

COMPOUNDS AS GLP-1R AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/313,160, filed on February 23, 2022, which is incorporated by reference herein in their entirety for all purposes.

FIELD

[0002] This invention relates to compositions for modulating glucagon-like peptide-1 (GLP-1) receptors and methods thereof.

BACKGROUND

[0003] Diabetes is a major public health concern because of its increasing prevalence and associated health risks. The disease is characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Two major forms of diabetes are recognized, Type 1 and Type 2. Type 1 diabetes (T1D) develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose. To survive, people with Type 1 diabetes must have insulin administered by injection or a pump. Type 2 diabetes mellitus (T2DM) usually begins with either insulin resistance or when there is insufficient production of insulin to maintain an acceptable glucose level.

[0004] Currently, various pharmacological approaches are available for treating hyperglycemia and subsequently, T2DM (Hampp, C. et al. Use of Antidiabetic Drugs in the U.S., 2003-2012, Diabetes Care 2014, 37, 1367-1374). One of them is glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g., liraglutide, albiglutide, exenatide, lixisenatide, dulaglutide, semaglutide), which enhance secretion of insulin by acting on the pancreatic beta-cells. Marketed GLP-1R agonists are peptides administered by subcutaneous injection. Liraglutide is additionally approved for the treatment of obesity.

[0005] GLP-1 is a 30 amino acid long incretin hormone secreted by the L-cells in the intestine in response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of

genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier et al. *Biodrugs*. 2003; 17 (2): 93-102).

[0006] In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll T, et al. *Diabetes*. 2001. 50; 609-613).

[0007] Holst (*Physiol. Rev.* 2007, 87, 1409) and Meier (*Nat. Rev. Endocrinol.* 2012, 8, 728) describe that GLP-1 receptor agonists, such as liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

[0008] There remains a need of developing GLP-1 receptor agonists for an easily-administered prevention and/or treatment for cardiometabolic and associated diseases.

SUMMARY

[0009] Disclosed are compounds that can be used as glucagon-like peptide-1 receptor (GLP-1R) agonists, compositions containing these compounds, and methods for treating diseases and/or conditions mediated by GLP-1R.

[0010] In one aspect, provided is a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof, as detailed herein.

[0011] Further provided is a pharmaceutical composition comprising a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0012] In another aspect, provided is a method of treating a disease or a condition mediated by GLP-1R in a subject in need thereof comprises administering to the subject a therapeutically

effective amount of a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease or the condition is a cardiometabolic disease. In some embodiments, the disease or the condition is diabetes. In some embodiments, the disease or the condition is a liver disease.

[0013] Also provided is a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof, as detailed herein, for the treatment.

[0014] Also provided is use of a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof, as detailed herein, in the manufacture of a medicament for the treatment.

[0015] Further provided is a kit comprising a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the kit comprises instructions for use according to a method described herein.

[0016] In yet another aspect, provided is a method of making a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof. Also provided are compound intermediates useful in synthesis of a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a compound selected from the group consisting of the compounds listed in Table 1, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

Definitions

[0017] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0018] As used herein and in the appended claims, the singular forms “a,” “an” and “the” include plural forms, unless the context clearly dictates otherwise.

[0019] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms “about” and “approximately,” when used in connection with a value, contemplate a variation within $\pm 15\%$, within $\pm 10\%$, within $\pm 5\%$, within $\pm 4\%$, within $\pm 3\%$, within $\pm 2\%$, within $\pm 1\%$, or within $\pm 0.5\%$ of the specified value. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[0020] “Comprising” is intended to mean that the compositions and methods include the recited elements, but not exclude others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination. For example, a composition consisting essentially of the elements as defined herein would not exclude other elements that do not materially affect the basic and novel characteristic(s) of the claimed invention. “Consisting of” shall mean excluding more than trace amount of, e.g., other ingredients and substantial method steps recited. Embodiments defined by each of these transition terms are within the scope of this invention.

[0021] The term “excipient” as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the invention as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbomers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc = “directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.;

materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0022] “Pharmaceutically acceptable” refers to safe and non-toxic, preferably for in vivo, more preferably, for human administration.

[0023] “Pharmaceutically acceptable salt” refers to a salt that is pharmaceutically acceptable. A compound described herein may be administered as a pharmaceutically acceptable salt.

[0024] “Salt” refers to an ionic compound formed between an acid and a base. When the compound provided herein contains an acidic functionality, such salts include, without limitation, alkali metal, alkaline earth metal, and ammonium salts. As used herein, ammonium salts include, salts containing protonated nitrogen bases and alkylated nitrogen bases. Exemplary and non-limiting cations useful in pharmaceutically acceptable salts include Na, K, Rb, Cs, NH₄, Ca, Ba, imidazolium, and ammonium cations based on naturally occurring amino acids. When the compounds utilized herein contain basic functionality, such salts include, without limitation, salts of organic acids, such as carboxylic acids and sulfonic acids, and mineral acids, such as hydrogen halides, sulfuric acid, phosphoric acid, and the likes. Exemplary and non-limiting anions useful in pharmaceutically acceptable salts include oxalate, maleate, acetate, propionate, succinate, tartrate, chloride, sulfate, bisulfate, mono-, di-, and tribasic phosphate, mesylate, tosylate, and the likes.

[0025] “Stereoisomer” or “stereoisomers” refer to compounds that differ in the stereogenicity of the constituent atoms such as, without limitation, in the chirality of one or more stereocenters or related to the cis or trans configuration of a carbon-carbon or carbon-nitrogen double bond. Stereoisomers include enantiomers and diastereomers.

[0026] As used herein, the term “subject” refers to an animal, including, but are not limited to, a primate (e.g., human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

[0027] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease or

disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delaying or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by “treatment” is a reduction of pathological consequence of the disease or disorder. The methods of this disclosure contemplate any one or more of these aspects of treatment.

[0028] “Therapeutically effective amount” or dose of a compound or a composition refers to that amount of the compound or the composition that results in reduction or inhibition of symptoms or a prolongation of survival in a patient. The results may require multiple doses of the compound or the composition.

[0029] “Alkyl” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 12 carbon atoms, preferably from 1 to 10 carbon atoms, and more preferably from 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), n-propyl ($\text{CH}_3\text{CH}_2\text{CH}_2-$), isopropyl ($(\text{CH}_3)_2\text{CH}-$), n-butyl ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-$), isobutyl ($(\text{CH}_3)_2\text{CHCH}_2-$), sec-butyl ($(\text{CH}_3)(\text{CH}_3\text{CH}_2)\text{CH}-$), t-butyl ($(\text{CH}_3)_3\text{C}-$), n-pentyl ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), and neopentyl ($(\text{CH}_3)_3\text{CCH}_2-$). C_x alkyl refers to an alkyl group having x number of carbon atoms.

[0030] “Alkylene” refers to a divalent saturated aliphatic hydrocarbyl group having from 1 to 12 carbon atoms, preferably from 1 to 10 carbon atoms, and more preferably from 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$ or $-\text{CH}(\text{Me})-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$ or $-\text{CH}(\text{Me})\text{CH}_2-$, or $-\text{CH}(\text{Et})-$) and the likes.

[0031] “Alkoxy” refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-pentoxy.

[0032] “Aryl” refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl (Ph)) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

[0033] “Cyano” refers to the group -CN.

[0034] “Cycloalkyl” refers to saturated or unsaturated but nonaromatic cyclic alkyl groups of from 3 to 10 carbon atoms, preferably from 3 to 8 carbon atoms, and more preferably from 3 to 6 carbon atoms, having single or multiple cyclic rings including fused, bridged, and spiro ring systems. C_x cycloalkyl refers to a cycloalkyl group having x number of ring carbon atoms. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl. One or more the rings can be aryl, heteroaryl, or heterocyclic provided that the point of attachment is through the non-aromatic, non-heterocyclic ring saturated carbocyclic ring. “Substituted cycloalkyl” refers to a cycloalkyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO₃H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0035] “Halo” or “halogen” refers to fluoro, chloro, bromo and iodo and preferably is fluoro or chloro.

[0036] “Hydroxy” or “hydroxyl” refers to the group -OH.

[0037] “Heteroaryl” refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridinyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N—>O), sulfinyl, or sulfonyl moieties. Preferred heteroaryls include 5 or 6 membered heteroaryls such as pyridinyl, pyrrolyl, thiophenyl, and furanyl. Other preferred heteroaryls include 9 or 10

membered heteroaryls, such as indolyl, quinolynyl, quinolonyl, isoquinolynyl, and isoquinolonyl.

[0038] “Heterocycle” or “heterocyclic” or “heterocycloalkyl” or “heterocyclyl” refers to a saturated or partially saturated, but not aromatic, group having from 1 to 10 ring carbon atoms, preferably from 1 to 8 carbon atoms, and more preferably from 1 to 6 carbon atoms, and from 1 to 4 ring heteroatoms, preferably from 1 to 3 heteroatoms, and more preferably from 1 to 2 heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. C_x heterocycloalkyl refers to a heterocycloalkyl group having x number of ring atoms including the ring heteroatoms. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl (S(O)), sulfonyl (S(O)₂) moieties.

[0039] Examples of heterocyclyl and heteroaryl include, but are not limited to, azetidiny, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, indolizyl, isoindolyl, indolyl, dihydroindolyl, indazolyl, purinyl, quinoliziny, isoquinolynyl, quinolynyl, phthalazinyl, naphthylpyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, carbazolyl, carboliny, phenanthridinyl, acridinyl, phenanthroliny, isothiazolyl, phenazinyl, isoxazolyl, phenoxazinyl, phenothiazinyl, imidazolidinyl, imidazoliny, piperidinyl, piperazinyl, indoliny, phthalimidyl, 1,2,3,4-tetrahydroisoquinoliny, 4,5,6,7-tetrahydrobenzo[b]thiophenyl, thiazolyl, thiazolidinyl, thiophenyl, benzo[b]thiophenyl, morpholiny, thiomorpholiny (also referred to as thiamorpholiny), 1,1-dioxothiomorpholiny, piperidinyl, pyrrolidinyl, and tetrahydrofuranyl.

[0040] “O_xo” refers to the atom (=O) or (O).

[0041] The terms “optional” or “optionally” as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “the nitrogen atom is optionally oxidized to provide for the N-oxide (N—>O) moiety” means that the nitrogen atom may but need not be oxidized, and the description includes situations where the nitrogen atom is not oxidized and situations where the nitrogen atom is oxidized.

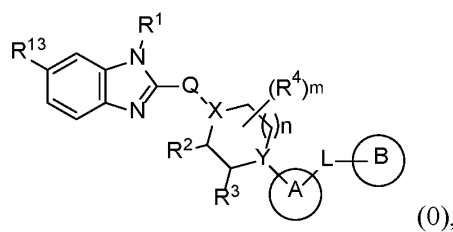
[0042] “Optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 1, 2, 3, 4 or 5) of the substituents listed for

that group in which the substituents may be the same or different. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. In some embodiments, an optionally substituted group has 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, or 2 to 5 substituents. In one embodiment, an optionally substituted group is unsubstituted.

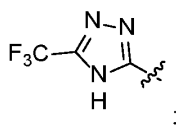
[0043] It is understood that an optionally substituted moiety can be substituted with more than five substituents, if permitted by the number of valences available for substitution on the moiety. For example, a propyl group can be substituted with seven halogen atoms to provide a perhalopropyl group. The substituents may be the same or different.

Compounds

[0044] In one aspects, provided is a compound of Formula (0):



or a pharmaceutically acceptable salt, wherein:



R^{13} is $-C(O)OH$ or

X is N or CR^x , wherein R^x is hydrogen, OH or C_1-C_6 alkyl;

Y is N or CR^y , wherein R^y is hydrogen, OH or C_1-C_6 alkyl;

n is 0 or 1;

Q is selected from the group consisting of $-C(R^7)(R^8)-$, $-O-$, $-N(R^9)-$, and $-S-$, wherein

R^7 and R^8 are independently hydrogen, halogen, or C_1-C_6 alkyl; and

R^9 is hydrogen or C_1-C_6 alkyl;

R^1 is optionally substituted $-C_1-C_6$ alkylene or $-C_1-C_6$ alkylene- R^5 , wherein R^5 is C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl, wherein each C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl substituent is independently optionally substituted by halo or CN;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_4 cycloalkyl ring; or

R^2 and R^x , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_5 cycloalkyl ring, and R^3 is hydrogen, oxo, or C_1 - C_6 alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or C_1 - C_6 alkyl;

Ring A is C_6 - C_{14} aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH, CN, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkyl optionally substituted by halo or OH;

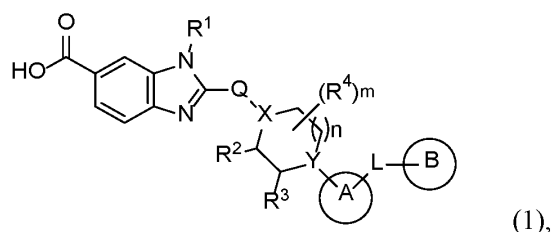
L is a bond, -O-, C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *-NR⁶- C_1 - C_6 alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

when L is C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *-NR⁶- C_1 - C_6 alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C_1 - C_6 alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

R^6 , when present, is hydrogen or C_1 - C_6 alkyl; and

Ring B is C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1 - C_6 alkyl optionally substituted by halo or CN, -OC₁₋₆ alkyl optionally substituted by halo or CN, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl optionally substituted by halo or CN.

[0045] In one aspect, provided is a compound of Formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^x, wherein R^x is hydrogen, OH or C_1 - C_6 alkyl, and

Y is N or CR^y, wherein R^y is hydrogen, OH or C_1 - C_6 alkyl;

n is 0 or 1;

Q is selected from the group consisting of $-C(R^7)(R^8)-$, $-O-$, $-N(R^9)-$, and $-S-$, wherein

R^7 and R^8 are independently hydrogen, halogen, or C_1-C_6 alkyl, and

R^9 is hydrogen or C_1-C_6 alkyl;

R^1 is $-C_1-C_6$ alkylene- R^5 , wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl, wherein each C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl substituent is independently optionally substituted by halo or CN;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3-C_4 cycloalkyl ring; or

R^2 and R^x , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3-C_5 cycloalkyl ring, and R^3 is hydrogen, oxo, or C_1-C_6 alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or C_1-C_6 alkyl;

Ring A is C_6-C_{14} aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH;

L is a bond, $-O-$, C_1-C_6 alkylene, $^*-O-C_1-C_6$ alkylene- ** , $^*-C_1-C_6$ alkylene- $O-^{**}$, or $^*-NR^6-C_1-C_6$ alkylene- ** , wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

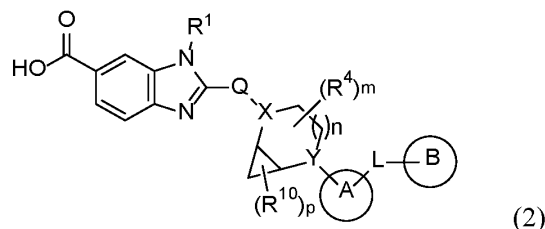
when L is C_1-C_6 alkylene, $^*-O-C_1-C_6$ alkylene- ** , $^*-C_1-C_6$ alkylene- $O-^{**}$, or $^*-NR^6-C_1-C_6$ alkylene- ** , L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C_1-C_6 alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl; and

R^6 , when present, is hydrogen or C_1-C_6 alkyl; and

Ring B is C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl optionally substituted by halo or CN, $-OC_1-C_6$ alkyl optionally substituted by halo or CN, $-COCH_3$, $-CONH_2$, $-S(O)_2CH_3$, and phenyl optionally substituted by halo or CN.

[0046] In some embodiments of Formula (0) or Formula (1), at least one of X and Y is N. In other embodiments of Formula (0) or Formula (1), both X and Y are N.

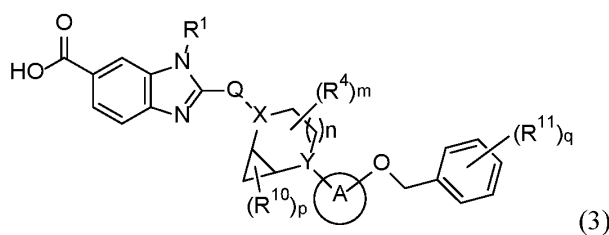
[0047] In some embodiments of Formula (0) or Formula (1), R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_4 cycloalkyl ring. In some embodiments, provided is a compound of Formula (2):



or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, or 2; each R^{10} is halo; and X , Y , n , Q , R^1 , m , R^4 , Ring A, L, and Ring B are as detailed herein for Formula (0) or Formula (1).

[0048] In some embodiments of Formula (2), at least one of X and Y is N. In other embodiments of Formula (2), both X and Y are N.

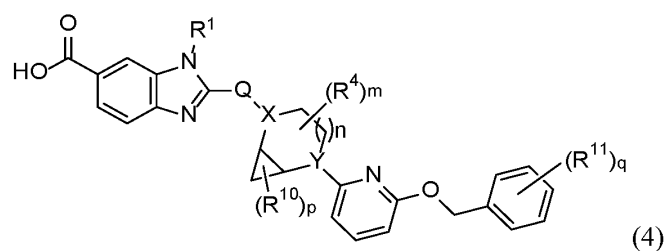
[0049] In some embodiments of Formula (2), L is $^*-OCH_2-^*$ and Ring B is phenyl. In some embodiments, provided is a compound of Formula (3):



or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3; R^{11} is selected from the group consisting of halo, CN, C_1 - C_6 alkyl optionally substituted by halo or CN, $-OC_1$ - C_6 alkyl optionally substituted by halo or CN, $-COCH_3$, $-CONH_2$, $-S(O)_2CH_3$, and phenyl optionally substituted by halo or CN; p and R^{10} are as detailed herein for Formula (2); and X , Y , n , Q , R^1 , m , R^4 , and Ring A are as detailed herein for Formula (0) or Formula (1).

[0050] In some such embodiments, each R^{11} is independently selected from halo and CN. In some embodiments of Formula (3), at least one of X and Y is N. In other embodiments of Formula (3), both X and Y are N.

[0051] In some embodiments of Formula (3), Ring A is pyridinyl. In some embodiments, provided is a compound of Formula (4):

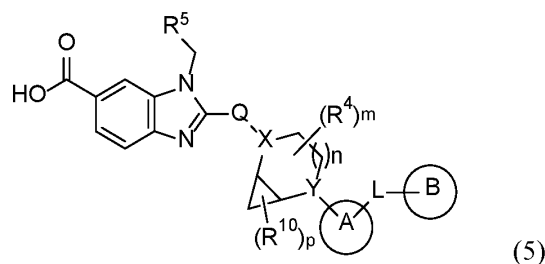


or a pharmaceutically acceptable salt thereof, wherein q and R^{11} are as detailed herein for Formula (3), p and R^{10} are as detailed herein for Formula (2), and X , Y , n , Q , R^1 , m , and R^4 are as detailed herein for Formula (0) or Formula (1).

[0052] In some such embodiments, each R^{11} is independently selected from halo and CN. In some embodiments of Formula (4), at least one of X and Y is N. In other embodiments of Formula (4), both X and Y are N.

[0053] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2) and subformulae thereof, if applicable), or a pharmaceutically acceptable salt thereof, R^1 is $-C_1-C_6$ alkylene- R^5 , wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl, wherein each C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl substituent is independently optionally substituted by halo or CN. In some embodiments, R^1 is $-CH_2-R^5$.

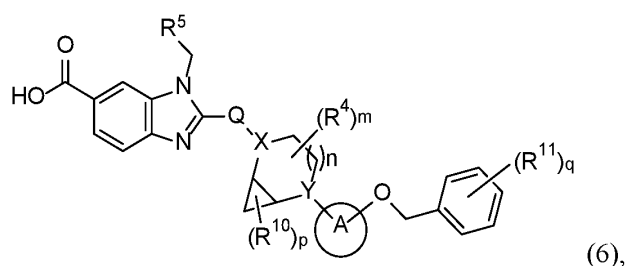
[0054] In some embodiments, provided is a compound of Formula (5):



or a pharmaceutically acceptable salt thereof, wherein p and R^{10} are as detailed herein for Formula (2), and X , Y , n , Q , R^5 , m , R^4 , Ring A, L, and Ring B are as detailed herein for Formula (0) or Formula (1).

[0055] In some embodiments of Formula (5), at least one of X and Y is N. In other embodiments of Formula (5), both X and Y are N.

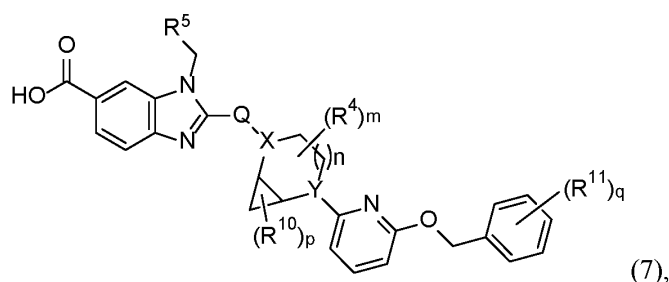
[0056] In some embodiments of Formula (5), L is $-OCH_2-$ and Ring B is phenyl. In some embodiments, provided is a compound of Formula (6):



wherein q is 0, 1, 2, or 3; R^{11} is halo, CN, C_1 - C_6 alkyl optionally substituted by halo or CN, $-OC_1$ - C_6 alkyl optionally substituted by halo or CN, $-COCH_3$, $-CONH_2$, $-S(O)_2CH_3$, or phenyl optionally substituted by halo or CN; p and R^{10} are as detailed herein for Formula (2); and X , Y , n , Q , R^5 , m , R^4 , and Ring A are as detailed herein for Formula (0) or Formula (1).

[0057] In some such embodiments, each R^{11} is independently selected from halo and CN. In some embodiments of Formula (6), at least one of X and Y is N. In other embodiments of Formula (6), both X and Y are N.

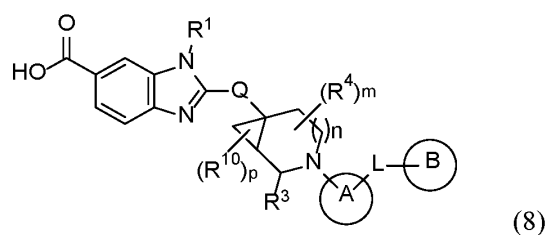
[0058] In some embodiments of Formula (6), Ring A is pyridinyl. In some embodiments, provided is a compound of Formula (7):



wherein q and R^{11} are as defined herein for Formula (6); p and R^{10} are as detailed herein for Formula (2); and X , Y , n , Q , R^5 , m , and R^4 are as detailed herein for Formula (0) or Formula (1).

[0059] In some such embodiments, each R^{11} is independently selected from halo and CN. In some embodiments of Formula (7), at least one of X and Y is N. In other embodiments of Formula (7), both X and Y are N.

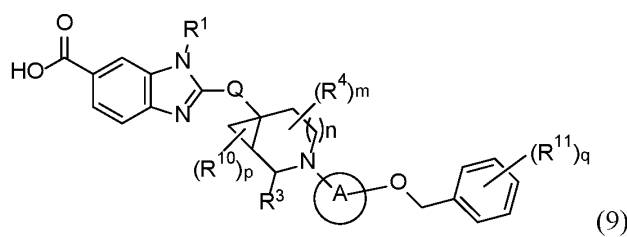
[0060] In some embodiments of a compound of Formula (0) or Formula (1), X is CR^x , and R^2 and R^x are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_5 cycloalkyl ring. In some embodiments, the compound is of Formula (8):



or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, or 2; each R^{10} is halo; and n, Q, R^1 , R^3 , m, R^4 , Ring A, L, and Ring B are as detailed herein for Formula (0) or Formula (1).

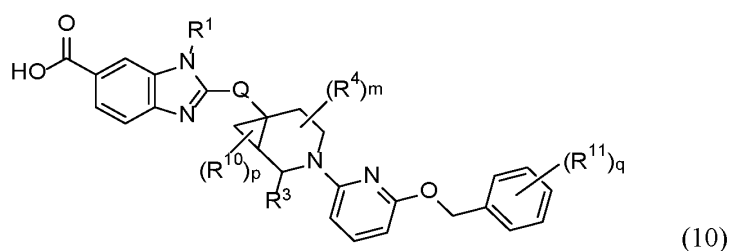
[0061] In some embodiments of Formula (8), R^2 and R^x are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 cycloalkyl ring. In other embodiments of Formula (8), R^2 and R^x are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 cycloalkyl ring.

[0062] In some embodiments of a compound of Formula (8), L is $^*-OCH_2-^*$ and Ring B is phenyl. In some embodiments, the compound is of Formula (9):



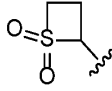
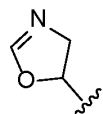
or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3; R^{11} is halo, CN, C_1 - C_6 alkyl optionally substituted by halo or CN, $-OC_1$ - C_6 alkyl optionally substituted by halo or CN, $-COCH_3$, $-CONH_2$, $-S(O)_2CH_3$, or phenyl optionally substituted by halo or CN; p and R^{10} are as detailed herein for Formula (8); and n, Q, R^1 , R^3 , m, R^4 , and Ring A are as detailed herein for Formula (0) or Formula (1).

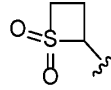
[0063] In some embodiments of a compound of Formula (9), Ring A is pyridinyl. In some embodiments, the compound is of Formula (10):



or a pharmaceutically acceptable salt thereof, wherein p and R^{10} are as detailed herein for Formula (8); q and R^{11} are as detailed herein for Formula (9); and n, Q, R^1 , R^3 , m, and R^4 are as detailed herein for Formula (0) or Formula (1).

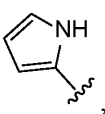
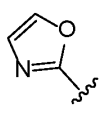
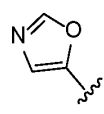
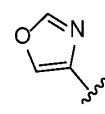
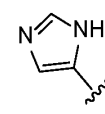
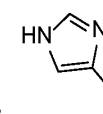
[0064] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), R^5 is optionally substituted 3- to 6-

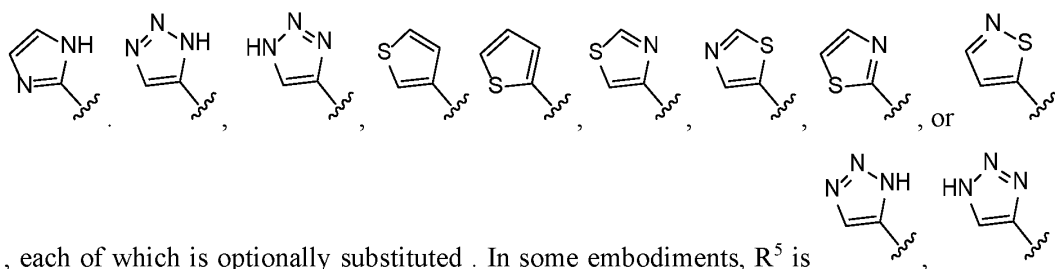
membered heterocyclyl. In some embodiments, R^5 is , , or , each

of which is optionally substituted. In some embodiments, R^5 is  or , each

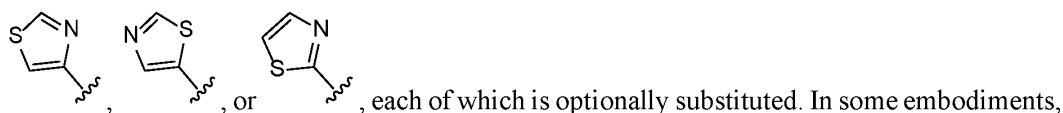
of which is optionally substituted. In some embodiments of any of the foregoing, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and $-OC_1$ - C_6 alkyl, wherein each C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and $-OC_1$ - C_6 alkyl substituent is independently optionally substituted by halo or CN. In some such embodiments, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and $-OC_1$ - C_6 alkyl. In some such embodiments, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1 - C_3 alkyl, and $-OC_1$ - C_3 alkyl. In some such embodiments, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, oxo, CN, C_1 - C_3 alkyl, and $-OC_1$ - C_3 alkyl. In some such embodiments, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, C_1 - C_3 alkyl, and $-OC_1$ - C_3 alkyl. In some such embodiments, R^5 is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, and C_1 - C_3 alkyl. In some embodiments, R^5 is unsubstituted.

[0065] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), R^5 is an optionally substituted 5- to 6-membered heteroaryl. In some embodiments, R^5 is an optionally substituted 5-membered heteroaryl. In some embodiments, R^5 is pyrrolyl, oxazolyl, imidazolyl, triazolyl, thiazolyl, or isothiazolyl, each of which is optionally substituted. In some embodiments, R^5 is oxazolyl, triazolyl, or thiazolyl, each of which is optionally substituted. In some embodiments, R^5 is optionally substituted triazolyl. In some embodiments, R^5 is optionally substituted thiazolyl. In

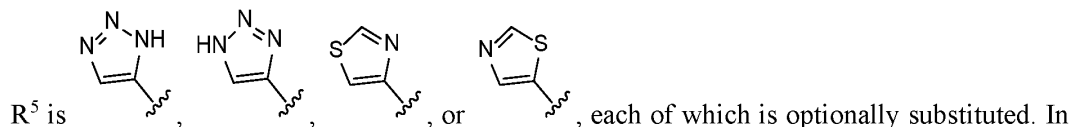
some embodiments, R^5 is , , , , , ,



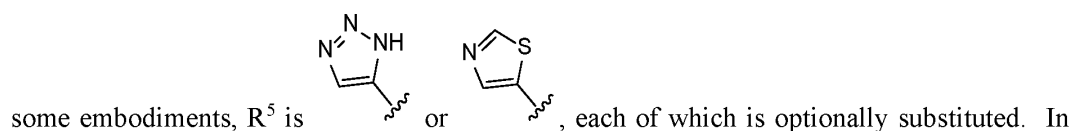
, each of which is optionally substituted. In some embodiments, R⁵ is



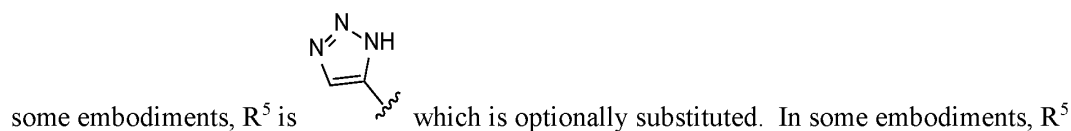
, each of which is optionally substituted. In some embodiments,



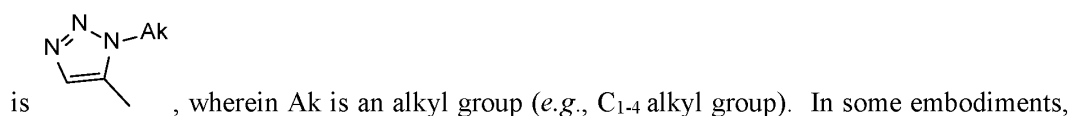
R⁵ is, each of which is optionally substituted. In



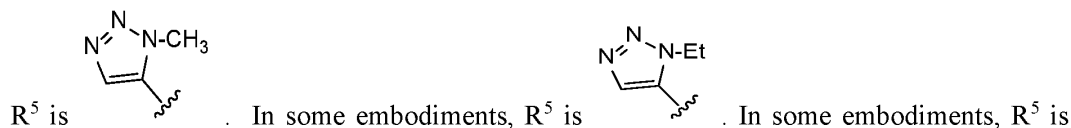
some embodiments, R⁵ is, each of which is optionally substituted. In



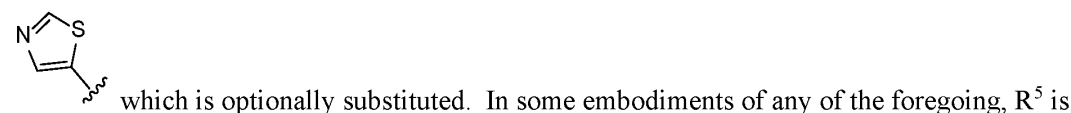
some embodiments, R⁵ is which is optionally substituted. In some embodiments, R⁵



is, wherein Ak is an alkyl group (*e.g.*, C₁₋₄ alkyl group). In some embodiments,



R⁵ is. In some embodiments, R⁵ is. In some embodiments, R⁵ is



which is optionally substituted. In some embodiments of any of the foregoing, R⁵ is

optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl substituent is independently optionally substituted by halo or CN. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, and -OC₁-C₆ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of

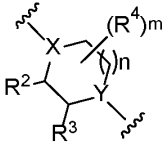
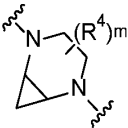
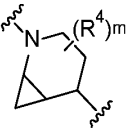
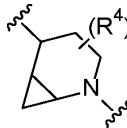
halo, oxo, CN, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, oxo, CN, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, and C₁-C₃ alkyl, such as methyl, ethyl, propyl, or isopropyl. In some embodiments, R⁵ is unsubstituted.

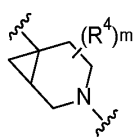
[0066] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), X is N, Y is N, and R² and R³ taken together with the carbon atoms to which they are attached form a C₃-C₄ cycloalkyl ring. In some embodiments, X is CR^x, wherein R^x is hydrogen, OH or C₁-C₆ alkyl, Y is N, and R² and R³ taken together with the carbon atoms to which they are attached form a C₃-C₄ cycloalkyl ring. In some embodiments, X is N, Y is CR^y wherein R^y is hydrogen, OH or C₁-C₆ alkyl, and R² and R³ taken together with the carbon atoms to which they are attached form a C₃-C₄ cycloalkyl ring. In some embodiments, X is CR^x, R^x is taken together with R² and the carbon atoms to which they are attached to form an optionally substituted C₃-C₄ cycloalkyl ring, Y is N, and R³ is hydrogen, oxo, or C₁-C₆ alkyl. In some embodiments of any of the foregoing, Q is CR⁷R⁸.

[0067] In some embodiments, when Q is -O-, -N(R⁹)-, or -S-, X is CR^x, wherein R^x is hydrogen, OH or C₁-C₆ alkyl, Y is N, and R² and R³ taken together with the carbon atoms to which they are attached form a C₃-C₄ cycloalkyl ring. In some embodiments, when Q is -O-, -N(R⁹)-, or -S-, X is CR^x, R^x is taken together with R² and the carbon atoms to which they are attached to form an optionally substituted C₃-C₄ cycloalkyl ring, Y is N, and R³ is hydrogen, oxo, or C₁-C₆ alkyl.

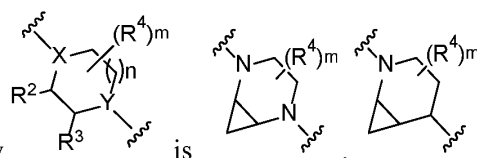
[0068] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), or a pharmaceutically acceptable salt thereof, n is 0. In other embodiments, n is 1.

[0069] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), or a pharmaceutically

acceptable salt thereof, the moiety  is , , , or

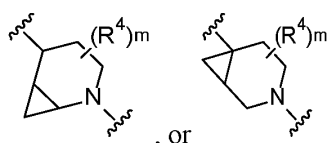


. In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), or a pharmaceutically



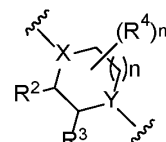
acceptable salt thereof, Q is CR^7R^8 and the moiety

is



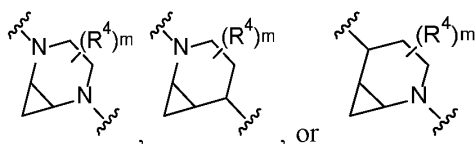
, or

. In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), or a



pharmaceutically acceptable salt thereof, Q is CR^7R^8 and the moiety

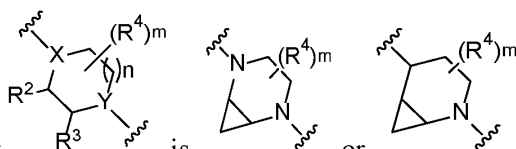
is



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, or

. In some such embodiments, Q is CR^7R^8 and the

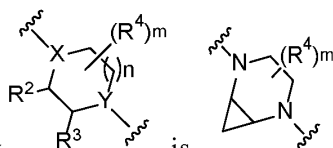


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. In some such embodiments, Q is CR^7R^8

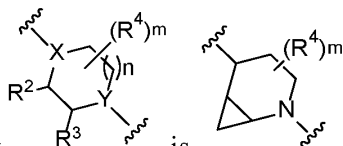


and the moiety

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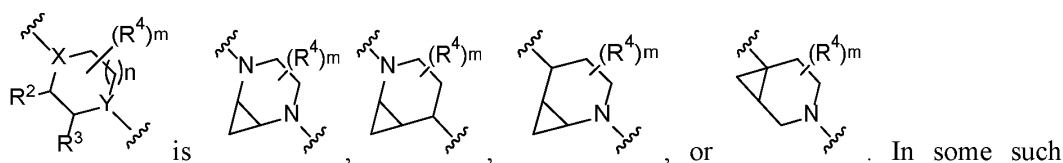
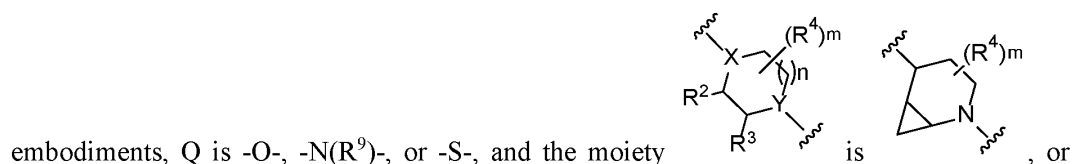
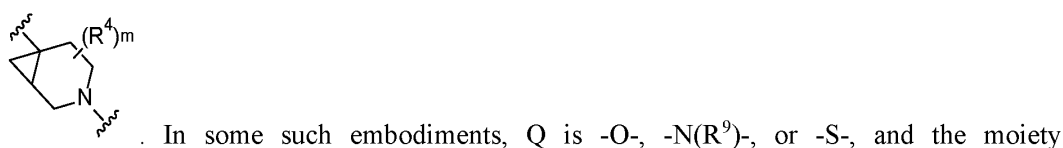
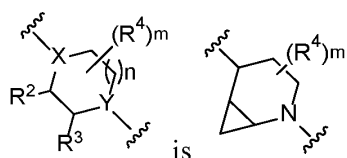
. In some such embodiments, Q is CR^7R^8 and the



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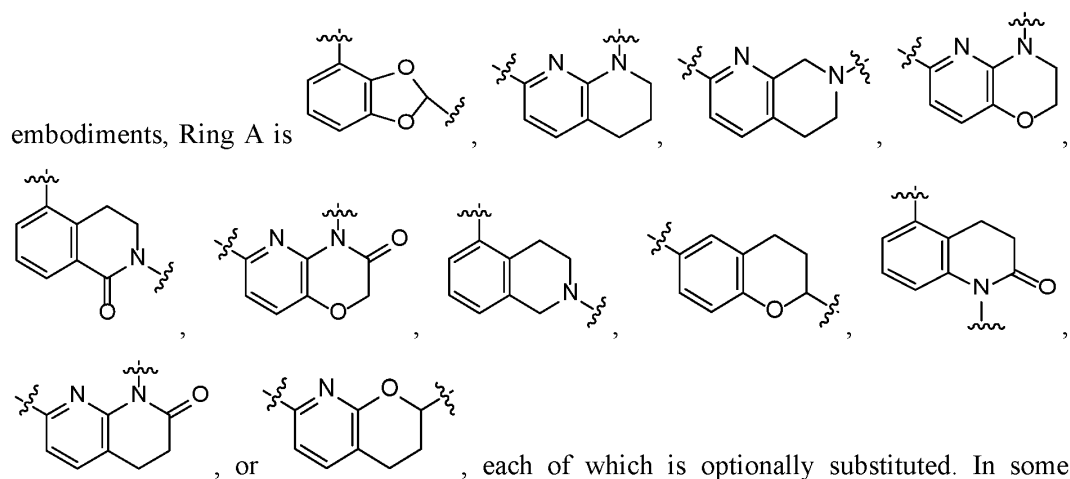
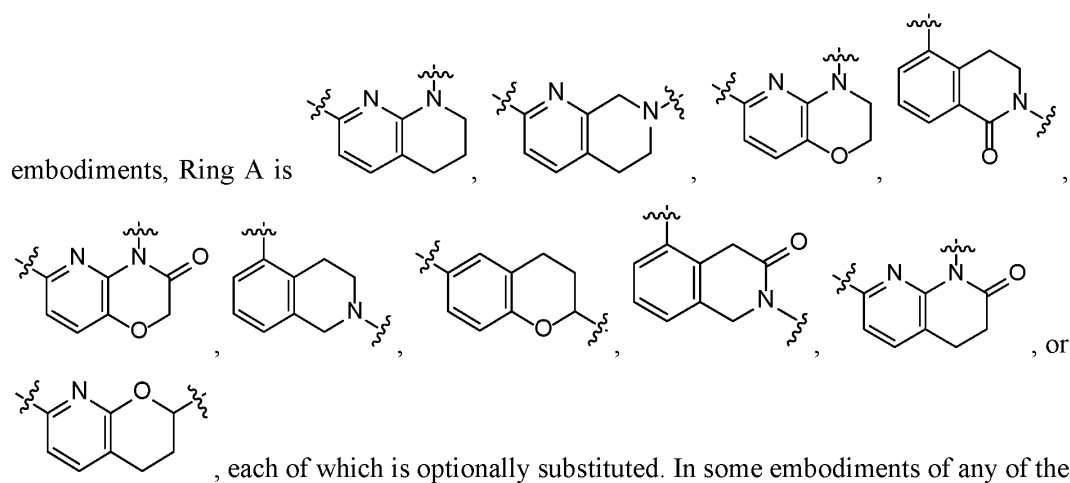
. In other embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), or a pharmaceutically acceptable salt thereof, Q is -O-, -N(R⁹)-, or -S-, and the moiety



[0070] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), or a pharmaceutically acceptable salt thereof, m is 0, 1, 2, or 3. In other embodiments, m is 0, 1, or 2. In other embodiments, m is 0 or 1. In some embodiments of any of the foregoing, each R⁴ is oxo or C₁-C₆ alkyl. In some such embodiments, each R⁴ is oxo or methyl. In some embodiments, m is 0.

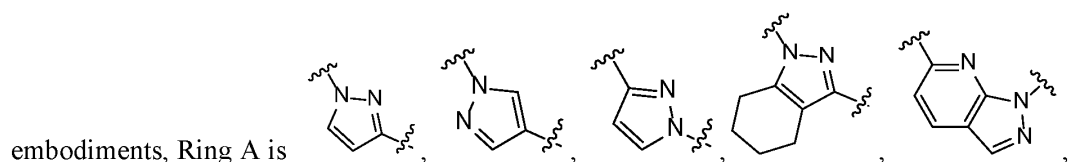
[0071] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), Q is selected from the group consisting of -C(R⁷)(R⁸)-, -O-, -N(R⁹)-, and -S-, wherein R⁷ and R⁸ are independently hydrogen, halogen, or C₁-C₆ alkyl; and R⁹ is hydrogen or C₁-C₆ alkyl. In some embodiments, Q is selected from the group consisting of -C(R⁷)(R⁸)-, -O-, -N(R⁹)-, and -S-, wherein R⁷ is hydrogen, halogen, or C₁-C₆ alkyl, and R⁸ is halogen or C₁-C₆ alkyl; and R⁹ is hydrogen or C₁-C₆ alkyl. Examples of suitable Q groups include, but are not limited to, -CH₂-, -CHF-, -C(H)(CH₃)-, -CF₂-, -C(CH₃)₂-, -NH-, -N(CH₃)-, -O-, -S-, and the like. In some embodiments, Q is not -CH₂-.

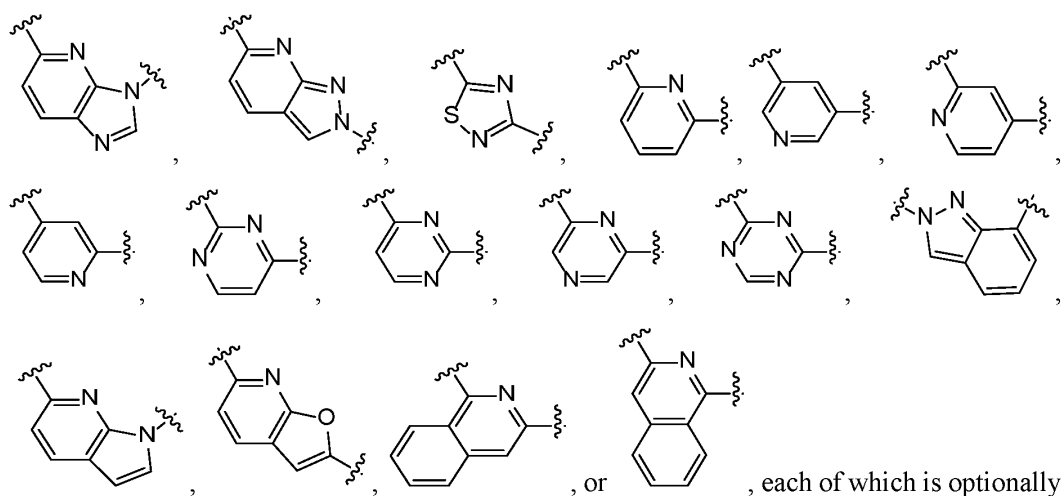
[0072] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), or a pharmaceutically acceptable salt thereof, Ring A is an optionally substituted 5- to 12-membered heterocycl. In some



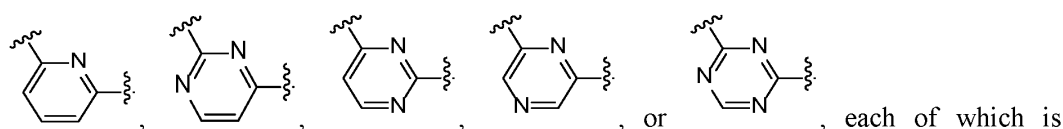
foregoing, Ring A is optionally substituted by halo, OH, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH. In some such embodiments, Ring A is optionally substituted by halo or OH. In some such embodiments, Ring A is optionally substituted by halo. In some embodiments, Ring A is unsubstituted.

[0073] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof), or a pharmaceutically acceptable salt thereof, Ring A is optionally substituted 5- to 12-membered heteroaryl. In some

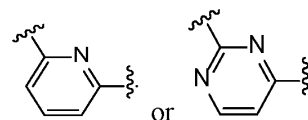




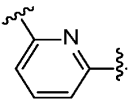
substituted. In some embodiments, Ring A is



optionally substituted. In some embodiments, Ring A is



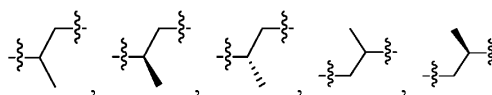
which is optionally substituted. In some embodiments, Ring A is



, which is optionally substituted. In some embodiments of any of the foregoing, Ring A is optionally substituted by halo, OH, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH. In some such embodiments, Ring A is optionally substituted by halo or OH. In some such embodiments, Ring A is optionally substituted by halo. In some embodiments, Ring A is unsubstituted.

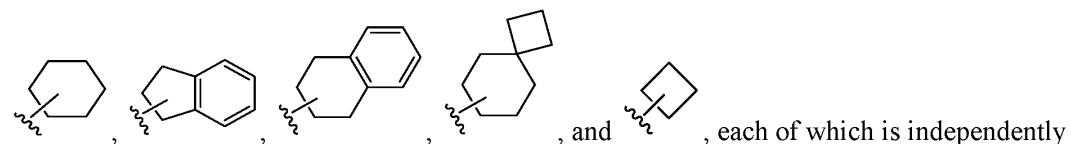
[0074] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (2)-(10) and subformulae thereof, if applicable), or a pharmaceutically acceptable salt thereof, L is a bond. In some embodiments, L is -O-. In some embodiments, L is C₁-C₆ alkylene. In some embodiments, L is unsubstituted C₁-C₆ alkylene. In some embodiments, L is C₁-C₆ alkylene optionally substituted by R^L, wherein each R^L is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl.

In some embodiments, L is unsubstituted C₁-C₂ alkylene. In some embodiments, L is C₁-C₂ alkylene optionally substituted by R^L, wherein each R^L is independently halo, OH, oxo, or C₁-C₆ alkyl. In some embodiments, L is unsubstituted C₂ alkylene. In some embodiments, L is C₂ alkylene optionally substituted by R^L, wherein each R^L is independently halo, OH, oxo, or C₁-

C₆ alkyl. In some such embodiments, L is , or

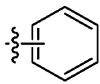
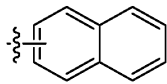
. In some embodiments, L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, wherein R⁶ is hydrogen or C₁-C₆ alkyl. For example, L can be *-OCH₂-**. In some embodiments, when L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, L is substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl. To give a specific example, when L is *-OC(R^L)₂-**, two R^L can be taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl. In some embodiments, L is *-O-C₁-C₆ alkylene-**. In some embodiments, L is *-O-C₁-C₃ alkylene-**. In some embodiments, L is *-OCH₂-**.

[0075] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (0)-(10) and subformulae thereof, if applicable), Ring B is optionally substituted C₃-C₁₀ cycloalkyl. Exemplary C₃-C₁₀ cycloalkyl include, but are not limited to,

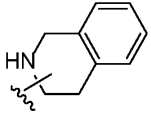
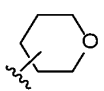
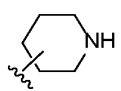
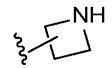
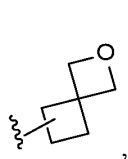
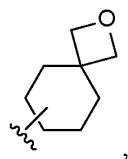
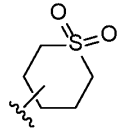
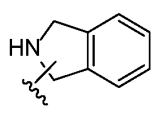
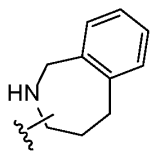


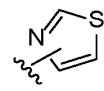
each of which is independently optionally substituted. In some embodiments of the foregoing, Ring B is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl optionally substituted by halo or CN, OC₁-C₆ alkyl optionally substituted by halo or CN, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl optionally substituted by halo or CN. In some such embodiments, Ring B is optionally substituted by one to three substituents independently selected from the group consisting of halo and CN. In some embodiments, Ring B is substituted by two substituents independently selected from F, Cl, and CN.

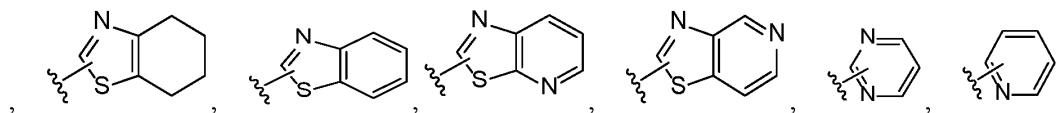
[0076] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (0)-(10) and subformulae thereof, if applicable), Ring B is optionally

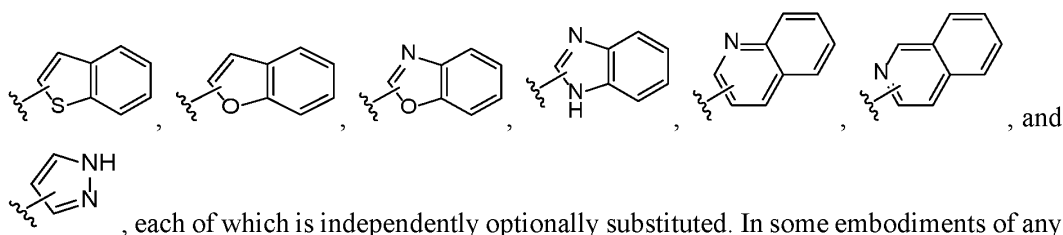
substituted C₆-C₁₄ aryl. For example, the C₆-C₁₄ aryl can be  or , each of which is independently optionally substituted. In some embodiments, Ring B is phenyl, which is optionally substituted. In some embodiments of any of the foregoing, Ring B is optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl. In some such embodiments, Ring B is optionally substituted by one to three substituents independently selected from the group consisting of halo and CN. In some embodiments, Ring B is substituted by two substituents independently selected from F, Cl, and CN.

[0077] In some embodiments of a compound of Formula (0) or Formula (1) (including compounds of Formula (0)-(10) and subformulae thereof, if applicable), Ring B is optionally substituted 4- to 12-membered heterocyclyl. Exemplary 4- to 12-membered heterocyclyl

include, but are not limited to, , , , , , , , , , and , each of which is independently optionally substituted. In some embodiments of any of the foregoing, Ring B is optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl. In some such embodiments, Ring B is optionally substituted by one to three substituents independently selected from the group consisting of halo and CN. In some embodiments, Ring B is substituted by two substituents independently selected from F, Cl, and CN.

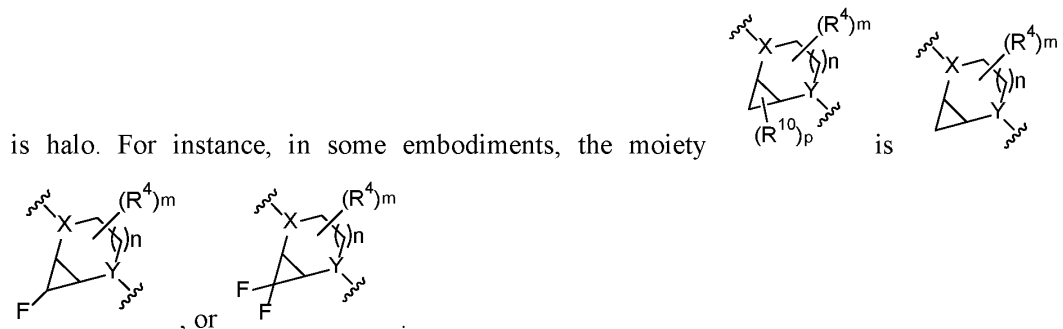
[0078] In some embodiments, Ring B is optionally substituted 5- to 12-membered heteroaryl. Exemplary 5- to 12-membered heteroaryl include, but are not limited to, ,





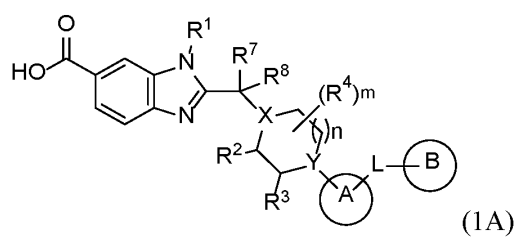
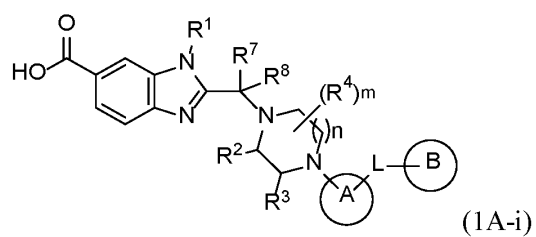
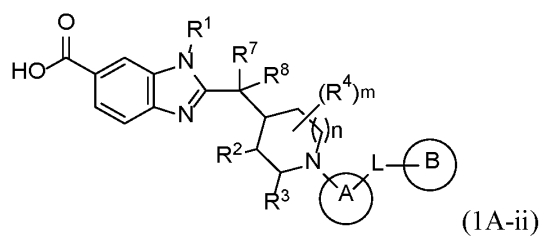
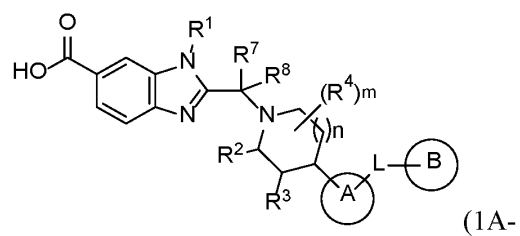
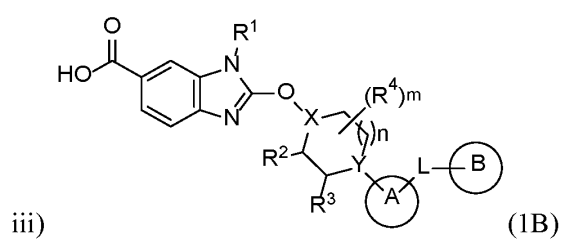
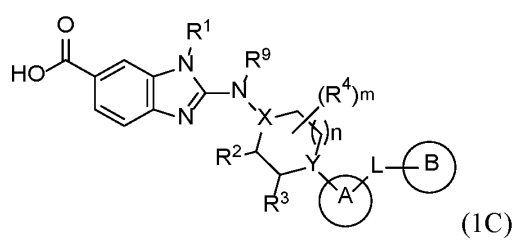
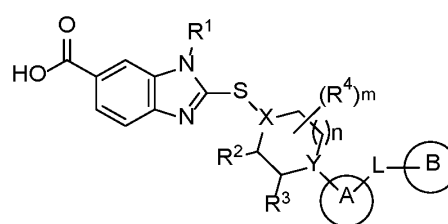
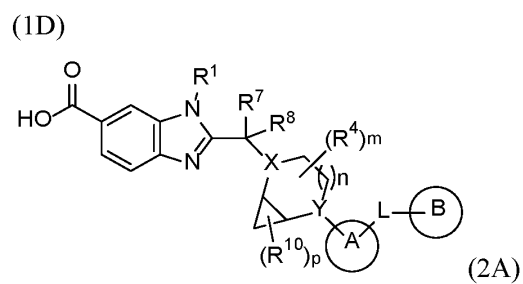
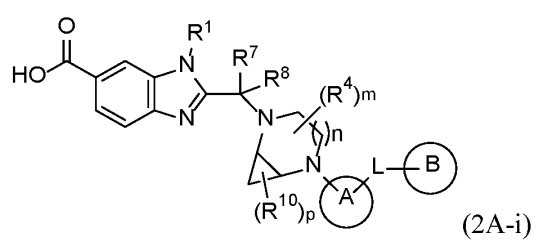
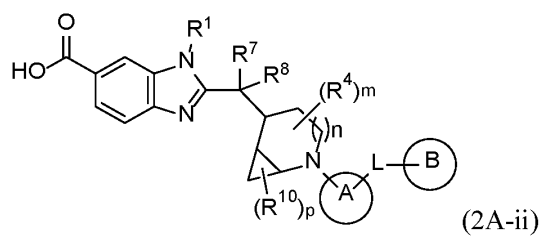
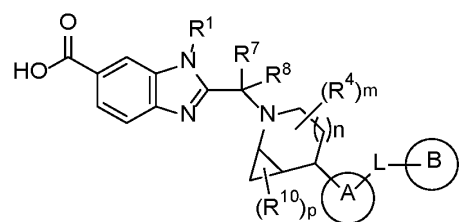
of the foregoing, Ring B is optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl. In some such embodiments, Ring B is optionally substituted by one to three substituents independently selected from the group consisting of halo and CN.

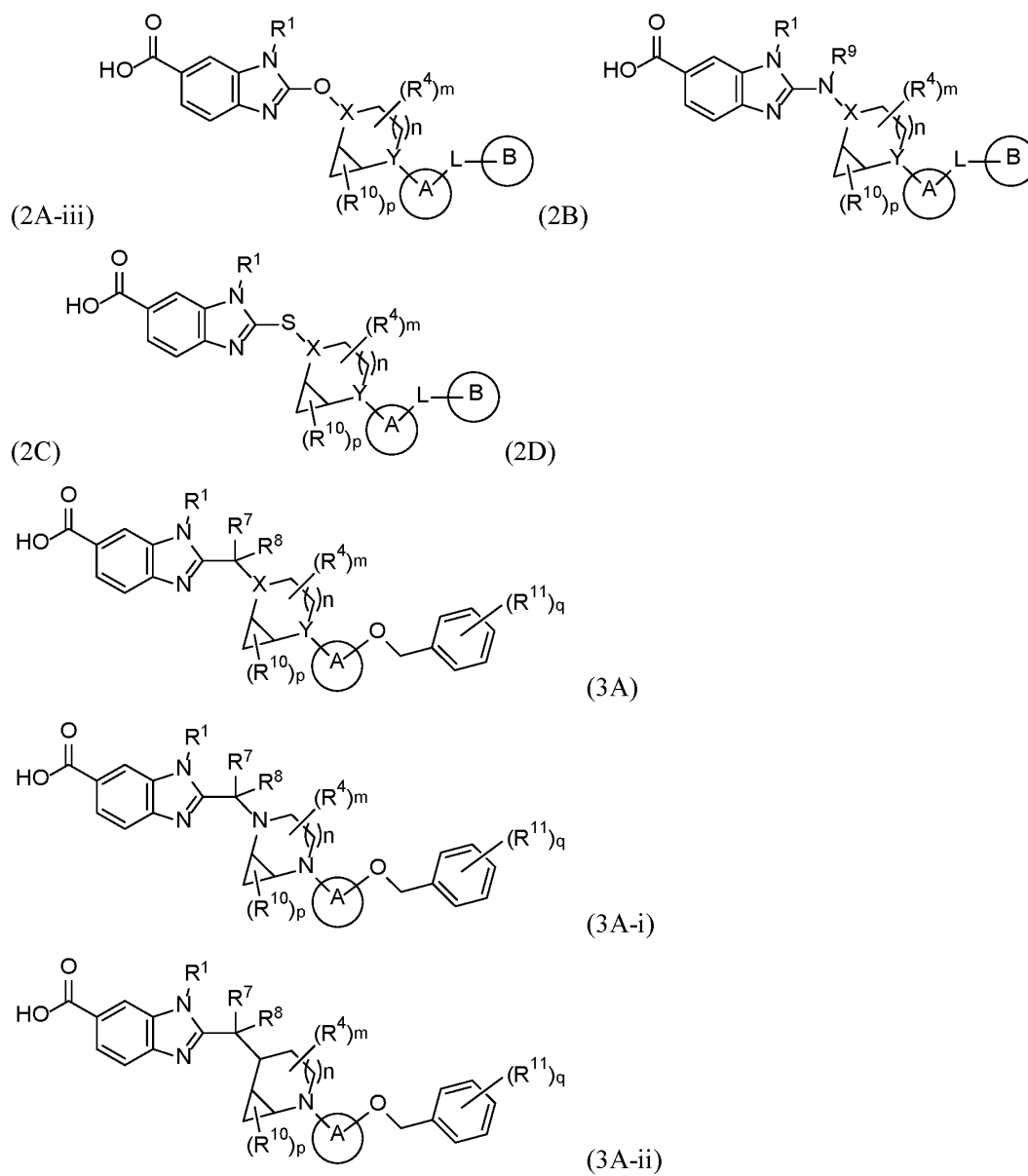
[0079] In some embodiments of Formula (2)-(10), or subformulae thereof if applicable, p is 0, 1, or 2 and each R¹⁰, when present, is halo. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 2 and each R¹⁰

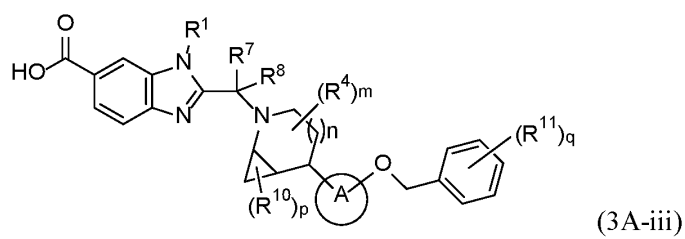
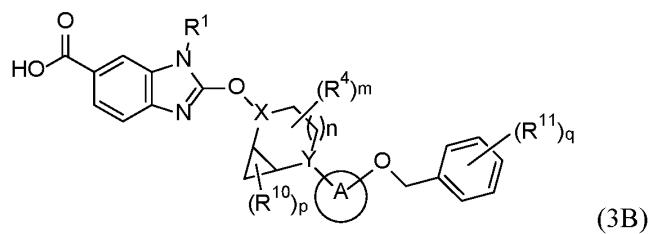
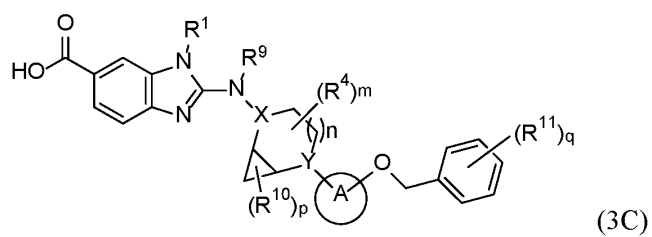
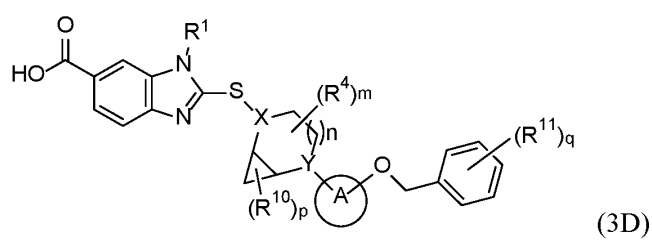
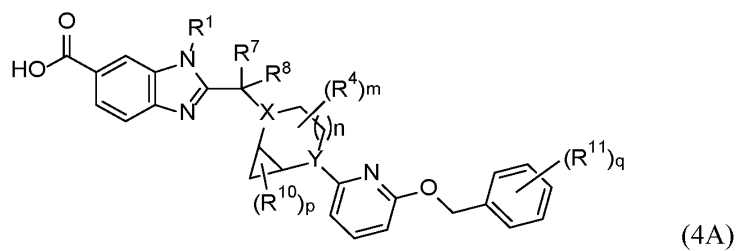
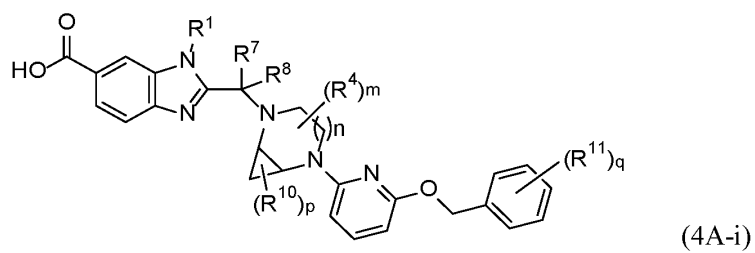


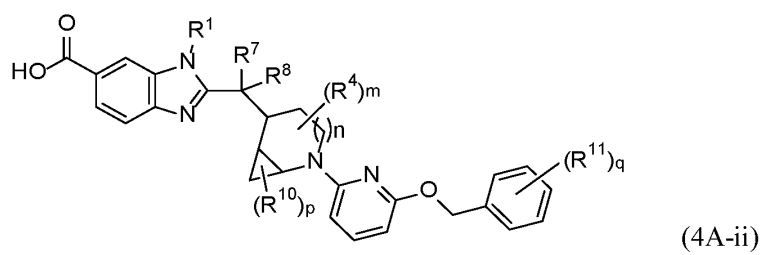
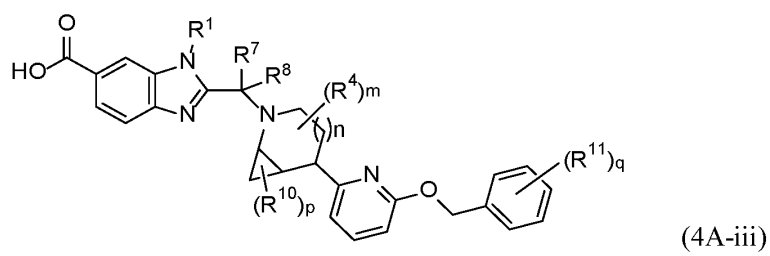
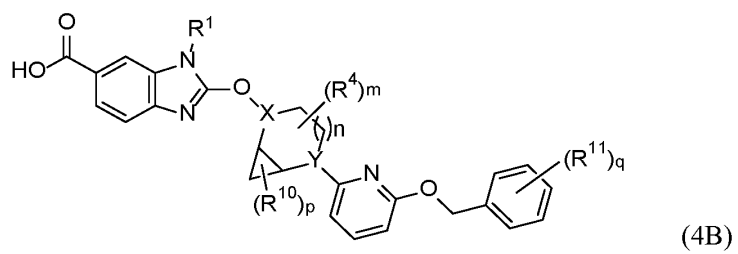
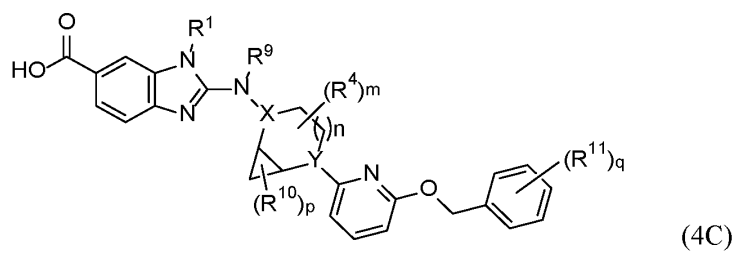
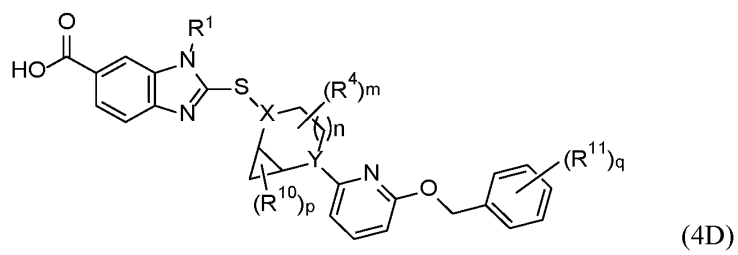
[0080] In some embodiments of Formula (3), (4), (6), (7), (9), and (10), or subformulae thereof if applicable, q is 0, 1, 2, or 3. In some embodiments, q is 2 or 3. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 2, and each R¹¹ is independently selected from halo or CN.

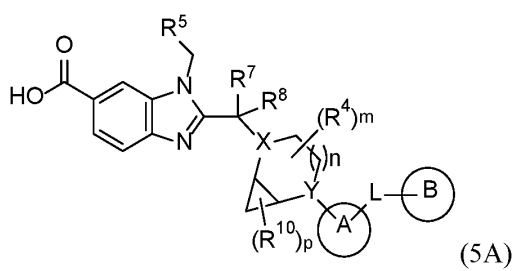
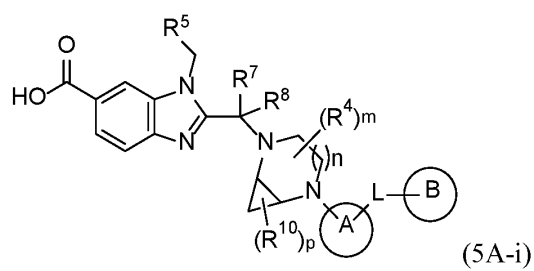
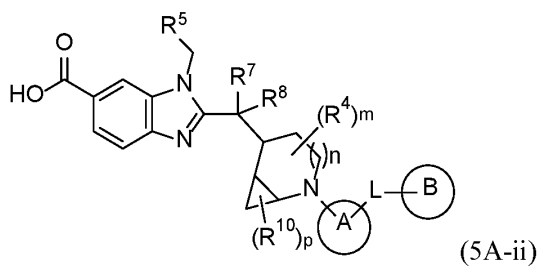
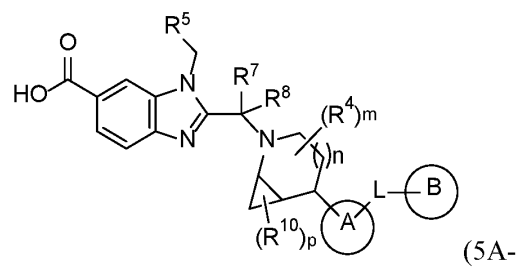
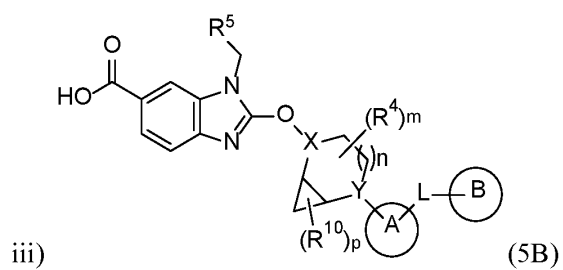
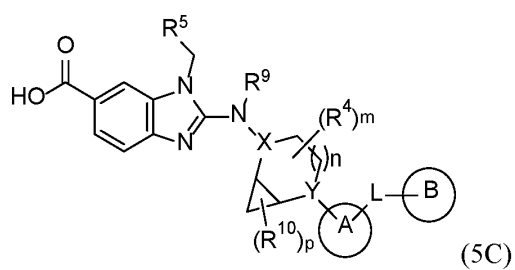
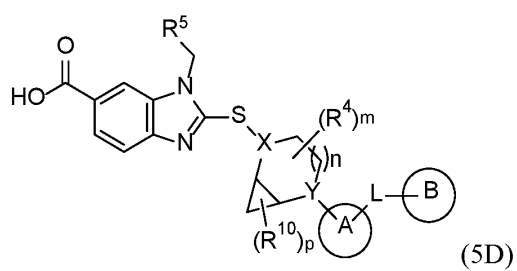
[0081] In the descriptions herein, it is understood that every description, variation, embodiment or aspect of a moiety/variable may be combined with every description, variation, embodiment or aspect of other moieties/variables the same as if each and every combination of descriptions is specifically and individually listed, for example, as shown in the subformulae below.

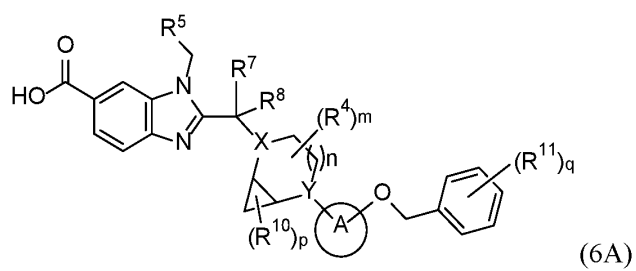
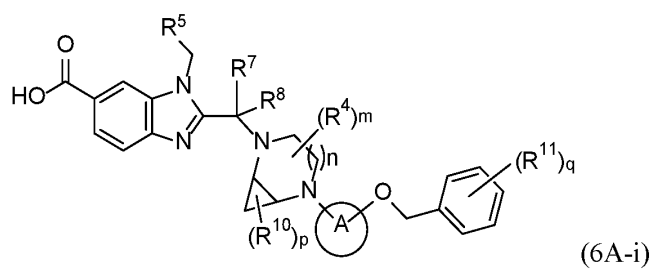
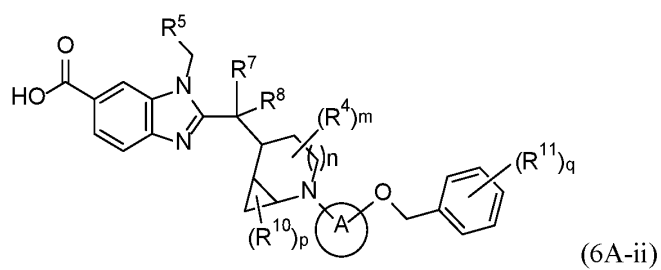
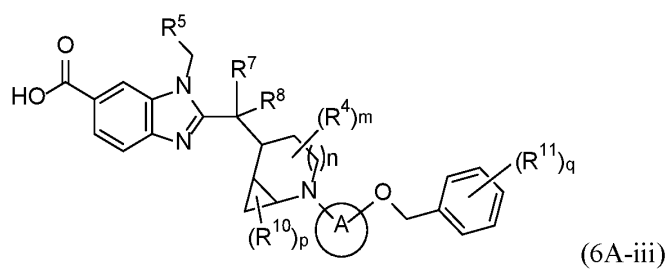
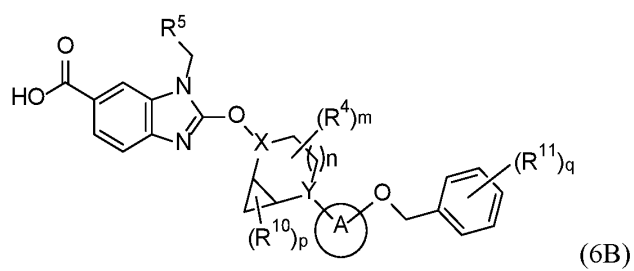


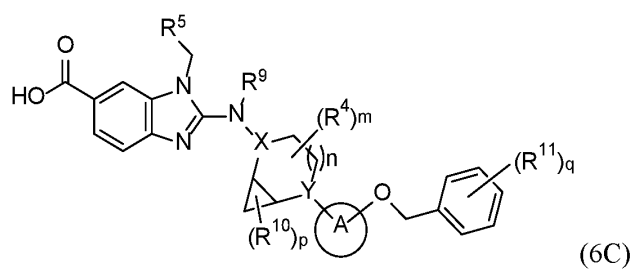
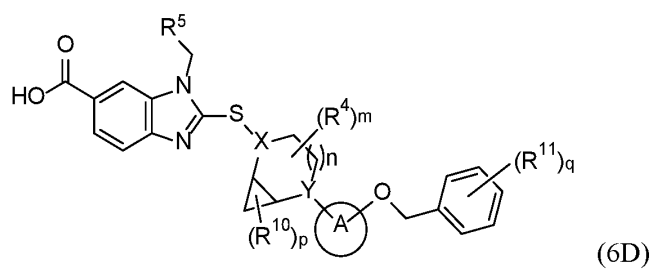
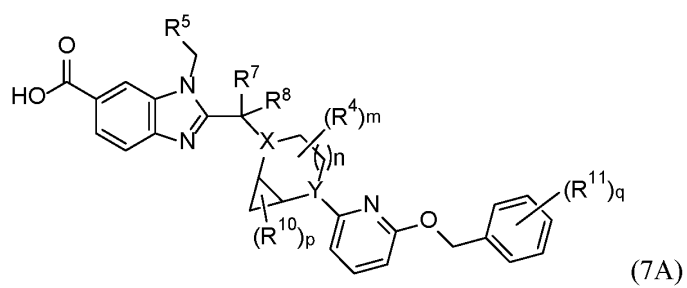
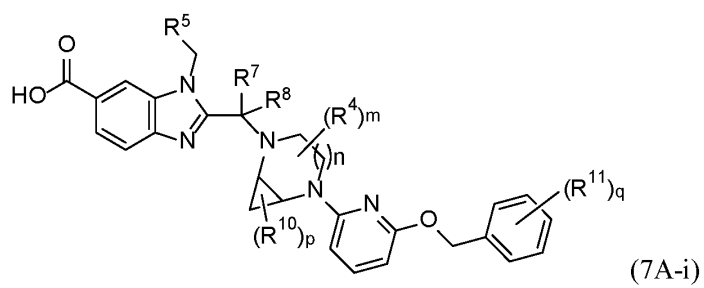












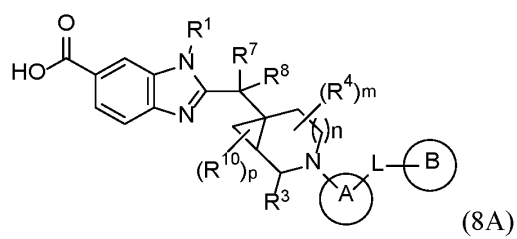
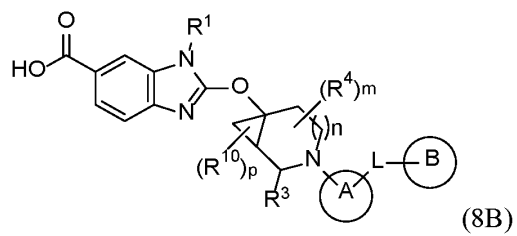
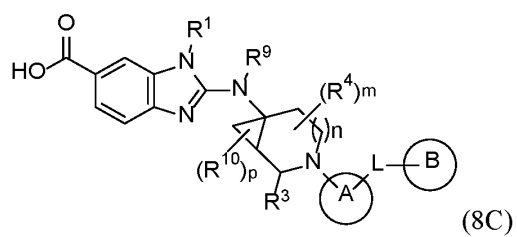
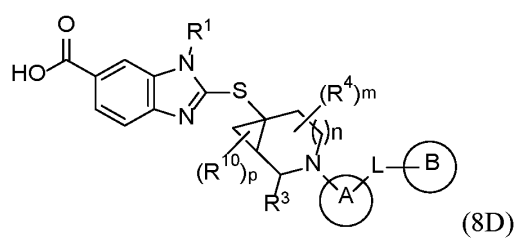
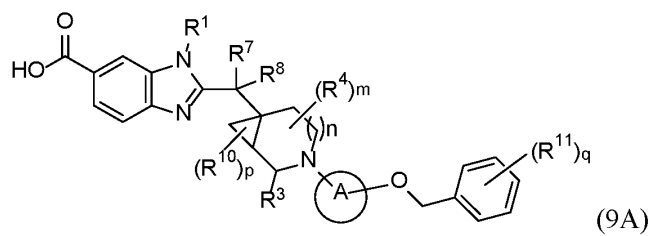
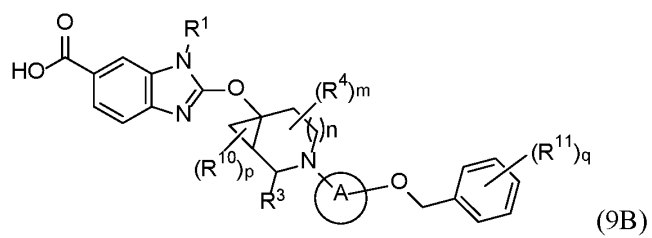
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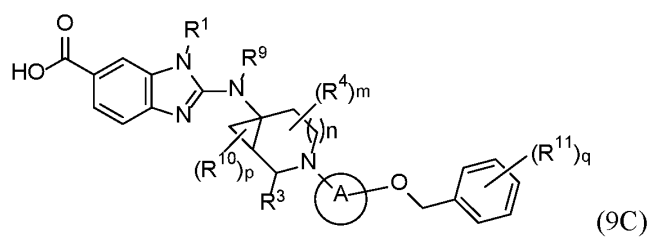
(7A-iii)

(7B)

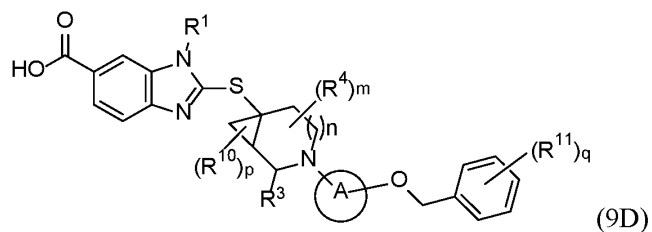
Chemical structure (7C) is a benzimidazole derivative. The benzimidazole ring is substituted at the 2-position with a side chain: $-N(R^9)-X-CH_2(R^4)_m-CH_2(R^{10})_p-Y$. The benzimidazole ring is also substituted at the 6-position with a carboxylic acid group ($-COOH$). The side chain contains a bicyclic system (a cyclopropane ring fused to a cyclobutane ring) where X and Y are the bridgehead atoms. The phenyl group is substituted with $(R^{11})_q$.

(7D)

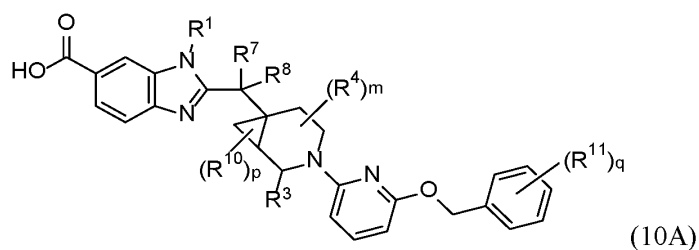




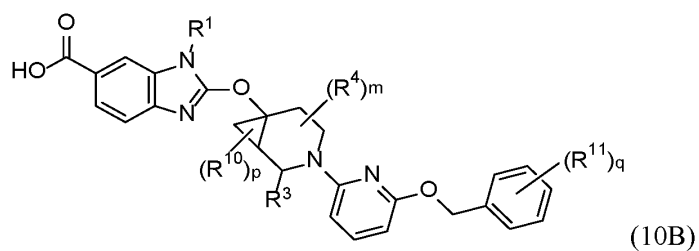
(9C)



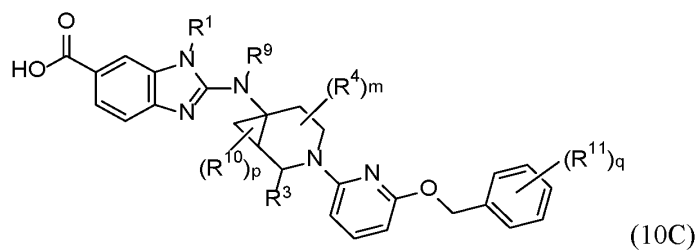
(9D)



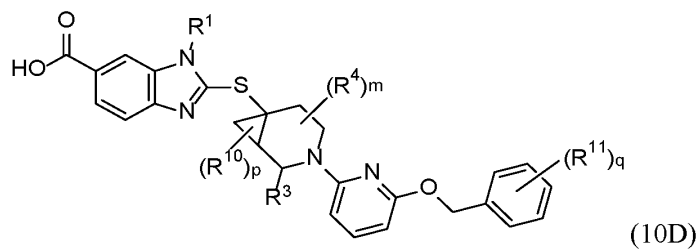
(10A)



(10B)



(10C)

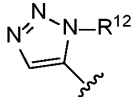


(10D)

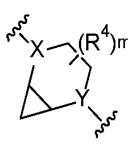
[0082] In some embodiments of Formula (1A), (1A-i), (1A-ii), (1A-iii), (1B), (1C), (1D), (2A), (2A-i), (2A-ii), (2A-iii), (2B), (2C), (2D), (3A), (3A-i), (3A-ii), (3A-iii), (3B), (3C), (3D),

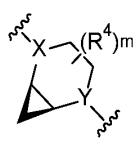
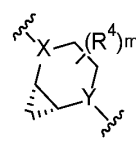
(4A), (4A-i), (4A-ii), (4A-iii), (4B), (4C), (4D), (5A), (5A-i), (5A-ii), (5A-iii), (5B), (5C), (5D), (6A), (6A-i), (6A-ii), (6A-iii), (6B), (6C), (6D), (7A), (7A-i), (7A-ii), (7A-iii), (7B), (7C), (7D), (8A), (8A-i), (8A-ii), (8A-iii), (8B), (8C), (8D), (9A), (9A-i), (9A-ii), (9A-iii), (9B), (9C), (9D), (10A), (10A-i), (10A-ii), (10A-iii), (10B), (10C), and (10D), R⁵ is triazolyl or thiazolyl, each of which is optionally substituted. In some embodiments, R⁵ is triazolyl which is unsubstituted. In some embodiments, R⁵ is thiazolyl which is optionally substituted. In some embodiments of any of the foregoing, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl substituent is independently optionally substituted by halo or CN. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, and -OC₁-C₆ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, oxo, CN, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, C₁-C₃ alkyl, and -OC₁-C₃ alkyl. In some such embodiments, R⁵ is optionally substituted by one to three substituents independently selected from the group consisting of Cl, F, Br, and C₁-C₃ alkyl, such as methyl, ethyl, propyl, or isopropyl. In some embodiments, R⁵ is unsubstituted.

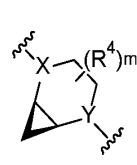
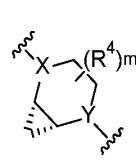
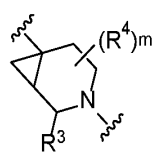
[0083] In some embodiments of Formula (1A), (1A-i), (1A-ii), (1A-iii), (1B), (1C), (1D), (2A), (2A-i), (2A-ii), (2A-iii), (2B), (2C), (2D), (3A), (3A-i), (3A-ii), (3A-iii), (3B), (3C), (3D), (4A), (4A-i), (4A-ii), (4A-iii), (4B), (4C), (4D), (5A), (5A-i), (5A-ii), (5A-iii), (5B), (5C), (5D), (6A), (6A-i), (6A-ii), (6A-iii), (6B), (6C), (6D), (7A), (7A-i), (7A-ii), (7A-iii), (7B), (7C), (7D), (8A), (8A-i), (8A-ii), (8A-iii), (8B), (8C), (8D), (9A), (9A-i), (9A-ii), (9A-iii), (9B), (9C), (9D),

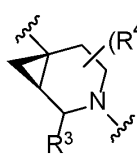
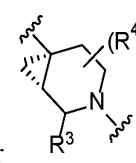
(10A), (10A-i), (10A-ii), (10A-iii), (10B), (10C), and (10D), R⁵ is , wherein R¹² is C₁-C₆ alkyl. In some such embodiments, R¹² is methyl. In other such embodiments, R¹² is ethyl. In other such embodiments, R¹² is isopropyl. In other such embodiments, R¹² is isobutyl.

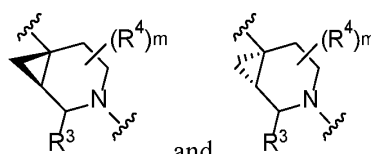
[0084] The present disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms of the compounds described. Compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric or diastereomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof in any ratio, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof in any ratio, unless a specific stereochemistry is otherwise indicated. Where a formula or a compound of Table 1 is depicted with a particular stereochemical configuration, also provided herein is any alternative stereochemical configuration of the compound, as well as a mixture of stereoisomers of the compound in any ratio. For example, where a formula or a compound of Table 1 has a stereocenter that is in an “S” stereochemical configuration, also provided herein is the enantiomer of the compound wherein that stereocenter is in an “R” stereochemical configuration. Likewise, when a formula or a compound of Table 1 has a stereocenter that is in an “R” configuration, also provided herein is enantiomer of the compound in an “S” stereochemical configuration. Also provided are mixtures of the compound with both the “S” and the “R” stereochemical configuration. As another example,

in Formula (0)-(7), and subformulae thereof, the moiety  includes variations

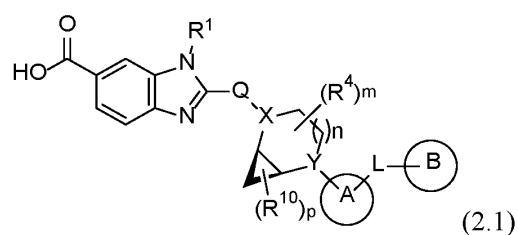
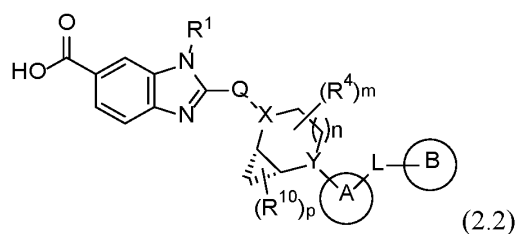
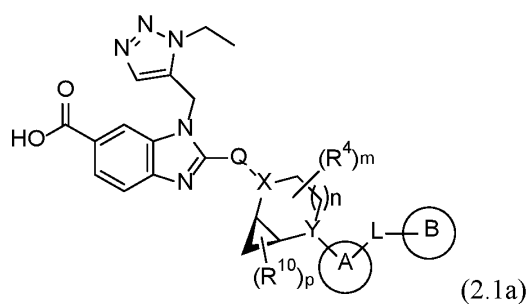
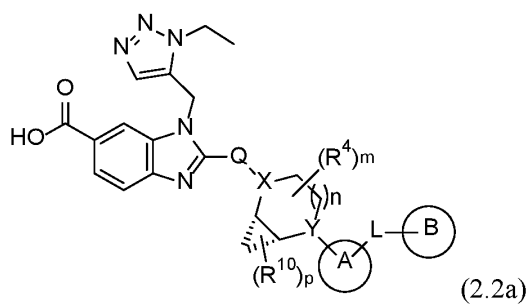
wherein the formula has the form  or . Also provided are mixtures

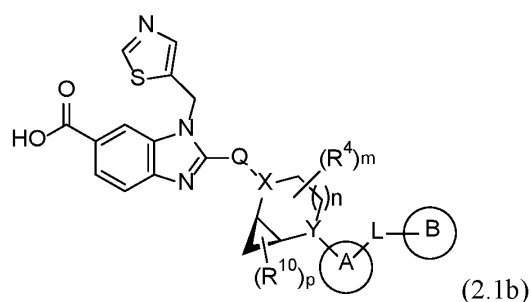
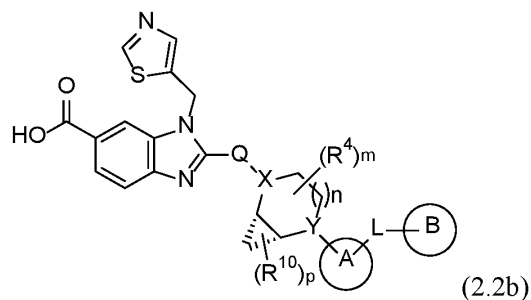
comprising both forms  and . Similarly, the moiety  includes variations

wherein the formula has the form  or . Also



provided are mixtures comprising both forms and . In some embodiments, one diastereomeric form may be preferred, for instance, compounds Formula (2) or subformulae thereof may be preferred with the configuration shown in Formula (2.1), Formula (2.1a), and Formula (2.1b) relative to the configuration shown in Formula (2.2), Formula (2.2a), and Formula (2.2b), respectively.





[0085] The compounds depicted herein may be present as salts even if salts are not depicted and it is understood that the present disclosure embraces all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts.

[0086] The invention also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or variations thereof described herein, where a fraction of one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl . Certain isotope labeled compounds (e.g. ^3H and ^{14}C) are useful in compound or substrate tissue distribution study. Incorporation of heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances.

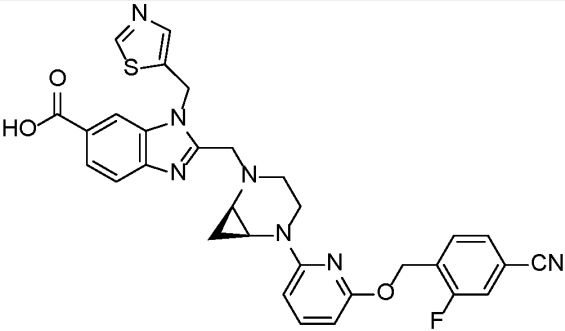
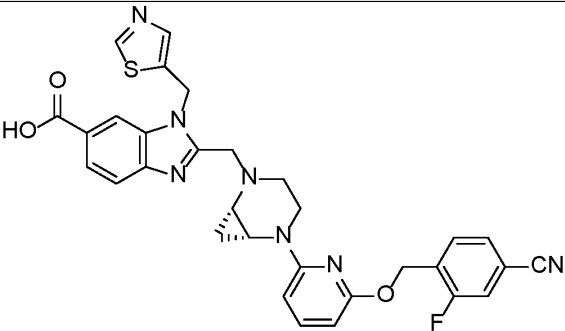
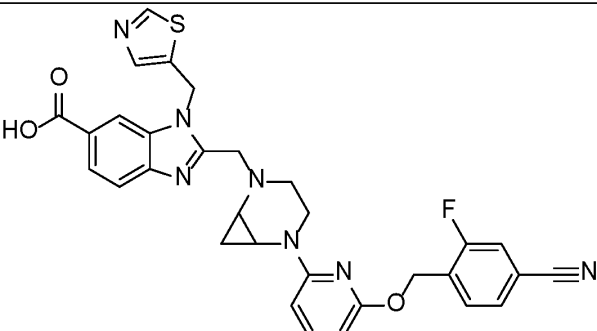
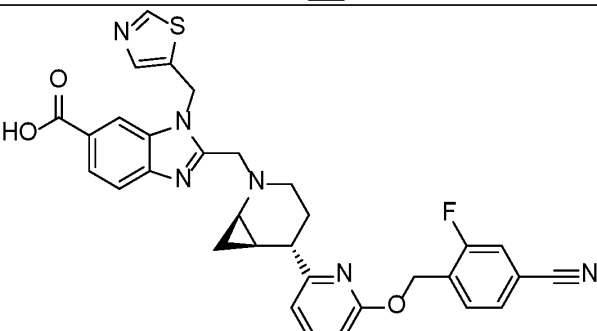
[0087] Isotopically-labeled compounds of the present invention can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar

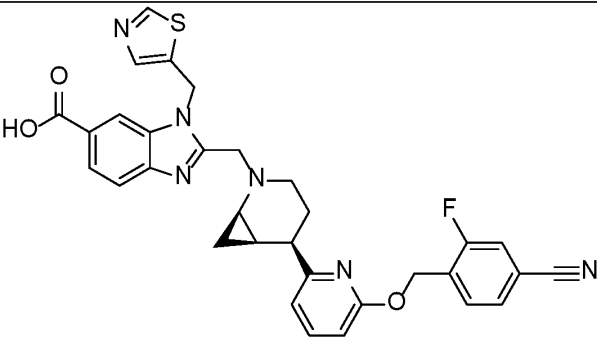
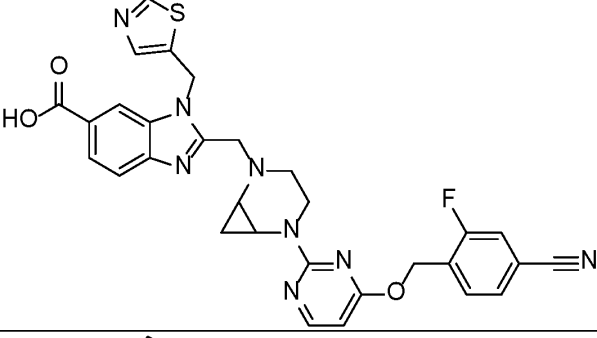
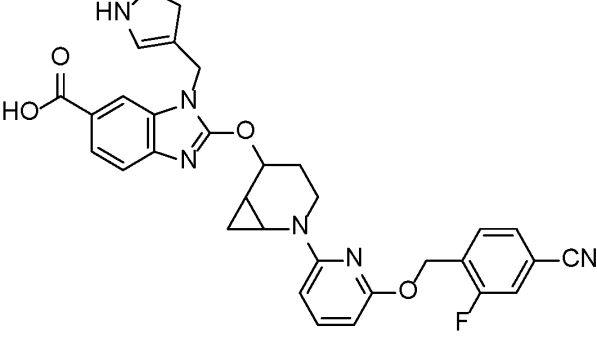
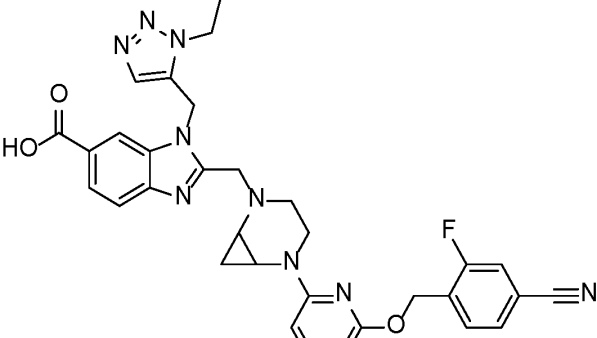
to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent.

[0088] The invention also includes any or all metabolites of any of the compounds described. The metabolites may include any chemical species generated by a biotransformation of any of the compounds described, such as intermediates and products of metabolism of the compound, such as would be generated in vivo following administration to a human.

[0089] Representative compounds are listed in Table 1 below. In some embodiments, provided is a compound, or a pharmaceutically acceptable salt thereof, which is selected from Compound Nos. 1-46 in Table 1. In some embodiments, provided is a compound, or a pharmaceutically acceptable salt thereof, which is Compound 1 in Table 1.

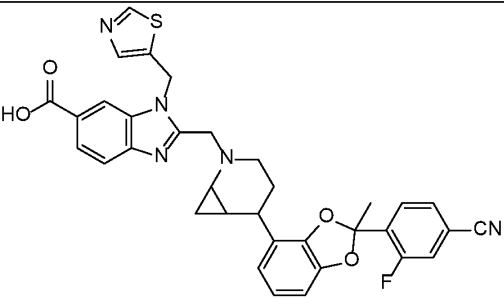
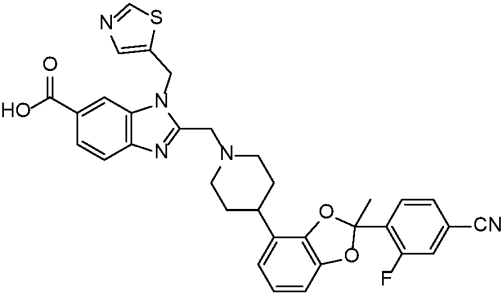
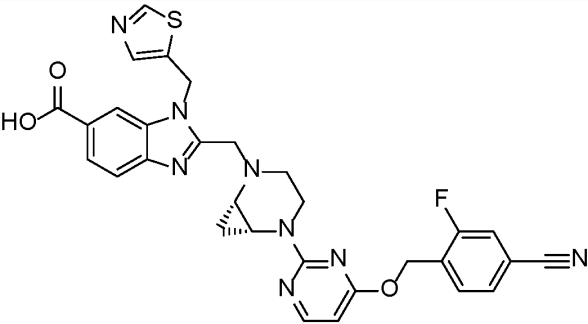
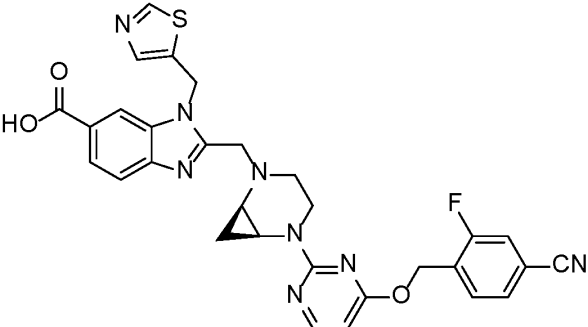
Table 1

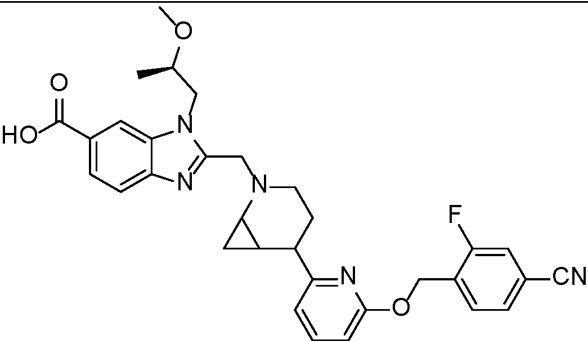
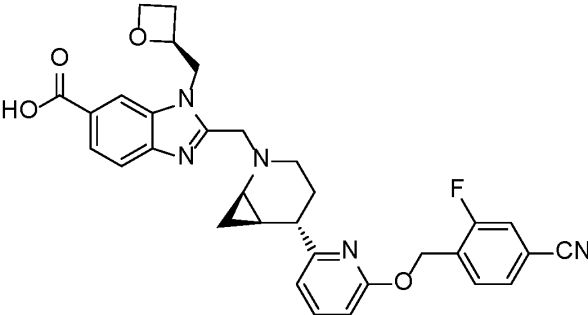
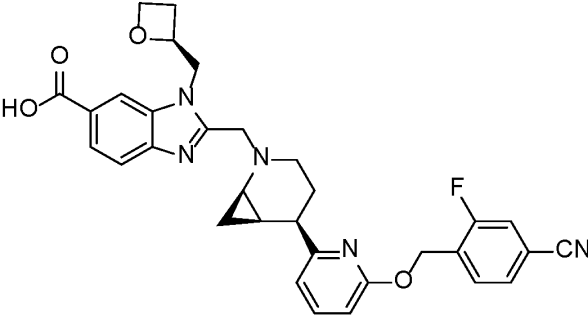
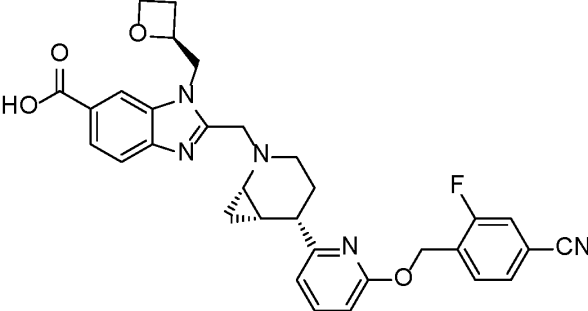
Compound No.	Structure
1	
2	
3	
4	

Compound No.	Structure
5	
6	
7	
8	

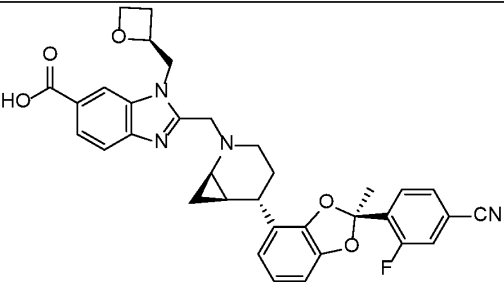
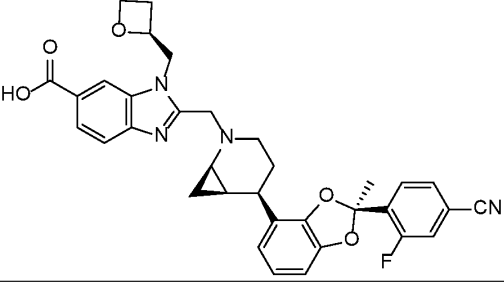
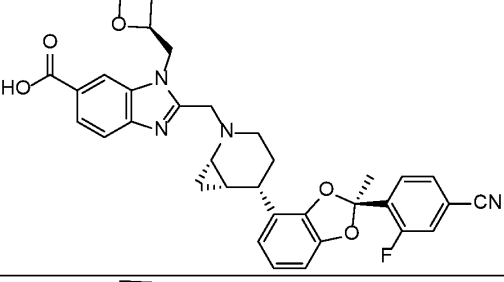
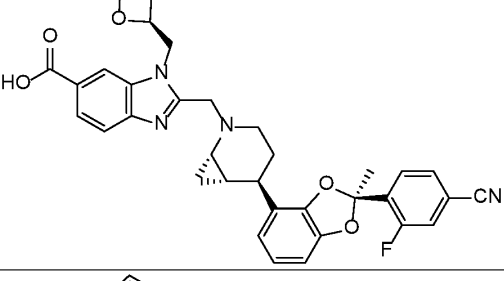
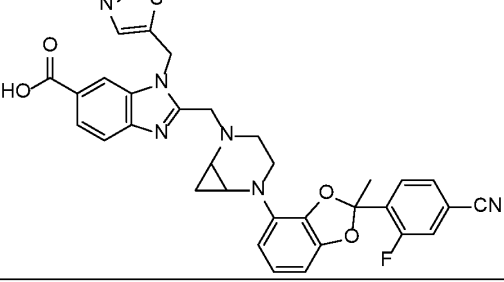
Compound No.	Structure
9	 <chem>CC1(CCN1c2ccc(O)nn2Cn3ccsc3)C4=CC=CC=C4COc5ccc(C#N)c(F)c5</chem>
10	 <chem>CC1(CCN1c2ccc(O)nn2CN3C=CN=N3)C4=CC=CC=C4COc5ccc(C#N)c(F)c5</chem>
11	 <chem>CN1C(CCN1c2ccc(O)nn2Cn3ccsc3)C4=CC=CC=C4COc5ccc(C#N)c(F)c5</chem>
12	 <chem>Cc1nn[nH]c1-c2ccc3c(c2)nn(Cn4ccsc4)c3C5=CC=CC=C5COc6ccc(C#N)c(F)c6</chem>

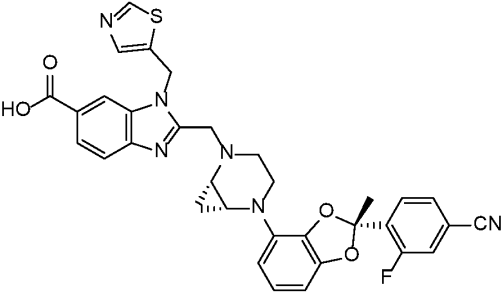
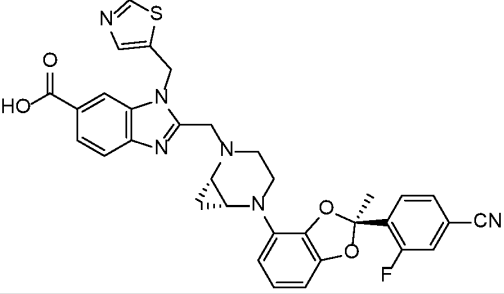
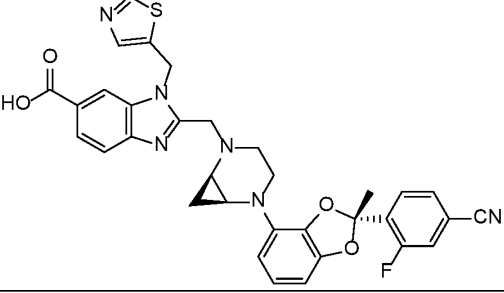
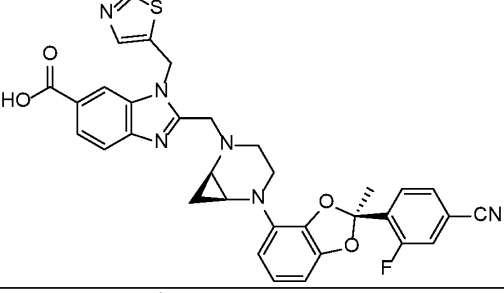
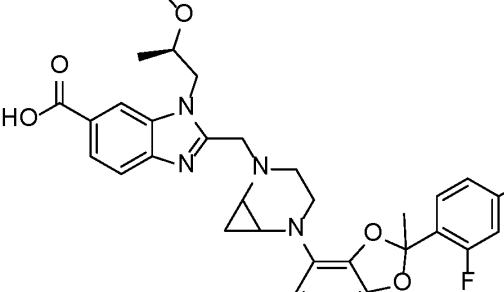
Compound No.	Structure
13	
14	
15	
16	

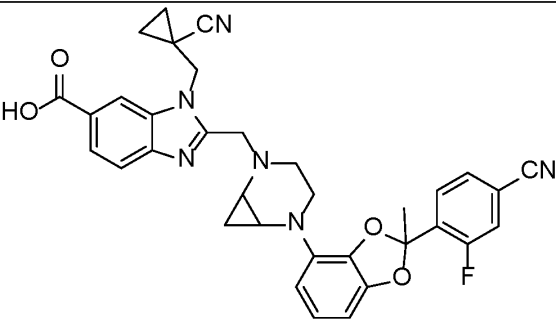
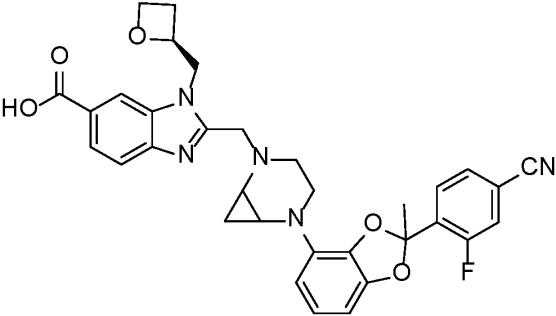
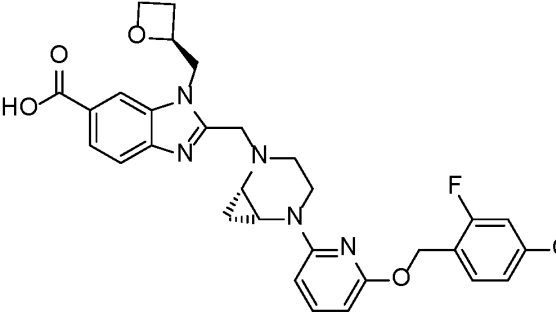
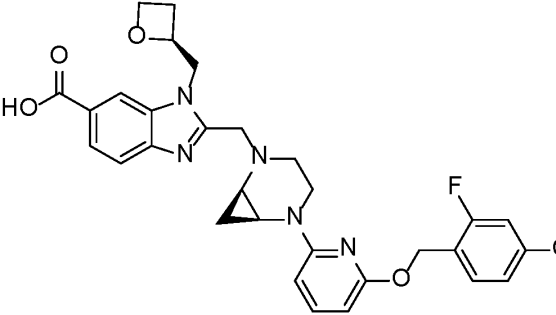
Compound No.	Structure
17	
18	
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20	

Compound No.	Structure
21	
22	
23	
24	

Compound No.	Structure
25	<chem>O=C(O)c1ccc2nc(CN(CCC1(C)CC[C@H]1c3ccc(nc3)COC4=CC=C(C=C4)C#N)CC5=CC=CC=C5F)nc2c1</chem>
26	<chem>O=C(O)c1ccc2nc(CN(CCC1(C)CC[C@H]1c3ccc(nc3)COC4=CC=C(C=C4)C#N)CC5=CC=CC=C5F)nc2c1</chem>
27	<chem>O=C(O)c1ccc2nc(CN(CCC1(C)CC[C@H]1c3ccc(nc3)COC4=CC=C(C=C4)C#N)CC5=CC=CC=C5F)nc2c1</chem>
28	<chem>O=C(O)c1ccc2nc(CN(CCC1(C)CC[C@H]1c3ccc(nc3)COC4=CC=C(C=C4)C#N)CC5=CC=CC=C5F)nc2c1</chem>
29	<chem>O=C(O)c1ccc2nc(CN(CCC1(C)CC[C@H]1c3ccc(nc3)COC4=CC=C(C=C4)C#N)CC5=CC=CC=C5F)nc2c1</chem>

Compound No.	Structure
30	
31	
32	
33	
34	

Compound No.	Structure
35	
36	
37	
38	
39	

Compound No.	Structure
40	
41	
42	
43	

Compound No.	Structure
44	
45	
46	

Pharmaceutically Acceptable Compositions and Formulations

[0090] Pharmaceutically acceptable compositions or simply “pharmaceutical compositions” of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0091] In some embodiments, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions

according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0092] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In one variation, “substantially pure” intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. For example, a composition of a substantially pure compound intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound or a salt thereof. In one variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 20% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 10% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 5% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 1% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 0.5% impurity. In yet other variations, a composition of substantially pure compound means that the composition contains no more than 15% or preferably no more than 10% or more preferably no more than 5% or even more preferably no more than 3% and most preferably no more than 1% impurity, which impurity may be the compound in a different stereochemical form.

[0093] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual such as a human. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier or excipient. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and

methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0094] The compounds may be formulated for any available delivery route, including an oral, mucosal (e.g., nasal, sublingual, vaginal, buccal or rectal), parenteral (e.g., intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (e.g., nasal spray or inhalers), gels, suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0095] Compounds described herein can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compounds as active ingredients with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (e.g., transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, e.g., in Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, 21st ed. (2005), which is incorporated herein by reference.

[0096] Compounds as described herein may be administered to individuals (e.g., a human) in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid polyols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0097] Compositions comprising two compounds utilized herein are described. Any of the compounds described herein can be formulated in a tablet in any dosage form described herein. In some embodiments, the composition comprises a compound of Formula (0), Formula (1),

including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a pharmaceutically acceptable salt thereof, as described herein. In some embodiments, provided herein is a dosage form comprises a therapeutically effective amount of a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or a pharmaceutically acceptable salt thereof is selected from Compound Nos. 1-46 in Table 1

Methods of Use and Uses

[0098] Compounds and compositions described herein may in some aspects be used in treatment of diseases and/or conditions described herein, for example, diseases and/or conditions mediated by GLP-1R. In some embodiments, the method of treating a disease or condition in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a compound of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or a pharmaceutically acceptable salt thereof. In some embodiments, the method of treating a disease or condition in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a compound selected from Compound Nos. 1-46 in Table 1, or a pharmaceutically acceptable salt thereof.

[0099] In accordance with the present application, a disease or condition to be treated and/or prevented is selected from the group consisting of cardiometabolic and associated diseases including diabetes (T1 D and/or T2DM, including pre-diabetes), idiopathic T1 D (Type 1 b), latent autoimmune diabetes in adults (LADA), early-onset T2DM (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease (e.g., acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules), diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity (including hypothalamic obesity and monogenic obesity) and related comorbidities (e.g., osteoarthritis and urine incontinence), eating disorders (including binge eating syndrome, bulimia nervosa, and syndromic obesity such as Prader-Willi and Bardet-Biedl syndromes), weight gain from use of other agents (e.g., from use of steroids and antipsychotics), excessive sugar craving, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, and low HDL cholesterol), hyperinsulinemia, liver diseases such as NAFLD, steatosis, NASH, fibrosis, cirrhosis, and hepatocellular carcinoma, cardiovascular disease, atherosclerosis (including

coronary artery disease), peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction (e.g. necrosis and apoptosis), stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome and addiction (e.g., alcohol and/or drug abuse), prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction (e.g., alcohol and/or drug abuse).

[0100] In some embodiments, provided herein is a method of treating a cardiometabolic disease in a subject (e.g., a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0101] In some embodiments, provided herein is a method of treating diabetes in a subject (e.g., a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof. Exemplary diabetes include, but are not limited to, T1 D, T2DM, pre-diabetes, idiopathic T1 D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, and gestational diabetes.

[0102] In some embodiments, provided herein is a method of treating a liver disorder in a subject (e.g., a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof. Exemplary liver disorders include, without limitation, liver inflammation, fibrosis, and steatohepatitis. In some embodiments, the liver disorder is selected from the list consisting of primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease

(NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and oti-antitrypsin deficiency. In some embodiments, the liver disorder is selected from the list consisting of liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). In some embodiments, the liver disorder is selected from the group consisting of liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, NAFLD, and NASH. In one embodiment, the liver disorder is NASH. In another embodiment, the liver disorder is liver inflammation. In another embodiment, the liver disorder is liver fibrosis. In another embodiment, the liver disorder is alcohol induced fibrosis. In another embodiment, the liver disorder is steatosis. In another embodiment, the liver disorder is alcoholic steatosis. In another embodiment, the liver disorder is NAFLD. In one embodiment, the treatment methods provided herein impedes or slows the progression of NAFLD to NASH. In one embodiment, the treatment methods provided herein impedes or slows the progression of NASH. NASH can progress, e.g., to one or more of liver cirrhosis, hepatic cancer, etc. In some embodiments, the liver disorder is NASH. In some embodiments, the patient has had a liver biopsy. In some embodiments, the method further comprising obtaining the results of a liver biopsy.

[0103] In accordance with the present application, a compound described herein, or a pharmaceutically acceptable salt thereof, can be administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. In some embodiments, it is a compound of any embodiment of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or selected from the compounds of Table 1, or a pharmaceutically acceptable salt thereof. The compounds and/or compositions described herein may be administered orally, rectally, vaginally, parenterally, or topically.

[0104] In some embodiments, the compounds and/or compositions may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

[0105] In some embodiments, the compounds and/or compositions may be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for

parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[0106] In some embodiments, the compounds and/or compositions may be administered topically to the skin or mucosa, that is, dermally or transdermally. In some embodiments, the compounds and/or compositions may be administered intranasally or by inhalation. In some embodiments, the compounds and/or compositions may be administered rectally or vaginally. In some embodiments, the compounds and/or compositions may be administered directly to the eye or ear.

[0107] The dosage regimen for the compounds and/or compositions described herein is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. In some embodiments, the total daily dose of the compounds of the present application is typically from about 0.001 to about 100 mg/kg (i.e., mg compound per kg body weight) for the treatment of the indicated conditions discussed herein. In one embodiment, total daily dose of the compounds of the present application is from about 0.01 to about 30 mg/kg, and in another embodiment, from about 0.03 to about 10 mg/kg, and in yet another embodiment, from about 0.1 to about 3. It is not uncommon that the administration of the compounds of the present application will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

[0108] For oral administration, the compounds and/or compositions described herein may be provided in the form of tablets containing 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 30.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

[0109] The compounds and/or compositions described herein can be used alone, or in combination with other therapeutic agents. The administration of two or more agents “in combination” means that all of the agents are administered closely enough in time that each may generate a biological effect in the same time frame. The presence of one agent may alter the biological effects of the other agent(s). The two or more agents may be administered

simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the agents prior to administration or by administering the compounds at the same point in time but as separate dosage forms at the same or different site of administration.

[0110] The present application provides any of the uses, methods or compositions as defined herein wherein a compound of any embodiment of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or selected from the compounds of Table 1 as described herein, or a pharmaceutically acceptable salt thereof, is used in combination with one or more other therapeutic agent. This would include a pharmaceutical composition comprising a compound of any embodiment of Formula (0), Formula (1), including compounds of Formula (2)-(10), or a subformula of any of the foregoing, or selected from the compounds of Table 1, or a pharmaceutically acceptable salt thereof, as defined in any of the embodiments described herein, in admixture with at least one pharmaceutically acceptable excipient and one or more other therapeutic agent.

[0111] In some embodiments, the one or more other therapeutic agent is an anti-diabetic agent including but not limited to a biguanide (e.g., metformin), a sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, or glipizide), a thiazolidinedione (e.g., pioglitazone, rosiglitazone, or lobeglitazone), a glitazar (e.g., saroglitazar, aleglitazar, muraglitazar or tesaglitazar), a meglitinide (e.g., nateglinide, repaglinide), a dipeptidyl peptidase 4 (DPP-4) inhibitor (e.g., sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, dutogliptin, or omarigliptin), a glitazone (e.g., pioglitazone, rosiglitazone, balaglitazone, rivoglitazone, or lobeglitazone), a sodium-glucose linked transporter 2 (SGLT2) inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, Ipragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a GPR40 agonist (FFAR1/FFA1 agonist, e.g. fasiglifam), glucose-dependent insulinotropic peptide (GIP) and analogues thereof, an alpha glucosidase inhibitor (e.g. voglibose, acarbose, or miglitol), or an insulin or an insulin analogue, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

[0112] In some embodiments, the one or more other therapeutic agent is an antiobesity agent including but not limited to peptide YY or an analogue thereof, a neuropeptide Y receptor type 2 (NPYR2) agonist, a NPYR1 or NPYR5 antagonist, a cannabinoid receptor type 1 (CB1 R) antagonist, a lipase inhibitor (e.g., orlistat), a human proislet peptide (HIP), a melanocortin

receptor 4 agonist (e.g., setmelanotide), a melanin concentrating hormone receptor 1 antagonist, a farnesoid X receptor (FXR) agonist (e.g. obeticholic acid), zonisamide, phentermine (alone or in combination with topiramate), a norepinephrine/dopamine reuptake inhibitor (e.g., bupropion), an opioid receptor antagonist (e.g., naltrexone), a combination of norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (e.g., a combination of bupropion and naltrexone), a GDF-15 analog, sibutramine, a cholecystokinin agonist, amylin and analogues thereof (e.g., pramlintide), leptin and analogues thereof (e.g., metreleptin), a serotonergic agent (e.g., lorcaserin), a methionine aminopeptidase 2 (MetAP2) inhibitor (e.g., beloranib or ZGN- 1061), phendimetrazine, diethylpropion, benzphetamine, an SGLT2 inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, Ipragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a dual SGLT2/SGLT1 inhibitor, a fibroblast growth factor receptor (FGFR) modulator, an AMP-activated protein kinase (AMPK) activator, biotin, a MAS receptor modulator, or a glucagon receptor agonist (alone or in combination with another GLP-1 R agonist, e.g., liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, or semaglutide), including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

[0113] In some embodiments, the one or more other therapeutic agent is an agent to treat NASH including but not limited to PF-05221304, an FXR agonist (e.g., obeticholic acid), a PPAR α/δ agonist (e.g., elafibranor), a synthetic fatty acid-bile acid conjugate (e.g., aramchol), a caspase inhibitor (e.g., emricasan), an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibody (e.g., simtuzumab), a galectin 3 inhibitor (e.g., GR-MD-02), a MAPK5 inhibitor (e.g., GS- 4997), a dual antagonist of chemokine receptor 2 (CCR2) and CCR5 (e.g., cenicriviroc), a fibroblast growth factor21 (FGF21) agonist (e.g., BMS-986036), a leukotriene D4 (LTD4) receptor antagonist (e.g., tielukast), a niacin analogue (e.g., ARI 3037MO), an ASBT inhibitor (e.g., volixibat), an acetyl-CoA carboxylase (ACC) inhibitor (e.g., NDI 010976), a ketohexokinase (KHK) inhibitor, a diacylglycerol acyltransferase 2 (DGAT2) inhibitor, a CB1 receptor antagonist, an anti- CB1 R antibody, or an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

Articles of Manufacture and Kits

[0114] The present disclosure further provides articles of manufacture comprising a compound, or a pharmaceutically acceptable salt thereof in accordance with the present application, a composition described herein, or one or more unit dosages described herein in

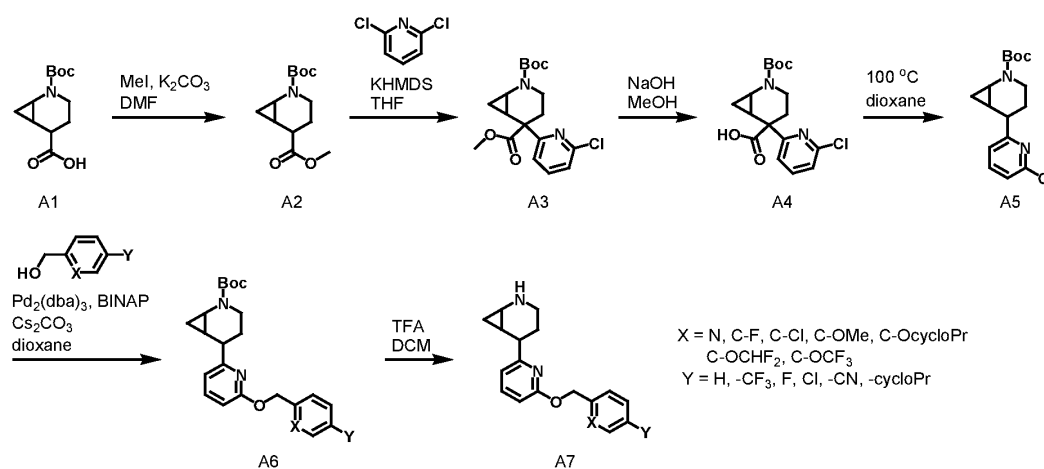
suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging (e.g., containers) is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[0115] The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound, or a pharmaceutically acceptable salt thereof in accordance with the present application, a composition described herein, and/or one or more other therapeutic agent useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds/compositions described herein and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

[0116] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

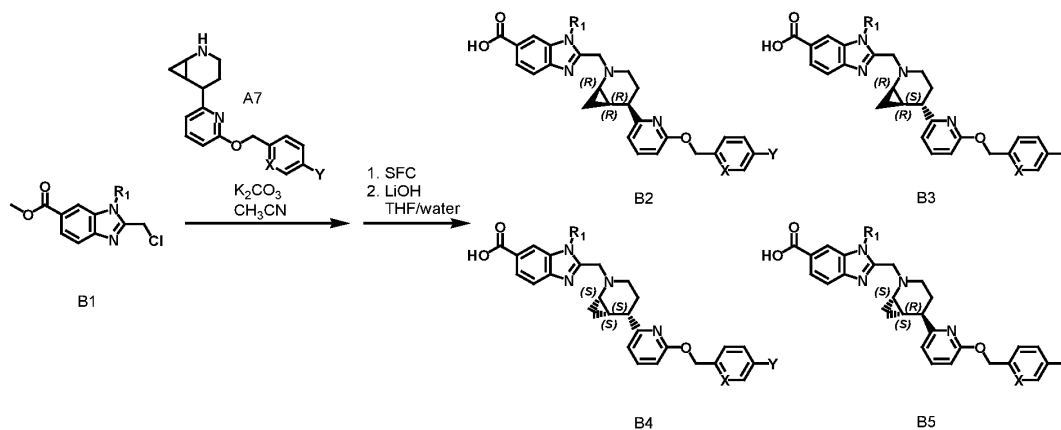
General Synthetic Schemes

[0117] Scheme A. Preparation of 5-(6-(Aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptane Intermediate A7.



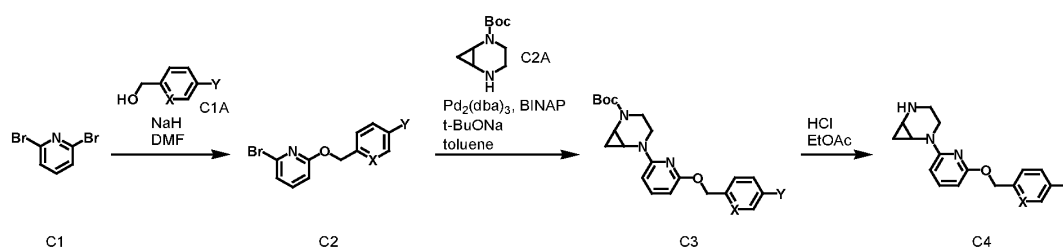
[0118] Pyridine substituted 2-azabicyclo[4.1.0]heptane intermediate **A7** may be prepared by S_NAr reaction of 2,6-dichloropyridine with the enolate **A2** prepared from commercially available 2-(tert-butyl) 5-methyl 2-azabicyclo[4.1.0]heptane-2,5-dicarboxylate and a base such as potassium or other alkali bis(trimethylsilyl)amide. The intermediate ester **A3** is saponified with an alkali hydroxide and thermally decarboxylated. Chloropyridine **A5** is reacted with a suitably substituted 2-(hydroxymethyl)aryl group under Buchwald-Hartwig etherification conditions and the resulting Boc-protected intermediate **A6** deprotected with a strong acid such as trifluoroacetic acid to provide **A7** as a salt.

[0119] Scheme B. Preparation of 5-(6-(Aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-substituted-1*H*-benzo[*d*]imidazole-6-carboxylic acids **B1**, **B2**, **B3** and **B4**.



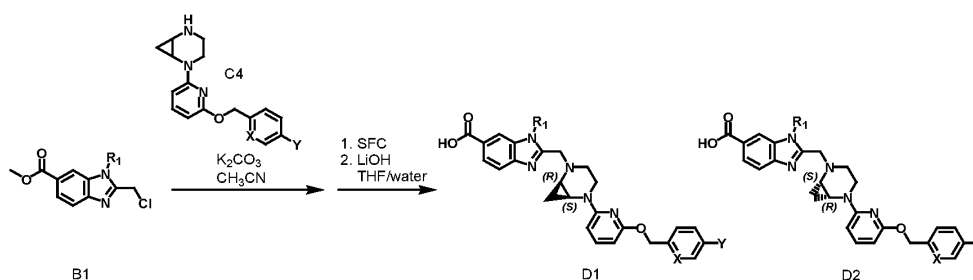
[0120] 5-(6-(Aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptane intermediate **A7** is reacted with an appropriately R_1 -substituted benzimidazole-6-carboxylic acid ester **B1** (prepared following various known synthetic methods such as those described in WO2019239371) in the presence of an acid scavenger such as an alkali carbonate to provide a mixture of 4 diastereomers with (1*R*, 5*R*, 6*R*), (1*R*, 5*S*, 6*R*), (1*S*, 5*R*, 6*S*) and (1*S*, 5*S*, 6*S*) configurations. The intermediate mixture of diastereomers is separated by supercritical fluid chromatography (SFC) and then each discrete compound saponified with an alkali hydroxide to provide final products **B2**, **B3**, **B4** and **B5**. Alternatively, intermediate **A7** may be prepared in a stereoselective synthesis or purified to obtain only the desired isomer for use in subsequent steps.

[0121] Scheme C. Preparation of 2-(6-(Aryloxy)pyridine-2-yl)-2,5-diazabicyclo[4.1.0]heptane Intermediate **C4**.



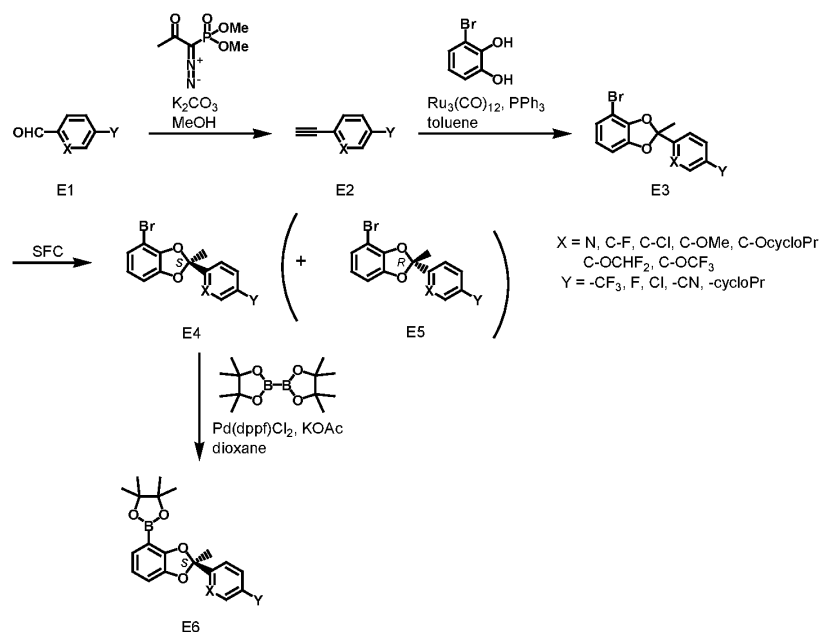
[0122] Pyridine substituted 2,5-diazabicyclo[4.1.0]heptane intermediate **C3** may be prepared by nucleophilic substitution of a 2,6-dihalopyridine **C1** with a suitably substituted 2-(hydroxymethyl)aryl group anion formed from **C1A** and a strong base such as sodium hydride. The 2-(aryloxy)-6-halopyridine **C2** is reacted with commercially available tert-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate **C2A** under Buchwald-Hartwig amination conditions and the resulting the resulting Boc-protected intermediate **C3** deprotected with a strong acid such as hydrochloric acid to provide intermediate **C4** as a salt.

[0123] Scheme D. Preparation of 2-((5-(6-(Aryloxy)pyridine-2-yl)-2,5-diazabicyclo[4.1.0]-heptan-2-yl)methyl)-1-substituted-*1H*-benzo[*d*]imidazole-6-carboxylic acids **D1** and **D2**.



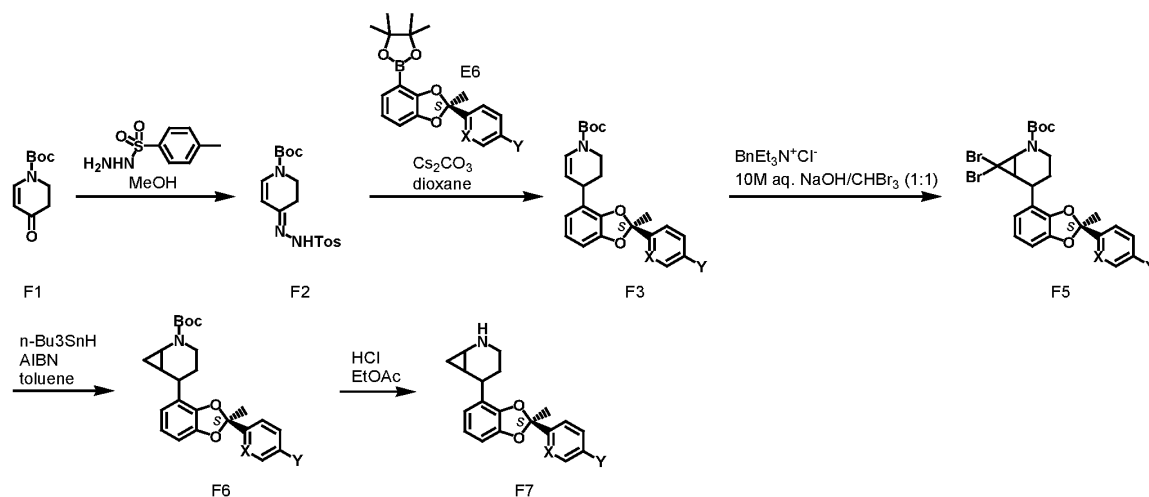
[0124] 2-(6-(Aryloxy)pyridine-2-yl)-2,5-diazabicyclo[4.1.0]heptane Intermediate **C4** is reacted with an appropriately R_1 -substituted benzimidazole-6-carboxylic acid ester **B1** (prepared following various known synthetic methods such as those described in WO2019239371) in the presence of an acid scavenger such as an alkali carbonate to provide a mixture of 2 diastereomers with (1*R*, 6*S*) and (1*S*, 6*R*) configurations. The intermediate mixture of diastereomers is separated by supercritical fluid chromatography (SFC) and then each discrete compound saponified with an alkali hydroxide to provide final products **D1** and **D2**. Alternatively, intermediate **C4** may be prepared in a stereoselective synthesis or purified to obtain only the desired isomer for use in subsequent steps.

[0125] Scheme E. Preparation of (*S*)-4, 4, 5, 5-Tetramethyl-2-(2-methyl-2-(substituted-aryl)benzo[*d*][1,3]dioxol-4-yl)-1, 3, 2-dioxaborolane Intermediate **E6**.



[0126] Seyferth-Gilbert homologation provides alkyne intermediate **E2** from the appropriately substituted aryl aldehyde **E1** and dimethyl (diazomethyl)phosphonate. The addition of 3-bromocatechol to alkyne **E2** in the presence of triruthenium dodecacarbonyl provides 4-bromo-2-methyl-2-arylbenzo[d][1,3]dioxole as a mixture of enantiomers **E4** and **E5** which may be separated by super critical fluid chromatography (SFC) to provide the desired (*S*)-isomer.

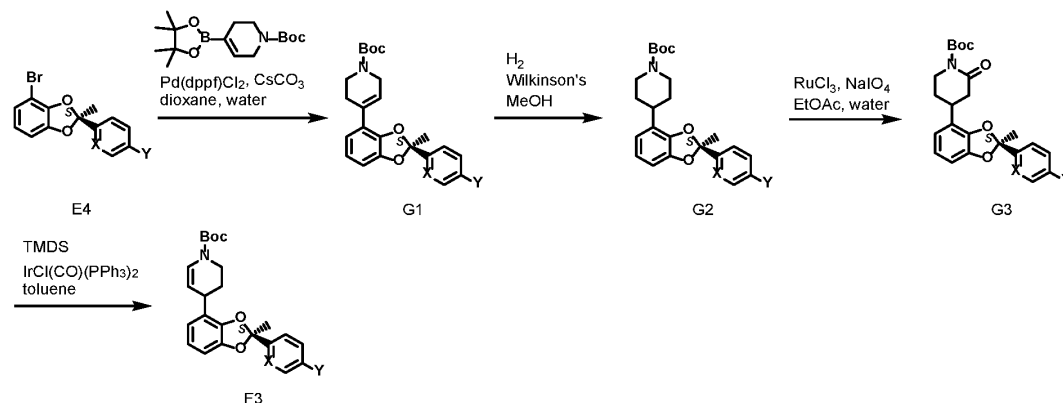
[0127] Scheme F. Preparation of 5-((*S*)-2-Methyl-2-substituted-arylbenzo[d][1,3]dioxol-4-yl)-2-azabicyclo[4.1.0]heptane Intermediate **F7**.



[0128] Metal free cross-coupling between sulfonylhydrazine **F2** and (*S*)-4, 4, 5, 5-tetramethyl-2-(2-methyl-2-(substituted-aryl)benzo[d][1,3]dioxol-4-yl)-1, 3, 2-dioxaborolane

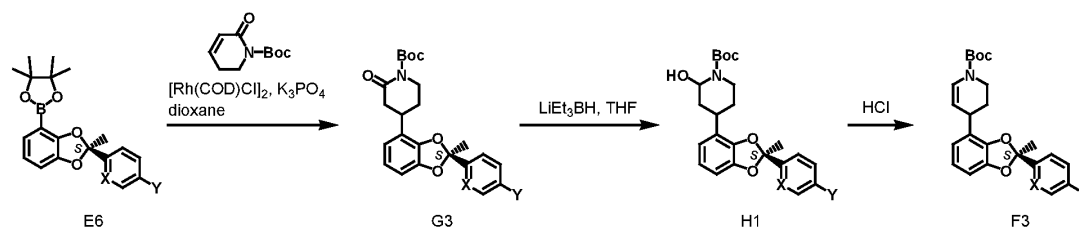
intermediate **E6** in the presence of a base, such as cesium carbonate, provides *tert*-butyl-((*S*)-2-methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate **F3**. Reaction of **F3** with dibromocyclopropane adduct **F5** which is reductively dehalogenated with tri-*n*-butyltin hydride. Deprotection of **F6** with strong acid, such as HCl or TFA, provides **F7**.

[0129] Scheme G. Alternate Preparation of *tert*-Butyl-((*S*)-2-methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate Intermediate **F3**.



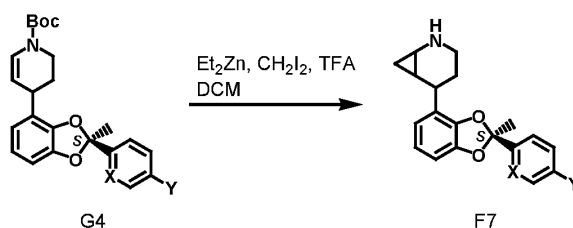
[0130] Alternatively, intermediate **F3** may be prepared by Suzuki coupling of commercially available *tert*-butyl 4-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate with intermediate **E4**. The resulting dihydropyridine **G1** is reduced and oxidized with catalytic ruthenium (III) chloride and sodium periodate to provide lactam **G3**. Lactam **G3** may be converted to dihydropyridine **F3** by an organic silane such as tetramethyldisiloxane and catalytic Vaska's Reagent.

[0131] Scheme H. Alternate Preparation of *tert*-Butyl-((*S*)-2-methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate Intermediate **F3**.



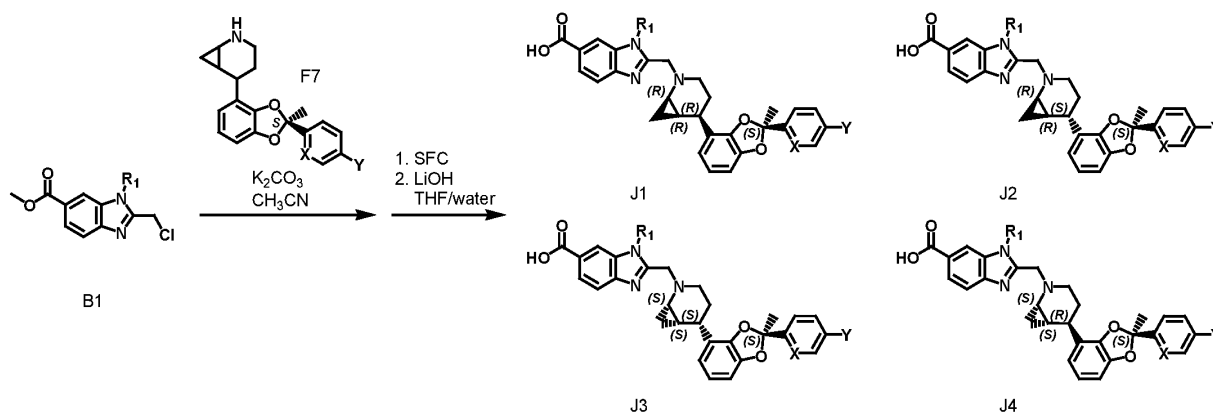
[0132] Alternatively, intermediate **F3** may be prepared by rhodium catalyzed cross-coupling of the commercial *tert*-butyl 6-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate with intermediate **E6**. Reduction of lactam **G3** provides hydroxypiperidine **H1** which is treated with aqueous acid to provide intermediate **F3**.

[0133] Scheme I. Alternate Preparation of 5-((*S*)-2-Methyl-2-substituted-arylbenzo[*d*]-[1,3]dioxol-4-yl)-2-azabicyclo[4.1.0]heptane Intermediate **F7**.



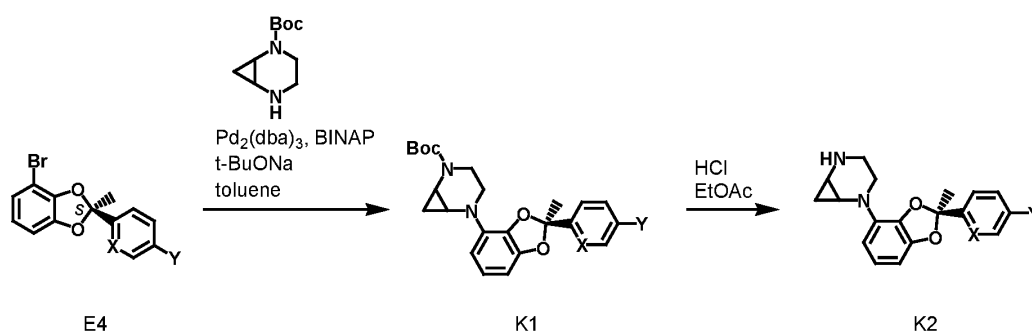
[0134] Intermediate **F7** may be obtained in very low yields from **G4** under traditional Simmons-Smith reaction conditions.

[0135] Scheme J. Preparation of 1-Substituted-2-((5-((*S*)-2-methyl-2-substituted-phenylbenzo[*d*][1,3]dioxol-4-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-*1H*-benzo[*d*]imidazole-6-carboxylic acids **J1**, **J2**, **J3** and **J4**.



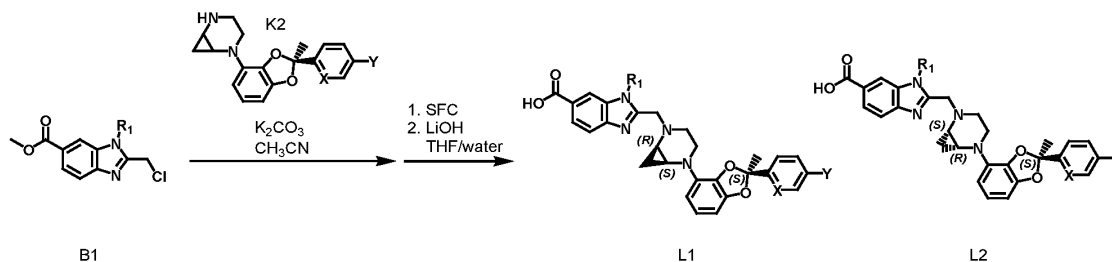
[0136] 5-((*S*)-2-Methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-2-azabicyclo[4.1.0]heptane Intermediate **F7** is reacted with an appropriately R_1 -substituted benzimidazole-6-carboxylic acid ester **B1** (prepared following various known synthetic methods such as those described in WO2019239371) in the presence of an acid scavenger such as an alkali carbonate to provide a mixture of 4 diastereomers with (1*R*, 5*R*, 6*R*), (1*R*, 5*S*, 6*R*), (1*S*, 5*R*, 6*S*) and (1*S*, 5*S*, 6*S*) configurations. The intermediate mixture of diastereomers is separated by supercritical fluid chromatography (SFC) and then each discrete compound saponified with an alkali hydroxide to provide final products **J1**, **J2**, **J3** and **J4**. Alternatively, intermediate **F7** may be prepared in a stereoselective synthesis or purified to obtain only the desired isomer for use in subsequent steps.

[0137] Scheme K. Preparation of 2-((*S*)-2-Methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptane Intermediate **K2**.



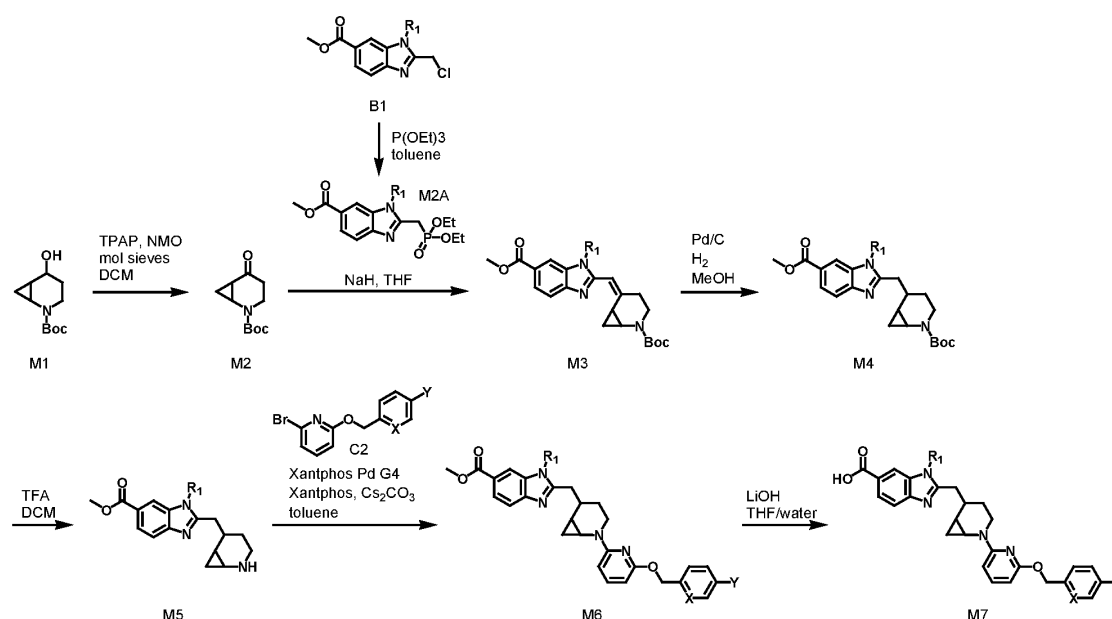
[0138] Commercially available *tert*-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate is reacted with **E4** under Buchwald amination conditions and the resulting intermediate deprotected with strong acid to provide **K2**.

[0139] Scheme L. 1-Substituted-2-((5-((*S*)-2-Methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptn-2-yl)methyl)-*1H*-benzo[*d*]imidazole-6-carboxylic acids **L1** and **L2**.



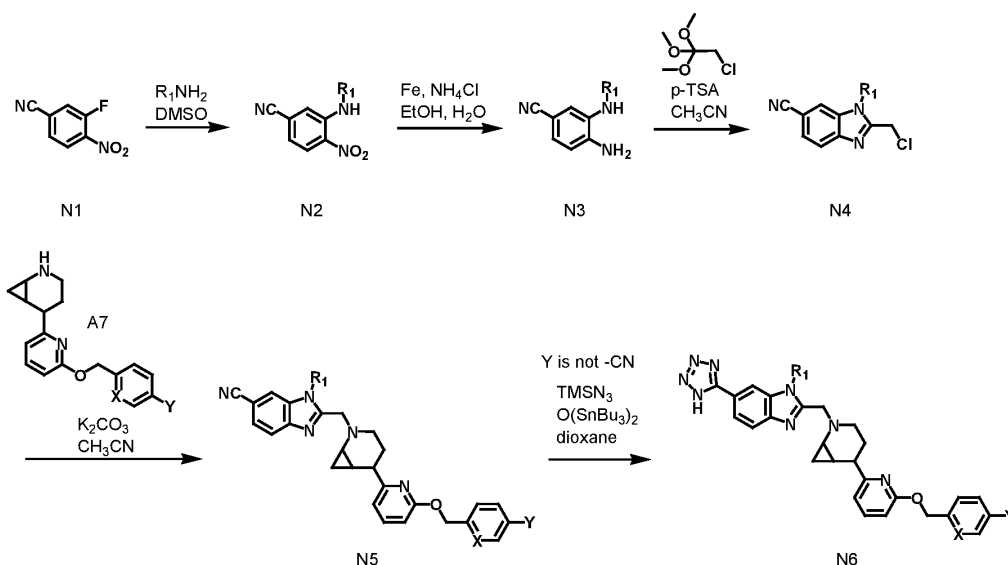
[0140] 2-((*S*))-2-Methyl-2-substituted-arylbenzo[*d*][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptane Intermediate **K2** is reacted with an appropriately R_1 -substituted benzimidazole-6-carboxylic acid ester **B1** (prepared following various known synthetic methods such as those described in WO2019239371) in the presence of an acid scavenger such as an alkali carbonate to provide a mixture of 2 diastereomers with (1*R*, 6*S*) and (1*S*, 6*R*) configurations. The intermediate mixture of diastereomers is separated by supercritical fluid chromatography (SFC) and then each discrete compound saponified with an alkali hydroxide to provide final products **L1** and **L2**. Alternatively, intermediate **K2** may be prepared in a stereoselective synthesis or purified to obtain only the desired isomer for use in subsequent steps.

[0141] Scheme M. Preparation of 2-((2-(6-(Aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-substituted-*1H*-benzo[*d*]imidazole-6-carboxylic acids **M7**.



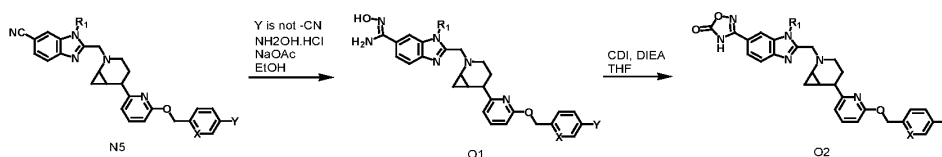
[0142] Horner-Wadsworth-Emmons olefination of commercially available tert-butyl 5-oxo-2-azabicyclo[4.1.0]heptane-2-carboxylate and phosphonate **M2A** provides methyl 2-((*tert*-butoxycarbonyl)-2-azabicyclo[4.1.0]heptan-5-ylidene)methyl)-1-substituted-1H-benzo[d]imidazole-6-carboxylate **M3** which is reduced and deprotected with strong acid. Amination of 2-(aryloxy)-6-bromopyridine **C2** under Buchwald conditions provides **M6** which is then saponified with an alkali hydroxide to provide **M7** as a mixture of 4 diastereomers. Alternatively, **M6** may be separated by supercritical fluid chromatography (SFC) to provide (1*S*, 5*R*, 6*S*), (1*S*, 5*S*, 6*S*), (1*R*, 5*R*, 6*R*) and (1*R*, 5*S*, 6*R*) discrete isomers which may be saponified with an alkali hydroxide to provide final products. Alternatively, intermediate **M6** may be prepared in a stereoselective synthesis or purified to obtain only the desired isomer for use in subsequent steps.

[0143] Scheme N. Preparation of 2-((5-(6-Substituted-aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-substituted-6-(1H-tetrazol-5-yl)-1*H*-benzo[d]imidazole **N6**.



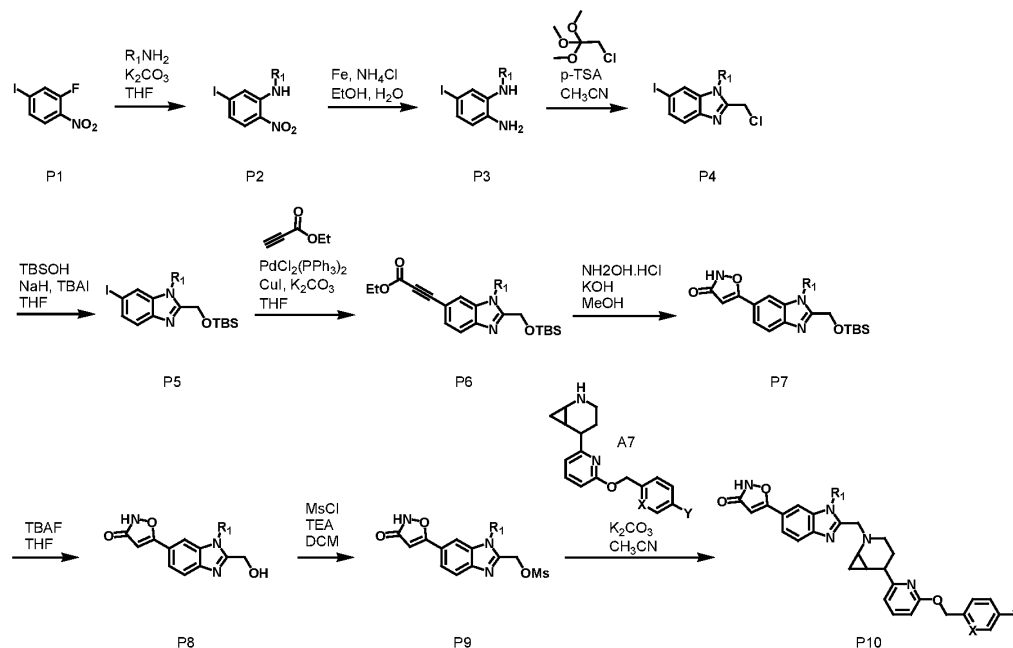
[0144] Nucleophilic substitution of commercially available 3-fluoro-4-nitrobenzonitrile with the desired amine, R_1NH_2 , followed by reduction and condensation with 2-chloro-1,1,1-trimethoxyethane provides 2-(chloromethyl)-1-substituted-1H-benzo[d]imidazole-6-carbonitrile **N4**. **N4** is reacted with 5-(6-(aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptane intermediate **A7** in the presence of an acid scavenger such as an alkali carbonate to provide **N5**. Cycloaddition of **N5** with azidotrimethylsilane in the presence of a catalyst such as tri-n-butyltin oxide provides **N6** as a mixture of 4 diastereomers. The mixture of diastereomers may be separated, if desired, by supercritical fluid chromatography (SFC).

[0145] Scheme O. Preparation of 3-(2-((5-(6-(Substituted-aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-substituted-1H-benzo[d]imidazole-6-yl)-1,2,4-oxadiazol-5(4H)-one **O2**.



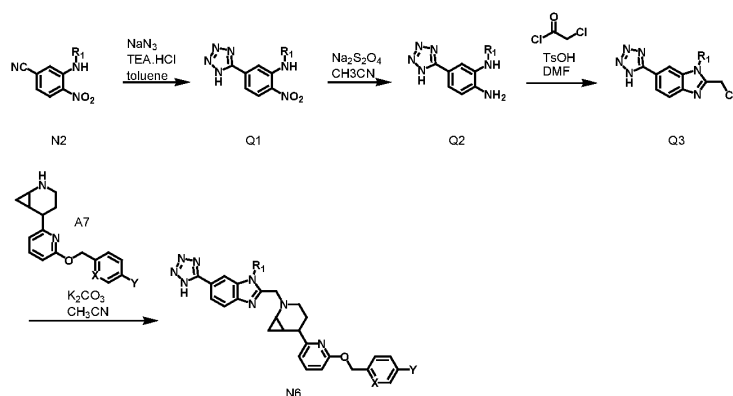
[0146] Reaction of hydroxylamine with **N5** yields 2-((5-(6-(substituted-aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-N'-hydroxy-1-substituted-1H-benzo[d]imidazole-6-carboximidamide **O1** which is further cyclized with 1,1'-carbonyldiimidazole or phosgene in the presence of a base to provide **O2**. The reaction may be conducted with discrete diastereomer **N5** or the mixture of 4 diastereomers separated by supercritical fluid chromatography (SFC).

[0147] Scheme P. Preparation of 5-(2-((5-(6-(Substituted-aryloxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)-1-substituted-1*H*-benzo[*d*]imidazol-6-yl)isoxazole-3(2*H*)-one **P10**.



[0148] 2-(Chloromethyl)-6-iodo-1-substituted-1*H*-benzo[*d*]imidazole **P4** is prepared following similar methods used to synthesize **N4**. Conversion to the TBS ether and Sonogashira coupling with ethyl propiolate yields alkyne **P6** which is cyclized with hydroxylamine to provide isoxazol-3-one **P7**. Deprotection, mesylation and reaction with 5-(6-(aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptane intermediate **A7** in the presence of an acid scavenger such as an alkali carbonate provides **P10**. The reaction may be conducted with discrete diastereomer **A7** or the mixture of 4 diastereomers separated by supercritical fluid chromatography (SFC).

[0149] Scheme Q. Alternative Preparation of 2-((5-(6-(Substituted-aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-substituted-6-(1*H*-tetrazol-5-yl)-1*H*-benzo[*d*]imidazole **N6**.



[0150] When Y = CN, it is advantageous to install the tetrazole heterocycle at an earlier stage in the synthesis. Azide cycloaddition of **N2** provides *N*-substituted-2-nitro-5-(1*H*-tetrazol-5-yl)aniline **Q1** which is reduced and condensed with 2-chloro-1, 1, 1-trimethoxyethane to provide 2-(chloromethyl)-1-substituted-6-(1*H*-tetrazol-5-yl)-1*H*-benzo[d]imidazole **Q3**. **Q3** is reacted with 5-(6-(aryloxy)pyridine-2-yl)-2-azabicyclo[4.1.0]heptane intermediate **A7** in the presence of an acid scavenger such as an alkali carbonate to provide **N6**.

[0151] GLP-1R Cell Assay

[0152] Stable cell lines expressing high and low GLP-1R surface expression are generated in CHO-K1 cells transfected (Fugene 6) with a puromycin selectable DNA plasmid encoding human GLP-1R receptor (accession number: NM_002062.5) under control of an EF1A promoter. Transfected cells are seeded into 24-well plates (9,000 cells/well) containing complete medium and incubated in a humidified incubator at 37°C with 5% carbon dioxide. After overnight incubation, medium is replaced with complete medium supplemented with puromycin (6 µg/mL) and refreshed every 2-3 days to select for stably transfected cells. Individual pools of selected cells are expanded prior to analysis for responsiveness to GLP-1 control peptide using a TR-FRET assay to detect cAMP (LANCE Ultra cAMP Assay, Perkin Elmer). Briefly, cells are collected in Versene solution, plated in 384-well plates (1,000 cells/well) and combined with serially diluted GLP-1R control peptide (10 nL) using an acoustic dispenser (ECHO). Plates are incubated for 30 minutes at 25°C prior to the addition of EU-cAMP tracer (5 µL) and Ulight-anti-cAMP (5 µL) reagents to each well, followed by 15 minutes incubation at 25°C. TR-FRET signal is detected using an EnVision Multimode Plate Reader (excitation=320 nm; emission= 615 and 655 nm). Dose-response curves are used to generate EC₅₀ values as a measure of responsiveness to the GLP-1R control peptide. Selected cell lines are monitored for responsiveness over multiple passages to ensure stability. CHO-

K1_hGLP-1Rhigh_clone16 and CHO-K1_hGLP-1Rlow_clone10 showed consistently high and low responsiveness to GLP-1R control peptide, respectively, and are chosen for further analysis to determine relative levels of GLP-1R surface expression. Briefly, GLP-1R expression is analyzed by flow cytometry using a fluorescein-labeled Exendin-4 peptide fluorescent probe (FLEX). Cells are harvested in Versene solution and washed 3-times with PBS+0.5% BSA before incubation with FLEX reagent (10 μ M) for 2 hours at room temperature. After incubation, cells are washed 3-times in PBS+0.5% BSA before final resuspension in PBS prior to analysis by flow cytometry to measure FLEX mean fluorescence intensity (MFI) as a measure of GLP-1R expression on the cell surface.

[0153] For compound testing in the CHO-K1_hGLP-1Rlow_clone10 cell lines, cells are seeded in 384-well plates (1,000 cells/well). Test compounds are serially diluted in DMSO (10-point, 3-fold dilution), added to wells using an ECHO dispenser (10 nL/well) and plates are centrifuged for 1 min and agitated for 2 min at room temperature prior to 30-minute incubation at 25°C. After incubation, Eu-cAMP (5 μ L) and Ulight-anti-cAMP (5 μ L) reagents are added to each well, followed by centrifugation for 1 minute, agitation for 2 minutes at room temperature, and final incubation of the plates at 25°C for 15 minutes. Plates are read using an EnVision microplate reader (excitation=320 nm; emission= 615 and 655 nm). Dose-response curves are generated from duplicate wells based on percent activation calculated relative to a control GLP-1 peptide agonist that was run in parallel. EC₅₀ values are determined by fitting percent activation as a function of compound concentration using the Hill equation (XLfit).

[0154] The EC₅₀ values of exemplary compounds **1** and **2** in the low expression assay are shown in the table below. The EC₅₀ values are compared to Reference Compound A and Reference Compound B. The compounds tested were compound samples prepared according to the General Procedures described in the Examples section.

[0155] Metabolic Stability in Hepatocytes

[0156] Test compounds are incubated in human hepatocytes and stability is assessed from the substrate depilation approach. Test compounds are dissolved in dimethyl sulfoxide (DMSO) to create a 10 mM Stock, and then further diluted to create a 1000 $\times$ Working Stock of 1 mM with DMSO in 96-well plates for test compounds and the positive control (midazolam). Vials containing cryopreserved hepatocytes are removed from the liquid nitrogen tank and immediately immersed in a 37°C water bath. The vials are shaken gently until the contents had thawed and were then immediately emptied into 48 mL of pre-warmed HT Medium in a 50 mL conical tube. Cells remaining in the vial are resuspended with 1.0 mL of

pre-warmed HT Medium and added to the conical tube. The tube is capped and then gently inverted several times to resuspend the hepatocytes. The cell suspension is centrifuged at 50 x g at room temperature for 5 minutes and the supernatant discarded. The cell pellet is loosened by gently swirling the centrifuge tube and is re-suspended in 4 mL of warm Dulbecco's Modified Eagle medium (DMEM). Cell density is determined by a cell counter by Nexcelom, and DMEM medium is added to obtain a target density of 1×10^6 cells/mL. The assay is carried out in 96-well microtiter plates. Test Compounds are incubated at $1 \mu\text{M}$ with 1×10^6 cells/mL hepatocytes in DMEM for 0, 30, 60, 120 and 240 minutes. The incubation is carried out with gentle shaking at 37°C under a humid atmosphere of 95% air/5% CO_2 . The volume of the incubation mixture is $37 \mu\text{L}$ with a final 0.1% DMSO. At each of the time points, the incubation is stopped by adding $150 \mu\text{L}$ quenching solution (100% acetonitrile, 0.1% formic acid containing bucecin as an internal standard for positive ESI mode). Subsequently, the mixtures are vortexed for 20 min and centrifuged at 4,000 RPM at 10°C . The supernatant ($80 \mu\text{L}$) is transferred to a clean 96-well plate and analyzed by LC-MS/MS. Midazolam at $1 \mu\text{M}$ with a final 0.1% DMSO is included as a positive control to verify assay performance. The percent parent remaining, intrinsic and predicted hepatic clearance and $t_{1/2}$ are calculated. All samples are analyzed by LC-MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Separation is achieved using a Waters Atlantis T3 dC18 reverse phase HPLC column (20 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in 100% acetonitrile (solvent B). Elution conditions are detailed below.

Time (min)	Flow ($\mu\text{L}/\text{min}$)	%A	%B
0	500	98	2
0.30	500	98	2
1.40	500	2	98
2.20	500	2	98
2.21	500	98	2
3.00	500	98	2

[0157] The ion optics of each test compound are optimized for their declustering potential (DP), collection energy (CE), collision-cell exit potential (CXP) and used in a selected ion monitoring experiment in the positive ion mode. The peak area ratio of each test compound to internal standard is then evaluated for stability. The extent of metabolism is calculated based on the disappearance of the test compound, compared to its initial concentration. The initial rates of clearance of the test compound are calculated using the linear regression plot of semi-

log % remaining of the compound versus time. The elimination rate constant (k) of the linear regression plot is then used to determine $t_{1/2}$ and the intrinsic clearance (CL_{int}) using the following formula, where $C_{hepatocyte}$ (million cells/mL) is the cell density of the incubation:

$$\begin{aligned} k &= -\text{slope} \\ t_{1/2} &= 0.693/k \\ CL_{int} &= k/C_{hepatocyte} \end{aligned}$$

[0158] This method of intrinsic clearance determination assumes that the test compound concentration is far below the Michaelis-Menten constant of the compound to its metabolizing enzymes.

[0159] The predicted hepatic clearance (CL_{hep}) was calculated using the well stirred method with the following formula with $CL_{int(in vivo)}$ normalized based on liver weight:

$$\begin{aligned} CL_{int(in vivo)} &= CL_{int} \times \text{Hepatocellularity} \times \text{liver weight} \\ CL_{hep predicted} &= (CL_{int(in vivo)} \times Q_{liver}) / (CL_{int(in vivo)} + Q_{liver}) \end{aligned}$$

Where Q_{liver} ((ml/min/kg) is Liver Blood Flow

[0160] The relevant physiological parameters of liver weight, blood flow, and hepatocellularity for humans are listed below:

Liver Weight (g liver/kg body weight)	Hepatocellularity (106 cells/g liver)	Liver Blood Flow (Q_{liver} , mL/min/kg)
25.7	135	20.7

[0161] Passive Permeability and Efflux Ratio

[0162] Caco-2 cells (clone C2BBel) are obtained, e.g., from American Type Culture Collection (Manassas, VA). Cell monolayers are grown to confluence on collagen-coated, microporous membranes in 12-well assay plates. The permeability assay buffer is Hanks' balanced salt solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.4. The buffer in the receiver chamber also contains 1% bovine serum albumin. The dosing solution concentration is 5 μ M of test article in the assay buffer. Cell monolayers are dosed on the apical side (A-to-B) or basolateral side (B-to-A) and incubated at 37°C with 5% CO₂ in a humidified incubator. Samples are taken from the donor and receiver chambers at 120 minutes. Each determination is performed in duplicate. The flux of lucifer yellow is also measured post-experimentally for each monolayer to ensure no damage is inflicted to the cell monolayers during the flux period. All samples are assayed by LC-MS/MS using electrospray ionization. The apparent permeability (P_{app}) and percent recovery were calculated as follows:

$$P_{app} = (dC_r/dt) \times V_r / (A \times C_A) \quad (1)$$

$$\text{Percent Recovery} = 100 \times ((V_r \times C_r^{\text{final}}) + (V_d \times C_d^{\text{final}})) / (V_d \times C_N) \quad (2),$$

where, dC_r/dt is the slope of the cumulative receiver concentration versus time in $\mu\text{M s}^{-1}$; V_r is the volume of the receiver compartment in cm^3 ; V_d is the volume of the donor compartment in cm^3 ; A is the area of the insert (1.13 cm^2 for 12-well); C_A is the average of the nominal dosing concentration and the measured 120-minute donor concentration in μM ; C_N is the nominal concentration of the dosing solution in μM ; C_r^{final} is the cumulative receiver concentration in μM at the end of the incubation period; C_d^{final} is the concentration of the donor in μM at the end of the incubation period. Efflux ratio (ER) is defined as $P_{app} \text{ (B-to-A)} / P_{app} \text{ (A-to-B)}$.

[0163] Rat Pharmacokinetics

[0164] Intravenous dosing: Compounds are formulated at 0.5 mg/mL in a solution comprising 5% polyethylene glycol 400 and 95% (12% (w/v) sulfobutyl- β -cyclodextrin in water) (v/v). Formulated compounds are sterile filtered through a 0.22 micron filter before dosing. Compounds are administered to male, 7–11-week-old Sprague-Dawley rats by jugular vein cannula infusion over 30 minutes at a dose of 1 mg/kg.

[0165] Oral dosing: Compounds are formulated at 0.3 mg/mL or 0.6 mg/mL in a solution comprising 5% polyethylene glycol 400 and 95% (12% (w/v) sulfobutyl- β -cyclodextrin in water) (v/v). Formulated compounds are administered to male, 7–11 week old Sprague-Dawley rats by oral gavage at a dose of 10 mL/kg.

[0166] Sample collection: Blood collections of about 0.2 mL per time point are performed from jugular vein or other suitable site of each animal, into pre-chilled commercial EDTA-K2 tubes and placed on wet ice until centrifugation. Blood samples are processed for plasma by centrifugation at approximately 4°C, 3,200 g for 10 min. Plasma is collected and transferred into pre-labeled 96 well plate or polypropylene tubes, quick frozen over dry ice and kept at -60°C or lower until LC-MS/MS analysis.

[0167] Data analysis: Plasma concentration versus time data are plotted in graph and analyzed by non-compartmental approaches using the Phoenix WinNonlin 6.3 software program. Related PK parameters are calculated according to dosing route, e.g., CL, V_{dss} and C_0 for intravenous administration, C_{max} , T_{max} or %F for extravascular administration, and $T_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $MRT_{(0-t)}$, $MRT_{(0-inf)}$ for all routes.

EXAMPLES

[0168] For exemplary purposes, neutral compounds of Formula (0) and Formula (1) are synthesized and tested in the examples. It is understood that the neutral compounds of Formula (0) and Formula (1) may be converted to the corresponding pharmaceutically acceptable salts of the compounds using techniques in the art (e.g., by saponification of an ester to the carboxylic acid salt, or by hydrolyzing an amide to form a corresponding carboxylic acid and then converting the carboxylic acid to a carboxylic acid salt).

[0169] It is understood that the values described in the examples are approximate and subject to experimental and instrumental variations.

Abbreviations:

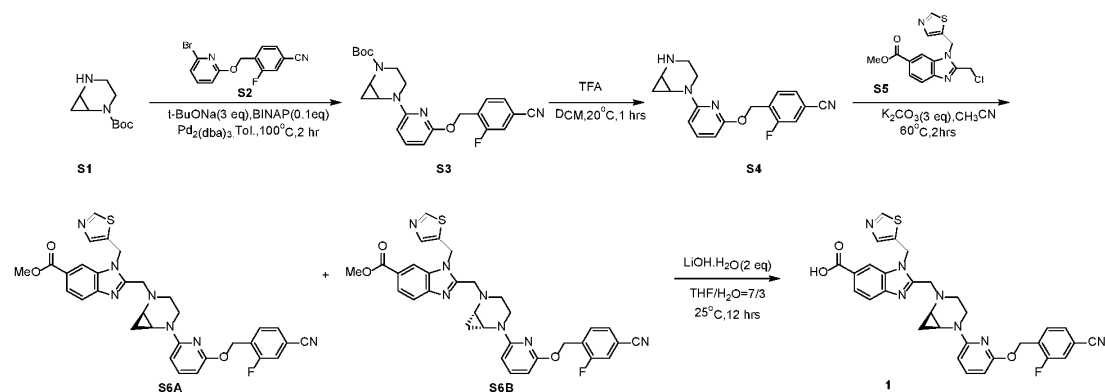
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
BOC	tert-butyl carbamate
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BTC	bis(trichloromethyl) carbonate
CDI	carbonyl diimidazole
DAD	diode array detector
DCM	Dichloromethane
DIEA/DIPEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
EA/EtOAc	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ELSD	evaporative light scattering detector
ES / ESI	electrospray ionisation
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOAT	1-hydroxy-7-azabenzotriazole
HOBT	hydroxy benzotriazole
HPLC	high-performance liquid chromatography
IPA	Isopropylalcohol
LC	liquid chromatography

LiHMDS	lithium hexamethyl disilazide
MS	mass spectrometry
NMR	nuclear magnetic resonance
Py	Pyridine
RT	retention time
SFC	supercritical fluid chromatography
TBAI	tetrabutyl ammonium iodide
TEA	Triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethyl silane
UV	Ultraviolet

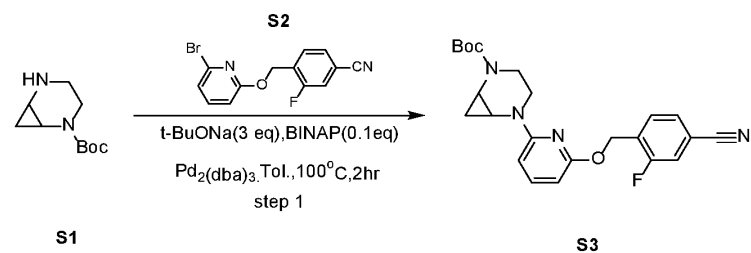
Example 1 (Synthesis of Compound 1)

[0170] Compound 1 was prepared by the synthetic method shown in Scheme 1.

Scheme 1



Procedure for the Preparation of Compound S3

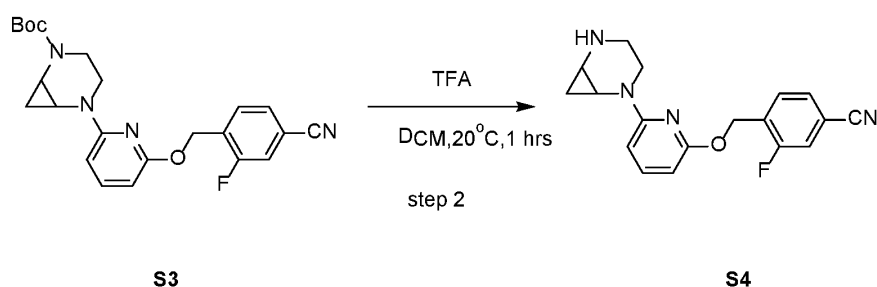


[0171] A mixture of **compound S1** (500 mg, 2.52 mmol, 1.1 eq), **compound S2** (704.12 mg, 2.29 mmol, 1 eq), Pd₂(dba)₃ (104.97 mg, 114.63 μmol, 0.05 eq), *rac*-BINAP (142.76 mg, 229.27 μmol, 0.1 eq), and *t*-BuONa (661.00 mg, 6.88 mmol, 3 eq) in Tol. (1 mL) was degassed and purged with N₂ x3, and then the mixture was stirred at 100 °C for 2 hr under N₂ atmosphere. LC-MS showed **compound S1** was consumed completely. The reaction mixture was cooled to 20°C, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1). **Compound S3** (440 mg, 1.04 mmol, 45% yield) was obtained as a white solid.

LCMS: RT = 2.142 min, MS cal.: 424.2, [M+H]⁺ = 325.2

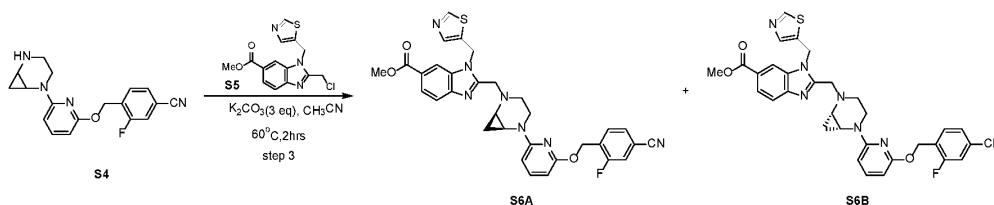
¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 0.39 (br s, 1 H) 1.02 - 1.21 (m, 1 H) 1.50 (s, 10 H) 2.75 - 2.91 (m, 1 H) 3.05 - 3.60 (m, 4 H) 3.83 - 4.08 (m, 1 H) 5.41 - 5.51 (m, 2 H) 6.18 (d, *J*=7.82 Hz, 1 H) 6.34 (br s, 1 H) 7.37 (dd, *J*=9.29, 1.22 Hz, 1 H) 7.43 - 7.51 (m, 2 H) 7.59 - 7.66 (m, 1 H).

General Procedure for Preparation of Compound S4



[0172] A mixture of **compound S3** (400 mg, 942.36 μmol, 1 eq), TFA (1 mL) in DCM (3 mL) was degassed and purged with N₂ x3 and then the mixture was stirred at 20 °C for 1 hr under an N₂ atmosphere at which point the reaction mixture was concentrated under reduced pressure. **Compound S4** was used directly as a yellow oil.

General Procedure for Preparation of Compound S6A and S6B



[0173] A mixture of **compound S4**, **compound S5** (300 mg, 924.92 μmol, 1 eq), K₂CO₃ (383.49 mg, 2.77 mmol, 3 eq) in CH₃CN (5 mL) was degassed and purged with N₂ x3, and

then the mixture was stirred at 50 °C for 3 hr under N₂ atmosphere. The reaction mixture was filtered and partitioned with 5 mL H₂O. The mixture was extracted with EtOAc (10 mL x3). The organic layers were combined and washed with 10 mL brine, concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(NH₄HCO₃)-ACN]; B%: 45%-80%,8min) to give desired compound (400 mg, yield 90%, purity 90%) as a white solid, which was further separated by SFC (condition: column: DAICEL CHIRALCEL OD(250mm*30mm, 10um);mobile phase: [0.1%NH₃H₂O MEOH];B%: 50%-50%,15min). **Compound S6A** (120 mg, 196.83 umol, 21.28% yield) was obtained as a white solid.

LCMS: RT = 2.532min, MS cal.:617.2, [M+H]⁺ = 618.2

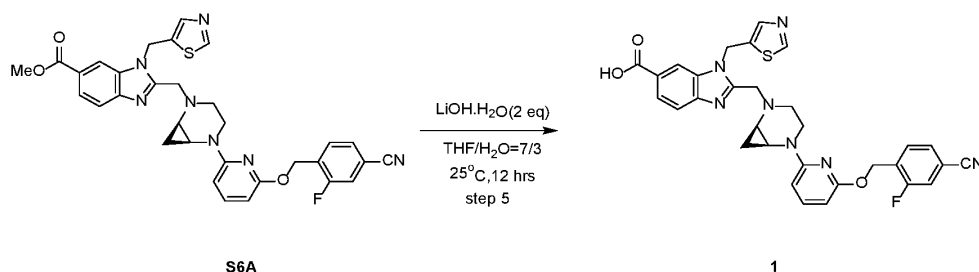
¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 0.46 - 0.61 (m, 1 H) 0.79 (q, *J*=6.30 Hz, 1 H) 1.22 (d, *J*=6.00 Hz, 1 H) 1.25 - 1.31 (m, 1 H) 2.37 - 2.45 (m, 1 H) 2.58 - 2.66 (m, 1 H) 2.72 - 2.83 (m, 2 H) 3.00 - 3.09 (m, 1 H) 3.96 (s, 3 H) 4.01 - 4.08 (m, 1 H) 4.10 - 4.21 (m, 3 H) 5.37 - 5.52 (m, 2 H) 5.86 (s, 2 H) 6.16 (d, *J*=7.88 Hz, 1 H) 6.31 (d, *J*=8.00 Hz, 1 H) 7.34 (d, *J*=9.26 Hz, 1 H) 7.41 - 7.51 (m, 2 H) 7.61 (t, *J*=7.50 Hz, 1 H) 7.79 (d, *J*=8.38 Hz, 1 H) 7.90 (s, 1 H) 8.02 (d, *J*=8.50 Hz, 1 H) 8.15 (s, 1 H) 8.74 - 8.77 (m, 1 H).

Compound S6B (80 mg, 131.22 umol, 14.19% yield) was obtained as a white solid.

LCMS: RT = 2.534min, MS cal.:617.2, [M+H]⁺ = 618.2

¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 0.50 - 0.60 (m, 1 H) 0.79 (q, *J*=6.34 Hz, 1 H) 1.20 - 1.29 (m, 1 H) 2.39 - 2.47 (m, 1 H) 2.59 - 2.67 (m, 1 H) 2.72 - 2.84 (m, 3 H) 3.05 (ddd, *J*=12.38, 9.76, 2.25 Hz, 1 H) 3.96 (s, 4 H) 4.03 - 4.21 (m, 4 H) 5.37 - 5.50 (m, 2 H) 5.86 (s, 2 H) 6.16 (d, *J*=7.88 Hz, 1 H) 6.31 (d, *J*=8.13 Hz, 1 H) 7.34 (d, *J*=9.38 Hz, 1 H) 7.41 - 7.50 (m, 3 H) 7.61 (t, *J*=7.44 Hz, 1 H) 7.79 (d, *J*=8.50 Hz, 1 H) 7.90 (s, 1 H) 8.02 (d, *J*=8.50 Hz, 1 H) 8.15 (s, 1 H) 8.74 - 8.77 (m, 1 H).

General procedure for Preparation of Compound 1



[0174] A mixture of **compound S6A** (90 mg, 147.62 μmol , 1 *eq*), $\text{LiOH}\cdot\text{H}_2\text{O}$ (12.39 mg, 295.24 μmol , 2 *eq*) in THF (0.7 mL) and H_2O (0.3 mL) was degassed and purged with N_2 x3, and then the mixture was stirred at 25 °C for 16 hr under an N_2 atmosphere. The reaction mixture was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10 μm ; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 20%-50%, 8min).

Compound 1 (29.88 mg, 50.16 μmol , 33.98% yield) was obtained as a white solid.

LCMS: RT = 2.508min, MS cal.: 595.2, $[\text{M}+\text{H}]^+ = 596.1$

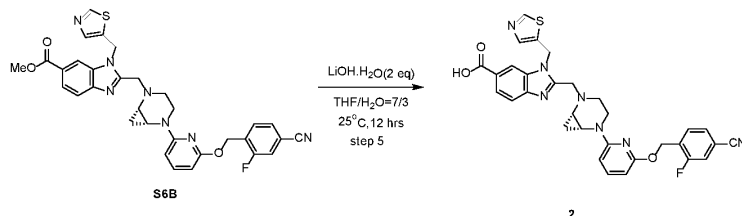
^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.49 - 0.55 (m, 1 H) 0.75 (q, $J=6.00$ Hz, 1 H) 2.37 - 2.45 (m, 1 H) 2.67 (td, $J=7.42, 5.42$ Hz, 1 H) 2.76 - 2.85 (m, 2 H) 3.00 (ddd, $J=12.84, 9.80, 2.62$ Hz, 1 H) 4.08 - 4.24 (m, 3 H) 5.46 (s, 2 H) 6.00 (s, 2 H) 6.13 (d, $J=7.75$ Hz, 1 H) 6.36 (d, $J=8.11$ Hz, 1 H) 7.48 (t, $J=7.93$ Hz, 1 H) 7.53 - 7.57 (m, 2 H) 7.62 - 7.68 (m, 1 H) 7.71 (d, $J=8.46$ Hz, 1 H) 8.01 (dd, $J=8.46, 1.43$ Hz, 1 H) 8.06 (s, 1 H) 8.27 (d, $J=0.83$ Hz, 1 H) 8.94 (d, $J=0.72$ Hz, 1 H).

LCMS: RT = 2.508min, MS cal.: 595.2, $[\text{M}+\text{H}]^+ = 596.1$

HPLC: RT = 11.351min

Example 2 (Synthesis of Compound 2)

[0175] **Compound 2** was prepared from **Compound S6B**. The preparation of **Compound S6B** was described in Example 1.



[0176] To a solution of **compound S6B** (70 mg, 114.82 μmol , 1 *eq*) in THF (0.7 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (9.64 mg, 229.63 μmol , 2 *eq*) in H_2O (0.3 mL). The mixture was stirred at 25 °C for 12 hr. The mixture was purified directly. The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 100*30mm*10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-60%, 8min). **Compound 2** (35 mg, 58.76 μmol , 51.18% yield) was obtained as a white solid.

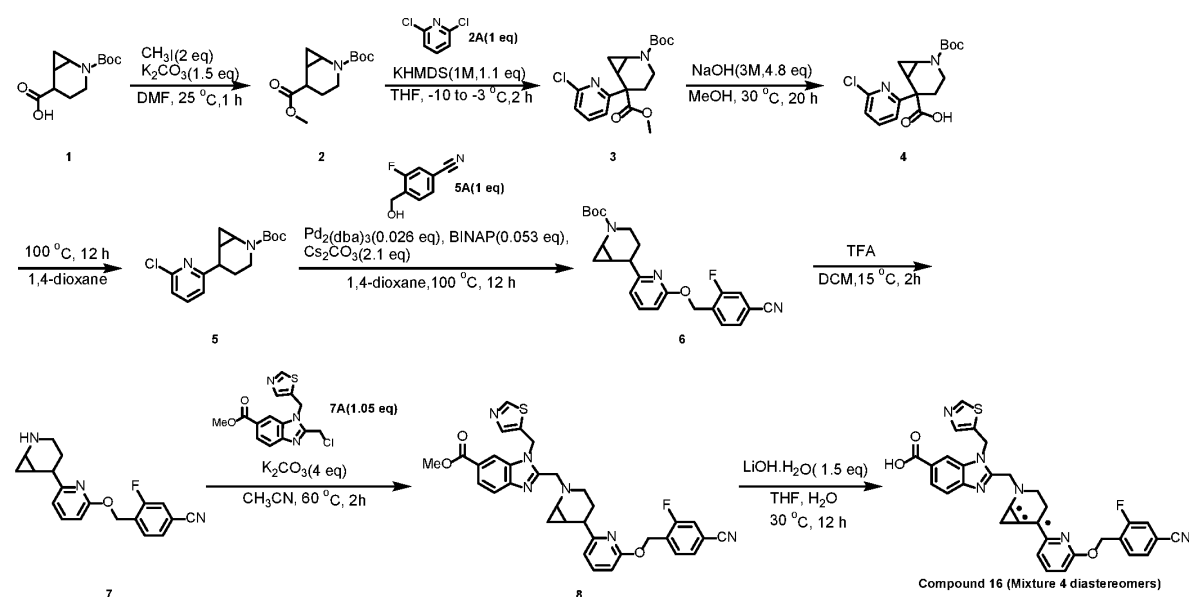
LCMS: Rt = 2.474 min, MS cal.: 595.65, $[\text{M}+\text{H}]^+ = 596.6$

HPLC: Rt = 11.346 min

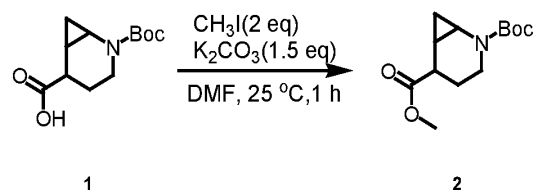
¹H NMR (400 MHz, METHANOL-d₄) δ = 0.47 - 0.54 (m, 1 H) 0.68 - 0.78 (m, 1 H) 2.35 - 2.45 (m, 1 H) 2.65 (td, J=7.43, 5.56 Hz, 1 H) 2.73 - 2.85 (m, 2 H) 2.93 - 3.02 (m, 1 H) 4.06 - 4.25 (m, 3 H) 5.44 (s, 2 H) 5.98 (s, 2 H) 6.11 (d, J=7.70 Hz, 1 H) 6.34 (d, J=8.07 Hz, 1 H) 7.46 (t, J=7.95 Hz, 1 H) 7.51 - 7.58 (m, 2 H) 7.60 - 7.66 (m, 1 H) 7.71 (d, J=8.44 Hz, 1 H) 7.99 (dd, J=8.56, 1.47 Hz, 1 H) 8.05 (s, 1 H) 8.27 (d, J=0.86 Hz, 1 H) 8.92 (d, J=0.73 Hz, 1 H)

Example 3 (Synthesis of Compound 16)

[0177] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers



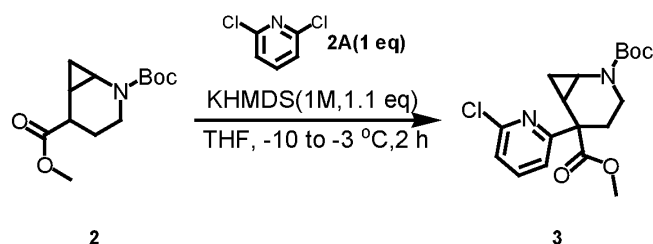
[0178] Preparation of 2-(tert-Butyl) 5-methyl 2-azabicyclo[4.1.0]heptane-2,5-dicarboxylate (2)



[0179] A mixture of 2-(tert-butoxycarbonyl)-2-azabicyclo[4.1.0]heptane-5-carboxylic acid (2.5 g, 10.4 mmol, 1 eq), CH₃I (2.94 g, 20.7 mmol, 1.29 mL, 2 eq), K₂CO₃ (2.15 g, 15.5 mmol, 1.5 eq) in DMF (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 1 h under N₂ atmosphere. TLC (Petroleum ether/Ethyl acetate=5/1 R_f = 0.46) indicated starting material was consumed completely. The combined

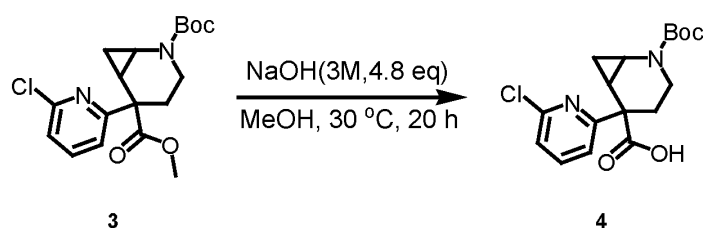
reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0 /1) to provide product as an oil (2.4 g, 9.40 mmol, 90.7% yield); ¹H NMR (400 MHz, DMSO-d₆) δ 3.67 (d, *J* = 10.8 Hz, 3H), 3.45 - 3.38 (m, 0.5H), 3.04 - 2.90 (m, 0.5H), 2.89 - 2.61 (m, 2H), 1.86 - 1.71 (m, 1H), 1.70 - 1.55 (m, 1H), 1.45 - 1.40 (m, 9.5H), 1.33 - 1.19 (m, 0.5H), 0.88 - 0.73 (m, 1H), 0.34 - 0.26 (m, 1H).

[0180] Preparation of 2-(tert-Butyl) 5-methyl 5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2,5-dicarboxylate (3)



[0181] To a solution of 2-(tert-butyl) 5-methyl 2-azabicyclo[4.1.0]heptane-2,5-dicarboxylate (1.5 g, 5.88 mmol, 1 eq) and 2,6-dichloropyridine (869 mg, 5.88 mmol, 1 eq) in THF (15 mL) was added slowly a solution of KHMDS (1 M, 6.46 mL, 1.1 eq) to control the internal temperature within -10~-3°C. Then the reaction mixture was kept stirring at -10~-5°C for 1.5~2 h. TLC indicated starting material was consumed completely. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to provide product as a white solid (1.5 g, 4.09 mmol, 69.6% yield).

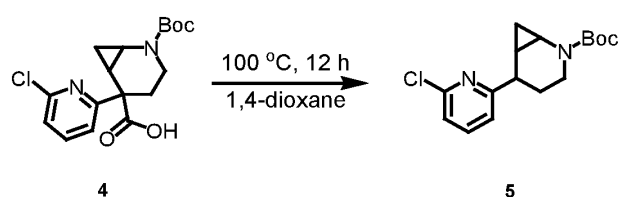
[0182] Preparation of 2-(tert-Butoxycarbonyl)-5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-5-carboxylic acid (4)



[0183] A mixture of 2-(tert-butyl) 5-methyl 5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2,5-dicarboxylate (1.4 g, 3.82 mmol, 1 eq), NaOH (2 M, 5.72 mL, 3 eq) in MeOH (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was

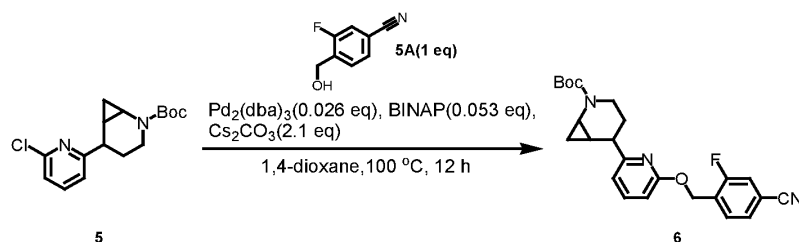
stirred at 45°C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The solution was concentrated under vacuum at ~ 40°C to remove ~ 1/2 solvents. The aqueous layer was neutralized by aq. HCl (2N, ~7 mL, 3.5eq) at -5°C~5°C to pH around 3~5. A white suspension was formed during the neutralization. The reaction mixture was filtered and the filter cake was washed with H₂O (10 mL*3). The filter cake was dissolved in DCM (30 mL), washed with brine (30 mL) and concentrated under reduced pressure to provide product as a white solid (1.3 g, 3.68 mmol, 96.6% yield); LCMS: RT = 1.262 min, MS cal.: 352.82, [M-55]⁺ = 297.1.

[0184] Preparation of tert-Butyl 5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (5)



[0185] A mixture of 2-(tert-butoxycarbonyl)-5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-5-carboxylic acid (1.3 g, 3.68 mmol, 1 eq) in dioxane (13 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated to give crude product as a white solid (1.2 g, crude); LCMS: RT = 2.127 min, MS cal.: 308.81, [M-55]⁺ = 253.1.

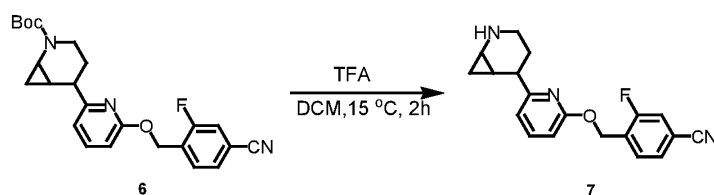
[0186] Preparation of tert-butyl 5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (6)



[0187] A mixture of tert-butyl 5-(6-chloropyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (0.8 g, 2.59 mmol, 1 eq), 3-fluoro-4-(hydroxymethyl)benzonitrile (392 mg, 2.59 mmol, 1 eq), Cs₂CO₃ (1.77 g, 5.44 mmol, 2.1 eq), Pd₂(dba)₃ (237 mg, 259 μmol, 0.1 eq) and BINAP (323 mg, 518 μmol, 0.2 eq) in dioxane (12 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100°C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The combined reaction mixture was

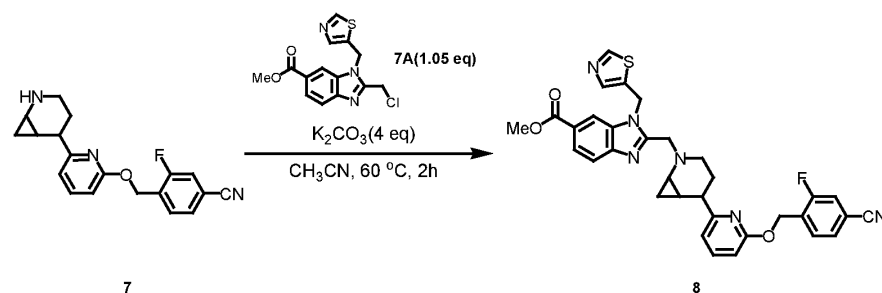
poured into water (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to provide product as a white solid (0.8 g, 1.89 mmol, 72.9% yield); ¹H NMR (400 MHz, DMSO-d₆) δ = 7.94 - 7.83 (m, 1H), 7.75 - 7.63 (m, 3H), 7.09 - 6.99 (m, 1H), 6.82 - 6.72 (m, 1H), 5.53 - 5.43 (m, 2H), 3.87 - 3.66 (m, 1H), 3.27 - 3.15 (m, 1H), 2.93 - 2.81 (m, 1H), 2.66 - 2.57 (m, 1H), 1.84 - 1.74 (m, 1H), 1.46 - 1.41 (m, 10H), 0.91 - 0.79 (m, 1H), 0.72 - 0.60 (m, 1H), 0.44 - 0.31 (m, 1H).

[0188] Preparation of 4-(((6-(2-Azabicyclo[4.1.0]heptan-5-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (7)



[0189] A mixture of tert-butyl 5-((6-(4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (0.7 g, 1.65 mmol, 1 eq) TFA (3.08 g, 27.0 mmol, 2 mL, 16.3 eq), in DCM (5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25°C for 1 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated to provide crude product as a white solid (0.73 g, crude, TFA); LCMS: RT =0.899 min, MS cal.: 323.37, [M+H]⁺ = 324.2.

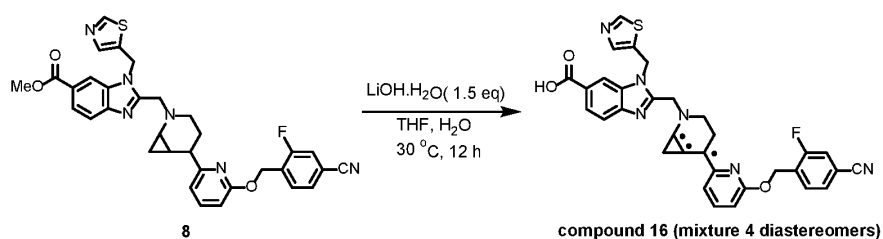
[0190] Preparation of Methyl 2-(((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (8)



[0191] A mixture of 4-(((6-(2-azabicyclo[4.1.0]heptan-5-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (483 mg, 1.50 mmol, 0.9 eq), methyl 2-(chloromethyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (0.73 g, 1.67 mmol, 1 eq, TFA), K₂CO₃ (1.38 g, 10.0 mmol, 6 eq) in ACN (5 mL) was degassed and purged with N₂ for 3 times, and then the

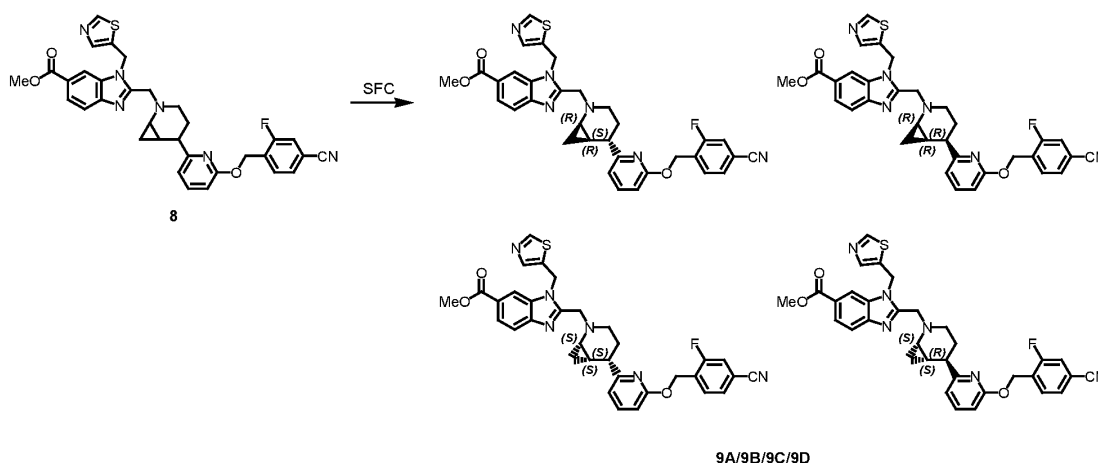
mixture was stirred at 60 °C for 2 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. TLC (Petroleum ether/Ethyl acetate=0/1 R_f = 0.45) indicated starting material was consumed completely. The combined reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to provide product as a white solid (0.6 g, 986 μmol, 59.1% yield); LCMS: RT = 1.029min, MS cal.: 608.89, [M+H]⁺ = 609.3.

[0192] Preparation of 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid (compound 16)



[0193] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (50 mg, 82.1 μmol, 1 eq), LiOH.H₂O (5.17 mg, 123 μmol, 1.5 eq) in THF (0.7 mL) and H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by reversed-phase HPLC (column: Phenomenex C18 75*30mm*3μm; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 25%-60%, 8 min) to provide product as a white solid (24.8 mg, 39.2 μmol, 47.7% yield, 94% purity) was obtained as a white solid; LCMS: RT = 1.654 min, MS cal.: 594.67, [M+H]⁺ = 595.2; HPLC: RT = 9.205 min, purity: 95.41%; ¹H NMR (400 MHz, METHANOL-d₄) δ 8.92 (s, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 8.01 - 7.94 (m, 1H), 7.72 - 7.49 (m, 5H), 7.00 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.03 (s, 2H), 5.57 (s, 2H), 4.23 - 4.08 (m, 2H), 3.28 - 3.20 (m, 1H), 2.74 - 2.60 (m, 2H), 2.55 - 2.45 (m, 1H), 1.75 - 1.62 (m, 2H), 1.49 - 1.38 (m, 1H), 0.67 - 0.60 (m, 1H), 0.44 - 0.32 (m, 1H).

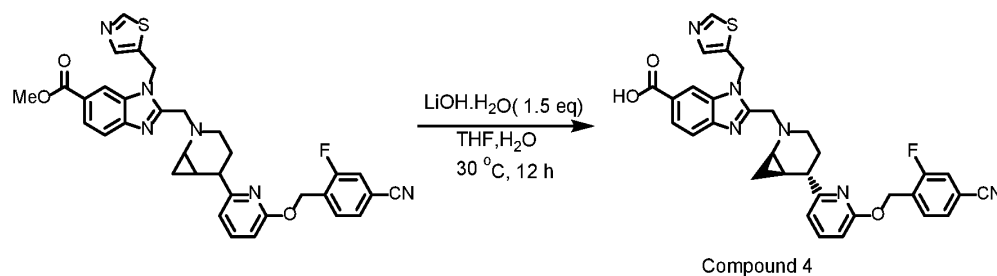
[0194] Intermediates for Examples 4-6



[0195] Methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (0.58 g) was purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10 μ m); mobile phase: [0.1%NH₃H₂O IPA]; B%: 40%-40%, 12 min) to provide **intermediate 9A** as a white solid (50 mg, 82.1 μ mol, 8.62% yield), **intermediate 9B** as a white solid (50 mg, 82.1 μ mol, 8.62% yield), **intermediate 9C** as a white solid (50 mg, 82.14 μ mol, 8.62% yield) and **intermediate 9D** as a white solid (50 mg, 82.14 μ mol, 8.62% yield).

Example 4 (Synthesis of Compound 4)

[0196] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 1

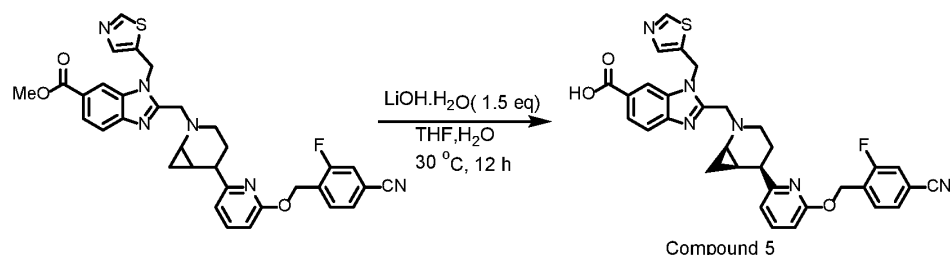


[0197] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (Intermediate 9A, 50 mg, 82.1 μ mol, 1 eq), LiOH.H₂O (5.17 mg, 123 μ mol, 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed starting material

was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-50%, 8 min). The crude product was purified by reversed-phase HPLC (column: C18-1 150*30mm*5 μ m; mobile phase: [water (FA)-ACN]; B%: 15%-40%, 20min) to provide product as a white solid (6.37 mg, 10.5 μ mol, 12.7% yield, 97.71% purity); LCMS: RT = 2.274 min, MS cal.: 594.67, [M+H]⁺ = 595.2; HPLC: RT = 9.259min, purity: 97.71%; SFC: RT = 10.562 min, purity: 99.34%; ¹H NMR (400 MHz, METHANOL-d₄) δ = 8.93 (s, 1H), 8.25 (s, 1H), 8.05 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.71 - 7.67 (m, 2H), 7.62 (m, 1H), 7.56 - 7.50 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H), 5.58 - 5.47 (m, 2H), 4.22 - 4.15 (d, *J* = 13.6 Hz, 1H), 4.09 - 4.03 (d, *J* = 13.6 Hz, 1H), 2.84 - 2.79 (m, 1H), 2.71 - 2.66 (m, 1H), 2.42 - 2.33 (m, 2H), 1.78 - 1.66 (m, 2H), 1.30 - 1.24 (m, 1H), 0.56 - 0.49 (m, 2H).

Example 5 (Synthesis of Compound 5).

[0198] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 2

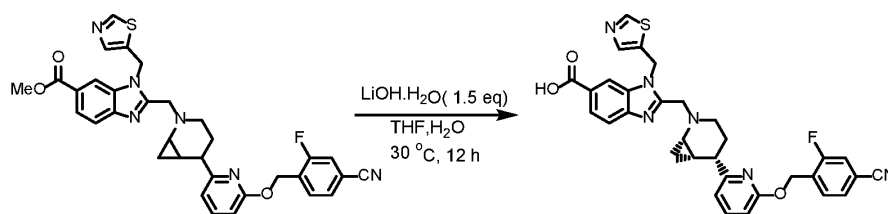


[0199] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (Intermediate 9B, 100 mg, 164 μ mol, 1 eq), LiOH.H₂O (10.34 mg, 246 μ mol, 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-50%, 8 min) to provide product as a white solid (51.4 mg, 83.3 μ mol, 50.7% yield, 96.4% purity); LCMS: RT = 2.258min, MS cal.: 594.67,

$[M+H]^+ = 595.2$; HPLC: RT = 9.326min, purity: 96.40%; SFC: RT = 9.504 min, purity: 98.74%; ^1H NMR (400 MHz, DMSO- d_6) δ = 9.03 (s, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.92 (d, J = 10.1 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.74 - 7.65 (m, 4H), 7.03 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.97 (s, 2H), 5.56 - 5.46 (m, 2H), 4.14 - 4.01 (m, 2H), 3.27 - 3.17 (m, 1H), 2.70 - 2.54 (m, 3H), 1.69 - 1.54 (m, 2H), 1.41 - 1.33 (m, 1H), 0.53 (m, 1H), 0.32 - 0.25 (m, 1H).

Example 6 (Synthesis of Compound 14).

[0200] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 3

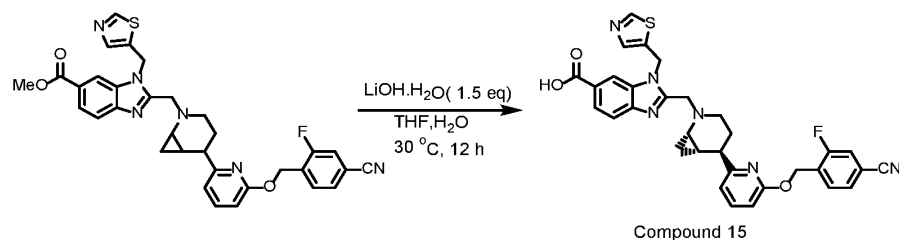


Compound 14

[0201] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (Intermediate 9C, 100 mg, 164 μmol , 1 eq), LiOH.H₂O (10.3 mg, 246 μmol , 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μm ; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-60%, 8 min) to provide product as a white solid (39.1 mg, 65.8 μmol , 40.0% yield); LCMS: RT = 1.646min, MS cal.: 594.67, $[M+H]^+ = 595.3$; HPLC: RT = 9.197min, purity: 96.20%; SFC: RT = 17.233 min, purity: 98.01%; ^1H NMR (400 MHz, DMSO- d_6) δ = 9.02 (s, 1H), 8.27 - 8.15 (m, 1H), 8.08 (m, 1H), 7.93 - 7.87 (m, 1H), 7.85 - 7.75 (m, 1H), 7.69 (m, 4H), 7.02 (d, J = 8.0 Hz, 1H), 6.76 - 6.72 (d, J = 8.0 Hz, 1H), 6.00 - 5.88 (s, 2H), 5.55 - 5.44 (m, 2H), 4.18 - 3.95 (s, 2H), 3.22 (m, 2H), 2.59 - 2.54 (m, 2H), 2.49 - 2.40 (m, 1H), 1.60 (m, 2H), 1.35 (m, 1H), 0.62 - 0.47 (m, 1H), 0.35 - 0.23 (m, 1H).

Example 7 (Synthesis of Compound 15).

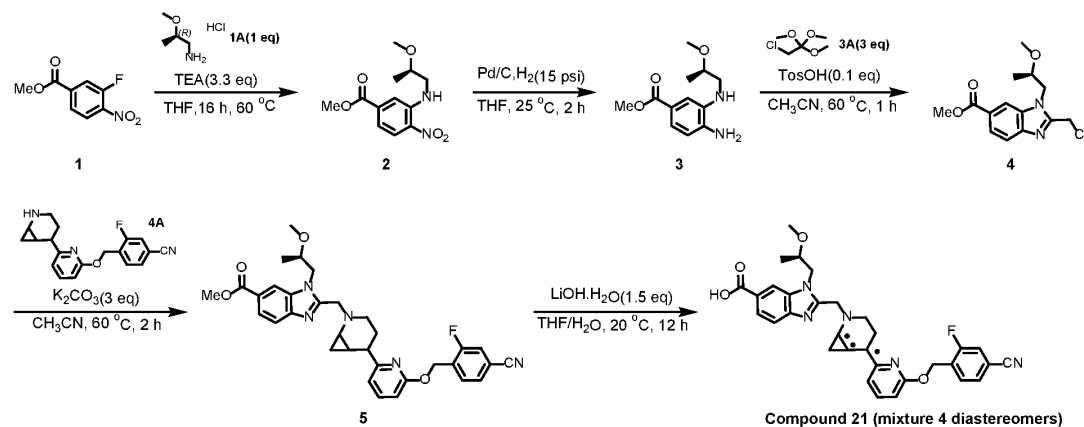
[0202] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 4



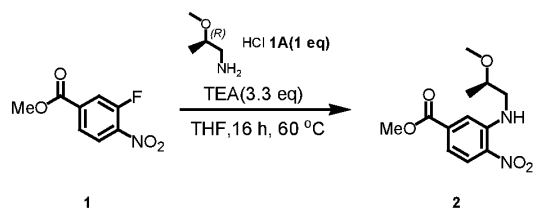
[0203] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (Intermediate 9D, 30 mg, 49.3 μ mol, 1 eq), LiOH.H₂O (3.10 mg, 73.9 μ mol, 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The mixture was used directly, no work-up. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-50%, 8 min) to provide product as a white solid (12.7 mg, 21.4 μ mol, 43.3% yield); LCMS: RT = 1.628min, MS cal.: 594.67, [M+H]⁺ = 595.2; HPLC: RT = 9.290 min, purity: 97.42%; SFC: RT = 8.630min, purity: 99.60%; ¹H NMR (400 MHz, DMSO-d₆) δ = 8.98 (s, 1H), 8.19 (s, 1H), 8.08 (s, 1H), 7.89 - 7.84 (m, 1H), 7.83 - 7.79 (m, 1H), 7.75 - 7.63 (m, 4H), 6.96 - 6.92 (d, *J* = 8.0 Hz, 1H), 6.76 - 6.71 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.52 - 5.43 (m, 2H), 4.16 - 4.08 (d, *J* = 13.6 Hz, 1H), 3.98 (d, *J* = 13.6 Hz, 1H), 2.81 - 2.74 (m, 1H), 2.66 - 2.57 (m, 1H), 2.44 - 2.36 (m, 1H), 2.31 - 2.21 (m, 1H), 1.67 - 1.58 (m, 2H), 1.22 - 1.13 (m, 1H), 0.55 - 0.46 (m, 1H), 0.44 - 0.35 (m, 1H).

Example 8 (Synthesis of Compound 21).

[0204] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture 4 diastereomers

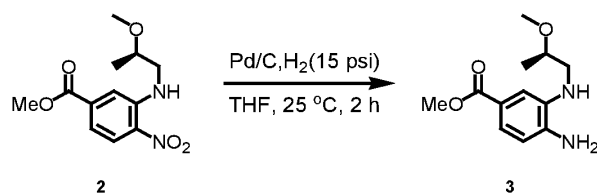


[0205] Preparation of Methyl (R)-3-((2-methoxypropyl)amino)-4-nitrobenzoate (2)



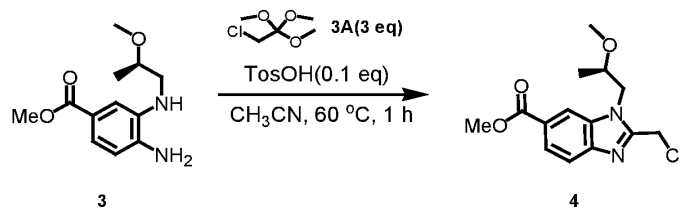
[0206] A mixture of methyl 3-fluoro-4-nitrobenzoate (2 g, 10.0 mmol, 1 eq), (R)-2-methoxypropan-1-amine (1.26 g, 10.0 mmol, 1 eq), TEA (3.35 g, 33.1 mmol, 4.61 mL, 3.3 eq) in THF (20 mL) was degassed and purged with N₂ for 3 times at 20 °C, and then the mixture was stirred at 60 °C for 16 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The residue was diluted with H₂O 100 mL and extracted with EtOAc 150 mL (50 mL * 3). The combined organic layers were washed with H₂O 15 mL (5 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1) to provide product as a yellow solid (2.6 g, 9.69 mmol, 96.50% yield); LCMS: RT = 0.746 min, MS cal.: 268.2, [M+H]⁺ = 269.0.

[0207] Preparation of methyl (R)-4-Amino-3-((2-methoxypropyl)amino)benzoate (3)



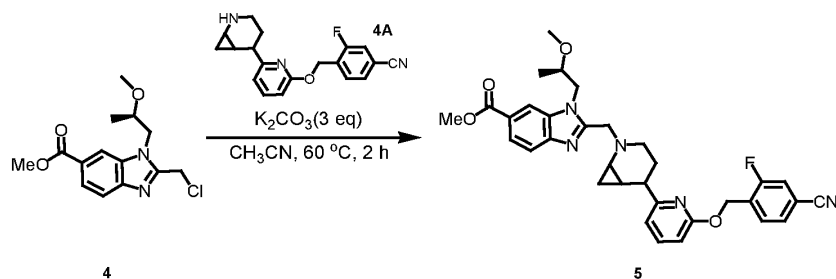
[0208] To a solution of methyl (R)-3-((2-methoxypropyl)amino)-4-nitrobenzoate (2.5 g, 9.32 mmol, 1 eq) in THF (30 mL) was added Pd/C (1 g, 10% purity) at 25 °C under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (15 psi) at 25°C for 2 h. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction was filtered, the filter cake washed with ethyl acetate and concentrated under reduced pressure to provide product as a white solid (2.2 g, 9.23 mmol, 99.1% yield); LCMS: RT = 0.494 min, MS cal.: 238.2, [M+H]⁺ = 239.0; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.91 - 3.85 (s, 3H), 3.80 (br s, 2H), 3.71 - 3.63 (m, 1H), 3.40 (s, 3H), 3.25 (m, 1H), 3.08 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H).

[0209] Preparation of Methyl (R)-2-(chloromethyl)-1-(2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (4)



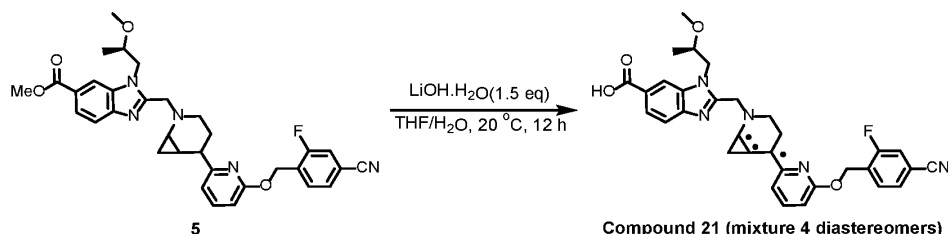
[0210] A mixture of methyl (R)-4-amino-3-((2-methoxypropyl)amino)benzoate (1 g, 4.20 mmol, 1 eq), 2-chloro-1,1,1-trimethoxyethane (1.95 g, 12.6 mmol, 1.69 mL, 3 eq), TosOH (72.3 mg, 420 μ mol, 0.1 eq) in CH₃CN (10 mL) was degassed and purged with N₂ for 3 times at 20 °C, and then the mixture was stirred at 60 °C for 1 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1) to provide product as a white solid (1 g, 3.37 mmol, 80.3% yield); LCMS: RT = 1.651 min, MS cal.: 296.7, [M+H]⁺ = 297.0.

[0211] Preparation of Methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-(R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (5)



[0212] A mixture of methyl (R)-2-(chloromethyl)-1-(2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (91.8 mg, 309 μ mol, 1 eq), 4-(((6-(2-azabicyclo[4.1.0]heptan-5-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (100 mg, 309 μ mol, 1 eq), K_2CO_3 (128 mg, 928 μ mol, 3 eq) in CH_3CN (1 mL) was degassed and purged with N_2 for 3 times at 20 $^{\circ}C$, and then the mixture was stirred at 60 $^{\circ}C$ for 2 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The residue was diluted with H_2O 1 mL, washed with EA (3 mL * 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 10/1) to provide product as a white solid (100 mg, 171 μ mol, 55.4% yield); LCMS: RT = 2.420 min, MS cal.: 583.6, $[M+H]^+ = 584.2$.

[0213] Preparation of 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers (Compound 21)

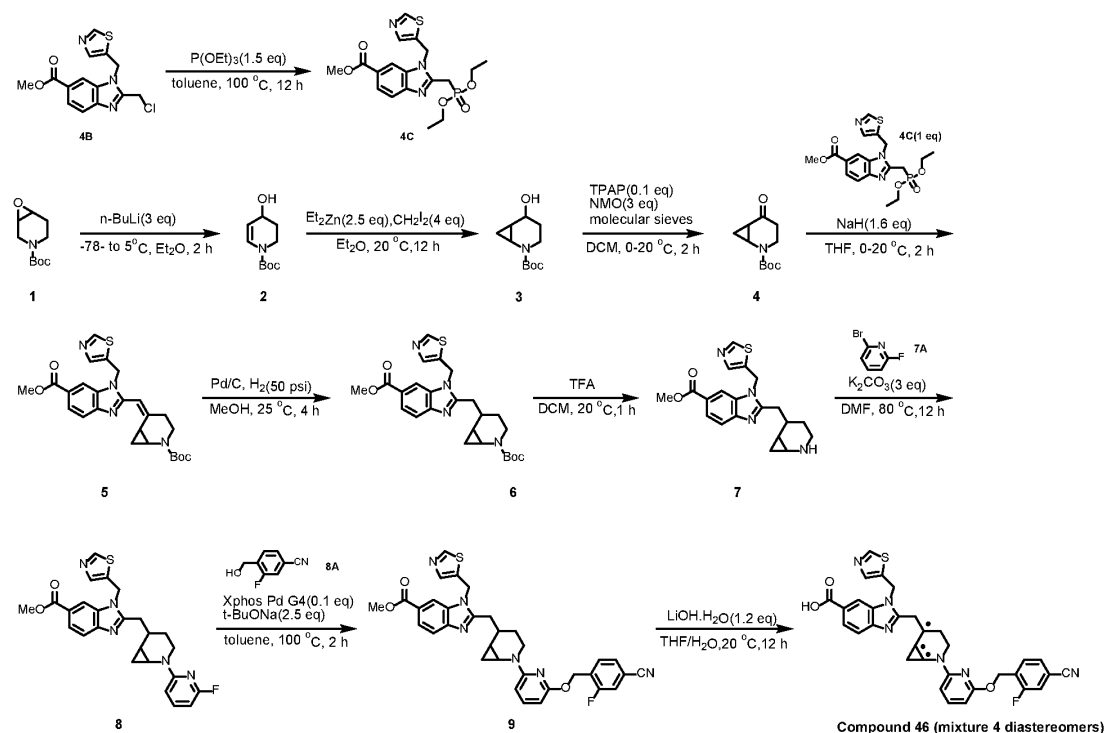


[0214] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (120 mg, 206 μ mol, 1 eq), $LiOH \cdot H_2O$ (12.9 mg, 308 μ mol, 1.5 eq) in THF (1.4 mL)/ H_2O (0.6 mL) was degassed and purged with N_2 for 3 times at 20 $^{\circ}C$, and then the mixture was stirred at 20 $^{\circ}C$ for 12 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge BEH C18 100*25mm*5 μ m; mobile phase: [water

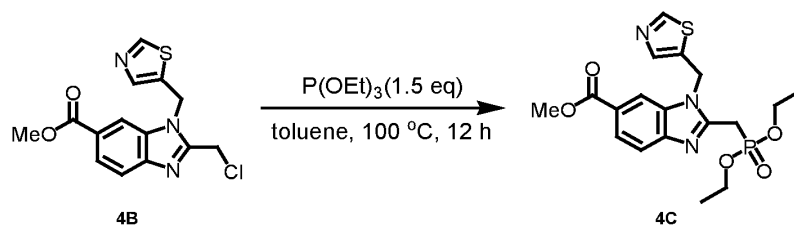
(NH_4HCO_3)-ACN]; B%: 30%- 65%, 8 min) to provide product as a white solid (36.8 mg, 61.3 μmol , 29.8% yield, 94.88% purity); LCMS: RT = 2.660min, MS cal.: 569.6, $[\text{M}+\text{H}]^+ = 570.3$; ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ = 8.24 (s, 1 H) 8.06 (d, J = 8.4 Hz, 1 H) 7.82 (d, J = 8.4 Hz, 1 H) 7.67 - 7.52 (m, 2 H) 7.48 - 7.34 (m, 2 H) 6.99 - 6.85 (d, J = 8.4 Hz, 1 H) 6.68 (d, J = 8.4 Hz, 1 H) 5.51 (s, 2 H) 4.61 (m, 1 H) 4.45 - 4.05 (m, 3 H) 3.89 - 3.75 (m, 1 H) 3.32 - 3.14 (m, 4 H) 2.74 - 2.60 (m, 2 H) 2.43 - 2.57 (m, 1 H) 1.84 - 1.57 (m, 2 H) 1.47 - 1.38 (m, 1 H) 1.34 - 1.26 (m, 3 H) 0.66 - 0.57 (m, 1 H) 0.53 - 0.39 (m, 1 H).

Example 9 (Synthesis of Compound 46).

[0215] 2-((2-((6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers

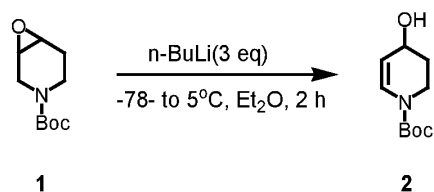


[0216] Preparation of Methyl 2-((diethoxyphosphoryl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (**4c**)



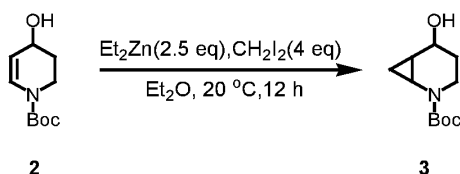
[0217] To a mixture of methyl 2-(chloromethyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (5 g, 15.5 mmol, 1 *eq*) in toluene (50 mL) was added triethyl phosphite (3.87 g, 23.3 mmol, 4.00 mL, 1.5 *eq*) in one portion at 20 °C. The mixture was stirred at 100 °C for 12 h. LC-MS showed ~58% of starting material remained. Several new peaks were shown on LC-MS and ~31% of desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 0/1) to provide product as a yellow oil (1.9 g, 4.49 mmol, 28.9% yield); LCMS: RT = 0.564 min, MS cal.: 423.10, [M+H]⁺ = 424.1; LCMS: RT = 1.395 min, MS cal.: 423.10, [M+H]⁺ = 424.1; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.75 (s, 1H), 8.12 (s, 1H), 8.03 - 7.97 (m, 1H), 7.81 - 7.70 (m, 2H), 5.89 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 4H), 3.94 (s, 3H), 3.59 - 3.51 (d, *J* = 21.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 6H)

[0218] Preparation of tert-Butyl 4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate (2)



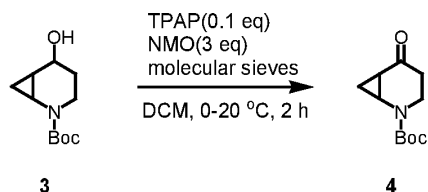
[0219] Et₂O (1000 mL) was charged to the 2 L three-necked round bottom flask, then tert-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (25 g, 125 mmol, 1 *eq*) was added at 20 °C. At -78 °C, n-BuLi (2.5 M, 151 mL, 3 *eq*) was added dropwise to the reaction mixture at -78 °C within 1 h. After the addition, the mixture was stirred at -78 °C for 1 h. The resulting mixture was stirred at 25 °C for 1 h. TLC indicated starting material was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was quenched with sat. aq. NaHCO₃ (350 mL) at 0 °C within 30 min. The mixture was extracted by EtOAc (200 mL * 3). Then organic phase was washed by aq. NaCl (300 mL). The organics were dried over Na₂SO₄, filtered and concentrated under reduced pressure at 30 °C to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=15/1 to 6/1) to provide product as a yellow oil (17 g, 85.3 mmol, 34% yield); LCMS: Rt = 1.368 min, MS cal.: 199.12, [M-tBu-OH]⁺ = 126.1; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.06 - 6.77 (m, 1H), 5.12 - 4.89 (m, 1H), 4.19 (m, 1H), 3.85 (m, 1H), 3.33 (m, 1H), 1.89 - 1.80 (m, 2H), 1.48 (s, 9H).

[0220] Preparation of tert-Butyl 5-hydroxy-2-azabicyclo[4.1.0]heptane-2-carboxylate (3)



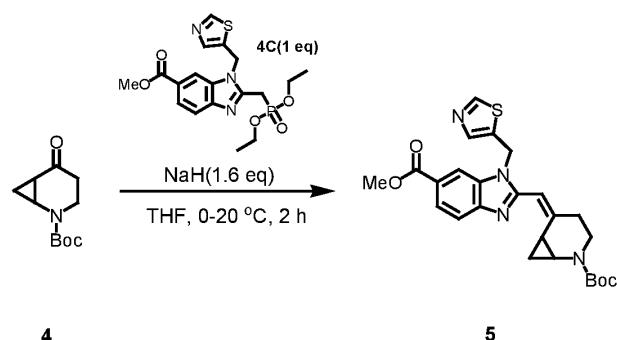
[0221] Et₂O (80 mL) was charged to the 500mL three-necked round bottom flask, then material **tert-butyl 4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate** (8 g, 40.2 mmol, 1 eq) was added at 20°C. At 0°C, ZnEt₂ (1 M, 100 mL, 2.5 eq) was added dropwise to the reaction mixture at 0 °C within 1 h. CH₂I₂ (43 g, 161 mmol, 13 mL, 4 eq) was added dropwise to the reaction mixture at 0 °C within 0.5 h. After the addition, the mixture was stirred at 20 °C for 12 h. TLC indicated starting material was consumed completely and many new spots formed. The reaction mixture was added to H₂O (100 ml) at 0 °C within 0.5 h. The mixture was extracted by EtOAc (50 mL * 3). Then organic phase was washed by NaCl (50 mL * 1). The organics were dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 3/1) to provide product as a yellow oil (3.5 g, 16.4 mmol, 20.4% yield); LCMS: RT = 1.307 min, MS cal.: 213.14, [M-tBu+H]⁺ = 158.1.

[0222] Preparation of **tert-Butyl 5-oxo-2-azabicyclo[4.1.0]heptane-2-carboxylate (4)**



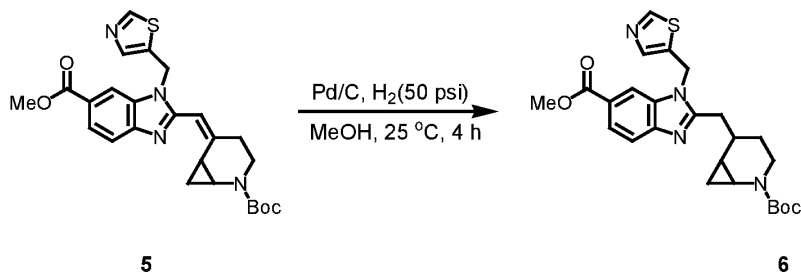
[0223] NMO (2.47 g, 21.1 mmol, 2.23 mL, 3eq) was added at 0 °C to a solution of **tert-butyl 5-hydroxy-2-azabicyclo[4.1.0]heptane-2-carboxylate** (1.5 g, 7.03 mmol, 1eq), molecular sieves 3A (2.5 g) and TPAP (247 mg, 703 μmol, 0.1eq) in DCM (25 mL). The reaction mixture was allowed to warm to 20 °C and stirred for 2 h. TLC indicated starting material was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was diluted with DCM (5 mL) and filtered through silica gel. The organic layer was washed with sat. Na₂S₂O₃ (5 mL), water (2 mL), brine (2 mL), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=15/1 to 8/1) to provide product as a yellow solid (1.05 g, 4.97 mmol, 70.7% yield); ¹H NMR (400 MHz, CHLOROFORM-d) δ = 4.21 - 3.89 (m, 1H), 3.58 - 3.21 (m, 2H), 2.46 - 2.21 (m, 2H), 1.87 (m, 1H), 1.49 (m, 10H), 1.23 - 1.06 (m, 1H).

[0224] Preparation of Methyl (Z)-2-((2-(tert-butoxycarbonyl)-2-azabicyclo[4.1.0]heptan-5-ylidene)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (5)



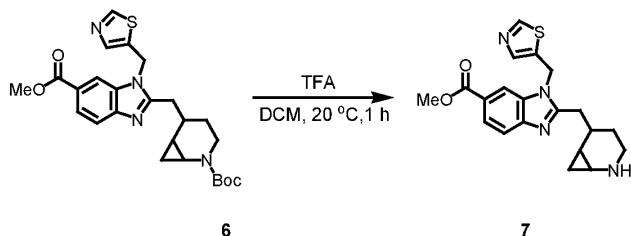
[0225] THF (10 mL) was charged to a 25 mL three-necked round bottom flask followed by methyl 2-((diethoxyphosphoryl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (1.82 g, 4.30 mmol, 1 eq). At 0 °C, NaH (275 mg, 6.89 mmol, 60% purity, 1.6 eq) was added portionwise to the reaction mixture. After 30 min, tert-butyl 5-oxo-2-azabicyclo[4.1.0]heptane-2-carboxylate (1 g, 4.73 mmol, 1.1 eq) was added to the reaction mixture at 0 °C. The mixture was stirred at 20 °C for 2 h. TLC showed starting material was consumed completely. The reaction mixture was added to NaHCO₃ at 0 °C. The mixture was extracted by EtOAc (10 mL * 2). Then organic phase was washed with brine 10mL. The organics were dried Na₂SO₄, filtered and concentrated under reduced pressure at 30 °C to give a residue. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 100/1 to 50/1) to provide product as an oil (1.3 g, 2.71 mmol, 62.9% yield); LCMS: RT = 0.633 min, MS cal.: 480.10, [M+H]⁺ = 481.1; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.75 (s, 1H), 8.09 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.83 - 7.73 (m, 2H), 6.56 - 6.34 (m, 1H), 5.63 (s, 2H), 4.16 - 3.97 (m, 0.5H), 3.95 (s, 3H), 3.93 - 3.81 (m, 1H), 3.53 - 3.44 (m, 0.5H), 3.35 - 3.18 (m, 1H), 3.01 - 2.74 (m, 1H), 2.48 - 2.36 (m, 1H), 2.34 - 2.18 (m, 0.5H), 2.10 - 1.96 (m, 0.5H), 1.71 - 1.57 (m, 0.5H), 1.53 - 1.48 (m, 9.5H), 0.96 - 0.82 (m, 1H).

[0226] Preparation of Methyl 2-((2-(tert-butoxycarbonyl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (6)



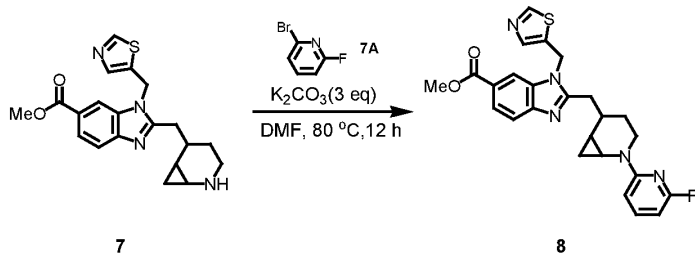
[0227] To a solution of methyl (Z)-2-((2-(tert-butoxycarbonyl)-2-azabicyclo[4.1.0]heptan-5-ylidene)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (1 g, 2.08 mmol, 1 *eq*) in MeOH (100 mL) was added Pd/C (1 g, 10% purity) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (50 psi) at 25 °C for 4 h. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to provide product as a white solid (1 g, 2.07 mmol, 99.6% yield); LCMS: RT = 1.306 min, MS cal.: 482.2, [M+H]⁺ = 483.3.

[0228] Preparation of Methyl 2-((2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (7)



[0229] To a solution of methyl 2-((2-(tert-butoxycarbonyl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (0.3 g, 622 μmol, 1 *eq*) in DCM (3 mL) was added TFA (924 mg, 8.10 mmol, 600.00 μL, 13.04 *eq*). The mixture was stirred at 20 °C for 1 h. TLC indicated starting material was consumed completely and one new spot was formed. The reaction mixture was diluted with Na₂CO₃ to pH = 8-9 and extracted with DCM 30 mL (15 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide product as a yellow solid (200 mg, 523 μmol, 84.1% yield); LCMS: RT= 0.740 min, MS cal.: 382.15, [M+H]⁺ = 383.1.

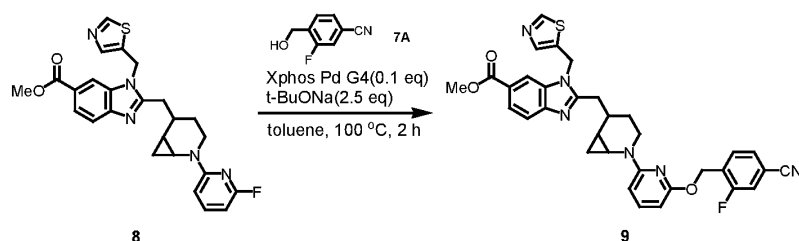
[0230] Preparation of Methyl 2-((2-(6-fluoropyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (8)



[0231] A mixture of methyl 2-((2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (143 mg, 375 μmol, 1.1 *eq*), 2-bromo-6-

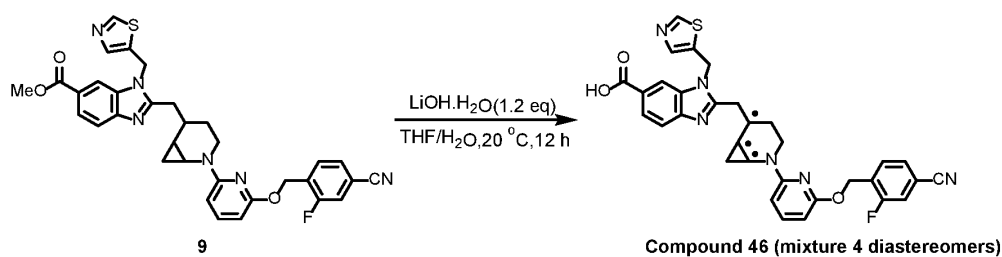
fluoropyridine (60 mg, 341 μmol , 1 *eq*), K_2CO_3 (141 mg, 1.02 mmol, 3 *eq*) in DMF (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 $^\circ\text{C}$ for 12 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with H_2O 20 mL and extracted with EtOAc 20 mL (10 mL * 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 10/1 to 0/1) to provide product as a white solid (100 mg, 186 μmol , 54.5% yield); LCMS: RT = 0.947 min, MS cal.: 477.17, $[\text{M}+\text{H}]^+ = 478.2$.

[0232] Preparation of Methyl 2-((2-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (9)



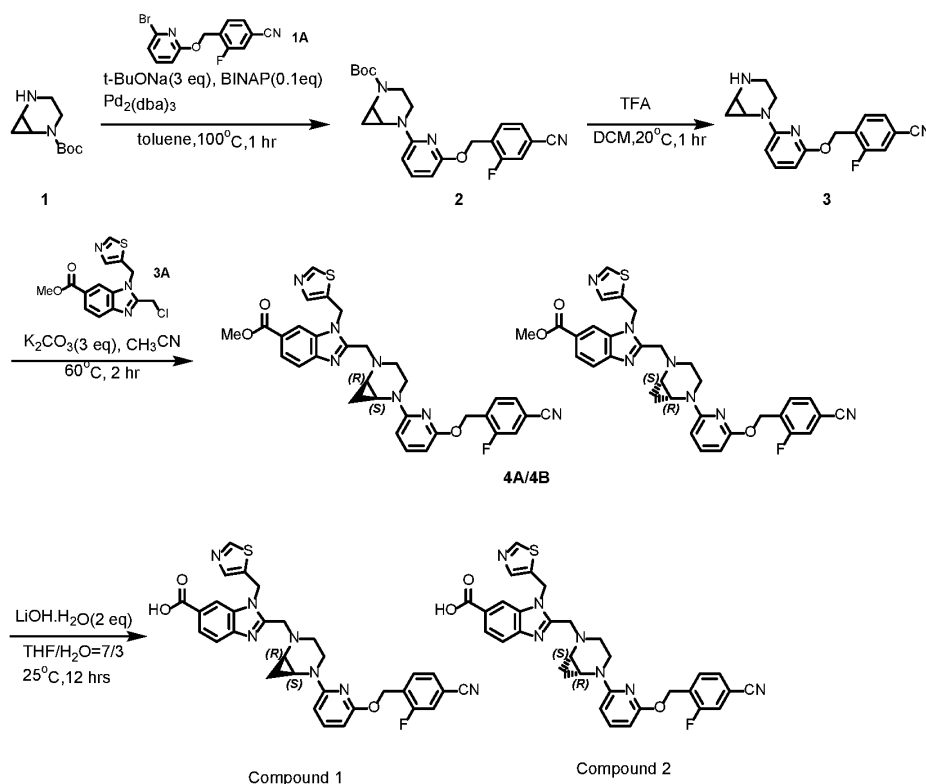
[0233] A mixture of methyl 2-((2-(6-fluoropyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (100 mg, 186 μmol , 1 *eq*), 3-fluoro-4-(hydroxymethyl)benzonitrile (28.07 mg, 186 μmol , 1 *eq*), Xphos Pd G4 (16 mg, 18.6 μmol , 0.1 *eq*), *t*-BuONa (44.6 mg, 464 μmol , 2.5 *eq*) in toluene (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 $^\circ\text{C}$ for 2 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with H_2O 20 mL and extracted with EtOAc 20 mL (20 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 0/1) to provide product (70 mg, 115 μmol , 61.9% yield); LCMS: Rt = 2.689 min, MS cal.: 608.2, $[\text{M}+\text{H}]^+ = 609.2$

[0234] Preparation of 2-((2-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers (Compound 46)

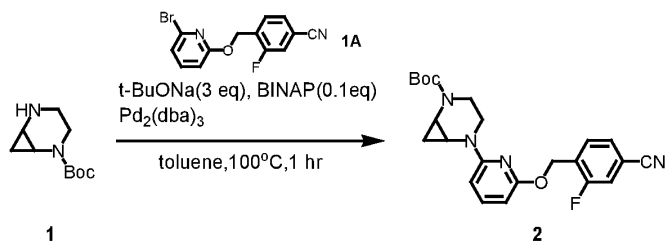


[0235] To a solution of methyl 2-((2-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-5-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (65 mg, 107 μmol , 1 *eq*) in THF (0.7 mL) was added LiOH.H₂O (5.38 mg, 128 μmol , 1.2 *eq*) in H₂O (0.3 mL). The mixture was stirred at 20 °C for 12 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10 μm ; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-70%, 8 min) to provide product as a white solid (28 mg, 47.1 μmol , 44.1% yield); LCMS: RT = 1.986 min, MS cal.: 594.18, [M+H]⁺ = 595.2; HPLC: RT = 3.096 min; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1 H) 8.27 (s, 1 H) 7.99 (s, 1 H) 7.90 - 7.85 (m, 1 H) 7.81 (m, 1 H) 7.72 - 7.62 (m, 3 H) 7.51 - 7.42 (m, 1 H) 6.35 - 6.28 (m, 1 H) 6.10 - 6.03 (m, 1 H) 5.96 - 5.88 (m, 2 H) 5.44 - 5.36 (m, 2 H) 4.40 - 4.31 (m, 1 H) 3.12 - 3.02 (m, 1 H) 3.00 - 2.90 (m, 1 H) 2.84 - 2.68 (m, 2 H) 2.61 - 2.55 (m, 1 H) 1.76 - 1.68 (m, 1 H) 1.54 - 1.43 (m, 1 H) 1.00 - 0.82 (m, 1 H) 0.79 - 0.69 (m, 1 H), 0.25-0.21 (m, 1 H).

[0236] Intermediates for Examples 10-11



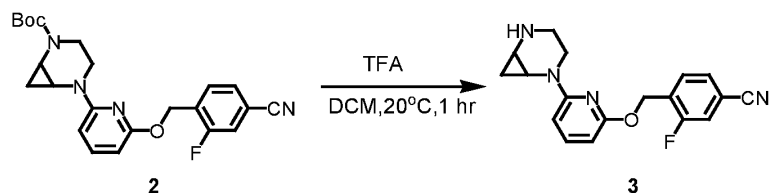
[0237] Preparation of tert-Butyl 5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (**2**)



[0238] A mixture of tert-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (500 mg, 2.52 mmol, 1.1 eq), 4-(((6-bromopyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (704 mg, 2.29 mmol, 1 eq), $\text{Pd}_2(\text{dba})_3$ (105 mg, 115 μmol , 0.05 eq), BINAP (143 mg, 229 μmol , 0.1 eq), and $t\text{-BuONa}$ (661 mg, 6.88 mmol, 3 eq) in toluene (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 1 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (50 mL). The organic layer was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 100/1 to 10/1) to provide product as a white solid (440 mg, 1.04 mmol, 45% yield); RT = 2.142 min; MS cal.:

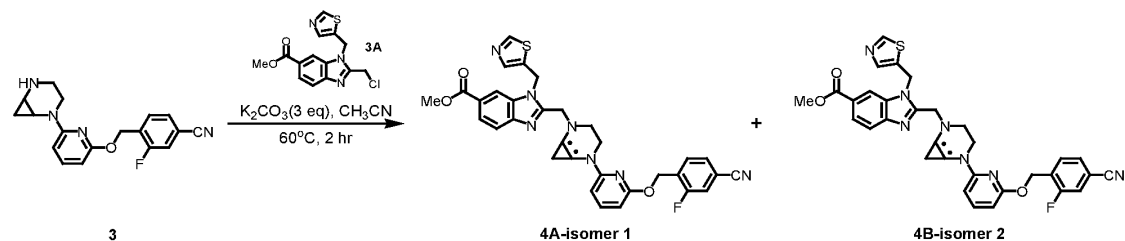
424.2, $[M+H]^+ = 325.2$; ^1H NMR (400 MHz, CHLOROFORM- d) δ 7.66 - 7.59 (m, 1H), 7.51 - 7.43 (m, 2H), 7.37 (d, $J = 9.2$ Hz, 1H), 6.34 (m, 1H), 6.18 (d, $J = 7.6$ Hz, 1H), 5.51 - 5.41 (m, 2H), 4.08 - 3.83 (m, 1H), 3.60 - 3.05 (m, 4H), 2.91 - 2.75 (m, 1H), 1.50 (s, 9H), 1.21 - 1.02 (m, 1H), 0.39 (m, 1H).

[0239] Preparation of 4-(((6-(2,5-Diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (3)



[0240] A mixture of tert-butyl 5-(6-(((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (400 mg, 942 μ mol, 1 eq), TFA (107 mg, 942 μ mol, 69.8 μ L, 1 eq) in DCM (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 1 h under N_2 atmosphere. TLC indicated starting material was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 45%-80% B over 8 min) to provide desired compound as a white solid (300 mg, yield 45%, purity 95%).

[0241] Preparation of Methyl 2-((5-(6-(((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (4A) and (4B)

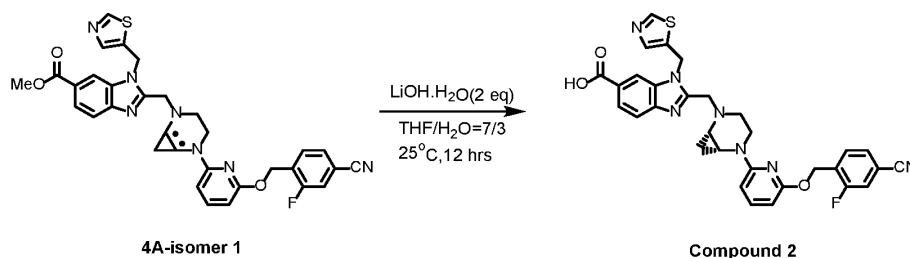


[0242] A mixture of 4-(((6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (298 mg, 925 μ mol, 1 eq), methyl 2-(chloromethyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (300 mg, 925 μ mol, 1 eq), K_2CO_3 (383 mg, 2.77 mmol, 3 eq) in CH_3CN (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The resulting

product was dissolved in EtOAc (20 ml) and filtered to remove insoluble material. The filtrate was concentrated in vacuo. The residue was purified by prep-HPLC (neutral condition: column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 45%-80%, 8min) to give a mixture of **intermediate 4A&4B** (400 mg, yield 90%, purity 90%) as a white solid, which was further separated by SFC (condition: column: DAICEL CHIRALCEL OD nv (250mm*30mm, 10 μ m); mobile phase: [0.1% NH₃H₂O MEOH]; B%: 50%-50%, 15 min). Intermediate **4A-isomer 1** was obtained as a white solid (120 mg, 197 μ mol, 21.3% yield); RT = 2.532 min, MS cal.: 617.2, [M+H]⁺ = 618.2; ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.77 (s, 1H), 8.15 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.51 - 7.41 (m, 2H), 7.34 (d, *J* = 9.2 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 2H), 5.52 - 5.37 (m, 2H), 4.21 - 4.10 (m, 3H), 4.08 - 4.01 (m, 1H), 3.96 (s, 3H), 3.09 - 3.00 (m, 1H), 2.83 - 2.72 (m, 2H), 2.66 - 2.58 (m, 1H), 2.45 - 2.37 (m, 1H), 0.81-0.79 (m, 1H), 0.61 - 0.46 (m, 1H). Intermediate **4B-isomer 2** was obtained as a white solid (80 mg, 131 μ mol, 14.2% yield); RT = 2.534min, MS cal.: 617.2, [M+H]⁺ = 618.2; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.77 (s, 1H), 8.15 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.34 (d, *J* = 9.4 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 2H), 5.50 - 5.37 (m, 2H), 4.21 - 4.03 (m, 4H), 3.96 (s, 3H), 3.05 (m, 1H), 2.84 - 2.72 (m, 2H), 2.67 - 2.59 (m, 1H), 2.47 - 2.39 (m, 1H), 0.81-0.79 (m, 1H), 0.60 - 0.50 (m, 1H).

Example 10 (Synthesis of Compound 2).

[0243] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 1

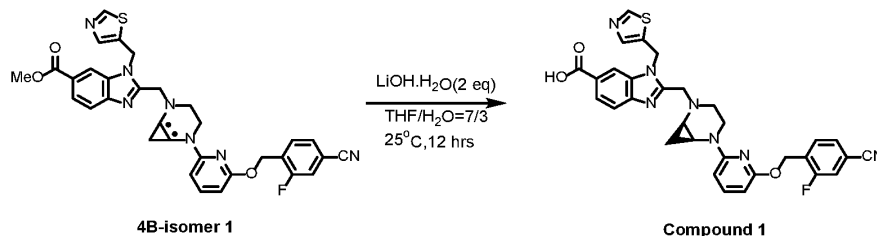


[0244] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-

carboxylate (90 mg, 148 μmol , 1 *eq*) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (12.4 mg, 295 μmol , 2 *eq*) in THF (0.7 mL) and H_2O (0.3 mL) was degassed and purged with N_2 for 3 times, and the mixture was stirred at 25 °C for 12 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10 μm ; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 20%-50%, 8 min) to provide product as a white solid (29.9 mg, 50.2 μmol , 34% yield); RT = 2.508 min, MS cal.: 595.2, $[\text{M}+\text{H}]^+ = 596.1$; ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.94 (s, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.68 - 7.62 (m, 1H), 7.57 - 7.53 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 6.00 (s, 2H), 5.46 (s, 2H), 4.24 - 4.08 (m, 3H), 3.00 (m, 1H), 2.85 - 2.76 (m, 2H), 2.67 (m, 1H), 2.45 - 2.37 (m, 1H), 0.75 (m, 1H), 0.55 - 0.49 (m, 1H).

Example 11 (Synthesis of Compound 1).

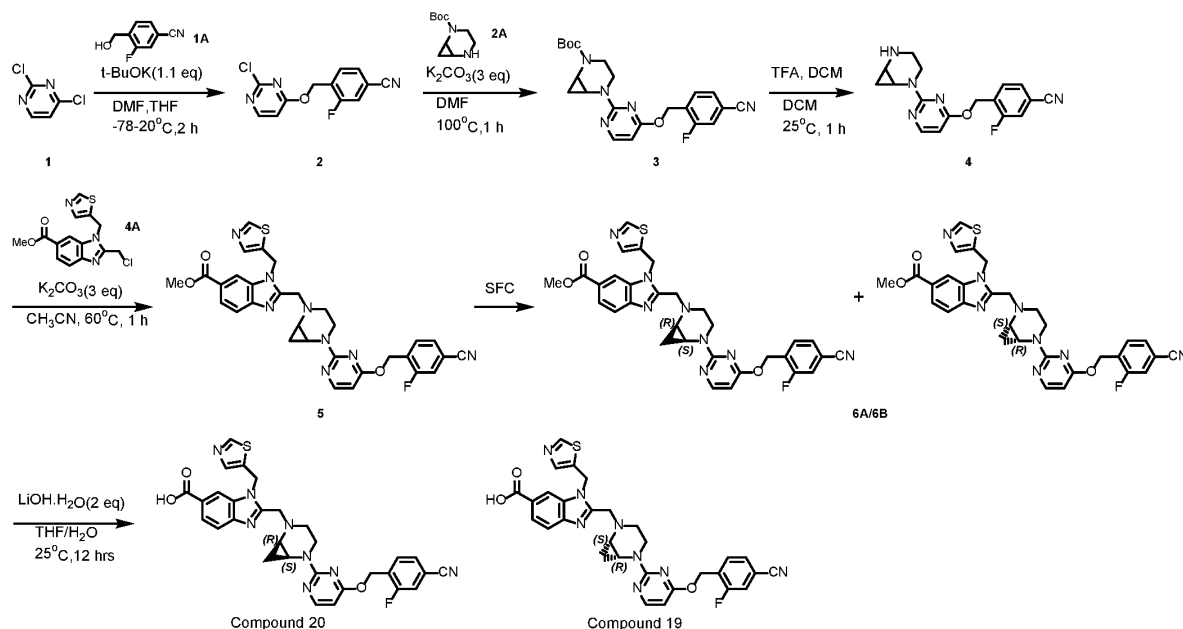
[0245] 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, diastereomer 2



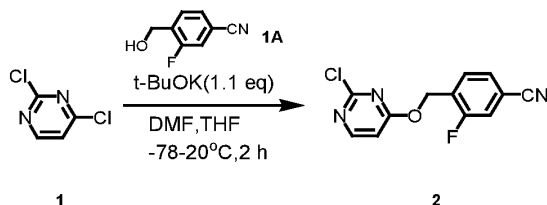
[0246] To a solution of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (70 mg, 115 μmol , 1 *eq*) in THF (0.7 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (9.64 mg, 230 μmol , 2 *eq*) in H_2O (0.3 mL). The mixture was stirred at 25 °C for 12 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was purified by prep-HPLC (neutral condition: column: Waters Xbridge BEH C18 100*30mm*10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-60%, 8 min) to provide product as a white solid (35 mg, 58.76 μmol , 51.2% yield); RT = 1.843 min, MS cal.: 595.65, $[\text{M}+\text{H}]^+ = 596$; ^1H NMR (400 MHz, METHANOL-d_4) δ 8.93 (s, 1H), 8.26 (s, 1H), 8.04 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.55 - 7.51 (m,

2H), 7.45 (t, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 8.0$ Hz, 1H), 6.11 (d, $J = 8.0$ Hz, 1H), 6.07 (s, 2H), 5.43 (s, 2H), 4.24 - 4.06 (m, 3H), 2.97 (m, 1H), 2.79 - 2.76 (m, 2H), 2.65 (m, 1H), 2.45 - 2.38 (m, 1H), 0.75 (m, 1H), 0.51 - 0.48 (m, 1H).

[0247] Intermediates for Examples 12-13



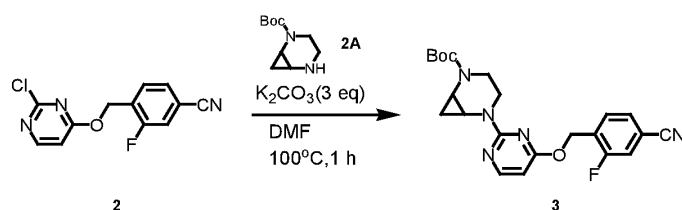
[0248] Preparation of 4-(((2-Chloropyrimidin-4-yl)oxy)methyl)-3-fluorobenzonitrile (2)



[0249] $t\text{-BuOK}$ (4.14 g, 36.9 mmol, 1.1eq) was added in portions to 3-fluoro-4-(hydroxymethyl)benzonitrile (5.33 g, 35.2 mmol, 1.05 eq) in THF (40 mL) at 20°C and then stirred until completely dissolved. This solution was added dropwise to 2,4-dichloropyrimidine (5 g, 33.6 mmol, 1 eq) in DMF (60 mL) at $< -65^\circ\text{C}$ over 1.5 hours under N_2 atmosphere. The reaction mixture was warmed to 10°C slowly over 1.5 hours and stirred for 0.5 h. LCMS showed 0.3% starting material and 85.9% product. The reaction mixture was poured into H_2O (300 mL) slowly at 0°C and a solid formed. The mixture was stirred for 15 mins and filtered. The solid was collected, dissolved in DCM (100 mL) and washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product (5 g). The crude product was stirred in MTBE (10 mL) and stirred for 5 mins, n-hexane (50 mL) was added to the mixture, stirred for 10 mins, filtered and the filter-cake collected.

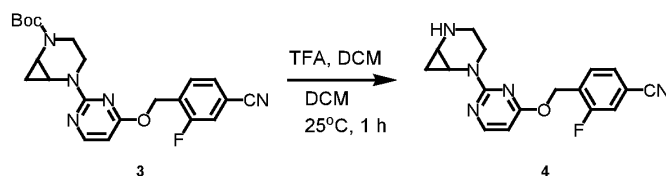
The cake was added into MTBE (5 mL) and stirred for 5 mins, n-hexane (25 mL) was added to the mixture, stirred for 5 mins, filtered and the cake was collected, dried under vacuum for 20 mins to afford the product as a yellow solid (4 g, 15.2 mmol, 45.2% yield); RT = 2.056 min, MS cal.: 263.0, $[M+H]^+ = 264.0$; ^1H NMR (400 MHz, CHLOROFORM- d) δ = 8.40 (d, J = 5.6 Hz, 1 H) 7.64 (t, J = 7.2 Hz, 1 H) 7.55 - 7.39 (m, 2 H) 6.80-6.71 (d, J = 5.6 Hz, 1 H, 1 H) 5.55 (s, 2 H).

[0250] Preparation of tert-Butyl 5-(4-((4-cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (3)



[0251] A mixture of 4-(((2-chloropyrimidin-4-yl)oxy)methyl)-3-fluorobenzonitrile (500 mg, 1.90 mmol, 1 *eq*), tert-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (490 mg, 2.09 mmol, 1.1 *eq*, HCl), K_2CO_3 (786 mg, 5.69 mmol, 3 *eq*), in DMF (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 1 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate= 20/1 to 0/1) to provide product as a white solid (500 mg, 1.18 mmol, 61.9% yield); RT = 2.522 min, MS cal.: 425.19, $[M+H]^+ = 426.2$; ^1H NMR (400 MHz, CHLOROFORM- d) δ = 8.24 (s, 1 H) 7.66-7.59 (m, 1 H) 7.53 (d, J = 9.6 Hz, 1 H) 7.42 (d, J = 9.6 Hz, 1 H) 6.19 (d, J = 5.6 Hz, 1 H) 5.60 (s, 2 H) 3.94-3.72 (m, 1 H) 3.71-3.31 (m, 3 H) 3.29-3.05 (m, 2 H) 1.59 - 1.70 (m, 1 H) 1.53 (s, 9 H).

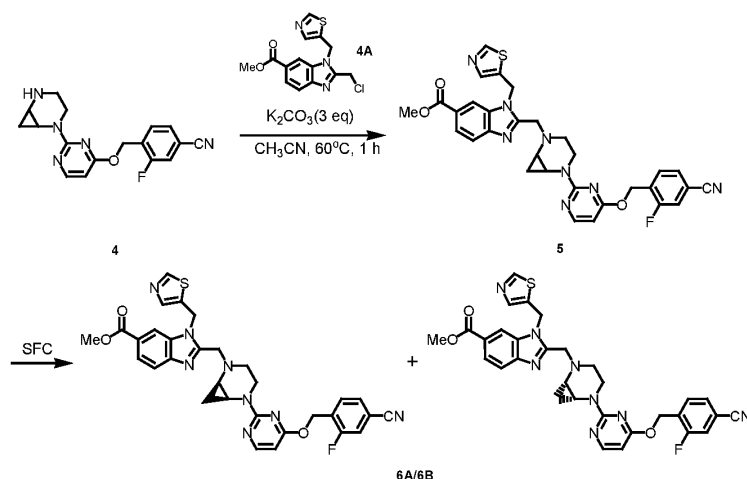
[0252] Preparation of 4-(((2-(2,5-Diazabicyclo[4.1.0]heptan-2-yl)pyrimidin-4-yl)oxy)methyl)-3-fluorobenzonitrile (4)



[0253] To a solution of tert-butyl 5-(4-((4-cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (0.3 g, 705 μ mol, 1 *eq*) in DCM (3 mL) was added

TFA (1.54 g, 13.5 mmol, 1.00 mL, 19.2 *eq*). The mixture was stirred at 25 °C for 1 h. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to provide product as a yellow oil (220 mg, 676 μ mol, 95.9 % yield); RT = 0.777 min, MS cal.: 325.13, $[M+H]^+ = 326.3$.

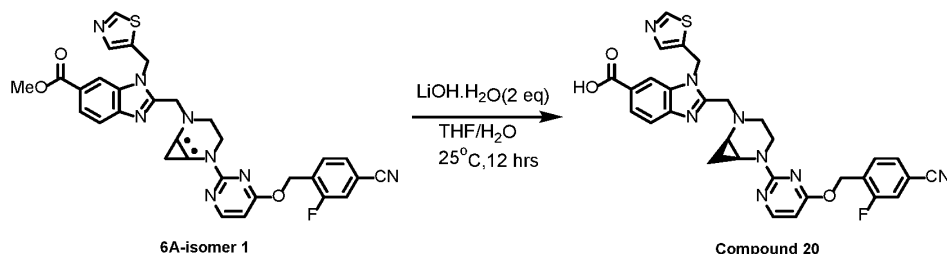
[0254] Preparation of Methyl 2-((5-(4-((4-cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (6A and 6B)



[0255] To a solution of 4-(((2-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyrimidin-4-yl)oxy)methyl)-3-fluorobenzonitrile (210 mg, 645 μ mol, 1 *eq*) in CH_3CN (1 mL) was added K_2CO_3 (268 mg, 1.94 mmol, 3 *eq*) and methyl 2-(chloromethyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (208 mg, 645 μ mol, 1 *eq*). The mixture was stirred at 60 °C for 1 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=0/1 to Dichloromethane/Methanol = 10/1). The residue was further separated by SFC (condition: column: DAICEL CHIRALPAK AD (250mm*30mm, 10 μ m); mobile phase: [0.1% NH_3H_2O MEOH]; B%: 60%-60%, 5min) to provide intermediate 6A as a white solid (120 mg, 197 μ mol, 30.4% yield); LCMS: RT = 2.229 min, MS cal.: 610.19, $[M+H]^+ = 611.2$; SFC: RT = 1.174 min, ee %: 100.0% and intermediate 6B as a white solid (120 mg, 197 μ mol, 30.4% yield); LCMS: RT = 2.229 min, MS cal.: 610.19, $[M+H]^+ = 611.1$; SFC: RT = 1.685 min, ee %: 97.9%.

Example 12 (Synthesis of Compound 20).

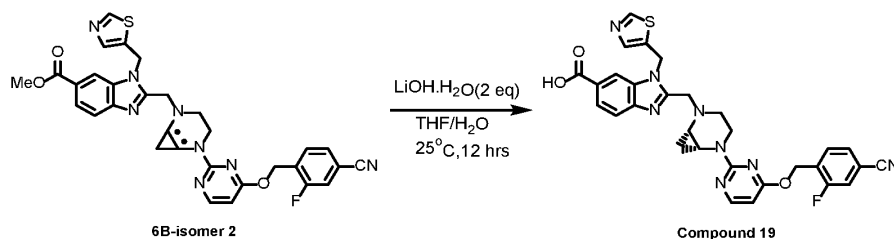
[0256] 2-((5-(4-((4-Cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0257] To a solution of methyl 2-((5-(4-((4-cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (100 mg, 164 μ mol, 1 *eq*) in THF (1.4 mL) was added LiOH.H₂O (13.7 mg, 328 μ mol, 2 *eq*) in H₂O (0.6 mL). The mixture was stirred at 20 °C for 12 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was purified by prep-HPLC (neutral condition: column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-60%, 8min) to provide product as a white solid (29 mg, 48.6 μ mol, 29.7% yield); LCMS: RT = 1.626 min, MS cal.: 596.18, [M+H]⁺ = 597.2; SFC: RT = 1.312 min, ee %: 99.64%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.94 (s, 1 H) 8.27 (s, 1 H) 8.16 - 8.04 (m, 2 H) 8.00 (d, *J* = 8.4 Hz, 1 H) 7.71 (d, *J* = 8.4 Hz, 1 H) 7.69 - 7.63 (m, 1 H) 7.60-7.53 (m, 2 H) 6.19 (d, *J* = 5.6 Hz, 1 H) 6.01 (s, 2 H) 5.67 (s, 2 H) 4.26 - 4.15 (m, 2 H) 4.13 - 4.08 (m, 1 H) 3.13-2.98 (m, 2 H) 2.87-2.78 (m, 1 H) 2.45-2.61 (m, 1 H) 2.55-2.42 (m, 1 H) 0.83-0.53 (m, 2 H).

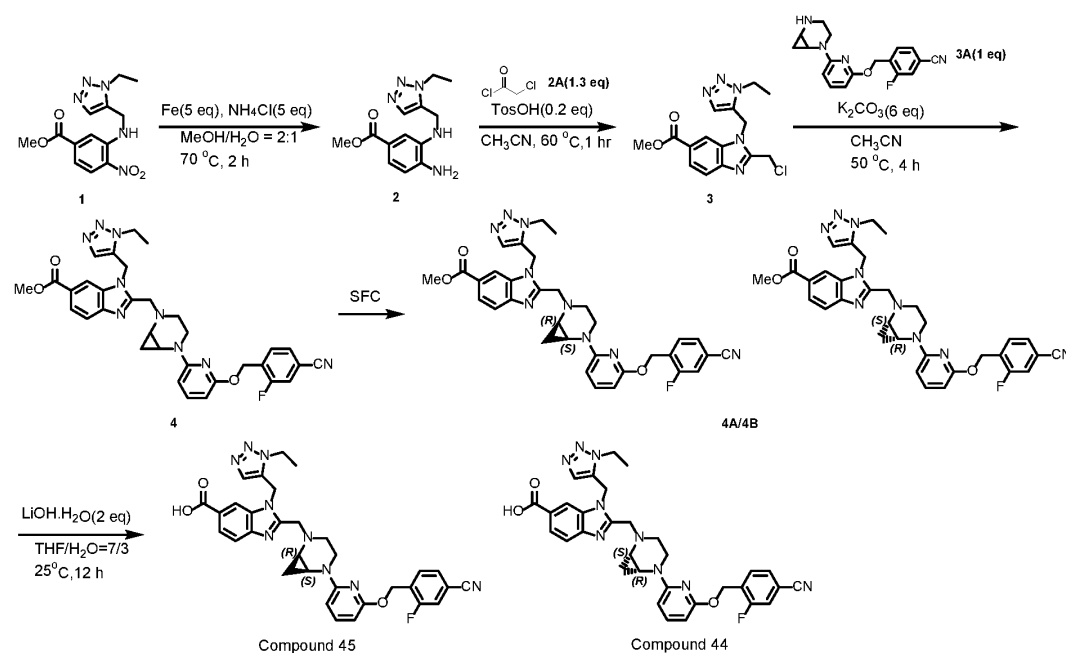
Example 13 (Synthesis of Compound 19).

[0258] 2-((5-(4-((4-Cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid

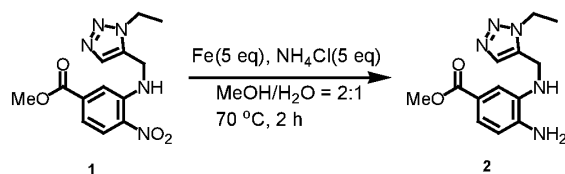


[0259] A mixture of methyl 2-((5-(4-((4-cyano-2-fluorobenzyl)oxy)pyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (110 mg, 180 μ mol, 1 eq), LiOH.H₂O (15.1 mg, 360 μ mol, 2 eq) in THF (3 mL) and H₂O (1.2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25°C for 12 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired m/z. The reaction solution was adjusted with citric acid to pH = 7. The residue was purified by prep-HPLC (neutral condition: column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 10%-45%, 8 min) to provide product as a white solid (26.2 mg, 43.8 μ mol, 24.3% yield); LCMS: RT = 1.631 min, MS cal.: 596.18, [M+H]⁺ = 597.2; SFC: RT = 1.381 min, ee %: 99.70%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = ppm 8.94 (s, 1 H) 8.27 (s, 1 H) 8.12 - 8.07 (m, 1 H) 8.05 (s, 1 H) 7.99 (d, *J*=8.6 Hz, 1 H) 7.73 - 7.63 (m, 2 H) 7.60 - 7.54 (m, 2 H) 6.19 (d, *J*=5.6 Hz, 1 H) 5.99 (s, 2 H) 5.52 (s, 2 H) 4.27 - 4.15 (m, 2 H) 4.14 - 4.08 (m, 1 H) 3.14 - 3.00 (m, 2 H) 2.82 (m, 1 H) 2.66 (m, 1 H) 2.52 - 2.43 (m, 1 H) 0.84 - 0.52 (m, 2 H).

[0260] Intermediates for Examples 14-15

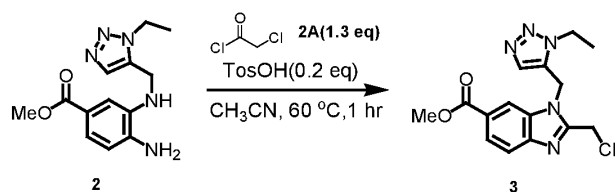


[0261] Preparation of Methyl 4-amino-3-(((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)amino)benzoate (2)



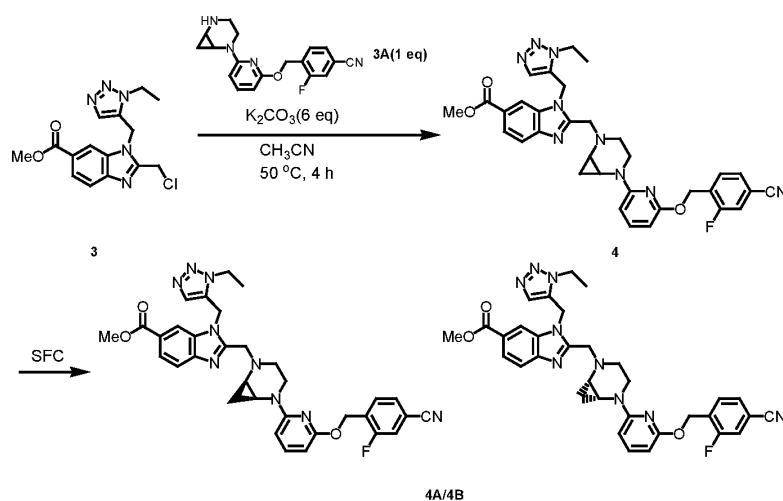
[0262] A mixture of **intermediate 1** (1 g, 3.28 mmol, 1 eq), Fe (915 mg, 16.4 mmol, 5 eq), NH₄Cl (876 mg, 16.4 mmol, 5 eq) in MeOH (10 mL) and H₂O (5 mL) was stirred at 70°C for 2 h under N₂ atmosphere. TLC indicated starting material was consumed completely and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated. The residue was diluted with H₂O (100 mL) and extracted with DCM (40 mL *3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the product as a white solid (800 mg, 2.91 mmol, 88.7% yield), which was used directly for next step.

[0263] Preparation of Methyl 2-(chloromethyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (**3**)



[0264] A mixture of methyl 4-amino-3-(((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)amino)benzoate (300 mg, 1.09 mmol, 1 eq), 2-chloroacetyl chloride (110.77 mg, 980.73 μmol, 78.00 μL, 0.9 eq) and TosOH (37.53 mg, 217.94 μmol, 0.2 eq) in CH₃CN (5 mL) was stirred at 60°C for 1 h under N₂ atmosphere. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to provide product as a brown solid (360 mg, 1.08 mmol, 99% yield), which was used directly in the next step; LCMS: RT = 0.697 min, MS cal.: 333.8, [M+H]⁺ = 334.2

[0265] Preparation of Methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (**4A** and **4B**)



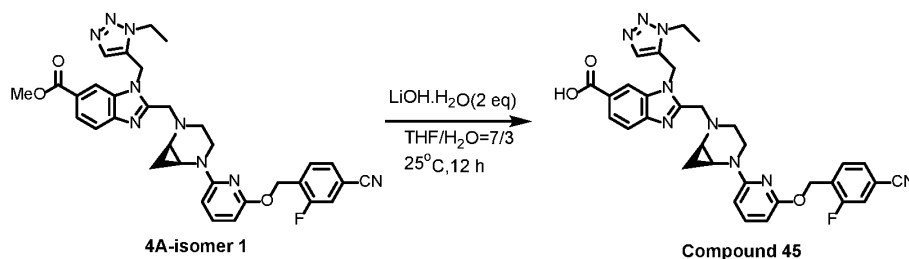
[0266] To a solution of methyl 2-(chloromethyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (320 mg, 958.74 μmol , 1 eq) and 4-(((6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (311 mg, 959 μmol , 1 eq) in CH_3CN (5 mL) was added K_2CO_3 (398 mg, 2.88 mmol, 3 eq). The mixture was stirred at 50°C for 4 h. LCMS showed starting material was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2 , Dichloromethane: Methanol=100/1 to 10/1) to provide product as a yellow solid (405 mg, 651 μmol , 68% yield); LCMS: RT = 2.439 min, MS cal.:621.7, $[\text{M}+\text{H}]^+ = 622.3$.

[0267] Product (400 mg) was further separated by SFC (condition, column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ MEOH]; B%: 60%-60%,20 min) to provide **intermediate 4A-isomer 1** as a yellow solid (150 mg, 241 μmol , 35% yield); LCMS: RT = 2.448 min, MS cal.:621.7, $[\text{M}+\text{H}]^+ = 622.3$; SFC: RT = 1.678 min, ee %: 100%; ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.04 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.34 (d, J = 9.2 Hz, 1H), 7.23 (s, 1H), 6.28 (d, J = 8.0 Hz, 1H), 6.15 (d, J = 8.0 Hz, 1H), 5.74 (s, 2H), 5.47 (d, J = 14 Hz, 1H), 5.42 (d, J = 14 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.09 - 3.97 (m, 3H), 3.95 (s, 3H), 2.92 - 2.83 (m, 1H), 2.75 - 2.61 (m, 2H), 2.57 - 2.49 (m, 1H), 2.38 - 2.29 (m, 1H), 1.56 - 1.43 (t, J = 7.2 Hz, 3H), 0.76-0.73 (m, 1H), 0.53 - 0.47 (m, 1H) and **intermediate 4B-isomer 2** as a yellow solid (154 mg, 248 μmol , 36% yield); LCMS: RT = 2.454 min, MS cal.:621.7, $[\text{M}+\text{H}]^+ = 622.3$; SFC: RT = 2.220 min, ee %: 100%; ^1H NMR (400 MHz, CHLOROFORM-d) δ =

8.07 - 8.02 (m, 2H), 7.83 (d, $J = 9.2$ Hz, 1H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.49 - 7.41 (m, 2H), 7.34 (d, $J = 9.2$ Hz, 1H), 7.24 (s, 1H), 6.28 (d, $J = 8.0$ Hz, 1H), 6.16 (d, $J = 8.0$ Hz, 1H), 5.74 (s, 2H), 5.46 (d, $J = 14$ Hz, 1H), 5.38 (d, $J = 14$ Hz, 1H), 4.40 (q, $J = 7.2$ Hz, 2H), 4.11 - 4.01 (m, 2H), 4.00 - 3.95 (m, 1H), 3.95 (s, 3H), 2.93 - 2.83 (m, 1H), 2.76 - 2.61 (m, 2H), 2.53 (m, 1H), 2.35 (m, 1H), 1.50 (t, $J = 7.2$ Hz, 3H), 0.76 (m, 1H), 0.51 (m, 1H).

Example 14 (Synthesis of Compound 45).

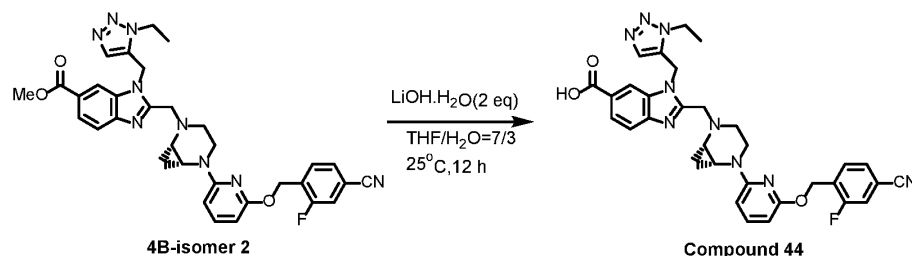
[0268] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0269] To a solution of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (80 mg, 129 μmol , 1 eq) in THF (0.7 mL) was added LiOH.H₂O (10.8 mg, 257 μmol , 2 eq) in H₂O (0.3 mL). The mixture was stirred at 25°C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction solution was adjusted with citric acid to pH 6-7. After concentration of the reagent, the residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge Prep OBD C18 150*40mm*10 μm ; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-60%, 8 min) to provide product as a white solid (43.93 mg, 72.30 μmol , 56.18% yield); LCMS: RT = 2.491 min, MS cal.: 607.7, [M+H]⁺ = 608.1; SFC: RT = 1.476 min, ee %: 100%; HPLC: RT=11.507 min, purity: 98.57%; ¹H NMR (400 MHz, METHANOL-d₄) δ = 8.17 (s, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.62 (t, $J = 7.2$ Hz, 1H), 7.56 - 7.50 (m, 2H), 7.44 (t, $J = 8$ Hz, 1H), 7.20 (s, 1H), 6.30 (d, $J = 8.0$ Hz, 1H), 6.09 (d, $J = 8.0$ Hz, 1H), 5.94 (s, 2H), 5.41 (s, 2H), 4.52 (q, $J = 7.2$ Hz, 2H), 4.20 (d, $J = 14.0$ Hz, 1H), 4.01 (m, 2H), 2.71 - 2.54 (m, 4H), 2.29 - 2.22 (m, 1H), 1.50 (t, $J = 7.2$ Hz, 3H), 0.69 (m, 1H), 0.46 - 0.41 (m, 1H).

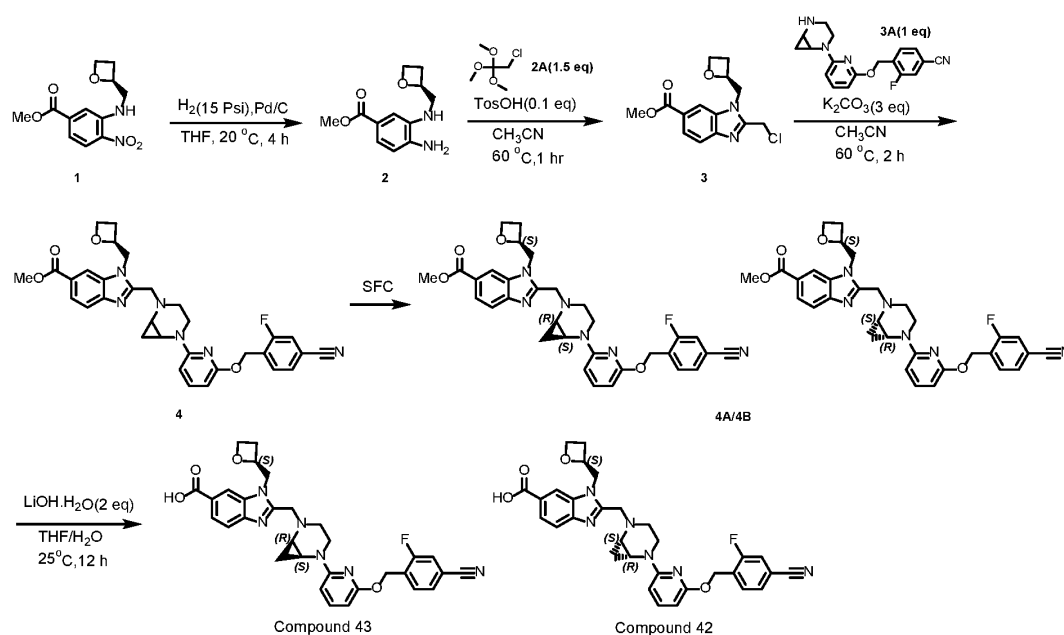
Example 15 (Synthesis of Compound 44).

[0270] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

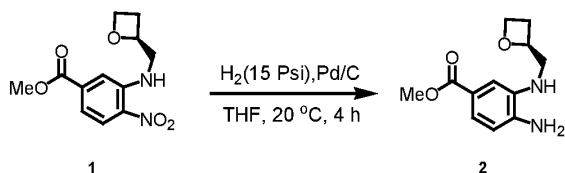


[0271] A mixture of methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-ethyl-1H-1,2,3-triazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (80 mg, 129 μ mol, 1 eq) and LiOH.H₂O (10.8 mg, 257 μ mol, 2 eq) in THF (0.7 mL) and H₂O (0.3 mL) was stirred at 25°C for 12 h under N₂ atmosphere. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction solution was adjusted with citric acid to pH 6-7. After concentration of the reagent, the residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 25%-55%, 8min) to provide product as a white solid (26.9 mg, 44.3 μ mol, 34% yield); LCMS: RT = 2.491 min, MS cal.: 607.7, [M+H]⁺ = 608.1; SFC: RT = 1.530 min, ee %: 100%; HPLC: RT = 11.539 min, purity: 98.67%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.15 (s, 1 H) 8.03 (d, *J* = 8.4 Hz, 1 H) 7.76 (d, *J* = 8.4 Hz, 1 H) 7.59 - 7.65 (m, 1 H) 7.51 - 7.55 (m, 2 H) 7.44 (t, *J* = 8.0 Hz, 1 H) 7.20 (s, 1 H) 6.30 (d, *J* = 8.0 Hz, 1 H) 6.10 (d, *J* = 8.0 Hz, 1 H) 5.93 (s, 2 H) 5.41 (s, 2 H) 4.52 (q, *J* = 7.2 Hz, 2 H) 4.20 (d, *J* = 14 Hz, 1 H) 3.95 - 4.05 (m, 2 H) 2.66 - 2.73 (m, 1 H) 2.54 - 2.65 (m, 3 H) 2.26 (m, 1 H) 1.50 (t, *J* = 7.2 Hz, 3 H) 0.69 (m, 1 H) 0.44 (m, 1 H).

[0272] Intermediates for Examples 16-17

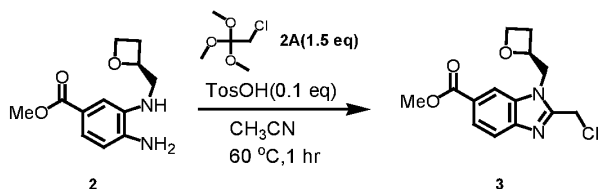


[0273] Preparation of Methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (2)



[0274] To a solution of methyl (S)-4-nitro-3-((oxetan-2-ylmethyl)amino)benzoate (0.5 g, 1.88 mmol, 1 eq) in THF (10 mL) was added Pd/C (0.1 g, 751 μmol, 10% purity) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (15 Psi) at 20 °C for 4 h. TLC indicated starting material was consumed completely and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to provide product as a colorless oil (400 mg, 1.69 mmol, 90.2% yield).

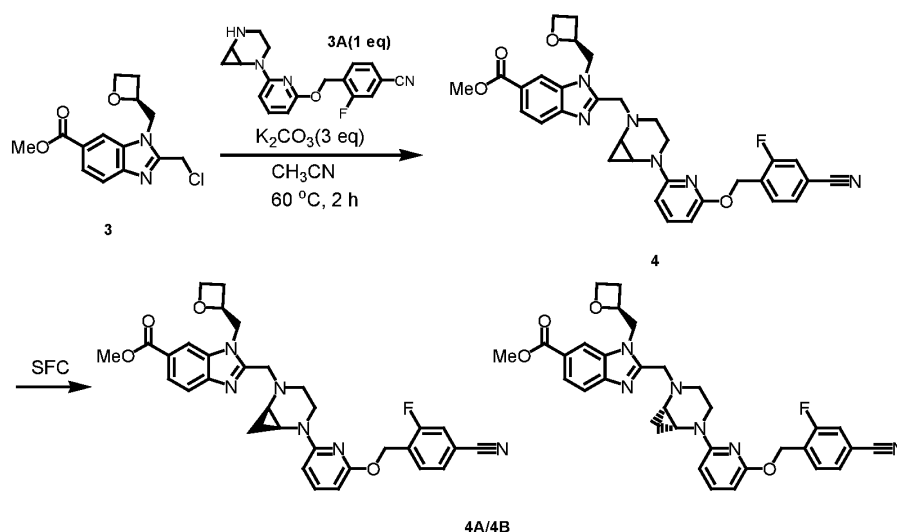
[0275] Preparation of Methyl (S)-2-(chloromethyl)-1-((oxetan-2-ylmethyl)amino)-1H-benzo[d]imidazole-6-carboxylate (3)



[0276] To a solution of methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (0.3 g, 1.27 mmol, 1 eq) in CH₃CN (3 mL) was added TosOH (21.9 mg, 127 μmol, 0.1 eq) and 2-

chloro-1,1,1-trimethoxyethane (206 mg, 1.33 mmol, 179 μ L, 1.05 *eq*). The mixture was stirred at 60 °C for 2 h. TLC showed starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to provide product as a white solid (370 mg, 1.26 mmol, 99% yield); LCMS: RT = 0.555 min, MS cal.: 294.74, $[M+H]^+ = 295.9$; ^1H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.15 (s, 1 H) 8.03 (d, *J* = 8.4 Hz, 1 H) 7.81 - 7.85 (d, *J* = 8.4 Hz, 1 H) 5.22 (m, 1 H) 5.08 (s, 2 H) 4.68 - 4.51 (m, 3 H) 4.35 (m, Hz, 1 H) 3.97 (s, 3 H) 2.83 - 2.72 (m, 1 H) 2.50 - 2.39 (m, 1 H).

[0277] Preparation of Methyl 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (4A and 4B)

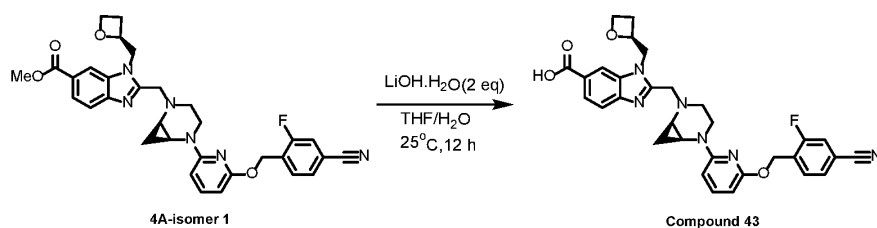


[0278] To a solution of methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (0.37 g, 1.26 mmol, 1 *eq*) in ACN (10 mL) was added K_2CO_3 (522 mg, 3.78 mmol, 3 *eq*) and 4-(((6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (409 mg, 1.26 mmol, 1 *eq*). The mixture was stirred at 60 °C for 2 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with H_2O 30 mL and extracted with EtOAc 30 mL (30 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 0/1) followed by SFC (column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 μ m); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ MEOH]; B%: 50%-50%, 40 min) to provide products **4A-isomer 1** as a white solid (180 mg, 309 μ mol, 36% yield) and **4B-**

isomer 2 as a white solid (180 mg, 309 μmol , 36% yield); LCMS: RT = 2.587 min, MS cal.: 582.64, $[\text{M}+\text{H}]^+ = 583.2$

Example 16 (Synthesis of Compound 43).

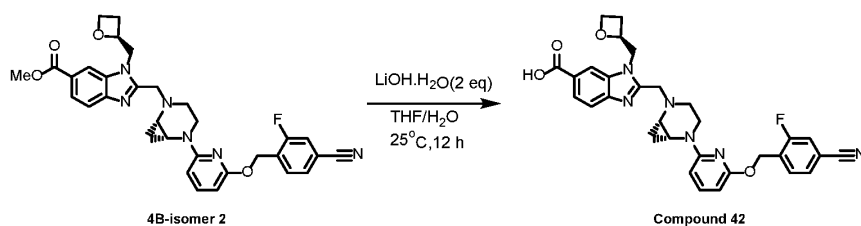
[0279] 2-((5-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0280] To a solution of **4A-isomer 1** (100 mg, 172 μmol , 1 *eq*) in THF (0.6 mL) was added LiOH.H₂O (14.4 mg, 343 μmol , 2 *eq*) in H₂O (0.2 mL). The mixture was stirred at 20 °C for 12 h. TLC indicated starting material was consumed completely and one new spot formed. The mixture was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40 mm*10 μm ; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%-60%, 8 min) to provide product as a white solid (53 mg, 93.2 μmol , 54.3% yield); LCMS: RT = 2.368 min, MS cal.: 568.61, $[\text{M}+\text{H}]^+ = 569.2$; HPLC: RT = 10.178 min, purity: 99.30%; SFC: RT = 1.443 min, ee %: 100%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.32 (s, 1 H) 7.97 (d, *J* = 8.4 Hz, 1 H) 7.67 (d, *J* = 8.4 Hz, 1 H) 7.65 - 7.55 (m, 3 H) 7.45 (t, *J* = 8.0 Hz, 1 H) 6.34 (d, *J* = 8.0 Hz, 1 H) 6.10 (d, *J* = 8.0 Hz, 1 H) 5.43 (s, 2 H) 5.24 (m, 1 H) 4.71 (m, 1 H) 4.66 - 4.59 (m, 1 H) 4.46 (m, 1 H) 4.29 (d, *J* = 13.6 Hz, 1 H) 4.15 - 4.09 (m, 1 H) 4.06 (d, *J* = 13.6 Hz, 1 H) 3.07 - 2.97 (m, 1 H) 2.84 - 2.64 (m, 4 H) 2.56 - 2.46 (m, 1 H) 2.42 - 2.33 (m, 1 H) 0.74 - 0.65 (m, 1 H) 0.48 - 0.40 (m, 1 H).

Example 17 (Synthesis of Compound 42).

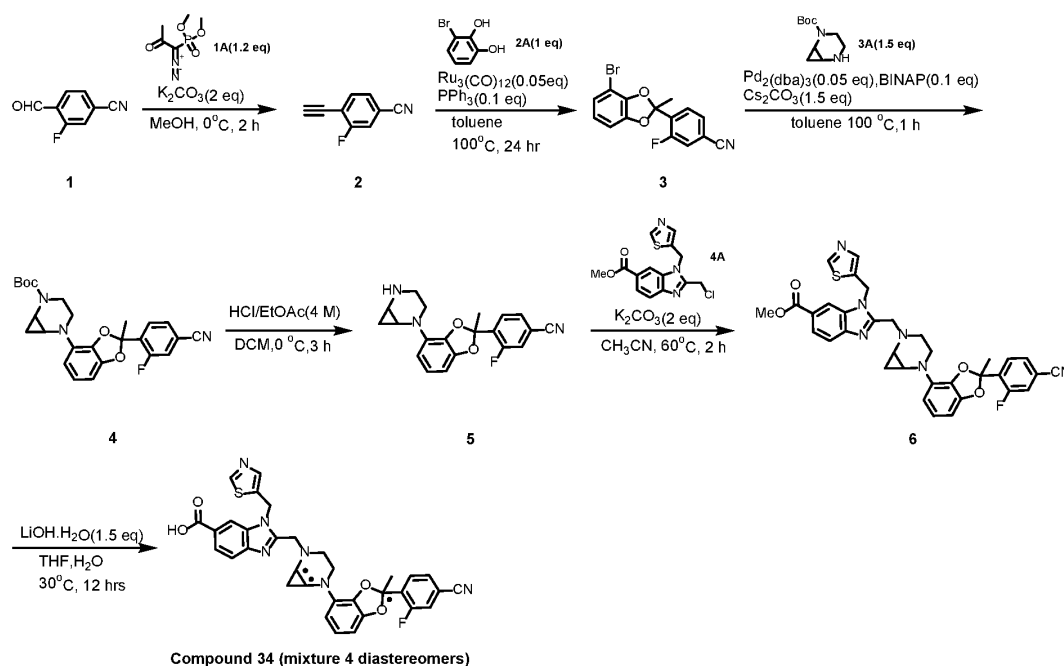
[0281] 2-((5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



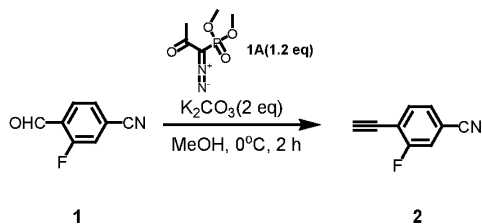
[0282] To a solution of **4B-isomer 2** (100 mg, 172 μ mol, 1 eq) in THF (1.5 mL) was added LiOH.H₂O (14.41 mg, 343 μ mol, 2 eq) in H₂O (0.3 mL). The mixture was stirred at 25 °C for 12 h. TLC indicated starting material was consumed completely. Adjust the solution to neutral with citric acid and concentrate solution. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40 mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 15%-45%, 8 min) to provide product as a white solid (31.9 mg, 56.0 μ mol, 32.6% yield); LCMS: RT = 1.824 min, MS cal.: 568.61, [M+H]⁺ = 569.2; HPLC: RT = 10.196 min, purity: 97.65%; SFC: RT = 1.916 min, ee %: 99.14%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.33 (s, 1 H) 8.00 (d, *J* = 8.4 Hz, 1 H) 7.71 (d, *J* = 8.4 Hz, 1 H) 7.69 - 7.63 (m, 1 H) 7.60 - 7.53 (m, 2 H) 7.48 - 7.45 (m, 1 H) 6.33 (d, *J* = 7.2 Hz, 1 H) 6.11 (d, *J* = 7.2 Hz, 1 H) 5.43 (s, 2 H) 5.27-5.25 (m, 1 H) 4.90-4.88 (m, 1 H) 4.75-4.73 (m, 1 H) 4.64-4.61 (m, 1 H) 4.50-4.48 (m, 1 H), 4.18 (s, 1 H) 4.17-4.15 (m, 1 H) 3.10-4.25 (m, 1 H) 2.73-2.77 (m, 3 H) 2.65-2.62 (m, 1 H) 4.50-4.48 (m, 1 H) 2.55 - 2.52 (m, 1 H) 2.45 - 2.49 (m, 1 H) 0.74-0.69 (m, 1 H) 0.47-0.44 (m, 1 H).

Example 18 (Synthesis of Compound 34).

[0283] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid

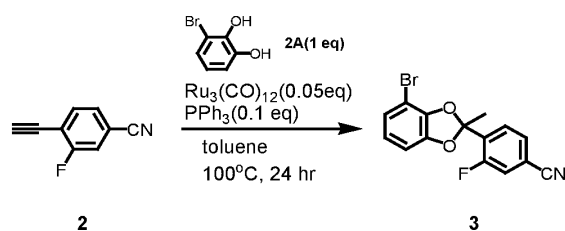


[0284] Preparation of 4-Ethynyl-3-fluorobenzonitrile (2)



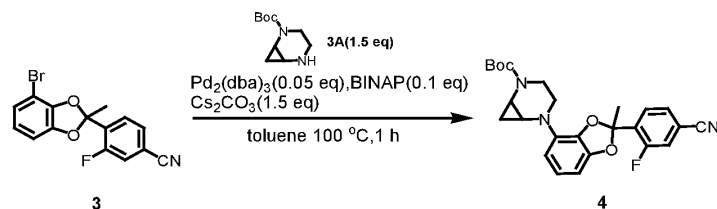
[0285] A mixture of **3-fluoro-4-formylbenzonitrile** (20 g, 134 mmol, 1 eq), **dimethyl (1-diazo-2-oxopropyl)phosphonate** (38.6 g, 201 mmol, 1.5 eq) K_2CO_3 (27.8 g, 201 mmol, 1.5 eq) in MeOH (200 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 2 h under N_2 atmosphere. TLC (Petroleum ether/Ethyl acetate = 5/1 R_f = 0.55) indicated starting material was consumed completely. The combined reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 0/1) to provide product as a white solid (12 g, 82.7 mmol, 61.7% yield).

[0286] Preparation of 4-(4-Bromo-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (3)



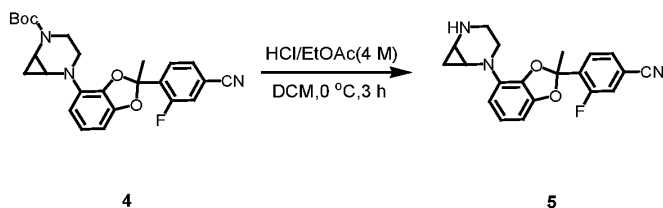
[0287] A mixture of 4-ethynyl-3-fluorobenzonitrile (15.6 g, 82.7 mmol, 1 eq), 3-bromobenzene-1,2-diol (12 g, 82.7 mmol, 1 eq), PPh₃ (2.17 g, 8.27 mmol, 0.1 eq), Ru₃(CO)₁₂ (2.64 g, 4.13 mmol, 0.05 eq) in toluene (120 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 24 h under N₂ atmosphere. HPLC showed the starting material was consumed completely. The combined reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The crude product was purified by reversed-phase HPLC (column: Welch Xtimate C18 250*100mm#10μm; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 50%-85%, 20 min to provide product as a black oil (13 g, 38.9 mmol, 47% yield).

[0288] Preparation of tert-Butyl 5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (4)



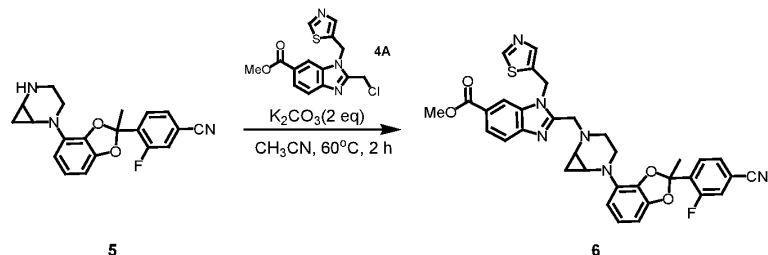
[0289] A mixture of tert-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (11.1 g, 56.1 mmol, 1.5 eq) 4-(4-bromo-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (12.5 g, 37.4 mmol, 1 eq) Cs₂CO₃ (18.3 g, 56.1 mmol, 1.5 eq) BINAP (2.33 g, 3.74 mmol, 0.1 eq) Pd₂(dba)₃ (1.71 g, 1.87 mmol, 0.05 eq) in toluene (120 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 1 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. TLC (Petroleum ether/Ethyl acetate=3:1 R_f=0.4) showed the starting material was consumed completely. The combined reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 0/1) to provide product as a yellow solid (5.6 g, 12.4 mmol, 33.2% yield); LCMS: RT =2.670 min, MS cal.: 451.5, [M-55]⁺ = 396.1.

[0290] Preparation of 4-(4-(2,5-Diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (5)



[0291] A mixture of tert-butyl 5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (334 mg, 740 μ mol, 1 eq) and HCl/EtOAc (4 M, 1.67 mL, 9.03 eq), in DCM (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 1 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated to give the crude product as a white solid (260 mg, crude); LCMS: RT =0.579 min, MS cal.: 351.3, [M+H]⁺ = 352.1.

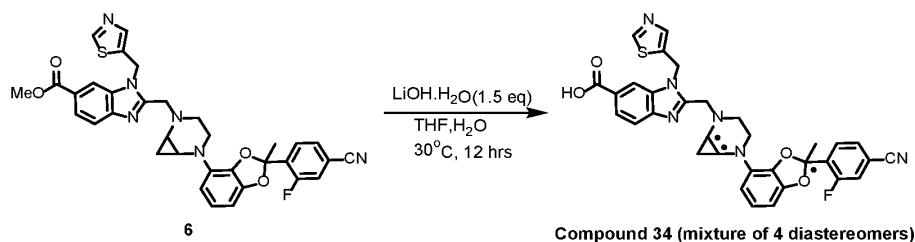
[0292] Preparation of Methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (6)



[0293] A mixture of 4-(4-(2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (238 mg, 740 μ mol, 1 eq), methyl 2-(chloromethyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (260 mg, 740 μ mol, 1 eq), K₂CO₃ (307 mg, 2.22 mmol, 3 eq) in ACN (5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60 °C for 2 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The combined reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic phase was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 0/1) to provide product as a white solid (330 mg, 518 μ mol, 70% yield); LCMS: RT =0.754 min, MS cal.: 636.70, [M+H]⁺ = 637.1; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.76 (s, 1 H) 8.15 (s, 1 H) 8.15 - 8.05

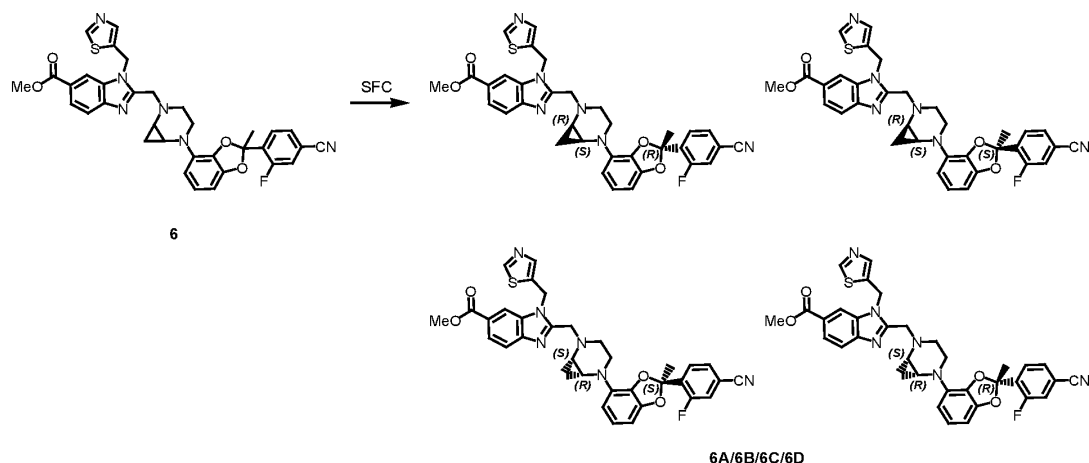
(d, $J = 8.4$ Hz, 1 H) 7.91 (s, 1 H) 7.81-7.66 (m, 2 H) 7.47 - 7.42 (m, 1 H) 7.41 - 7.34 (m, 1 H) 6.77 (m, 1 H) 6.49 (m, 1 H) 6.40 (m, 1 H) 5.95 (m, 2 H) 4.19 - 4.08 (m, 1 H) 4.06 - 4.00 (m, 1 H) 3.99 - 3.92 (m, 3 H) 3.86 - 3.66 (m, 1 H) 3.44 - 3.30 (m, 1 H) 2.96 - 2.83 (m, 2 H) 2.65 - 2.42 (m, 2 H) 2.01 (s, 3 H) 0.59 - 0.78 (m, 2 H).

[0294] Preparation of 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid (Compound 34)



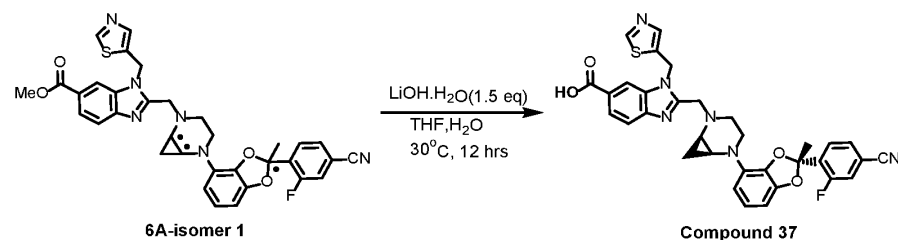
[0295] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (330 mg, 518 μ mol, 1 eq), LiOH.H₂O (30.5 mg, 726 μ mol, 1.4 eq) in THF (2.8 mL) H₂O (1.2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%:25%-55%, 8 min) to provide product as a white solid (25.3 mg, 37.3 μ mol, 7.2% yield, 92% purity); LCMS: RT =1.882 min, MS cal.: 622.8, [M+H]⁺ = 623.2; HPLC: RT =11.63 min, purity: 91.76%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.94 (d, $J = 9.6$ Hz, 1 H) 8.26 (s, 1 H) 8.06 (s, 1 H) 8.01-7.97 (m, 1 H) 7.80 - 7.67 (m, 2 H) 7.64 - 7.53 (m, 2 H) 6.69 - 6.77 (m, 1 H) 6.50 (m, 1 H) 6.31 - 6.36 (m, 1 H) 5.99 (s, 2 H) 4.24 - 4.14 (m, 1 H) 4.13 - 4.03 (m, 1 H) 3.80 - 3.71 (m, 1 H) 3.29 - 3.23 (m, 1 H) 2.95 - 2.74 (m, 2 H) 2.67 - 2.43 (m, 2 H) 2.05 (s, 3 H) 0.74 - 0.50 (m, 2 H).

[0296] Intermediates for Examples 19-22



Example 19 (Synthesis of Compound 37).

[0297] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid

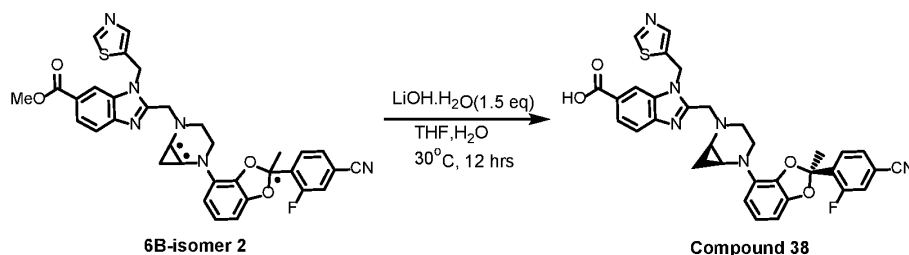


[0298] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (90 mg, 141 μmol , 1 eq), LiOH.H₂O (8.90 mg, 212 μmol , 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-60%, 8 min) to provide product as a white solid (21.2 mg, 34.1 μmol , 24.1% yield); LCMS: RT =1.733 min, MS cal.: 622.68, [M+H]⁺ = 623.2; HPLC: RT =11.744 min, purity: 94.48%; SFC: RT =5.660 min, purity: 100.00%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.97 (s, 1 H) 8.27 (s Hz, 1 H) 8.06 (s, 1 H) 7.99 (d, *J* = 8.4 Hz, 1 H) 7.78 (t, *J* = 7.6 Hz, 1 H) 7.70 (d, *J* = 8.4 Hz, 1 H) 7.66 - 7.54 (m, 2 H) 6.69 - 6.78 (m, 1 H) 6.52 - 6.48 (m, 1 H) 6.36 -

6.33 (m, 1 H) 5.99 (s, 2 H) 4.22-4.16 (m, 1 H) 4.12 - 4.07 (m, 1 H) 3.80-3.73 (m, 1 H) 3.29 - 3.24 (m, 1 H) 2.91 (m, 1 H) 2.80 (m, 1 H) 2.64 - 2.50 (m, 2 H) 2.03 (s, 3 H) 0.63 - 0.55 (m, 2 H).

Example 20 (Synthesis of Compound 38).

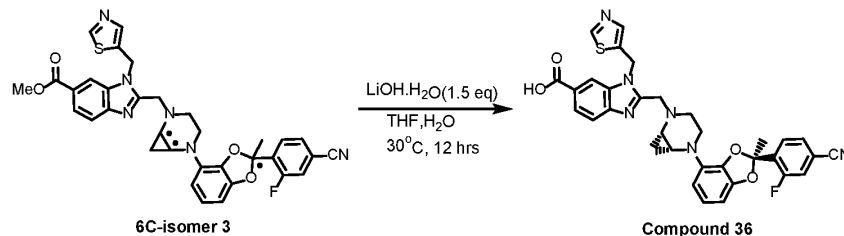
[0299] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0300] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (50 mg, 78.5 μ mol, 1 eq), LiOH.H₂O (4.94 mg, 118 μ mol, 1.5 eq) in H₂O (0.1 mL) THF (0.4 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. 71% of desired compound was detected by LC-MS. Adjust the solution to neutral with citric acid and concentrate solution. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-60%, 8 min) to provide product as a white solid (17.5 mg, 28.1 μ mol, 35.7% yield); LCMS: RT =1.722 min, MS cal.: 622.68, [M+H]⁺ = 623.2; HPLC: RT =11.691min, purity: 91.87%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.93 (s, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.78 - 7.68 (m, 2H), 7.63 - 7.54 (m, 2H), 6.77 - 6.71 (m, 1H), 6.52 (m, 1H), 6.37 - 6.32 (m, 1H), 5.99 (s, 2H), 4.24 - 4.16 (d, *J* = 13.6 Hz, 1H), 4.11 - 4.04 (d, *J* = 13.6 Hz, 1H), 3.79 - 3.71 (m, 1H), 2.87 - 2.75 (m, 2H), 2.67 - 2.60 (m, 1H), 2.48 (m, 1H), 2.02 (s, 3H), 0.72 - 0.60 (m, 2H).

Example 21 (Synthesis of Compound 36).

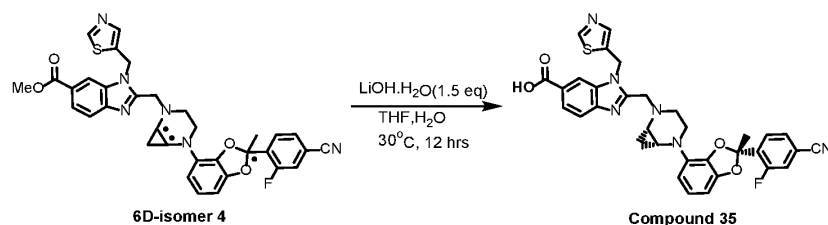
[0301] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0302] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (110 mg, 173 μ mol, 1 eq), LiOH.H₂O (10.9 mg, 259 μ mol, 1.5 eq) in THF (0.7 mL) H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 12 h under N₂ atmosphere. TLC showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 35%-65%, 8 min) to provide product as a white solid (15.2 mg, 24.4 μ mol, 14.1% yield); LCMS: RT =1.733min, MS cal.: 622.68, [M+H]⁺ = 623.2; HPLC: RT =11.770 min, purity: 93.95%; SFC: RT =5.825 min, purity: 100.00%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.92 (s, 1 H) 8.26 (s, 1 H) 8.06 (s, 1 H) 7.99 (d, *J* = 8.4 Hz, 1 H) 7.77 - 7.68 (m, 2 H) 7.61 - 7.454 (m, 2 H) 6.76 - 6.71 (m, 1 H) 6.51 (m, 1 H) 6.34 (m, 1 H) 5.98 (s, 2 H) 4.22 - 4.16 (m, 1 H) 4.10 - 4.04 (m, 1 H) 3.79 - 3.71 (m, 1 H) 3.29 - 3.23 (m, 1 H) 2.85 - 2.76 (m, 2 H) 2.66 - 2.60 (m, 1 H) 2.50 - 2.44 (m, 1 H) 2.02 (s, 3 H) 0.71 - 0.60 (m, 2 H).

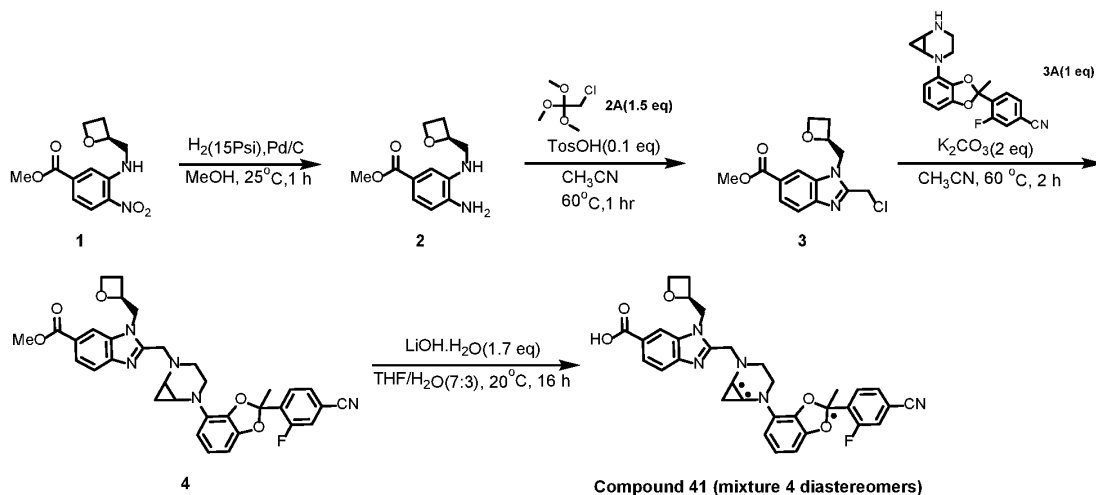
Example 22 (Synthesis of Compound 35).

[0303] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid

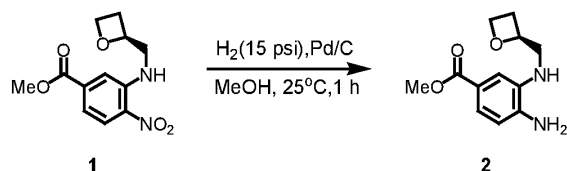


[0304] To a solution of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (100 mg, 157 μ mol, 1 eq) in THF (0.7 mL) was added LiOH.H₂O (9.89 mg, 236 μ mol, 1.5 eq) in H₂O (0.3 mL). The mixture was stirred at 20 °C for 12 h. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8 min) to provide product as a white solid (34.6 mg, 55.5 μ mol, 35.3% yield); LCMS: RT = 2.118 min, MS cal.: 622.68, [M+H]⁺ = 623.2; HPLC: RT = 11.544 min, purity: 93.04%; SFC: RT = 1.914 min, purity: 100.00%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.96 (s, 1 H) 8.27 (s, 1 H) 8.14 (s, 1 H) 8.00 (dd, *J* = 8.4 Hz, 1 H) 7.78 (t, *J* = 7.6 Hz, 1 H) 7.70 (d, *J* = 8.4 Hz, 1 H) 7.66 - 7.53 (m, 2 H) 6.78 - 6.67 (m, 1 H) 6.50 (m, 1 H) 6.41 - 6.30 (m, 1 H) 6.00 (s, 2 H) 4.30 - 4.04 (m, 2 H) 3.81 - 3.70 (m, 1 H) 3.29 - 3.24 (m, 1 H) 2.98 - 2.88 (m, 1 H) 2.85 - 2.73 (m, 1 H) 2.65 - 2.43 (m, 2 H) 2.04 (s, 3 H) 0.67 - 0.53 (m, 2 H).

Example 23 (Synthesis of Compound 41) 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers

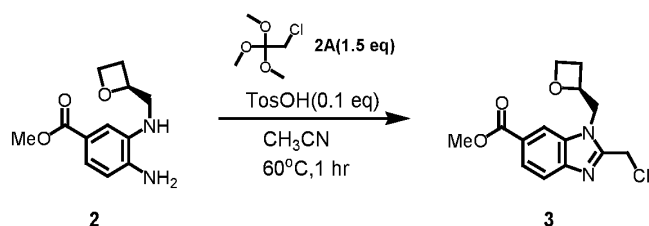


[0305] Preparation of Methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (2)



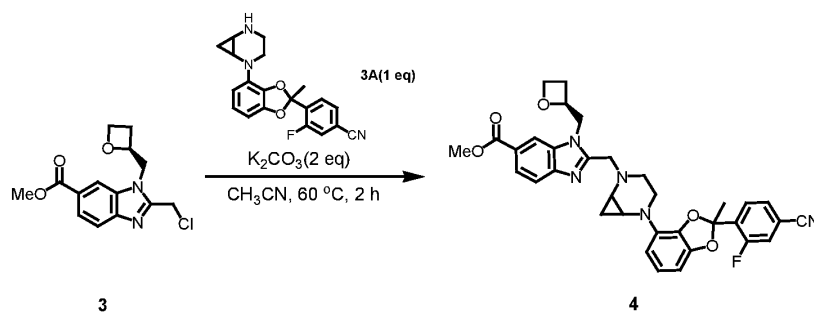
[0306] To a solution of methyl (S)-4-nitro-3-((oxetan-2-ylmethyl)amino)benzoate (500 mg, 1.88 mmol, 1 eq) in MeOH (5 mL) was added Pd/C (10%, 200 mg) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (15 Psi.) at 25°C for 1 h. TLC indicated starting material was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction solution was filtered and the filtrate was concentrated to provide product (400 mg, 1.69 mmol, 90.2% yield) as a white solid.

[0307] Preparation of Methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (3)



[0308] A mixture of methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (300 mg, 1.27 mmol, 1 eq), 2-chloro-1,1,1-trimethoxyethane (393 mg, 2.54 mmol, 341 μ L, 2 eq), TosOH (43.7 mg, 254 μ mol, 0.2 eq) in CH₃CN (3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60°C for 1 h under N₂ atmosphere. TLC indicated starting material was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to give product as a white solid (350 mg, 1.19 mmol, 93.5% yield); LCMS: RT = 1.590 min, MS cal.: 294.74, [M+H]⁺ = 295.0.

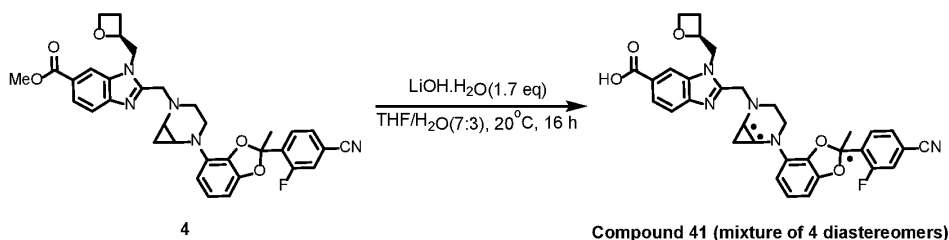
[0309] Preparation of Methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (4)



[0310] A mixture of methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (247 mg, 840 μ mol, 1 eq), 4-(4-(2,5-

diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (295 mg, 840 μ mol, 1 eq), K_2CO_3 (232 mg, 1.68 mmol, 2 eq) in ACN (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60°C for 2 h under N_2 atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O 50 mL and extracted with EtOAc 150mL (50mL *3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 0/1) to provide product as a white solid (250 mg, 410 μ mol, 49% yield); **LCMS**: RT = 2.624 min, MS cal.: 609.66, $[M+H]^+ = 610.2$.

[0311] Preparation of 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers (Compound 41)

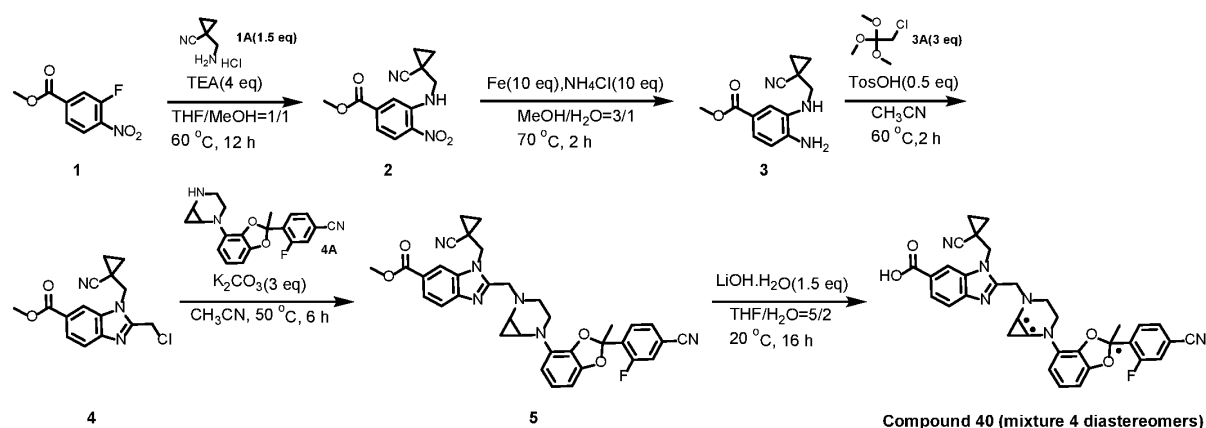


[0312] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (150 mg, 246 μ mol, 1 eq), $LiOH \cdot H_2O$ (17.6 mg, 418 μ mol, 1.7 eq) in THF (1.2 mL) and H_2O (0.3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20°C for 16 h under N_2 atmosphere. LC-MS showed 22% of starting material remained. Several new peaks were shown on LC-MS and 62% of desired compound was detected. Adjust the solution to neutral with citric acid and concentrated. The residue was purified by prep-HPLC (neutral condition column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 20%-60%, 8 min) to provide product as a white solid (30 mg, 50.4 μ mol, 20.5% yield) was obtained; **LCMS**: RT = 1.865 min, MS cal.: 595.63, $[M+H]^+ = 596.3$; **HPLC**: RT = 10.534 min, purity: 96.05%; ^1H NMR (400 MHz, METHANOL- d_4) δ = 8.33 (s, 1 H) 7.97 (d, J = 8.4 Hz, 1 H) 7.77-7.70 (m, 1 H) 7.68 (d, J = 8.4 Hz, 1 H) 7.66-7.60 (m, 1 H) 7.55 (d, J = 8.0 Hz, 1 H) 6.73-6.72 (m, 1 H) 6.53-6.49 (m, 1 H) 6.35-6.32 (m, 1 H) 5.26-5.24 (m, 1 H) 4.90-4.89 (m, 1 H) 4.74-4.70 (m, 1 H) 4.64-4.62 (m, 1 H) 4.47-4.46 (m, 1 H) 4.28-4.26 (m, 0.5 H) 4.17-4.18

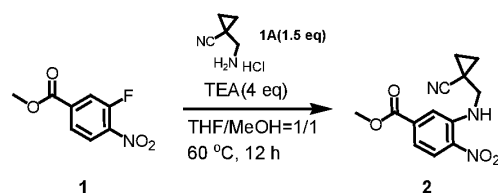
(m, 1 H) 4.10-4.05 (m, 0.5 H) 3.706-3.7 (m, 1 H) 3.33-3.31 (m, 1 H) 2.80-2.78 (m, 4 H) 2.55-2.51 (m, 2 H) 2.03-2.01 (d, $J = 4.8$ Hz, 3 H) 0.69-0.52 (m, 2 H).

Example 24 (Synthesis of Compound 40).

[0313] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers



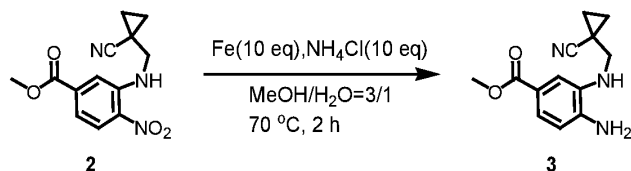
[0314] Preparation of Methyl 3-(((1-cyanocyclopropyl)methyl)amino)-4-nitrobenzoate (2)



[0315] A mixture of methyl 3-fluoro-4-nitrobenzoate (1.90 g, 9.55 mmol, 1 eq), 1-(aminomethyl)cyclopropane-1-carbonitrile (1.9 g, 14.3 mmol, 1.5 eq), TEA (3.87 g, 38.2 mmol, 5.32 mL, 4 eq) in THF (10 mL) and MeOH (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60°C for 12 h under N_2 atmosphere. TLC (Petroleum ether/Ethyl acetate = 3/1, $R_f = 0.46$) indicated starting material was consumed completely and one new spot formed. The reaction was clean according to TLC. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL*3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 100/1 to 0/1) to provide product as a yellow solid (2.5 g, 9.08 mmol, 95.07% yield); LCMS: RT = 1.948 min, MS cal.: 275.26, $[M+H]^+ = 276.2$; ^1H NMR (400 MHz, $CHCl_3$ -d) δ = 8.25 (d, $J = 8.8$ Hz, 1H), 8.15 (br s, 1H), 7.58 (s, 1H), 7.35

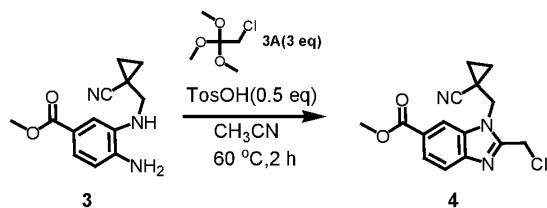
(d, $J = 8.8$ Hz, 1H), 4.01 (s, 3H), 3.57 (d, $J = 5.6$ Hz, 2H), 1.48 - 1.42 (m, 2H), 1.14 - 1.08 (m, 2H).

[0316] Preparation of Methyl 4-amino-3-(((1-cyanocyclopropyl)methyl)amino)benzoate (3)



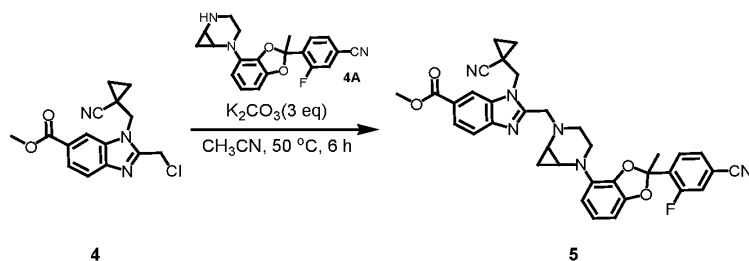
[0317] A mixture of methyl 3-(((1-cyanocyclopropyl)methyl)amino)-4-nitrobenzoate (2.5 g, 9.08 mmol, 1 eq), Fe (5.07 g, 90.8 mmol, 10 eq), NH₄Cl (4.86 g, 90.8 mmol, 10 eq) in H₂O (8 mL) and MeOH (24 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 70°C for 2 h under N₂ atmosphere. TLC (Petroleum ether/Ethyl acetate = 3/1, $R_f = 0.35$) indicated starting material was consumed completely and one new spot formed. The resulting product was dissolved in MeOH and filtered to remove the insoluble. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to provide product as a yellow solid (1.94 g, 7.91 mmol, 87% yield); LCMS: RT = 1.529 min, MS cal.: 245.28, $[M+H]^+ = 246.1$; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.22 (d, $J = 8.0$ Hz, 1H), 7.04 (s, 1H), 6.56 (d, $J = 8.0$ Hz, 1H), 5.55 (br s, 2H), 4.94 (br t, $J = 5.6$ Hz, 1H), 3.72 (s, 3H), 3.23 (d, $J = 5.6$ Hz, 2H), 1.30 - 1.21 (m, 2H), 1.10 - 1.01 (m, 2H).

[0318] Preparation of Methyl 2-(chloromethyl)-1-(((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate (4)



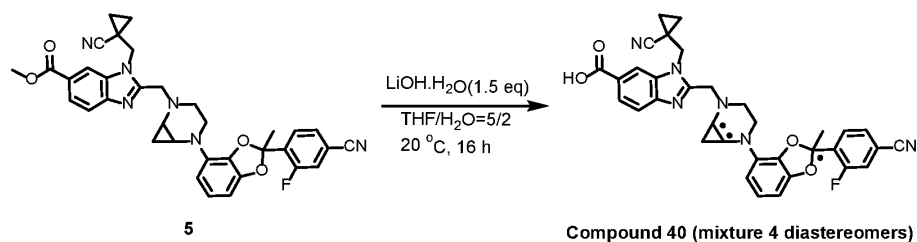
[0319] A mixture of methyl 4-amino-3-(((1-cyanocyclopropyl)methyl)amino)benzoate (300 mg, 1.22 mmol, 1 eq), 2-chloro-1,1,1-trimethoxyethane (567 mg, 3.67 mmol, 493 μ L, 3 eq), TosOH (105 mg, 612 μ mol, 0.5 eq) in ACN (5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60°C for 2 h under N₂ atmosphere. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to provide product as a white solid (372 g, crude); LCMS: RT = 1.588 min, MS cal.: 303.72, $[M+H]^+ = 304.1$.

[0320] Preparation of Methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate (5)



[0321] A mixture of methyl 2-(chloromethyl)-1-((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate (216 mg, 711 μmol , 1 eq), 4-(4-(2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (250 mg, 711 μmol , 1 eq), K_2CO_3 (295 mg, 2.13 mmol, 3 eq) in ACN (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at $50^\circ C$ for 6 h under N_2 atmosphere. LC-MS showed the starting material was consumed completely. TLC (Petroleum ether/Ethyl acetate = 0/1, R_f = 0.47) indicated starting material was consumed completely. The residue was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 100/1 to 0/1) to give product as a yellow solid (240 mg, 388 μmol , 54.5% yield); LCMS: RT = 2.630 min, MS cal.: 618.66, $[M+H]^+ = 619.3$.

[0322] Preparation of 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (Compound 40)

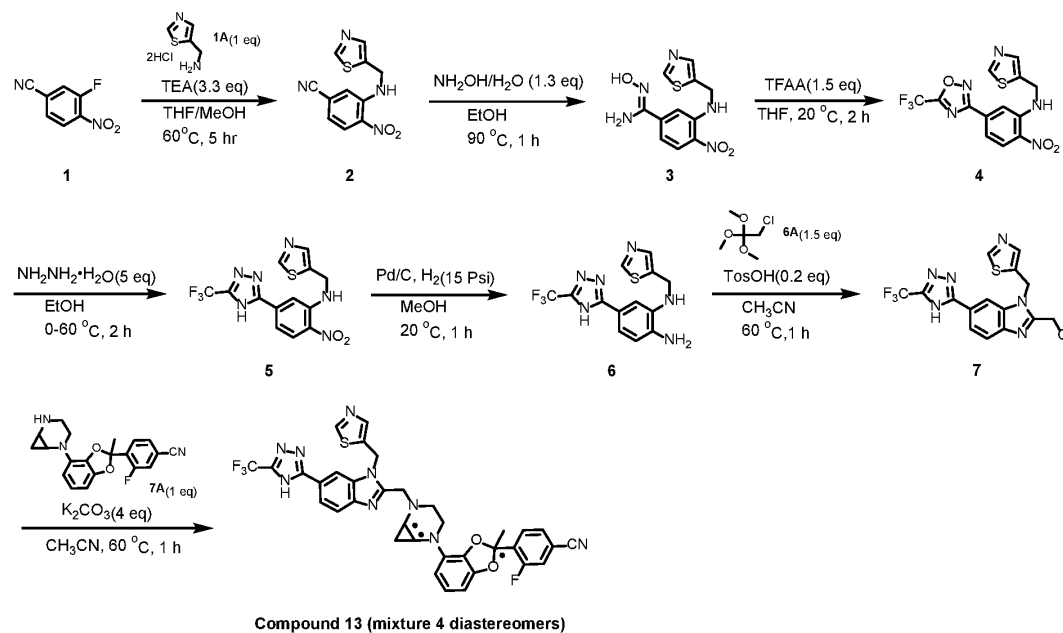


[0323] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((1-cyanocyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate (100 mg, 162 μmol , 1 eq), $LiOH \cdot H_2O$ (10.17 mg, 242.46 μmol , 1.5 eq) in THF (1.5 mL) and H_2O (0.6 mL) was degassed

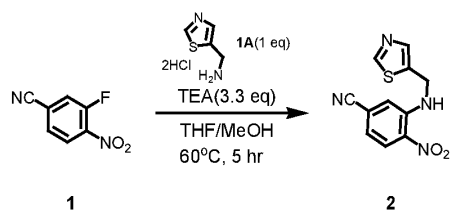
and purged with N₂ for 3 times, and then the mixture was stirred at 20°C for 16 h under N₂ atmosphere. LCMS showed the starting material was consumed completely. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 20%- 50%, 8 min) to provide product as a white solid (18 mg, 29.8 umol, 18.4% yield); LCMS: RT = 2.510min, MS cal.: 604.63, [M+H]⁺ = 605.3; HPLC: purity = 93.9%; ¹H NMR (400 MHz, METHANOL-d₄) δ = 8.35 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 7.65 - 7.59 (m, 1H), 7.58 - 7.54 (m, 1H), 6.73 (m, 1H), 6.51 (m, 1H), 6.37 - 6.31 (m, 1H), 4.81 - 4.77 (m, 2H), 4.36 - 4.26 (m, 1H), 4.20 - 4.13 (m, 1H), 3.83 - 3.71 (m, 1H), 3.40 - 3.33 (m, 1H), 2.90 - 2.84 (m, 2H), 2.68 - 2.60 (m, 1H), 2.58 - 2.45 (m, 1H), 2.02 (d, *J* = 4.6 Hz, 3H), 1.52 - 1.43 (m, 4H), 0.72 - 0.49 (m, 2H).

Example 25 (Synthesis of Compound 13)

[0324] 3-Fluoro-4-(2-methyl-4-(5-((1-(thiazol-5-ylmethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)benzo[d][1,3]dioxol-2-yl)benzonitrile, mixture of 4 diastereomers

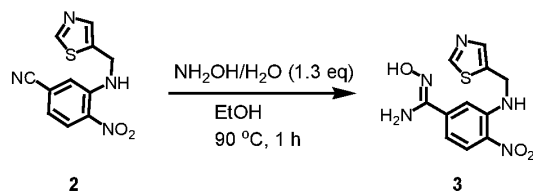


[0325] Preparation of 4-Nitro-3-((thiazol-5-ylmethyl)amino)benzonitrile (2)



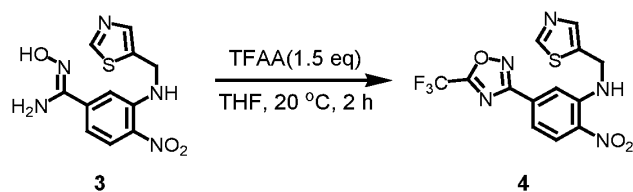
[0326] To a solution of 3-fluoro-4-nitrobenzonitrile (2 g, 12.0 mmol, 1 eq) and thiazol-5-ylmethanamine (2.25 g, 12.0 mmol, 1 eq, 2HCl) in THF (10 mL) and MeOH (10 mL) was added TEA (4.02 g, 39.7 mmol, 5.53 mL, 3.3 eq). The mixture was stirred at 60°C for 5 hours. TLC indicated starting material was consumed completely and one new spot formed. The reaction mixture was poured into H₂O (60 mL) slowly at 0°C and the solid formed. The mixture was stirred for 15 mins and filtered. The solid was collected and under reduced pressure to give product as a yellow solid (3 g, 11.5 mmol, 95.7% yield); LCMS: RT = 0.774 min, MS cal.: 260.3, [M+H]⁺ = 261.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1 H) 8.72 (br t, *J* = 6.0 Hz, 1 H) 8.19 (d, *J* = 8.8 Hz, 1 H) 7.96 (s, 1 H) 7.67 (s, 1 H) 7.06 (d, *J* = 8.8 Hz, 1 H) 4.93 (d, *J* = 6.0 Hz, 2 H).

[0327] Preparation of N'-hydroxy-4-nitro-3-((thiazol-5-ylmethyl)amino)benzimidamide (3)



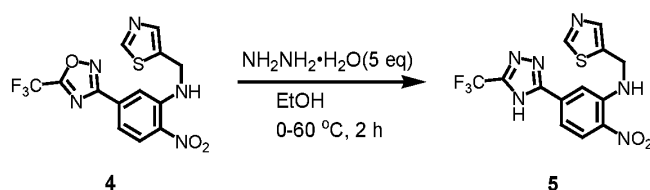
[0328] To a solution of 4-nitro-3-((thiazol-5-ylmethyl)amino)benzonitrile (1.3 g, 4.99 mmol, 1 eq) in EtOH (15 mL) was added hydroxylamine (429 mg, 6.49 mmol, 50% purity, 1.3 eq). The mixture was stirred at 90°C for 1 hour. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was obtained as a yellow solid (1.46 g); LCMS: RT = 1.290 min, MS cal.: 293.3, [M+H]⁺ = 294.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.10 (br s, 1 H) 8.98 (s, 1 H) 8.71 (br t, *J* = 6.0 Hz, 1 H) 8.03 (d, *J* = 9.2 Hz, 1 H) 7.90 (s, 1 H) 7.34 (s, 1 H) 7.05 (d, *J* = 9.2 Hz, 1 H) 6.02 (br s, 2 H) 4.96 (d, *J* = 6.0 Hz, 2 H).

[0329] Preparation of 2-Nitro-N-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)aniline (4)



[0330] To a solution of N'-hydroxy-4-nitro-3-((thiazol-5-ylmethyl)amino)benzimidamide (1.3 g, 4.43 mmol, 1 eq) in THF (8 mL) was added TFAA (1.40 g, 6.65 mmol, 924.76 μ L, 1.5 eq). The mixture was stirred at 20°C for 2 hours. LC-MS showed starting material was consumed completely and desired mass was detected. The residue was diluted with NaHCO₃ (30 mL) and extracted with EtOAc (30 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 30/1 to 1/1) to provide product as a yellow solid (1.5 g, 4.04 mmol, 91% yield); LCMS: RT = 2.324 min, MS cal.: 371.3, [M+H]⁺ = 372.0; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.81 (s, 1 H) 8.45 (br s, 1 H) 8.40 (d, *J* = 8.8 Hz, 1 H) 7.95 (s, 1 H) 7.72 (s, 1 H) 7.48 (d, *J* = 8.8 Hz, 1 H) 4.90 (d, *J* = 5.6 Hz, 2 H).

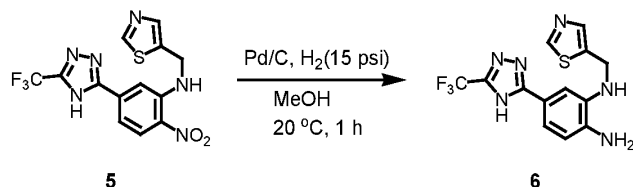
[0331] Preparation of 2-Nitro-N-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)aniline (5)



[0332] To a solution of 2-nitro-N-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)aniline (0.8 g, 2.15 mmol, 1 eq) in EtOH (10 mL) was added NH₂NH₂·H₂O (539 mg, 10.8 mmol, 524 μ L, 5 eq) dropwise at 0-5°C. The mixture was stirred at 60°C for 2 hours. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure at 30°C to give a residue. The residue was diluted with H₂O (20 mL) and extracted with EtOAc/*i*-PrOH = 2/1 (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Phenomenex luna C18 250*50mm*10 μ m; mobile phase: [water (TFA)-ACN]; B%: 25%-55%, 10 min) to provide product as a yellow solid (500 mg, 1.35 mmol, 62.7% yield); LCMS: RT = 1.815 min, MS cal.: 370.3, [M+H]⁺ =

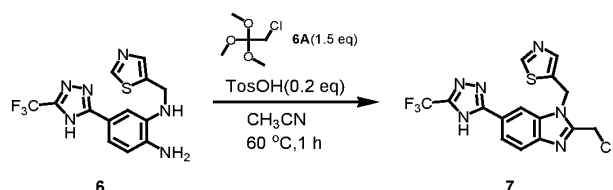
=371.1; ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.03 (s, 1 H) 8.36 (d, J = 8.8 Hz, 1 H) 8.01 (s, 1 H) 7.78 (s, 1 H) 7.35 (d, J = 8.8 Hz, 1 H) 5.02 (s, 2 H).

[0333] Preparation of N1-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)benzene-1,2-diamine (6)



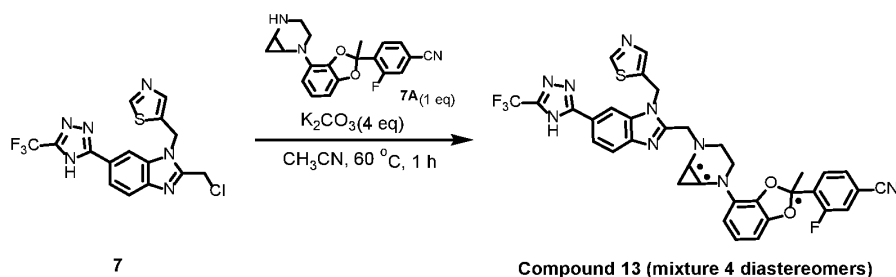
[0334] To a solution of 2-nitro-N-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)aniline (130 mg, 351 μmol , 1 eq) in MeOH (5 mL) was added Pd/C under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 20°C for 1 hour. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to provide product as a yellow solid (119 mg, 350 μmol , 99.6% yield); LCMS: Rt = 1.327 min, MS cal.: 340.3, $[\text{M}+\text{H}]^+ = 341.0$.

[0335] Preparation of 5-((2-(Chloromethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)thiazole (7)



[0336] To a solution of N1-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)benzene-1,2-diamine (0.11 g, 323 μmol , 1 eq) in CH_3CN (1 mL) was added TosOH (11.1 mg, 64.6 μmol , 0.2 eq) and 2-chloro-1,1,1-trimethoxyethane (75 mg, 485 μmol , 65.2 μL , 1.5 eq). The mixture was stirred at 60°C for 1 hour. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to provide product as a yellow solid (120 mg, 301 μmol , 93.1% yield); LCMS: RT = 1.284 min, MS cal.: 398.8, $[\text{M}+\text{H}]^+ = 399.0$.

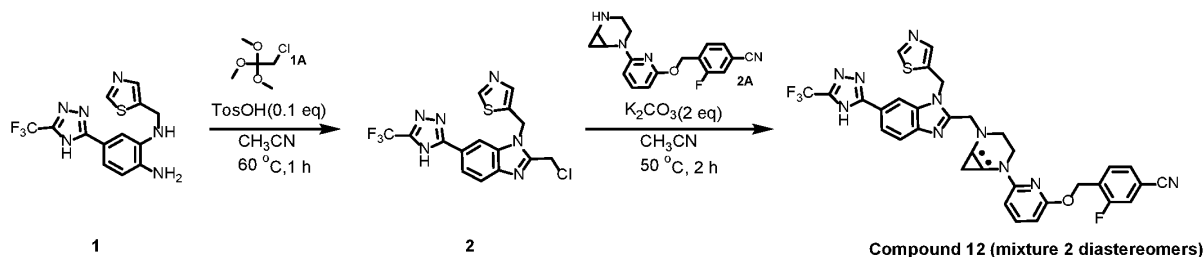
[0337] Preparation of 3-Fluoro-4-(2-methyl-4-(5-((1-(thiazol-5-ylmethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)benzo[d][1,3]dioxol-2-yl)benzonitrile, mixture of 4 diastereomers (Compound 13)



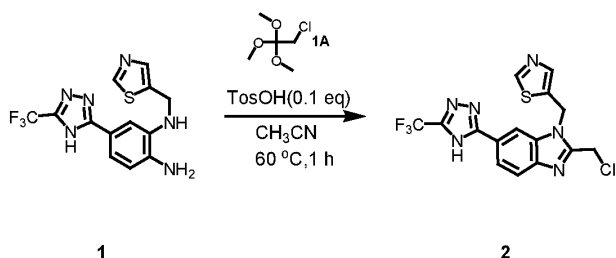
[0338] To a solution of 5-((2-(chloromethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)thiazole (110 mg, 166 μ mol, 60% purity, 1 eq) in CH₃CN (2 mL) was added K₂CO₃ (91.5 mg, 662 μ mol, 4 eq) and 4-(4-(2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (64 mg, 166 μ mol, 1 eq, HCl). The mixture was stirred at 60°C for 1 hour. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Phenomenex C18 75*30mm*3 μ m; mobile phase: [water (NH₃H₂O+NH₄HCO₃)-ACN]; B%: 40%-65%, 8 min) to provide product as a white solid (8.88 mg, 12.4 μ mol, 7.5% yield); LCMS: RT = 2.201 min, MS cal.: 713.7, [M+H]⁺ = 714.2; HPLC: RT = 4.071 min, purity: 87.6%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.94 (d, *J* = 11.4 Hz, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.96 - 7.91 (m, 1H), 7.83 - 7.79 (m, 1H), 7.79 - 7.73 (m, 1H), 7.65 - 7.54 (m, 2H), 6.74 (dt, *J* = 2.8, 8.1 Hz, 1H), 6.54 - 6.48 (m, 1H), 6.35 (dd, *J* = 1.3, 7.8 Hz, 1H), 6.00 (s, 2H), 4.24 - 4.17 (m, 1H), 4.13 - 4.05 (m, 1H), 3.80 - 3.72 (m, 1H), 3.30 - 3.25 (m, 1H), 2.95 - 2.77 (m, 2H), 2.69 - 2.59 (m, 1H), 2.59 - 2.45 (m, 1H), 2.03 (d, *J* = 4.8 Hz, 3H), 0.73 - 0.55 (m, 2H).

Example 26 (Synthesis of Compound 12).

[0339] 3-Fluoro-4-(((6-(5-((1-(thiazol-5-ylmethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)benzonitrile, mixture of 2 diastereomers

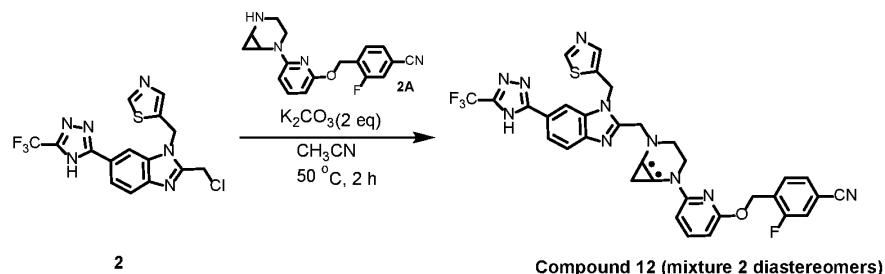


[0340] Preparation of 5-((2-(Chloromethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)thiazole (2)



[0341] A mixture of N1-(thiazol-5-ylmethyl)-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)benzene-1,2-diamine (100 mg, 294 μ mol, 1 eq), 2-chloro-1,1,1-trimethoxyethane (114 mg, 735 μ mol, 98.8 μ L, 2.5 eq), TosOH (5.06 mg, 294 μ mol, 0.1 eq) in CH₃CN (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60°C for 1 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak desired mass was detected. The reaction solution was concentrated to provide product as a white solid (80 mg, 201 μ mol, 68.3% yield); LCMS: RT = 1.140 min, MS cal.: 398.1, [M+H]⁺ = 399.0.

[0342] Preparation of 3-Fluoro-4-(((6-(5-((1-(thiazol-5-ylmethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)benzonitrile (Compound 12)

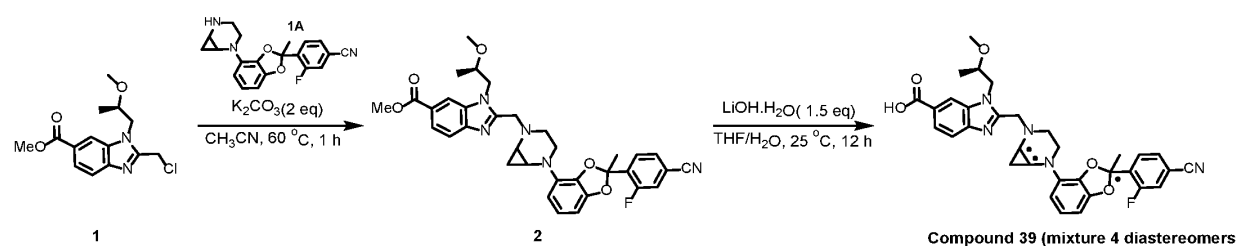


[0343] A mixture of 5-((2-(chloromethyl)-6-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)thiazole (80 mg, 201 μ mol, 1 eq), 4-(((6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (65.1 mg, 201 μ mol, 1 eq), K₂CO₃ (55 mg, 401 μ mol, 2 eq) in ACN (3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 50°C for 2 h under N₂ atmosphere. LCMS showed starting material was consumed completely and one main desired mass was detected. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc 60 mL (20 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD

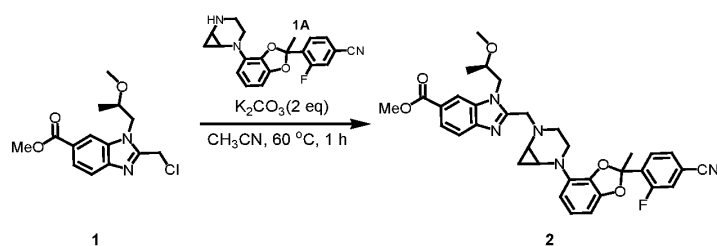
C18 150*40mm*10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-70%, 8 min) to provide product as a white solid (2.73 mg, 3.98 umol, 1.98% yield); LCMS: RT = 2.673 min, MS cal.: 686.1, [M+H]⁺ = 687.2; HPLC: RT = 3.232 min, purity: 91.2%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.91 (s, 1 H) 8.27 (s, 1 H) 8.08 (s, 1 H) 7.94 (d, *J* = 8.4 Hz, 1 H) 7.84 - 7.79 (m, 1 H) 7.64 (t, *J* = 7.6 Hz, 1 H) 7.56 - 7.51 (m, 2 H) 7.49 - 7.44 (m, 1 H) 6.37 (d, *J* = 8.4 Hz, 1 H) 6.14 (d, *J* = 8.4 Hz, 1 H) 5.99 (s, 2 H) 5.44 (s, 2 H) 4.24 - 4.08 (m, 3 H) 2.98 (m, 1 H) 2.84 - 2.74 (m, 2 H) 2.71 - 2.63 (m, 1 H) 2.44 - 2.36 (m, 1 H) 0.75-0.71 (m, 1 H) 0.54 - 0.47 (m, 1 H).

Example 27 (Synthesis of Compound 39)

[0344] 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylic acid



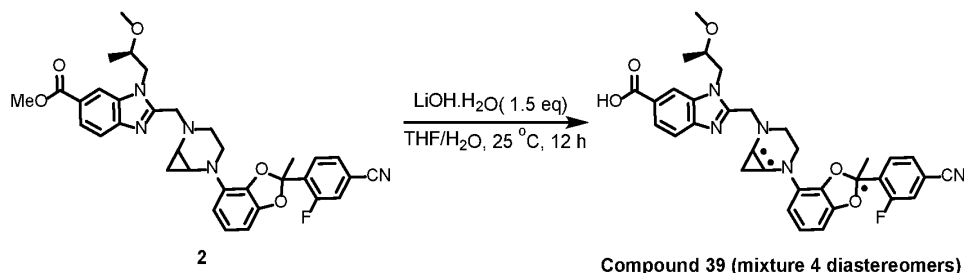
[0345] Preparation of Methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (2)



[0346] A mixture of methyl (R)-2-(chloromethyl)-1-(2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (250 mg, 842 umol, 1.29 eq), 4-(4-(2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-methylbenzo[d][1,3]dioxol-2-yl)-3-fluorobenzonitrile (230 mg, 655 umol, 1 eq), K₂CO₃ (271 mg, 1.96 mmol, 3 eq), in CH₃CN (3 mL) was degassed and purged with N₂ for 3 times at 25°C, and then the mixture was stirred at 60 °C for 1 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure

to remove solvent. The residue was diluted with H₂O 25 mL and extracted with DCM 45 mL (15 mL * 3). The combined organic layers were washed with H₂O 35 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to product as a white solid (200 mg, 327 μ mol, 50% yield); LCMS: RT = 2.437 min, MS cal.: 611.6, [M+H]⁺ = 612.2.

[0347] Preparation of 2-((5-(2-(4-Cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylic acid, mixture of 4 diastereomers (Compound 39)



[0348] A mixture of methyl 2-((5-(2-(4-cyano-2-fluorophenyl)-2-methylbenzo[d][1,3]dioxol-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)methyl)-1-((R)-2-methoxypropyl)-1H-benzo[d]imidazole-6-carboxylate (120 mg, 196 μ mol, 1 eq), LiOH.H₂O (12.4 mg, 294 μ mol, 1.5 eq), in H₂O (0.6 mL)/THF (1.4 mL) was degassed and purged with N₂ for 3 times at 25°C, and then the mixture was stirred at 25 °C for 12 h under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 30%-65%, 8 min) to provide product as a white solid (26 mg, 43.5 μ mol, 22.2% yield); LCMS: RT = 2.427 min, MS cal.: 597.6, [M+H]⁺ = 598.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.19 (s, 1 H) 7.99 - 7.93 (m, 1 H) 7.80 (d, *J*=8.4 Hz, 1 H) 7.76 - 7.69 (m, 2 H) 7.64 (d, *J*=8.4 Hz, 1 H) 6.74 (m, 1 H) 6.45 - 6.53 (m, 1 H) 6.39 (m, 1 H) 4.52 - 4.37 (m, 2 H) 4.23 - 4.13 (m, 1 H) 3.99 - 3.84 (m, 1 H) 3.82 - 3.74 (m, 1 H) 3.58 - 3.73 (m, 1 H) 3.21 (m, 1 H) 3.13 (s, 3 H) 2.89 - 2.60 (m, 3 H) 2.47 - 2.29 (m, 1 H) 2.06 (s, 3 H) 1.27 - 1.17 (m, 3 H) 0.66 - 0.41 (m, 2 H).

Biological Assays

Example B1: GLP-1R cell assay

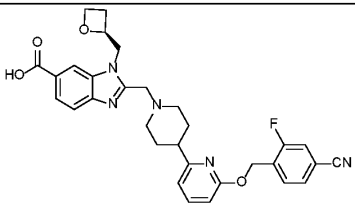
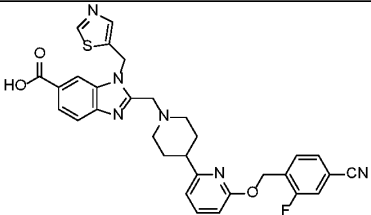
[0349] Stable cell lines expressing high and low GLP-1R surface expression were generated in CHO-K1 cells transfected (Fugene 6) with a puromycin selectable DNA plasmid encoding human GLP-1R receptor (accession number: NM_002062.5) under control of an

EF1A promoter. Transfected cells were seeded into 24-well plates (9,000 cells/well) containing complete medium and incubated in a humidified incubator at 37°C with 5% carbon dioxide. After overnight incubation, medium was replaced with complete medium supplemented with puromycin (6 µg/mL) and refreshed every 2-3 days to select for stably transfected cells. Individual pools of selected cells were expanded prior to analysis for responsiveness to GLP-1 control peptide using a TR-FRET assay to detect cAMP (LANCE Ultra cAMP Assay, Perkin Elmer). Briefly, cells were collected in Versene solution, plated in 384-well plates (1,000 cells/well) and combined with serially diluted GLP-1R control peptide (10 nL) using an acoustic dispenser (ECHO). Plates were incubated for 30 minutes at 25°C prior to the addition of EU-cAMP tracer (5 µL) and Ulight-anti-cAMP (5 µL) reagents to each well, followed by 15 minutes incubation at 25°C. TR-FRET signal was detected using an EnVision Multimode Plate Reader (excitation=320 nm; emission= 615 and 655 nm). Dose-response curves were used to generate EC₅₀ values as a measure of responsiveness to the GLP-1R control peptide. Selected cell lines were monitored for responsiveness over multiple passages to ensure stability. CHO-K1_hGLP-1R_{high}_clone16 and CHO-K1_hGLP-1R_{low}_clone10 showed consistently high and low responsiveness to GLP-1R control peptide, respectively, and were chosen for further analysis to determine relative levels of GLP-1R surface expression. Briefly, GLP-1R expression was analyzed by flow cytometry using a fluorescein-labeled Exendin-4 peptide fluorescent probe (FLEX). Cells were harvested in Versene solution and washed 3-times with PBS+0.5% BSA before incubation with FLEX reagent (10 µM) for 2 hours at room temperature. After incubation, cells were washed 3-times in PBS+0.5% BSA before final resuspension in PBS prior to analysis by flow cytometry to measure FLEX mean fluorescence intensity (MFI) as a measure of GLP-1R expression on the cell surface. Both cell lines showed higher MFI values relative to control CHO-K1 cells, confirming GLP-1R surface expression; CHO-K1_hGLP-1R_{high}_clone16 cells showed significantly higher MFI levels relative to CHO-K1_hGLP-1R_{low}_clone10 cells.

[0350] For compound testing in the CHO-K1_hGLP-1R_{low}_clone10 cell lines, cells were seeded in 384-well plates (1,000 cells/well). Test compounds were serially diluted in DMSO (10-point, 3-fold dilution), added to wells using an ECHO dispenser (10 nL/well) and plates were centrifuged for 1 min and agitated for 2 min at room temperature prior to 30-minute incubation at 25°C. After incubation, Eu-cAMP (5 µL) and Ulight-anti-cAMP (5 µL) reagents were added to each well, followed by centrifugation for 1 minute, agitation for 2 minutes at room temperature, and final incubation of the plates at 25°C for 15 minutes. Plates were read

using an EnVision microplate reader (excitation=320 nm; emission= 615 and 655 nm). Dose-response curves were generated from duplicate wells based on percent activation calculated relative to a control GLP-1 peptide agonist that was run in parallel. EC₅₀ values were determined by fitting percent activation as a function of compound concentration using the Hill equation (XLfit).

[0351] The EC₅₀ values of exemplary compounds in the low expression assay are shown in the table below. The EC₅₀ values are compared to Reference Compound A and Reference Compound B. The compounds tested were compound samples prepared according to the General Procedures described in the Examples section.

Compound No.	GLP-1R Low Expression Cell Assay EC50
 <p>Reference Compound A</p>	D
 <p>Reference Compound B</p>	D
1	D
2	B
4	D
5	C
12	A
13	A
14	C
15	C
16	C
18	D
19	A
20	C
21	C
34	D
35	A
36	C
37	D
38	A
39	B

40	D
41	D
42	B
43	D
44	A
45	D
46	B

A: >100 nM; **B:** 50-100 nM; **C:** 5.0-50 nM; **D:** <5.0 nM

Example B2: Metabolic Stability in Hepatocytes

[0352] Test compounds were incubated in human hepatocytes and stability was assessed from the substrate depilation approach. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to create a 10 mM Stock, and then further diluted to create a 1000× Working Stock of 1 mM with DMSO in 96-well plates for test compounds and the positive control (midazolam). Vials containing cryopreserved hepatocytes were removed from the liquid nitrogen tank and immediately immersed in a 37°C water bath. The vials were shaken gently until the contents had thawed and were then immediately emptied into 48 mL of pre-warmed HT Medium in a 50 mL conical tube. Cells remaining in the vial were resuspended with 1.0 mL of pre-warmed HT Medium and added to the conical tube. The tube was capped and then gently inverted several times to resuspend the hepatocytes. The cell suspension was centrifuged at 50 x g at room temperature for 5 minutes and the supernatant discarded. The cell pellet was loosened by gently swirling the centrifuge tube and was re-suspended in 4 mL of warm Dulbecco's Modified Eagle medium (DMEM). Cell density was determined by a cell counter by Nexcelom, and DMEM medium was added to obtain a target density of 1×10^6 cells/mL. The assay was carried out in 96-well microtiter plates. Test Compounds were incubated at 1 μ M with 1×10^6 cells/mL hepatocytes in DMEM for 0, 30, 60, 120 and 240 minutes. The incubation was carried out with gentle shaking at 37°C under a humid atmosphere of 95% air/5% CO₂. The volume of the incubation mixture was 37 μ L with a final 0.1% DMSO. At each of the time points, the incubation was stopped by adding 150 μ L quenching solution (100% acetonitrile, 0.1% formic acid containing buccetin as an internal standard for positive ESI mode). Subsequently, the mixtures were vortexed for 20 min and centrifuged at 4,000 RPM at 10°C. The supernatant (80 μ L) was transferred to a clean 96-well plate and analyzed by LC-MS/MS. Midazolam at 1 μ M with a final 0.1% DMSO was

included as a positive control to verify assay performance. The percent parent remaining, intrinsic and predicted hepatic clearance and $t_{1/2}$ were calculated. All samples were analyzed by LC-MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Separation was achieved using a Waters Atlantis T3 dC18 reverse phase HPLC column (20 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in 100% acetonitrile (solvent B). Elution conditions are detailed below.

Time (min)	Flow (μ L/min)	%A	%B
0	500	98	2
0.30	500	98	2
1.40	500	2	98
2.20	500	2	98
2.21	500	98	2
3.00	500	98	2

[0353] The ion optics of each test compound were optimized for their declustering potential (DP), collection energy (CE), collision-cell exit potential (CXP) and used in a selected ion monitoring experiment in the positive ion mode. The peak area ratio of each test compound to internal standard was then evaluated for stability. The extent of metabolism was calculated based on the disappearance of the test compound, compared to its initial concentration. The initial rates of clearance of the test compound were calculated using the linear regression plot of semi-log % remaining of the compound versus time. The elimination rate constant (k) of the linear regression plot was then used to determine $t_{1/2}$ and the intrinsic clearance (CL_{int}) using the following formula, where $C_{hepatocyte}$ (million cells/mL) is the cell density of the incubation:

$$\begin{aligned}
 k &= -\text{slope} \\
 t_{1/2} &= 0.693/k \\
 CL_{int} &= k/C_{hepatocyte}
 \end{aligned}$$

[0354] This method of intrinsic clearance determination assumes that the test compound concentration is far below the Michaelis-Menten constant of the compound to its metabolizing enzymes.

[0355] The predicted hepatic clearance (CL_{hep}) was calculated using the well stirred method with the following formula with $CL_{int(in vivo)}$ normalized based on liver weight:

$$\begin{aligned}
 CL_{int(in vivo)} &= CL_{int} \times \text{Hepatocellularity} \times \text{liver weight} \\
 CL_{hep predicted} &= (CL_{int(in vivo)} \times Q_{liver}) / (CL_{int(in vivo)} + Q_{liver})
 \end{aligned}$$

Where Q_{liver} ((ml/min/kg) is Liver Blood Flow

[0356] The relevant physiological parameters of liver weight, blood flow, and hepatocellularity for humans are listed below:

Liver Weight (g liver/kg body weight)	Hepatocellularity (106 cells/g liver)	Liver BloodFlow (Q_{liver} , mL/min/kg)
25.7	135	20.7

[0357] Results are presented in the Table below for the intrinsic clearance (mL/min/kg) and half-life ($t_{1/2}$).

Table 2

Cmpd No.	hHep CL_{int} (mL/min/kg)	hHep $t_{1/2}$ (min)
Reference Compound B	15.5	156
1	11.9	201.8
2	5.01	480
4	14	172
5	7.46	322
14	7.86	306
15	9.24	260
18	17.5	13.8
19	5.01	480
20	6.4	376
40	5.86	411
42	5.01	480
43	7.09	339
44	5.01	480
45	6.46	372

Example B3. Passive Permeability and Efflux Ratio

[0358] Caco-2 cells (clone C2BBel) were obtained from American Type Culture Collection (Manassas, VA). Cell monolayers were grown to confluence on collagen-coated, microporous membranes in 12-well assay plates. Details of the plates and their certification are shown below. The permeability assay buffer was Hanks' balanced salt solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.4. The buffer in the receiver chamber also contained 1% bovine serum albumin. The dosing solution concentration was 5 μM of test article in the assay buffer. Cell monolayers were dosed on the apical side (A-to-B) or basolateral side (B-to-A) and incubated at 37°C with 5% CO_2 in a humidified incubator. Samples were taken from the donor and receiver chambers at 120 minutes. Each determination was performed in

duplicate. The flux of lucifer yellow was also measured post-experimentally for each monolayer to ensure no damage was inflicted to the cell monolayers during the flux period. All samples were assayed by LC-MS/MS using electrospray ionization. The apparent permeability (P_{app}) and percent recovery were calculated as follows:

$$P_{app} = (dC_r/dt) \times V_r / (A \times C_A) \quad (1)$$

$$\text{Percent Recovery} = 100 \times ((V_r \times C_r^{\text{final}}) + (V_d \times C_d^{\text{final}})) / (V_d \times C_N) \quad (2),$$

where, dC_r/dt is the slope of the cumulative receiver concentration versus time in $\mu\text{M s}^{-1}$; V_r is the volume of the receiver compartment in cm^3 ; V_d is the volume of the donor compartment in cm^3 ; A is the area of the insert (1.13 cm^2 for 12-well); C_A is the average of the nominal dosing concentration and the measured 120-minute donor concentration in μM ; C_N is the nominal concentration of the dosing solution in μM ; C_r^{final} is the cumulative receiver concentration in μM at the end of the incubation period; C_d^{final} is the concentration of the donor in μM at the end of the incubation period. Efflux ratio (ER) is defined as $P_{app} \text{ (B-to-A)} / P_{app} \text{ (A-to-B)}$.

Table 3

Compound #	P_{app} (A-to-B)	ER
1	15	2.51
5	27.9	1.71
18	16.8	1.31
34	19.9	1.82
40	17.5	2.27

Example B4: Rat Pharmacokinetics

[0359] Intravenous dosing: Compounds were formulated at 0.5 mg/mL in a solution comprising 5% polyethylene glycol 400 and 95% (12% (w/v) sulfobutyl- β -cyclodextrin in water) (v/v). Formulated compounds were sterile filtered through a 0.22 micron filter before dosing. Compounds were administered to male, 7–11-week-old Sprague-Dawley rats by jugular vein cannula infusion over 30 minutes at a dose of 1 mg/kg.

[0360] Oral dosing: Compounds were formulated at 0.3 mg/mL or 0.6 mg/mL in a solution comprising 5% polyethylene glycol 400 and 95% (12% (w/v) sulfobutyl- β -cyclodextrin in water) (v/v). Formulated compounds were administered to male, 7-11 week old Sprague-Dawley rats by oral gavage at a dose of 10 mL/kg.

[0361] Sample collection: Blood collections of about 0.2 mL per time point were performed from jugular vein or other suitable site of each animal, into pre-chilled commercial EDTA-K2

tubes and placed on wet ice until centrifugation. Blood samples were processed for plasma by centrifugation at approximately 4°C, 3,200 g for 10 min. Plasma was collected and transferred into pre-labeled 96 well plate or polypropylene tubes, quick frozen over dry ice and kept at -60°C or lower until LC-MS/MS analysis.

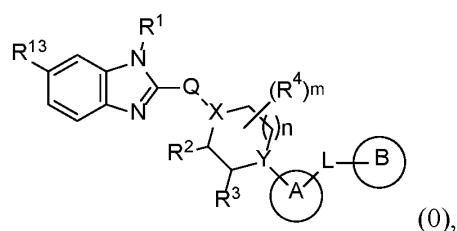
[0362] Data analysis: Plasma concentration versus time data was plotted in graph and analyzed by non-compartmental approaches using the Phoenix WinNonlin 6.3 software program. Related PK parameters were calculated according to dosing route, e.g., CL, V_{dss} and C_0 for intravenous administration, C_{max} , T_{max} or %F for extravascular administration, and $T_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $MRT_{(0-t)}$, $MRT_{(0-inf)}$ for all routes.

Table 4

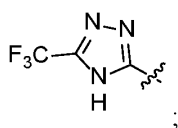
Compound No.	Rat Cmax (ng/mL)	Rat T _{1/2} (h)	Rat AUC (ng.h/mL)
1	34.7 ± 13.7	4.58	71.8 ± 90.3
2	44.1 ± 6.5	2.41	63.5 ± 11.1
4	70 ± 31.99	0.92	86.3 ± 27.2
5	282 ± 4.04	1.31	418 ± 49.6
14	59.3 ± 5.68	0.645	66.8 ± 7.06
15	77.4 ± 16.2	0.597	71.7 ± 16.1
18	89.5 ± 23.6	0.89	84.9 ± 32.2
20	15.5 ± 7.15	0.578	22.9 ± 30
36	19.3 ± 2.70	1.8	20.7 ± 12.6
37	20 ± 7.7	ND	15.8 ± 7.6
38	58.3 ± 9.74	1.6	109 ± 21.5
40	28.3 ± 6.42	2.78	44.2 ± 8.62
43	64.5 ± 17.8	1.19	118 ± 10.0
45	9.62	ND	9.48

Exemplary Embodiments

Exemplary Embodiment No. 1. A compound of Formula (0):



or a pharmaceutically acceptable salt, wherein:



R^{13} is -C(O)OH or

X is N or CR^x, wherein R^x is hydrogen, OH or C₁-C₆ alkyl;

Y is N or CR^y, wherein R^y is hydrogen, OH or C₁-C₆ alkyl;

n is 0 or 1;

Q is selected from the group consisting of -C(R⁷)(R⁸)-, -O-, -N(R⁹)-, and -S-, wherein

R⁷ and R⁸ are independently hydrogen, halogen, or C₁-C₆ alkyl; and

R⁹ is hydrogen or C₁-C₆ alkyl;

R¹ is optionally substituted -C₁-C₆ alkylene or -C₁-C₆ alkylene-R⁵, wherein R⁵ is C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl substituent is independently optionally substituted by halo or CN;

R² and R³ are taken together with the carbon atoms to which they are attached to form an optionally substituted C₃-C₄ cycloalkyl ring; or

R² and R^x, when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted C₃-C₅ cycloalkyl ring, and R³ is hydrogen, oxo, or C₁-C₆ alkyl;

m is 0, 1, 2, or 3;

R⁴ is oxo or C₁-C₆ alkyl;

Ring A is C₆-C₁₄ aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

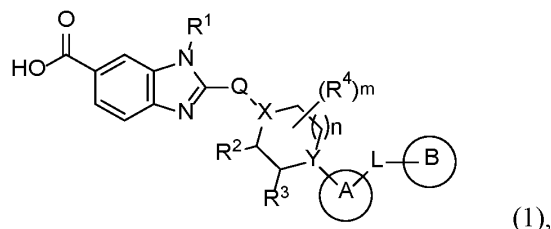
when L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C₁-C₆ alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

R⁶, when present, is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl

optionally substituted by halo or CN, $-\text{OC}_1\text{-C}_6$ alkyl optionally substituted by halo or CN, $-\text{COCH}_3$, $-\text{CONH}_2$, $-\text{S(O)}_2\text{CH}_3$, and phenyl optionally substituted by halo or CN.

Exemplary Embodiment No. 2. A compound of Formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^x , wherein R^x is hydrogen, OH or $\text{C}_1\text{-C}_6$ alkyl, and

Y is N or CR^y , wherein R^y is hydrogen, OH or $\text{C}_1\text{-C}_6$ alkyl;

n is 0 or 1;

Q is selected from the group consisting of $-\text{C(R}^7\text{)(R}^8\text{)}-$, $-\text{O}-$, $-\text{N(R}^9\text{)}-$, and $-\text{S}-$, wherein

R^7 and R^8 are independently hydrogen, halogen, or $\text{C}_1\text{-C}_6$ alkyl, and

R^9 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^1 is $-\text{C}_1\text{-C}_6$ alkylene- R^5 , wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, and $-\text{OC}_1\text{-C}_6$ alkyl, wherein each $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, and $-\text{OC}_1\text{-C}_6$ alkyl substituent is independently optionally substituted by halo or CN;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted $\text{C}_3\text{-C}_4$ cycloalkyl ring; or

R^2 and R^x , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl ring, and R^3 is hydrogen, oxo, or $\text{C}_1\text{-C}_6$ alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or $\text{C}_1\text{-C}_6$ alkyl;

Ring A is $\text{C}_6\text{-C}_{14}$ aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH , CN, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo or OH ;

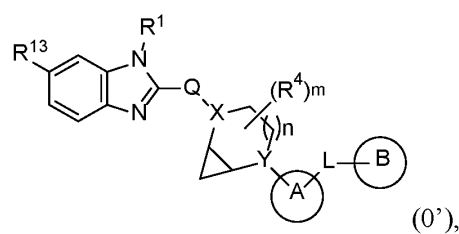
L is a bond, $-\text{O}-$, $\text{C}_1\text{-C}_6$ alkylene, $^*\text{-O-C}_1\text{-C}_6$ alkylene- ** , $^*\text{-C}_1\text{-C}_6$ alkylene- O-^{**} , or $^*\text{-NR}^6\text{-C}_1\text{-C}_6$ alkylene- ** , wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B , and wherein:

when L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C₁-C₆ alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

R⁶, when present, is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl optionally substituted by halo or CN, -OC₁-C₆ alkyl optionally substituted by halo or CN, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl optionally substituted by halo or CN.

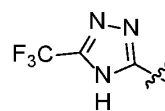
Exemplary Embodiment No. 3. The compound of Exemplary Embodiments No. 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (0'):



or a pharmaceutically acceptable salt thereof.

Exemplary Embodiment No. 4. The compound of Exemplary Embodiments No. 1-3, or a pharmaceutically acceptable salt thereof, wherein R¹³ is -C(O)OH.

Exemplary Embodiment No. 5. The compound of Exemplary Embodiments No. 1-3, or a



pharmaceutically acceptable salt thereof, wherein R¹³ is

Exemplary Embodiment No. 6. The compound of Exemplary Embodiments No. 1-5, or a pharmaceutically acceptable salt thereof, wherein X is N and Y is CR^y.

Exemplary Embodiment No. 7. The compound of Exemplary Embodiments No. 1-5, or a pharmaceutically acceptable salt thereof, wherein X is CR^x and Y is N.

Exemplary Embodiment No. 8. The compound of Exemplary Embodiments No. 1-5, or a pharmaceutically acceptable salt thereof, wherein X is N and Y is N.

Exemplary Embodiment No. 9. The compound of Exemplary Embodiments No. 1-8, wherein n is 0.

Exemplary Embodiment No. 10. The compound of Exemplary Embodiments No. 1-8, or a pharmaceutically acceptable salt thereof, wherein n is 1.

Exemplary Embodiment No. 11. The compound of Exemplary Embodiments No. 1-10, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{C}(\text{R}^7)(\text{R}^8)-$.

Exemplary Embodiment No. 12. The compound of Exemplary Embodiments No. 1-10, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{CH}_2-$.

Exemplary Embodiment No. 13. The compound of Exemplary Embodiments No. 1-10, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{O}-$.

Exemplary Embodiment No. 14. The compound of Exemplary Embodiments No. 1-10, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{N}(\text{R}^9)-$.

Exemplary Embodiment No. 15. The compound of Exemplary Embodiments No. 1-14, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-\text{CH}_2-\text{R}^5$.

Exemplary Embodiment No. 16. The compound of Exemplary Embodiments No. 1-15, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_3 - C_6 cycloalkyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

Exemplary Embodiment No. 17. The compound of Exemplary Embodiment No. 16, or a pharmaceutically acceptable salt thereof, wherein R^5 is cyclopropyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

Exemplary Embodiment No. 18. The compound of Exemplary Embodiments No. 1-15, or a pharmaceutically acceptable salt thereof, wherein R^5 is 4- to 5-membered heterocyclyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

Exemplary Embodiment No. 19. The compound of Exemplary Embodiment No. 18, or a pharmaceutically acceptable salt thereof, wherein R^5 is 4-membered heterocyclyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

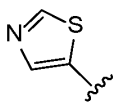
Exemplary Embodiment No. 20. The compound of Exemplary Embodiment No. 19, or a pharmaceutically acceptable salt thereof, wherein R^5 is oxetanyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

Exemplary Embodiment No. 21. The compound of Exemplary Embodiments No. 1-15, or a pharmaceutically acceptable salt thereof, wherein R^5 is 5-membered heteroaryl optionally substituted by halo, $-\text{O}-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

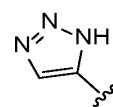
Exemplary Embodiment No. 22. The compound of Exemplary Embodiment No. 21, or a pharmaceutically acceptable salt thereof, wherein R^5 is oxazolyl, triazolyl, thiazolyl or isothiazolyl, each of which is optionally substituted by halo, $-\text{O}-\text{C}_{1-6}$ alkyl, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

Exemplary Embodiment No. 23. The compound of Exemplary Embodiment No. 22, or a pharmaceutically acceptable salt thereof, wherein R⁵ is triazolyl or thiazolyl, each of which is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl.

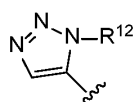
Exemplary Embodiment No. 24. The compound of Exemplary Embodiment No. 23, or a

pharmaceutically acceptable salt thereof, wherein R⁵ is  optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl.

Exemplary Embodiment No. 25. The compound of Exemplary Embodiment No. 23, or a

pharmaceutically acceptable salt thereof, wherein R⁵ is  optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl.

Exemplary Embodiment No. 26. The compound of Exemplary Embodiment No. 23, or a

pharmaceutically acceptable salt thereof wherein R⁵ is , wherein R¹² is C₁₋₆ alkyl.

Exemplary Embodiment No. 27. The compound of Exemplary Embodiment No. 26, or a pharmaceutically acceptable salt thereof, wherein R¹² is methyl.

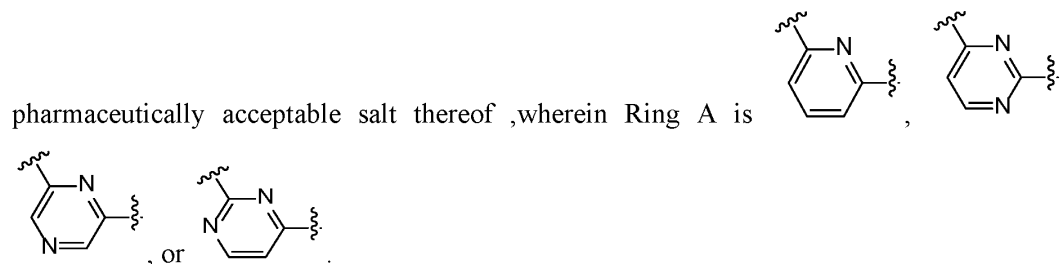
Exemplary Embodiment No. 28. The compound of Exemplary Embodiment No. 26, or a pharmaceutically acceptable salt thereof, wherein R¹² is ethyl.

Exemplary Embodiment No. 29. The compound of Exemplary Embodiments No. 1-28, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 6-membered heteroaryl optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH.

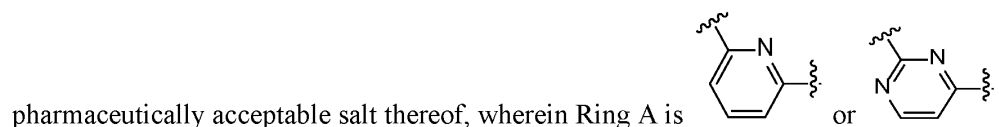
Exemplary Embodiment No. 30. The compound of Exemplary Embodiment No. 29, or a pharmaceutically acceptable salt thereof, wherein Ring A is 6-membered heteroaryl optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH.

Exemplary Embodiment No. 31. The compound of Exemplary Embodiment No. 30, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyridyl, pyrimidinyl, or pyrazinyl, each of which is optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH.

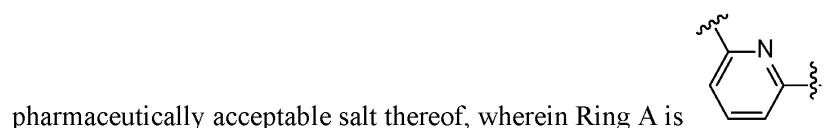
Exemplary Embodiment No. 32. The compound of Exemplary Embodiment No. 31, or a



Exemplary Embodiment No. 33. The compound of Exemplary Embodiment No. 32, or a



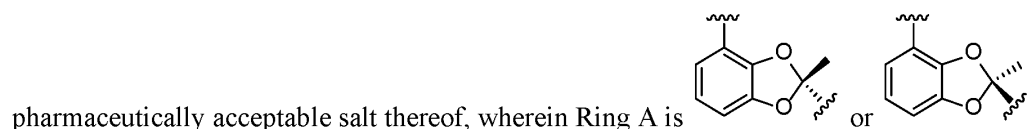
Exemplary Embodiment No. 34. The compound of Exemplary Embodiment No. 33, or a



Exemplary Embodiment No. 35. The compound of Exemplary Embodiments No. 1-28, or a pharmaceutically acceptable salt thereof, wherein Ring A is 10- to 12-membered heterocyclyl or 10- to 12-membered heteroaryl optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH.

Exemplary Embodiment No. 36. The compound of Exemplary Embodiment No. 35, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted benzodioxole.

Exemplary Embodiment No. 37. The compound of Exemplary Embodiment No. 36, or a



Exemplary Embodiment No. 38. The compound of Exemplary Embodiments No. 1-37, or a pharmaceutically acceptable salt thereof, wherein L is *-O-C₁-C₆ alkylene-* optionally substituted by R^L.

Exemplary Embodiment No. 39. The compound of Exemplary Embodiment No. 38, or a pharmaceutically acceptable salt thereof, wherein L is *-O-CH₂-*.

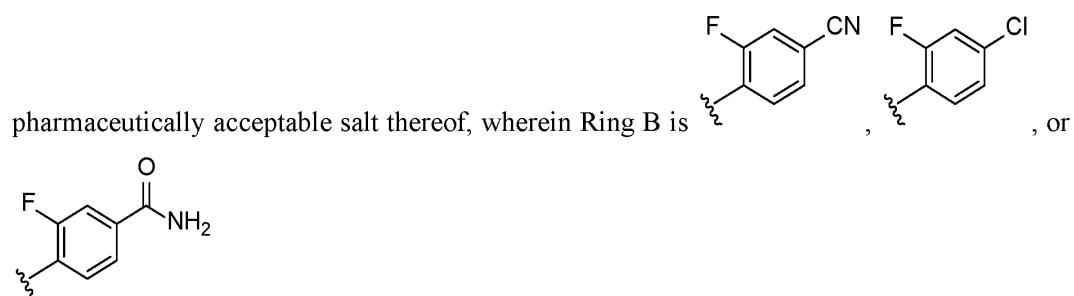
Exemplary Embodiment No. 40. The compound of Exemplary Embodiments No. 1-37, or a pharmaceutically acceptable salt thereof, wherein L is -O-.

Exemplary Embodiment No. 41. The compound of Exemplary Embodiments No. 1-37, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

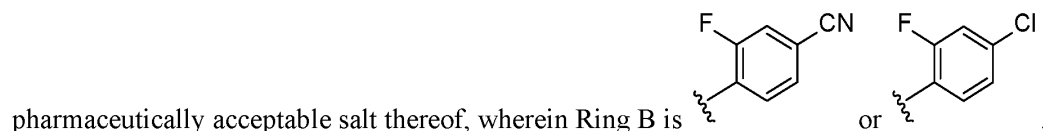
Exemplary Embodiment No. 42. The compound of Exemplary Embodiments No. 1-41, or a pharmaceutically acceptable salt thereof, wherein Ring B is C₆-C₁₄ aryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 43. The compound of Exemplary Embodiment No. 42, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 44. The compound of Exemplary Embodiment No. 43, or a



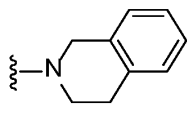
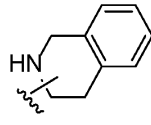
Exemplary Embodiment No. 45. The compound of Exemplary Embodiment No. 44, or a



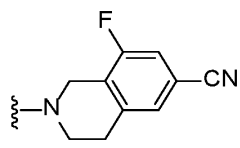
Exemplary Embodiment No. 46. The compound of Exemplary Embodiments No. 1-41, or a pharmaceutically acceptable salt thereof, wherein Ring B is 4- to 12-membered heterocyclyl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 47. The compound of Exemplary Embodiment No. 46, or a pharmaceutically acceptable salt thereof, wherein Ring B is tetrahydroisoquinolinyl optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 48. The compound of Exemplary Embodiment No. 47, or a

pharmaceutically acceptable salt thereof, wherein Ring B is  or  or optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

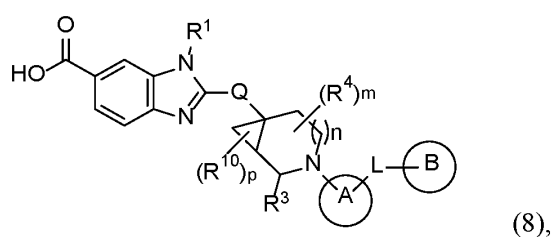
Exemplary Embodiment No. 49. The compound of Exemplary Embodiment No. 48, or a

pharmaceutically acceptable salt thereof, wherein Ring B is .

Exemplary Embodiment No. 50. The compound of Exemplary Embodiments No. 1-41, or a pharmaceutically acceptable salt thereof, wherein Ring B is 5- to 12-membered heteroaryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 51. The compound of Exemplary Embodiment No. 50, or a pharmaceutically acceptable salt thereof, wherein Ring B is 9-membered heteroaryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

Exemplary Embodiment No. 52. The compound of Exemplary Embodiment No. 1, wherein the compound is of Formula (8):



or a pharmaceutically acceptable salt thereof.

Exemplary Embodiment No. 53. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from any one of the compounds in Table 1.

Exemplary Embodiment No. 54. A pharmaceutical composition comprising the compound of Exemplary Embodiments No. 1-53, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable excipient.

Exemplary Embodiment No. 55. A method of treating a disease mediated by glucagon-like peptide-1 receptor (GLP-1R) in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the compound of Exemplary Embodiments No. 1-53, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of Exemplary Embodiment No. 54.

Exemplary Embodiment No. 56. The method of Exemplary Embodiment No. 55, wherein the disease is a liver disease.

Exemplary Embodiment No. 57. The method of Exemplary Embodiment No. 56, wherein the liver disease is primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or oti-antitrypsin deficiency.

Exemplary Embodiment No. 58. The method of Exemplary Embodiment No. 55, wherein the disease is diabetes.

Exemplary Embodiment No. 59. The method of Exemplary Embodiment No. 55, wherein the disease is a cardiometabolic disease.

Exemplary Embodiment No. 60. The method of Exemplary Embodiment No. 55, wherein the disease is obesity.

Exemplary Embodiment No. 61. Use of the compound of Exemplary Embodiments No. 1-53, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease mediated by GLP-1R.

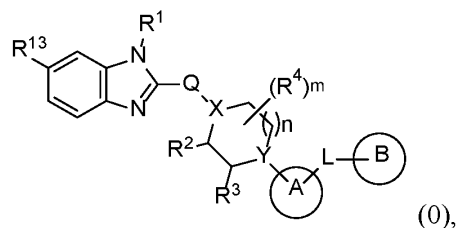
EQUIVALENTS

[0352] It is understood that the invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended

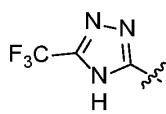
claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

1. A compound of Formula (0):



or a pharmaceutically acceptable salt, wherein:



R^{13} is $-\text{C}(\text{O})\text{OH}$ or

X is N or CR^x , wherein R^x is hydrogen, OH or $\text{C}_1\text{-C}_6$ alkyl;

Y is N or CR^y , wherein R^y is hydrogen, OH or $\text{C}_1\text{-C}_6$ alkyl;

n is 0 or 1;

Q is selected from the group consisting of $-\text{C}(\text{R}^7)(\text{R}^8)-$, $-\text{O}-$, $-\text{N}(\text{R}^9)-$, and $-\text{S}-$, wherein

R^7 and R^8 are independently hydrogen, halogen, or $\text{C}_1\text{-C}_6$ alkyl; and

R^9 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^1 is optionally substituted $-\text{C}_1\text{-C}_6$ alkylene or $-\text{C}_1\text{-C}_6$ alkylene- R^5 , wherein R^5 is $\text{C}_3\text{-C}_6$ cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN , $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, and $-\text{OC}_1\text{-C}_6$ alkyl, wherein each $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, and $-\text{OC}_1\text{-C}_6$ alkyl substituent is independently optionally substituted by halo or CN ;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted $\text{C}_3\text{-C}_4$ cycloalkyl ring; or

R^2 and R^3 , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl ring, and R^3 is hydrogen, oxo, or $\text{C}_1\text{-C}_6$ alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or $\text{C}_1\text{-C}_6$ alkyl;

Ring A is $\text{C}_6\text{-C}_{14}$ aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH , CN , $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo or OH ;

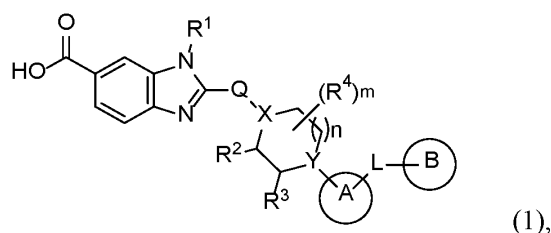
L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

when L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C₁-C₆ alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

R⁶, when present, is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl optionally substituted by halo or CN, -OC₁-C₆ alkyl optionally substituted by halo or CN, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl optionally substituted by halo or CN.

2. A compound of Formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^x, wherein R^x is hydrogen, OH or C₁-C₆ alkyl, and

Y is N or CR^y, wherein R^y is hydrogen, OH or C₁-C₆ alkyl;

n is 0 or 1;

Q is selected from the group consisting of -C(R⁷)(R⁸)-, -O-, -N(R⁹)-, and -S-, wherein

R⁷ and R⁸ are independently hydrogen, halogen, or C₁-C₆ alkyl, and

R⁹ is hydrogen or C₁-C₆ alkyl;

R¹ is -C₁-C₆ alkylene-R⁵, wherein R⁵ is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and -OC₁-C₆ alkyl substituent is independently optionally substituted by halo or CN;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_4 cycloalkyl ring; or

R^2 and R^3 , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3 - C_5 cycloalkyl ring, and R^3 is hydrogen, oxo, or C_1 - C_6 alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or C_1 - C_6 alkyl;

Ring A is C_6 - C_{14} aryl, 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, OH, CN, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkyl optionally substituted by halo or OH;

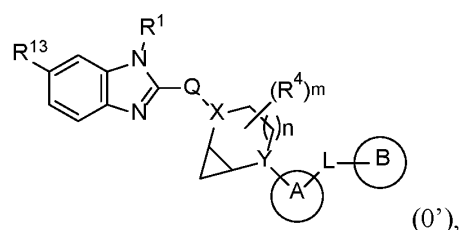
L is a bond, -O-, C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *- NR^6 - C_1 - C_6 alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

when L is C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *- NR^6 - C_1 - C_6 alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C_1 - C_6 alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl; and

R^6 , when present, is hydrogen or C_1 - C_6 alkyl; and

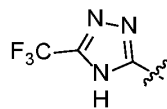
Ring B is C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1 - C_6 alkyl optionally substituted by halo or CN, -OC $_1$ - C_6 alkyl optionally substituted by halo or CN, -COCH $_3$, -CONH $_2$, -S(O) $_2$ CH $_3$, and phenyl optionally substituted by halo or CN.

3. The compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (0'):



or a pharmaceutically acceptable salt thereof.

4. The compound of any one of the preceding claims, or a pharmaceutically acceptable



salt thereof, wherein R^{13} is $-C(O)OH$ or

5. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X is N and Y is CR^y ;
- (ii) X is CR^x and Y is N; or
- (iii) X is N and Y is N.

6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Q is $-C(R^7)(R^8)-$, $-CH_2-$, $-O-$, or $-N(R^9)-$.

8. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2-R^5$.

9. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

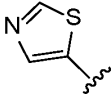
- (i) C_3 - C_6 cycloalkyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl;
- (ii) 4- to 5-membered heterocyclyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl; or
- (iii) 5-membered heteroaryl optionally substituted by halo, $-O-C_{1-6}$ alkyl, C_{1-6} alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl.

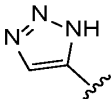
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

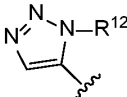
- (i) cyclopropyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl;
- (ii) oxetanyl optionally substituted by halo, oxo, C_1 - C_6 alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl; or

(iii) oxazolyl, triazolyl, thiazolyl or isothiazolyl, each of which is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R⁵ is:

(i)  optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl;

(ii)  optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁₋₆ haloalkyl; or

(iii) , wherein R¹² is C₁₋₆ alkyl.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R¹² is methyl or ethyl.

13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Ring A is:

(i) 5- to 6-membered heteroaryl optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH; or

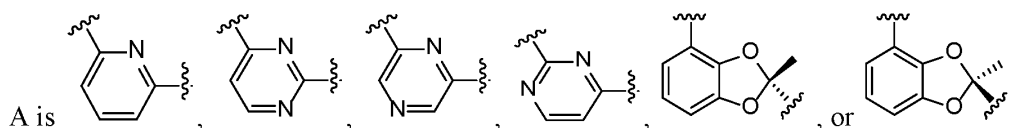
(ii) 10- to 12-membered heterocyclyl or 10- to 12-membered heteroaryl optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein Ring A is:

(i) pyridyl, pyrimidinyl, or pyrazinyl, each of which is optionally substituted by halo, CN, C₃₋₆ cycloalkyl, or C₁₋₆ alkyl optionally substituted by halo or OH; or

(ii) optionally substituted benzodioxole.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein Ring



16. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein L is *-O-C₁-C₆ alkylene-* optionally substituted by R^L.

17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein L is *-O-CH₂-*.

18. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein L is:

(i) -O-; or

(ii) a bond.

19. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Ring B is:

(i) C₆-C₁₄ aryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl;

(ii) 4- to 12-membered heterocyclyl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl; or

(iii) 5- to 12-membered heteroaryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

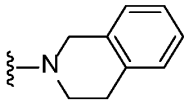
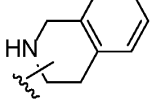
20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein Ring B is:

(i) phenyl optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl;

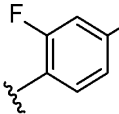
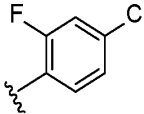
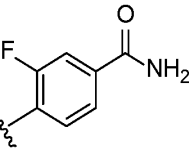
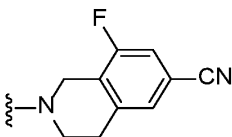
(ii) tetrahydroisoquinoliny optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl; and/or

(iii) 9-membered heteroaryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

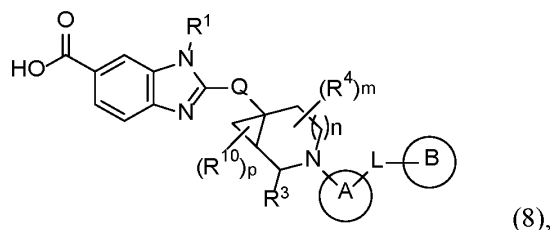
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein Ring

B is  or  optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃ and phenyl.

22. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein Ring

B is , , , or .

23. The compound of claim 1, wherein the compound is of Formula (8):



or a pharmaceutically acceptable salt thereof.

24. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from any one of the compounds in Table 1.

25. A pharmaceutical composition comprising the compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable excipient.

26. A method of treating a disease mediated by glucagon-like peptide-1 receptor (GLP-1R) in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25.

27. The method of claim 26, wherein the disease is a liver disease.

28. The method of claim 27, wherein the liver disease is primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or oti-antitrypsin deficiency.

29. The method of claim 26, wherein the disease is:

- (i) diabetes;
- (ii) a cardiometabolic disease; and/or
- (iii) obesity.

30. Use of the compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease mediated by GLP-1R.