m, 2H), 7.73 - 7.53 (m, 7H), 6.75 (d, J = 9.2 Hz, 2H), 4.75 - 4.65 (m, 1H), 3.82 - 3.65 (m, 1H), 3.47 - 3.27 (m, 1H).

Example 47 (for illustrative purposes)

[0449]





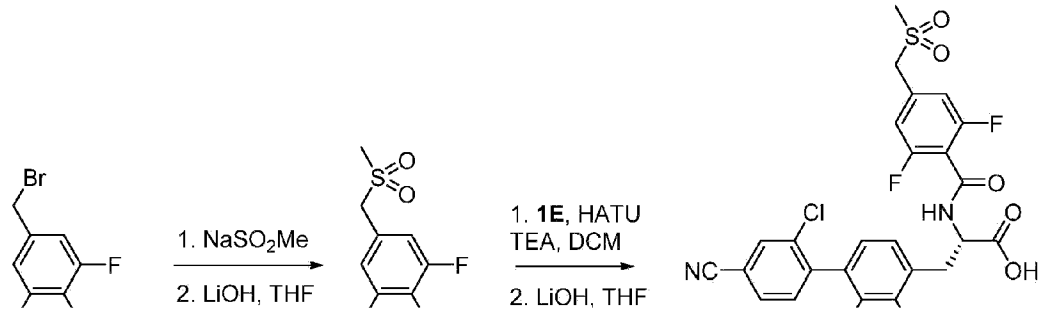
47A 47

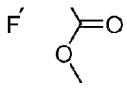
[0450] Synthesis methyl (S)-3-(8-bromoquinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoate **(47A):** The title compound was prepared according to the method presented for the synthesis of compound **16** of Example 16 starting with 2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzoic acid.

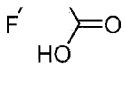
[0451] Synthesis of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoic acid **(47):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and 3 starting with **47A.** MS (m/z) 742.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 11.21 (s, 1H), 9.11 (d, J = 8.1 Hz, 1H), 8.81 (dd, J = 4.1, 1.6 Hz, 1H), 8.59 (dd, J = 8.6, 1.7 Hz, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.09 - 8.03 (m, 2H), 8.01 - 7.94 (m, 2H), 7.89 (dd, J = 7.9, 1.6 Hz, 1H), 7.72 (dt, J = 5.4, 1.8 Hz, 1H), 7.64 - 7.51 (m, 5H), 6.78 (d, J = 9.2 Hz, 2H), 4.83 - 4.59 (m, 1H), 3.71 (s, 1H), 3.34 (s, 1H).

Example 48 (for illustrative purposes)

[0452] Synthesis of 2,6-difluoro-4-((methylsulfonyl)methyl)benzoic acid **(48A):** To a stirred solution of methyl 4-(bromomethyl)-2,6-difluorobenzoate (125 mg, 0.47 mmol) in DMF was added methyl sodium sulfinate (96.28 mg, 0.94 mmol). This was heated to 65°C and stirred for 1 h. EA and water were added. The combined organics were washed with brine, dried, and concentrated. The material was then converted to the title compound according to the method presented for the synthesis of compound **1G.**







48A

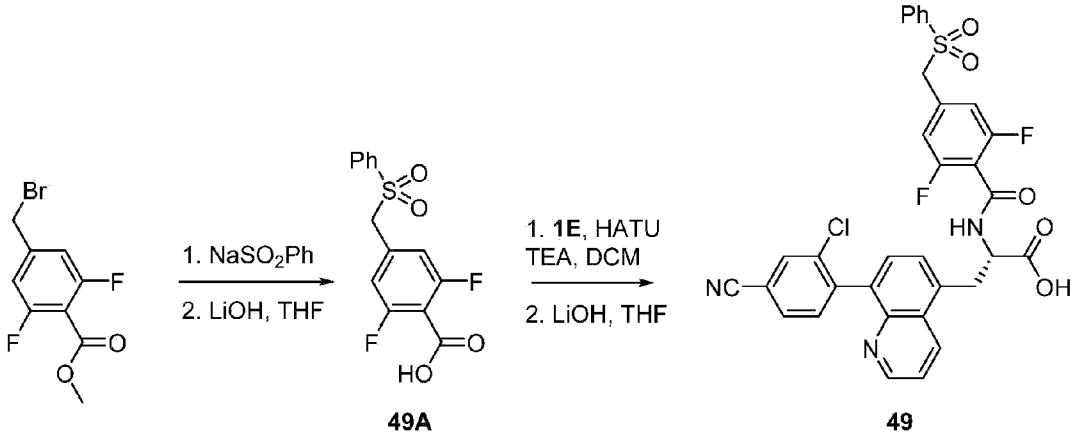


48

[0453] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((methylsulfonyl) methyl)benzamido)propanoic acid **(48):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **48A.** MS (m/z) 584.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.2 Hz, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.68 - 7.53 (m, 4H), 7.16 (d, J = 8.1 Hz, 2H), 4.84 - 4.73 (m, 1H), 4.55 (s, 2H), 3.77 (s, 1H), 3.40 (s, 1H), 2.93 (s, 3H).

Example 49 (for illustrative purposes)

[0454]



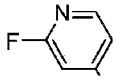
49A

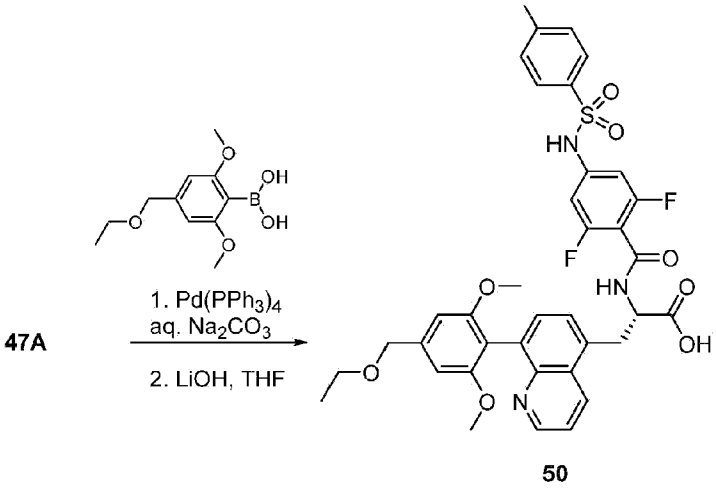
49

[0455] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((phenylsulfonyl) methyl)benzamido)propanoic acid **(49):** The title compound was prepared according to the method presented for the synthesis of compound **48A** of Example 48 starting with phenyl sodium sulfinate, followed by the method presented for **16** and **16C** starting with **49A.** MS (m/z) 646.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.28 (d, J = 8.2 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.81 - 7.69 (m, 3H), 7.69 - 7.50 (m, 6H), 6.88 (d, J = 8.1 Hz, 2H), 4.82 - 4.73 (m, 1H), 4.77 (s, 2H), 3.76 (s, 1H), 3.40 (s, 1H).

Example 50 (for illustrative purposes)

[0456]

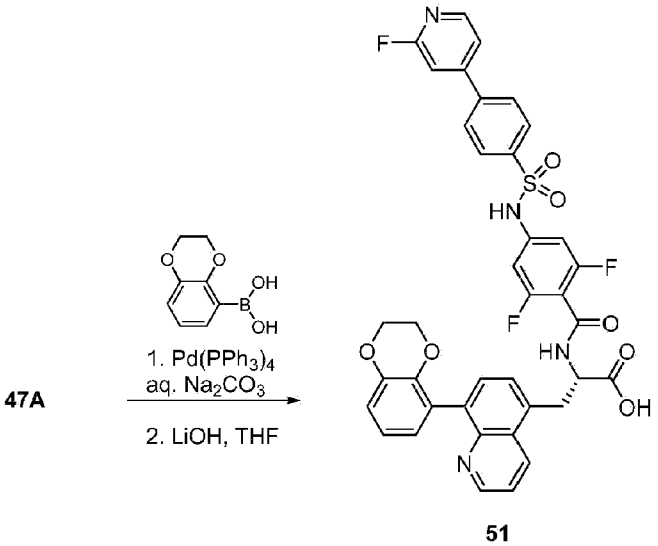




[0457] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(4-(ethoxymethyl)-2,6-dimethoxyphenyl)quinolin-5-yl)propanoic acid **(50):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and (4-(ethoxymethyl)-2,6-dimethoxyphenyl)boronic acid. MS (m/z) 802.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.24 (s, 1H), 9.16 (d, J = 8.0 Hz, 1H), 8.83 (s, 2H), 8.35 (d, J = 5.3 Hz, 1H), 8.12 - 8.04 (m, 2H), 8.03 - 7.95 (m, 2H), 7.82 - 7.43 (m, 5H), 6.81 (d, J = 9.0 Hz, 2H), 6.74 (s, 2H), 4.72 (q, J = 8.3 Hz, 1H), 4.54 (s, 2H), 3.73 (dd, J = 13.3, 3.5 Hz, 1H), 3.59 (d, J = 7.0 Hz, 1H), 3.54 (d, J = 2.0 Hz, 6H), 3.43 (s, 1H), 1.22 (t, J = 7.0 Hz, 3H).

Example 51 (for illustrative purposes)

[0458]

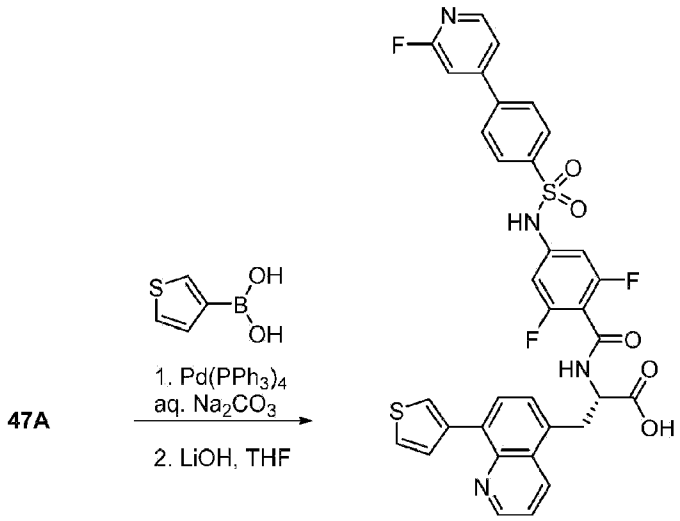


[0459] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((methylsulfonyl)methyl)benzamido)propanoic acid **(51):** The title compound was prepared according to the

method presented for the synthesis of compound **3B** and **3** starting with **47A** and (2,3-dihydrobenzo[b][1,4]dioxin-5-yl)boronic acid. MS (m/z) 741.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.21 (s, 1H), 9.12 (d, J = 8.1 Hz, 1H), 8.87 (s, 1H), 8.71 (s, 1H), 8.38 - 8.26 (m, 1H), 8.10 - 8.02 (m, 2H), 8.02 - 7.93 (m, 2H), 7.78 - 7.47 (m, 5H), 6.90 (d, J = 9.3 Hz, 2H), 6.79 (t, J = 8.8 Hz, 2H), 4.67 (s, 1H), 4.20 (s, 2H), 4.05 (s, 2H), 3.71 (d, J = 14.0 Hz, 1H), 3.42 - 3.27 (m, 1H).

Example 52 (for illustrative purposes)

[0460]

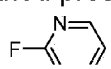


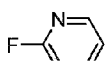
52

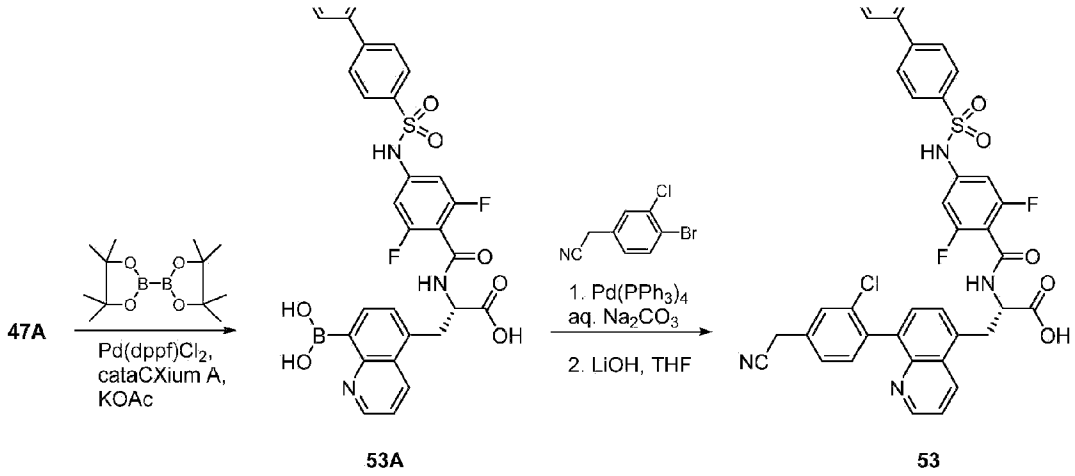
[0461] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(thiophen-3-yl)quinolin-5-yl)propanoic acid **(52):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and thiophen-3-ylboronic acid. MS (m/z) 689.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.23 (s, 1H), 9.11 (d, J = 8.1 Hz, 1H), 8.97 (dd, J = 4.1, 1.7 Hz, 1H), 8.60 (dd, J = 8.6, 1.7 Hz, 1H), 8.37 - 8.32 (m, 1H), 8.09 - 8.04 (m, 3H), 8.01 - 7.96 (m, 2H), 7.86 (d, J = 7.5 Hz, 1H), 7.74 (dt, J = 5.4, 1.8 Hz, 1H), 7.69 - 7.59 (m, 4H), 7.51 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 9.1 Hz, 2H), 4.66 (ddd, J = 10.1, 8.1, 4.4 Hz, 1H), 3.69 (dd, J = 14.3, 4.4 Hz, 1H), 3.31 (dd, J = 14.5, 10.1 Hz, 1H).

Example 53 (for illustrative purposes)

[0462] Synthesis of (S)-3-(8-boronoquinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoic acid **(53A):** The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **47A.**





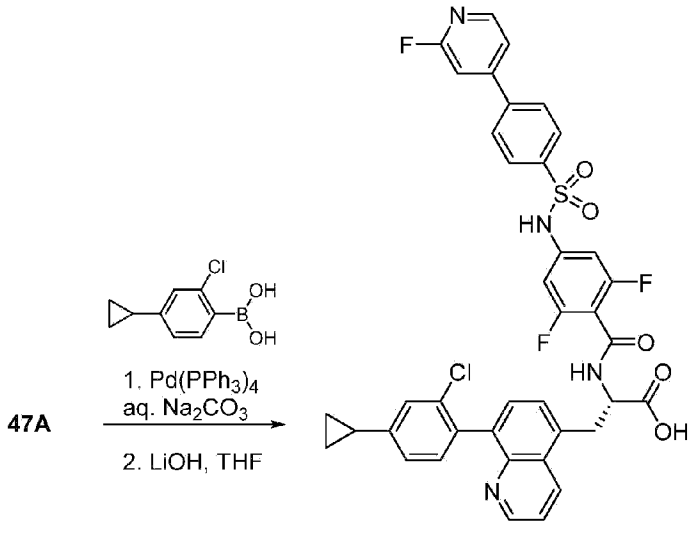


53A 53

[0463] (S)-3-(8-(2-chloro-4-(cyanomethyl)phenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoic acid **(53):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **53A** and 2-(4-bromo-3-chlorophenyl)acetonitrile. MS (m/z) 756.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.19 (s, 1H), 9.10 (d, J = 8.1 Hz, 1H), 8.81 (dd, J = 4.1, 1.6 Hz, 1H), 8.58 (dd, J = 8.7, 1.7 Hz, 1H), 8.33 (dt, J = 5.3, 0.6 Hz, 1H), 8.09 - 8.02 (m, 2H), 8.01 - 7.94 (m, 2H), 7.72 (dt, J = 5.4, 1.8 Hz, 1H), 7.62 - 7.49 (m, 5H), 7.43 - 7.32 (m, 2H), 6.79 (d, J = 9.1 Hz, 2H), 4.67 (d, J = 11.2 Hz, 1H), 4.14 (s, 2H), 3.36 (s, 2H).

Example 54 (for illustrative purposes)

[0464]



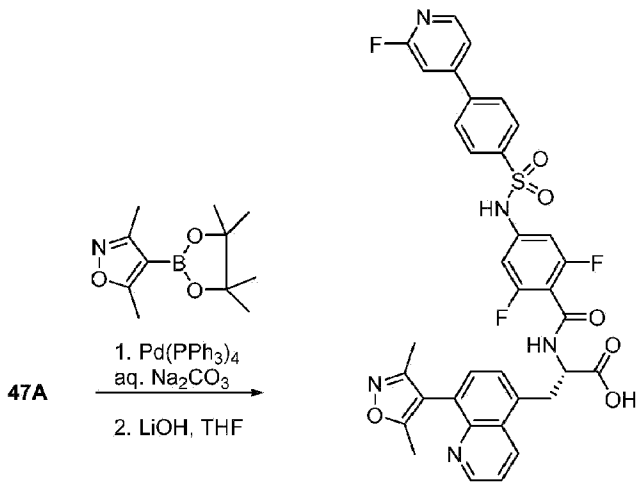
54

[0465] (S)-3-(8-(2-chloro-4-cyclopropylphenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoic acid **(54):** The title compound was

prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and (2-chloro-4-cyclopropylphenyl)boronic acid. MS (m/z) 757.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.23 (s, 1H), 9.12 (d, J = 8.1 Hz, 1H), 8.82 (d, J = 4.3 Hz, 1H), 8.61 (d, J = 8.7 Hz, 1H), 8.35 (d, J = 5.3 Hz, 1H), 8.13 - 8.05 (m, 2H), 8.03 - 7.95 (m, 2H), 7.74 (dt, J = 5.3, 1.8 Hz, 1H), 7.66 - 7.52 (m, 4H), 7.25 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.11 (dd, J = 8.1, 1.8 Hz, 1H), 6.80 (d, J = 9.1 Hz, 2H), 4.76 - 4.64 (m, 1H), 3.82 - 3.62 (m, 1H), 3.45 - 3.25 (m, 1H), 2.02 (tt, J = 8.4, 5.1 Hz, 1H), 1.07 - 0.99 (m, 2H), 0.84 - 0.73 (m, 2H).

Example 55 (for illustrative purposes)

[0466]

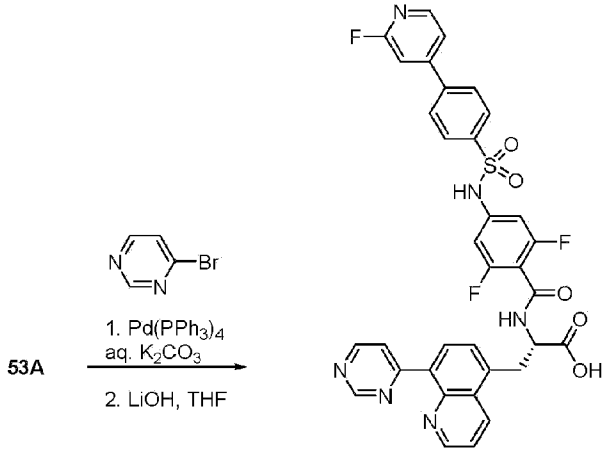


[0467] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(3,5-dimethylisoxazol-4-yl)quinolin-5-yl)propanoic acid (55): The title compound was prepared according to the method presented for the synthesis of compound **3B** and 3 starting with **47A** and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole. MS (m/z) 702.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.19 (s, 1H), 9.07 (d, J = 8.2 Hz, 1H), 8.88 (dd, J = 4.1, 1.6 Hz, 1H), 8.58 (dd, J = 8.7, 1.6 Hz, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.05 (s, 1H), 8.01 - 7.93 (m, 2H), 7.72 (dt, J = 5.4, 1.8 Hz, 1H), 7.65 - 7.57 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 9.1 Hz, 2H), 4.69 (s, 1H), 3.75-3.60 (m, 1 H), 3.30 (dd, J = 14.4, 10.6 Hz, 1H), 2.22 (s, 3H), 2.01 (s, 3H).

Example 56 (for illustrative purposes)

[0468] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(pyrimidin-4-yl)quinolin-5-yl)propanoic acid **(56):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **53A** and 4-bromopyrimidine. MS (m/z) 685.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.21 (s, 1H), 9.30

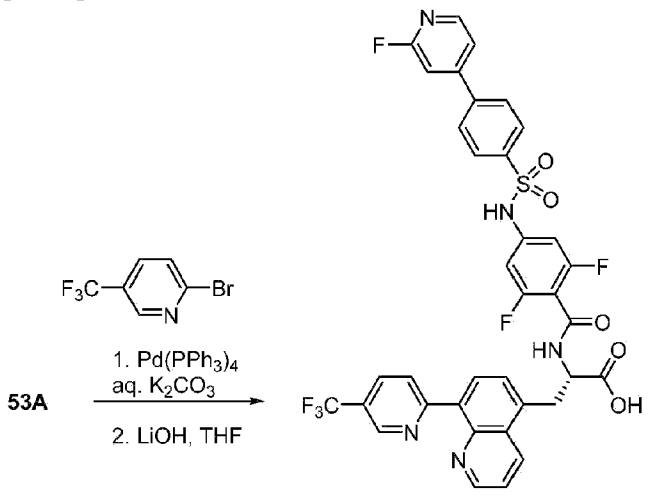
(d, J = 1.4 Hz, 1H), 9.11 (d, J = 8.2 Hz, 1H), 8.99 (dd, J = 4.2, 1.6 Hz, 1H), 8.86 (d, J = 5.4 Hz, 1H), 8.67 (dd, J = 8.7, 1.7 Hz, 1H), 8.42 - 8.25 (m, 2H), 8.19 (d, J = 7.5 Hz, 1H), 8.10-8.00 (m, 2H), 8.01 - 7.92 (m, 2H), 7.74 - 7.70 (m, 1H), 7.71 - 7.66 (m, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 9.1 Hz, 2H), 4.68 (ddd, J = 10.3, 8.2, 4.4 Hz, 1H), 3.81 - 3.65 (m, 1H), 3.34 (d, J = 7.0 Hz, 1H).



56

Example 57 (for illustrative purposes)

[0469]



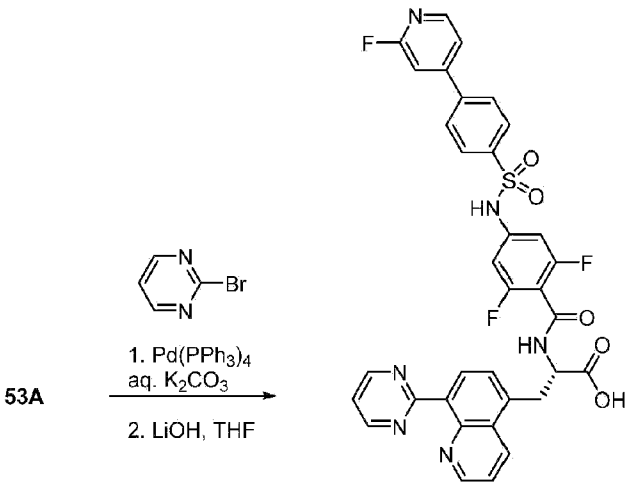
57

[0470] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(5-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(57):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with 53A and 2-bromo-5-(trifluoromethyl)pyridine. MS (m/z) 752.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.21 (s, 1H), 9.20 - 9.05 (m, 2H), 8.98 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 8.7, 1.7 Hz, 1H), 8.38 - 8.23 (m, 3H), 8.11 (d, J = 7.5 Hz, 1H), 8.09 - 8.02 (m, 2H), 8.00 - 7.90

(m, 2H), 7.76 - 7.65 (m, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 1.7 Hz, 1H), 6.78 (d, J = 9.1 Hz, 2H), 4.78 - 4.62 (m, 1H), 3.74 (dd, J = 14.5, 4.4 Hz, 1H), 3.36 (dd, J = 14.5, 10.2 Hz, 1H).

Example 58 (for illustrative purposes)

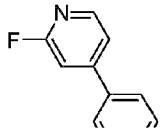
[0471]

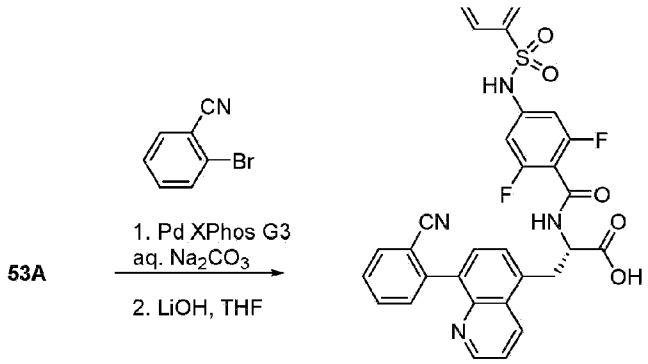


[0472] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(pyrimidin-2-yl)quinolin-5-yl)propanoic acid **(58):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **53A** and 2-bromopyrimidine. MS (m/z) 685.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.22 (s, 1H), 9.29 (d, J = 4.9 Hz, 1H), 9.23 (d, J = 8.7 Hz, 1H), 9.15 - 9.02 (m, 3H), 8.76 (s, 1H), 8.33 (dd, J = 5.3, 0.6 Hz, 1H), 8.10 - 8.00 (m, 2H), 8.00 - 7.92 (m, 2H), 7.86 (d, J = 7.7 Hz, 1H), 7.71 (dt, J = 5.3, 1.8 Hz, 1H), 7.67 (t, J = 4.9 Hz, 1H), 7.58 (p, J = 0.7 Hz, 1H), 6.76 (d, J = 9.1 Hz, 2H), 4.77 (ddd, J = 10.4, 8.3, 4.4 Hz, 1H), 3.92 - 3.79 (m, 1H), 3.47 (dd, J = 14.6, 10.4 Hz, 1H).

Example 59 (for illustrative purposes)

[0473] (S)-3-(8-(2-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)propanoic acid **(59):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **53A** and 2-bromobenzonitrile. MS (m/z) 708.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.22 (d, J = 15.6 Hz, 1H), 9.23 - 9.03 (m, 1H), 8.90 - 8.77 (m, 1H), 8.77 - 8.47 (m, 1H), 8.33 (dd, J = 5.3, 2.2 Hz, 1H), 8.18 - 7.82 (m, 5H), 7.82 - 7.15 (m, 7H), 6.89 - 6.72 (m, 2H), 4.78 - 4.36 (m, 1H), 3.72 (d, J = 10.6 Hz, 1H), 3.30 (m, 1H).

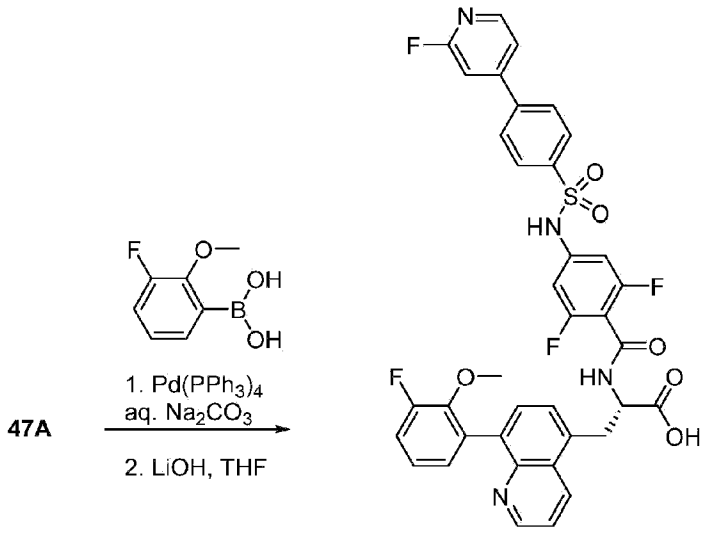




59

Example 60 (for illustrative purposes)

[0474]

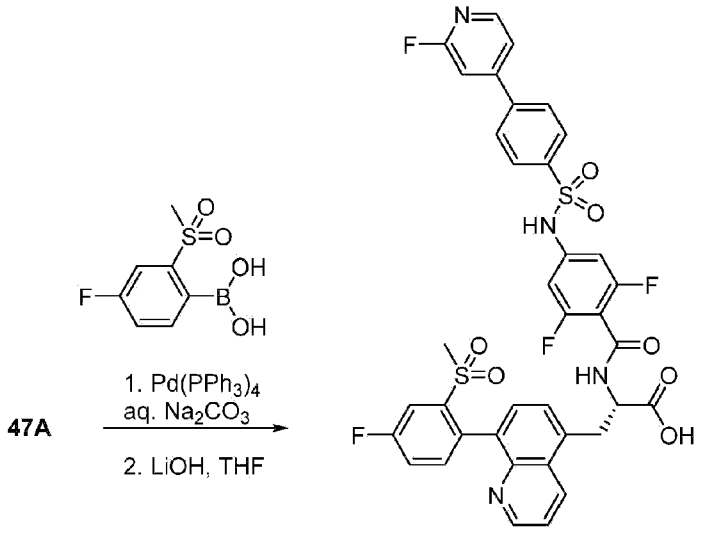


60

[0475] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(3-fluoro-2-methoxyphenyl)quinolin-5-yl)propanoic acid **(60):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and 3 starting with **47A** and (3-fluoro-2-methoxyphenyl)boronic acid. MS (m/z) 731.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.20 (s, 1H), 9.11 (d, J = 8.1 Hz, 1H), 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.61 (d, J = 8.6 Hz, 1H), 8.37 - 8.29 (m, 1H), 8.11 - 8.02 (m, 2H), 8.02 - 7.93 (m, 2H), 7.72 (dt, J = 5.3, 1.8 Hz, 1H), 7.65 - 7.50 (m, 4H), 7.31 (ddd, J = 11.8, 8.2, 1.6 Hz, 1H), 7.15 (td, J = 8.0, 5.1 Hz, 1H), 7.06 - 7.01 (m, 1H), 6.79 (d, J = 9.1 Hz, 2H), 4.74 - 4.62 (m, 1H), 3.71 (dd, J = 14.4, 4.4 Hz, 1H), 3.48 (d, J = 1.4 Hz, 3H), 3.38 - 3.28 (m, 1H).

Example 61 (for illustrative purposes)

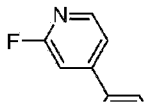
[0476]

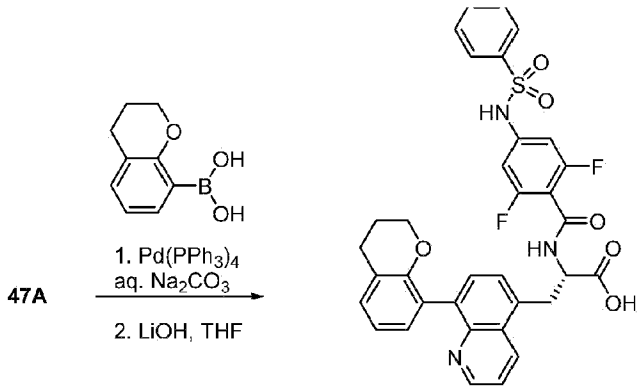


[0477] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(4-fluoro-2-(methylsulfonyl)phenyl)quinolin-5-yl)propanoic acid **(61):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and (4-fluoro-2-(methylsulfonyl)phenyl)boronic acid. MS (m/z) 779.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) (mixture of 50:50 diastereomers) δ 11.21 (s, 1H), 9.12 (dd, J = 8.1, 3.4 Hz, 1H), 8.80 (td, J = 3.8, 3.3, 1.5 Hz, 1H), 8.60 (t, J = 7.4 Hz, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.10 - 8.02 (m, 2H), 8.01 - 7.94 (m, 2H), 7.87 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 7.73 (dd, J = 5.3, 1.7 Hz, 1H), 7.68 - 7.57 (m, 3H), 7.61 - 7.48 (m, 2H), 7.41 - 7.32 (m, 1H), 6.79 (dd, J = 9.1, 1.9 Hz, 2H), 4.76 - 4.61 (m, 1H), 3.77 (dd, J = 14.3, 4.0 Hz, 0.5H), 3.62 (dd, J = 14.7, 5.1 Hz, 0.5H), 3.44 (dd, J = 14.6, 9.6 Hz, 0.5H), 3.27 (dd, J = 14.5, 10.5 Hz, 0.5H), 2.85 (s, 1.5H), 2.80 (s, 1.5H).

Example 62 (for illustrative purposes)

[0478] (S)-3-(8-(chroman-8-yl)quinolin-5-yl)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl) phenyl)sulfonamido)benzamido)propanoic acid **(62):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and chroman-8-ylboronic acid. MS (m/z) 739.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.22 (s, 1H), 9.12 (d, J = 8.1 Hz, 1H), 8.88 (s, 1H), 8.33 (dt, J = 5.4, 0.6 Hz, 1H), 8.10 - 8.01 (m, 2H), 8.01 - 7.90 (m, 2H), 7.72 (dt, J = 5.4, 1.8 Hz, 1H), 7.59 (q, J = 1.1 Hz, 3H), 7.14 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.86 - 6.64 (m, 2H), 4.75 - 4.57 (m, 1H), 3.97 - 3.85 (m, 2H), 3.72 (d, J = 14.3 Hz, 1H), 3.43 - 3.27 (m, 1H), 2.82 (t, J = 6.5 Hz, 2H), 1.87 (t, J = 5.6 Hz, 3H).

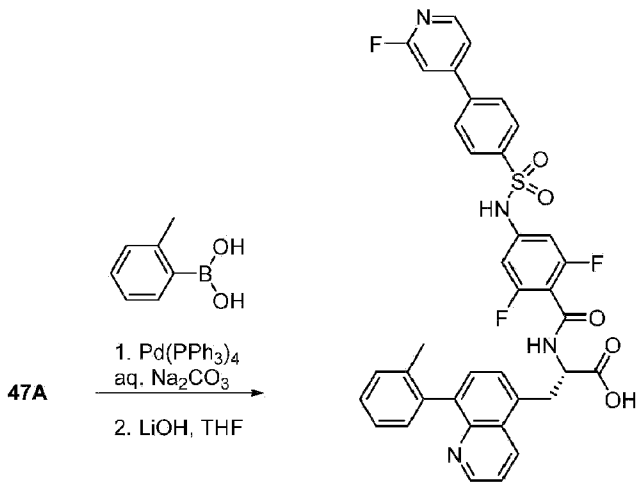




62

Example 63 (for illustrative purposes)

[0479]

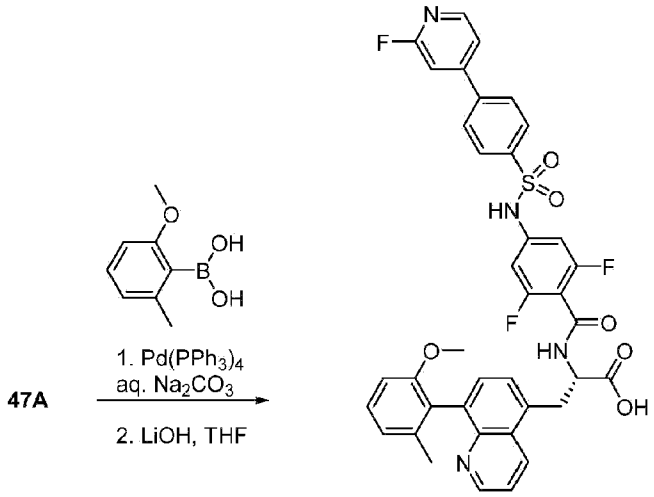


63

[0480] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(o-tolyl)quinolin-5-yl)propanoic acid **(63):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and o-tolylboronic acid. MS (m/z) 697.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.20 (s, 1H), 9.09 (d, J = 8.2 Hz, 1H), 8.81 (dd, J = 4.2, 1.6 Hz, 1H), 8.62 (d, J = 8.7 Hz, 1H), 8.36 - 8.28 (m, 1H), 8.11 - 8.01 (m, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.72 (dt, J = 5.4, 1.8 Hz, 1H), 7.65 - 7.55 (m, 2H), 7.55 - 7.41 (m, 2H), 7.34 - 7.17 (m, 3H), 7.13 (d, J = 7.0 Hz, 1H), 6.78 (d, J = 9.5 Hz, 2H), 4.70 (s, 1H), 3.72 (dd, J = 14.4, 4.4 Hz, 1H), 3.32 (dd, J = 14.4, 10.3 Hz, 1H), 1.87 (s, 3H).

Example 64 (for illustrative purposes)

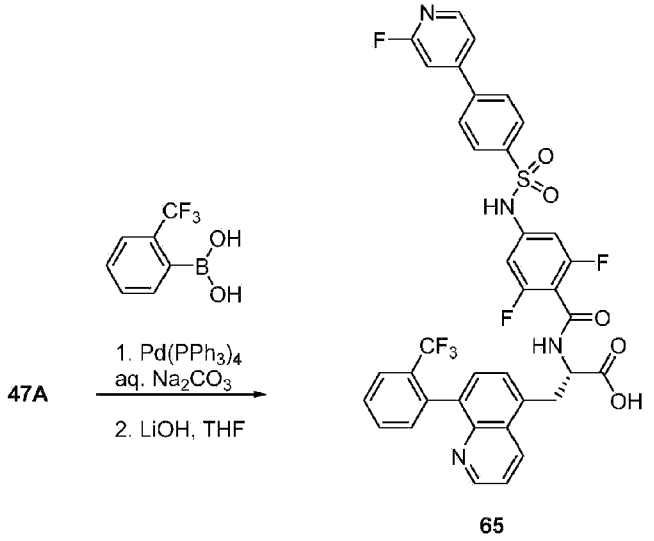
[0481]



[0482] (2S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(2-methoxy-6-methylphenyl)quinolin-5-yl)propanoic acid **(64):** The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and (2-methoxy-6-methylphenyl)boronic acid. MS (m/z) 727.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 11.20 (s, 1H), 9.08 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 42.8 Hz, 2H), 8.33 (d, J = 5.3 Hz, 1H), 8.13 - 7.89 (m, 4H), 7.72 (dt, J = 5.3, 1.7 Hz, 1H), 7.69 - 7.37 (m, 4H), 7.28 (t, J = 7.9 Hz, 1H), 6.90 (t, J = 8.9 Hz, 2H), 6.83 - 6.71 (m, 2H), 4.79 - 4.66 (m, 1H), 3.77 (d, J = 14.2 Hz, 1H), 3.49 (s, 3H), 3.28 (dd, J = 14.4, 10.6 Hz, 1H), 1.74 (s, 3H).

Example 65 (for illustrative purposes)

[0483]

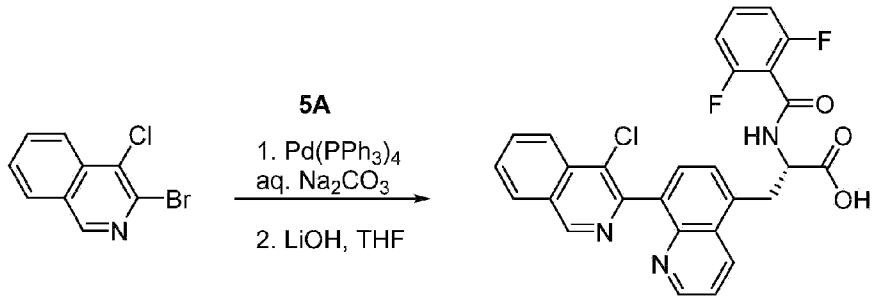


[0484] (S)-2-(2,6-difluoro-4-((4-(2-fluoropyridin-4-yl)phenyl)sulfonamido)benzamido)-3-(8-(2-

(trifluoromethyl)phenyl)quinolin-5-yl)propanoic acid (65): The title compound was prepared according to the method presented for the synthesis of compound **3B** and **3** starting with **47A** and (2-(trifluoromethyl)phenyl)boronic acid. MS (m/z) 751.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.20 (d, J = 2.3 Hz, 1H), 9.10 (dd, J = 8.2, 6.2 Hz, 1H), 8.77 (dt, J = 4.0, 1.9 Hz, 1H), 8.59 (d, J = 8.5 Hz, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.10 - 8.02 (m, 2H), 8.01 - 7.93 (m, 2H), 7.82 (dt, J = 7.9, 1.9 Hz, 1H), 7.75 - 7.54 (m, 6H), 7.51 (d, J = 1.9 Hz, 2H), 7.32 (dd, J = 7.7, 4.4 Hz, 1H), 6.78 (dd, J = 9.0, 3.5 Hz, 2H), 4.69 (ddd, J = 10.2, 8.1, 4.6 Hz, 1H), 3.71 (ddd, J = 29.9, 14.4, 4.4 Hz, 1H), 3.34 (ddd, J = 25.9, 14.5, 10.2 Hz, 1H).

Example 66 (for illustrative purposes)

[0485]

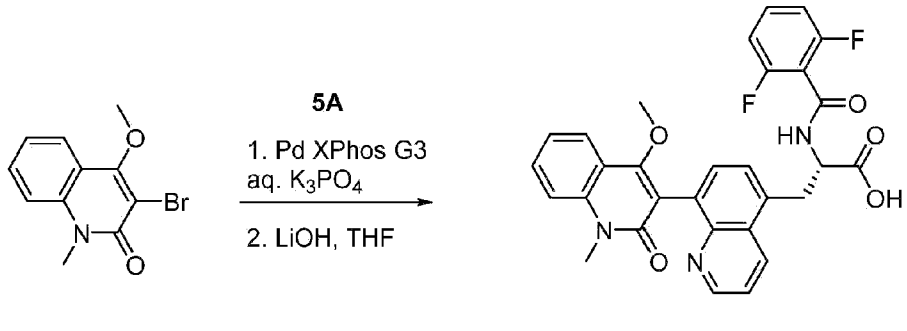


66

[0486] (S)-3-(8-(4-chloroisoquinolin-3-yl)quinolin-5-yl)-2-(2,6-difluorobenzamido)propanoic acid **(66):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **5A** and 3-bromo-4-chloroisoquinoline. MS (m/z) 514.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 8.1 Hz, 1H), 8.88 (d, J = 4.3 Hz, 1H), 8.77 (s, 1H), 7.98 (s, 1H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.70 - 7.56 (m, 3H), 7.49 (tt, J = 8.4, 6.5 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.18 - 7.08 (m, 2H), 4.75 (td, J = 9.5, 4.5 Hz, 1H), 3.77 (dd, J = 14.5, 4.5 Hz, 1H), 3.68 (s, 3H), 3.44 (dd, J = 14.5, 9.9 Hz, 1H).

Example 67 (for illustrative purposes)

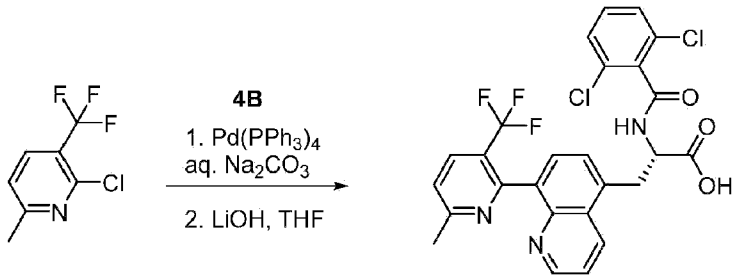
[0487]



[0488] (S)-2-(2,6-difluorobenzamido)-3-(4-methoxy-1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(67):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **5A** and 3-bromo-4-methoxy-1-methylquinolin-2(1H)-one. MS (m/z) 518.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.41 (d, J = 0.8 Hz, 1H), 9.31 (d, J = 8.1 Hz, 1H), 8.81 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 8.7, 1.7 Hz, 1H), 8.38 - 8.29 (m, 1H), 8.24 (dq, J = 8.5, 0.9 Hz, 1H), 8.02 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.87 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.72 - 7.64 (m, 2H), 7.48 (tt, J = 8.5, 6.6 Hz, 1H), 7.16 - 7.07 (m, 2H), 4.80 (ddd, J = 10.1, 8.1, 4.4 Hz, 1H), 3.81 (dd, J = 14.5, 4.4 Hz, 1H), 3.46 (dd, J = 14.5, 10.1 Hz, 1H).

Example 68 (for illustrative purposes)

[0489]

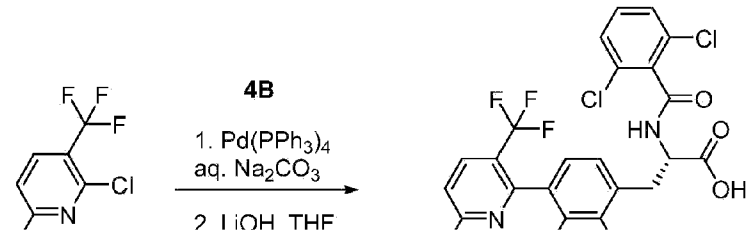


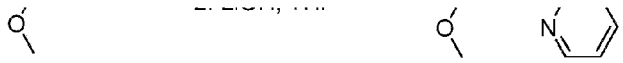
68

[0490] (S)-2-(2,6-dichlorobenzamido)-3-(8-(6-methyl-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(68):** The title compound was prepared according to the method presented for the synthesis of compound **4C** and **4** starting with **4B** and 2-chloro-6-methyl-3-(trifluoromethyl)pyridine. MS (m/z) 549.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.31 (d, J = 8.3 Hz, 1H), 8.81 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 8.7, 1.7 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.70 - 7.52 (m, 4H), 7.48 - 7.35 (m, 3H), 4.84 (td, J = 9.3, 4.3 Hz, 1H), 3.75 (dd, J = 14.6, 4.4 Hz, 1H), 3.44 (dd, J = 14.6, 10.1 Hz, 1H), 2.58 (s, 3H).

Example 69 (for illustrative purposes)

[0491]



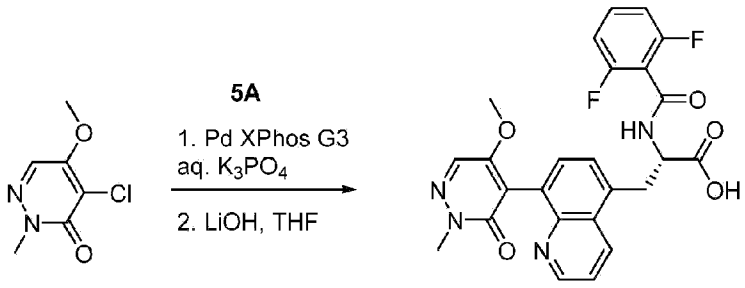


69

[0492] (S)-2-(2,6-dichlorobenzamido)-3-(8-(6-methoxy-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(69):** The title compound was prepared according to the method presented for the synthesis of compound **4C** and **4** starting with **4B** and 2-chloro-6-methoxy-3-(trifluoromethyl)pyridine. MS (m/z) 565.9 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.28 (s, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (d, J = 8.9 Hz, 1H), 7.70 - 7.58 (m, 3H), 7.47 - 7.34 (m, 3H), 7.06 (dt, J = 8.7, 0.8 Hz, 1H), 4.86 (m, 1H), 3.81 (s, 3H), 3.78 (m, 1H), 3.43 (m, 1H).

Example 70 (for illustrative purposes)

[0493]

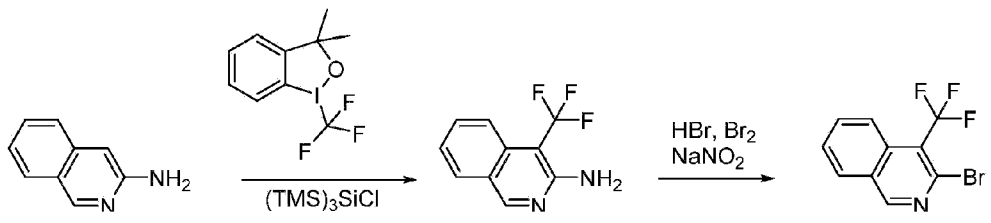


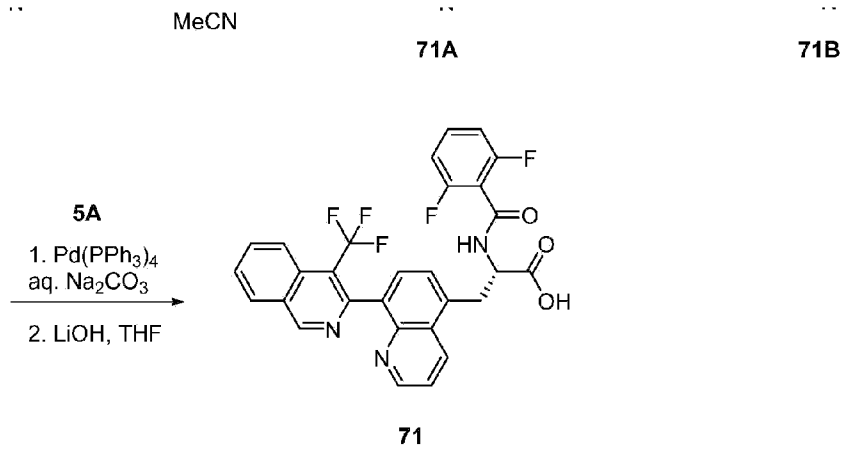
70

[0494] (S)-2-(2,6-difluorobenzamido)-3-(8-(5-methoxy-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)quinolin-5-yl)propanoic acid **(70):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **5A** and 4-chloro-5-methoxy-2-methylpyridazin-3(2H)-one. MS (m/z) 495.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 7.6 Hz, 1H), 8.88 (d, J = 4.4 Hz, 1H), 8.75 (d, J = 8.6 Hz, 1H), 8.27 (s, 1H), 7.77 - 7.65 (m, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.48 (tt, J = 8.5, 6.6 Hz, 1H), 7.12 (dd, J = 8.4, 7.6 Hz, 2H), 4.74 (s, 1H), 3.86 - 3.63 (m, 7H), 3.43 (q, J = 13.6 Hz, 1H).

Example 71 (for illustrative purposes)

[0495]





[0496] Synthesis of 4-(trifluoromethyl)isoquinolin-3-amine **(71A):** 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 h. The reaction mixture was filtered through celite, rinsed with EA and purified by silica gel chromatography using EA in hexanes as eluent to give the title compound.

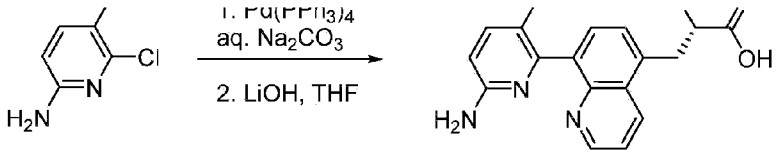
[0497] Synthesis of 3-bromo-4-(trifluoromethyl)isoquinoline (**71B**): To a stirred solution of **71A** (91 mg, 0.43 mmol) in HBr (6.9 mL) was added Br_2 (0.13 ml, 2.57 mmol). The reaction mixture was kept at 0 °C for 10 minutes at which time $NaNO_2$ (147.96 mg, 2.14 mmol) was added as a premade solution 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/EA to give the title compound.

[0498] (S)-2-(2,6-difluorobenzamido)-3-(8-(4-(trifluoromethyl)isoquinolin-3-yl)quinolin-5-yl)propanoic acid **(71):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **4B** and **71B.** MS (m/z) 552.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.60 (d, J = 3.3 Hz, 1H), 9.29 (t, J = 7.6 Hz, 1H), 8.75 (dt, J = 3.9, 1.8 Hz, 1H), 8.65 (ddd, J = 8.7, 5.6, 1.7 Hz, 1H), 8.38 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.05 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 7.70 (dd, J = 7.3, 4.7 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.55 - 7.41 (m, 1H), 7.12 (q, J = 8.2 Hz, 2H), 4.77 (dtd, J = 18.5, 8.8, 4.4 Hz, 1H), 3.77 (ddd, J = 25.7, 14.5, 4.5 Hz, 1H), 3.49 - 3.34 (m, 1H).

Example 72 (for illustrative purposes)

[0499]



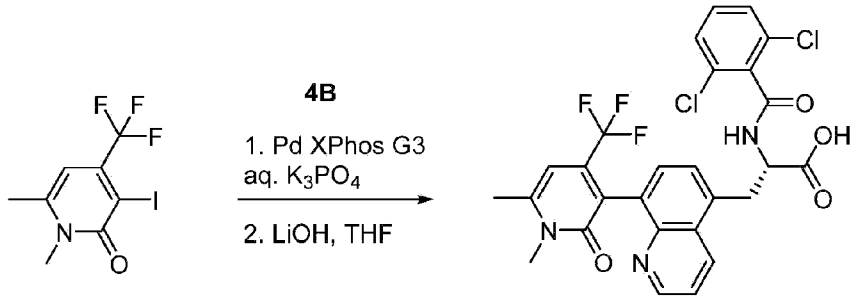


72

[0500] (S)-3-(8-(6-amino-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)-2-(2,6-dichloro benzamido)propanoic acid **(72):** The title compound was prepared according to the method presented for the synthesis of compound **4C** and **4** starting with **4B** and 6-chloro-5-(trifluoromethyl)pyridin-2-amine. MS (m/z) 550.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.33 (d, J = 8.3 Hz, 1H), 8.89 (dd, J = 4.1, 1.6 Hz, 1H), 8.70 (dd, J = 8.7, 1.6 Hz, 1H), 7.97 (d, J = 9.1 Hz, 1H), 7.74 - 7.63 (m, 3H), 7.49 - 7.36 (m, 3H), 6.81 (d, J = 9.1 Hz, 1H), 4.80 (td, J = 9.2, 4.4 Hz, 1H), 3.74 (dd, J = 14.5, 4.4 Hz, 1H), 3.43 (dd, J = 14.6, 9.9 Hz, 1H).

Example 73 (for illustrative purposes)

[0501]



73

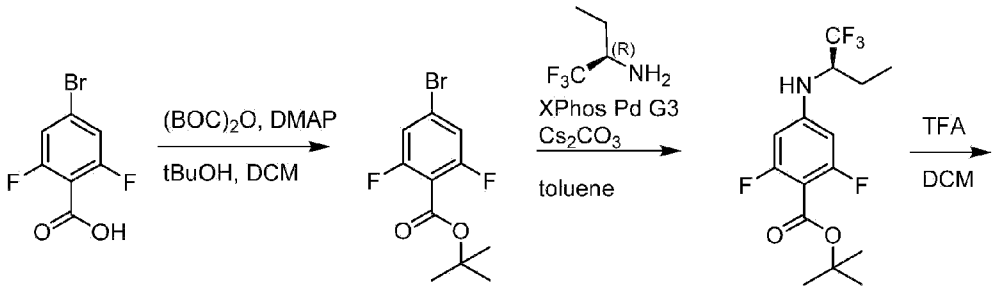
[0502] (S)-2-(2,6-dichlorobenzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(73):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **4B** and 3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one. MS (m/z) 578.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.00 (s, 1H), 9.27 (dd, J = 27.2, 8.3 Hz, 1H), 8.83 (dt, J = 4.2, 2.0 Hz, 1H), 8.69 (d, J = 8.6 Hz, 1H), 7.72 - 7.59 (m, 2H), 7.49 - 7.31 (m, 4H), 6.55 (d, J = 4.7 Hz, 1H), 4.90 - 4.71 (m, 1H), 3.73 (td, J = 14.4, 4.0 Hz, 1H), 3.47 (d, J = 4.2 Hz, 3H), 3.38 (ddd, J = 24.5, 14.7, 10.5 Hz, 1H), 2.52 (m, 3H).

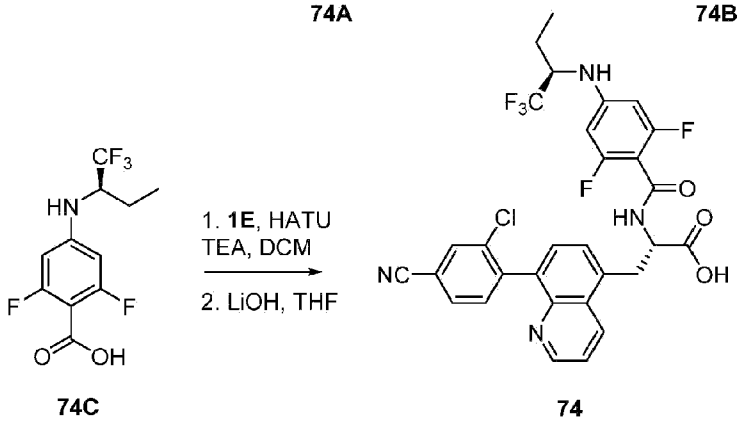
Example 74 (for illustrative purposes)

[0503] Synthesis of *tert*-butyl 4-bromo-2,6-difluorobenzoate **(74A):** To a stirred solution of 4-bromo-2,6-difluorobenzoic acid (5 g, 21.1 mmol) in DCM (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 material. This material was suspended in hexanes, the solid was filtered off and the filtrate was evaporated under reduced pressure to afford compound **74A.** 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 **(74B):** To a stirred suspension of tert-butyl 4-bromo-2,6-difluorobenzoate **(74A)** (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 **74B.** MS (m/z) 284.1 $[M+H-C_4H_8]^+$.



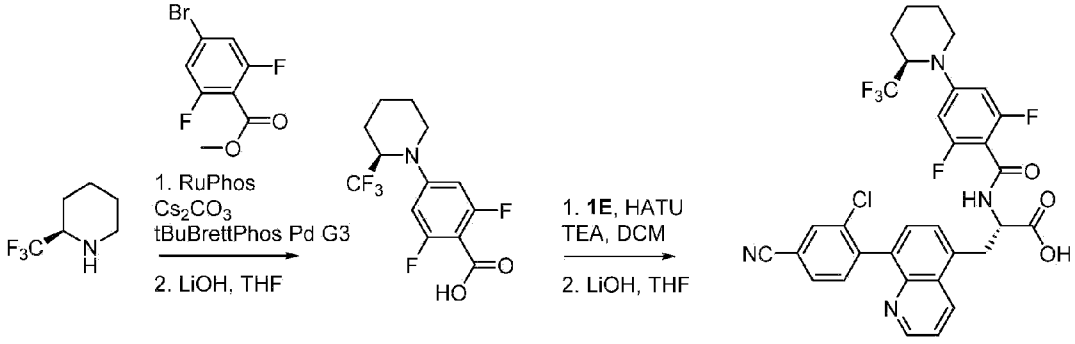


[0505] Synthesis of (R)-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid **(74C):** To a stirred solution of tert-butyl (R)-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoate **(74B)** (188 mg, 0.55 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was allowed to stir at RT for 20 mins. The reaction mixture was concentrated under reduced pressure to afford material that was purified by silica gel column chromatography and eluted by ethyl acetate in hexane to afford compound **74C.** MS (m/z) 338.1 $[M+H]^+$.

[0506] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoro butan-2-yl)amino)benzamido)propanoic acid **(74):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **74C.** MS (m/z) 617.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.87 - 8.77 (m, 2H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.73 - 7.44 (m, 4H), 6.76 (d, J = 9.4 Hz, 1H), 6.43 (d, J = 11.6 Hz, 2H), 4.68 (s, 1H), 4.29 (d, J = 10.2 Hz, 1H), 3.73 (s, 1H), 3.49 - 3.33 (m, 1H), 1.75 (ddt, J = 10.1, 7.5, 3.8 Hz, 1H), 1.51 (ddt, J = 17.6, 14.4, 7.3 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H).

Example 75 (for illustrative purposes)

[0507]



75A **75**

[0508] Synthesis of (R)-2,6-difluoro-4-(2-(trifluoromethyl)piperidin-1-yl)benzoic acid **(75A):** To a 150 mL pressure vessel containing a stir bar was added methyl 4-bromo-2,6-difluoro benzoate (700 mg, 1.8 mmol), RuPhos (169 mg, 0.36 mmol), tBuBrettPhos Pd G3 (155 mg, 0.18 mmol), Cs_2CO_3 (2.95 g, 9.1 mmol), (R)-2-(trifluoromethyl)piperidine (416 mg, 2.7 mmol) and toluene (18 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 EA and the filtrate was evaporated to dryness under reduced pressure. The material was purified by silica gel chromatography using EA in Hexane as eluent. To this material was added THF (6 mL) and aqueous LiOH (6.2 mL, 1.0 M). The reaction mixture was stirred at 60°C for 20 hrs. The reaction mixture was cooled to RT and acidified with 1.0 M HCl before extracting with EA. Organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **75A.**

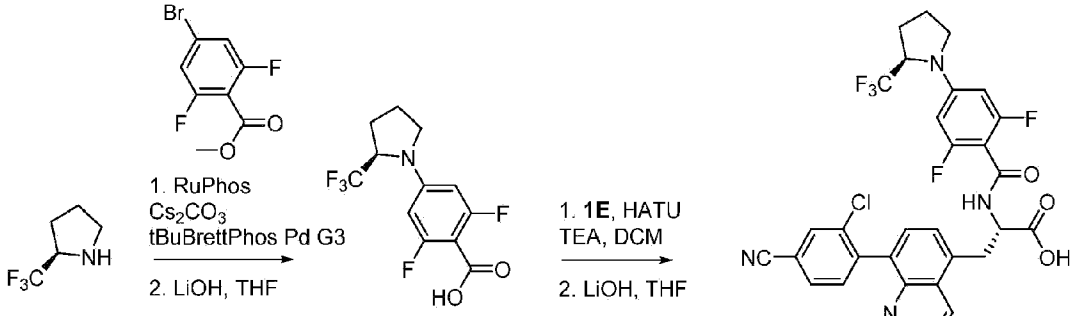
[0509] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-2-(trifluoromethyl)piperidin-1-yl)benzamido)propanoic acid **(75):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **75A.** MS (m/z) 645.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 8.1 Hz, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.64 (dd, J = 8.6, 1.7 Hz, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.67 - 7.52 (m, 4H), 6.72 (d, J = 12.0 Hz, 2H), 4.93 (d, J =

9.0 Hz, 1H), 4.70 (dt, J = 9.7, 4.9 Hz, 1H), 3.74 (s, 1H), 3.59 (d, J = 12.9 Hz, 1H), 3.41 (s, 1H), 2.99 (t, J = 12.2 Hz, 1H), 1.94 (d, J = 14.4 Hz, 1H), 1.85 - 1.67 (m, 2H), 1.67 - 1.42 (m, 3H).

Example 76 (for illustrative purposes)

[0510] Synthesis of (R)-2,6-difluoro-4-(2-(trifluoromethyl)pyrrolidin-1-yl)benzoic acid **(76A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (R)-2-(trifluoromethyl)pyrrolidine.

[0511] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-2-(trifluoro methyl)pyrrolidin-1-yl)benzamido)propanoic acid **(76):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **76A.** MS (m/z) 629.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 8.2 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.96 - 7.83 (m, 1H), 7.66 - 7.58 (m, 3H), 7.56 (dt, J = 7.9, 0.6 Hz, 1H), 6.48 (d, J = 11.5 Hz, 2H), 4.82 - 4.63 (m, 2H), 3.72 (d, J = 13.0 Hz, 1H), 3.56 (t, J = 8.5 Hz, 1H), 3.41 (s, 1H), 3.15 (q, J = 8.7 Hz, 1H), 2.16 - 1.91 (m, 4H).

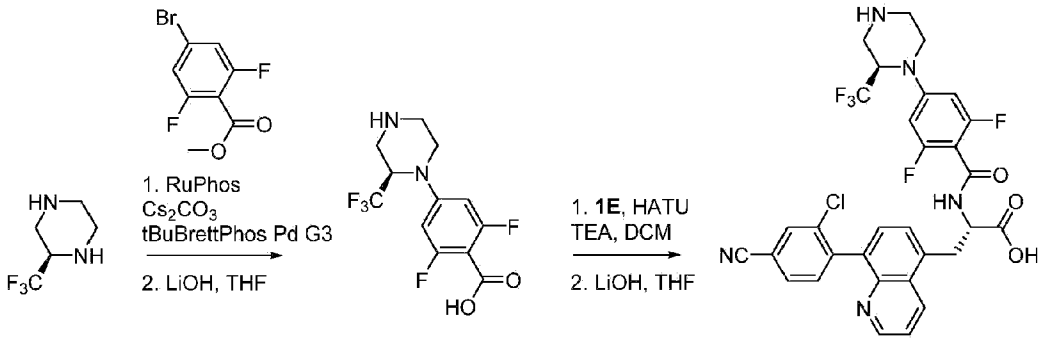


76A

76

Example 77 (for illustrative purposes)

[0512]



77A

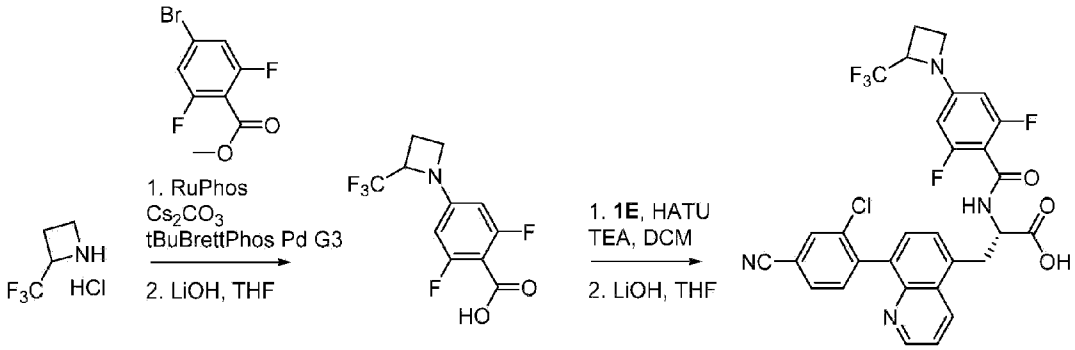
77

[0513] Synthesis of (R)-2,6-difluoro-4-(2-(trifluoromethyl)piperazin-1-yl)benzoic acid **(77A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (R)-2-(trifluoromethyl)piperazine.

[0514] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-2-(trifluoro methyl)piperazin-1-yl)benzamido)propanoic acid **(77):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **77A.** MS (m/z) 644.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 8.1 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.63 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (dd, J = 1.6, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.67 - 7.57 (m, 3H), 7.58 - 7.53 (m, 1H), 6.79 (d, J = 11.5 Hz, 2H), 4.71 (td, J = 9.2, 8.2, 4.3 Hz, 1H), 4.26 (br, 1H), 4.05 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 10.9 Hz, 1H), 3.75 (s, 1H), 3.42 (s, 1H), 3.29 (d, J = 10.7 Hz, 1H), 3.12 - 2.96 (m, 3H).

Example 78 (for illustrative purposes)

[0515]

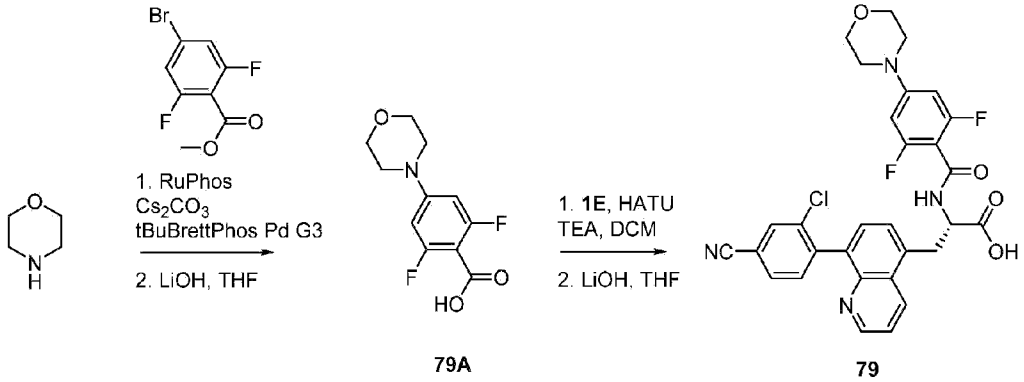


[0516] Synthesis of 2,6-difluoro-4-(2-(trifluoromethyl)azetidin-1-yl)benzoic acid **(78A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with 2-(trifluoromethyl)azetidine hydrochloride.

[0517] (2S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(2-(trifluoromethyl) azetidin-1-yl)benzamido)propanoic acid **(78):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **78A.** MS (m/z) 617.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.93 (dd, J = 8.1, 3.2 Hz, 1H), 8.87 - 8.77 (m, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (d, J = 1.7 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.67 - 7.50 (m, 4H), 6.24 (d, J = 9.9 Hz, 2H), 4.91 (q, J = 6.3 Hz, 1H), 4.71 (d, J = 9.6 Hz, 1H), 4.16 - 3.97 (m, 1H), 3.84 - 3.62 (m, 2H), 3.40 (s, 1H), 2.68 - 2.53 (m, 1H), 2.37 (ddd, J = 11.7, 5.6, 2.6 Hz, 1H).

Example 79 (for illustrative purposes)

[0518]



79A

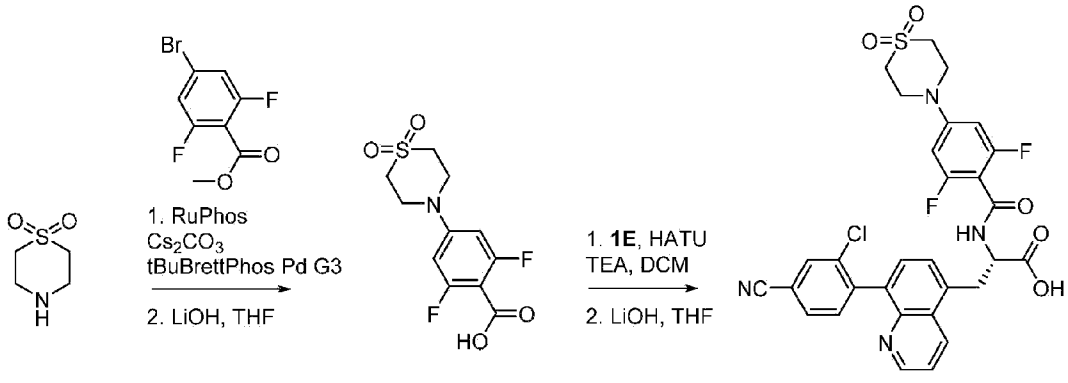
79

[0519] Synthesis of 2,6-difluoro-4-morpholinobenzoic acid **(79A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with morpholine.

[0520] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-morpholino benzamido)propanoic acid **(79):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **79A.** MS (m/z) 577.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J = 8.0 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.96 - 7.84 (m, 1H), 7.67 - 7.58 (m, 3H), 7.56 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 11.8 Hz, 2H), 4.69 (q, J = 5.9, 4.3 Hz, 1H), 3.74 (s, 1H), 3.70 - 3.61 (m, 4H), 3.42 (s, 1H), 3.22 - 3.12 (m, 4H).

Example 80 (for illustrative purposes)

[0521]



80A

80

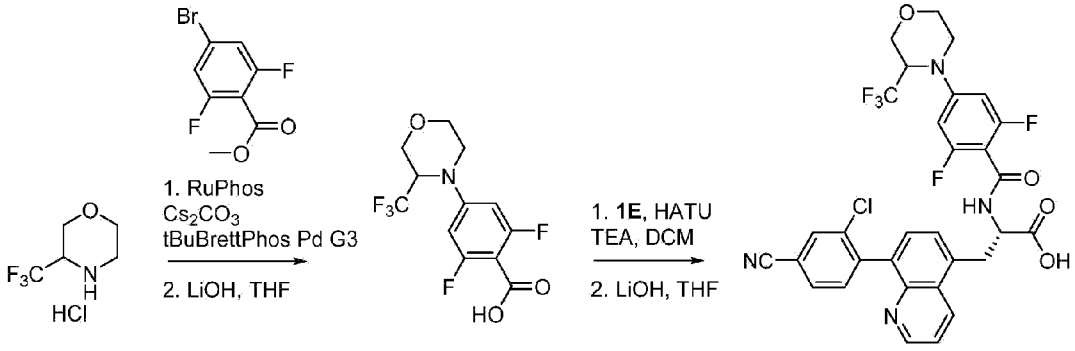
[0522] Synthesis of 4-(1,1-dioxidothiomorpholino)-2,6-difluorobenzoic acid **(80A):** The title compound was prepared according to the method presented for the synthesis of compound

75A starting with thiomorpholine 1,1-dioxide.

[0523] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(4-(1,1-dioxidothiomorpholino)-2,6-difluorobenzamido)propanoic acid **(80):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **80A.** MS (m/z) 625.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 8.1 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.6, 1.7 Hz, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.67 - 7.58 (m, 3H), 7.56 (dd, J = 7.9, 0.4 Hz, 1H), 6.76 (d, J = 11.7 Hz, 2H), 4.78 - 4.64 (m, 1H), 3.85 (s, 4H), 3.75 (s, 1H), 3.42 (s, 1H), 3.06 (s, 4H).

Example 81 (for illustrative purposes)

[0524] Synthesis of 2,6-difluoro-4-morpholinobenzoic acid **(81A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with 3-(trifluoromethyl)morpholine hydrochloride.

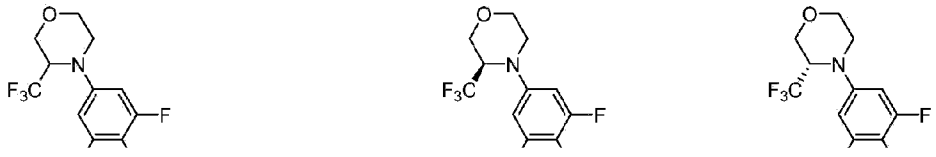


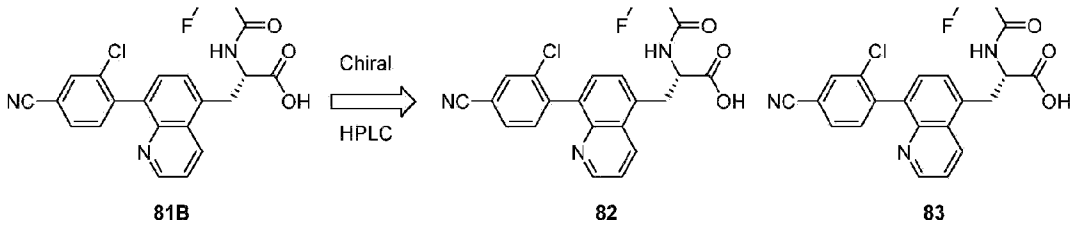
81A **81**

[0525] 2,6-difluoro-4-(3-(trifluoromethyl)morpholino)benzoic acid **(81):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **81A.** MS (m/z) 645.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.96 (dd, J = 8.0, 2.7 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.65 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (dd, J = 1.6, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.68 - 7.59 (m, 3H), 7.57 (dt, J = 7.9, 0.6 Hz, 1H), 6.74 (d, J = 11.7 Hz, 2H), 4.89 (dd, J = 8.7, 3.6 Hz, 1H), 4.71 (d, J = 6.2 Hz, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.93 (dd, J = 11.5, 3.8 Hz, 1H), 3.72 (d, J = 13.0 Hz, 2H), 3.59 - 3.45 (m, 1H), 3.40 (d, J = 12.7 Hz, 2H), 3.21 (t, J = 12.2 Hz, 1H).

Examples 82 and 83 (for illustrative purposes)

[0526]



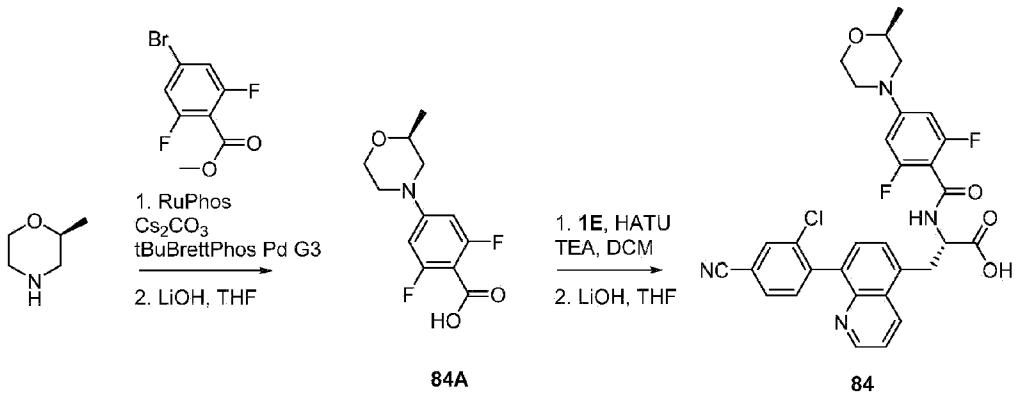


[0527] Preparation of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(82): 81** was separated into its 2 stereoisomers by supercritical fluid chromatography using 25% MeOH/DEA co-solvent, at a flow rate of 50 mL/min, using a Chiralpak AD-H 5um 21x250mm column. The title compound was identified as the first eluting peak. MS (m/z) 645.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.74 (s, 1H), 8.14 (dd, J = 1.6, 0.4 Hz, 1H), 8.0-8.4 (br, 1H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.61 - 7.49 (m, 4H), 6.74 (d, J = 11.9 Hz, 2H), 4.88 (d, J = 9.0 Hz, 1H), 4.43 (s, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.93 (dd, J = 11.5, 3.7 Hz, 1H), 3.72 (d, J = 12.6 Hz, 2H), 3.60 - 3.48 (m, 1H), 3.41 (d, J = 12.9 Hz, 1H), 3.21 (t, J = 13.1 Hz, 2H).

[0528] Preparation of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((S)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(83): 81** was separated into its 2 stereoisomers by supercritical fluid chromatography using 25% EtOH/TFA cosolvent, at a flow rate of 50 mL/min, using a Chiralpak AD-H 5 µm 21x250 mm column. The title compound was identified as the second eluting peak. MS (m/z) 645.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.77 (dd, J = 4.1, 1.5 Hz, 2H), 8.13 (dd, J = 1.7, 0.4 Hz, 1H), 8.08 (s, 1H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.65 - 7.42 (m, 4H), 6.74 (d, J = 11.9 Hz, 2H), 4.88 (dt, J = 9.4, 4.7 Hz, 1H), 4.40 (d, J = 6.6 Hz, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.93 (dd, J = 11.5, 3.7 Hz, 1H), 3.71 (d, J = 13.0 Hz, 2H), 3.60 - 3.46 (m, 1H), 3.41 (d, J = 13.0 Hz, 2H), 3.23 (d, J = 11.8 Hz, 1H).

Example 84 (for illustrative purposes)

[0529]



[0530] Synthesis of (S)-2,6-difluoro-4-(2-methylmorpholino)benzoic acid **(84A):** The title

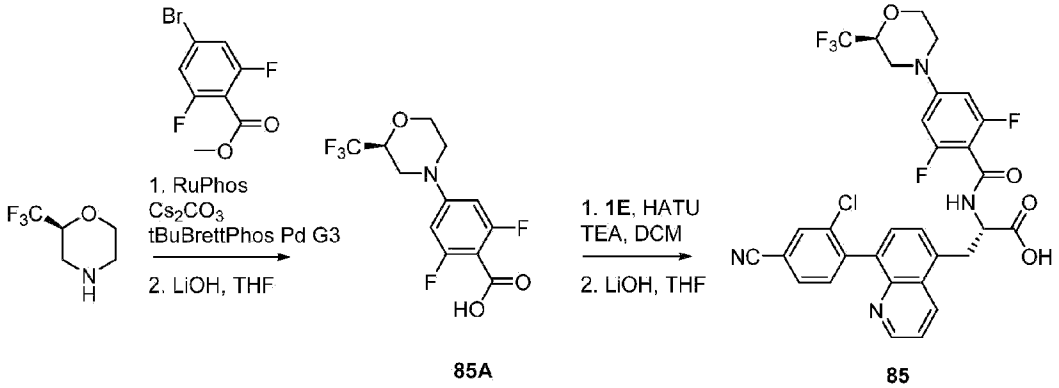
compound was prepared according to the method presented for the synthesis of compound **75A** starting with (S)-2-methylmorpholine.

[0531] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((S)-2-methyl morpholino)benzamido)propanoic acid **(84):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **84A.** MS (m/z) 591.8 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 8.1 Hz, 1H), 8.85 (dd, J = 4.2, 1.5 Hz, 1H), 8.65 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 7.9, 1.6 Hz, 1H), 7.69 - 7.55 (m, 4H), 6.62 (d, J = 11.9 Hz, 2H), 4.71 (t, J = 11.2 Hz, 1H), 3.87 (dd, J = 11.2, 3.4 Hz, 1H), 3.71 (d, J = 12.4 Hz, 2H), 3.66 - 3.50 (m, 3H), 3.44 (s, 1H), 2.70 (td, J = 11.8, 3.6 Hz, 1H), 2.38 (dd, J = 12.3, 10.4 Hz, 1H), 1.13 (d, J = 6.2 Hz, 3H).

Example 85 (for illustrative purposes)

[0532] Synthesis of (S)-2,6-difluoro-4-(2-methylmorpholino)benzoic acid **(85A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (S)-2-(trifluoromethyl)morpholine.

[0533] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((S)-2-(trifluoro methyl)morpholino)benzamido)propanoic acid **(85):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **85A.** MS (m/z) 645.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.93 (d, J = 8.1 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.64 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.67 - 7.57 (m, 3H), 7.56 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 11.6 Hz, 2H), 4.77 - 4.66 (m, 1H), 4.29 (dq, J = 6.7, 3.3 Hz, 1H), 4.03 (dd, J = 10.9, 3.3 Hz, 1H), 3.86 (d, J = 12.2 Hz, 1H), 3.75 (m, 1H), 3.69 (t, J = 10.4 Hz, 2H), 3.41 (s, 1H), 2.92 - 2.72 (m, 2H).



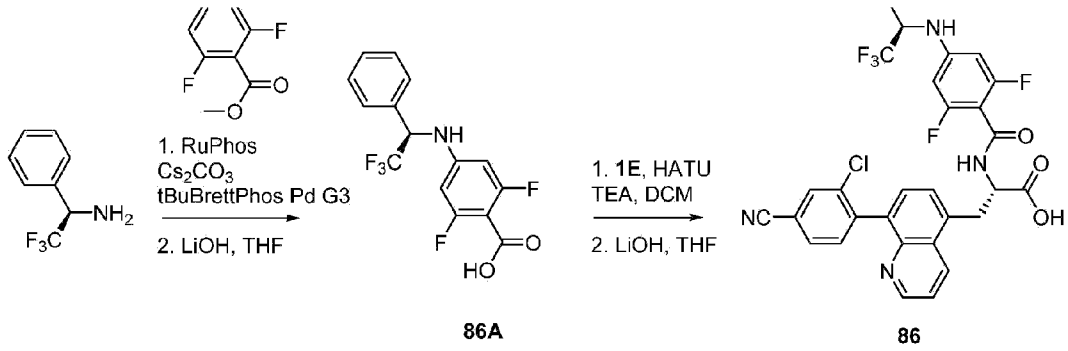
85A

85

Example 86 (for illustrative purposes)

[0534]





86A

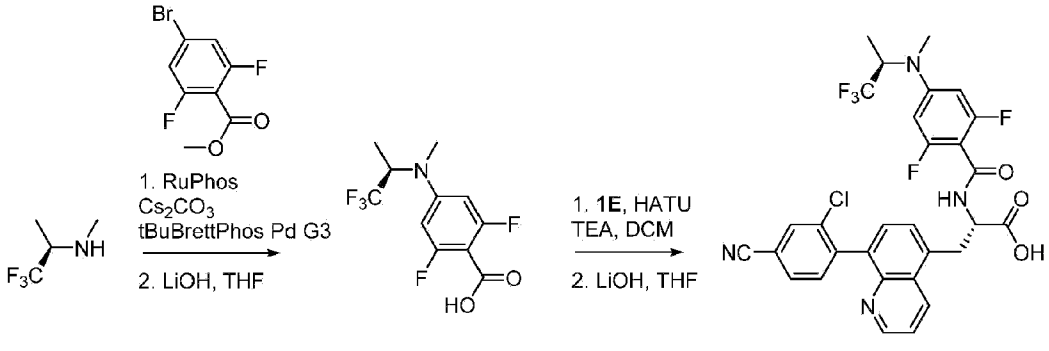
86

[0535] Synthesis of (R)-2,6-difluoro-4-((2,2,2-trifluoro-1-phenylethyl)amino)benzoic acid **(86A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (R)-2,2,2-trifluoro-1-phenylethan-1-amine.

[0536] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(((R)-2,2,2-trifluoro-1-phenylethyl)amino)benzamido)propanoic acid **(86):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **86A.** MS (m/z) 665.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 - 8.77 (m, 2H), 8.61 (dd, J = 8.8, 1.7 Hz, 1H), 8.15 (dd, J = 1.6, 0.4 Hz, 1H), 7.89 (dd, J = 7.9, 1.6 Hz, 1H), 7.66 - 7.48 (m, 7H), 7.46 - 7.32 (m, 3H), 6.53 (d, J = 11.6 Hz, 2H), 5.67 (q, J = 8.7 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 3.71 (s, 1H), 3.37 (s, 1H).

Example 87 (for illustrative purposes)

[0537]



87A

87

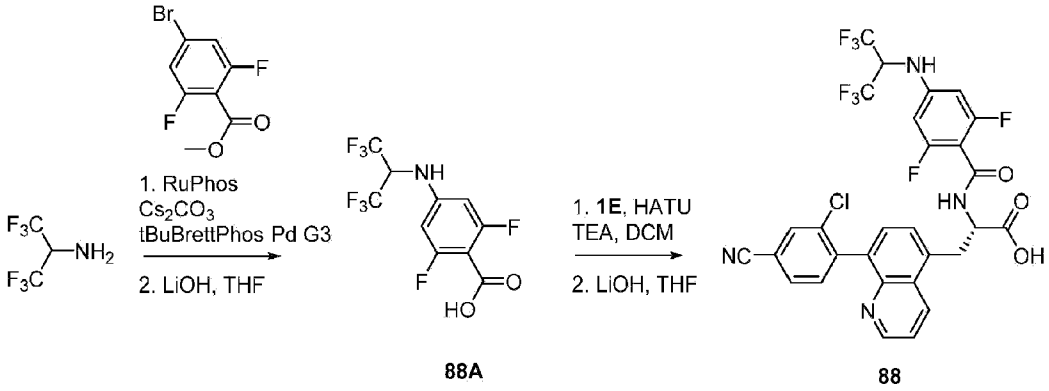
[0538] Synthesis of (R)-2,6-difluoro-4-(methyl(1,1,1-trifluoropropan-2-yl)amino)benzoic acid **(87A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (R)-1,1,1-trifluoro-N-methylpropan-2-amine.

[0539] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-(methyl((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)propanoic acid **(87):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with

87A. MS (m/z) 617.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.92 - 8.81 (m, 2H), 8.65 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.68 - 7.53 (m, 4H), 6.63 (d, J = 12.0 Hz, 2H), 4.93 (p, J = 7.4 Hz, 1H), 4.70 (s, 1H), 3.74 (s, 1H), 3.41 (s, 1H), 2.83 - 2.77 (m, 3H), 1.36 (d, J = 6.8 Hz, 3H).

Example 88 (for illustrative purposes)

[0540]



88A

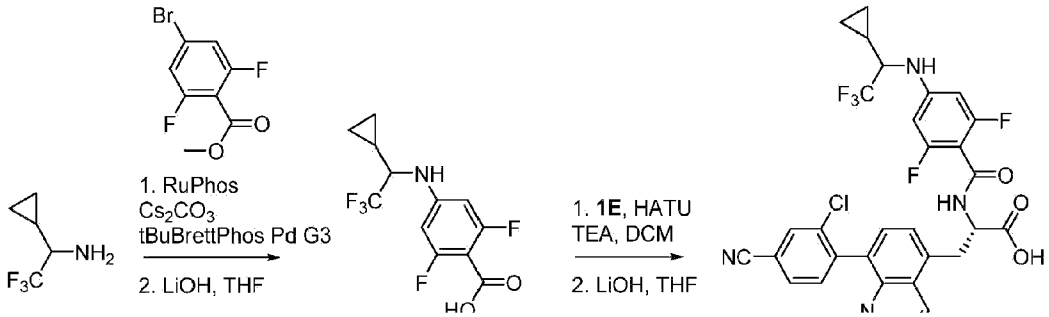
88

[0541] Synthesis of 2,6-difluoro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)amino)benzoic acid (88A): The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with 1,1,1,3,3,3-hexafluoropropan-2-amine.

[0542] (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)amino)benzamido)propanoic acid **(88):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **88A.** MS (m/z) 657.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.93 (d, J = 8.0 Hz, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.66 - 8.59 (m, 1H), 8.15 (d, J = 1.7 Hz, 1H), 7.90 (dd, J = 7.8, 1.6 Hz, 1H), 7.67 - 7.53 (m, 5H), 6.69 (d, J = 11.1 Hz, 2H), 5.93 (s, 1H), 4.70 (s, 1H), 3.62 (s, 1H), 3.40 (s, 1H).

Example 89 (for illustrative purposes)

[0543]





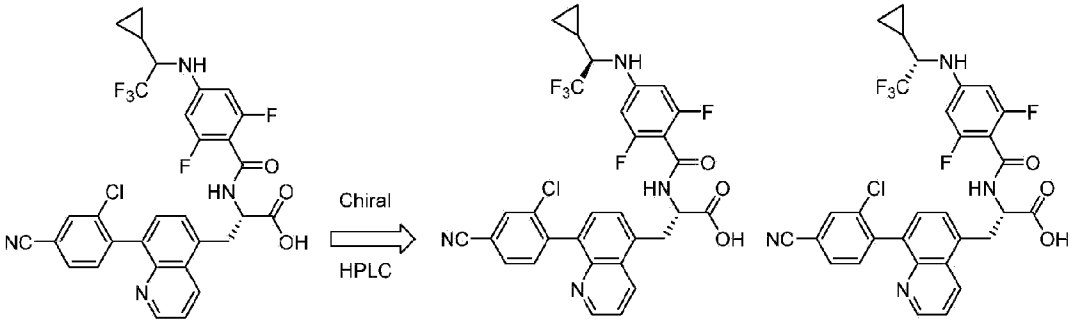
89A 89

[0544] Synthesis of 4-((1-cyclopropyl-2,2,2-trifluoroethyl)amino)-2,6-difluorobenzoic acid **(89A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with 1-cyclopropyl-2,2,2-trifluoroethan-1-amine.

[0545] (2S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(4-((1-cyclopropyl-2,2,2-trifluoro ethyl)amino)-2,6-difluorobenzamido)propanoic acid **(89):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **89A.** MS (m/z) 629.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.86 - 8.75 (m, 2H), 8.63 (dd, J = 8.7, 1.6 Hz, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.67 - 7.53 (m, 4H), 6.93 (d, J = 9.5 Hz, 1H), 6.40 (d, J = 11.8 Hz, 2H), 4.67 (s, 1H), 3.91 (q, J = 8.1 Hz, 1H), 3.72 (s, 1H), 3.40 (s, 1H), 1.08 - 0.96 (m, 1H), 0.60 (dq, J = 8.5, 4.1, 3.3 Hz, 1H), 0.49 (dd, J = 11.1, 5.8 Hz, 2H), 0.34 - 0.23 (m, 1H).

Example 90 (for illustrative purposes)

[0546]

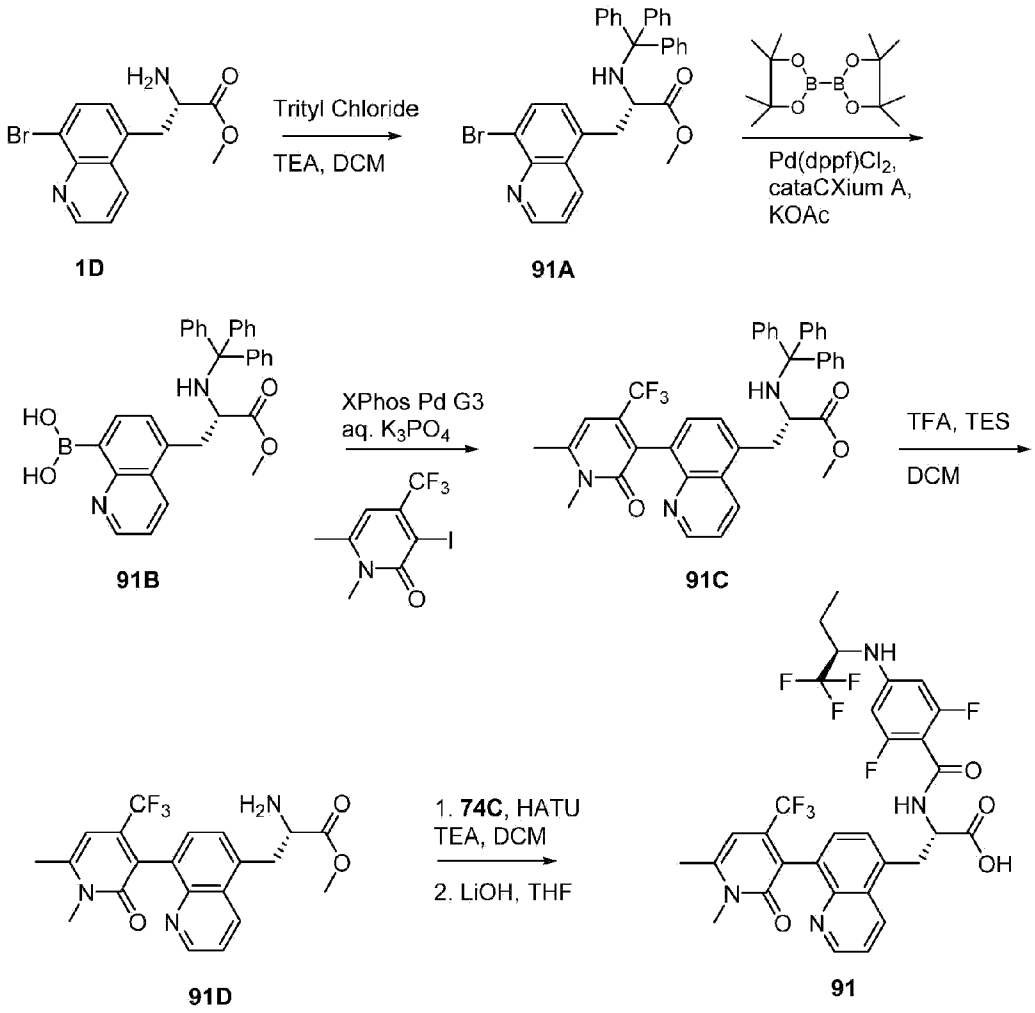


89 90 148

[0547] Preparation of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid (90): 89 was separated into its 2 stereoisomers by supercritical fluid chromatography using 30% EtOH/TFA co-solvent, at a flow rate of 45 mL/min, using an IE 5 µm 21x250 mm column. The title compound was identified as the first eluting peak. MS (m/z) 629.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.86 - 8.75 (m, 2H), 8.66 - 8.59 (m, 1H), 8.15 (dd, J = 1.7, 0.4 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.67 - 7.49 (m, 4H), 6.92 (d, J = 9.5 Hz, 1H), 6.40 (d, J = 11.8 Hz, 2H), 4.67 (s, 1H), 3.91 (d, J = 7.8 Hz, 1H), 3.72 (s, 1H), 3.39 (s, 1H), 1.08 - 1.00 (m, 1H), 0.66 - 0.56 (m, 1H), 0.53 - 0.42 (m, 2H), 0.33 - 0.26 (m, 1H).

Example 91 (for illustrative purposes)

[0548]



[0549] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(tritylamino)propanoate (91A): To a stirred solution of 1D (15 g, 43.4 mmol) in DCM was added TEA (15.12 mL, 108.5 mmol) and trityl chloride (12.7 g, 45.57 mmol). The reaction mixture was stirred for 2 hours then filtered through celite, and washed 3x with EA. The filtrate was concentrated and purified by silica gel chromatography eluting with EA/hexanes to give the title compound.

[0550] Synthesis of (S)-(5-(3-methoxy-3-oxo-2-(tritylamino)propyl)quinolin-8-yl)boronic acid (91B): The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **91A.**

[0551] Synthesis of methyl (S)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro pyridin-3-yl)quinolin-5-yl)-2-(tritylamino)propanoate **(91C):** The title compound was prepared according to the method presented for the synthesis of compound **11A** starting with **91B** and 3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one.

[0552] Synthesis of methyl (S)-2-amino-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-

dihydropyridin-3-yl)quinolin-5-yl)propanoate **(91D):** To a stirred solution of **91C** (0.3 g, 0.46 mmol) in DCM was added triethylsilane (0.064 g, 0.49 mmol) and TFA (0.18 mL, 2.0 mmol). The reaction mixture was allowed to stir at RT for 1 h then concentrated under reduced pressure to give a material that was used without further purification.

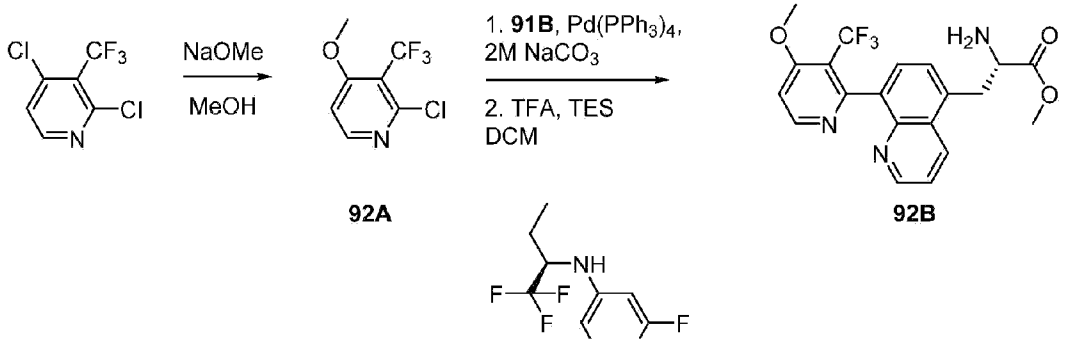
[0553] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(91):** The title compound was prepared according to the method presented for the synthesis of compound **74** starting with **91D.** MS (m/z) 671.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.84 - 8.70 (m, 2H), 8.62 (s, 1H), 7.55 (s, 2H), 7.42 (s, 1H), 6.75 (dd, J = 9.4, 5.5 Hz, 1H), 6.54 (s, 1H), 6.42 (dd, J = 11.4, 4.2 Hz, 2H), 4.66 (s, 1H), 4.29 (s, 1H), 3.66 (d, J = 13.6 Hz, 1H), 3.59 - 3.21 (m, 5H), 2.51 (s, 2H), 1.79 - 1.70 (m, 1H), 1.51 (ddd, J = 13.7, 10.4, 7.1 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

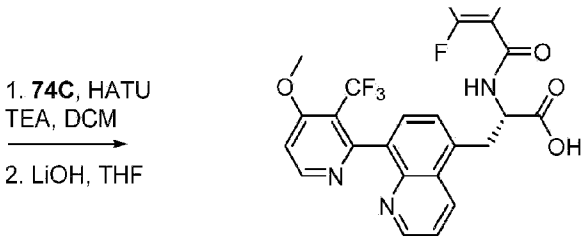
Example 92 (for illustrative purposes)

[0554] Synthesis of 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine (92A): To a stirred solution of 2,4-dichloro-3-(trifluoromethyl)pyridine (157.5 mg, 0.729 mmol) in methanol at 0 °C was added sodium methoxide powder (118.19 mg, 2.188 mmol). The reaction mixture was allowed to warm to RT and was stirred for 16 hours. The solvent was removed under reduced pressure, and the resulting residue was purified by silica gel chromatography using EA in hexanes as eluent to afford the title compound.

[0555] Synthesis of methyl (S)-2-amino-3-(8-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoate **(92B):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with **92A.**

[0556] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(92):** The title compound was prepared according to the method presented for the synthesis of compound **74** starting with 92B. MS (m/z) 657.8 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 8.9 Hz, 2H), 8.73 (d, J = 5.9 Hz, 1H), 8.62 (t, J = 7.9 Hz, 1H), 7.60 (t, J = 6.8 Hz, 3H), 7.44 (d, J = 6.0 Hz, 1H), 6.76 (t, J = 8.2 Hz, 1H), 6.45 (dd, J = 11.7, 7.2 Hz, 2H), 4.68 (d, J = 19.6 Hz, 1H), 4.30 (s, 1H), 4.07 (s, 3H), 3.74 (d, J = 15.1 Hz, 1H), 3.69 - 3.64 (m, 1H), 1.77 (s, 1H), 1.53 (s, 1H), 0.93 (t, J = 7.4 Hz, 3H).

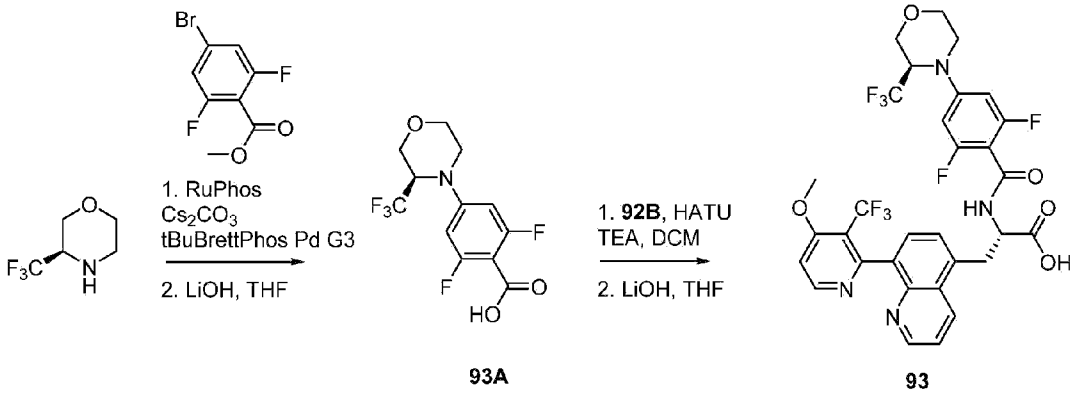




92

Example 93 (for illustrative purposes)

[0557]



93A

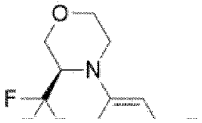
93

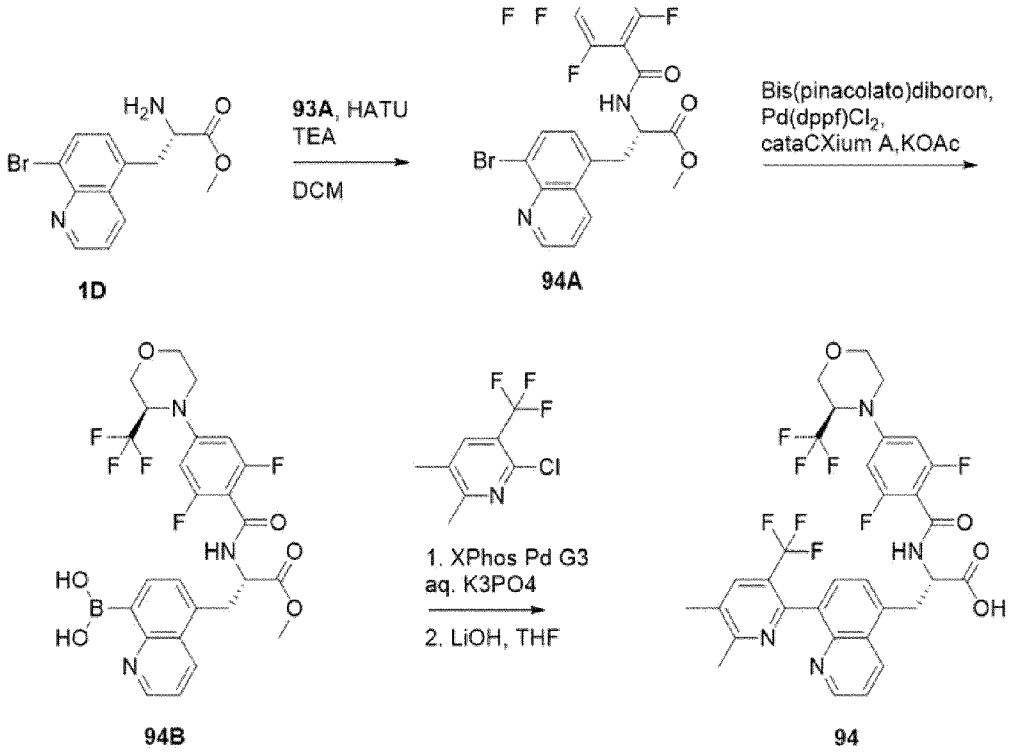
[0558] Synthesis of (R)-2,6-difluoro-4-(3-(trifluoromethyl)morpholino)benzoic acid (93A): The title compound was prepared according to the method presented for the synthesis of compound 75A starting with (R)-3-(trifluoromethyl)morpholine.

[0559] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid (93): The title compound was prepared according to the method presented for the synthesis of compound 16A and 16 starting with **92B** and 93A. MS (m/z) 685.9 [M+H]+. 1H NMR (500 MHz, DMSO-d6) δ 8.95 (dd, J = 11.7, 8.0 Hz, 1H), 8.80 (d, J = 3.7 Hz, 1H), 8.74 (d, J = 6.0 Hz, 1H), 8.63 (t, J = 8.7 Hz, 1H), 7.61 (dd, J = 13.0, 5.4 Hz, 3H), 7.46 (d, J = 6.1 Hz, 1H), 6.76 (t, J = 11.2 Hz, 2H), 4.91 (d, J = 9.3 Hz, 1H), 4.77 -4.64 (m, 1H), 4.19 - 4.13 (m, 1H), 4.08 (s, 3H), 3.95 (d, J = 11.7 Hz, 1H), 3.80 - 3.66 (m, 2H), 3.55 (t, J = 11.8 Hz, 1H), 3.51 - 3.36 (m, 2H), 3.23 (t, J = 12.5 Hz, 1H).

Example 94 (for illustrative purposes)

[0560]





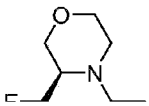
[0561] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoate **(94A):** The title compound was prepared according to the method presented for the synthesis of compound **16A** in Example 16 starting with **93A.**

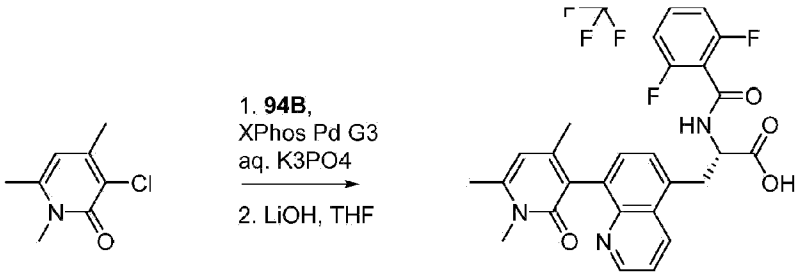
[0562] Synthesis of (5-((S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-methoxy-3-oxopropyl)quinolin-8-yl)boronic acid **(94B):** The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **94A.**

[0563] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(5,6-dimethyl-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(94):** The title compound was prepared according to the method presented for the synthesis of compound 11A and 11 starting with 94B and 2-chloro-5,6-dimethyl-3-(trifluoromethyl)pyridine. MS (m/z) 683.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 8.0 Hz, 1H), 8.77 (dd, J = 4.0, 1.5 Hz, 1H), 8.67 - 8.59 (m, 1H), 8.03 (s, 1H), 7.68 - 7.47 (m, 3H), 6.74 (d, J = 11.7 Hz, 2H), 4.95 - 4.84 (m, 1H), 4.72 - 4.61 (m, 1H), 4.14 (d, J = 12.8 Hz, 1H), 3.98 - 3.86 (m, 1H), 3.72 (d, J = 13.1 Hz, 2H), 3.58 - 3.30 (m, 3H), 3.21 (s, 1H), 2.50 (s, 3H), 2.41 (s, 3H).

Example 95 (for illustrative purposes)

[0564]



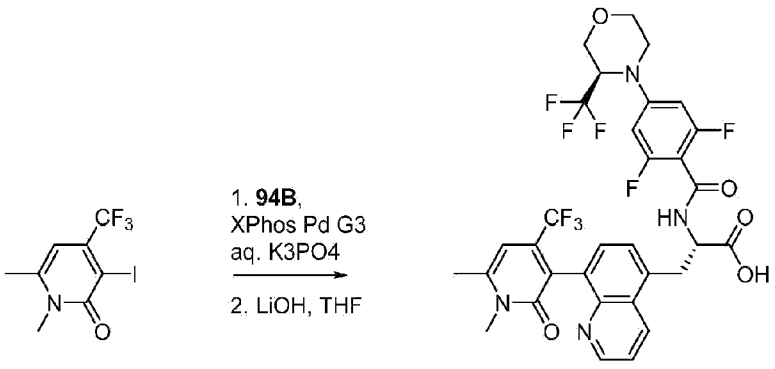


95

[0565] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(95):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **94B** and 3-chloro-1,4,6-trimethylpyridin-2(1H)-one. MS (m/z) 645.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.99 - 8.81 (m, 3H), 7.76 (s, 1H), 7.65 (dd, J = 13.5, 7.3 Hz, 1H), 7.53 (t, J = 8.1 Hz, 1H), 6.72 (dd, J = 11.5, 2.7 Hz, 2H), 6.20 (s, 1H), 4.88 (d, J = 9.4 Hz, 1H), 4.74 -4.69 (m, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.93 (dd, J = 11.5, 3.8 Hz, 1H), 3.79 (s, 1H), 3.70 (t, J = 9.9 Hz, 1H), 3.51 (d, J = 10.7 Hz, 2H), 3.46 - 3.34 (m, 4H), 3.21 (t, J = 12.3 Hz, 1H), 2.40 (s, 3H), 1.73 (d, J = 10.6 Hz, 3H).

Example 96 (for illustrative purposes)

[0566]



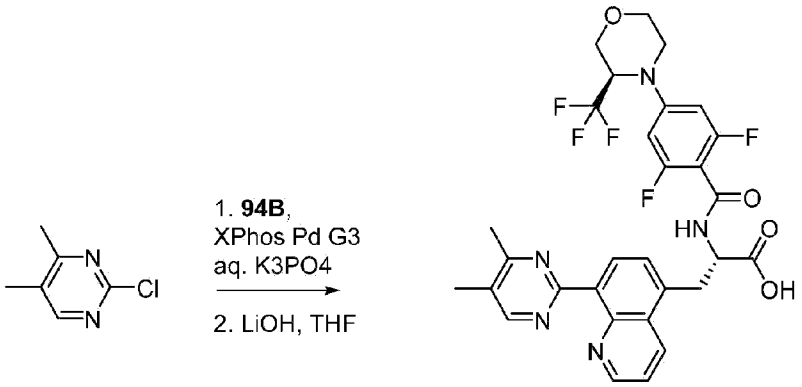
96

[0567] (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)quinolin-5-yl)propanoic acid **(96):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **94B** and 3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one. MS (m/z) 699.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.96 (dd, J = 7.9, 4.2 Hz, 1H), 8.86 - 8.79 (m, 1H), 8.67 (s, 1H), 7.60 (dt, J = 25.1, 8.5 Hz, 2H), 7.48 - 7.39 (m, 1H), 6.74 (dd, J = 11.6, 4.3 Hz, 2H), 6.54 (s, 1H), 4.90 (dd, J = 8.7, 3.6 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.14 (d, J = 12.7 Hz, 1H), 3.93 (dd, J = 11.5, 3.8 Hz, 1H), 3.75 - 3.62 (m, 2H), 3.60 - 3.32 (m, 6H), 3.23 (d,

J = 12.4 Hz, 1H), 2.52 (s, 3H).

Example 97 (for illustrative purposes)

[0568]

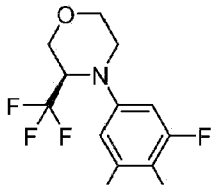


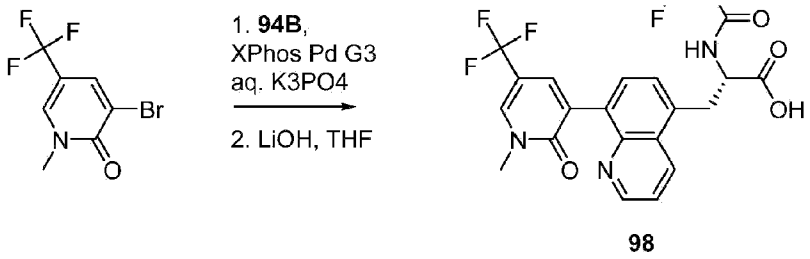
97

[0569] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4,5-dimethylpyrimidin-2-yl)quinolin-5-yl)propanoic acid **(97):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **94B** and 2-chloro-4,5-dimethylpyrimidine. MS (m/z) 617.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.37 (s, 1H), 9.31 (s, 1H), 8.94 (d, J = 8.3 Hz, 1H), 8.78 (s, 2H), 8.11 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 6.77 (dd, J = 37.8, 12.3 Hz, 2H), 4.97 - 4.75 (m, 2H), 4.16 (dd, J = 12.9, 8.0 Hz, 1H), 3.91 (ddd, J = 25.2, 12.9, 4.2 Hz, 2H), 3.72 (d, J = 13.1 Hz, 1H), 3.59-3.53 (m, 2H),3.41-3.36 (m, 1H), 3.22 (dd, J = 14.4, 11.1 Hz, 1H), 2.66 (s, 3H), 2.39 (s, 3H).

Example 98 (for illustrative purposes)

[0570] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid (98): The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **94B** and 3-bromo-1-methyl-5-(trifluoromethyl)pyridin-2(1H)-one. MS (m/z) 685.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 8.96 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 4.2 Hz, 1H), 8.71 (d, J = 8.6 Hz, 1H), 8.50 (s, 1H), 7.73 - 7.64 (m, 3H), 7.61 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 11.8 Hz, 2H), 4.91 (d, J = 9.7 Hz, 1H), 4.68 (s, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.95 (d, J = 11.4 Hz, 1H), 3.73 (d, J = 13.4 Hz, 2H), 3.57 (s, 4H), 3.44 (dd, J = 14.0, 9.3 Hz, 2H), 3.24 (t, J = 12.5 Hz, 1H).

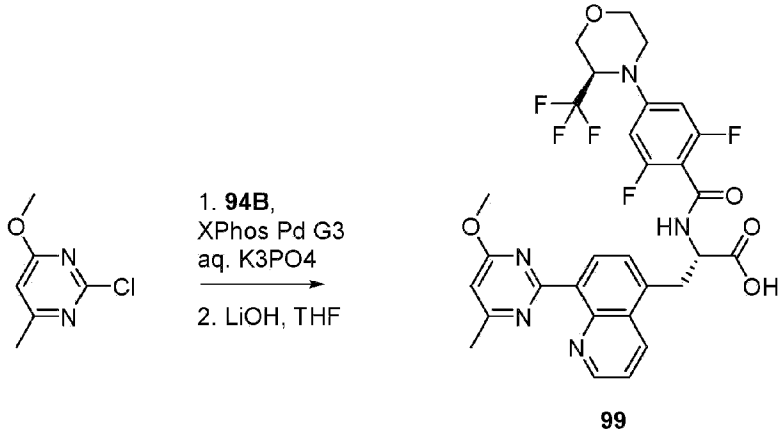




98

Example 99 (for illustrative purposes)

[0571]

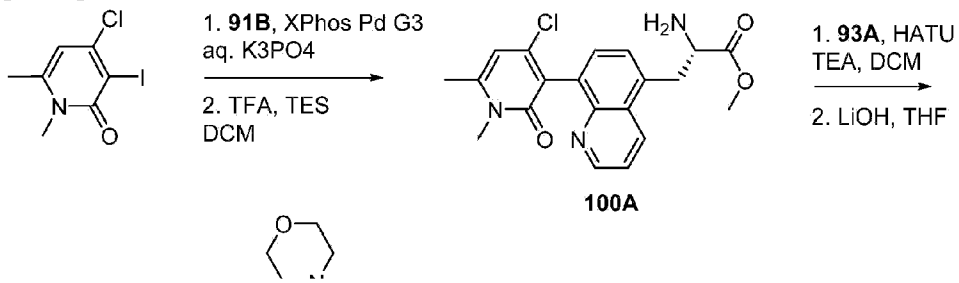


99

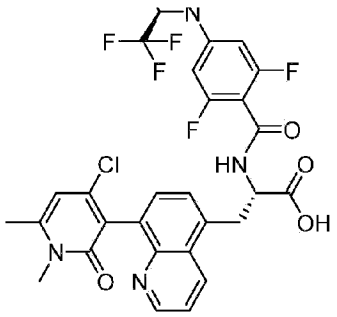
[0572] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-methoxy-6-methylpyrimidin-2-yl)quinolin-5-yl)propanoic acid **(99):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **94B** and 2-chloro-4-methoxy-6-methylpyrimidine. MS (m/z) 632.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.49 (d, J = 4.9 Hz, 1H), 9.39 (d, J = 8.7 Hz, 1H), 9.04 (d, J = 7.5 Hz, 1H), 8.95 (d, J = 8.4 Hz, 1H), 8.18 (dd, J = 8.7, 5.0 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.72 (d, J = 12.2 Hz, 2H), 4.94 - 4.78 (m, 2H), 4.15 (s, 4H), 4.00 - 3.84 (m, 2H), 3.74 (t, J = 16.0 Hz, 1H), 3.65 - 3.46 (m, 2H), 3.39 (d, J = 12.8 Hz, 1H), 3.21 (t, J = 12.5 Hz, 1H), 2.70 (s, 3H).

Example 100 (for illustrative purposes)

[0573]



100A



100

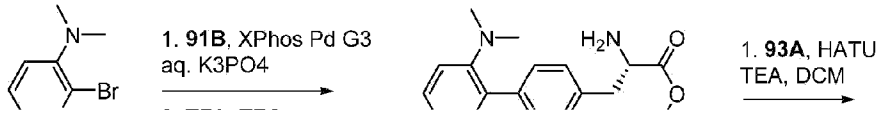
[0574] Synthesis of methyl (S)-2-amino-3-(8-(4-chloro-1,6-dimethyl-2-oxo-1,2-dihydro pyridin-3-yl)quinolin-5-yl)propanoate **(100A):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with 4-chloro-3-iodo-1,6-dimethylpyridin-2(1H)-one.

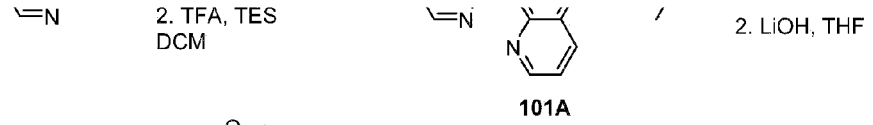
[0575] (S)-3-(8-(4-chloro-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(100):** The title compound was prepared according to the method presented for the synthesis of compound **93** starting with **100A.** MS (m/z) 665.7 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J = 7.9 Hz, 1H), 8.87 (d, J = 4.3 Hz, 1H), 8.73 (s, 1H), 7.67 (d, J = 9.1 Hz, 1H), 7.63 (dd, J = 7.6, 4.2 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 6.76 (dd, J = 11.7, 3.9 Hz, 2H), 6.49 (d, J = 2.8 Hz, 1H), 4.91 (dd, J = 8.9, 3.6 Hz, 1H), 4.70 (dd, J = 12.5, 7.4 Hz, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.97 - 3.93 (m, 2H), 3.73 (dd, J = 12.0, 8.5 Hz, 2H), 3.52 (d, J = 22.8 Hz, 1H), 3.45 (d, J = 1.9 Hz, 3H), 3.41 (d, J = 3.5 Hz, 1H), 3.24 (t, J = 12.4 Hz, 1H), 2.46 (s, 3H).

Example 101 (for illustrative purposes)

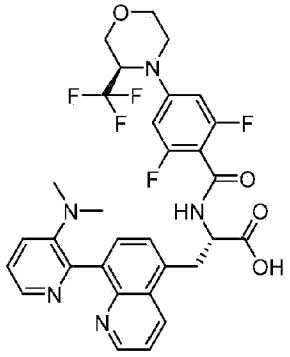
[0576] Synthesis of methyl (S)-2-amino-3-(8-(3-(dimethylamino)pyridin-2-yl)quinolin-5-yl)propanoate **(101A):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with 2-bromo-N,N-dimethylpyridin-3-amine.

[0577] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(3-(dimethylamino)pyridin-2-yl)quinolin-5-yl)propanoic acid **(101):** The title compound was prepared according to the method presented for the synthesis of compound 93 starting with **101A.** MS (m/z) 630.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.04 - 8.92 (m, 2H), 8.77 (dd, J = 8.8, 1.6 Hz, 1H), 8.32 (d, J = 5.3 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.91 (t, J = 7.9 Hz, 2H), 7.81 - 7.71 (m, 2H), 6.74 (d, J = 11.8 Hz, 2H), 4.90 (dd, J = 8.8, 3.5 Hz, 1H), 4.81 - 4.72 (m, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.96 (dd, J = 11.4, 3.7 Hz, 1H), 3.82 (dd, J = 14.2, 4.4 Hz, 1H), 3.73 (d, J = 12.8 Hz, 1H), 3.62 - 3.36 (m, 3H), 3.23 (t, J = 12.1 Hz, 1H), 2.50 (m, 6H).





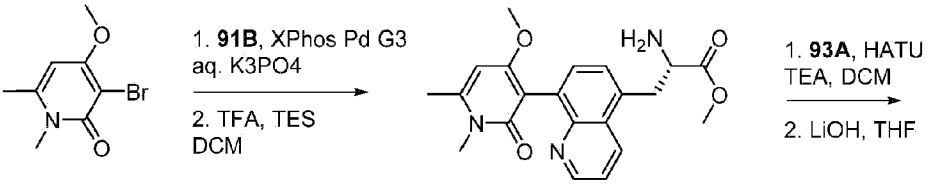
101A



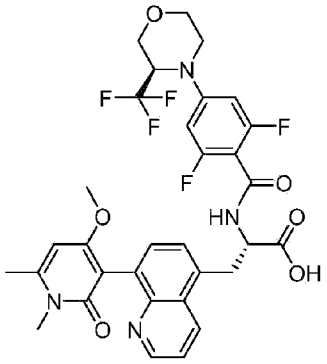
101

Example 102 (for illustrative purposes)

[0578]



102A



102

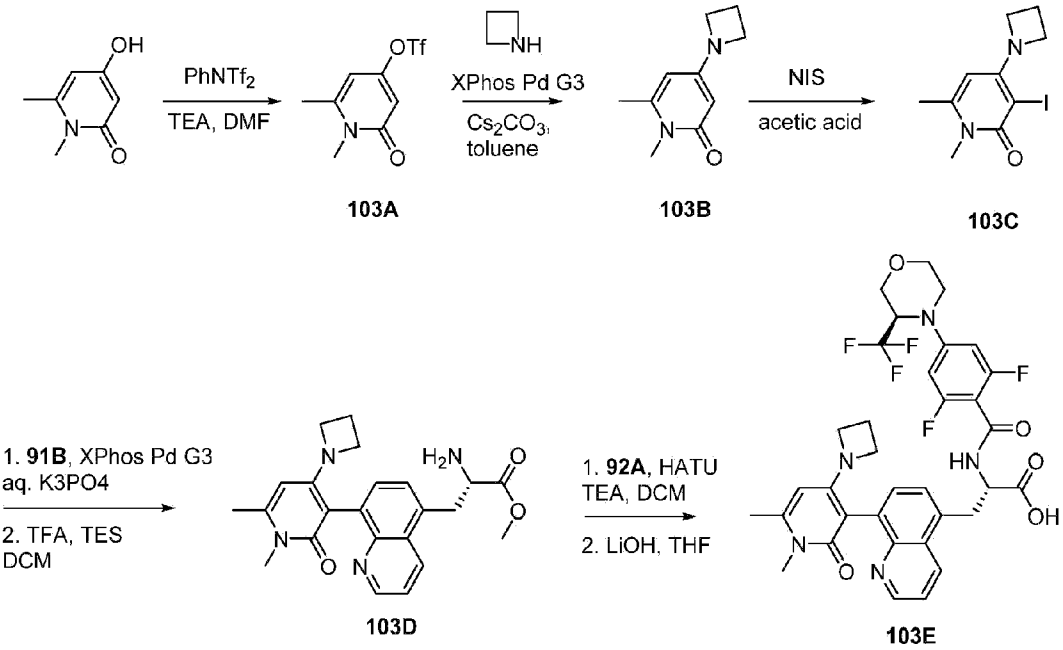
[0579] Synthesis of methyl (S)-2-amino-3-(8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoate **(102A):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with 3-bromo-4-methoxy-1,6-dimethylpyridin-2(1H)-one.

[0580] (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)quinolin-5-yl)propanoic acid **(102):** The title compound was prepared according to the method presented for the synthesis of compound 93 starting with **102A.** MS (m/z) 661.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H),

9.09 (s, 1H), 9.04 - 8.93 (m, 2H), 7.91 (s, 1H), 7.71 (d, J = 14.6 Hz, 2H), 6.76 (d, J = 11.8 Hz, 2H), 6.46 (s, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 4.16 (d, J = 12.7 Hz, 1H), 4.00-3.91 (m, 1H), 3.70 (m, 5H), 3.61 - 3.37 (m, 6H), 3.23 (t, J = 12.3 Hz, 1H).

Example 103 (for illustrative purposes)

[0581]



[0582] Synthesis of 1,6-dimethyl-2-oxo-1,2-dihydropyridin-4-yl 4-methylbenzenesulfonate (103A): To a stirred suspension of 4-hydroxy-1,6-dimethylpyridin-2(1H)-one (1.5 g, 10.8 mmol) in TEA (1.8 mL, 12.9 mmol) in DMF (27 mL) was added N-Ph triflimide (3.85 g, 10.8 mmol). The reaction mixture was stirred for 15 min during which the suspended solids went into solution. The solution was concentrated under reduced pressure and purified by silica gel chromatography using EA in hexanes to afford the title compound.

[0583] Synthesis of 4-(azetidin-1-yl)-1,6-dimethylpyridin-2(1H)-one (103B): To a pressure tube was added **103A** (450 mg, 1.66 mmol), azetidine (0.11 mL, 1.66 mmol), XPhos Pd G3 (140 mg, 0.17 mmol), and Cs_2CO_3 (1.08 g, 3.3 mmol) in toluene (5.5 mL). After sparging with N_2, the mixture was heated at 90 °C and allowed to stir vigorously for 90 min. The reaction mixture was cooled and filtered through a pad of Celite rinsing with EA. The solution was concentrated under reduced pressure and purified by silica gel chromatography using MeOH in DCM to afford the title compound.

[0584] Synthesis of 4-(azetidin-1-yl)-3-iodo-1,6-dimethylpyridin-2(1H)-one (103C): To a stirred solution of **103B** (90 mg, 0.5 mmol) in acetic acid (0.5 mL) was added N-iodosuccinimide (125 mg, 0.56 mmol). After 10 min concentrated and added a 1:1 mixture of aq sat $NaHCO_3$ and aq

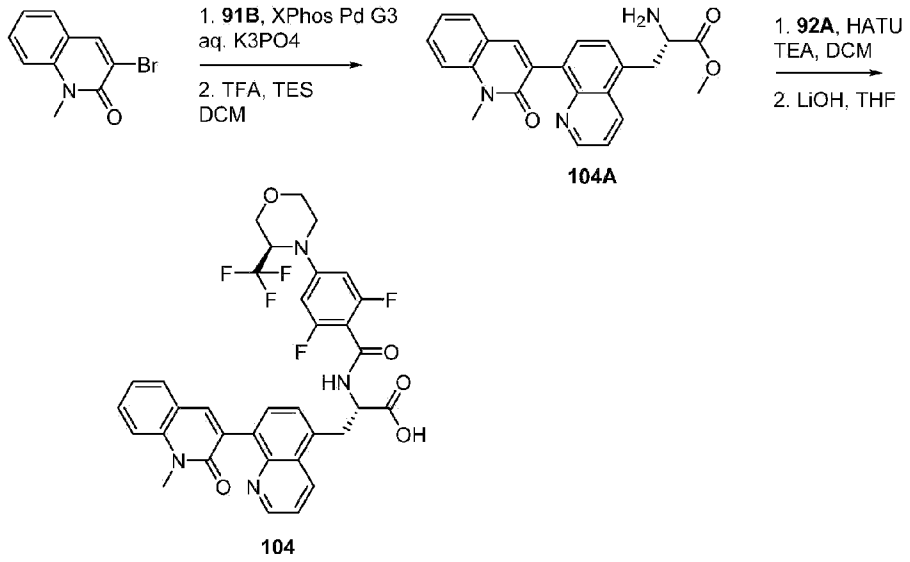
sat $Na_2S_2O_3$. The aqueous layer was extracted with EA. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The material was purified by silica gel chromatography using EA in hexanes to afford the title compound.

[0585] Synthesis of methyl (S)-2-amino-3-(8-(4-(azetidin-1-yl)-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoate **(103D):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with **103C.**

[0586] (S)-3-(8-(4-(azetidin-1-yl)-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(103E):** The title compound was prepared according to the method presented for the synthesis of compound **93** starting with **103D.** MS (m/z) 686.4 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.20 (s, 1H), 9.05 (d, J = 4.9 Hz, 1H), 8.91 (dd, J = 8.3, 3.5 Hz, 1H), 7.98 (d, J = 27.1 Hz, 1H), 7.84 - 7.55 (m, 2H), 6.73 (dd, J = 17.5, 11.8 Hz, 2H), 5.74 (d, J = 2.8 Hz, 1H), 4.90 (s, 1H), 4.82 - 4.70 (m, 1H), 4.16 (dd, J = 12.6, 4.0 Hz, 1H), 4.01 -3.88 (m, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.68 - 3.48 (m, 2H), 3.35 (d, J = 5.2 Hz, 4H), 3.21 (s, 3H), 2.42 - 2.36 (m, 3H), 1.83 (dt, J = 27.5, 7.6 Hz, 1H).

Example 104 (for illustrative purposes)

[0587]



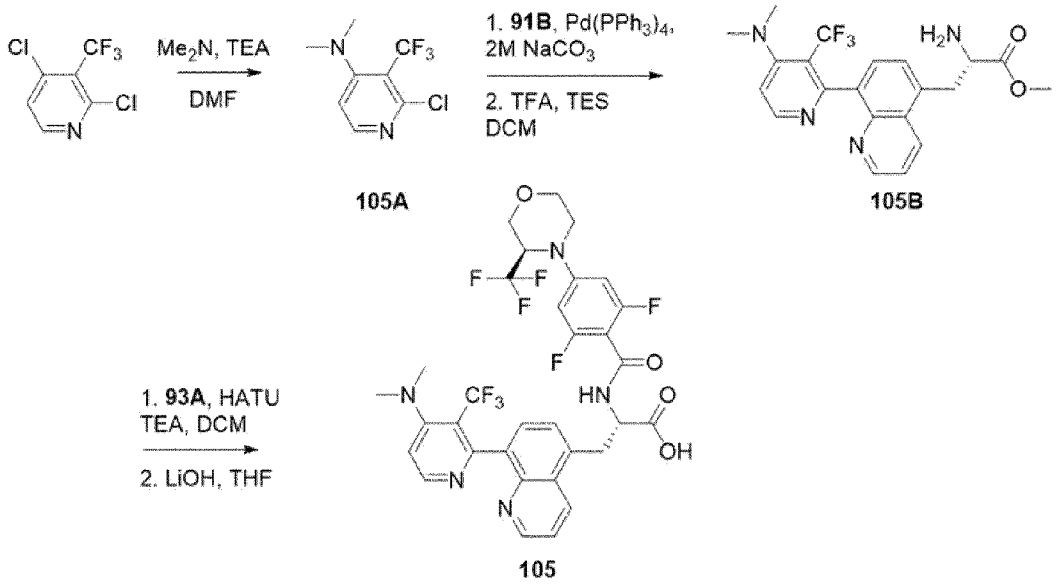
[0588] Synthesis of methyl (S)-2-amino-3-(1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoate (104A): The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with 3-bromo-1-methylquinolin-2(1H)-one.

[0589] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(1-methyl-2-oxo-

1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid (104): The title compound was prepared according to the method presented for the synthesis of compound 93 starting with **104A.** MS (m/z) 667.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.99 (1H, d, J = 8.0 Hz), 8.90 (1H, d, J = 4.2 Hz), 8.79 (1H, m), 7.99 (1H, s), 7.82 - 7.58 (6H, m), 7.32 (1H, t, J = 7.4 Hz), 6.78 (2H, d, J = 11.8 Hz), 4.95 - 4.88 (1H, m), 4.76 - 4.66 (1H, m), 4.16 (1H, d, J = 12.7 Hz), 3.96 (2H, dd, J = 11.4, 3.9 Hz), 3.70 (4H, m), 3.50 (3H, ddd, J = 44.1, 17.5, 11.8 Hz), 3.24 (1H, t, J = 12.6 Hz).

Example 105 (for illustrative purposes)

[0590]



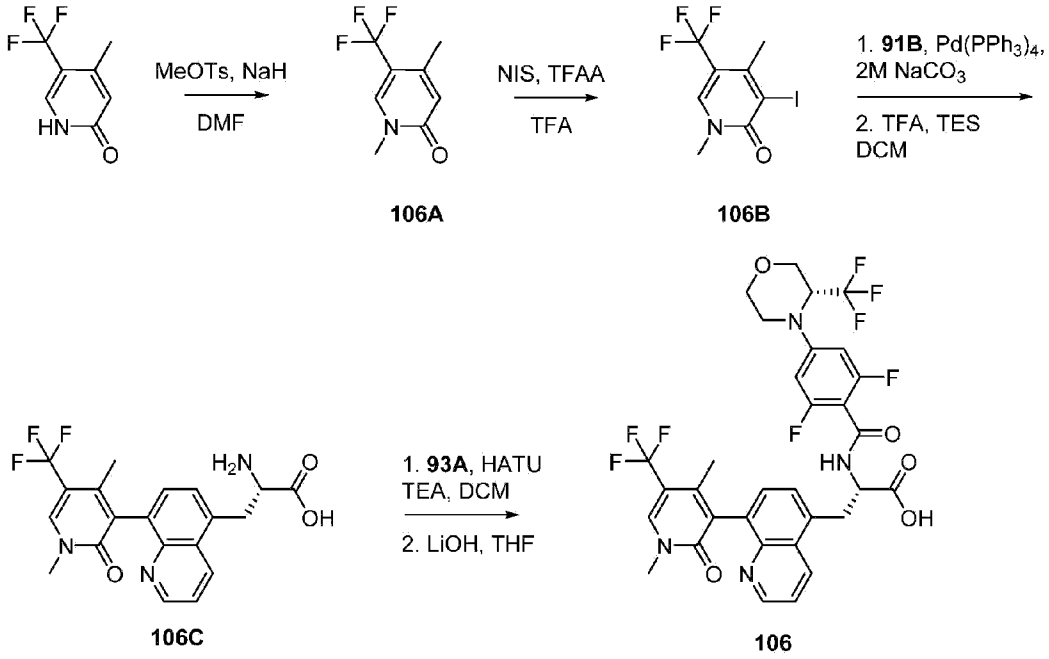
[0591] Synthesis of 2-chloro-N,N-dimethyl-3-(trifluoromethyl)pyridin-4-amine (105A): The title compound was prepared according to the method presented for the synthesis of compound 92A in Example 92 starting with dimethyl amine.

[0592] Synthesis of methyl (S)-2-amino-3-(8-(4-(dimethylamino)-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoate **(105B):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with **105A.**

[0593] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(4-(dimethylamino)-3-(trifluoromethyl)pyridin-2-yl)quinolin-5-yl)propanoic acid **(105):** The title compound was prepared according to the method presented for the synthesis of compound **93** starting with **105B.** MS (m/z) 698.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 13.08 (s, 1H), 9.00 (dd, J = 30.1, 6.7 Hz, 2H), 8.74 (s, 1H), 8.38 (d, J = 7.5 Hz, 1H), 7.96 (s, 1H), 7.72 (d, J = 21.3 Hz, 2H), 7.43 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 11.7 Hz, 2H), 4.91 (s, 1H), 4.74 (s, 1H), 4.16 (d, J = 12.7 Hz, 1H), 3.96 (dd, J = 11.4, 3.8 Hz, 1H), 3.85 (d, J = 14.5 Hz, 1H), 3.74 (d, J = 13.0 Hz, 2H), 3.55 (t, J = 12.1 Hz, 1H), 3.41 (d, J = 12.5 Hz, 1H), 3.31 (s, 6H), 3.23 (s, 1H).

Example 106 (for illustrative purposes)

[0594]



[0595] Synthesis of 1,4-dimethyl-5-(trifluoromethyl)pyridin-2(1H)-one **(106A):** To a stirred solution of 4-methyl-5-(trifluoromethyl)pyridin-2(1H)-one (100 mg, 0.056 mmol) in DMF was added NaH (25 mg, 0.62 mmol) and the reaction mixture was allowed to stir for 30 min at which time the bubbling ceased. The reaction mixture was cooled to 0°C and methyl p-toluene sulfonate (116 mg, 0.062 mmol) was added dropwise. After 4 hrs the reaction mixture was allowed to warm to RT, concentrated under reduced pressure, and purified on silica gel chromatography eluting with Hex/EA 0-100% to afford the title compound.

[0596] Synthesis of 3-iodo-1,4-dimethyl-5-(trifluoromethyl)pyridin-2(1H)-one **(106B):** To a stirred solution of **106A** (0.72 g, 4 mmol) neat TFA was added TFAA (1.6 g, 8 mmol). The reaction mixture was heated to 100°C for 5 min in a sealed vial, followed by the addition of NIS (1.08 g, 5 mmol) and further heating at 60°C for 3 hrs. The reaction mixture was cooled and the TFA removed under reduced pressure. The residue was dissolved in EA and washed with sat. sodium bicarbonate then brine. The organic layer was filtered then concentrated to give the title compound without further purification.

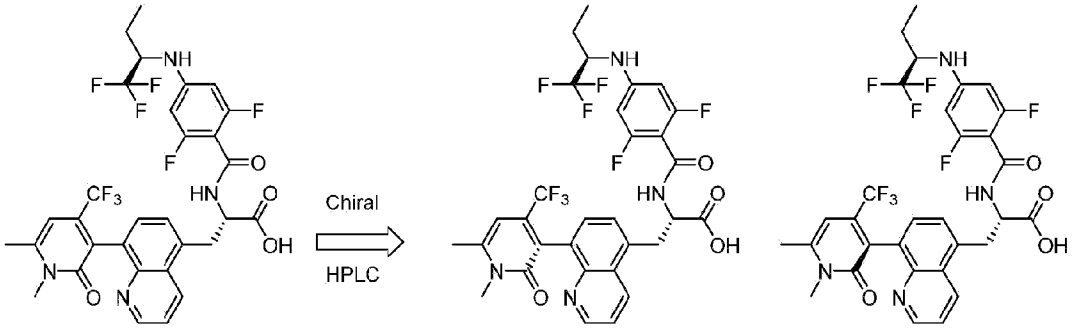
[0597] Synthesis of (S)-2-amino-3-(8-(1,4-dimethyl-2-oxo-5-(trifluoromethyl)-1,2-dihydro pyridin-3-yl)quinolin-5-yl)propanoic acid **(106C):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with **106B.**

[0598] (S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,4-dimethyl-2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(106):** The title

compound was prepared according to the method presented for the synthesis of compound **93** starting **with** 106C. MS (m/z) 699.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 12.94 (s, **1H),** 8.94 (t, J = 7.2 Hz, 1H), 8.86 (t, J = 3.0 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.39 (s, 1H), 7.74 - 7.58 (m, 2H), 7.53 (dd, J = 11.4, 7.3 Hz, 1H), 6.74 (d, J = 12.3 Hz, 2H), 4.90 (d, J = 9.0 Hz, 1H), 4.74 (dd, J = 9.1, 5.0 Hz, 1H), 4.16 (d, J = 12.7 Hz, 1H), 4.00 - 3.90 (m, 1H), 3.86 - 3.64 (m, 2H), 3.56 (d, J = 13.1 Hz, 1H), 3.51 (d, J = 1.7 Hz, 3H), 3.46 - 3.31 (m, 2H), 3.23 (t, J = 12.4 Hz, 1H), 1.83 (d, J = 10.2 Hz, 3H).

Example 107 (for illustrative purposes)

[0599]



91 107 147

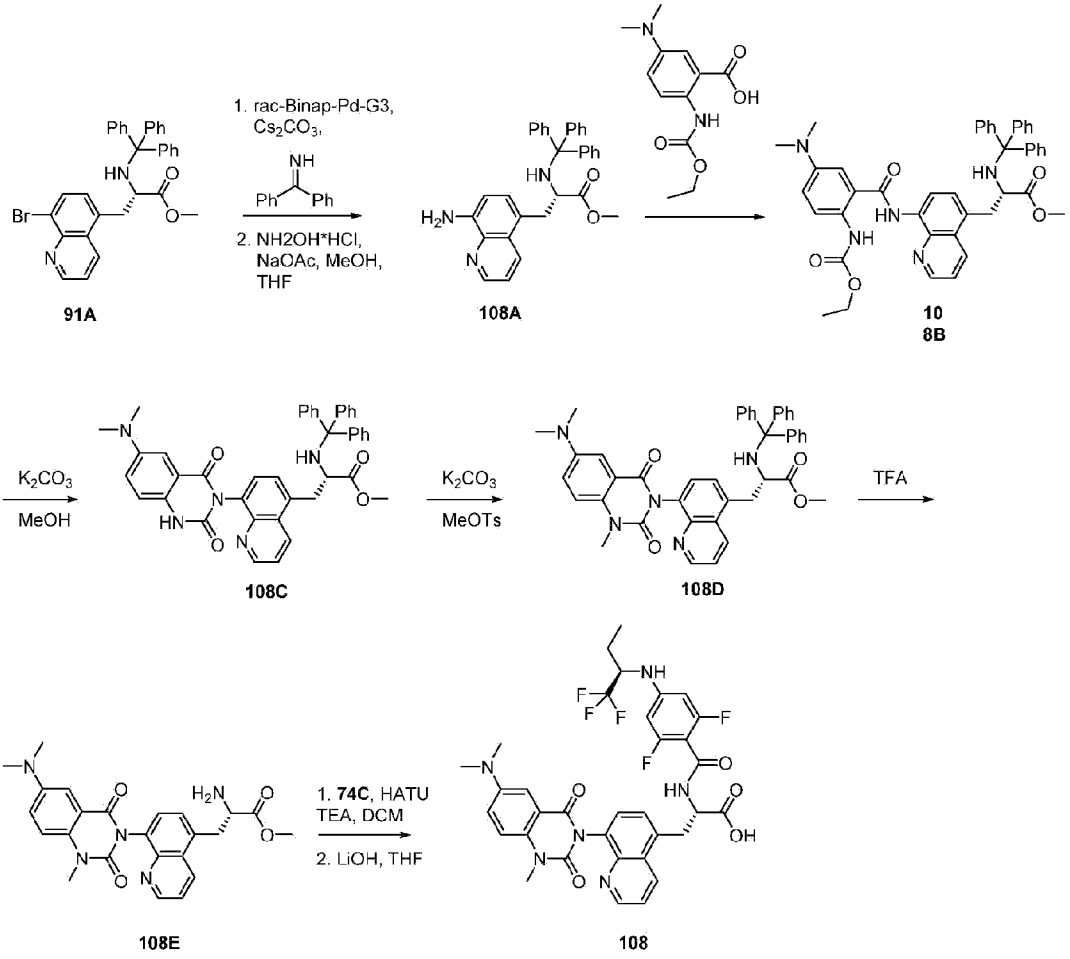
[0600] Preparation of (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido) -3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid (107): 91 was separated into its 2 atropisomeric enantiomers by supercritical fluid chromatography using 30% MeOH co-solvent, at a flow rate of 60 mL/min, using an IC 5 µm 21x250 mm column. The title compound was identified as the first eluting peak. MS (m/z) 671.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.85 - 8.72 (m, 2H), 8.63 (d, J = 8.1 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 9.2 Hz, 1H), 6.54 (s, 1H), 6.42 (d, J = 11.8 Hz, 2H), 4.66 (s, 1H), 4.29 (s, 1H), 3.75 - 3.66 (m, 1H), 3.41 (m, 7H), 1.75 (s, 1H), 1.58 - 1.46 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 108 (for illustrative purposes)

[0601] Synthesis of methyl (S)-3-(8-aminoquinolin-5-yl)-2-(tritylamino)propanoate (108A). To a stirred solution of (91A) (1.148 g, 2.08 mmol) in dioxane (5 mL) was added cesium carbonate (2.04 g, 6 mmol), benzophenone imine, (755 mg, 4.16 mmol), rac-Binap-Pd-G3 (103 mg, 0.1 mmol). The mixture was heated at 90 °C overnight, cooled to RT diluted with THF and added hydroxylamine hydrochloride (289 mg, 4.1 mmol) and sodium acetate (850 mg, 6 mmol) and methanol (1 mL) and let stir for 4 h. The mixture was diluted with ethyl acetate and washed with water. The organic extracts were dried over magnesium sulfate and chromatographed on

silica gel eluting with hexanes and ethyl acetate to afford the title compound.

[0602] Synthesis of methyl (S)-3-(8-(5-(dimethylamino)-2-((ethoxycarbonyl)amino) benzamido)quinolin-5-yl)-2-(tritylamino)propanoate (108B). A stirred solution of 2-amino-5-(dimethylamino)benzoic acid (299 mg, 1.6 mmol) and acetonitrile (3 mL) was cooled to 0° C and added pyridine (672 uL, 8.3 mmol), and ethyl chloroformate (0.635 mL, 6.645 mmol). The mixture was removed from an ice bath and let warm to RT over 30 minutes. Ethanol was then added and the mixture stirred a further 1h. This entire mixture was then added to **108A** (675 mg, 1.38 mmol) dissolved in DMF (4mL) and left to stir for 4h. Solvents were removed on a rotary evaporator and the product mixture was slurried with DCM and added to silica gel which was eluted with hexanes and ethyl acetate to provide the afford the title compound.



[0603] Synthesis of methyl (S)-3-(8-(6-(dimethylamino)-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)quinolin-5-yl)-2-(tritylamino)propanoate (108C). To a stirred solution of 108B (100 mg, 0.14 mmol) in DMF (2 mL) was added potassium carbonate (96 mg, 0.695mmol) and methanol (1mL). The mixture was stirred overnight and then the adsorbed directly onto silica gel and chromatographed eluting with hexanes and ethyl acetate to afford the title compound.

[0604] Synthesis of methyl (S)-3-(8-(6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydro quinazolin-3(2H)-yl)quinolin-5-yl)-2-(tritylamino)propanoate **(108D):** To a stirred solution of

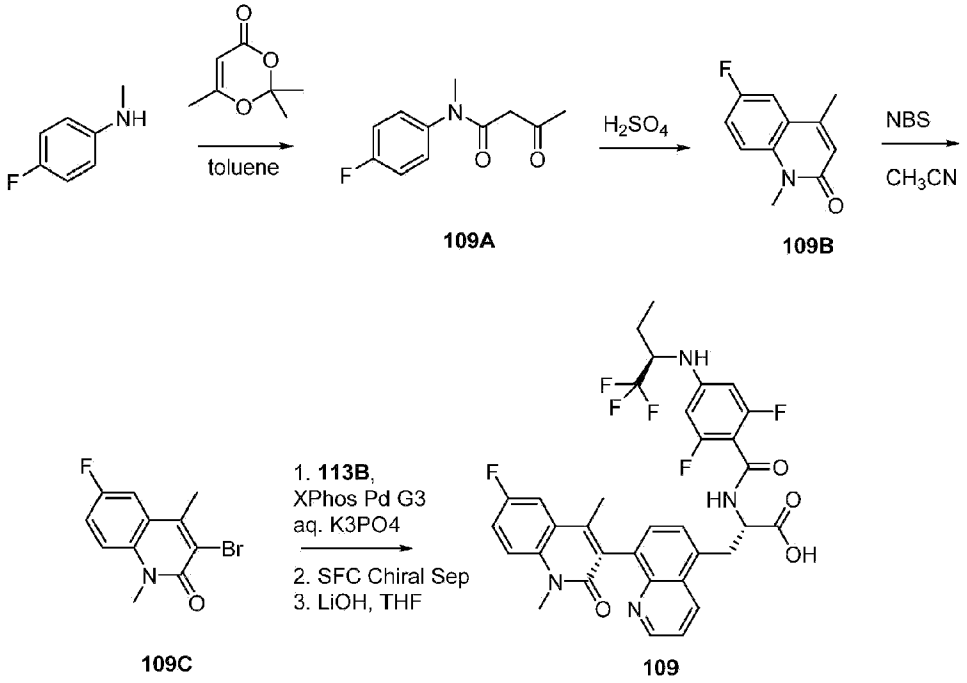
108C (250 mg, 0.37 mol) in DMF (1 mL) was added potassium carbonate (51 mg, 0.37 mmol) and methyl tosylate (103 mg, 0.55 mmol). The reaction mixture was stirred overnight and concentrated under reduced pressure to afford material that was chromatographed on silica gel column eluting with EA in hexane to afford the title compound.

[0605] Synthesis of methyl (S)-2-amino-3-(8-(6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)quinolin-5-yl)propanoate **(108E). 108D** was dissolved in DCM (1 mL) and added TFA (1 mL) and let stir for 4h. The mixture was concentrated and used without further purification.

[0606] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)quinolin-5-yl)propanoic acid (108): The title compound was prepared according to the method presented for the synthesis of compound **74** starting with **108E.** MS (m/z) 699.8 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.00 - 8.79 (m, 2H), 8.64 (d, J = 8.4 Hz, 1H), 7.78 - 7.55 (m, 3H), 7.44 (d, J = 9.1 Hz, 1H), 7.37 (dd, J = 9.5, 2.9 Hz, 1H), 7.25 (s, 1H), 6.78 (d, J = 9.4 Hz, 1H), 6.45 (d, J = 11.7 Hz, 3H), 5.74 (s, 1H), 4.66 (s, 1H), 3.51 (d, J = 1.7 Hz, 3H), 3.49 - 3.30 (m, 1H), 2.94 (s, 6H).

Example 109 (for illustrative purposes)

[0607]



[0608] Synthesis of *N*-(4-fluorophenyl)-*N*-methyl-3-oxobutanamide (109A): To a solution of 4-fluoro-N-methylaniline (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-4*H*-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).

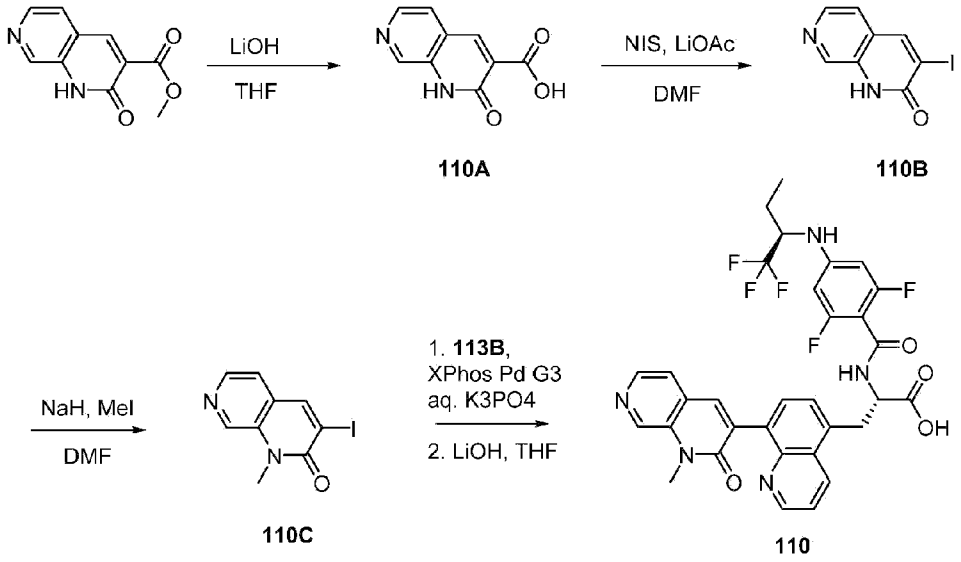
[0609] Synthesis of 6-fluoro-1,4-dimethylquinolin-2(1H)-one **(109B):** A mixture of **109A** (0.250 g, 1.20 mmol) and concentrated H_2SO_4 (5.53 g, 56.4 mmol) was heated at 95 °C for 2 h. Upon completion, the reaction mixture was poured over ice. The precipitate was filtered off to afford the product that was used without further purification.

[0610] Synthesis of 6-fluoro-1,4-dimethylquinolin-2(1H)-one **(109C):** To a microwave vial was added **109B** (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.

[0611] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(6-fluoro-1,4-dimethyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid (109): The title compound was prepared according to the method presented for the synthesis of compound 113 starting with **109C.** MS (m/z) 671.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.82 (dd, J = 9.8, 6.2 Hz, 3H), 7.80 - 7.49 (m, 6H), 6.76 (d, J = 9.4 Hz, 1H), 6.49 - 6.38 (m, 2H), 4.72 (ddd, J = 10.6, 8.3, 4.2 Hz, 1H), 4.29 (d, J = 8.5 Hz, 2H), 3.81 (d, J = 4.1 Hz, 3H), 3.65 (d, J = 2.6 Hz, 1H), 3.35 (dd, J = 14.3, 10.5 Hz, 1H), 2.06 (d, J = 9.3 Hz, 3H), 1.75 (ddd, J = 13.8, 7.4, 3.3 Hz, 1H), 1.51 (ddd, J = 13.7, 10.4, 7.0 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 110 (for illustrative purposes)

[0612]



[0613] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(110A):** To a suspension of methyl 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylate (0.109 g, 0.534

mmol) in THF/H_2O (1:1/0.76 mL) was added LiOH (64.0 mg, 2.67 mmol), and the mixture was heated at 65 °C for 3 h. The precipitate was filtered off to afford the title compound and used without further purification.

[0614] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(110B):** To a microwave vial was added **110A** (0.200 g, 1.05 mmol), NIS (0.828 g, 3.68 mmol), LiOAc (0.104 g, 1.58 mmol) and a mixture of DMF/water (9:1, 12 mL). The reaction mixture was then stirred under microwave heating at 120 °C for 1 h. The solvent was removed under reduced pressure and the material was used without further purification.

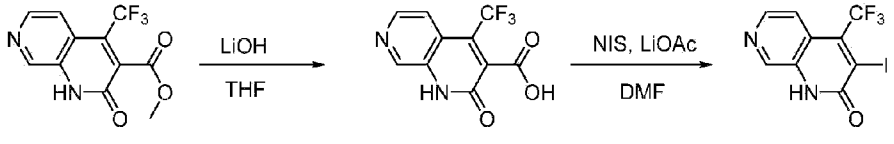
[0615] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(110C):** To a solution of **110B** (0.275 g, 1.01 mmol) in DMF (5 mL) at 0 °C was added NaH (32.0 mg, 1.00 mmol). The mixture was stirred for 5 min at 0 °C, followed by the addition of iodomethane (0.187 g, 1.31 mmol). The cold bath was removed, and the mixture was stirred for 45 min at RT. Upon completion, the solvent was removed under reduced pressure and the material was purified by flash chromatography using MeOH in DCM (0-25%) to afford the title compound.

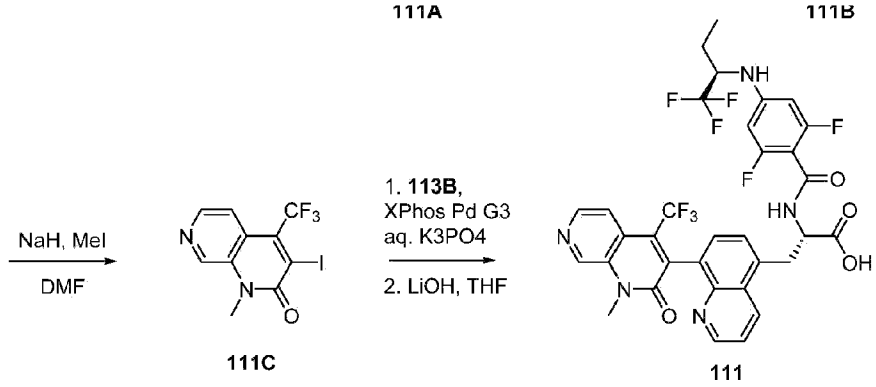
[0616] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-3-yl)quinolin-5-yl)propanoic acid **(110):** The title compound was prepared according to the method presented for the synthesis of compound **113** starting with **110C.** MS (m/z) 640.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.87 - 8.79 (m, 2H), 8.65 (s, 1H), 8.49 (d, J = 5.1 Hz, 1H), 8.01 (s, 1H), 7.77 - 7.68 (m, 2H), 7.65 - 7.57 (m, 2H), 6.78 (d, J = 9.4 Hz, 1H), 6.50 - 6.42 (m, 2H), 4.72 - 4.64 (m, 1H), 4.36 - 4.25 (m, 1H), 3.77 (s, 5H), 3.75 - 3.69 (m, 8H), 3.43 (dd, J = 13.8, 9.4 Hz, 3H), 1.83 - 1.73 (m, 1H), 1.60 - 1.47 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H).

Example 111 (for illustrative purposes)

[0617] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(111A):** To a suspension of methyl 2-oxo-4-(trifluoromethyl)-1,2-dihydro-1,7-naphthyridine-3-carboxylate (0.109 g, 0.534 mmol) in THF/H_2O (1:1/0.76 mL) was added LiOH (64.0 mg, 2.67 mmol), and the mixture was heated at 65 °C for 3 h. The precipitate was filtered off to afford the title compound and used without further purification.

[0618] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(111B):** To a microwave vial was added **111A** (0.200 g, 1.05 mmol), NIS (0.828 g, 3.68 mmol), LiOAc (0.104 g, 1.58 mmol) and a mixture of DMF/water (9:1, 12 mL). The reaction mixture was then stirred under microwave heating at 120 °C for 1 h. The solvent was removed under reduced pressure and the material was used without further purification.



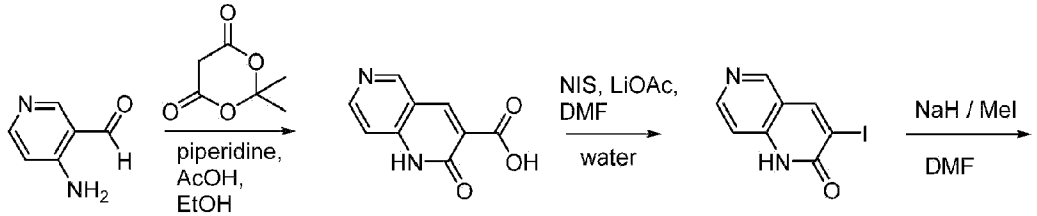


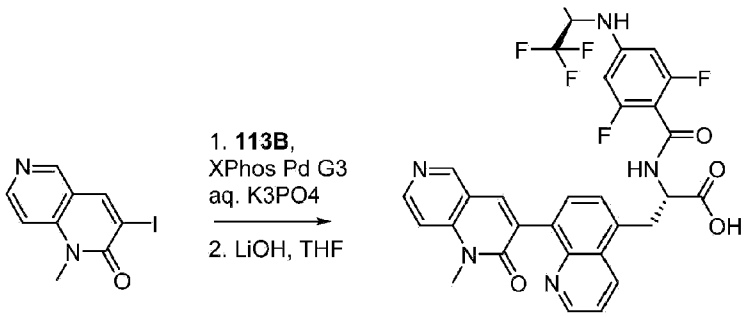
[0619] Synthesis of 2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylic acid **(111C):** To a solution of **111B** (0.275 g, 1.01 mmol) in DMF (5 mL) at 0 °C was added NaH (32.0 mg, 1.00 mmol). The mixture was stirred for 5 min at 0 °C, followed by the addition of iodomethane (0.187 g, 1.31 mmol). The cold bath was removed, and the mixture was stirred for 45 min at RT. Upon completion, the solvent was removed under reduced pressure and the material was purified by flash chromatography using MeOH in DCM (0-25%) to afford the title compound.

[0620] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro-1,7-naphthyridin-3-yl)quinolin-5-yl)propanoic acid **(111):** The title compound was prepared according to the method presented for the synthesis of compound **113** starting with **111C.** MS (m/z) 708.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.15 (d, J = 2.2 Hz, 1H), 8.86 - 8.75 (m, 2H), 8.61 (t, J = 8.8 Hz, 2H), 7.76 (d, J = 5.2 Hz, 1H), 7.60 (ddd, J = 18.7, 8.8, 5.3 Hz, 3H), 7.24 (dd, J = 36.0, 7.8 Hz, 1H), 6.76 (t, J = 7.4 Hz, 1H), 6.57 - 6.36 (m, 2H), 4.70 (s, 1H), 4.32 (s, 1H), 3.79 (s, 3H), 3.77 - 3.61 (m, 1H), 2.89 (d, J = 2.2 Hz, 1H), 2.81 -2.65 (m, 1H), 1.77 (dd, J = 14.3, 7.2 Hz, 1H), 1.61 - 1.44 (m, 1H), 1.24 (s, 1H), 0.93 (t, J = 7.4 Hz, 3H).

Example 112 (for illustrative purposes)

[0621] Synthesis of 2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylic acid **(112A):** To a stirred solution of 4-aminonicotinaldehyde (0.15 g, 1.2 mmol) in EtOH (2 mL) was added Meldrum's acid (0.17 g, 1.2 mmol), piperidine (10 µL, 0.13 mmol), and acetic acid (20 µL, 0.36 mmol).The reaction mixture was stirred at RT for 20 min and then heated at 100 °C for 2 h. After cooling to RT, the product was filtered, washed with EtOH, and dried in vacuo to give the title compound.





112C 112

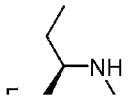
[0622] Synthesis of 3-iodo-1,6-naphthyridin-2(1H)-one **(112B):** In a microwave vial (10 mL) that contained a solution of compound **112A** (80 mg, 0.42 mmol) in a mixture of DMF/water (9:1, 5 mL) were added NIS (331 mg, 1.47 mmol) and LiOAc (42 mg, 0.63 mmol). The vial was sealed and then heated under microwave heating at 120 °C for 30 min. After cooling, water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound which was used without further purification.

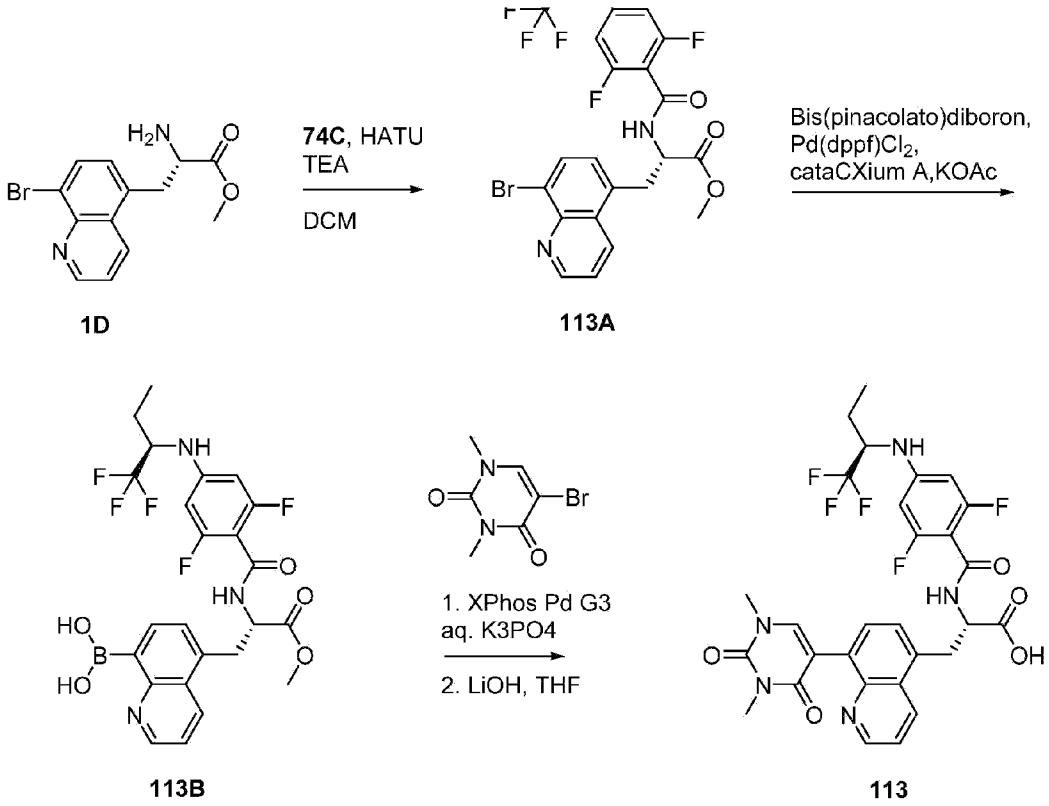
[0623] Synthesis of 3-iodo-1-methyl-1,6-naphthyridin-2-one **(112C):** To a stirred solution of compound **112B** (114 mg, 0.42 mmol) in DMF (4 mL) at 0 °C was added sodium hydride (60%, 20 mg, 0.5 mmol) and the mixture was stirred for 10 min at 0 °C, followed by the addition of MeI (31 µL, 0.5 mmol). Ice bath was removed, and the reaction mixture was stirred at RT for 30 minutes. EA and water was added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The material was purified by silica gel chromatography using MeOH in DCM as eluent to afford the title compound.

[0624] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)quinolin-5-yl)propanoic acid **(112):** The title compound was prepared according to the method presented for the synthesis of compound **113** starting with **112C.** MS (m/z) 640.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 8.87 - 8.81 (m, 2H), 8.79 (d, J = 6.6 Hz, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 7.87 (d, J = 6.6 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.67 (dd, J = 8.6, 4.2 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 9.4 Hz, 1H), 6.46 (d, J = 11.6 Hz, 2H), 4.76 - 4.61 (m, 1H), 4.31 (d, J = 8.8 Hz, 1H), 3.76 (d, J = 4.6 Hz, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.5, 9.9 Hz, 1H), 1.78 (ddd, J = 13.7, 7.2, 3.2 Hz, 1H), 1.61 - 1.50 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Example 113 (for illustrative purposes)

[0625]





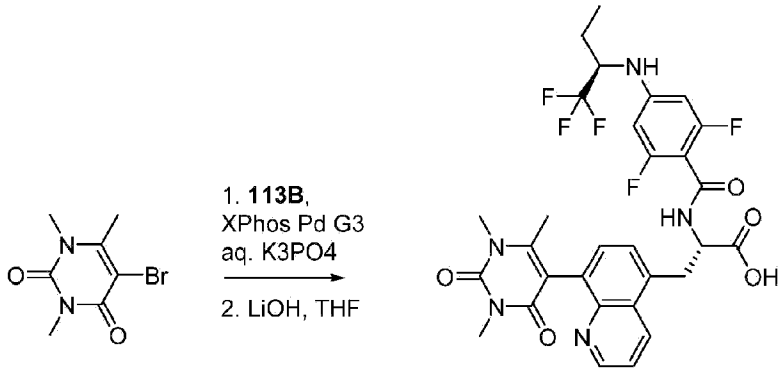
[0626] Synthesis of methyl (S)-3-(8-bromoquinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoro methyl)morpholino)benzamido)propanoate **(113A):** The title compound was prepared according to the method presented for the synthesis of compound 16A in Example 16 starting with **74C.**

[0627] Synthesis of (5-((S)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido) -3-methoxy-3-oxopropyl)quinolin-8-yl)boronic acid **(113B):** The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **113A.**

[0628] (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)quinolin-5-yl)propanoic acid **(113):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 5-bromo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione. MS (m/z) 620.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.98 - 8.83 (m, 1H), 8.78 (dd, J = 15.0, 8.3 Hz, 2H), 7.92 (s, 1H), 7.79 - 7.64 (m, 2H), 7.60 (d, J = 7.4 Hz, 1H), 6.84 - 6.69 (m, 1H), 6.43 (d, J = 11.6 Hz, 2H), 4.63 (td, J = 9.3, 4.5 Hz, 1H), 4.30 (d, J = 10.0 Hz, 1H), 3.70 (dd, J = 14.4, 4.5 Hz, 1H), 3.39 (s, 4H), 3.24 (s, 3H), 1.75 (ddt, J = 15.0, 7.7, 3.9 Hz, 1H), 1.51 (ddt, J = 17.8, 14.5, 7.3 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 114 (for illustrative purposes)

[0629]

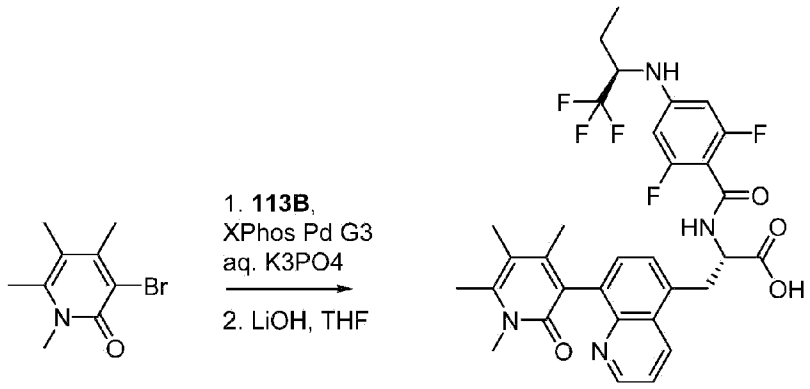


114

[0630] (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)quinolin-5-yl)propanoic acid **(114):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 5-bromo-1,3,6-trimethylpyrimidine-2,4(1H,3H)-dione. MS (m/z) 634.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.91 (d, J = 4.3 Hz, 1H), 8.78 (dd, J = 8.0, 2.3 Hz, 1H), 7.76 - 7.44 (m, 3H), 6.78 - 6.67 (m, 1H), 6.41 (dd, J = 11.3, 3.5 Hz, 2H), 4.73 - 4.57 (m, 1H), 4.29 (s, 1H), 3.72 (ddd, J = 56.2, 14.3, 4.5 Hz, 1H), 3.45 (d, J = 1.6 Hz, 4H), 3.21 (d, J = 2.4 Hz, 3H), 1.92 (d, J = 10.1 Hz, 3H), 1.75 (ddd, J = 13.6, 7.3, 3.2 Hz, 1H), 1.50 (ddd, J = 13.7, 10.3, 7.0 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H).

Example 115 (for illustrative purposes)

[0631]



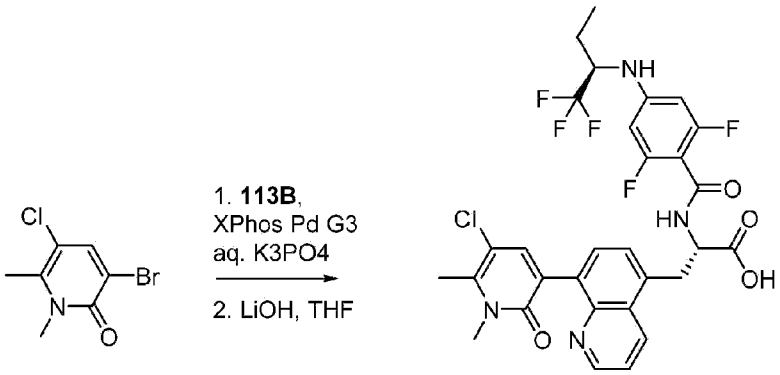
115

[0632] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,4,5,6-tetramethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(115):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 3-bromo-1,4,5,6-tetramethylpyridin-2(1H)-one. MS (m/z) 631.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.91 - 8.86 (m, 1H), 8.79 (dd, J = 7.8, 3.0 Hz,

1H), 7.80 - 7.71 (m, 1H), 7.66 (dd, J = 11.8, 7.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 6.76 (dd, J = 9.2, 4.4 Hz, 1H), 6.47 - 6.39 (m, 2H), 4.77 - 4.66 (m, 1H), 4.36 - 4.25 (m, 1H), 3.71 - 3.64 (m, 2H), 3.53 (s, 1H), 3.49 (s, 3H), 3.37 (dd, J = 13.8, 10.2 Hz, 1H), 2.43 (s, 3H), 2.32 (s, 1H), 2.09 (d, J = 6.8 Hz, 3H), 1.75 (d, J = 10.8 Hz, 3H), 1.58 - 1.47 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H).

Example 116 (for illustrative purposes)

[0633]



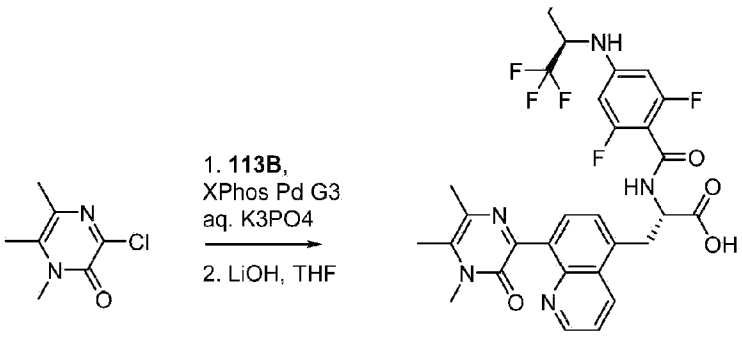
116

[0634] (S)-3-(8-(5-chloro-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid **(116):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 3-bromo-5-chloro-1,6-dimethylpyridin-2(1H)-one. MS (m/z) 637.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.96 (dd, J = 4.5, 1.5 Hz, 1H), 8.87 (d, J = 8.5 Hz, 1H), 8.81 (d, J = 8.0 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H), 6.78 (d, J = 9.4 Hz, 1H), 6.45 (d, J = 11.7 Hz, 2H), 4.72 - 4.62 (m, 1H), 4.37 - 4.23 (m, 1H), 3.74 (dd, J = 14.5, 4.6 Hz, 1H), 3.56 (s, 3H), 3.44 (dd, J = 14.5, 9.8 Hz, 1H), 2.58 (s, 3H), 1.84 - 1.70 (m, 1H), 1.60 - 1.45 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Example 117 (for illustrative purposes)

[0635] (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)quinolin-5-yl)propanoic acid **(117):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 3-chloro-1,5,6-trimethylpyrazin-2(1H)-one. MS (m/z) 618.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.91 (d, J = 4.4 Hz, 1H), 8.80 (d, J = 7.9 Hz, 2H), 7.84 - 7.69 (m, 2H), 7.64 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 9.4 Hz, 1H), 6.45 (d, J = 11.6 Hz, 2H), 4.68 (dt, J = 8.6, 4.1 Hz, 1H), 4.36 - 4.29 (m, 1H), 3.73 (dd, J = 14.4, 4.6 Hz, 1H), 3.53 (s, 3H), 3.45 (dd, J = 14.4, 9.7 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 1.77 (ddd, J = 13.8, 7.2, 3.3 Hz, 1H), 1.57 - 1.47 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

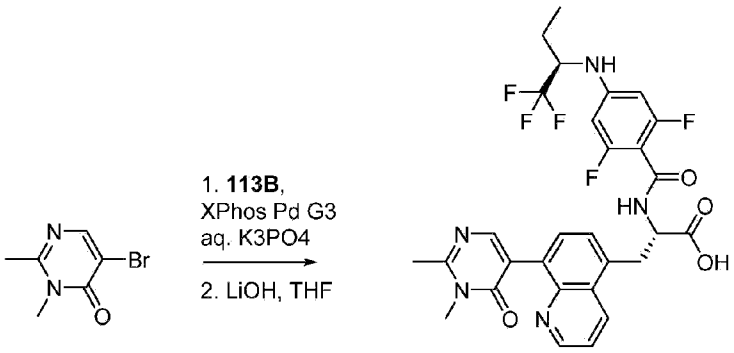
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117

Example 118 (for illustrative purposes)

[0636]

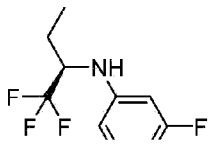


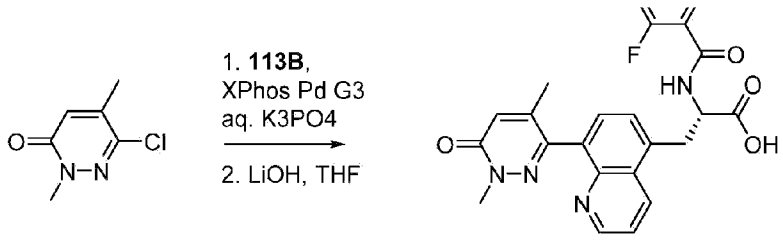
118

[0637] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,2-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)quinolin-5-yl)propanoic acid **(118):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 5-bromo-2,3-dimethylpyrimidin-4(3H)-one. MS (m/z) 604.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.89 (dd, J = 4.3, 1.5 Hz, 1H), 8.80 (d, J = 7.9 Hz, 1H), 8.70 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.68 (dd, J = 7.9, 3.9 Hz, 2H), 7.59 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 9.4 Hz, 1H), 6.44 (d, J = 11.5 Hz, 2H), 4.70 - 4.55 (m, 1H), 4.30 (s, 1H), 3.70 (dd, J = 14.4, 4.6 Hz, 1H), 3.53 (s, 3H), 3.41 (dd, J = 14.5, 9.8 Hz, 1H), 2.62 (s, 3H), 1.77 (ddd, J = 13.7, 7.3, 3.2 Hz, 1H), 1.52 (ddd, J = 13.7, 10.4, 7.2 Hz, 1H), 0.92 (t, J = 7.3 Hz, 3H).

Example 119 (for illustrative purposes)

[0638]



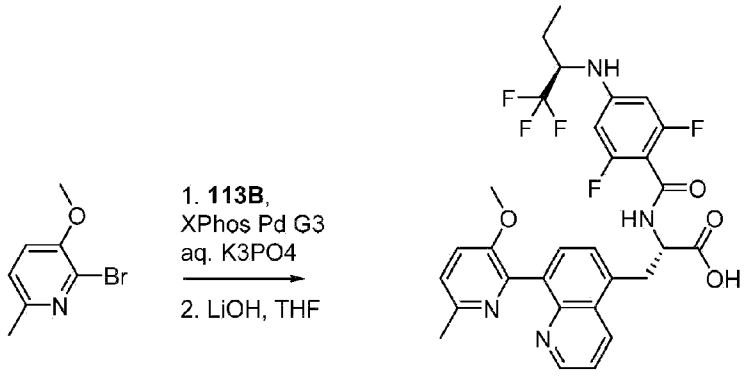


119

[0639] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,4-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)quinolin-5-yl)propanoic acid **(119):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 6-chloro-2,5-dimethylpyridazin-3(2H)-one. MS (m/z) 604.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.76 (d, J = 8.1 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 7.70 - 7.56 (m, 3H), 6.86 (d, J = 1.4 Hz, 1H), 6.75 (d, J = 9.4 Hz, 1H), 6.42 (d, J = 11.6 Hz, 2H), 4.67 (t, J = 11.3 Hz, 1H), 4.29 (d, J = 9.4 Hz, 1H), 3.72 (dd, J = 14.3, 4.5 Hz, 1H), 3.64 (s, 3H), 3.39 (dd, J = 14.3, 10.1 Hz, 1H), 1.74 (d, J = 1.2 Hz, 4H), 1.50 (ddd, J = 13.7, 10.4, 7.1 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H).

Example 120 (for illustrative purposes)

[0640]

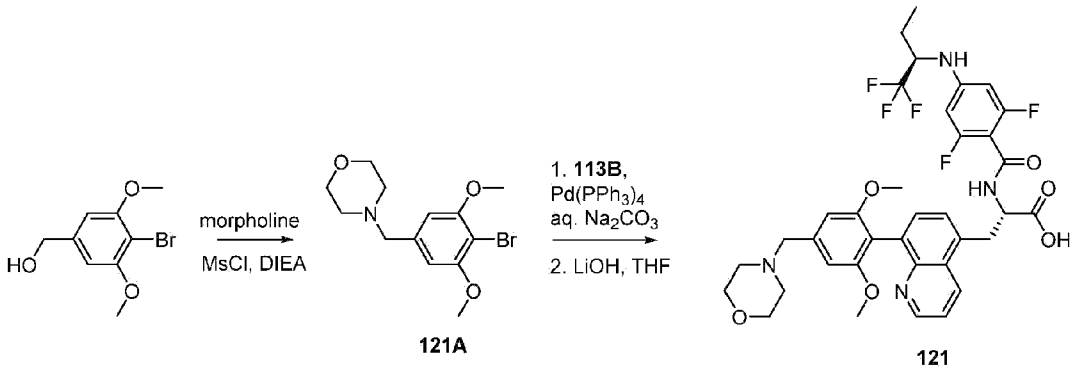


120

[0641] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(3-methoxy-6-methylpyridin-2-yl)quinolin-5-yl)propanoic acid **(120):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 2-bromo-3-methoxy-6-methylpyridine. MS (m/z) 603.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.88 (dd, J = 11.7, 5.9 Hz, 2H), 8.74 (d, J = 8.6 Hz, 1H), 8.16 (s, 1H), 7.85 (d, J = 24.9 Hz, 2H), 7.71 (d, J = 7.1 Hz, 2H), 6.79 (d, J = 9.4 Hz, 1H), 6.46 (d, J = 12.0 Hz, 2H), 4.70 (s, 1H), 4.31 (d, J = 10.1 Hz, 1H), 3.79 (s, 4H), 3.50 - 3.41 (m, 1H), 2.62 (s, 3H), 1.77 (s, 1H), 1.54 (dd, J = 15.7, 7.7 Hz, 1H), 0.93 (t, J = 7.0 Hz, 3H).

Example 121 (for illustrative purposes)

[0642]

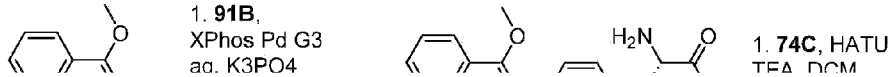


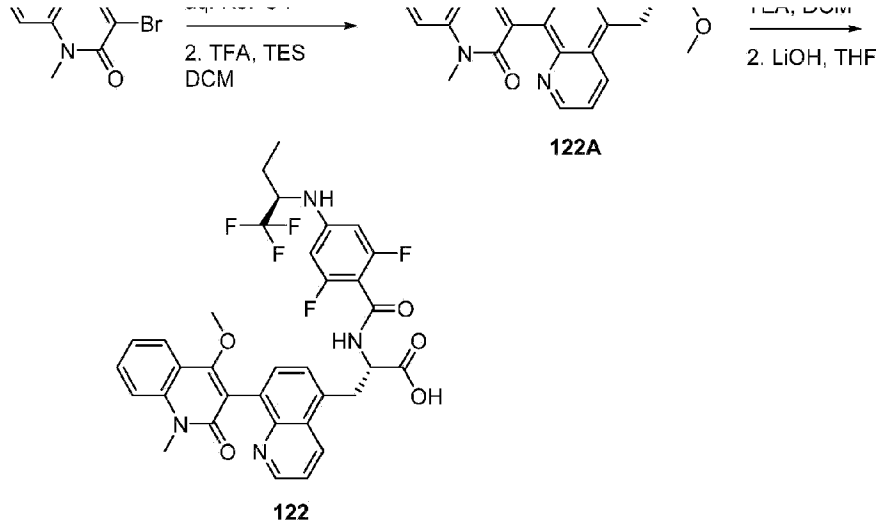
[0643] Synthesis of 4-(4-bromo-3,5-dimethoxybenzyl)morpholine **(121A):** To a stirred solution of (4-bromo-3,5-dimethoxyphenyl)methanol (300 mg, 1.214 mmol) in DCM (3 mL) was added N,N-diisopropylethyl amine (0.306 mL, 2.428 mmol). Methanesulfonyl chloride (0.094 mL, 1.214 mmol) was added dropwise and the reaction mixture was allowed to stir at RT for 5 min. Morpholine (0.134 mL, 3.642 mmol) was added dropwise and the reaction mixture was allowed to stir at RT for 14 hrs. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (2 mL) and again concentrated under reduced pressure to afford the title compound without further purification.

[0644] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(2,6-dimethoxy-4-(morpholinomethyl)phenyl)quinolin-5-yl)propanoic acid **(121):** The title compound was prepared according to the method presented for the synthesis of compound **5B** and **5** starting with **113B** and **121A.** MS (m/z) 717.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 12.93 (s, 1H), 10.01 (s, 1H), 8.84 (d, J = 7.9 Hz, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.60 (d, J = 8.5 Hz, 1H), 7.57 (dd, J = 16.9, 8.0 Hz, 2H), 7.40 (d, J = 7.3 Hz, 1H), 6.91 (q, J = 1.3 Hz, 2H), 6.78 (d, J = 9.4 Hz, 1H), 6.44 (d, J = 11.5 Hz, 2H), 4.66 (td, J = 8.8, 8.1, 4.3 Hz, 1H), 4.39 (s, 2H), 4.30 (d, J = 9.5 Hz, 1H), 4.02 (d, J = 12.6 Hz, 2H), 3.70 (t, J = 12.1 Hz, 5H), 3.58 (d, J = 5.6 Hz, 6H), 3.38 (dd, J = 14.2, 10.2 Hz, 3H), 3.19 (d, J = 10.8 Hz, 3H), 1.76 (ddt, J = 10.7, 7.3, 3.1 Hz, 1H), 1.51 (ddt, J = 17.5, 14.2, 7.3 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 122 (for illustrative purposes)

[0645] Synthesis of methyl (S)-2-amino-3-(4-methoxy-1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoate **(122A):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** starting with 3-bromo-4-methoxy-1-methylquinolin-2(1H)-one.

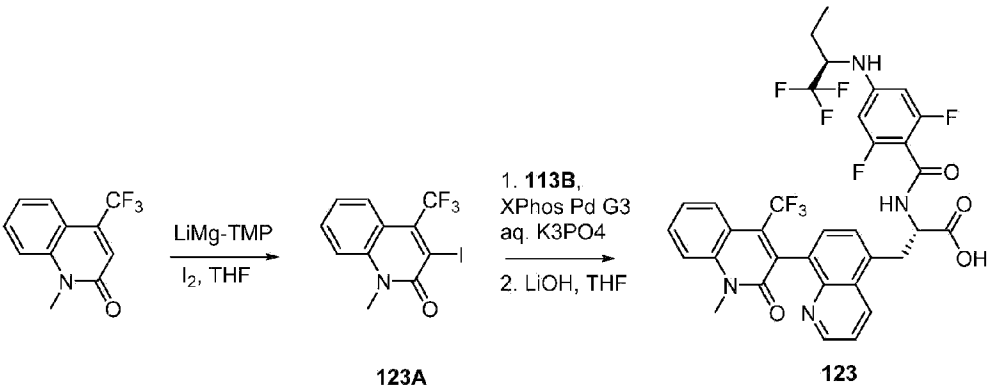




[0646] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(4-methoxy-1-methyl-2-oxo-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(122):** The title compound was prepared according to the method presented for the synthesis of compound **74** starting with **122A.** MS (m/z) 669.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 5.1 Hz, 2H), 8.81 (dd, J = 8.2, 2.6 Hz, 1H), 7.97 (dt, J = 8.0, 1.9 Hz, 1H), 7.89 - 7.66 (m, 4H), 7.68 - 7.59 (m, 1H), 7.42 - 7.32 (m, 1H), 6.77 (d, J = 9.4 Hz, 1H), 6.44 (dd, J = 11.5, 8.0 Hz, 2H), 4.80 - 4.69 (m, 1H), 4.37 - 4.22 (m, 1H), 3.76 - 3.52 (m, 4H), 3.30 (d, J = 2.1 Hz, 3H), 1.84 - 1.70 (m, 1H), 1.61 - 1.44 (m, 1H), 0.92 (td, J = 7.4, 2.4 Hz, 3H).

Example 123 (for illustrative purposes)

[0647]



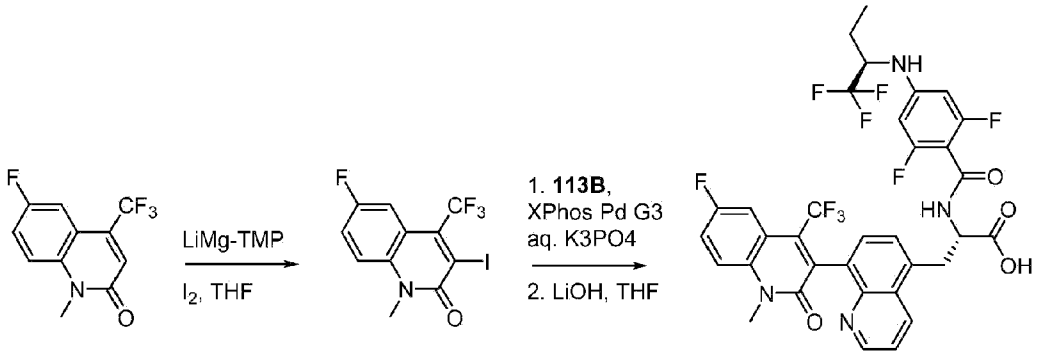
[0648] Synthesis of 3-iodo-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one **(123A):** To a stirred solution of 1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one (243 mg, 1.07 mmol) in THF was added LiMg-TMP (1.74 mL, 1M) dropwise at -78 °C. The reaction mixture was allowed to stir for 30 min, then a solution of iodine (488 mg, 2 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 EA/hexanes as the eluent to afford the title compound.

[0649] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(123):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and **123A.** MS (m/z) 707.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 - 8.77 (m, 2H), 8.65 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.85 - 7.72 (m, 2H), 7.67 - 7.57 (m, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 6.76 (dd, J = 9.4, 5.6 Hz, 1H), 6.45 (dd, J = 11.4, 3.7 Hz, 2H), 4.70 (tt, J = 8.8, 4.7 Hz, 1H), 4.39 - 4.24 (m, 1H), 3.80 - 3.63 (m, 4H), 3.44 (ddd, J = 35.4, 14.5, 9.8 Hz, 1H), 1.85 - 1.69 (m, 1H), 1.60 - 1.43 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Example 124 (for illustrative purposes)

[0650]



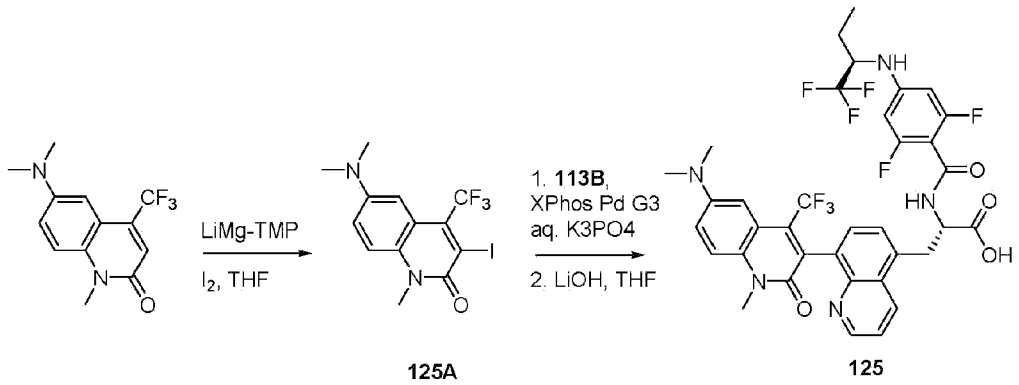
124A **124**

[0651] Synthesis of 3-iodo-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one **(124A):** The title compound was prepared according to the method presented for the synthesis of compound **123A** starting with 6-fluoro-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one.

[0652] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(124):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and **124A.** MS (m/z) 724.9 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.95 - 8.70 (m, 2H), 8.62 (d, J = 8.6 Hz, 1H), 6.75 (dd, J = 9.4, 5.6 Hz, 1H), 6.43 (dd, J = 11.3, 3.7 Hz, 2H), 4.76 - 4.62 (m, 1H), 4.28 (s, 2H), 3.69 (d, J = 2.0 Hz, 3H), 3.43 (d, J = 47.0 Hz, 1H), 1.89 - 1.69 (m, 1H), 1.51 (dt, J = 17.5, 7.4 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 125 (for illustrative purposes)

[0653]



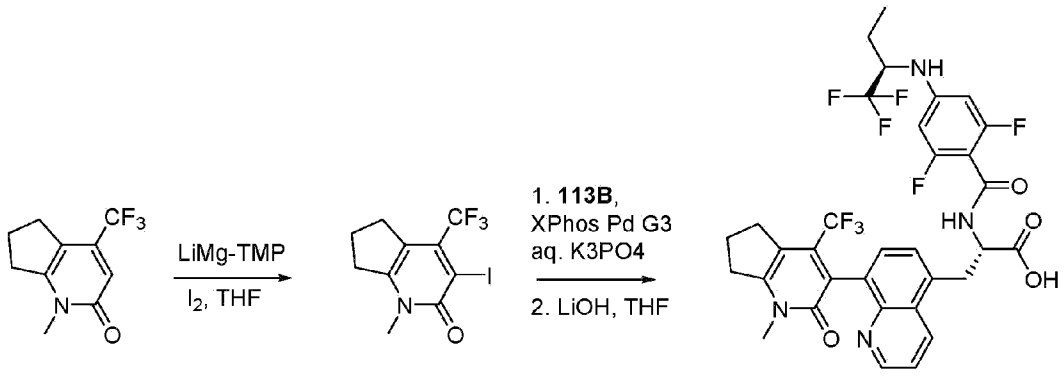
125A **125**

[0654] Synthesis of 3-iodo-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one **(125A):** The title compound was prepared according to the method presented for the synthesis of compound 123A starting with 6-(dimethylamino)-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one.

[0655] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(6-(dimethyl amino)-1-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(125):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and **125A.** MS (m/z) 724.9 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.95 - 8.70 (m, 2H), 8.62 (d, J = 8.6 Hz, 1H), 6.75 (dd, J = 9.4, 5.6 Hz, 1H), 6.43 (dd, J = 11.3, 3.7 Hz, 2H), 4.76 - 4.62 (m, 1H), 4.28 (s, 2H), 3.69 (d, J = 2.0 Hz, 3H), 3.43 (d, J = 47.0 Hz, 1H), 1.89 - 1.69 (m, 1H), 1.51 (dt, J = 17.5, 7.4 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 126 (for illustrative purposes)

[0656]



126A **126**

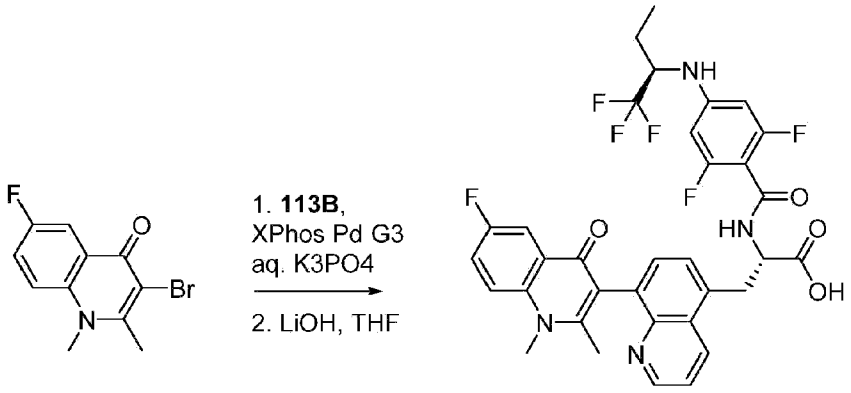
[0657] Synthesis of 3-iodo-1-methyl-4-(trifluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta [b]pyridin-2-one **(126A):** The title compound was prepared according to the method presented for the synthesis of compound **123A** starting with 1-methyl-4-(trifluoromethyl)-1,5,6,7-

tetrahydro-2H-cyclopenta[b]pyridin-2-one.

[0658] (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)quinolin-5-yl)propanoic acid **(126):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and **126A.** MS (m/z) 697.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.89 - 8.75 (m, 2H), 8.68 (d, J = 8.1 Hz, 1H), 7.65 (dt, J = 8.9, 4.9 Hz, 1H), 7.58 (dd, J = 7.4, 5.8 Hz, 1H), 7.43 (dd, J = 7.3, 5.4 Hz, 1H), 6.76 (dd, J = 9.4, 6.4 Hz, 1H), 6.56 (q, J = 1.1 Hz, 1H), 6.44 (dd, J = 11.4, 4.9 Hz, 2H), 4.77 - 4.53 (m, 1H), 4.30 (s, 1H), 3.86 - 3.56 (m, 1H), 3.10 (q, J = 7.2, 6.8 Hz, 2H), 2.98 (dt, J = 17.6, 7.4 Hz, 3H), 2.85 - 2.72 (m, 2H), 2.24 - 1.98 (m, 3H), 1.89 - 1.67 (m, 1H), 1.53 (ddd, J = 13.7, 10.3, 7.0 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H)..

Example 127 (for illustrative purposes)

[0659]

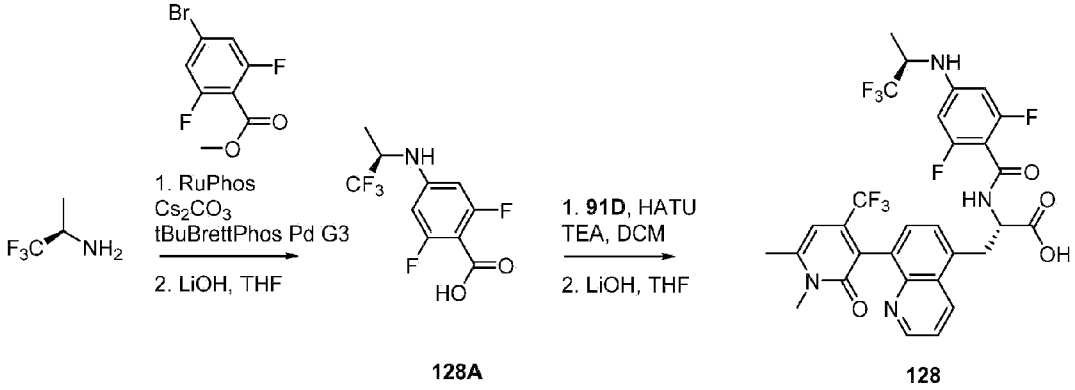


127

[0660] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(6-fluoro-1,2-dimethyl-4-oxo-1,4-dihydro-[3,8'-biquinolin]-5'-yl)propanoic acid **(127):** The title compound was prepared according to the method presented for the synthesis of compound **11A** and **11** starting with **113B** and 3-bromo-6-fluoro-1,2-dimethylquinolin-4(1H)-one. MS (m/z) 671.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J = 3.9 Hz, 2H), 8.84 - 8.78 (m, 1H), 8.01 (dd, J = 9.6, 4.4 Hz, 1H), 7.84 - 7.79 (m, 1H), 7.78 - 7.65 (m, 3H), 7.60 (dd, J = 12.7, 8.4 Hz, 1H), 6.76 (dd, J = 10.0, 2.5 Hz, 1H), 6.44 (d, J = 13.0 Hz, 2H), 4.78 - 4.68 (m, 1H), 4.35 - 4.25 (m, 2H), 3.90 - 3.88 (m, 3H), 3.84 (dd, J = 14.8, 3.8 Hz, 1H), 3.71 - 3.66 (m, 1H), 3.58 - 3.51 (m, 1H), 3.38 (dd, J = 14.6, 10.5 Hz, 1H), 2.16 (d, J = 8.7 Hz, 3H), 1.83 - 1.71 (m, 1H), 1.59 - 1.47 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H).

Example 128 (for illustrative purposes)

[0661] Synthesis of (R)-2,6-difluoro-4-((1,1,1-trifluoropropan-2-yl)amino)benzoic acid **(128A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** Example 75 starting with (R)-1,1,1-trifluoropropan-2-amine.

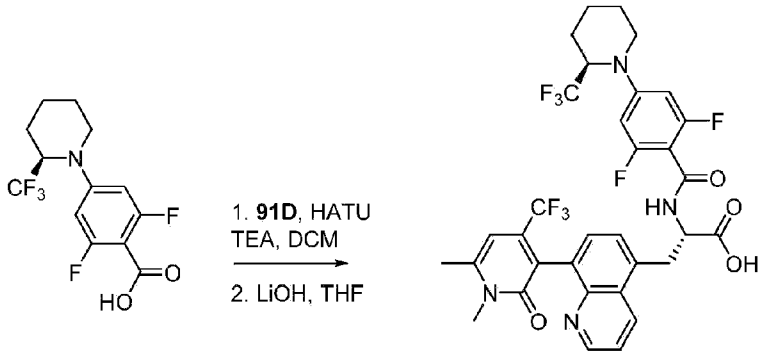


128A 128

[0662] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluoropropan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(128):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **128A.** MS (m/z) 657.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.80 (t, J = 6.0 Hz, 2H), 8.60 (d, J = 8.7 Hz, 1H), 7.63 - 7.51 (m, 2H), 7.46 - 7.33 (m, 1H), 6.88 - 6.76 (m, 1H), 6.53 (s, 1H), 6.40 (dd, J = 11.2, 4.3 Hz, 2H), 4.65 (dt, J = 13.4, 4.7 Hz, 1H), 4.50 (dd, J = 15.4, 7.7 Hz, 1H), 3.73 - 3.56 (m, 2H), 3.47 (d, J = 2.2 Hz, 4H), 3.16 - 3.03 (m, 1H), 2.51 (s, 2H), 1.27 - 1.23 (m, 4H).

Example 129 (for illustrative purposes)

[0663]



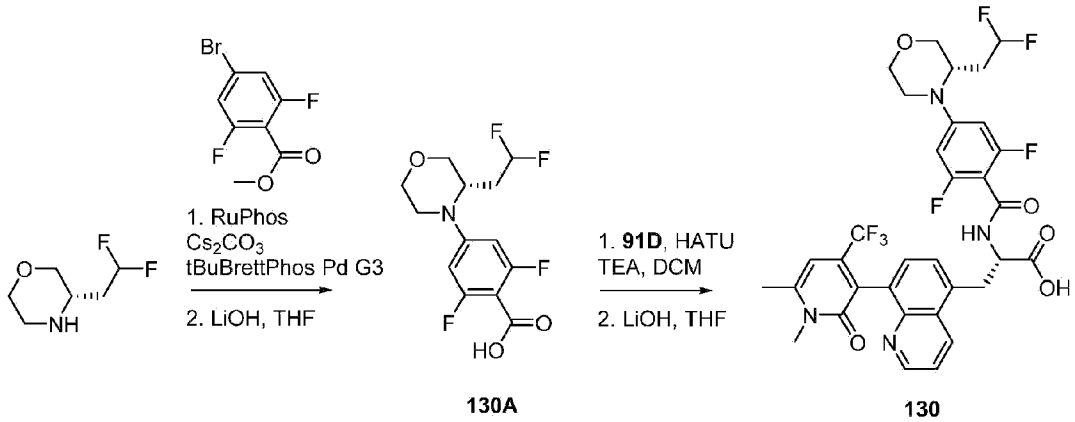
75A 129

[0664] (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)quinolin-5-yl)propanoic acid **(129):** The title compound was prepared according to the method presented for the synthesis of compound **75** starting with **91D.** MS (m/z) 697.8 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.92 (dd, J = 7.8, 4.2 Hz, 1H), 8.86 (d, J = 4.0 Hz, 1H), 8.73 (d, J = 7.7 Hz, 1H), 7.74 - 7.64 (m, 1H),

7.61 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 7.1, 3.7 Hz, 1H), 6.73 (dd, J = 11.9, 4.0 Hz, 2H), 6.57 (s, 1H), 5.00 - 4.87 (m, 1H), 4.77 - 4.71 (m, 1H), 3.73 (td, J = 19.1, 14.5, 4.2 Hz, 1H), 3.66 - 3.56 (m, 1H), 3.53 - 3.37 (m, 4H), 3.02 (t, J = 12.4 Hz, 1H), 2.54 (s, 3H), 1.97 (d, J = 14.5 Hz, 1H), 1.87 - 1.67 (m, 2H), 1.67 - 1.43 (m, 3H).

Example 130 (for illustrative purposes)

[0665]



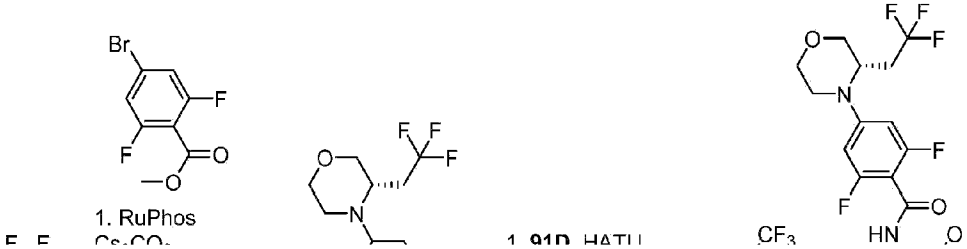
130A **130**

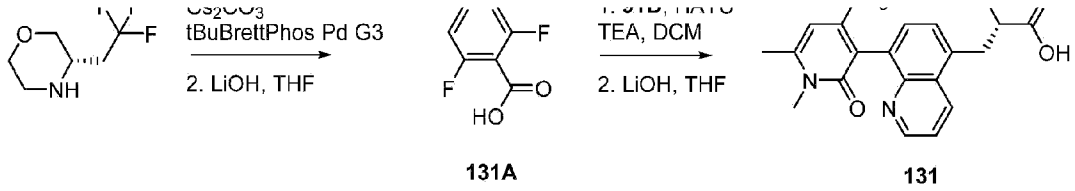
[0666] Synthesis of (S)-4-(3-(2,2-difluoroethyl)morpholino)-2,6-difluorobenzoic acid **(130A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (S)-3-(2,2-difluoroethyl)morpholine.

[0667] (S)-2-(4-((S)-3-(2,2-difluoroethyl)morpholino)-2,6-difluorobenzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid (130): The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **130A.** MS (m/z) 695.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 10.4 Hz, 2H), 8.72 (s, 1H), 7.65 (s, 1H), 7.52 (d, J = 10.0 Hz, 1H), 6.78 (d, J = 9.3 Hz, 1H), 6.46 (d, J = 12.0 Hz, 2H), 6.40 (d, J = 3.6 Hz, 1H), 4.67 (s, 1H), 4.32 (s, 1H), 3.66 (d, J = 3.2 Hz, 7H), 3.44 (s, 5H), 1.77 (s, 1H), 1.55 (d, J = 15.1 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Example 131 (for illustrative purposes)

[0668]



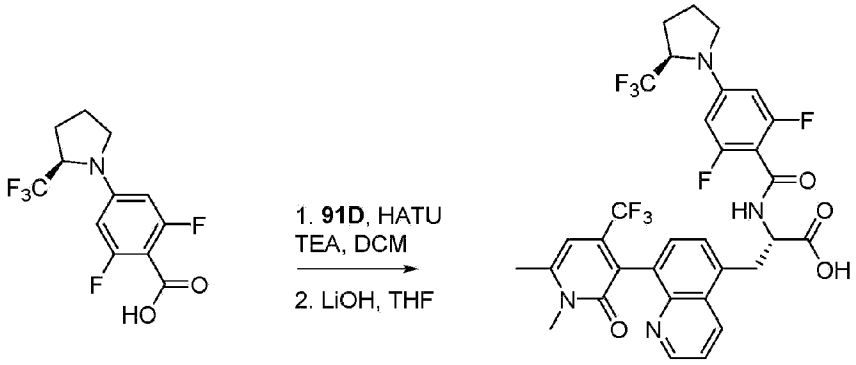


[0669] Synthesis of (S)-2,6-difluoro-4-(3-(2,2,2-trifluoroethyl)morpholino)benzoic acid **(131A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (S)-3-(2,2,2-trifluoroethyl)morpholine

[0670] (S)-2-(2,6-difluoro-4-((S)-3-(2,2,2-trifluoroethyl)morpholino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(131):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **131A.** MS (m/z) 713.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.90 (dd, J = 7.9, 4.2 Hz, 1H), 8.86 - 8.77 (m, 1H), 8.65 (s, 1H), 7.63 (dd, J = 8.7, 4.4 Hz, 1H), 7.57 (t, J = 7.1 Hz, 1H), 7.44 (dd, J = 7.3, 4.5 Hz, 1H), 6.66 - 6.50 (m, 3H), 4.78 - 4.66 (m, 1H), 4.28 (s, 1H), 3.89 (dd, J = 11.4, 3.6 Hz, 1H), 3.78 (d, J = 11.9 Hz, 1H), 3.67 (dd, J = 22.0, 13.3 Hz, 2H), 3.57 - 3.36 (m, 6H), 3.07 (td, J = 12.6, 3.8 Hz, 1H), 2.77 (ddd, J = 15.4, 11.8, 8.1 Hz, 1H), 2.53 (s, 3H), 2.39 - 2.20 (m, 1H).

Example 132 (for illustrative purposes)

[0671]

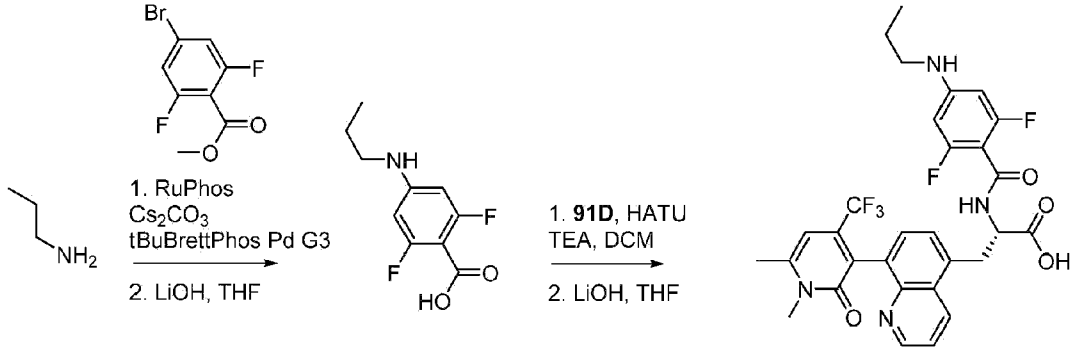


[0672] (S)-2-(2,6-difluoro-4-((R)-2-(trifluoromethyl)pyrrolidin-1-yl)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(132):** The title compound was prepared according to the method presented for the synthesis of compound **76** starting with **91D.** MS (m/z) 683.7 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.89 (dd, J = 8.0, 3.8 Hz, 1H), 8.84 (dd, J = 4.3, 1.5 Hz, 1H), 8.70 (t, J = 7.6 Hz, 1H), 7.71 - 7.63 (m, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.3, 4.1 Hz, 1H), 6.56 (t, J = 1.1 Hz, 1H), 6.49 (dd, J = 11.3, 4.1 Hz, 2H), 4.83 - 4.66 (m, 2H), 3.72 (td, J = 15.5, 4.6 Hz, 1H), 3.58 (t, J = 8.5 Hz, 1H), 3.53 - 3.36 (m, 4H), 3.18 (q, J = 8.8 Hz, 1H), 2.54 (s, 3H), 2.19 - 1.93 (m, 4H).

Example 133 (for illustrative purposes)

[0673] Synthesis of 2,6-difluoro-4-(propylamino)benzoic acid **(133A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with propan-1-amine.

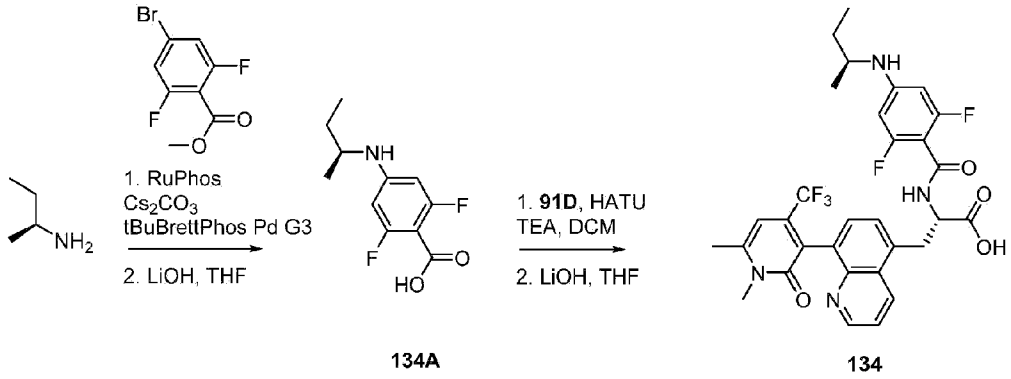
[0674] (S)-2-(2,6-difluoro-4-(propylamino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(133):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **133A.** MS (m/z) 603.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.1 Hz, 1H), 8.65 (dd, J = 7.8, 5.4 Hz, 2H), 7.63 (dd, J = 8.4, 4.1 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.44 (dd, J = 7.3, 3.0 Hz, 1H), 6.55 (s, 1H), 6.15 (dd, J = 11.6, 4.4 Hz, 2H), 4.74 - 4.61 (m, 1H), 3.78 - 3.61 (m, 1H), 3.49 (d, J = 1.9 Hz, 3H), 3.47 - 3.36 (m, 1H), 2.97 (t, J = 7.0 Hz, 2H), 2.53 (s, 3H), 1.51 (h, J = 7.3 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H).



133A **133**

Example 134 (for illustrative purposes)

[0675]



134A **134**

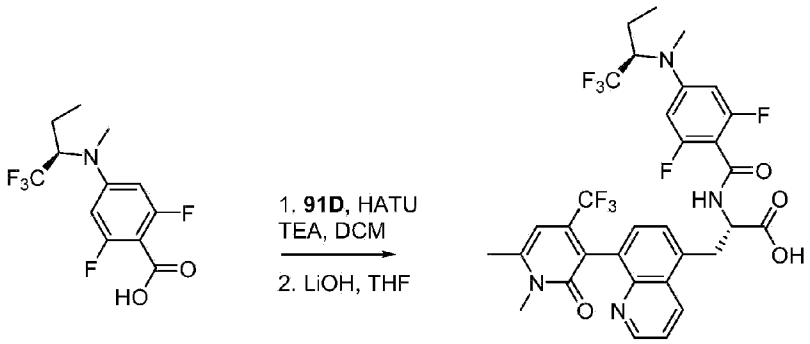
[0676] Synthesis of (S)-4-(sec-butylamino)-2,6-difluorobenzoic acid **(134A):** The title

compound was prepared according to the method presented for the synthesis of compound **75A** starting with (S)-butan-2-amine.

[0677] (S)-2-(4-(((S)-sec-butyl)amino)-2,6-difluorobenzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(134):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **134A.** MS (m/z) 617.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.86 - 8.77 (m, 1H), 8.73 - 8.57 (m, 2H), 7.63 (dd, J = 8.4, 4.1 Hz, 1H), 7.58 (t, J = 6.4 Hz, 1H), 7.48 - 7.40 (m, 1H), 6.55 (s, 1H), 6.33 (s, 1H), 6.15 (dd, J = 11.7, 4.4 Hz, 2H), 4.67 (dt, J = 14.5, 5.6 Hz, 1H), 3.77 - 3.62 (m, 1H), 3.49 (d, J = 2.0 Hz, 3H), 3.47 - 3.24 (m, 2H), 2.53 (s, 3H), 1.57 - 1.31 (m, 2H), 1.06 (d, J = 6.3 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H).

Example 135 (for illustrative purposes)

[0678]



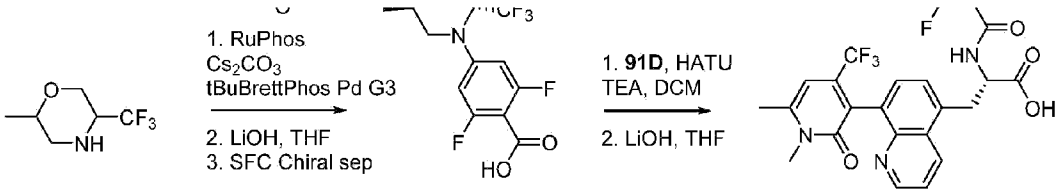
87A **135**

[0679] (S)-2-(2,6-difluoro-4-(methyl((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(135):** The title compound was prepared according to the method presented for the synthesis of compound **87** starting with **91D.** MS (m/z) 671.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.89 (dd, J = 7.9, 2.5 Hz, 1H), 8.84 (dd, J = 4.3, 1.5 Hz, 1H), 8.69 (s, 1H), 7.72 - 7.54 (m, 2H), 7.46 (dd, J = 7.4, 3.3 Hz, 1H), 6.64 (dd, J = 12.0, 4.4 Hz, 2H), 6.56 (d, J = 1.5 Hz, 1H), 5.02 - 4.90 (m, 1H), 4.70 (dt, J = 4.7, 2.4 Hz, 1H), 3.72 (td, J = 15.0, 4.5 Hz, 1H), 3.54 - 3.35 (m, 4H), 2.82 (s, 3H), 2.54 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H).

Example 136 (for illustrative purposes)

[0680]





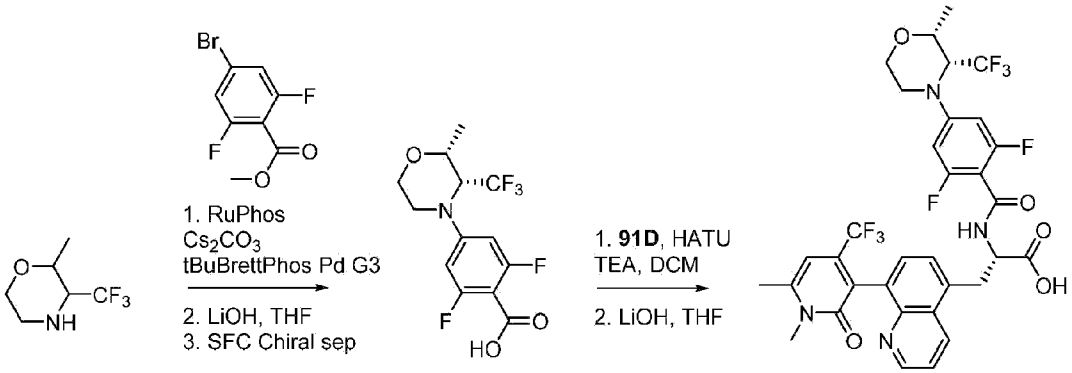
136A 136

[0681] Synthesis of 2,6-difluoro-4-((2R,5R)-2-methyl-5-(trifluoromethyl)morpholino)benzoic acid **(136A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with 2-methyl-5-(trifluoromethyl)morpholine. The mixture of stereoisomers was separated into four peaks by supercritical fluid chromatography via chiral SFC (OJ-H column) eluting with 5% TFA in EtOH to yield intermediate 136A. The title compound was identified as the first eluting peak.

[0682] (S)-2-(2,6-difluoro-4-((2R,5R)-2-methyl-5-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(136):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **136A.** MS (m/z) 713.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 7.7 Hz, 1H), 8.80 (d, J = 4.1 Hz, 1H), 8.61 (d, J = 8.4 Hz, 1H), 7.66 - 7.51 (m, 2H), 7.47 - 7.35 (m, 1H), 6.75 (dd, J = 11.5, 4.4 Hz, 2H), 6.54 (s, 1H), 4.85 (s, 1H), 4.70 (s, 1H), 4.10 (s, 13H), 3.87 (d, J = 12.9 Hz, 1H), 3.69 (d, J = 16.9 Hz, 1H), 3.49 (d, J = 2.1 Hz, 3H), 3.42 (d, J = 20.5 Hz, 4H), 2.53 (s, 4H), 1.20 (d, J = 6.6 Hz, 3H).

Example 137 (for illustrative purposes)

[0683]



137A 137

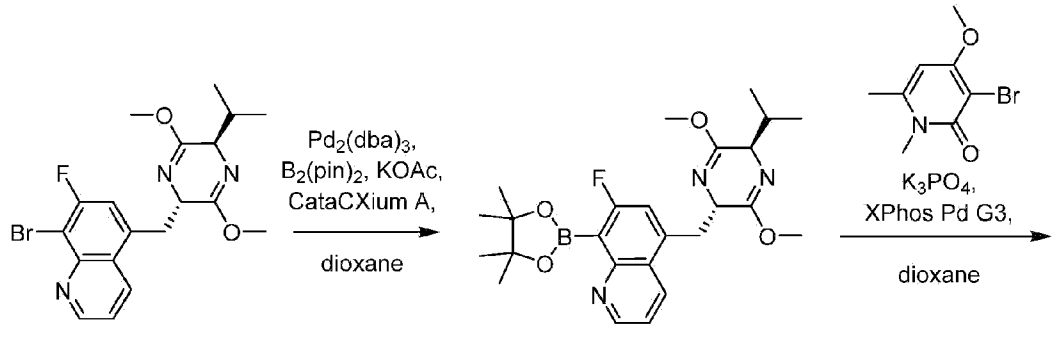
[0684] Synthesis of 2,6-difluoro-4-((2R,3R)-2-methyl-3-(trifluoromethyl)morpholino)benzoic acid **(137A):** The title compound was prepared according to the method presented for the synthesis of compound **75A** starting with (cis)-2-methyl-3-(trifluoromethyl)morpholine. The mixture of stereoisomers was separated into two peaks by supercritical fluid chromatography

via chiral SFC (IG-H column) eluting with 10% TFA in EtOH to yield intermediate 137A. The title compound was identified as the first eluting peak.

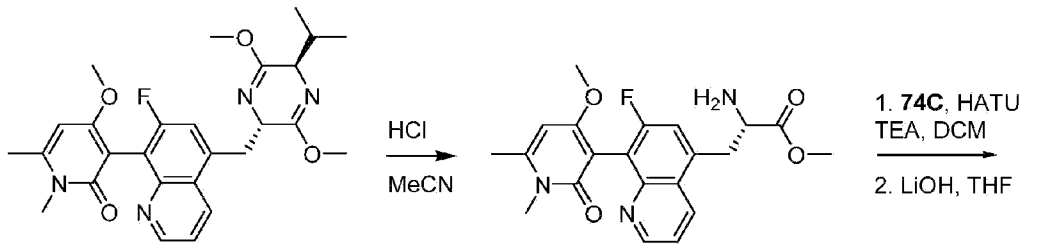
[0685] (S)-2-(2,6-difluoro-4-((2R,3R)-2-methyl-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(137):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **137A.** MS (m/z) 712.7 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.95 (dd, J = 7.9, 3.4 Hz, 1H), 8.80 (dd, J = 4.2, 1.5 Hz, 1H), 8.61 (d, J = 8.7 Hz, 1H), 7.65 - 7.52 (m, 2H), 7.48 - 7.38 (m, 1H), 6.74 (dd, J = 11.7, 4.5 Hz, 2H), 6.53 (s, 1H), 4.86 (d, J = 6.9 Hz, 1H), 4.69 (td, J = 9.1, 8.7, 4.3 Hz, 1H), 3.94 (dd, J = 11.4, 3.7 Hz, 1H), 3.85 (s, 1H), 3.48 (d, J = 2.0 Hz, 3H), 3.46 (s, 2H), 3.39 (dd, J = 13.9, 9.6 Hz, 1H), 3.08 (dd, J = 14.3, 10.6 Hz, 1H), 2.52 (s, 4H), 1.34 - 1.24 (m, 3H).

Example 138 (for illustrative purposes)

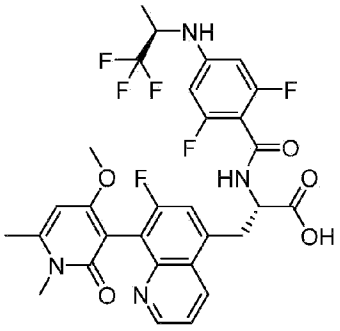
[0686] Synthesis of 7-fluoro-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline **(138A):** To **34C** (676 mg, 1.601 mmol), bis(pinacolato)diboron (813 mg, 3.202 mmol), potassium acetate (471 mg, 4.802 mmol), CataCXium A (86 mg, 0.192 mmol), and tris(dibenzylideneacetone)dipalladium(0) (46 mg, 0.080 mmol) were added dioxane (13.5 mL) and the reaction mixture was purged with N_2 for 10 min. The reaction mixture was sealed, affixed with a N_2 balloon, and allowed to stir at 105° C for 14 hrs. The reaction mixture was cooled to RT, diluted with EA, and filtered. The filtrate was collected and concentrated under reduced pressure to afford the title compound without further purification.



34C **138A**



138B **138C**



138

[0687] Synthesis of 3-(7-fluoro-5-(((2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)quinolin-8-yl)-4-methoxy-1,6-dimethylpyridin-2(1H)-one **(138B):** To a stirred solution of **138A** (325 mg, 0.277 mmol), 3-bromo-4-methoxy-1,6-dimethylpyridin-2(1H)-one (128 mg, 0.554 mmol), and XPhos Pd G3 (70 mg, 0.083 mmol), in dioxane (5 mL) were added 1M potassium phosphate (0.96 mL, 0.989 mmol). The reaction mixture was purged with N_2 for 5 min, sealed, and allowed to stir at 90° C for 2 hrs. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography eluting with Hex/EA 0-100% then DCM/MeOH 0-30% to afford the title compound.

[0688] Synthesis of methyl (S)-2-amino-3-(7-fluoro-8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoate **(138C):** To a stirred solution of **138B** (80 mg, 0.162 mmol) in acetonitrile (3.8 mL) was added 2M HCl (0.404 mL, 0.809 mmol). The reaction mixture was allowed to stir at RT for 2 hrs then concentrated under reduced pressure to yield the title compound without further purification.

[0689] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(7-fluoro-8-(4-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(138):** The title compound was prepared according to the method presented for the synthesis of compound **74** of starting with **137C.** MS (m/z) 650.6 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 10.4 Hz, 2H), 8.72 (s, 1H), 7.65 (s, 1H), 7.52 (d, J = 10.0 Hz, 1H), 6.78 (d, J = 9.3 Hz, 1H), 6.46 (d, J = 12.0 Hz, 2H), 6.40 (d, J = 3.6 Hz, 1H), 4.67 (s, 1H), 4.32 (s, 1H), 3.66 (d, J = 3.2 Hz, 7H), 3.44 (s, 5H), 1.77 (s, 1H), 1.55 (d, J = 15.1 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Example 139 (for illustrative purposes)

[0690] Synthesis of methyl (S)-3-(8-bromo-3-fluoroquinolin-5-yl)-2-(tritylamino)propanoate (139A): The title compound was prepared according to the method presented for the synthesis of compound **91A** starting with **30K.**

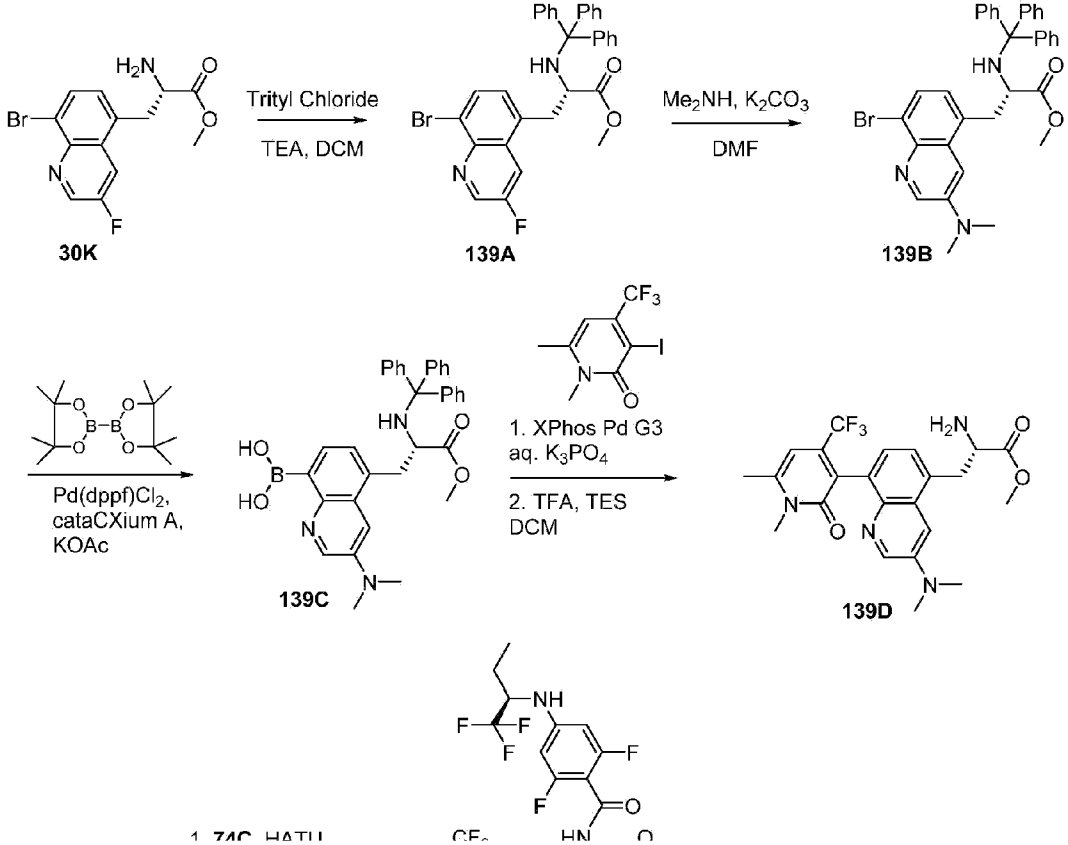
[0691] Synthesis of methyl (S)-3-(8-bromo-3-(dimethylamino)quinolin-5-yl)-2-(tritylamino) propanoate **(139B): 139A** (445 mg, 0.781 mmol) was dissolved in DMF (2.4 mL), and to this was added K_2CO_3 (113 mg, 0.82 mmol) and dimethylamine (4.69 mmol, 2.3 mL, 2.0M in THF).

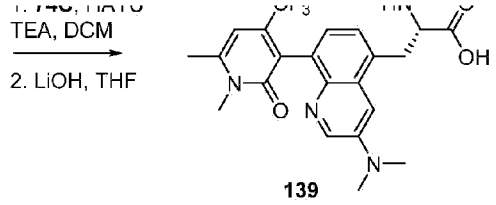
The reaction was heated to 100 °C and stirred for 21.5 hours. After cooling to RT, EA and water were added to the reaction mixture. The aqueous layer was extracted and the organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The material was purified by silica gel chromatography using 0-50% EA in hexanes to afford the title compound.

[0692] Synthesis of (S)-(3-(dimethylamino)-5-(3-methoxy-3-oxo-2-(tritylamino)propyl) quinolin-8-yl)boronic acid **(139C):** The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **91A.**

[0693] Synthesis of methyl (S)-2-amino-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)-3-(dimethylamino)quinolin-5-yl)propanoate **(139D):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and 91**D** in starting with **139C** and3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one.

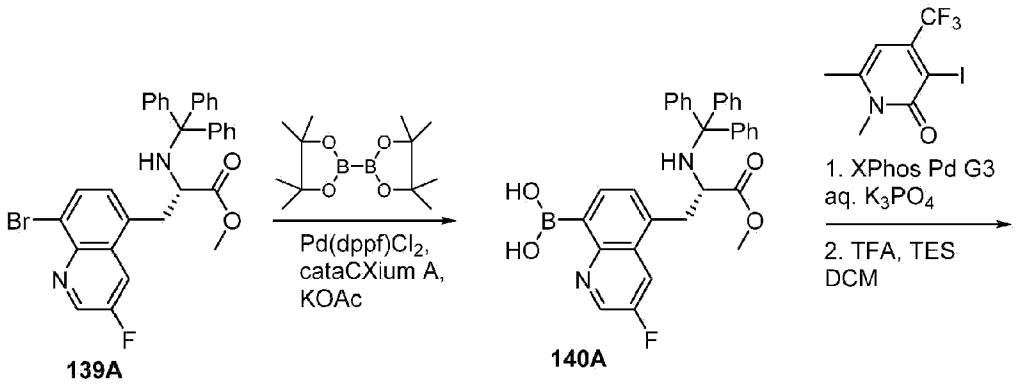
[0694] (S)-2-(2,6-difluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)-3-(dimethylamino)quinolin-5-yl)propanoic acid **(139):** The title compound was prepared according to the method presented for the synthesis of compound **74** starting with **139D.** MS (m/z) 714.5 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 7.8 Hz, 1H), 8.62 (t, J = 3.0 Hz, 1H), 7.58 (s, 1H), 7.44 (t, J = 5.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 6.84 - 6.73 (m, 1H), 6.55 (d, J = 2.7 Hz, 1H), 6.45 (dd, J = 11.3, 3.9 Hz, 2H), 4.67 (dt, J = 13.4, 9.0 Hz, 1H), 4.31 (d, J = 8.8 Hz, 1H), 3.65 - 3.54 (m, 1H), 3.48 (d, J = 1.7 Hz, 3H), 3.39 - 3.26 (m, 1H), 3.10 (d, J = 3.9 Hz, 6H), 2.53 (s, 3H), 1.77 (ddd, J = 10.7, 7.5, 3.7 Hz, 1H), 1.61 - 1.46 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

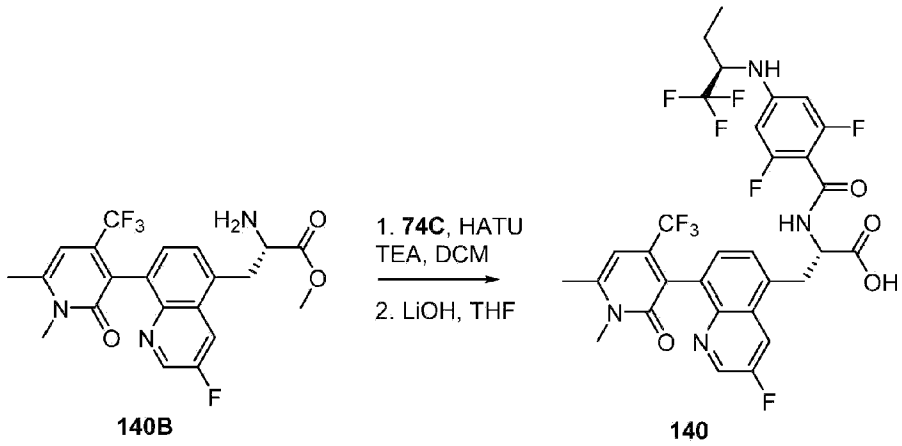




Example 140 (for illustrative purposes)

[0695] Synthesis of (S)-(3-fluoro-5-(3-methoxy-3-oxo-2-(tritylamino)propyl)quinolin-8-yl)boronic acid **(140A):** The title compound was prepared according to the method presented for the synthesis of compound **4B** starting with **139A.**





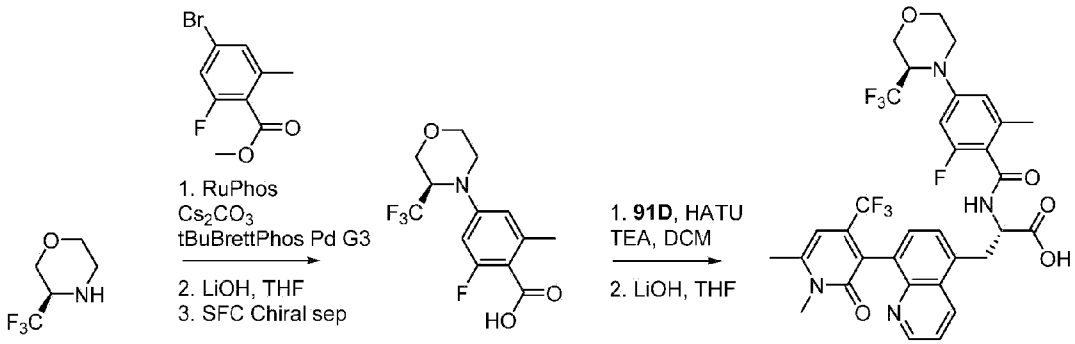
[0696] Synthesis of methyl (S)-2-amino-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)-3-fluoroquinolin-5-yl)propanoate **(140B):** The title compound was prepared according to the method presented for the synthesis of compound **91C** and **91D** in starting with **140A** and3-iodo-1,6-dimethyl-4-(trifluoromethyl)pyridin-2(1H)-one.

[0697] (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)-3-fluoroquinolin-5-yl)propanoic acid **(140):** The title compound was prepared according to the method presented for the synthesis

of compound **74** starting with **140B.** MS (m/z) 689.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 2.6 Hz, 1H), 8.81 (d, J = 7.9 Hz, 1H), 8.37 (dt, J = 10.6, 3.3 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.41 (dd, J = 7.3, 5.2 Hz, 1H), 6.77 (d, J = 9.3 Hz, 1H), 6.54 (s, 1H), 6.44 (d, J = 11.8 Hz, 2H), 4.68 (td, J = 8.8, 4.5 Hz, 1H), 4.31 (d, J = 9.1 Hz, 1H), 3.62 (td, J = 14.1, 4.4 Hz, 1H), 3.48 (d, J = 1.7 Hz, 3H), 3.41 (td, J = 15.3, 9.9 Hz, 1H), 2.52 (s, 3H), 1.77 (ddd, J = 13.9, 7.1, 3.3 Hz, 1H), 1.52 (ddd, J = 13.6, 10.2, 6.9 Hz, 1H), 0.92 (t, J = 7.3 Hz, 3H).

Example 141 (for illustrative purposes)

[0698]



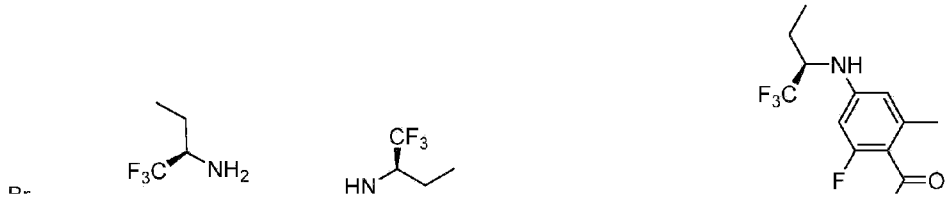
141A **141**

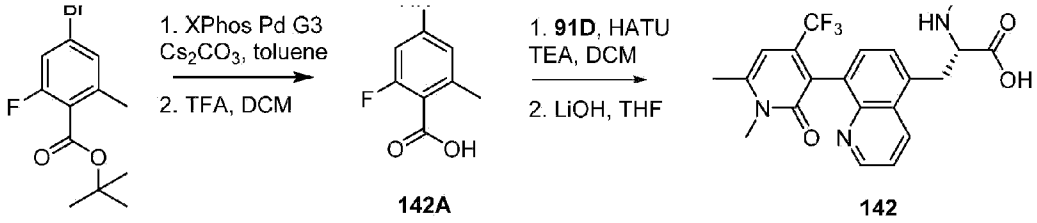
[0699] Synthesis of (R)-2-fluoro-6-methyl-4-(3-(trifluoromethyl)morpholino)benzoic acid **(141A):** The title compound was prepared according to the method presented for the synthesis of compound **93A** starting with methyl 4-bromo-2-fluoro-6-methylbenzoate.

[0700] (S)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(141):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **141A** and **91D.** MS (m/z) 695.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.89 - 8.77 (m, 2H), 8.63 (d, J = 8.6 Hz, 1H), 7.68 - 7.53 (m, 2H), 7.43 (t, J = 7.2 Hz, 1H), 6.71 - 6.61 (m, 2H), 6.55 (d, J = 3.2 Hz, 1H), 4.89 - 4.69 (m, 2H), 4.14 (d, J = 12.6 Hz, 1H), 3.94 (d, J = 9.6 Hz, 1H), 3.80 - 3.64 (m, 2H), 3.59 - 3.19 (m, 7H), 2.53 (s, 3H), 1.99 - 1.97 (m, 3H).

Example 142 (for illustrative purposes)

[0701]





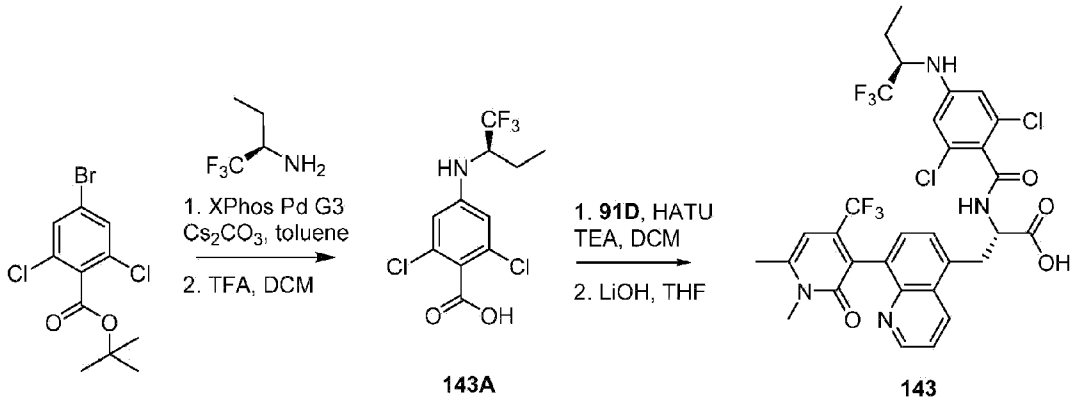
142A 142

[0702] Synthesis of (R)-2-fluoro-6-methyl-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid **(142A):** The title compound was prepared according to the method presented for the synthesis of compound **74B** and **74C** starting with methyl 4-bromo-2-fluoro-6-methylbenzoate.

[0703] (S)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2-fluoro-6-methyl-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid **(142):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **142A** and **91D.** MS (m/z) 667.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.81 (dt, J = 3.9, 1.8 Hz, 1H), 8.71 (dd, J = 9.9, 8.1 Hz, 1H), 8.63 (d, J = 8.5 Hz, 1H), 7.61 (ddd, J = 20.7, 9.0, 4.6 Hz, 2H), 7.43 (t, J = 6.8 Hz, 1H), 6.55 (d, J = 3.5 Hz, 1H), 6.41 - 6.34 (m, 2H), 6.28 (d, J = 9.2 Hz, 1H), 4.80 - 4.67 (m, 1H), 4.18 (br s, 1H), 3.71 (ddd, J = 28.0, 14.6, 4.0 Hz, 1H), 3.53 - 3.29 (m, 4H), 2.53 (s, 3H), 1.95 - 1.91 (m, 3H), 1.80 - 1.70 (m, 1H), 1.59 - 1.47 (m, 1H), 0.96 - 0.87 (m, 3H).

Example 143 (for illustrative purposes)

[0704] Synthesis of (R)-2,6-dichloro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid **(143A):** The title compound was prepared according to the method presented for the synthesis of compound **74B** and **74C** starting with tert-butyl 4-bromo-2,6-dichlorobenzoate.



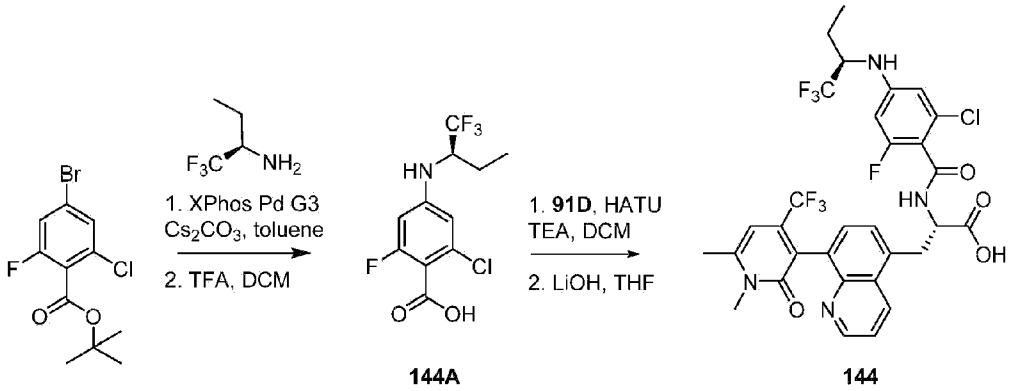
143A 143

[0705] (S)-2-(2,6-dichloro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(143):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **143A** and **91D.** MS (m/z) 703.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.01 (dd, J = 26.1, 8.3 Hz, 1H), 8.82 (d, J = 3.5 Hz, 1H), 8.66 (d, J = 8.6 Hz,

1H), 7.65 (dd, J = 18.5, 9.6 Hz, 2H), 7.43 (dd, J = 7.4, 3.8 Hz, 1H), 6.77 (s, 1H), 6.55 (q, J = 5.9 Hz, 2H), 4.85 - 4.63 (m, 1H), 4.33 (s, 1H), 3.69 (ddd, J = 19.3, 14.5, 4.0 Hz, 1H), 3.49 (d, J = 4.0 Hz, 3H), 3.42 - 3.31 (m, 1H), 2.53 (s, 3H), 1.85 - 1.60 (m, 1H), 1.51 (dt, J = 11.8, 7.9 Hz, 1H), 0.93 (td, J = 7.3, 3.0 Hz, 3H).

Example 144 (for illustrative purposes)

[0706] Synthesis of (R)-2-chloro-6-fluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid **(144A):** The title compound was prepared according to the method presented for the synthesis of compound **74B** and **74C** starting with tert-butyl 4-bromo-2-chloro-6-fluorobenzoate.

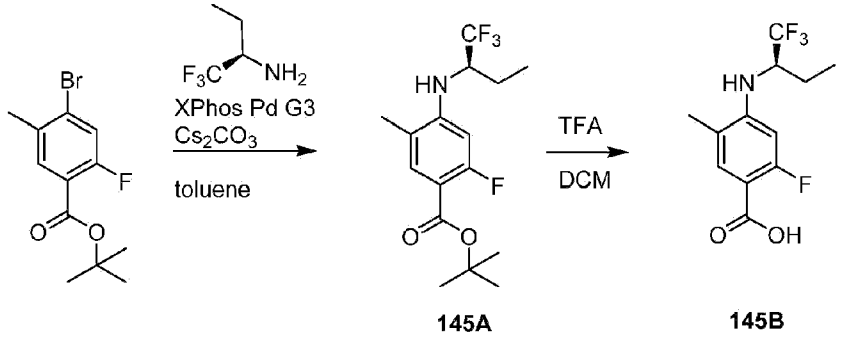


144A **144**

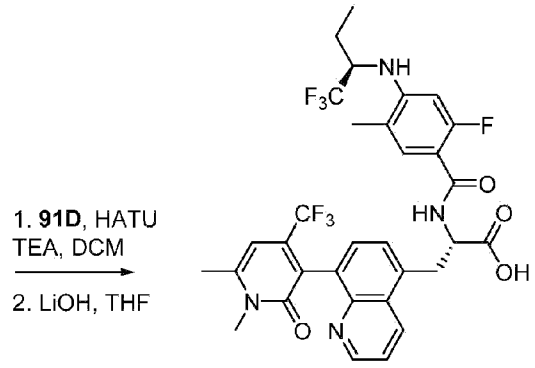
[0707] (S)-2-(2-chloro-6-fluoro-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(144):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **144A** and **91D.** MS (m/z) 687.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.97 (dd, J = 12.0, 8.1 Hz, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 7.69 - 7.54 (m, 2H), 7.43 (d, J = 6.2 Hz, 1H), 6.67 - 6.61 (m, 2H), 6.61 - 6.51 (m, 2H), 4.71 (dd, J = 23.5, 11.8 Hz, 1H), 4.31 (s, 1H), 3.76 - 3.63 (m, 1H), 3.49 (d, J = 3.4 Hz, 3H), 3.48 - 3.28 (m, 1H), 2.53 (s, 3H), 1.75 (d, J = 8.3 Hz, 1H), 1.66 - 1.46 (m, 1H), 1.01 - 0.88 (m, 3H).

Example 145 (for illustrative purposes)

[0708]



145A **145B**



145

[0709] Synthesis of tert-butyl (R)-2-fluoro-5-methyl-4-((1,1,1-trifluorobutan-2-yl)amino) benzoate **(145B):** The title compound was prepared according to the method presented for the synthesis of compound **74B** and **74C** starting with tert-butyl 4-bromo-2-fluoro-5-methylbenzoate.

[0710] (S)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)-2-(2-fluoro-5-methyl-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzamido)propanoic acid **(145):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **145B** and **91D.** MS (m/z) 667.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.0 Hz, 1H), 8.75 (t, J = 11.1 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.60 (dd, J = 24.9, 7.1 Hz, 2H), 7.53 - 7.41 (m, 1H), 7.36 - 7.18 (m, 1H), 6.76 - 6.61 (m, 1H), 6.55 (s, 1H), 5.52 (d, J = 8.6 Hz, 1H), 4.78 (s, 1H), 4.38 (s, 1H), 3.73 (t, J = 13.5 Hz, 1H), 3.59 (dd, J = 15.9, 9.6 Hz, 1H), 3.53 - 3.41 (m, 3H), 2.53 (d, J = 2.3 Hz, 3H), 2.10 (t, J = 2.9 Hz, 3H), 1.96 - 1.62 (m, 2H), 0.98 - 0.82 (m, 3H).

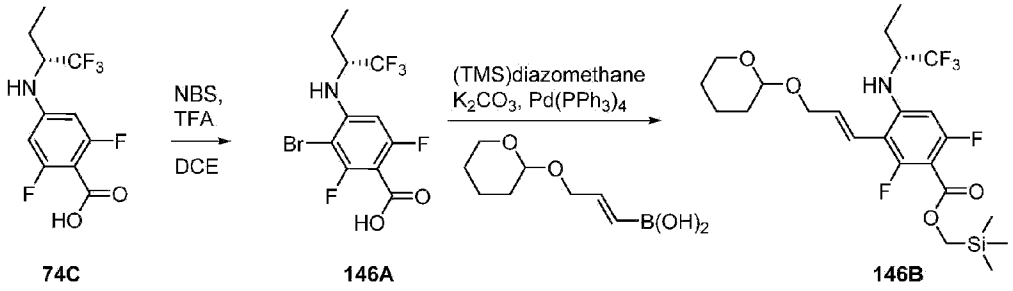
Example 146 (for illustrative purposes)

[0711] Synthesis of (R)-3-bromo-2,6-difluoro-4-((1,1,1-trifluorobutan-2-yl)amino)benzoic acid **(146A).** To stirred solution of **74C** (216 mg, 0.76mmol) in dichloroethane (4 mL) was added TFA (0.292 mL, 3.8 mmol), and N-bromosuccinimide (143 mg, 0.80 mmol) and the mixture was heated to 50 °C. After 1h the mixture was added to silica gel and chromatographed eluting with ethyl acetate in hexanes to the title compound.

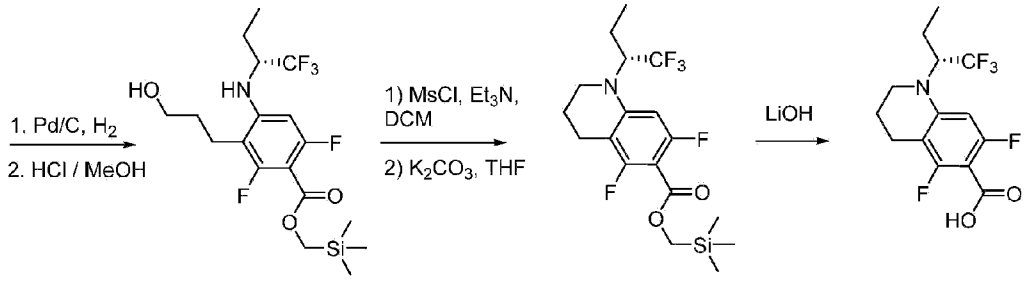
[0712] Synthesis of (trimethylsilyl)methyl 2,6-difluoro-3-((E)-3-((tetrahydro-2H-pyran-2-yl) oxy)prop-1-en-1-yl)-4-(((R)-1,1,1-trifluorobutan-2-yl)amino)benzoate **(146B).** To a microwave vial was added **146A** (230 mg, 0.635 mmol), dioxane (4 mL), (Trimethylsilyl)diazomethane solution (1N ether) (0.635 mL, 0.635 mmol), potassium carbonate (176 mg, 1.3 mmol) palladium tetrakis triphenylphosphine (73.4 mg, 0.06 mmol), and (E)-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-en-1-yl)boronic acid (236.31 mg, 1.27 mmol). The vessel was sealed and heated to 110 °C for 35 minutes. The mixture was then added to silica gel and

chromatographed eluting with ethyl acetate in hexanes to afford the title compound.

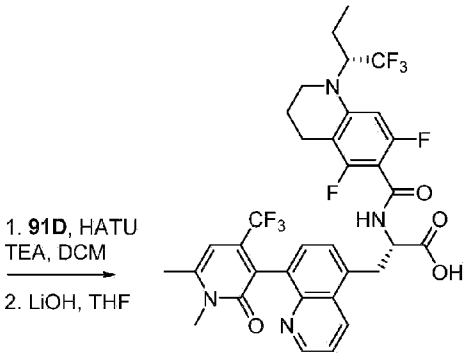
[0713] Synthesis of (trimethylsilyl)methyl (R)-2,6-difluoro-3-(3-hydroxypropyl)-4-((1,1,1-trifluorobutan-2-yl)amino)benzoate **(146C). 146B** (160 mg, 0.314 mmol), was added to a Parr shaker bottle with 5% palladium on charcoal (25 mg) and the mixture was shaken overnight under 50 PSI of H2. The mixture was filtered and HCl in methanol was added (9 mL, 3N) and the mixture was stirred for 4h. Volatile components of the mixture were removed on a rotary evaporator, dissolved in DCM, washed with sodium bicarbonate (aq) and the residue was chromatographed on silica gel eluting with methanol in DCM to afford the title compound.



74C 146A 146B



146C 146D 146E



146

[0714] Synthesis of (trimethylsilyl)methyl (R)-5,7-difluoro-1-(1,1,1-trifluorobutan-2-yl)-1,2,3,4-tetrahydroquinoline-6-carboxylate **(146D).** To a stirred solution of **146C** (107 mg, 0.215 mmol), and TEA (0.1 ml, 0.9 mmol) in DCM (1 mL) was added methanesulfonyl chloride (39 uL, 0.5 mmol) and let stir for ten minutes. The mixture was washed with sodium bicarbonate (aq) and the volatile components of the organic layer were removed on a rotary evaporator and diluted with THF (2 mL) and potassium carbonate was added (173 mg, 1.25 mmol) and the mixture

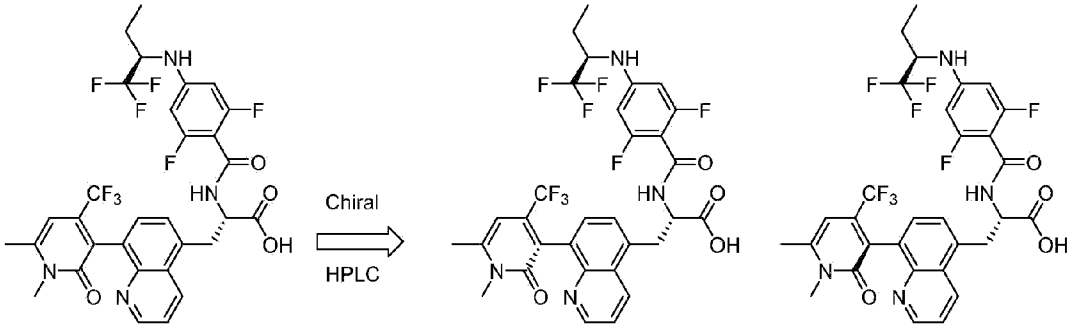
was heated to 70 °C overnight. The mixture was chromatographed on silica gel eluting with ethyl acetate in hexanes to afford the title compound.

[0715] Synthesis of (R)-5,7-difluoro-1-(1,1,1-trifluorobutan-2-yl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid **(146E).** To **146D** (95 mg, 0.2 mmol) was added methanol (10 mL) and lithium hydroxide (4 mg) and water (2 mL) and the mixture was stirred over the weekend at 85 °C. The mixture was neutralized with HCl in dioxane and the solvents were removed on a rotary evaporator. The title compound thus obtained was used without further purification.

[0716] (S)-2-(5,7-difluoro-1-((R)-1,1,1-trifluorobutan-2-yl)-1,2,3,4-tetrahydroquinoline-6-carboxamido)-3-(8-(1,6-dimethyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)quinolin-5-yl)propanoic acid **(146):** The title compound was prepared according to the method presented for the synthesis of compound **16A** and **16** starting with **91D** and **146E.** MS (m/z) 711.3 [M+H]+. 1H NMR (400 MHz, Chloroform-d) δ 9.30 (dd, J = 86.9, 8.7 Hz, 1H), 7.87 - 7.50 (m, 3H), 7.00 (d, J = 35.4 Hz, 1H), 6.53 (d, J = 12.4 Hz, 1H), 6.24 (dd, J = 14.4, 6.2 Hz, 1H), 5.00 (dd, J = 29.5, 6.2 Hz, 1H), 4.22 - 3.85 (m, 1H), 3.89 - 3.64 (m, 1H), 3.56 (d, J = 7.5 Hz, 3H), 3.25 (s, 2H), 2.74 - 2.61 (m, 2H), 2.10 - 1.66 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H).

Example 147 (for illustrative purposes)

[0717]

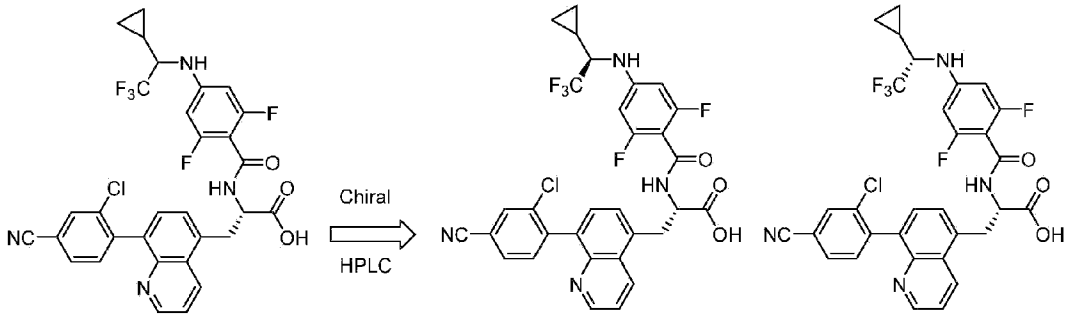


91 **107** **147**

[0718] Preparation of (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)quinolin-5-yl)propanoic acid **(147): 91** was separated into its 2 atropisomeric enantiomers by supercritical fluid chromatography using 30% MeOH co-solvent, at a flow rate of 60 mL/min, using an IC 5 µm 21x250 mm column. The title compound was identified as the second eluting peak. MS (m/z) 671.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.82 (t, J = 6.4 Hz, 2H), 8.67 (d, J = 8.7 Hz, 1H), 7.70 - 7.50 (m, 2H), 7.45 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 9.3 Hz, 1H), 6.55 (s, 1H), 6.43 (d, J = 11.9 Hz, 2H), 4.68 (m, 1H), 4.37 - 4.24 (m, 1H), 3.67 - 3.63 (m, 1H), 3.48 (m, 4H), 2.52 (s, 3H), 1.74 (m, 1H), 1.53 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

Example 148 (for illustrative purposes)

[0719] Preparation of (S)-3-(8-(2-chloro-4-cyanophenyl)quinolin-5-yl)-2-(2,6-difluoro-4-((R)-3-(trifluoromethyl)morpholino)benzamido)propanoic acid **(148): 89** was separated into its 2 enantiomers by supercritical fluid chromatography using 30% EtOH/TFA co-solvent, at a flow rate of 45 mL/min, using an IE 5 µm 21x250 mm column. The title compound was identified as the second eluting peak. MS (m/z) 629.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d6) δ 8.86 - 8.75 (m, 2H), 8.63 (dd, J = 8.6, 1.6 Hz, 1H), 8.15 (dd, J = 1.6, 0.4 Hz, 1H), 7.89 (dd, J = 7.9, 1.7 Hz, 1H), 7.66 - 7.51 (m, 4H), 6.92 (d, J = 9.4 Hz, 1H), 6.40 (d, J = 11.8 Hz, 2H), 4.67 (s, 1H), 3.97 - 3.89 (m, 1H), 3.72 (s, 1H), 3.40 (s, 1H), 1.03 (ddt, J = 13.0, 8.1, 4.2 Hz, 1H), 0.66 - 0.55 (m, 1H), 0.55 - 0.43 (m, 2H), 0.30 (dd, J = 9.7, 4.9 Hz, 1H).



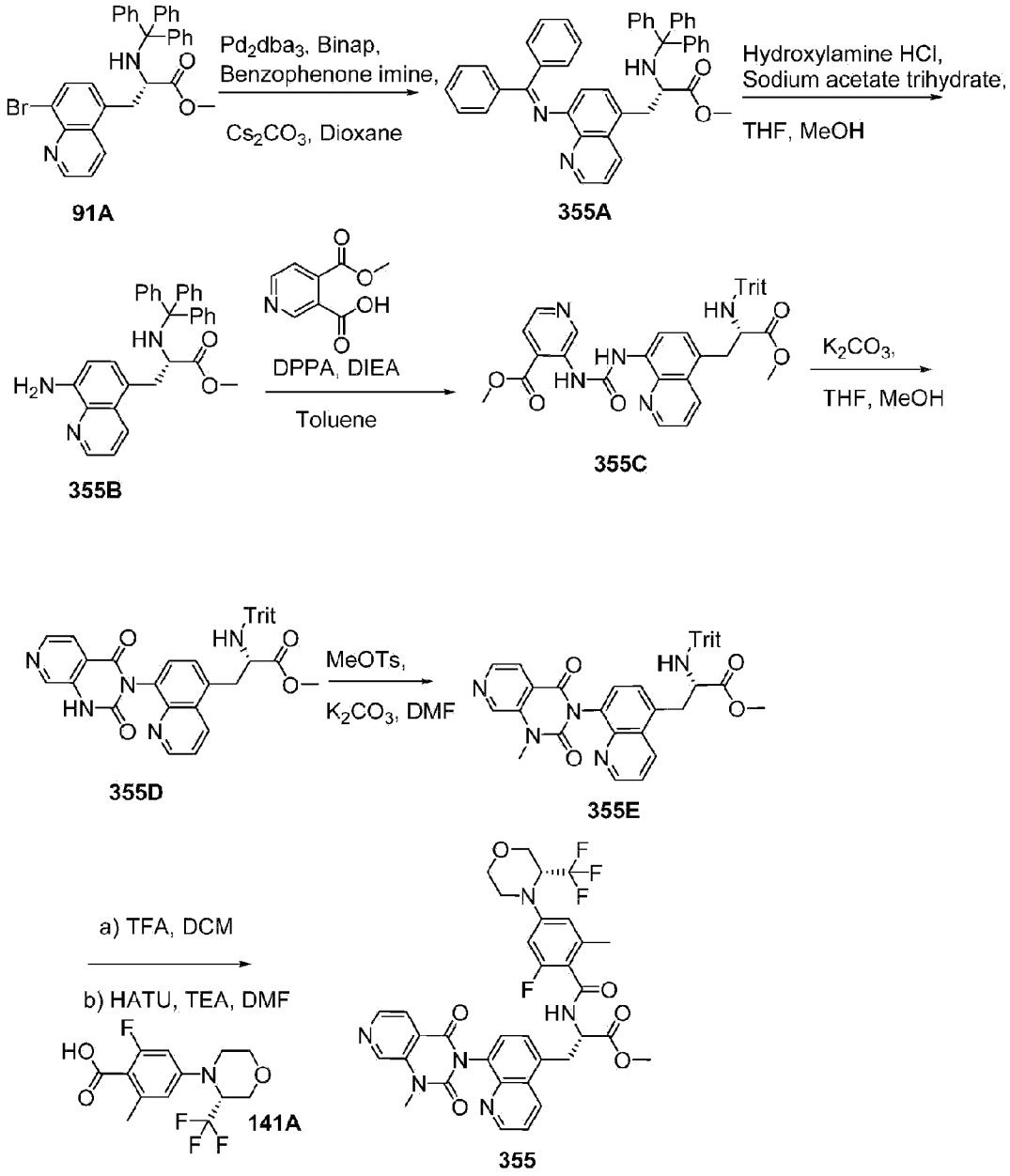
89 90 148

Example 355 (for illustrative purposes)

[0720] Synthesis of methyl (S)-3-(8-((diphenylmethylene)amino)quinolin-5-yl)-2-(tritylamino)propanoate **(355A):** To a flame-dried 200 mL flask equipped with a stir bar was added 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (Binap ligand) (1.26 g, 2.029 mmol, 0.10 eq) in dioxane (101 mL, 0.2 M) and the flask was vacuum purged then flushed with N_2 3 times. Bis(dibenzylideneacetone)palladium (Palladium dba) (0.93 g, 1.015 mmol, 0.05 eq) was added and the reaction was allowed to stir at room temperature for 10 minutes. Cesium carbonate (19.83 g, 60.87 mmol, 3 eq.), benzophenone imine (6.81 mL, 40.58 mmol, 2 eq.), and methyl (S)-3-(8-bromoquinolin-5-yl)-2-(tritylamino)propanoate **(91A)** (11.19 g, 20.29 mmol, 1 eq.) were added and the reaction was heated to 100 °C under a N_2 balloon and stirred overnight. The reaction was cooled to room temperature and quenched by the addition of water (100 mL). The reaction mixture was then extracted with ethyl acetate (100 mL, 3x), the combined organic phases were washed with brine (100 mL) and dry packed onto silica gel. Purification was performed via silica gel chromatography eluting with 20% EtOAc in hexanes until excess benzophenone imine was eluted (~20 min), then the percentage of EtOAc was increased to 25% in hexanes to elute product. Product containing fractions were concentrated under vacuum.

[0721] Synthesis of methyl (S)-3-(8-aminoquinolin-5-yl)-2-(tritylamino)propanoate **(355B): 355A** (11.19 g, 17.17 mmol, 1 eq.) was dissolved in THF (100 mL) to which was added

hydroxylamine HCl (4.77 g, 68.67 mmol, 4 eq.), and sodium acetate trihydrate (14.02 g, 103.01 mmol, 6 eq.). MeOH (50 mL) was added and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was concentrated under vacuum and absorbed onto pre-packed silica gel. Purification was performed via silica gel chromatography using 20% EtOAc in Hexanes until excess hydroxyl-imine was eluted (~20 min), then the percentage of EtOAc was increased to 25% in hexanes to elute product. Product containing fractions were concentrated under vacuum.



[0722] Synthesis of methyl (S)-3-(3-(5-(3-methoxy-3-oxo-2-(tritylamino)propyl)quinolin-8-yl)ureido)isonicotinate **(355C):** To a flame-dried flask equipped with a stir bar was added 4-methoxycarbonylpyridine-3-carboxylic acid (0.22 g, 1.23 mmol, 1.2 eq.), triethylamine (0.43 ml, 3.08 mmol, 3 eq.), DPPA (0.24 mL, 1.13 mmol, 1.1 eq.), **355B,** and toluene (5.12 mL, 0.2 M). The reaction was affixed with a condenser (open to atmosphere) and heated to 50° C for 2 h.

The reaction was quenched with water (50 mL) and extracted with EtOAc (50 mL, 3x). The combined organic phases were washed with sat. sodium bicarbonate (25 mL), brine, and dried over anhydrous Na_2SO_4. Organic phases were concentrated and used without further purification.

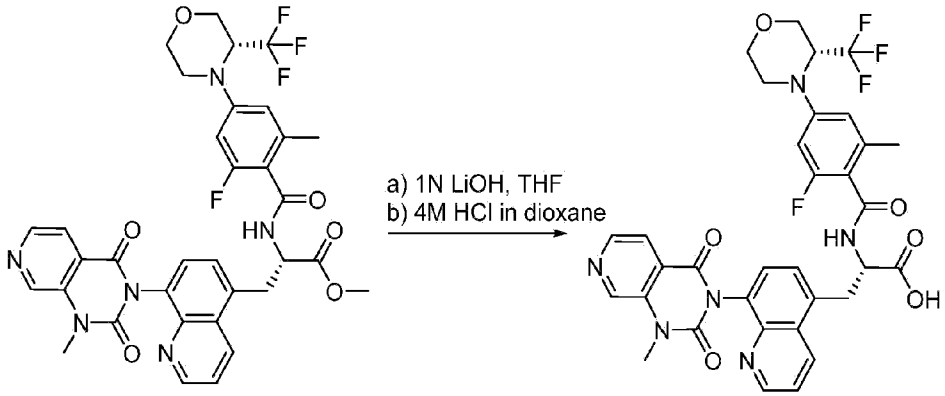
[0723] Synthesis of methyl (S)-3-(8-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)-2-(tritylamino)propanoate **(355D): 355C** (0.68 g, 1.03 mmol, 1.0 eq.) was dissolved in THF (4 mL) and MeOH (4 mL), to which was added solid potassium carbonate (0.71 g, 5.13 mmol, 5 eq.). The reaction mixture was allowed to stir 1 h at room temperature. The reaction was diluted with water and sat. NH_4Cl (4 mL), extracted with EtOAc (20 mL, 3x), washed with brine, and dried over Na_2SO_4. The combined organic phases were concentrated, EtOAc (~10 mL) was added, then hexanes was added dropwise under stirring to form a precipitate. The filtrate was collected and dried under high vacuum.

[0724] Synthesis of methyl (S)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)-2-(tritylamino)propanoate **(355E):** To a flame-dried flask was added Intermediate **355D** (4.05 g, 6.396 mmol, 1.0 eq.), potassium carbonate (0.88 g, 6.4 mmol, 1.0 eq.) and DMF (32 mL, 0.2 M). The reaction mixture was stirred for 10 minutes at room temperature, then methyl tosylate (0.97 mL, 6.4 mmol, 1.0 eq.) was added and the reaction was allowed to stir overnight at room temperature. The reaction was concentrated and purified via silica gel chromatography eluting with DCM/MeOH 0-5%.

[0725] Synthesis of methyl (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl) morpholino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoate **(355): 355E** (1.49 g, 2.29 mmol, 1 eq.) was dissolved in DCM (51 mL) and triethylsilane (0.44 mL, 2.75 mmol, 1.2 eq.), and TFA (0.53 ml, 6.88 mmol, 3 eq.) were added. The reaction mixture was allowed to stir at room temperature for 2 h, then concentrated. The resulting material was re-suspended in DCM and concentrated again under vacuum to remove residual TFA. The material was used without further purification. The resulting material (1.47 g, 2.31 mmol, 1.0 eq.), **141A** (0.85 g, 2.78 mmol, 1.2 eq.), and HATU (1.06 g, 2.78 mmol, 1.2 eq.) were added to a vial and dissolved in DMF (10 mL). DIEA (2.42 mL, 13.89 mmol, 6.0 eq.) was added and the reaction was allowed to stir at room temperature for 2 h. The reaction was quenched with water and extracted with EtOAc, organic phases were washed with brine, and dried over Na_2SO_4. The organic phases were concentrated and purified via silica gel chromatography using DCM/MeOH 0-5%. ES/MS m/z [M+H]: 695.198; 1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.95 - 8.80 (m, 2H), 8.71 (dd, J = 8.7, 1.6 Hz, 1H), 8.60 (dd, J = 4.9, 1.4 Hz, 1H), 7.92 (ddd, J = 4.8, 3.8, 0.7 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.75 - 7.63 (m, 2H), 6.73 - 6.63 (m, 2H), 4.90 - 4.72 (m, 2H), 4.14 (d, J = 12.6 Hz, 1H), 3.94 (dd, J = 11.4, 3.6 Hz, 1H), 3.83 - 3.69 (m, 3H), 3.66 (d, J = 2.5 Hz, 3H), 3.51 (ddd, J = 25.5, 13.6, 9.8 Hz, 2H), 3.35 (d, J = 12.2 Hz, 1H), 3.26 (d, J = 12.3 Hz, 1H), 2.09 - 1.95 (m, 3H).

Example 356 (for illustrative purposes)

[0726]

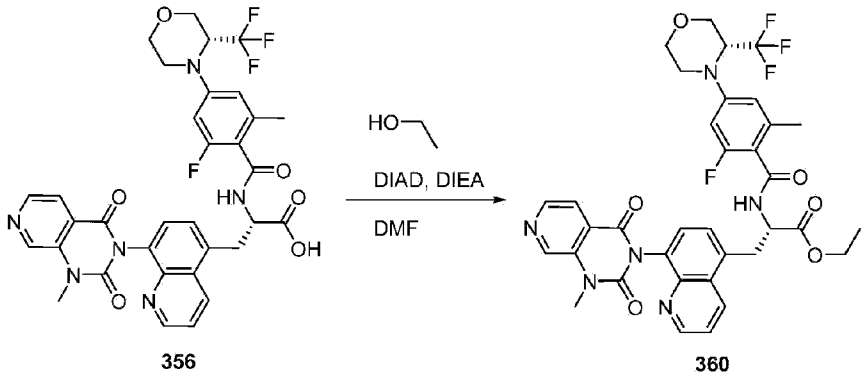


355 356

[0727] (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoic acid **(356):** **355** (0.49 g, 0.70 mmol, 1.0 eq.) was dissolved in THF (10 mL) and 1M LiOH (3.5 ml, 5 eq.) was added. The reaction mixture was allowed to stir at room temperature for 2 h. 4 M HCl in dioxane (1.75 mL, 10 eq.) was then added to re-cyclize, and the reaction mixture was allowed to stir for 1 h. The reaction was concentrated and purified via reverse phase HPLC, lyophilized to afford the title compound as a mono-TFA salt. ES/MS (m/z) [M+H]: 681.151 1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.92 - 8.77 (m, 2H), 8.68 (d, J = 8.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (t, J = 4.3 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.67 (dd, J = 8.3, 4.5 Hz, 2H), 6.74 - 6.58 (m, 2H), 5.00 - 4.59 (m, 2H), 4.14 (d, J = 12.6 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.66 (d, J = 2.4 Hz, 4H), 3.59 - 3.40 (m, 1H), 3.31 (dd, J = 35.1, 12.3 Hz, 3H), 2.03 (s, 3H).

Example 360

[0728]



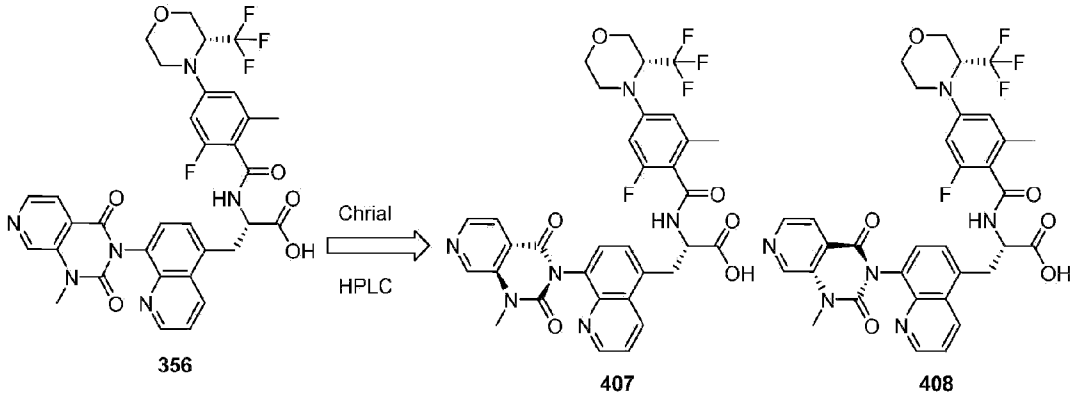
356 360

[0729] Ethyl (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino)benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoate **(360):** To a solution of **356** (150 mg, 0.22 mmol) in DMF (1.0 mL) was added triphenylphosphine (173

mg, 0.66 mmol) followed by DIEA (117 µL, 0.66 mmol) and ethanol (129 µL, 2.2 mmol). DIAD (217 µL, 1.1 mmol) was then added and the reaction mixture was allowed to stir for 2 hours. The reaction mixture was then diluted with EtOAc and washed with water, 10% citric acid, saturated sodium bicarbonate, and brine followed by drying the combined organics over sodium sulfate. After filtration, the solvent was removed under reduced pressure and the product was purified by normal phase using an elution gradient of 0-30%, 30-60%, and 60-100% 9:1 DCM:MeOH in DCM. ES/MS (m/z) [M+H]: 709.2. 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.2, 1.4 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.91 (dd, J = 5.0, 2.2 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.66 (dt, J = 8.6, 2.5 Hz, 2H), 6.76 - 6.63 (m, 2H), 4.82 (td, J = 14.4, 12.1, 5.3 Hz, 2H), 4.20 - 4.04 (m, 3H), 3.95 (dd, J = 11.5, 3.6 Hz, 1H), 3.80 - 3.66 (m, 2H), 3.65 (d, J = 1.6 Hz, 3H), 3.60 - 3.46 (m, 2H), 3.36 (d, J = 13.7 Hz, 1H), 3.31 -3.18 (m, 1H), 2.07 (s, 3H), 1.16 (td, J = 7.1, 1.1 Hz, 3H).

Examples 407 and 408

[0730]



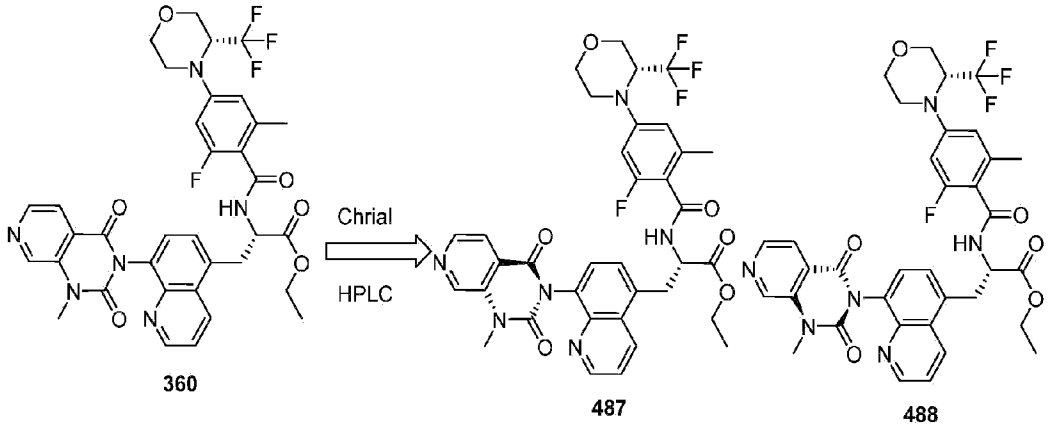
[0731] Preparation of (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoic acid **(407): 356** was separated into its 2 atropisomeric enantiomers by supercritical fluid chromatography using 30% EtOH co-solvent, at a flow rate of 3 mL/min, using an AD-H 5 µm 4.6x100 mm column. The title compound was identified as the second eluting peak. ES/MS (m/z) 681.2 (M+H)+. 1H NMR (400 MHz, Chloroform-d) δ 8.84 - 8.72 (m, 2H), 8.66 (d, J = 8.6 Hz, 1H), 8.55 (s, 1H), 8.00 (s, 1H), 7.58 (s, 2H), 7.44 (dd, J = 8.6, 4.2 Hz, 1H), 6.66 (d, J = 6.5 Hz, 1H), 6.46 (s, 1H), 6.37 (d, J = 13.6 Hz, 1H), 5.08 (d, J = 7.0 Hz, 1H), 4.29 (d, J = 12.4 Hz, 1H), 4.11 (dd, J = 8.2, 3.8 Hz, 1H), 4.04 (dd, J = 11.3, 3.5 Hz, 1H), 3.84 - 3.70 (m, 3H), 3.68 (s, 3H), 3.65 - 3.56 (m, 1H), 3.50 (t, J = 12.0 Hz, 1H), 3.26 (d, J = 12.2 Hz, 1H), 2.38 (s, 3H).

[0732] Preparation (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-

yl)propanoic acid **(408): 356** was separated into its 2 atropisomeric enantiomers by supercritical fluid chromatography using 30% EtOH co-solvent, at a flow rate of 3 mL/min, using an AD-H 5 µm 4.6x100 mm column. The title compound was identified as the first eluting peak. ES/MS (m/z) 681.2 (M+H)+. 1H NMR (400 MHz, Chloroform-d) δ 8.83 - 8.72 (m, 2H), 8.64 (d, J = 8.6 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.59 (q, J = 7.6 Hz, 2H), 7.46 (dd, J = 8.6, 4.2 Hz, 1H), 6.63 (d, J = 6.1 Hz, 1H), 6.47 (s, 1H), 6.38 (dd, J = 13.4, 2.4 Hz, 1H), 5.13 - 5.02 (m, 1H), 4.30 (d, J = 12.4 Hz, 1H), 4.12 (dd, J = 8.0, 3.8 Hz, 1H), 4.04 (dd, J = 11.2, 3.5 Hz, 1H), 3.86 - 3.78 (m, 1H), 3.72 (t, J = 5.6 Hz, 2H), 3.69 (s, 3H), 3.65 - 3.59 (m, 1H), 3.51 (t, J = 11.7 Hz, 1H), 3.27 (d, J = 12.3 Hz, 1H), 2.39 (s, 3H).

Examples 487 and 488

[0733] Preparation ethyl (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoate **(487): 360** was separated into its 2 atropisomeric enantiomers by supercritical fluid chromatography using 30% EtOH co-solvent, at a flow rate of 3 mL/min, using an AD-H 5 µm 4.6x100 mm column. The title compound was identified as the first eluting peak. ES/MS (m/z) 709.2 (M+H)+. 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.1, 1.5 Hz, 1H), 8.64 (dd, J = 8.6, 1.6 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.91 (dd, J = 4.9, 0.7 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.69 - 7.63 (m, 2H), 6.76 - 6.63 (m, 2H), 4.90 - 4.74 (m, 2H), 4.19 - 4.06 (m, 3H), 3.95 (dd, J = 11.4, 3.6 Hz, 1H), 3.78 - 3.67 (m, 2H), 3.65 (s, 3H), 3.61 - 3.46 (m, 2H), 3.37 (s, 1H), 3.31 - 3.18 (m, 1H), 2.07 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H).



360 487 488

[0734] Preparation ethyl (S)-2-(2-fluoro-6-methyl-4-((R)-3-(trifluoromethyl)morpholino) benzamido)-3-(8-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)quinolin-5-yl)propanoate **(488): 360** was separated into its 2 atropisomeric enantiomers by Simulated moving bed (SMB) chromatography using EA/heptanes (80/20), using a ChiralPak IC column. The title compound was identified as the second eluting peak. ES/MS (m/z) 709.2 (M+H)+. 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.2, 1.5 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 4.9 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.69 - 7.63 (m, 2H), 6.75 - 6.62 (m, 2H), 4.91 - 4.75 (m, 2H), 4.20 - 4.07 (m,

3H), 3.95 (dd, J = 11.4, 3.6 Hz, 1H), 3.78 - 3.67 (m, 2H), 3.66 (s, 3H), 3.60 - 3.47 (m, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.25 (t, J = 12.3 Hz, 1H), 2.07 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H).

α4β7 Integrin Cell Capture Assay

[0735] 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. 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.

[0736] RPMI8866 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 ECso of the test compounds. Results were presented in Tables 1 and 2.

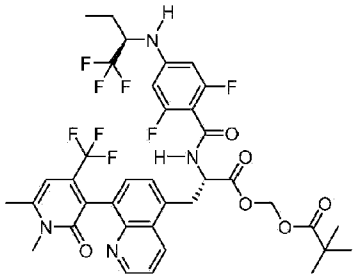
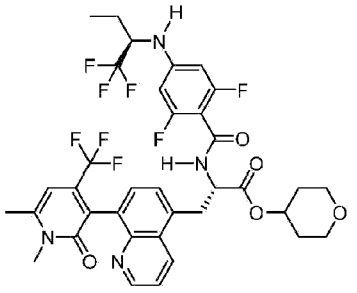
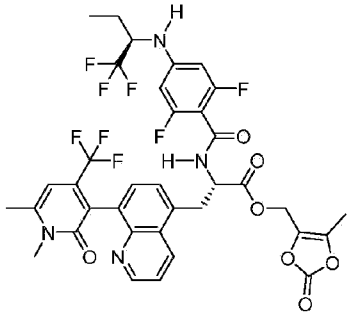
TABLE 1

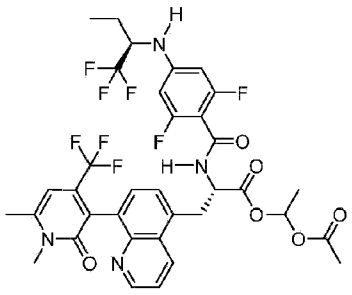
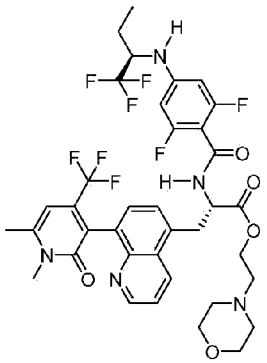
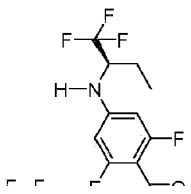
Example#	**α4β7 EC_{50} (nM)**	**Example#**	**α4β7 EC_{50} (nM)**	**Example#**	**α4β7 EC_{50} (nM)**	**Example#**	**α4β7 EC_{50} (nM)**
1	21.2	**38**	29.7	**75**	80.4	**112**	0.4
2	31.1	**39**	81.6	**76**	78.4	**113**	1.2
3	63.8	**40**	8.6	**77**	90.7	**114**	0.6
4	6.7	**41**	7.7	**78**	134.3	**115**	0.6
5	17.4	**42**	13.4	**79**	26.1	**116**	1.2
6	4.5	**43**	4.6	**80**	18.1	**117**	0.7
7	1.9	**44**	10.9	**81**	6.0	**118**	1.5
8	41.4	**45**	3.4	**82**	4.7	**119**	20.5
9	25.1	**46**	20.0	**83**	32.9	**120**	1.3
10	21.2	**47**	2.4	**84**	11.7	**121**	1.7
11	22.9	**48**	52.1	**85**	25.4	**122**	0.2
12	7.0	**49**	33.7	**86**	8.3	**123**	0.9

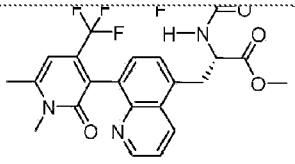
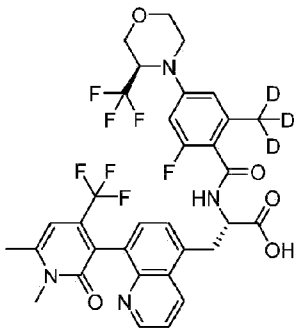
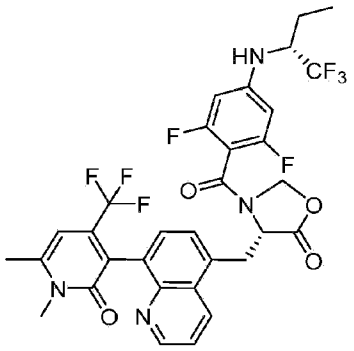
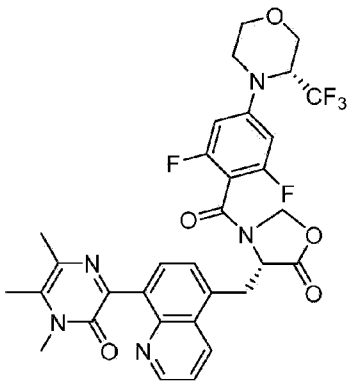
Example#	α4β7 EC_{50} (nM)	Example#	α4β7 EC_{50} (nM)	Example#	α4β7 EC_{50} (nM)	Example#	α4β7 EC_{50} (nM)
13	8.5	**50**	0.4	**87**	15.0	**124**	0.6
14	3.7	**51**	2.9	**88**	8.2	**125**	1.0
15	9.3	**52**	91.5	**89**	14.4	**126**	0.6
16	67.4	**53**	3.0	**90**	11.3	**127**	9.3
17	36.7	**54**	37.4	**91**	0.3	**128**	0.3
18	9.0	**55**	27.4	**92**	2.0	**129**	0.7
19	50.0	**56**	9.1	**93**	0.4	**130**	0.5
20	185.8	**57**	30.0	**94**	0.5	**131**	0.8
21	96.6	**58**	2.0	**95**	0.3	**132**	1.3
22	48.5	**59**	3.2	**96**	0.2	**133**	3.2
23	46.7	**60**	3.0	**97**	3.2	**134**	4.2
24	56.7	**61**	4.2	**98**	1.4	**135**	0.4
25	3.3	**62**	1.8	**99**	11.2	**136**	0.2
26	32.8	**63**	30.5	**100**	0.7	**137**	0.4
27	12.8	**64**	0.8	**101**	4.1	**138**	0.8
28	33.5	**65**	8.4	**102**	0.3	**139**	11.7
29	68.7	**66**	18.9	**103**	0.7	**140**	0.5
30	16.9	**67**	1.6	**104**	0.5	**141**	0.1
31	19.3	**68**	14.0	**105**	4.1	**142**	0.2
32	75.9	**69**	28.9	**106**	0.3	**143**	0.3
33	60.5	**70**	10.7	**107**	0.2	**144**	0.2
34	39.5	**71**	9.5	**108**	1.0	**145**	3.1
35	6.2	**72**	5.5	**109**	0.3	**146**	0.6
36	21.0	**73**	2.5	**110**	0.3	**147**	1.9
37	69.6	**74**	13.6	**111**	0.1	**148**	60.6

[0737] Examples 346-354 in Table 2 were prepared by processes described herein.

TABLE 2

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
346		1H NMR (400 MHz, DMSO-d6) δ 9.00 (dd, J = 12.1, 7.5 Hz, 1H), 8.82 (d, J = 4.2 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H), 7.68 - 7.56 (m, 2H), 7.44 (dd, J = 7.2, 2.9 Hz, 1H), 6.81 - 6.73 (m, 1H), 6.55 (s, 1H), 6.45 (dd, J = 11.5, 5.6 Hz, 2H), 5.76 (dd, J = 11.1, 6.1 Hz, 2H), 4.74 (dd, J = 13.7, 7.1 Hz, 1H), 4.34 (d, J = 2.1 Hz, 1H), 3.70 - 3.61 (m, 1H), 3.51 (s, 3H), 3.43 (d, J = 10.0 Hz, 1H), 2.53 (s, 3H), 1.76 (d, J = 8.0 Hz, 1H), 1.53 (dq, J = 13.7, 7.1 Hz, 1H), 1.16 (d, J = 1.9 Hz, 9H), 0.92 (t, J = 7.3 Hz, 3H).	785.2	NA
347		1H NMR (400 MHz, DMSO-d6) δ 8.98 (t, J = 6.8 Hz, 1H), 8.82 (d, J = 4.2 Hz, 1H), 8.62 (d, J = 8.6 Hz, 1H), 7.63 (dd, J = 8.5, 4.3 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 6.79 (dd, J = 9.5, 4.4 Hz, 1H), 6.55 (s, 1H), 6.47 (dd, J = 11.4, 3.9 Hz, 2H), 4.86 (d, J = 9.4 Hz, 1H), 4.69 (d, J = 13.6 Hz, 1H), 4.35 - 4.28 (m, 1H), 3.82 - 3.60 (m, 3H), 3.57 - 3.36 (m, 6H), 2.53 (s, 3H), 1.85 - 1.65 (m, 3H), 1.53 (ddd, J = 17.2, 8.9, 5.3 Hz, 2H), 1.39 (t, J = 9.7 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H).	755.2	NA
348		1H NMR (400 MHz, DMSO-d6) δ 9.00 (t, J = 7.1 Hz, 1H), 8.83 (d, J = 4.2 Hz, 1H), 8.63 (s, 1H), 7.62 (dd, J = 8.9, 4.6 Hz, 1H), 7.55 (t, J = 7.0 Hz, 1H), 7.44 (t, J = 6.6 Hz, 1H), 6.78 (d, J = 9.8 Hz, 1H), 6.55 (s, 1H), 6.45 (d, J = 11.9 Hz, 2H), 5.06 - 4.96 (m, 2H), 4.74 (d, J = 7.9 Hz, 1H), 4.32 (d, J = 9.2 Hz, 1H), 3.67 (dt, J = 12.6, 5.8 Hz, 1H), 3.49 (s, 4H), 2.53 (s,	783.2	NA

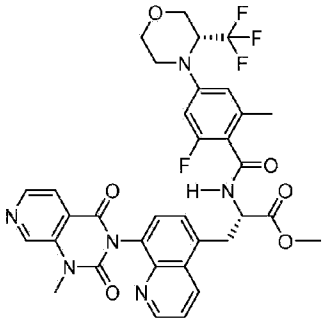
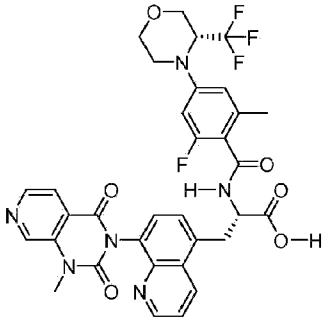
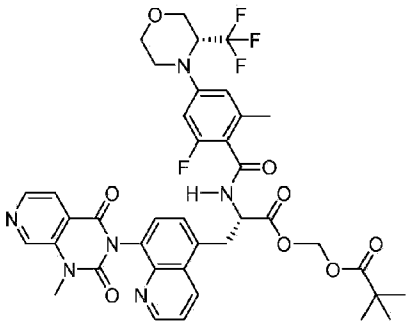
Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		3H), 2.14 (d, J = 3.7 Hz, 3H), 1.76 (d, J = 10.4 Hz, 1H), 1.53 (d, J = 9.1 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H).		
349		1H NMR (400 MHz, DMSO-d6) δ 9.06 - 8.93 (m, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.56 (t, J = 10.6 Hz, 1H), 7.65 - 7.51 (m, 2H), 7.44 (d, J = 6.4 Hz, 1H), 6.85 - 6.69 (m, 2H), 6.54 (s, 1H), 6.50 - 6.35 (m, 2H), 4.79 - 4.65 (m, 1H), 4.32 (s, 1H), 3.63 (d, J = 13.8 Hz, 1H), 3.49 (s, 4H), 2.53 (s, 3H), 2.08 - 1.97 (m, 2H), 1.77 (s, 1H), 1.55 (d, J = 15.3 Hz, 1H), 1.44 (t, J = 5.0 Hz, 1H), 1.29 (d, J = 5.4 Hz, 1H), 0.93 (q, J = 6.5, 5.8 Hz, 2H), -0.00 (d, J = 1.6 Hz, 3H).	757.2	NA
350		1H NMR (400 MHz, DMSO-d6) δ 9.81 (d, J = 41.6 Hz, 1H), 9.08 (t, J = 8.0 Hz, 1H), 8.83 (t, J = 5.3 Hz, 1H), 8.58 (dd, J = 37.4, 9.3 Hz, 1H), 7.66 - 7.56 (m, 1H), 7.46 (dd, J = 9.5, 6.6 Hz, 1H), 6.85 (d, J = 9.6 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 6.49 (dd, J = 11.5, 2.6 Hz, 2H), 4.86 - 4.76 (m, 1H), 4.47 - 4.37 (m, 1H), 4.38 - 4.29 (m, 1H), 4.24-4.14 (m, 1H), 3.99 - 3.90 (m, 1H), 3.73 (dd, J = 15.6, 4.8 Hz, 1H), 3.70 - 3.60 (m, 2H), 3.59 - 3.52 (m, 1H), 3.50 (s, 2H), 3.43 - 3.34 (m, 1H), 3.34 - 3.26 (m, 2H), 3.22 - 3.08 (m, 2H), 2.54 (d, J = 2.3 Hz, 3H), 1.83 - 1.72 (m, 1H), 1.57 - 1.46 (m, 1H), 0.96-0.90 (m, 3H).	784. 2	NA
351		1H NMR (400 MHz, DMSO-d6) δ 9.01 - 8.91 (m, 1H), 8.79 (d, J = 4.3 Hz, 1H), 8.57 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 8.5, 4.2 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H),	685.2	NA

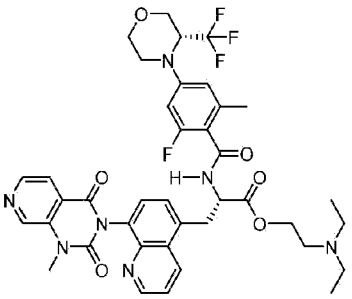
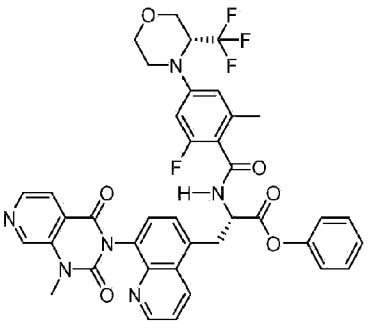
Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		6.78 (dd, J = 9.4, 6.0 Hz, 1H), 6.53 (d, J = 0.9 Hz, 1H), 6.44 (dd, J = 11.5, 5.7 Hz, 2H), 4.72 (dd, J = 10.4, 7.2 Hz, 1H), 4.30 (s, 1H), 3.72 - 3.29 (m, 6H), 2.51 (s, 3H), 1.80 - 1.71 (m, 1H), 1.58 - 1.45 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H).		
352		1H NMR (400 MHz, DMSO-d6) δ 8.88 - 8.77 (m, 2H), 8.66 (d, J = 8.7 Hz, 1H), 7.70 - 7.56 (m, 2H), 7.45 (t, J = 7.2 Hz, 1H), 6.71 - 6.60 (m, 2H), 6.55 (d, J = 3.3 Hz, 1H), 4.89 - 4.69 (m, 2H), 4.14 (d, J = 12.6 Hz, 1H), 3.99 - 3.89 (m, 1H), 3.81 - 3.73 (m, 2H), 3.55 - 3.42 (m, 4H), 3.41 - 3.30 (m, 1H), 3.30 - 3.17 (m, 1H), 2.53 (s, 3H).	698.13	NA
353		1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.64 (d, J = 8.5 Hz, 1H), 7.54 (s, 1H), 7.52 - 7.35 (m, 2H), 7.00 (t, J = 10.6 Hz, 1H), 6.50 (d, J = 30.6 Hz, 3H), 5.31 (d, J = 6.2 Hz, 1H), 5.08 (s, 1H), 4.67 (s, 1H), 4.57 (s, 1H), 4.35 (s, 1H), 3.49 (s, 3H), 2.53 (s, 3H), 1.78 (s, 1H), 1.53 (d, J = 15.1 Hz, 1H), 1.25 (d, J = 6.4 Hz, 1H), 0.93 (d, J = 6.2 Hz, 3H).	683.2	NA
354		1H NMR (400 MHz, DMSO-d6) δ 8.86 (m, 2H), 7.75 (s, 1H), 7.67 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 9.4 Hz, 1H), 6.54 (d, J = 12.4 Hz, 2H), 5.36 (d, J = 4.4 Hz, 1H), 5.03 (m, 2H), 3.79 (d, J = 6.2 Hz, 1H), 3.53 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H), 1.79 (m, 1H), 1.55 (s, 1H), 0.94 (t, J = 7.4 Hz, 3H)	630.2	NA

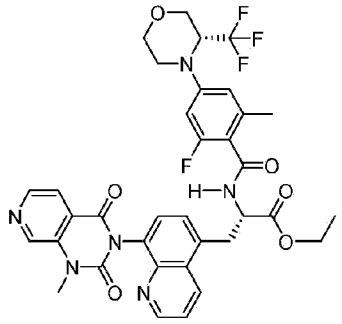
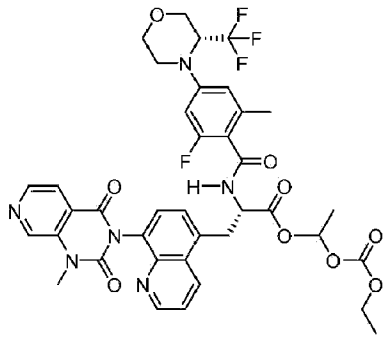
[0738] Examples 355-368, 408, 474, 487, 488, and 494 in Table 3 were prepared by

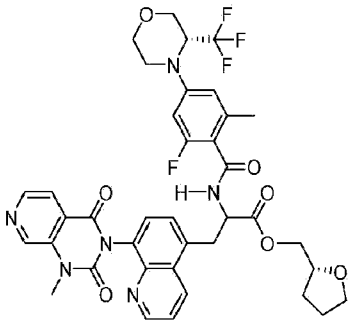
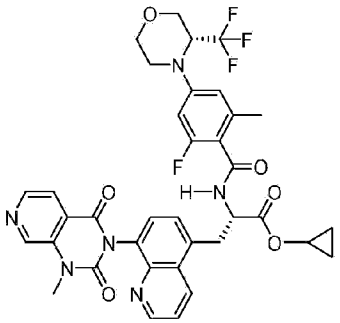
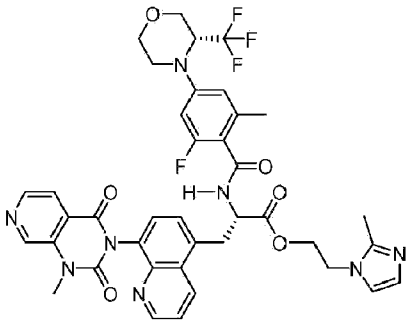
processes described herein.

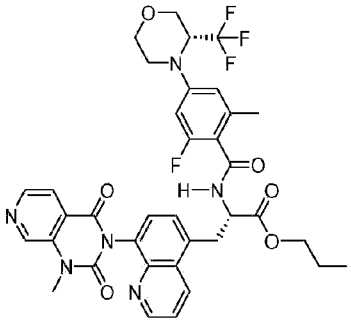
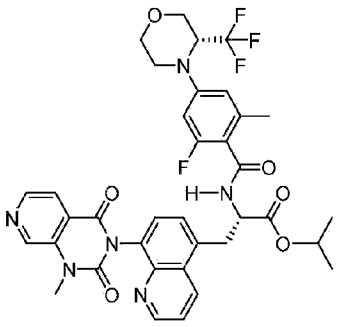
TABLE 3

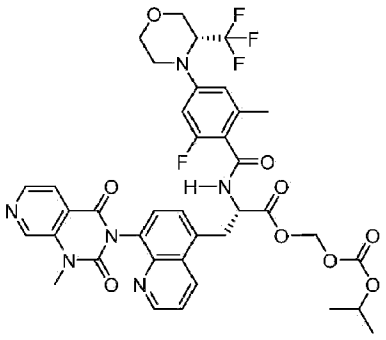
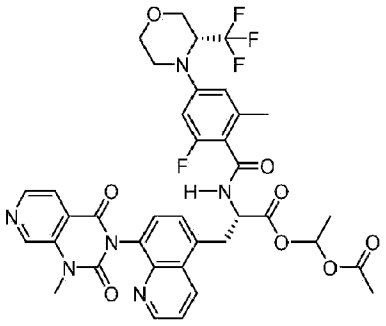
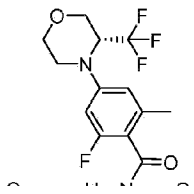
Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
355		1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 9.00 (d, J = 7.7 Hz, 1H), 8.85 (d, J = 4.1 Hz, 1H), 8.66 (dd, J = 8.7, 1.5 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.91 (dd, J = 4.9, 3.2 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.72 - 7.58 (m, 2H), 6.79 - 6.61 (m, 2H), 4.83 (td, J = 9.2, 8.4, 4.4 Hz, 2H), 4.15 (d, J = 12.6 Hz, 1H), 3.93 (d, J = 3.7 Hz, 1H), 3.68 (s, 3H), 3.66 (d, J = 2.3 Hz, 4H), 3.53 (dp, J = 14.9, 5.8, 5.2 Hz, 2H), 3.40 - 3.18 (m, 2H), 2.05 (s, 3H).	695.2	NA
356		1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.92 - 8.77 (m, 2H), 8.68 (d, J = 8.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (t, J = 4.3 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.67 (dd, J = 8.3, 4.5 Hz, 2H), 6.74 - 6.58 (m, 2H), 5.00 - 4.59 (m, 2H), 4.14 (d, J = 12.6 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.66 (d, J = 2.4 Hz, 4H), 3.59 - 3.40 (m, 1H), 3.31 (dd, J = 35.1, 12.3 Hz, 3H), 2.03 (s, 3H).	681.2	0.05
357		1H NMR (400 MHz, DMSO-d6) δ 9.15 - 9.00 (m, 2H), 8.85 (d, J = 3.9 Hz, 1H), 8.67 - 8.57 (m, 2H), 7.91 (ddd, J = 5.0, 3.1, 0.8 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.73 - 7.61 (m, 2H), 5.83 (s, 2H), 4.85 (d, J = 9.2 Hz, 2H), 4.14 (d, J = 12.6 Hz, 1H), 4.06 - 3.88 (m, 1H), 3.84 - 3.68 (m, 2H), 3.65 (d, J = 2.2 Hz, 3H), 3.53 (dt, J = 14.8, 9.7	795.3	NA

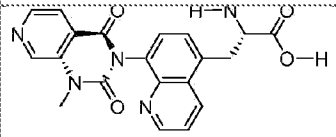
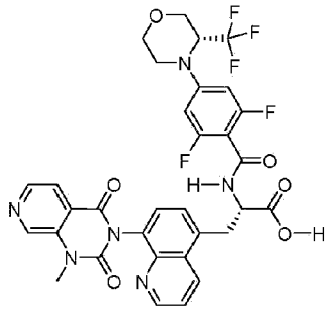
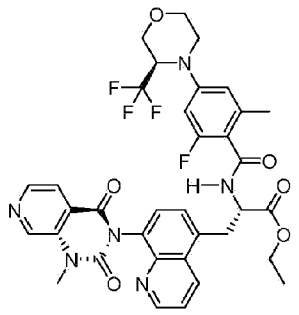
Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		Hz, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 12.1 Hz, 1H), 2.03 (s, 3H), 1.18 (s, 9H).		
358		1H NMR (400 MHz, Chloroform-d) δ 9.28 (dt, J = 4.8, 1.6 Hz, 1H), 9.20 (ddd, J = 8.7, 4.6, 1.5 Hz, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.62 (dd, J = 5.0, 1.6 Hz, 1H), 8.04 (dd, J = 24.7, 5.0 Hz, 1H), 7.83 (dd, J = 8.6, 4.7 Hz, 1H), 7.75 (d, J = 1.2 Hz, 2H), 7.46 (d, J = 7.0 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.43 - 6.27 (m, 1H), 5.18 (q, J = 7.6 Hz, 1H), 4.97 (dd, J = 12.8, 6.4 Hz, 1H), 4.53 (td, J = 9.2, 7.8, 4.6 Hz, 1H), 4.31 (d, J = 12.4 Hz, 1H), 4.16 (ddt, J = 19.3, 8.0, 3.3 Hz, 1H), 4.10 - 3.90 (m, 2H), 3.82 (dd, J = 12.5, 2.2 Hz,1H), 3.72 (d, J = 9.4 Hz, 3H), 3.60 (ddt, J = 32.1, 17.2, 8.3 Hz, 3H), 3.28 (d, J = 12.0 Hz, 1H), 3.22 - 3.09 (m, 1H), 3.03 (s, 4H), 2.32 (s, 3H), 1.49 -1.10 (m, 9H), 1.02 (d, J = 7.6 Hz, 2H).	780.3	NA
359		1H NMR (400 MHz, DMSO-d6) δ 9.22 (d, J = 7.1 Hz, 1H), 9.05 (s, 1H), 8.86 (dd, J = 4.1, 1.5 Hz, 1H), 8.76 (dd, J = 8.7, 1.5 Hz, 1H), 8.61 (d, J = 4.9 Hz, 1H), 7.93 (d, J = 4.9 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (dd, J = 8.6, 4.2 Hz, 1H), 7.44 (td, J = 8.4, 7.9, 1.4 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.06 (ddd, J = 8.5, 2.3, 1.1 Hz, 2H), 6.73 (d, J = 13.4 Hz, 1H), 6.70 - 6.64 (m, 1H), 5.05 (q, J = 7.3 Hz,	757.2	NA

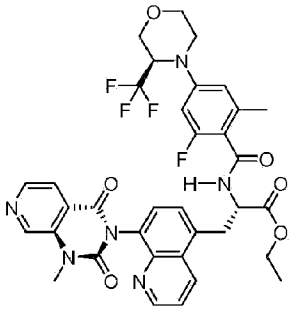
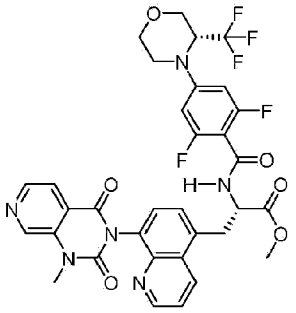
Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		1H), 4.93 - 4.78 (m, 1H), 4.15 (d, J = 12.5 Hz, 1H), 3.95 (dd, J = 11.4, 3.6 Hz, 1H), 3.86 (dd, J = 14.6, 5.6 Hz, 1H), 3.72 (dd, J = 14.3, 9.9 Hz, 2H), 3.67 (s, 3H), 3.60 - 3.49 (m, 1H), 3.37 (d, J = 12.4 Hz, 1H), 3.26 (t, J = 12.1 Hz, 1H), 2.10 (d, J = 1.7 Hz, 3H).		
360		1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.2, 1.4 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.91 (dd, J = 5.0, 2.2 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.66 (dt, J = 8.6, 2.5 Hz, 2H), 6.76 - 6.63 (m, 2H), 4.82 (td, J = 14.4, 12.1, 5.3 Hz, 2H), 4.20 - 4.04 (m, 3H), 3.95 (dd, J = 11.5, 3.6 Hz, 1H), 3.80 - 3.66 (m, 2H), 3.65 (d, J = 1.6 Hz, 3H), 3.60 - 3.46 (m, 2H), 3.36 (d, J = 13.7 Hz, 1H), 3.31 - 3.18 (m, 1H), 2.07 (s, 3H), 1.16 (td, J = 7.1, 1.1 Hz, 3H).	709.2	NA
361		1H NMR (400 MHz, DMSO-d6) δ 9.05 (d, J = 5.5 Hz, 2H), 8.90 - 8.81 (m, 1H), 8.70 - 8.57 (m, 2H), 7.91 (d, J = 5.1 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.9 Hz, 2H), 6.74 - 6.64 (m, 2H), 4.86 (s, 2H), 4.35 - 4.06 (m, 3H), 3.95 (d, J = 11.0 Hz, 1H), 3.74 (d, J = 13.2 Hz, 6H), 3.53 (q, J = 14.3, 13.3 Hz, 2H), 3.42 - 3.13 (m, 2H), 2.03 (d, J = 20.9 Hz, 3H), 1.53 (d, J = 5.4 Hz, 1H), 1.38 (d, J = 5.4 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).	797.2	NA

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
362		1H NMR (400 MHz, DMSO-d6) δ 9.03 (d, J = 13.5 Hz, 2H), 8.85 (d, J = 4.3 Hz, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.72 - 7.61 (m, 2H), 6.81 - 6.59 (m, 2H), 4.86 (d, J = 11.5 Hz, 2H), 4.21 - 4.05 (m, 2H), 3.95 (dd, J = 11.7, 3.9 Hz, 1H), 3.75 (dd, J = 15.2, 9.4 Hz, 3H), 3.66 (s, 4H), 3.36 (d, J = 13.6 Hz, 1H), 3.27 (d, J = 11.9 Hz, 1H), 2.41 - 2.22 (m, 1H), 2.07 (d, J = 6.2 Hz, 2H), 1.87 (ddt, J = 33.9, 14.4, 7.2 Hz, 2H), 1.76 - 1.36 (m, 1H).	765.3	NA
363		1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.98 (d, J = 7.6 Hz, 1H), 8.83 (dd, J = 4.1, 1.5 Hz, 1H), 8.68 - 8.56 (m, 2H), 7.91 (dt, J = 4.9, 1.0 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.71 - 7.60 (m, 2H), 6.76 - 6.59 (m, 2H), 4.89 - 4.72 (m, 2H), 4.14 (dt, J = 9.3, 3.7 Hz, 2H), 3.95 (dd, J = 11.1, 3.6 Hz, 1H), 3.80 - 3.62 (m, 5H), 3.52 (q, J = 14.4, 13.6 Hz, 2H), 3.36 (d, J = 12.2 Hz, 1H), 3.22 (s, 1H), 2.04 (s, 3H), 0.75 - 0.52 (m, 4H).	721.3	NA
364		1H NMR (400 MHz, DMSO-d6) δ 9.04 (d, J = 8.2 Hz, 2H), 8.87 (d, J = 4.1 Hz, 1H), 8.64 - 8.57 (m, 2H), 7.91 (t, J = 4.8 Hz, 1H), 7.77 (d, 1H), 7.71 - 7.59 (m, 3H), 7.56 (s, 1H), 6.74 - 6.65 (m, 2H), 4.90 - 4.76 (m, 2H), 4.52 - 4.42 (m, 1H), 4.41 - 4.28 (m, 3H),	789.3	NA

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		4.15 (d, J = 12.6 Hz, 1H), 3.94 (d, J = 3.5 Hz, 1H), 3.73 (d, J = 12.7 Hz, 1H), 3.69 - 3.60 (m, 4H), 3.59 - 3.47 (m, 2H), 3.34 (d, 1H), 3.25 (t, 1H), 2.53 (s, 3H), 2.03 (s, 3H).		
365		1H NMR (400 MHz, DMSO-d6) δ 9.04 (d, J = 2.1 Hz, 1H), 8.99 (d, J = 7.8 Hz, 1H), 8.89 - 8.79 (m, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (dt, J = 4.9, 2.4 Hz, 1H), 7.77 (dd, J = 7.5, 2.1 Hz, 1H), 7.71 - 7.63 (m, 2H), 6.76 - 6.61 (m, 2H), 4.84 (d, J = 9.4 Hz, 2H), 4.14 (d, J = 12.6 Hz, 1H), 4.05 (q, J = 6.7 Hz, 2H), 3.95 (d, J = 11.3 Hz, 1H), 3.73 (dd, J = 14.0, 4.4 Hz, 2H), 3.65 (d, J = 2.3 Hz, 3H), 3.54 (t, J = 8.7 Hz, 2H), 3.36 (d, J = 12.4 Hz, 1H), 3.25 (t, J = 12.6 Hz, 1H), 2.05 (s, 3H), 1.58 (h, J = 7.0 Hz, 2H), 0.88 (td, J = 7.4, 2.1 Hz, 3H).	723.3	NA
366		1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.97 (d, J = 7.7 Hz, 1H), 8.84 (d, J = 4.1 Hz, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.71 - 7.62 (m, 2H), 6.71 (d, J = 13.1 Hz, 1H), 6.68 - 6.63 (m, 1H), 4.97 - 4.90 (m, 1H), 4.84 (dd, J = 29.2, 20.4 Hz, 2H), 4.15 (d, J = 12.7 Hz, 1H), 3.95 (d, J = 11.3 Hz, 1H), 3.73 (d, J = 13.7 Hz, 2H), 3.66 (s, 3H), 3.53 (q, J = 13.5, 11.7 Hz, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.27 (d, J = 12.5 Hz,	723.3	NA

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		1H), 2.08 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H).		
367		1H NMR (400 MHz, DMSO-d6) δ 9.15 - 9.00 (m, 2H), 8.85 (d, J = 3.9 Hz, 1H), 8.67 - 8.57 (m, 2H), 7.91 (ddd, J = 5.0, 3.1, 0.8 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.73 - 7.61 (m, 2H), 5.83 (s, 2H), 4.85 (d, J = 9.2 Hz, 2H), 4.14 (d, J = 12.6 Hz, 1H), 4.06 - 3.88 (m, 1H), 3.84 - 3.68 (m, 2H), 3.65 (d, J = 2.2 Hz, 3H), 3.53 (dt, J = 14.8, 9.7 Hz, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 12.1 Hz, 1H), 2.03 (s, 3H), 1.18 (s, 9H).	795.3	NA
368		1H NMR (400 MHz, DMSO-d6) δ 9.02 (d, J = 18.4 Hz, 2H), 8.85 (d, J = 4.1 Hz, 1H), 8.63 (dd, J = 22.3, 7.3 Hz, 2H), 7.92 (d, J = 4.9 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 6.5 Hz, 2H), 6.82 (dq, J = 27.7, 5.5 Hz, 1H), 6.75 - 6.63 (m, 2H), 4.84 (d, J = 10.7 Hz, 2H), 4.15 (d, J = 12.7 Hz, 1H), 3.95 (d, J = 11.4 Hz, 1H), 3.81 - 3.61 (m, 5H), 3.53 (q, J = 13.5, 12.8 Hz, 2H), 3.36 (d, J = 12.5 Hz, 1H), 3.26 (d, J = 12.5 Hz, 1H), 2.15 - 1.96 (m, 6H), 1.42 (dd, J = 53.9, 5.5 Hz, 3H).	767.2	NA
408		1H NMR (400 MHz, Chloroform-d) δ 8.83 - 8.72 (m, 2H), 8.64 (d, J = 8.6 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.59 (q, J = 7.6 Hz,	681.2	0.049

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		2H), 7.46 (dd, J = 8.6, 4.2 Hz, 1H), 6.63 (d, J = 6.1 Hz, 1H), 6.47 (s, 1H), 6.38 (dd, J = 13.4, 2.4 Hz, 1H), 5.13 - 5.02 (m, 1H), 4.30 (d, J = 12.4 Hz, 1H), 4.12 (dd, J = 8.0, 3.8 Hz, 1H), 4.04 (dd, J = 11.2, 3.5 Hz, 1H), 3.86 - 3.78 (m, 1H), 3.72 (t, J = 5.6 Hz, 2H), 3.69 (s, 3H), 3.65 - 3.59 (m, 1H), 3.51 (t, J = 11.7 Hz, 1H), 3.27 (d, J = 12.3 Hz, 1H), 2.39 (s, 3H).		
474		1H NMR (400 MHz, DMSO-d6) δ 13.24-12.63 (bs, 1H), 9.05 (s, 1H), 9.02 (d, J = 7.9 Hz, 1H), 8.84 (d, J = 4.1 Hz, 1H), 8.68 (d, J = 8.7 Hz, 1H), 8.60 (d, J = 5.1 Hz, 1H), 7.91 (dd, J = 5.0, 2.3 Hz, 1H), 7.76 (dd, J = 7.6, 1.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 6.78 (d, J = 11.9 Hz, 2H), 4.91 (d, J = 9.9 Hz, 1H), 4.71 (s, 1H), 4.16 (d, J = 12.7 Hz, 1H), 4.00-3.92 (m, 1H), 3.74 (d, J = 13.0 Hz, 2H), 3.65 (s, 3H), 3.61 - 3.40 (m, 3H), 3.26 (d, J = 12.4 Hz, 1H).	685.3	0.112
487		1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.1, 1.5 Hz, 1H), 8.64 (dd, J = 8.6, 1.6 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.91 (dd, J = 4.9, 0.7 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.69 - 7.63 (m, 2H), 6.76 - 6.63 (m, 2H), 4.90 - 4.74 (m, 2H), 4.19 - 4.06 (m, 3H), 3.95 (dd, J = 11.4, 3.6 Hz, 1H), 3.78 - 3.67 (m, 2H), 3.65 (s, 3H), 3.61 - 3.46 (m, 2H), 3.37 (s, 1H), 3.31 - 3.18 (m, 1H), 2.07 (s,	709.2	NA

Example	Structure	1H-NMR	M/Z [M+H]+	α4β7 EC_{50} (nM)
		3H), 1.16 (t, J = 7.1 Hz, 3H).		
488		1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.99 (d, J = 7.7 Hz, 1H), 8.84 (dd, J = 4.2, 1.5 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 4.9 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.69 - 7.63 (m, 2H), 6.75 - 6.62 (m, 2H), 4.91 - 4.75 (m, 2H), 4.20 - 4.07 (m, 3H), 3.95 (dd, J = 11.4, 3.6 Hz, 1H), 3.78 - 3.67 (m, 2H), 3.66 (s, 3H), 3.60 - 3.47 (m, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.25 (t, J = 12.3 Hz, 1H), 2.07 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H).	709.2	NA
494		1H NMR (400 MHz, DMSO-d6) δ 9.15 (d, J = 7.5 Hz, 1H), 9.05 (s, 1H), 8.86 (d, J = 4.2 Hz, 1H), 8.64 (dd, J = 28.6, 6.8 Hz, 2H), 7.91 (dd, J = 4.9, 1.9 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.72 - 7.55 (m, 2H), 6.79 (d, J = 11.8 Hz, 2H), 4.96 - 4.82 (m, 1H), 4.77 (q, J = 8.0 Hz, 1H), 4.17 (d, J = 12.7 Hz, 1H), 3.96 (dd, J = 11.6, 3.6 Hz, 1H), 3.82 - 3.68 (m, 2H), 3.56 (dd, J = 14.0, 9.9 Hz, 2H), 3.44 (d, J = 13.3 Hz, 1H), 3.24 (t, J = 12.0 Hz, 1H)	699.2	NA

α4β1 Cell Capture Assay

[0739] The potency of inhibitors in preventing α4β1 integrin interaction with VCAM-1 was measured by monitoring the capture of α4β1 expressing cells to a recombinant VCAM-1 extracellular domain-coated plate.

[0740] 384-well plates (Corning 3702) were coated with VCAM-1 extracellular domain by dispensing 20 µL of VCAM-1 at 0.5 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.

[0741] Jurkat cells were spun down and re-suspended in assay medium (DMEM + 0.5%FBS + 0.5 mM $MnCl_2$) at a density of 0.5X106 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, VCAM-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 Hoechst 33342 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 EC50 of the test compounds.

[0742] The parent carboxylic acids in Table 3 display at least 70 folds selectivity over α4β1, as calculated from the ratio of EC50 values in cell capture assays for α4β1 and α4β7. These assays measure the capture of α4β1 or α4β7 expressing cells by a recombinant VCAM-1 or MadCAM-1 extracellular domain-coated plate, respectively.

Dog Bioavailability Experiments

[0743] Pharmacokinetic studies for were performed in non-naive male beagle dogs (three animals per dosing route) following federal and Institutional Animal Care and Use Committee in humans (IACUC) guidelines. Intravenous (iv) administration was dosed via infusion over 30 minutes. The intravenous dose for dogs was formulated in a sterile solution. One solution formulation was 20% polyethylene glycol 300 and 80% water, pH 8-9. Oral dosing in dogs was administered by gavage as a solution. One formulation for dog was 72% 10 mM HCl, 5% N-methylpyrrolidone, 20% polyethylene glycol 200, and 3% Vitamin E TPGS, pH 2-3. Blood samples were collected over a 24 h period post-dose, plasma was isolated, and the concentration of the test compound in plasma was determined with LC/MS/MS after protein precipitation with acetonitrile. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data.

[0744] Bioavailability (%F) is defined as the area under the concentration/time curve (AUC) of parent carboxylic acid in systemic circulation following oral administration of ester prodrug divided by the AUC of amount of parent carboxylic acid in circulation following intravenous administration of the parent carboxylic acid, normalized to the same dose. Results for dog oral bioavailability are presented in Table 4.

Table 4

Prodrug Example	%F	Parent carboxylic acid
346	5	Example 91
347	11	Example 91
348	3	Example 91
349	9	Example 91
351	35	Example 91
355	18	Example 356
357	9	Example 356
358	2	Example 356
359	12	Example 356
360	37	Example 356
361	5	Example 356
363	37	Example 356
364	3	Example 356
365	16	Example 356
368	8	Example 356
487	20	Example 408
494	8	Example 474

REFERENCES CITED IN THE DESCRIPTION

Cited references

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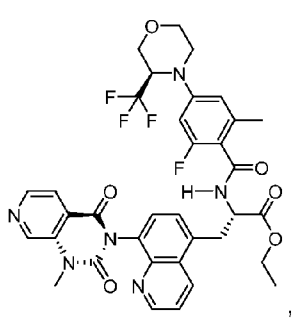
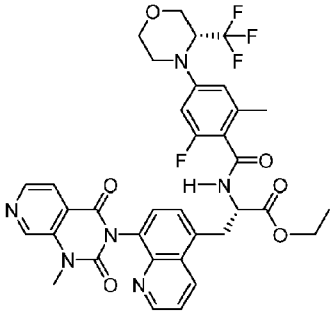
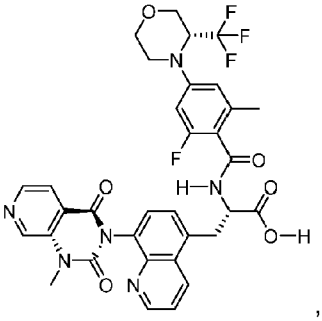
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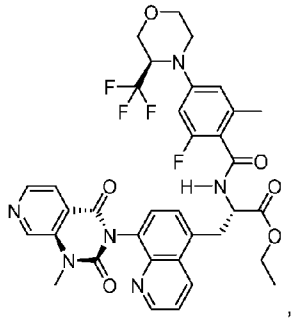
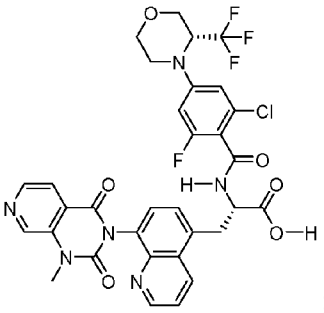
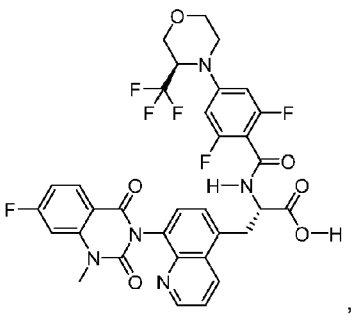
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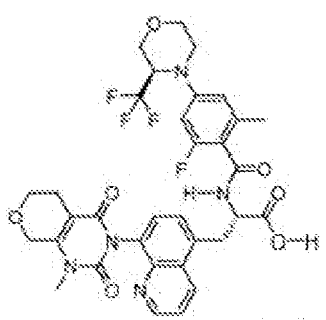
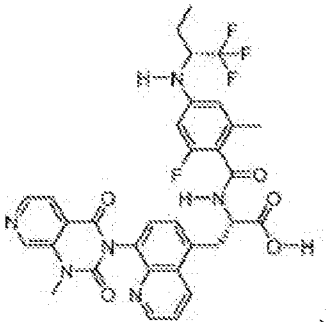
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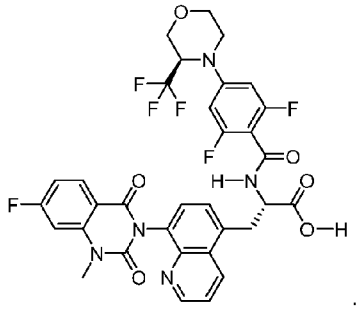
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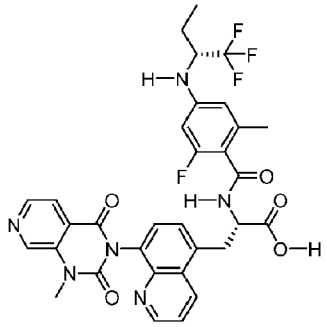

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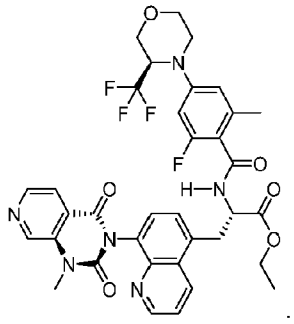
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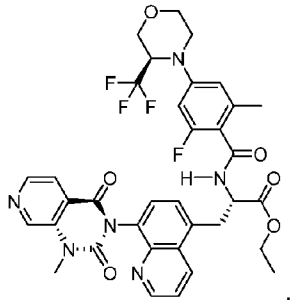
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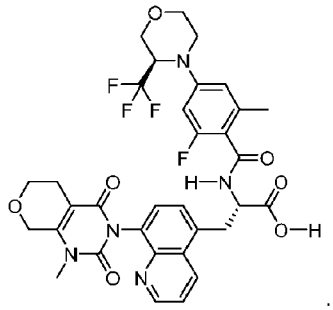
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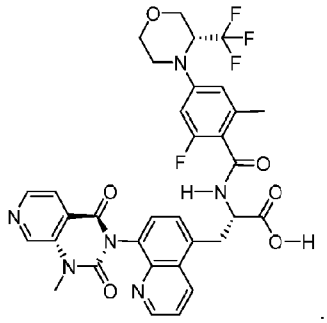
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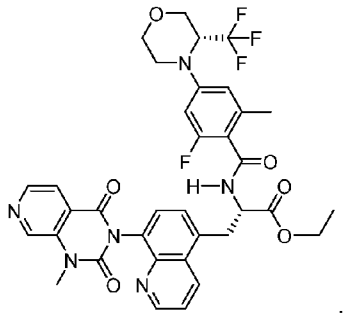
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9. Forbindelse ifølge krav 1 eller et farmaceutisk acceptabelt salt deraf, hvor forbindelsen er

