
***BICYCLIC HETEROARYL-CONTAINING PIPERIDINE
INHIBITORS OF SLC6A19 FUNCTION***

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application Serial Nos. 63/532,264, filed August 11, 2023; and 63/633,404, filed April 12, 2024.

BACKGROUND

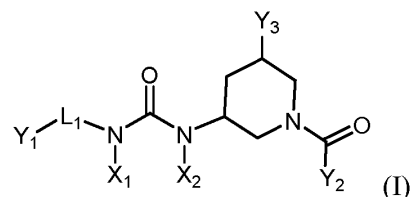
Phenylketonuria (PKU) is an inborn error of metabolism caused by mutations in phenylalanine hydroxylase (PAH), the enzyme responsible for metabolizing phenylalanine. PKU is an autosomal recessive metabolic disorder in which phenylalanine is not properly metabolized and results in abnormally high levels of plasma phenylalanine. People who have PKU have abnormally high blood levels of phenylalanine, which if untreated can lead to irreversible neurological damage resulting in a spectrum of complications such as intellectual disabilities, seizures, neurodevelopmental and behavioral disorders. PKU is difficult to treat because blood levels of phenylalanine are directly related to diet. Patients must adhere to a life-long and strict diet that impacts all aspects of patients' lives. Current standard of care are enzyme co-factor and enzyme substitution therapy but these therapies are not effective in all patients, and carry potential risk for adverse events.

The enzyme responsible for metabolizing phenylalanine, and thus maintaining phenylalanine homeostasis is phenylalanine hydroxylase (PAH). Loss-of-function (LOF) mutations at PAH gene at chromosome 12q23.2 are known to cause most forms of PKU. These LOF mutations resulting in PKU can be diagnosed as classical PKU (the most severe form), and "mild PKU" or "hyperphe" a less severe form. In addition to PAH, mutations in other enzymes that affect phenylalanine metabolism, such as dihydropteridine reductase (DHPR), the enzyme responsible for synthesis of co-factors required for PAH activity, may also result in elevated levels of phenylalanine. In addition to diet, blood amino acid levels, including levels of phenylalanine, are regulated by SLC6A19. SLC6A19 is located in the proximal tubule of the kidney and is responsible for reabsorption of amino acids back into the blood.

SUMMARY

One aspect of the invention provides compounds, compositions, and methods useful for treating or preventing a disease or disorder associated with abnormal levels of amino acids by modulation of SLC6A19 transport.

Accordingly, provided herein is a compound having the structure of Formula (I):



wherein:

L₁ is -alkyl-;

X₁ and X₂ are independently selected from -H and cycloalkyl; provided that X₁ and X₂ are not both -H;

Y₁ is an optionally substituted 5,6-fused bicyclic heteroaryl;

Y₂ is selected from -NH(Y₂'), -OY₂'', alkyl, and hydroxyalkyl;

Y₂' is selected from -H, alkyl, and -O-alkyl;

Y₂'' is alkyl; and

Y₃ is selected from -H, hydroxyalkyl, and halogen;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention relates to methods of treating or preventing a disease or disorder associated with a genetic defect in phenylalanine hydroxylase in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

Another aspect of the invention relates to methods of treating or preventing phenylketonuria, hyperphenylalaninemia, tyrosinemia, nonketotic hyperglycinemia, isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

Another aspect of the invention relates to methods of modulating SLC6A19 transport in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the

present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features, objects, and advantages of the invention will be apparent from the detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a table summarizing isoleucine transport data for exemplary compounds of the invention. A = $IC_{50} < 500$ nM; B = IC_{50} 500 nM – 1500 nM; C = IC_{50} >1500 nM – 5000 nM; D = IC_{50} >5000 nM – 10000 nM; and E = IC_{50} >10000 nM.

DETAILED DESCRIPTION

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of”

shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

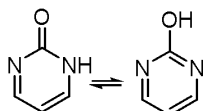
Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

“Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in “atropisomeric” forms or as “atropisomers.” Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from a mixture of isomers. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by

resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

The term "tautomer" as used herein means structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. For example, the two tautomers of 2-pyrimidinone are recited below. A single tautomer may be provided in a structural representation of a given compound. However, the present invention contemplates all such tautomers of a given compound.



Percent purity by mole fraction is the ratio of the moles of the enantiomer (or diastereomer) or over the moles of the enantiomer (or diastereomer) plus the moles of its optical isomer. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by

the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

The term “prodrug” as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term “pharmaceutically acceptable salts” refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate,

naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

The term "pharmaceutically acceptable cocrystals" refers to solid cofomers that do not form formal ionic interactions with the small molecule.

A "therapeutically effective amount" (or "effective amount") of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "patient" or "subject" refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term “aliphatic group” refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

“Alkyl” refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chains, C₃-C₃₀ for branched chains), and more preferably 20 or fewer. Alkyl groups may be substituted or unsubstituted.

As used herein, the term “heteroalkyl” refers to an alkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms.

As used herein, the term “haloalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one halogen.

As used herein, the term “hydroxyalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one hydroxyl.

As used herein, the term “alkylene” refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene -(CH₂)-, ethylene -(CH₂CH₂)-, n-propylene -(CH₂CH₂CH₂)-, isopropylene -(CH₂CH(CH₃))-, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

“Cycloalkyl” means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted.

As used herein, the term “halocycloalkyl” refers to a cycloalkyl group as hereinbefore defined substituted with at least one halogen.

“Cycloheteroalkyl” refers to an cycloalkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms. Preferred cycloheteroalkyls have from 4-8 carbon atoms and heteroatoms in their ring structure, and more preferably have 4-6 carbons and heteroatoms in the ring structure. Cycloheteroalkyl groups may be substituted or unsubstituted.

Unless the number of carbons is otherwise specified, “lower alkyl,” as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, “lower alkenyl” and “lower alkynyl” have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

“Alkenyl” refers to any cyclic or acyclic, branched or unbranched unsaturated carbon chain moiety having the number of carbon atoms specified, or up to 26 carbon atoms if no limitation on the number of carbon atoms is specified; and having one or more double bonds in the moiety. Alkenyl of 6 to 26 carbon atoms is exemplified by hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, eicosenyl, heneicosenyl, docosenyl, tricosenyl, and tetracosenyl, in their various isomeric forms, where the unsaturated bond(s) can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

“Alkynyl” refers to hydrocarbonyl moieties of the scope of alkenyl, but having one or more triple bonds in the moiety.

The term “aryl” as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Carbocyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-

membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

The term “halo”, “halide”, or “halogen” as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

The terms “heterocyclyl” or “heterocyclic group” refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, and the like.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds.

The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. In preferred embodiments, the substituents on substituted alkyls are selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, halogen, carbonyl, cyano, or hydroxyl. In more preferred embodiments, the substituents on substituted alkyls are selected from fluoro, carbonyl, cyano, or hydroxyl. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, “small molecules” refers to small organic or inorganic molecules of molecular weight below about 3,000 Daltons. In general, small molecules useful for the invention have a molecular weight of less than 3,000 Daltons (Da). The small molecules can be, e.g., from at least about 100 Da to about 3,000 Da (e.g., between about 100 to about 3,000 Da, about 100 to about 2500 Da, about 100 to about 2,000 Da, about 100 to about 1,750 Da, about 100 to about 1,500 Da, about 100 to about 1,250 Da, about 100 to about 1,000 Da, about 100 to about 750 Da, about 100 to about 500 Da, about 200 to about 1500, about 500 to about 1000, about 300 to about 1000 Da, or about 100 to about 250 Da).

In some embodiments, a “small molecule” refers to an organic, inorganic, or organometallic compound typically having a molecular weight of less than about 1000. In some embodiments, a small molecule is an organic compound, with a size on the order of 1 nm. In some embodiments, small molecule drugs of the invention encompass oligopeptides and other biomolecules having a molecular weight of less than about 1000.

An “effective amount” is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a composition depends on the composition selected. The compositions can be administered from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments.

The terms “decrease,” “reduce,” “reduced,” “reduction,” “decrease,” and “inhibit” are all used herein generally to mean a decrease by a statistically significant amount relative to a reference. However, for avoidance of doubt, “reduce,” “reduction” or “decrease” or “inhibit” typically means a decrease by at least 10% as compared to a reference level and can include, for example, a decrease by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, up to and including, for example, the complete absence of the given entity or parameter as compared to the reference level, or any decrease between 10-99% as compared to the absence of a given treatment.

The terms “increased,” “increase” or “enhance” or “activate” are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms “increased,” “increase” or “enhance” or “activate” means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

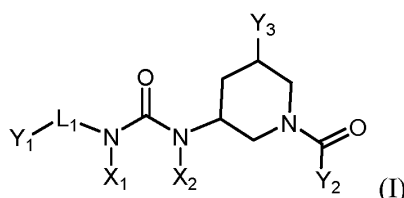
As used herein, the term “modulate” includes up-regulation and down-regulation, e.g., enhancing or inhibiting a response.

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

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Compounds of the Invention

Provided herein is a compound having the structure of Formula (I):



wherein:

L₁ is -alkyl-;

X₁ and X₂ are independently selected from -H and cycloalkyl; provided that X₁ and X₂ are not both -H;

Y₁ is an optionally substituted 5,6-fused bicyclic heteroaryl;

Y₂ is selected from -NH(Y₂'), -OY₂", alkyl, and hydroxyalkyl;

Y₂' is selected from -H, alkyl, and -O-alkyl;

Y₂" is alkyl; and

Y₃ is selected from -H, hydroxyalkyl, and halogen;

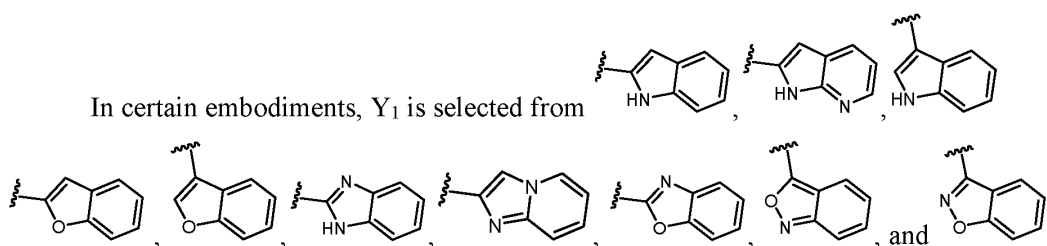
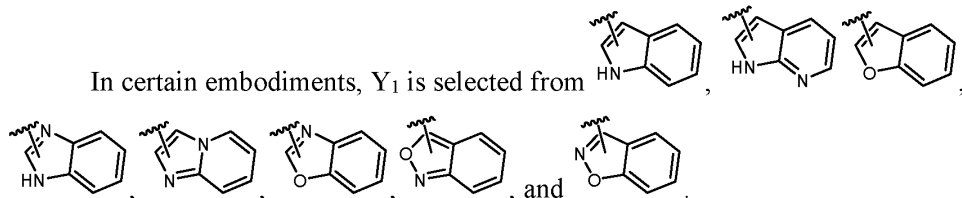
or a pharmaceutically acceptable salt thereof.

In certain embodiments, one of X_1 and X_2 is $-H$; and the other of X_1 and X_2 is .

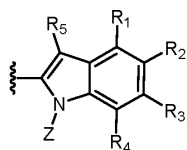
In certain embodiments, X_1 is $-H$; and X_2 is .

In certain embodiments, L_1 is $-C_1-C_4$ alkyl-. In other embodiments, L_1 is $-CH_2-$.

In certain embodiments, Y_1 is an unsubstituted 5,6-fused bicyclic heteroaryl.



In certain embodiments, Y_1 is a substituted 5,6-fused bicyclic heteroaryl.



In certain embodiments, Y_1 is ; and

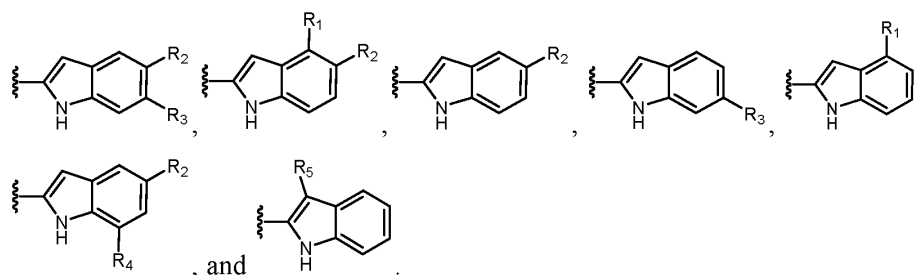
each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; and

Z is H or alkyl; provided that at least one of R_1 , R_2 , R_3 , R_4 , R_5 , and Z is not $-H$.

In certain embodiments, each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, alkyl, cycloalkyl, halogen, $-CN$, $-CF_3$, and $-OCF_3$; and Z is $-H$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

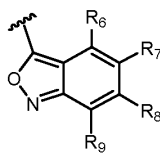
In certain embodiments, each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

In certain embodiments, Y_1 is selected from



In certain embodiments, each of R_1 , R_2 , R_3 , R_4 , and R_5 is a halogen.

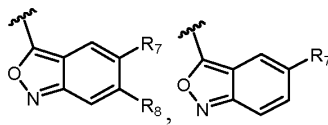
In certain embodiments, each of R_1 , R_2 , R_3 , R_4 , and R_5 is $-F$.



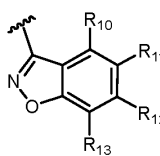
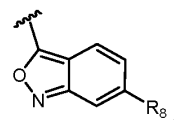
In certain embodiments, Y_1 is ; and

each occurrence of R_6 , R_7 , R_8 , and R_9 is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

In certain embodiments, each occurrence of R_6 , R_7 , R_8 , and R_9 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.



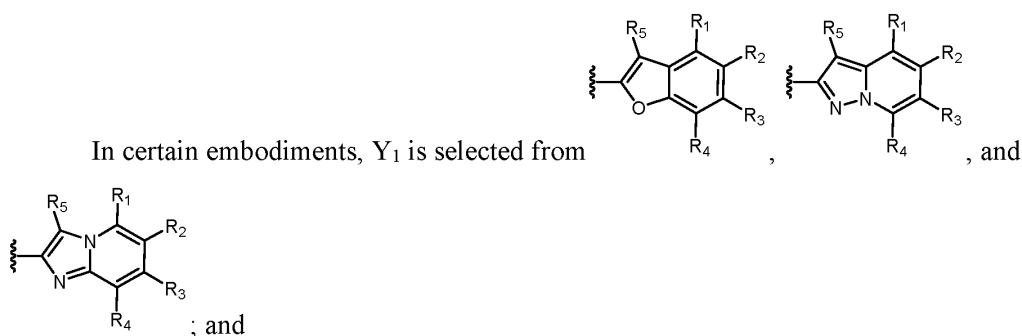
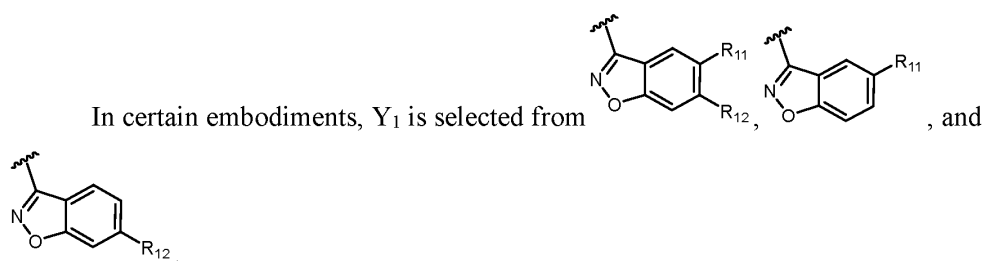
In certain embodiments, Y_1 is selected from



In certain embodiments, Y_1 is ; and

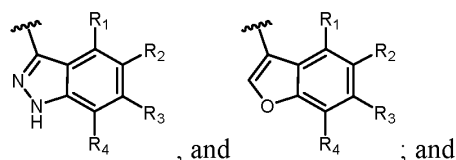
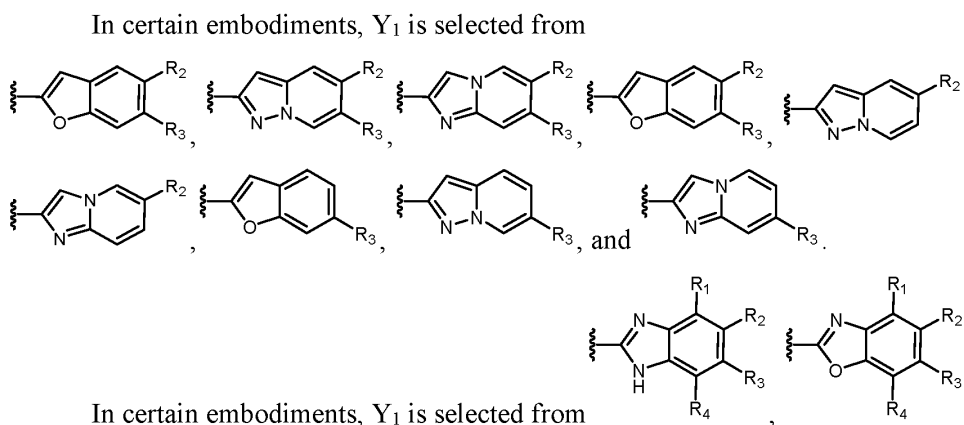
each occurrence of R_{10} , R_{11} , R_{12} , and R_{13} is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

In certain embodiments, each occurrence of R_{10} , R_{11} , R_{12} , and R_{13} is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.



each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, halogen, alkyl, alkoxy, cyclopropyl, -OH, -CN, -CF₃, -OCHF₂, and -OCF₃; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

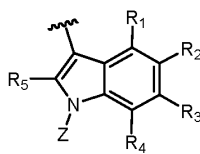
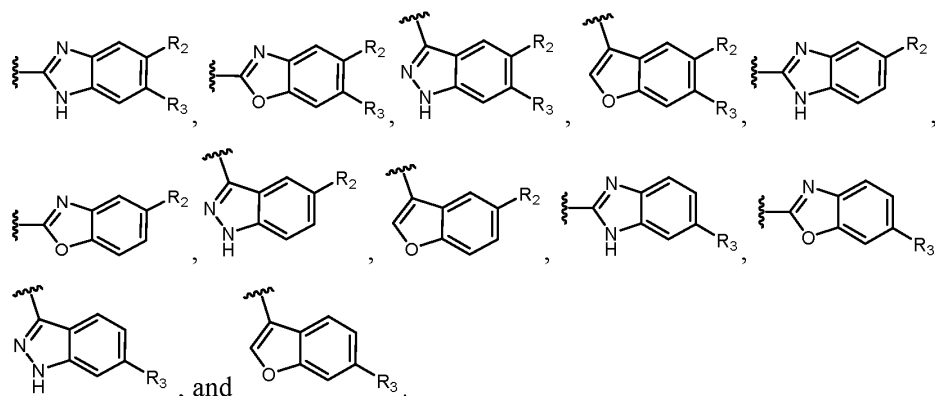
In certain embodiments, each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, -Cl, -Br, -F, -CH₃, , -CF₃, and -OCF₃; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

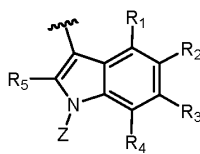


each occurrence of R_1 , R_2 , R_3 , and R_4 is independently selected from $-H$, alkyl, alkoxy, cyclopropyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , and R_4 is not $-H$.

In certain embodiments, each occurrence of R_1 , R_2 , R_3 , and R_4 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , and R_4 is not $-H$.

In certain embodiments, Y_1 is selected from



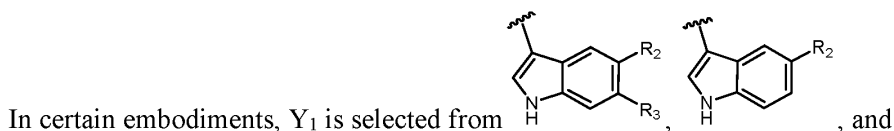
In certain embodiments, Y_1 is ; and

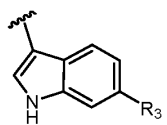
each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; and

Z is H or alkyl; provided that at least one of R_1 , R_2 , R_3 , R_4 , R_5 , and Z is not $-H$.

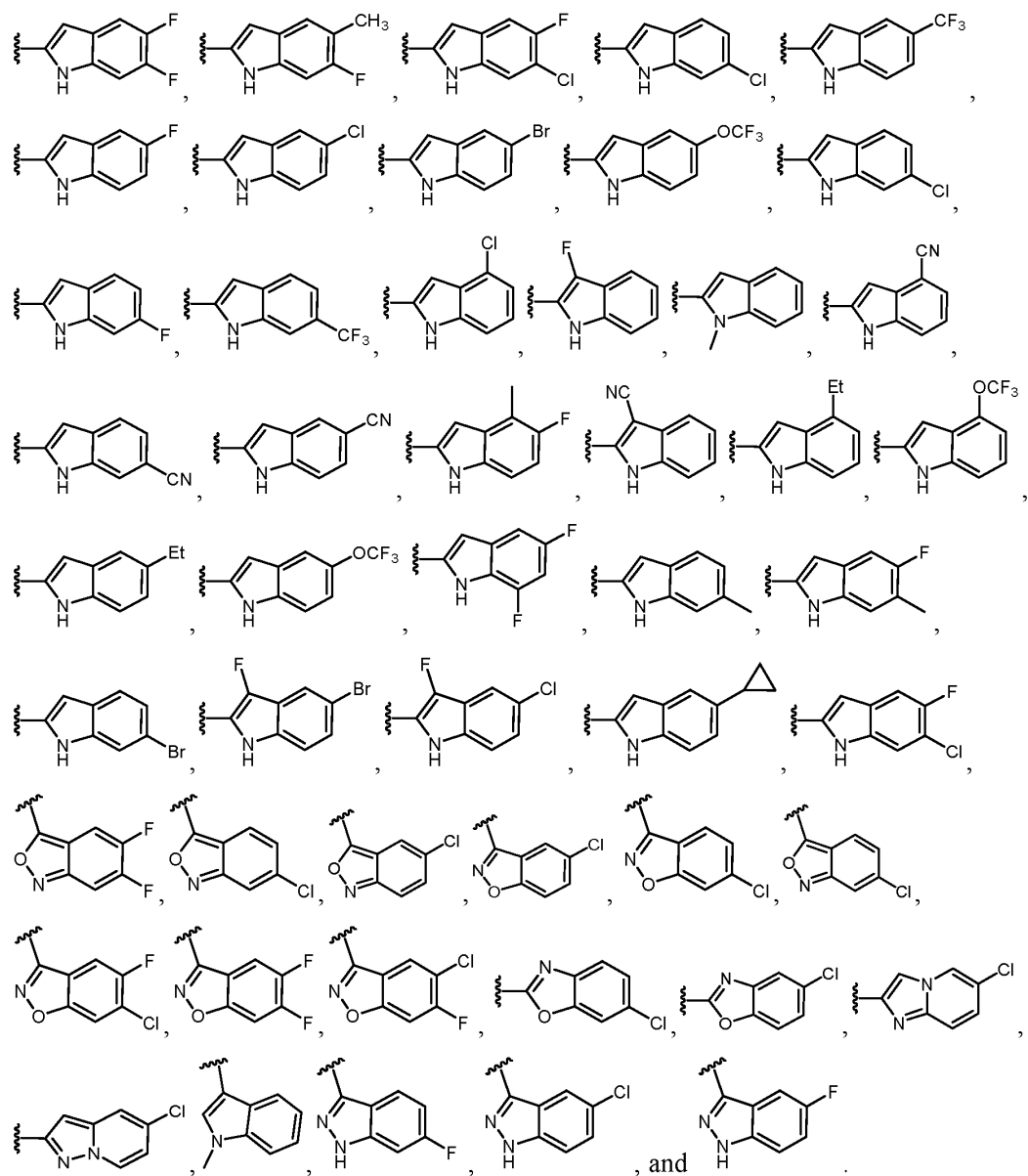
In certain embodiments, each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, alkyl, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; and Z is $-H$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

In certain embodiments, each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; and Z is $-H$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

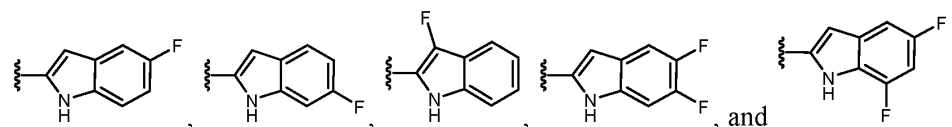




In certain embodiments, Y₁ is selected from



In certain embodiments, Y₁ is selected from



In certain embodiments, Y_2 is $-\text{NH}(Y_2')$. In other embodiments, Y_2' is $\text{C}_1\text{-C}_4$ alkyl, for example, $-\text{CH}_3$. In other embodiments, Y_2' is $-\text{H}$.

In certain embodiments, Y_2' is $-\text{O-alkyl}$. In certain embodiments, Y_2' is $-\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, for example, $-\text{OCH}_3$.

In certain embodiments, Y_2 is $-\text{OY}_2''$.

In certain embodiments, Y_2'' is $\text{C}_1\text{-C}_4$ alkyl, for example $-\text{CH}_3$.

In certain embodiments, Y_2 is alkyl.

In certain embodiments, Y_2 is $\text{C}_1\text{-C}_4$ alkyl, for example, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$. In certain embodiments, Y_2 is hydroxyalkyl. In certain embodiments, Y_2 is $(\text{C}_1\text{-C}_4 \text{ alkyl})\text{-OH}$, for example, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$.

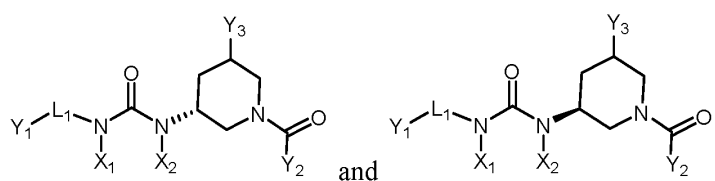
In certain embodiments, Y_3 is $-\text{H}$. In other embodiments, Y_3 is hydroxyalkyl.

In certain embodiments, Y_3 is $(\text{C}_1\text{-C}_4 \text{ alkyl})\text{-OH}$, for example, $-\text{CH}_2\text{OH}$.

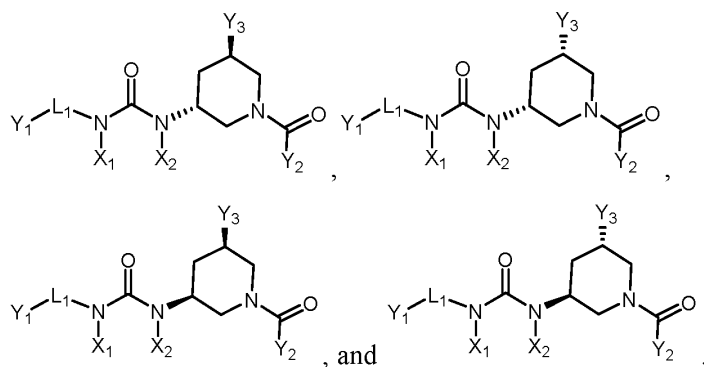
In certain embodiments, Y_3 is halogen.

In certain embodiments, Y_3 is $-\text{F}$.

In certain embodiments, the compound having the structure selected from:



In certain embodiments, the compound having structure selected from:



In certain embodiments, L_1 is $-\text{alkyl-}$; X_1 and X_2 are independently selected from $-\text{H}$ and cyclopropyl; provided that X_1 and X_2 are not both $-\text{H}$; Y_1 is an optionally substituted indolyl; Y_2 is $-\text{NH}(Y_2')$; Y_2' is alkyl; and Y_3 is $-\text{H}$ or halogen; or a pharmaceutically acceptable salt thereof.

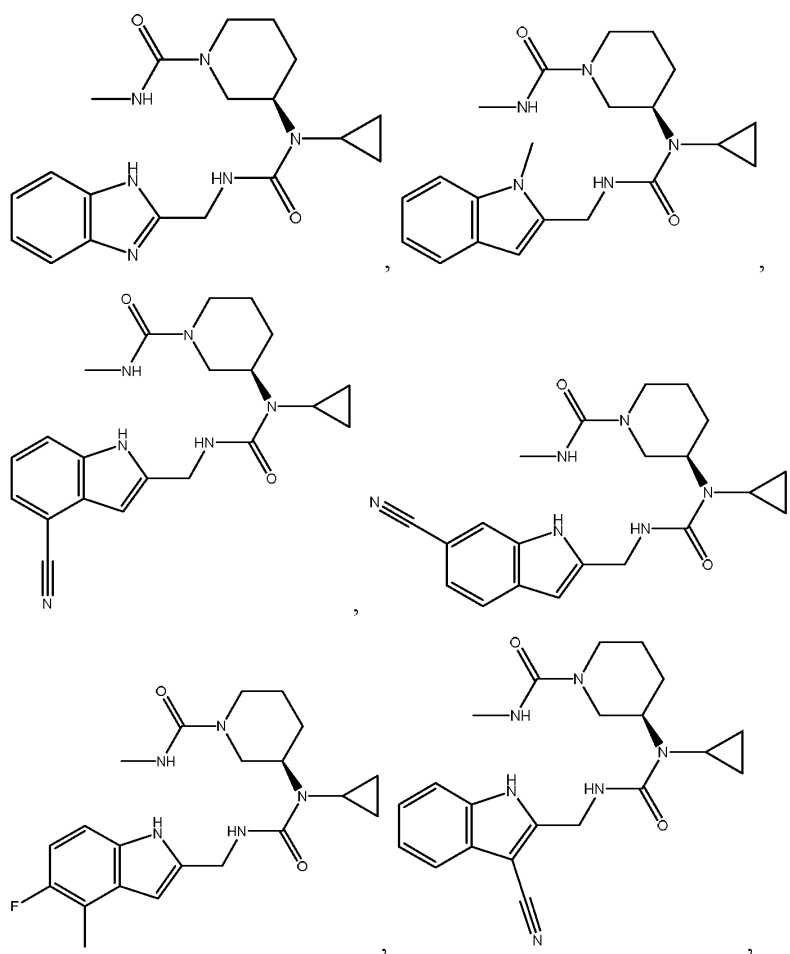
In certain embodiments, L_1 is $-\text{alkyl}-$; X_1 and X_2 are independently selected from $-\text{H}$ and cyclopropyl; provided that X_1 and X_2 are not both $-\text{H}$; Y_1 is an optionally substituted indolyl; Y_2 is alkyl; and Y_3 is $-\text{H}$ or halogen; or a pharmaceutically acceptable salt thereof.

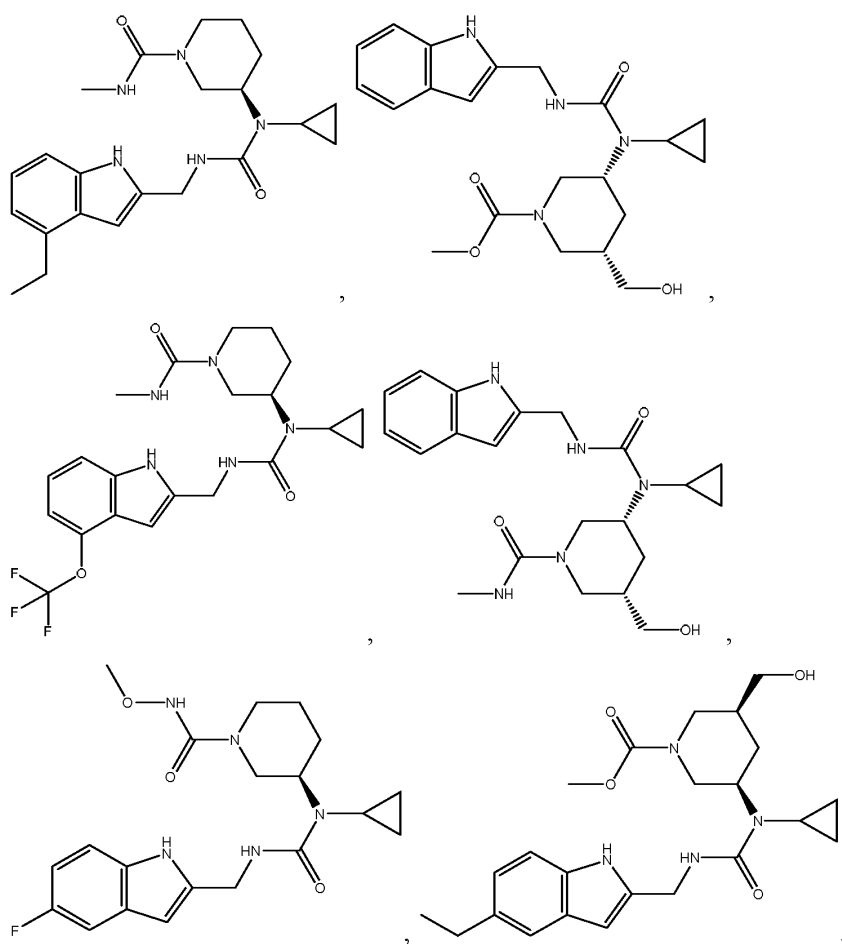
In certain embodiments, Y_1 is substituted indolyl.

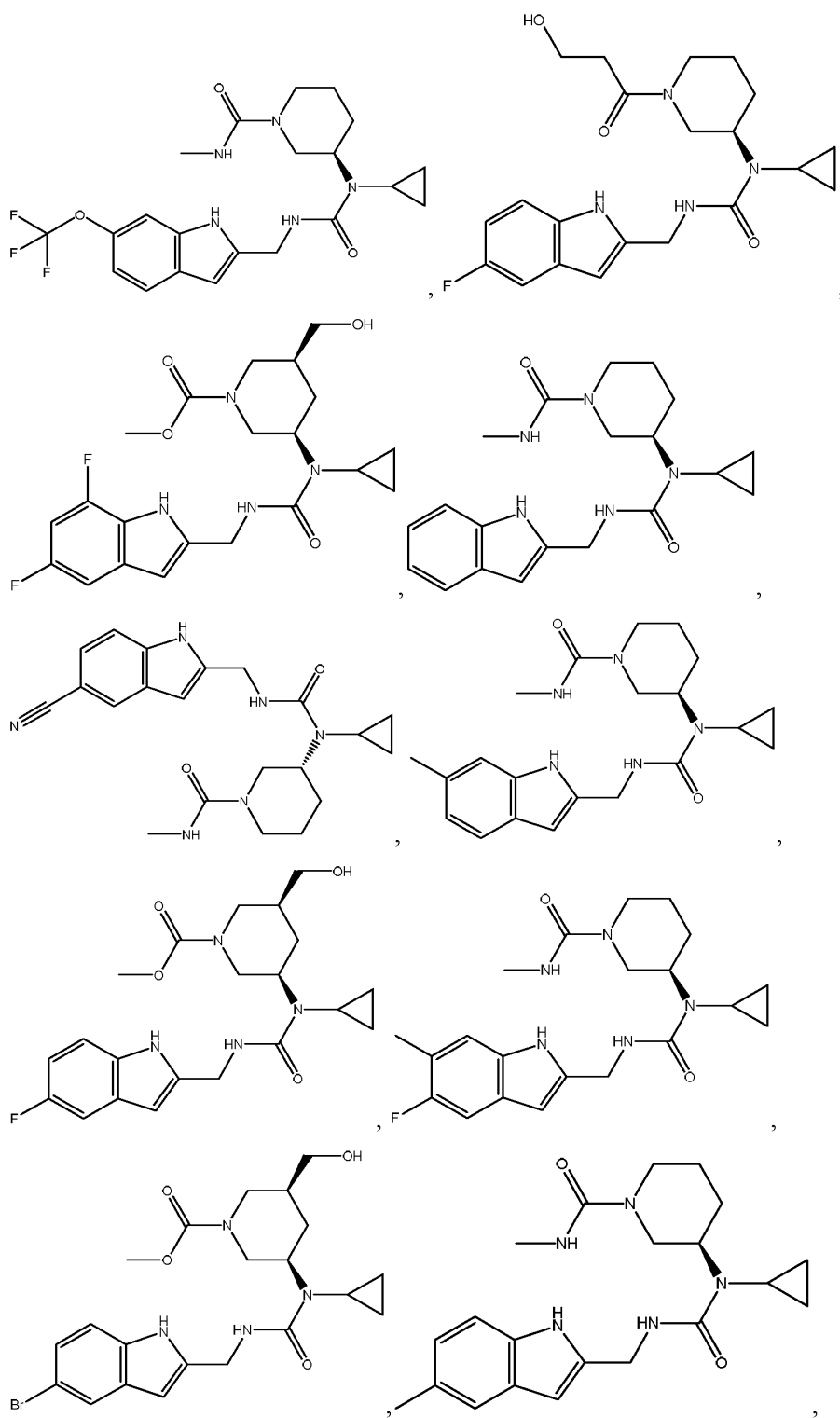
In certain embodiments, Y_3 is halogen.

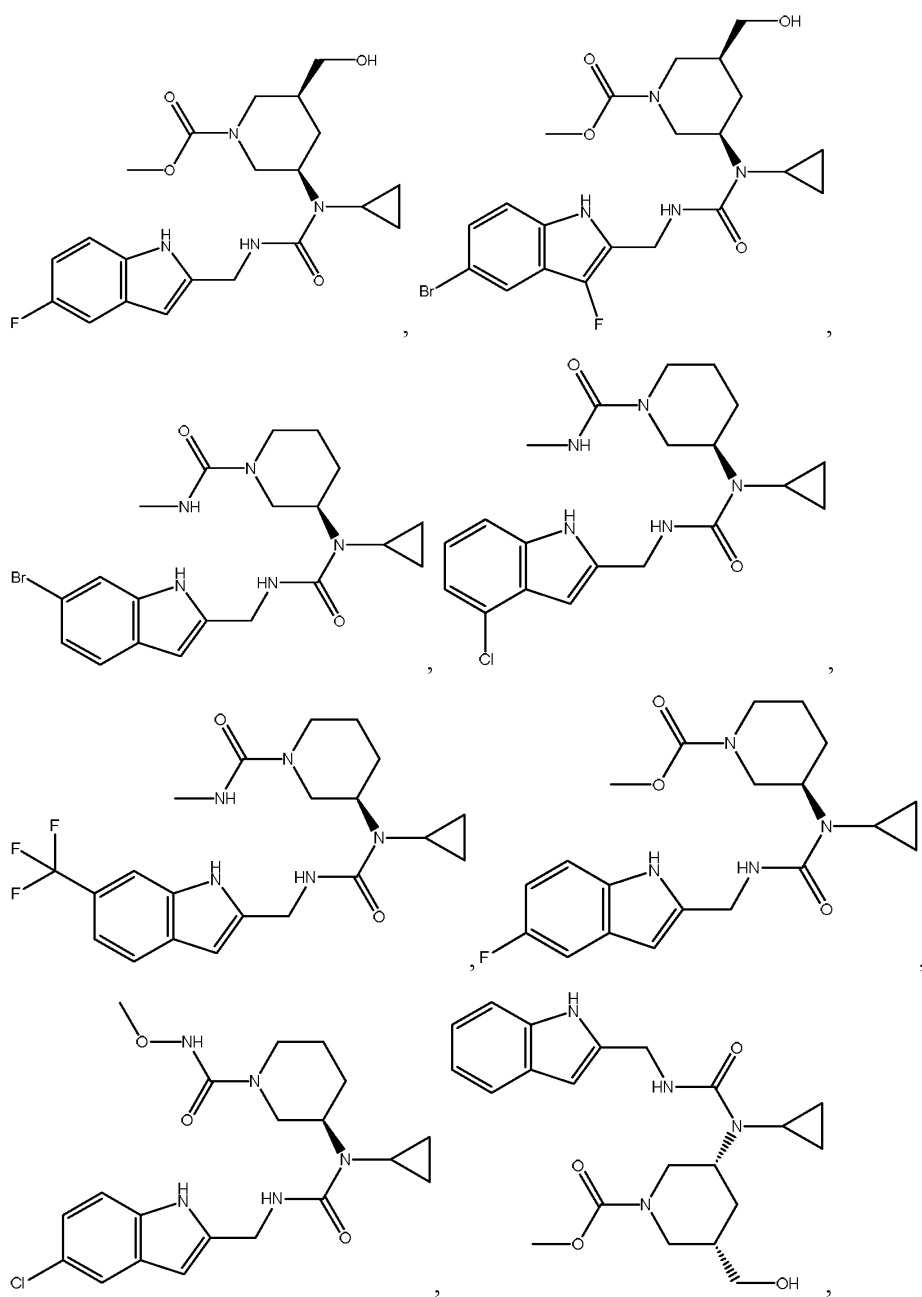
In certain embodiments, Y_3 is $-\text{F}$.

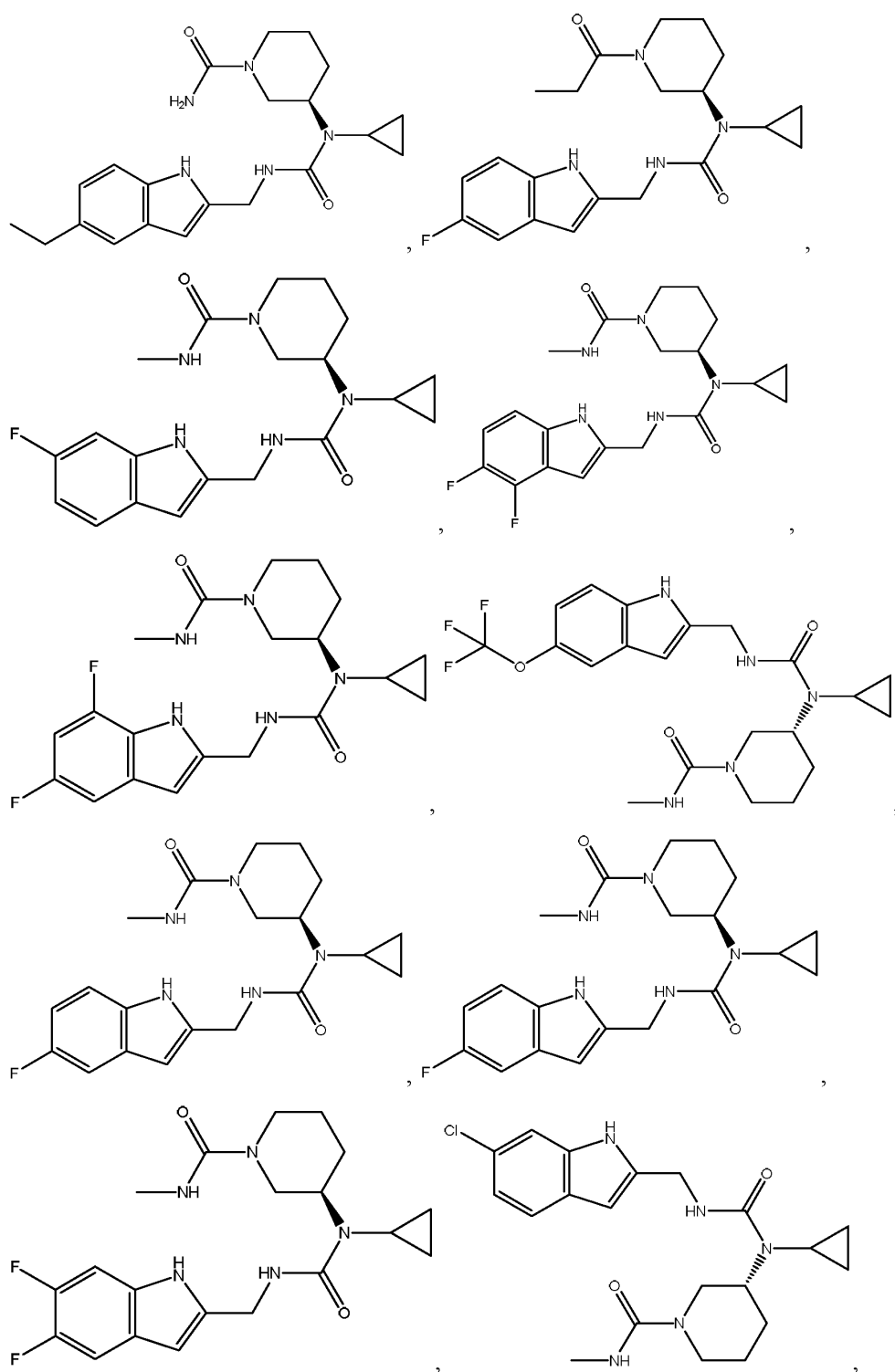
Exemplary Compounds of Formula (I):

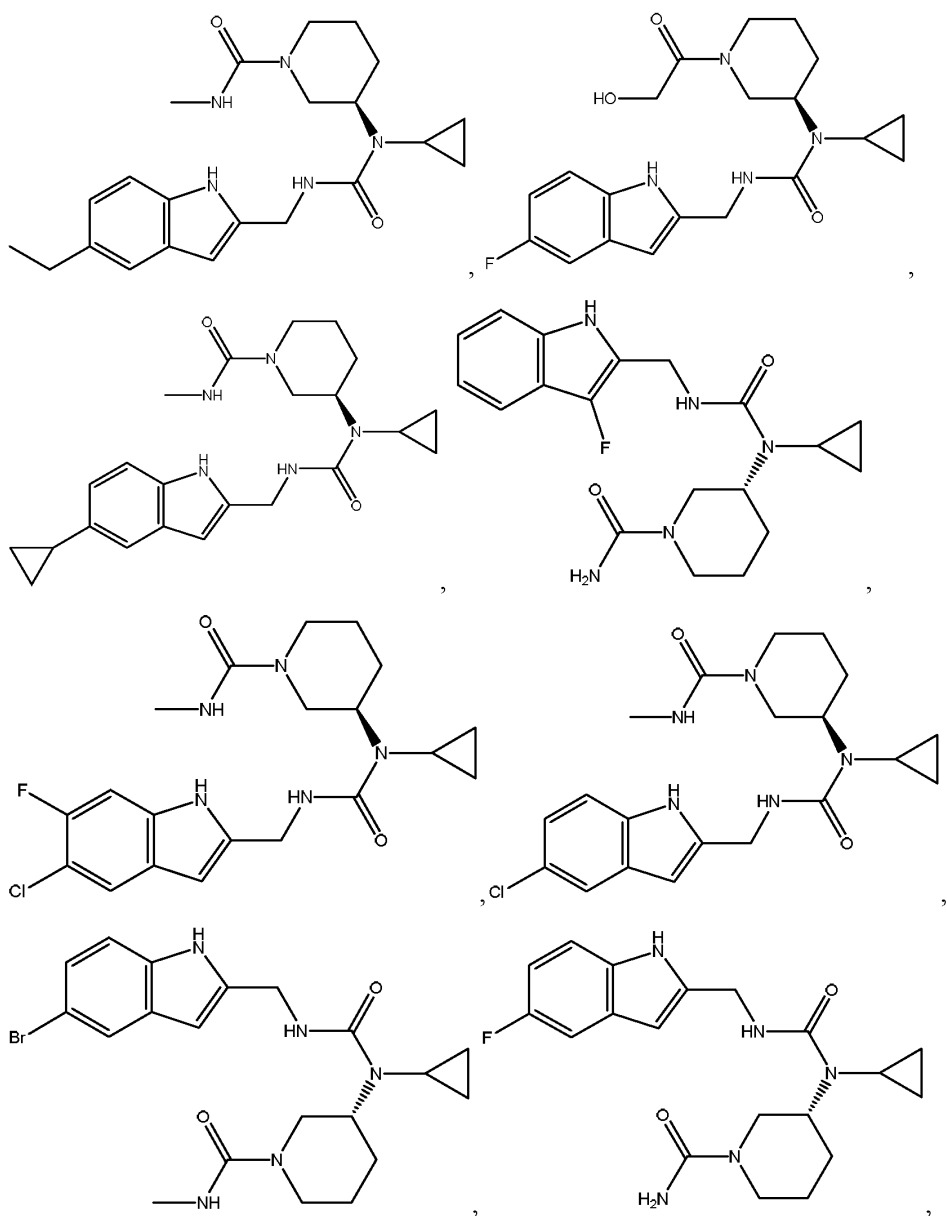


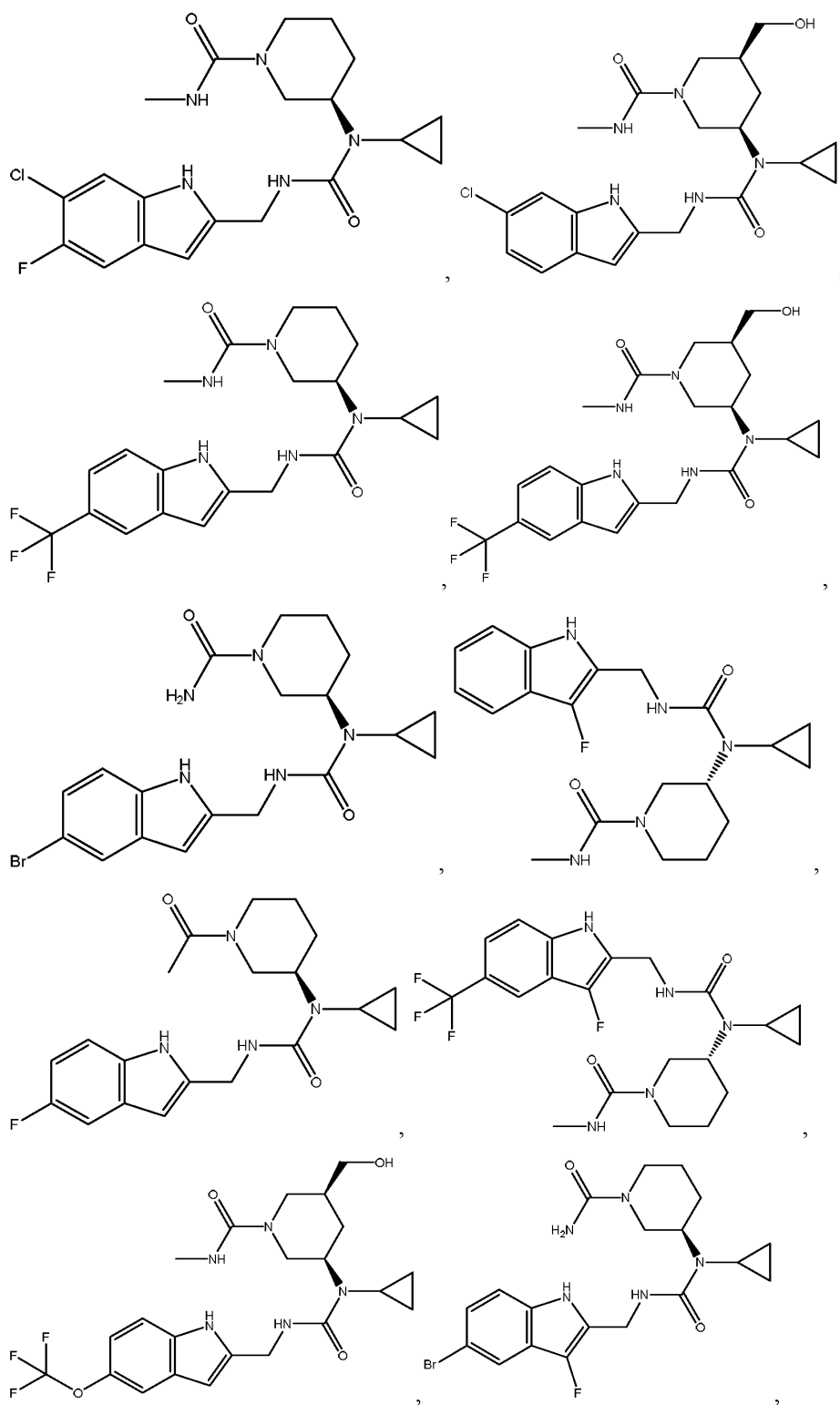


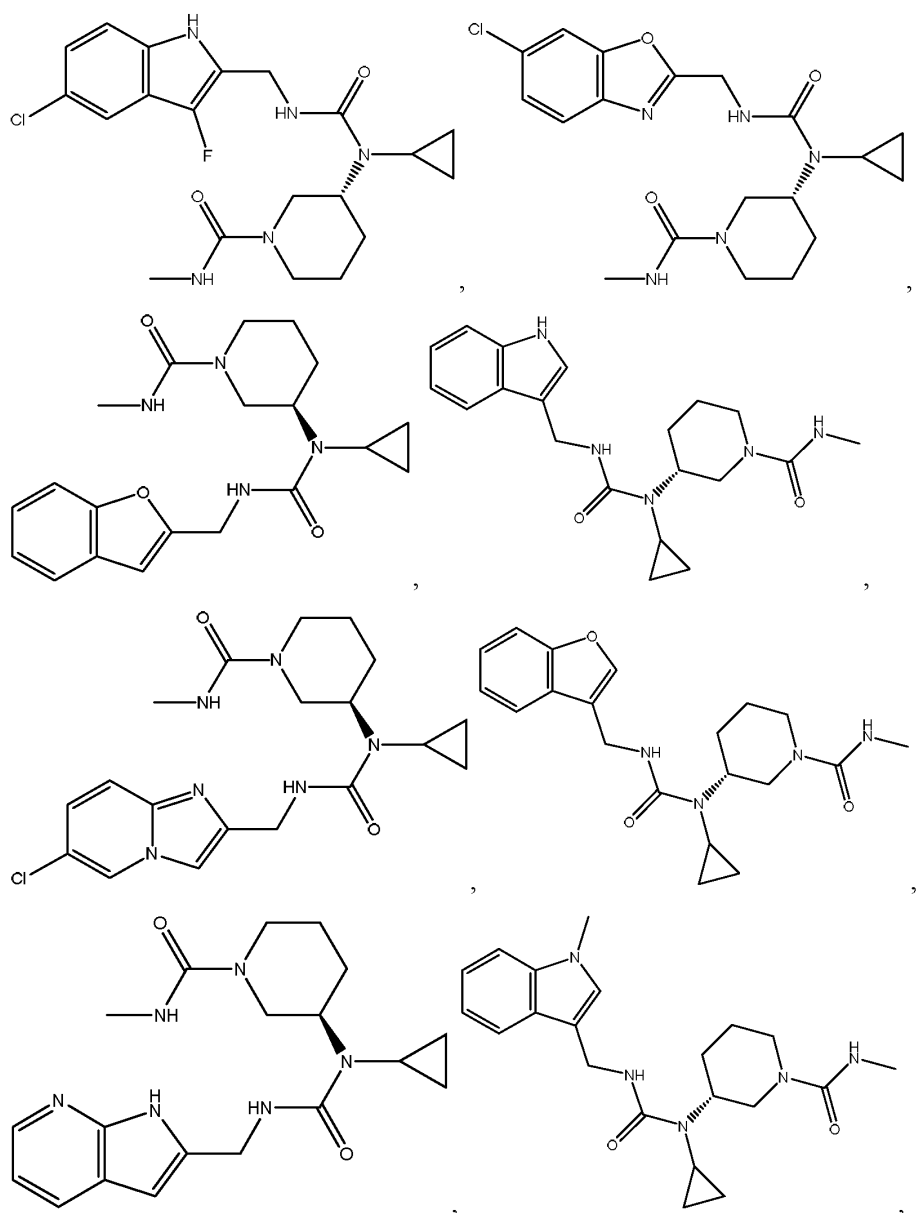


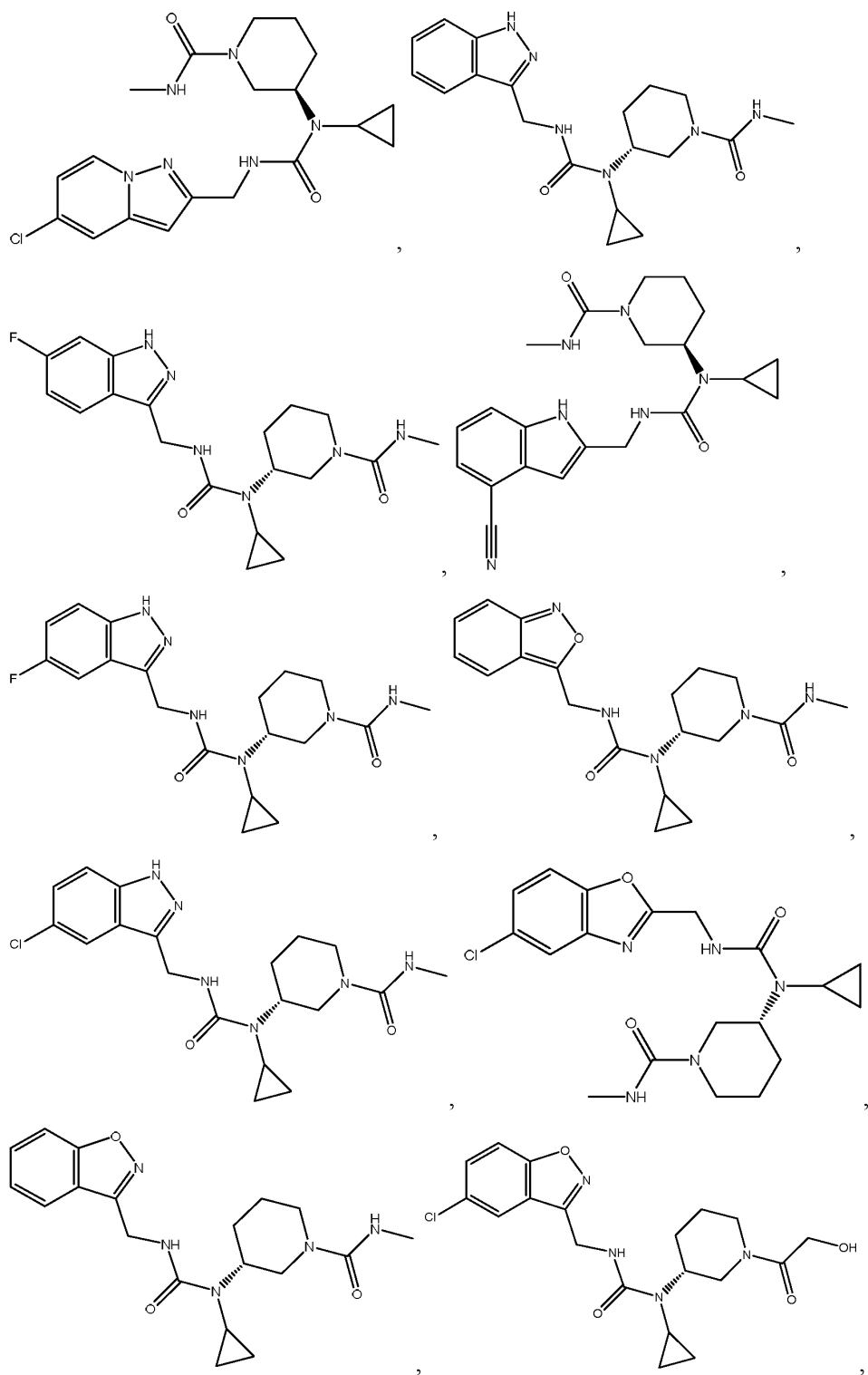


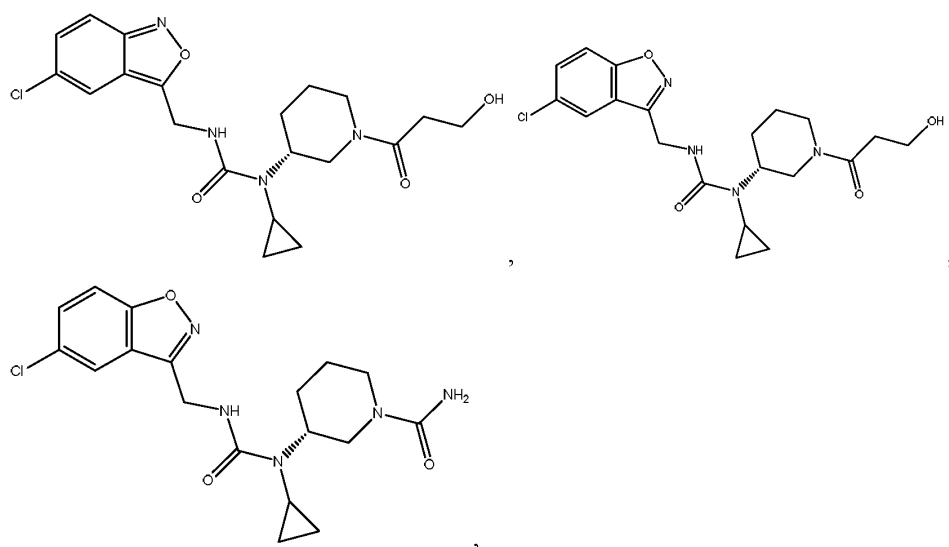


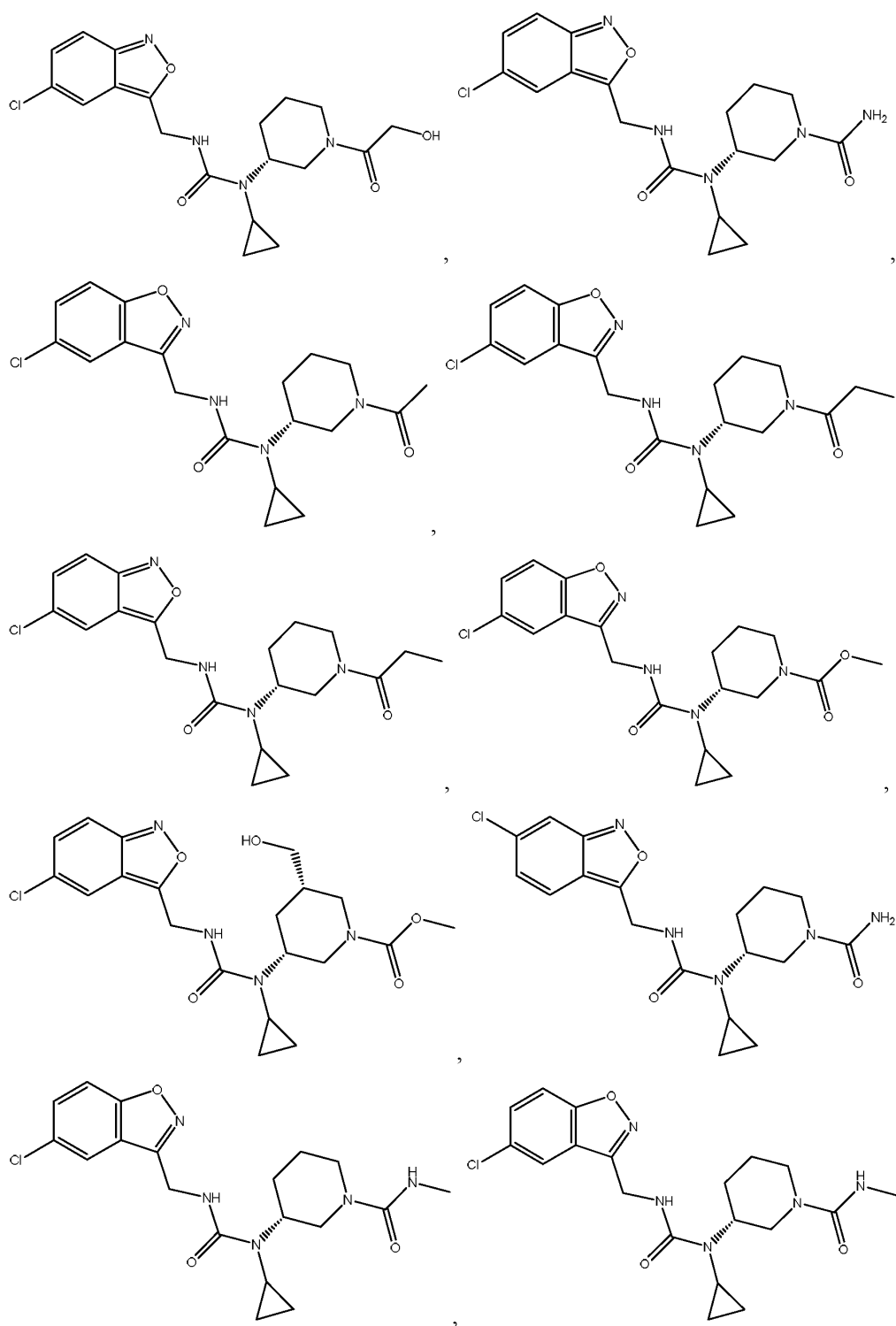


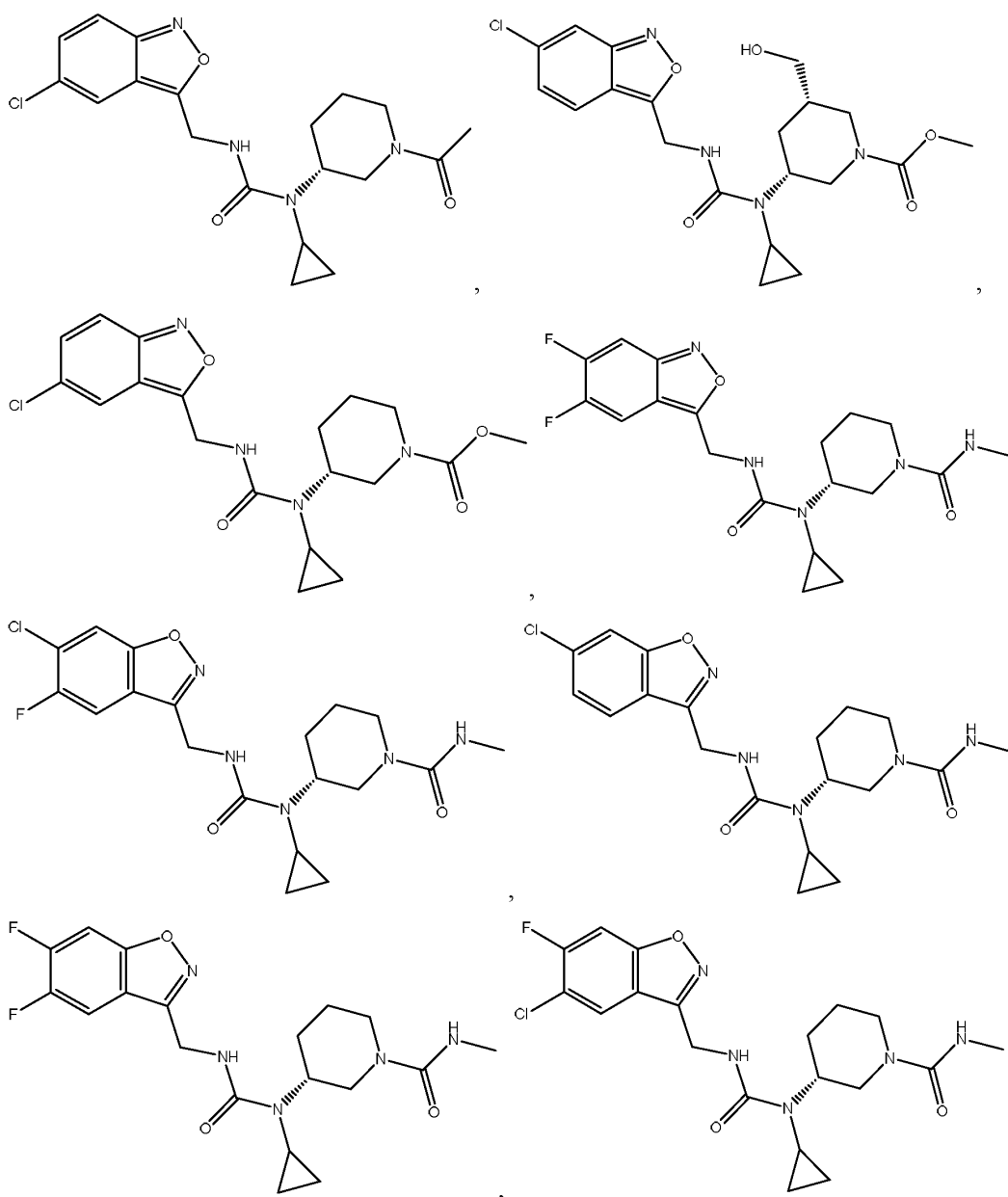


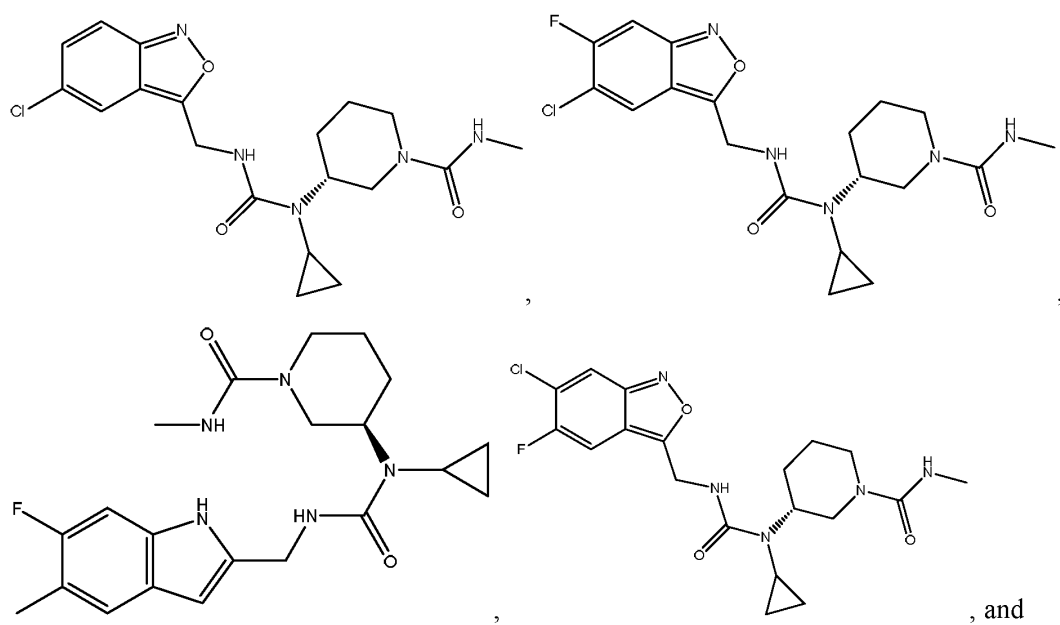


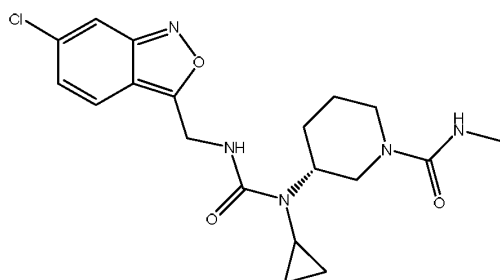






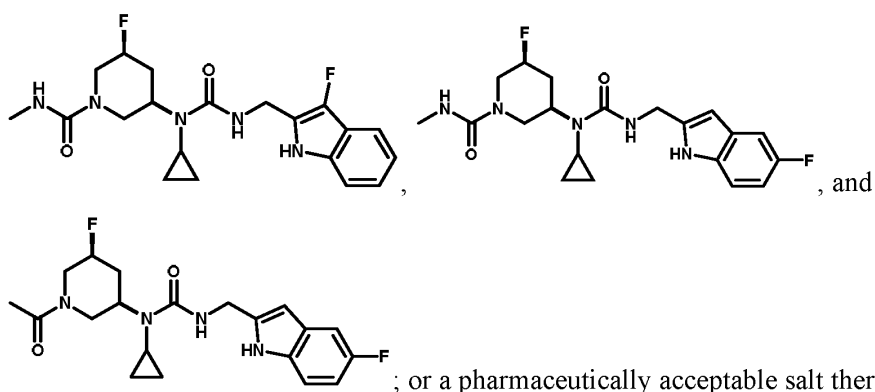






; or a pharmaceutically acceptable salt thereof.

Additional Exemplary Compounds of Formula (I):



; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are atropisomers. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. For example, in the case of variable R^1 , the $(\text{C}_1\text{-C}_4)\text{alkyl}$ or the $-\text{O}-(\text{C}_1\text{-C}_4)\text{alkyl}$ can be suitably deuterated (*e.g.*, $-\text{CD}_3$, $-\text{OCD}_3$).

Any compound of the invention can also be radiolabeled for the preparation of a radiopharmaceutical agent.

Methods of Treatment

One aspect of the invention provides compounds, compositions, and methods useful for treating or preventing a disease or disorder associated with abnormal levels of amino acids by modulation of SLC6A19 transport.

Another aspect of the invention relates to methods of modulating SLC6A19 transport in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

Another aspect of the invention relates to methods of treating or preventing a disease or disorder associated with a genetic defect in phenylalanine hydroxylase in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

In some embodiments, the invention relates to methods of treating or preventing phenylketonuria in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

In some embodiments, the invention relates to methods of treating or preventing hyperphenylalaninemia in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

In some embodiments, the compound reduces systemic phenylalanine levels in the subject.

In some embodiments, the invention relates to methods of treating or preventing tyrosinemia (Type I, II, or III) in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

In some embodiments, the compound reduces systemic glycine levels in the subject.

In some embodiments, the invention relates to methods of treating or preventing isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

In some embodiments of any one of the disclosed methods, the compound modulates SLC6A19 in the subject.

In some embodiments of any one of the disclosed methods, the compound inhibits SLC6A19 in the subject.

In some embodiments of any one of the disclosed methods, the compound modulates SLC6A19 transport in the subject.

In some embodiments of any one of the disclosed methods, the compound inhibits SLC6A19 transport in the subject.

In some embodiments, the compound reduces systemic levels of an amino acid in the subject.

In some embodiments of any one of the disclosed methods, wherein the subject is a mammal. In some embodiments of any one of the disclosed methods, the mammal is a human.

Pharmaceutical Compositions, Routes of Administration, and Dosing

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of the invention and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition comprises a plurality of compounds of the invention and a pharmaceutically acceptable carrier.

In certain embodiments, a pharmaceutical composition of the invention further comprises at least one additional pharmaceutically active agent other than a compound of the invention.

Pharmaceutical compositions of the invention can be prepared by combining one or more compounds of the invention with a pharmaceutically acceptable carrier and, optionally, one or more additional pharmaceutically active agents.

As stated above, an “effective amount” refers to any amount that is sufficient to achieve a desired biological effect. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial unwanted toxicity and yet is effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular compound of the invention being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular compound of the invention and/or other therapeutic agent without necessitating undue experimentation. A maximum dose may be used, that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient’s peak or sustained plasma level of the drug. “Dose” and “dosage” are used interchangeably herein.

In certain embodiments, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 2 mg/kg/day. In one embodiment,

intravenous administration of a compound may typically be from 0.5 mg/kg/day to 5 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 10 mg/kg/day.

Generally, daily oral doses of a compound will be, for human subjects, from about 0.01 milligrams/kg per day to 1000 milligrams/kg per day. It is expected that oral doses in the range of 0.5 to 50 milligrams/kg, in one or more administrations per day, will yield therapeutic results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending upon the mode of administration. For example, it is expected that intravenous administration would be from one order to several orders of magnitude lower dose per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of the compound.

For any compound described herein the therapeutically effective amount can be initially determined from animal models. A therapeutically effective dose can also be determined from human data for compounds which have been tested in humans and for compounds which are known to exhibit similar pharmacological activities, such as other related active agents. Higher doses may be required for parenteral administration. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention can be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the compound can be administered to a subject by any mode that delivers the compound to the desired surface. Administering a pharmaceutical composition may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to intravenous, intramuscular, intraperitoneal, intravesical (urinary bladder), oral, subcutaneous, direct injection (for example, into a tumor or abscess), mucosal (e.g., topical to eye), inhalation, and topical.

For intravenous and other parenteral routes of administration, a compound of the invention can be formulated as a lyophilized preparation, as a lyophilized preparation of liposome-intercalated or -encapsulated active compound, as a lipid complex in aqueous suspension, or as a salt complex. Lyophilized formulations are generally reconstituted in suitable aqueous solution, e.g., in sterile water or saline, shortly prior to administration.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers, e.g., EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of the above component or components. The component or components may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of acid hydrolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Abuchowski and Davis, "Soluble Polymer-Enzyme Adducts", In: *Enzymes as Drugs*, Hoenberg and Roberts, eds., Wiley-Interscience, New York, N.Y., pp. 367-383 (1981); Newmark et al., *J Appl Biochem* 4:185-9 (1982). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. For pharmaceutical usage, as indicated above, polyethylene glycol moieties are suitable.

For the component (or derivative) the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound of the invention (or derivative) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic (e.g., powder); for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the invention (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates, especially mannitol, α -lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may be also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents which can be used and can include benzalkonium chloride and benzethonium chloride. Potential non-ionic detergents that could be included in the formulation as surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the compound of the invention or derivative either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For topical administration, the compound may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art. Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

For administration by inhalation, compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Also contemplated herein is pulmonary delivery of the compounds disclosed herein (or salts thereof). The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of inhaled molecules include Adjei et al., *Pharm Res* 7:565-569 (1990); Adjei et al., *Int J Pharmaceutics* 63:135-144 (1990) (leuprolide acetate); Braquet et al., *J Cardiovasc Pharmacol* 13(suppl. 5):143-146 (1989) (endothelin-1); Hubbard et al., *Annal Int Med* 3:206-212 (1989) (α 1-antitrypsin); Smith et al., 1989, *J Clin Invest* 84:1145-1146 (a-1-proteinase); Oswein et al., 1990, "Aerosolization of Proteins", Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, March, (recombinant human growth hormone); Debs et al., 1988, *J*

Immunol 140:3482-3488 (interferon-gamma and tumor necrosis factor alpha) and Platz et al., U.S. Pat. No. 5,284,656 (granulocyte colony stimulating factor; incorporated by reference). A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Pat. No. 5,451,569 (incorporated by reference), issued Sep. 19, 1995 to Wong et al.

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Mo.; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colo.; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Mass.

All such devices require the use of formulations suitable for the dispensing of the compounds of the invention. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically modified compound of the invention may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise a compound of the invention (or derivative) dissolved in water at a concentration of about 0.1 to 25 mg of biologically active compound of the invention per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for inhibitor stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the compound of the invention caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound of the invention (or derivative) suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane,

dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing compound of the invention (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation. The compound of the invention (or derivative) should advantageously be prepared in particulate form with an average particle size of less than 10 micrometers (μm), most preferably 0.5 to 5 μm , for most effective delivery to the deep lung.

Nasal delivery of a pharmaceutical composition of the present invention is also contemplated. Nasal delivery allows the passage of a pharmaceutical composition of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. Preferably, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as

suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethylcellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, a compound may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical

compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R, *Science* 249:1527-33 (1990).

The compound of the invention and optionally other therapeutics may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt or cocrystal. When used in medicine the salts or cocrystals should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts or cocrystals may conveniently be used to prepare pharmaceutically acceptable salts or cocrystals thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonc, tartaric, citric, methane sulphonc, formic, malonic, succinic, naphthalene-2-sulphonc, and benzene sulphonc. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

Pharmaceutical compositions of the invention contain an effective amount of a compound as described herein and optionally therapeutic agents included in a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

The therapeutic agent(s), including specifically but not limited to a compound of the invention, may be provided in particles. Particles as used herein means nanoparticles or microparticles (or in some instances larger particles) which can consist in whole or in part of the compound of the invention or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero-order release, first-order

release, second-order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the compound of the invention in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described in Sawhney H S et al. (1993) *Macromolecules* 26:581-7, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, gluten, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The term “controlled release” is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including but not limited to sustained release and delayed release formulations. The term “sustained release” (also referred to as “extended release”) is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term “delayed release” is used in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug there from. “Delayed release” may or may not involve gradual release of drug over an extended period of time, and thus may or may not be “sustained release.”

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. “Long-term” release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7

days, and preferably 30-60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1: SLC6A19 Isoleucine transport assay

Cell line generation and maintenance

The Flp-In™ T-REx™ 293 cell line was purchased from Thermo Fisher Scientific. The line was used to generate a stable cell line inducibly expressing human SLC6A19 with a C-terminal V5 tag and stably expressing human TMEM27 (also known as Collectrin) with a C-terminal myc-DDK tag. The stable cell line was generated by transfecting SLC6A19- and TMEM27-encoding plasmids using standard protocols, followed by antibiotic selection. Stable cells were maintained in DMEM/F12 supplemented with Glutamax, 10% fetal bovine serum, 100 U/mL penicillin, 100 ug/mL streptomycin, 200 ug/mL hygromycin, 10 ug/mL blasticidin and 300 ug/mL neomycin (Thermo Fisher).

Assay: Isoleucine transport assay in 96-well format

Stable cell lines were seeded at a density of 35,000 cells per well in a poly-D-lysine coated 96-well cell culture-treated plate on day 0. On day 1 the expression of SLC6A19 was induced by dispensing tetracycline at a final concentration of 1 ug/mL using a Tecan D300e digital dispenser. On day 2 the transport assay was run. Media was removed from the plate using the GentleSpin setting of a Centrifugal Blue Washer (Blue Cat Bio) and cells were washed with 175 uL live cell imaging solution (Thermo Fisher) using the Blue Washer.

Following washing, cells were treated with 70 uL of either DMSO, positive control or compound, diluted in Krebs buffer (140 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgCl₂, 11 mM HEPES, 10 mM Glucose, pH 7.4) at room temperature. After 20-60 minutes 30 uL of a 3.3 mM solution of ¹³C₆, ¹⁵N-L-isoleucine (Cambridge Isotope Laboratories) was added. After 20 min incubation with the isoleucine substrate at room temperature cells were washed with 175 uL live cell imaging solution using the Blue Washer. Cells were then lysed in 150 uL of 15 uM D-Leucine-d10 (CDN Isotopes) in ultrapure water. Plates were put on a shaker at 700 rpm for a minimum of 40 minutes to facilitate lysis. Following lysis, a standard dilution curve of ¹³C₆, ¹⁵N-L-isoleucine was added to wells containing lysates of untreated cells. Plates were returned to the shaker for a minimum of 2 minutes to ensure proper mixing of the standard curve. Plates were then centrifuged for 5 min at 4,000 rpm to pellet cellular debris and precipitate. Supernatants were diluted 1:10 in acetonitrile + 0.1% formic acid in polypropylene plates.

Assay: Isoleucine transport assay in 384-well format

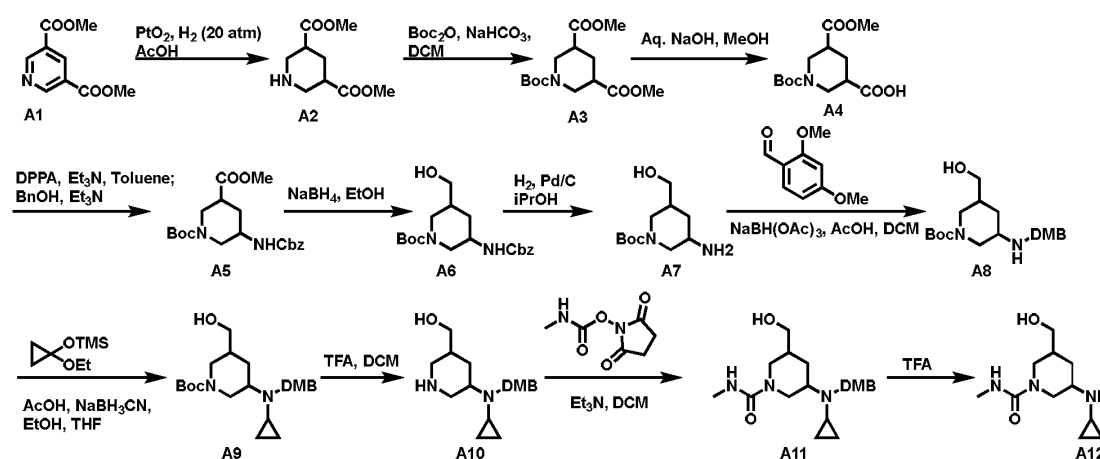
On day 0, stable cell lines were seeded at a density of 20,000 cells per well in a poly-D-lysine coated 384-well cell culture-treated plate in media containing 1 ug/mL tetracycline using a Viaflo 384-well pipette. Transport assays were run the following day (day 1). Media was removed from the plate using the GentleSpin setting of a Centrifugal Blue Washer (Blue Cat Bio) and cells were washed with 80 uL live cell imaging solution (Thermo Fisher) using the Blue Washer. Following washing, cells were treated with 20 uL of either DMSO, positive control or compound, diluted in Krebs buffer (140 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgCl₂, 11 mM HEPES, 10 mM Glucose, pH 7.4) using a TECAN liquid handler. After 20-60 minutes incubation at room temperature 8.6 uL of a 3.3 mM solution of ¹³C₆, ¹⁵N-L-isoleucine (Cambridge Isotope Laboratories) was added. After 20 min incubation with the isoleucine substrate at room temperature cells were washed with 80 uL live cell imaging solution using the Blue Washer. Cells were then lysed in 80 uL of 15 uM D-Leucine-d10 (CDN Isotopes) in ultrapure water. Plates were put on a shaker at 700 rpm for a minimum of 2 hours to facilitate lysis. Following lysis, a standard dilution curve of ¹³C₆, ¹⁵N-L-isoleucine was added to wells containing lysates of untreated cells. Plates were returned to the shaker for a minimum of 5 minutes to ensure proper mixing of the standard curve. Plates were then centrifuged for 10 min at 4,000 rpm to pellet cellular debris and precipitate. Supernatants were diluted 1:10 in acetonitrile + 0.1% formic acid in polypropylene plates.

$^{13}\text{C}_6$, ^{15}N -L-isoleucine analysis was performed using a RapidFire365-QTOF 6545 (Agilent). Quantitative sample analysis utilizes automated solid-phase extraction (HILIC H6 cartridge) prior to mass spec injection. Samples were loaded using 95% acetonitrile, 0.1% formic acid and eluted from the cartridge with 5% acetonitrile, 0.1% formic acid directly for ESI-MS (electrospray ionization) analysis. Quantification of the analytes were performed using Agilent Masshunter Quant software from the high-resolution full scan data.

Example 2: Synthesis of Exemplary Compounds

Synthesis of Common Intermediates

Synthesis of A12



Step 1: Synthesis of A2

To a solution of **A1** (50 g, 256.2 mmol) in AcOH (120 mL) was added PtO₂ (5g, 22.0 mmol). The resulting mixture was stirred at 50 °C for 16 hrs under H₂ atmosphere (20 atm). Then the mixture was filtered and concentrated under reduced pressure to give crude **A2** (50 g, 97% yield) which was used in next step directly without further purification. LC/MS (ESI) *m/z*: 202 (M+H)⁺.

Step 2: Synthesis of A3

To a solution of **A2** (50 g, 248.5 mmol) in DCM (500 mL) were added NaHCO₃ (76 g, 904.7 mmol) and Boc₂O (66.4 g, 304.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 hrs. The mixture was diluted with water (500 mL) and extracted with DCM (500 mL x 2). The combined organic layers were washed with brine (500 mL), dried

over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~15% EtOAc in PE) to give the cis isomer **A3** (24.0 g, 32% yield) as white solid. **LC/MS (ESI) *m/z***: 246 (M+H-56)⁺. ¹H NMR (400 MHz, CDCl₃) δ 4.35 (br s, 2H), 3.69 (s, 6H), 2.88 – 2.36 (m, 6H), 1.45 (s, 9H); and the trans isomer (9.1 g, 12% yield) as a colorless oil. **LC/MS (ESI) *m/z***: 246 (M+H-56)⁺. ¹H NMR (400 MHz, CDCl₃) δ 3.82 – 3.70 (m, 2H), 3.68 (s, 6H), 3.60 – 3.42 (m, 2H), 2.85 – 2.77 (m, 2H), 2.15 – 1.96 (m, 2H), 1.44 (s, 9H).

Step 3: Synthesis of A4

To a solution of **A3** (24 g, 79.6 mmol) in MeOH (240 mL) were added 2M NaOH (42 mL, 84.0 mmol, aq.) at 0 °C. The resulting mixture was stirred at room temperature for 16 hrs. Then the mixture was diluted with water (250 mL) and extracted with EtOAc (250 mL). The aqueous layer was adjusted with HCl (1M) to pH=4, then extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~70% EtOAc in PE) to give **A4** (16 g, 70% yield) as white solid. **LC/MS (ESI) *m/z***: 232 (M+H-56)⁺.

Step 4: Synthesis of A5

To a solution of **A4** (16 g, 55.7 mmol) in toluene (160 mL) were added DPPA (18.4 g, 66.8 mmol) and TEA (6.8 g, 66.8 mmol) at 0 °C. The resulting mixture was stirred at 110 °C for 2 hrs under N₂ atmosphere. Then BnOH (30.1 g, 278.5 mmol) and TEA (6.8 g, 66.8 mmol) was added into the above mixture at 0 °C. The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the mixture was diluted with water (250 mL) and extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~40% EtOAc in PE) to give **A5** (12.8 g, 59% yield) as white solid. **LC/MS (ESI) *m/z***: 293 (M+H-100)⁺.

Step 5: Synthesis of A6

To a solution of **A5** (12.8 g, 32.6 mmol) in EtOH (150 mL) was added NaBH₄ (3.0 g, 81.5 mmol) at 0 °C in portions. The resulting mixture was stirred at room temperature for 16 hrs. Then the mixture was quenched with water (200 mL) and extracted with EtOAc (200 mL x

2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~60% EtOAc in PE) to give **A6** (10.2 g, 28.0 mmol) as white solid. **LC/MS (ESI)** m/z : 265 ($\text{M}+\text{H}-100$)⁺.

Step 6: Synthesis of A7

To a solution of **A6** (10.0 g, 27.5 mmol) in *i*-PrOH (150 mL) was added Pd/C (1.0 g, 10 wt%) at room temperature under nitrogen atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The resulting mixture was stirred at room temperature for 18 hrs under H_2 atmosphere. Then the mixture was filtered through a pad of Celite®, the filter cake was washed with MeOH (100 mL). The combined filtrates were concentrated to dryness to give crude **A7** (6.1 g, 97% yield) which was used in next step directly without further purification. **LC/MS (ESI)** m/z : 231 ($\text{M}+\text{H}$)⁺.

Step 7: Synthesis of A8

To a solution of **A7** (2.4 g, 10.4 mmol) in DCM (50 mL) were added AcOH (1.2 g, 20.8 mmol) and 2,4-dimethoxybenzaldehyde (8.9 g, 71.5 mmol) at room temperature. The resulting mixture was stirred for 1 hr under N_2 atmosphere. Then $\text{NaBH}(\text{OAc})_3$ (2.65 g, 12.48 mmol) was added into the above mixture in portions at 0 °C and the resulting mixture was stirred at room temperature for 3 hrs under N_2 atmosphere. Then the mixture was filtered and rinsed with DCM (50 mL x 2). The filtrate was diluted with water (70 mL) and extracted with DCM (40 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **A8** (2.7 g, 68% yield) as light-yellow oil. **LC/MS (ESI)** m/z : 381 ($\text{M}+\text{H}$)⁺.

Step 8: Synthesis of A9

To a solution of **A8** (2.7 g, 7.1 mmol) in THF/EtOH (60 mL, v/v = 2:1) was added AcOH (4.3 g, 71 mmol), (1-ethoxycyclopropoxy)trimethylsilane (2.5 g, 14.2 mmol) and NaBH_3CN (1.3 g, 21.3 mmol). The resulting mixture was stirred at 80 °C for 4 hrs under N_2 atmosphere. Then the mixture was neutralized with NaHCO_3 (aq.) until the pH was adjusted to pH = 8. The mixture was diluted with water (80 mL) and extracted with EtOAc (70 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and

concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **A9** (2.0 g, 67% yield) as colorless oil. LC/MS (ESI) m/z : 421 (M+H)⁺.

Step 9: Synthesis of A10

To a solution of **A9** (2.0 g, 4.8 mmol) in DCM (20 mL) was added TFA (4 mL) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 6 hrs. Then the reaction mixture was concentrated under reduced pressure. The residue was diluted with DCM (20 mL), neutralized with NaHCO₃ (aq.) until the pH was adjusted to pH = 8. Then the mixture was extracted with DCM (40 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 10~15% MeOH in DCM) to give **A10** (1.3 g, 86% yield) as light-yellow oil. LC/MS (ESI) m/z : 321 (M+H)⁺.

Step 10: Synthesis of A11

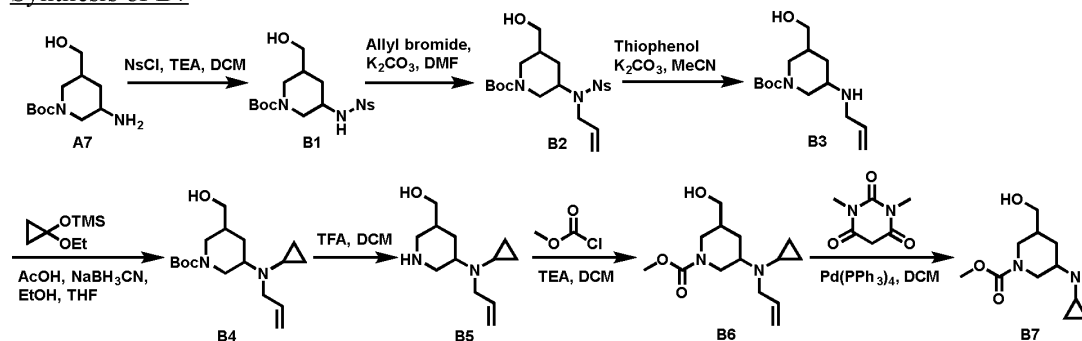
To a solution of **A10** (1.3 g, 4.1 mmol) in DCM (20 mL) was added TEA (1.2 g, 8.2 mmol) and 2,5-dioxopyrrolidin-1-yl methylcarbamate (0.8 g, 4.9 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 12 hrs. Then the mixture was diluted with water (30 mL) and extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 10~15% MeOH in DCM) to give **A11** (1.2 g, 80% yield) as colorless oil. LC/MS (ESI) m/z : 378 (M+H)⁺.

Step 11: Synthesis of A12

To a solution of **A11** (1.2 g, 3.2 mmol) in DCM (20 mL) was added TFA (5 mL) dropwise at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with DCM (30 mL), neutralized with NaHCO₃ (aq.) until the pH was adjusted to pH = 8. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column

chromatography (eluted with 25~30% MeOH in DCM) to give **A12** (0.6 g, 83% yield) as light-yellow oil. **LC/MS (ESI) m/z** : 228 (M+H)⁺.

Synthesis of B7



Step 1: Synthesis of B1

To a solution of **A7** (6.1 g, 26.5 mmol) in DCM (100 mL) was added TEA (4.0 g, 40.0 mmol) and NsCl (6.4 g, 29.1 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was diluted with water (150 mL) and extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **B1** (6.5 g, 59% yield) as white solid. **LC/MS (ESI) m/z** : 360 (M+H-56)⁺.

Step 2: Synthesis of B2

To a mixture of **B1** (6.5 g, 15.7 mmol) and K₂CO₃ (4.3 g, 31.4 mmol) in DMF (100 mL) was added allyl bromide (3.8 g, 31.4 mmol) in portions at 0 °C and the resulting mixture was stirred at room temperature for 18 hrs under N₂ atmosphere. Then the mixture was filtered and rinsed with DCM (50 mL x 2). The filtrate was diluted with water (150 mL) and extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **B2** (6.5 g, 91% yield) as a yellow oil. **LC/MS (ESI) m/z** : 400 (M+H-56)⁺.

Step 3: Synthesis of B3

To a solution of **B2** (6.5 g, 14.3 mmol) in MeCN (120 mL) were added K₂CO₃ (9.9 g, 71.5 mmol) and thiophenol (8.9 g, 71.5 mmol). The resulting mixture was stirred at 80 °C for 18 hrs under N₂ atmosphere. Then the mixture was diluted with water (150 mL) and extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **B3** (3.1 g, 83% yield) as light-yellow oil. **LC/MS (ESI) m/z**: 271 (M+H)⁺.

Step 4: Synthesis of B4

A mixture of **B3** (3.1 g, 11.5 mmol), (1-ethoxycyclopropoxy)trimethylsilane (4.0 g, 23.0 mmol), AcOH (6.9 g, 115 mmol) and NaBH₃CN (2.2 g, 34.5 mmol) in a solution of THF/EtOH (90 mL, V/V=2:1) were stirred at 80 °C for 4 hrs under N₂ atmosphere. Then the mixture was neutralized with NaHCO₃ (aq., sat.) until the pH was adjusted to pH = 8. The mixture was diluted with water (60 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **B4** (3.2 g, 90% yield) as colorless oil. **LC/MS (ESI) m/z**: 311 (M+H)⁺.

Step 5: Synthesis of B5

To a solution of **B4** (1.0 g, 3.2 mmol) in DCM (12 mL) were added TFA (3 mL) at 0 °C in portions under N₂ atmosphere. The resulting mixture was stirred at room temperature for 5 hrs. Then the reaction mixture was concentrated under reduced pressure to dryness. The residue was diluted with water (20 mL), neutralized with NaHCO₃ (aq., sat.) until the pH was adjusted to pH = 8, then extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 20~30% MeOH in DCM) to give **B5** (0.62 g, 92% yield) as light-yellow oil. **LC/MS (ESI) m/z**: 211 (M+H)⁺.

Step 6: Synthesis of B6

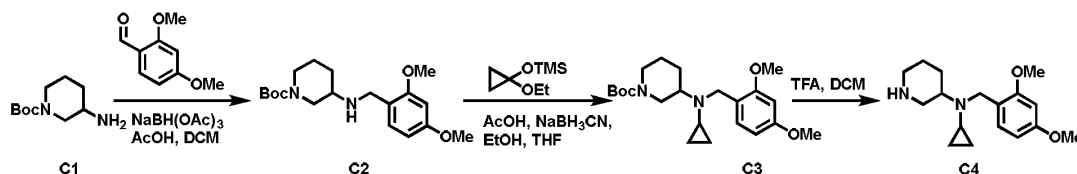
To a mixture of **B5** (200 mg, 0.95 mmol) and TEA (144 mg, 1.4 mmol) in dry DCM (12 mL) was added methyl chloroformate (89 mg, 0.95 mmol) dropwise at 0 °C under N₂ atmosphere.

The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was diluted with water (20 mL) and extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 10~15% MeOH in DCM) to give **B6** (140 mg, 55% yield) as colorless oil. LC/MS (ESI) *m/z*: 269 (M+H)⁺.

Step 7: Synthesis of B7

To a solution of **B6** (140 mg, 0.52 mmol) in DCM (8 mL) was added Pd(PPh₃)₄ (57 mg, 0.05 mmol) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (162 mg, 1.04 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was warmed up to room temperature and stirred for 50 min. Then the mixture was diluted with water (30 mL) and extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 20~25% MeOH in DCM) to give **B7** (107 mg, 90% yield) as brown oil. LC/MS (ESI) *m/z*: 229 (M+H)⁺.

Synthesis of C4



Step 1: Synthesis of C2

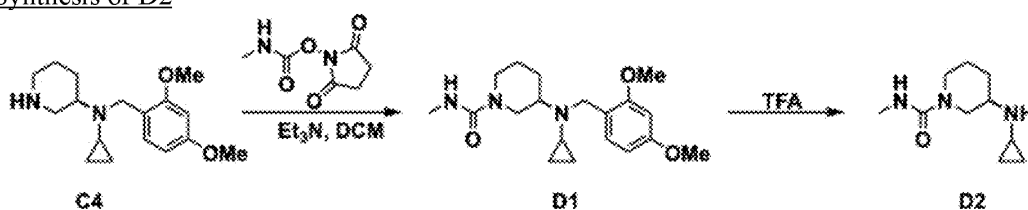
To a solution of **C1** (7.0 g, 34.9 mmol) in DCM (140 mL) was added 2,4-dimethoxybenzene-1-carbaldehyde (5.8 g, 34.9 mmol) and HOAc (5.9 mL, 104.8 mmol) at room temperature under N₂ atmosphere. After stirring at room temperature for 1 hr, Sodium triacetoxyborohydride (22.1 g, 104.8 mmol) was added into the above mixture in portions and the resulting mixture was stirred at room temperature for another 6 hrs. Then the mixture was quenched with H₂O (150 mL) and extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **C2** (7.3 g, 60% yield) as yellow oil. LC/MS (ESI) *m/z*: 351 (M+H)⁺.

Step 2: Synthesis of C3

To a mixture of **C2** (7.3 g, 20.8 mmol) in THF (200 mL) and EtOH (50 mL) was added acetic acid (17.9 mL, 312 mmol), (1-ethoxycyclopropoxy)trimethylsilane (12.5 mL, 62.4 mmol) and sodium cyanoborohydride (3.2 g, 52.0 mmol) at room temperature under N₂ atmosphere. The resulting mixture was stirred at 80 °C for 8 hrs. Then the mixture was concentrated under reduced pressure and the residue was diluted with H₂O (160 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (120 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **C3** (6.7 g, 82% yield) as yellow oil. **LC/MS (ESI) *m/z***: 391 (M+H)⁺.

Step 3: Synthesis of C4

To a solution of **C3** (6.7 g, 17.1 mmol) in DCM (50 mL) was added TFA (8 mL) dropwise at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in DCM (50 mL) and neutralized with NaHCO₃ (aq., sat.) until the pH was adjusted to pH= 8. Then the resulting mixture was diluted with H₂O (150 mL) and extracted with DCM (120 mL x 2). The combined organic layers were washed with brine (120 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **C4** (4.5 g, 91% yield) as yellow oil. **LC/MS (ESI) *m/z***: 291 (M+H)⁺.

Synthesis of D2**Step 1: Synthesis of D1**

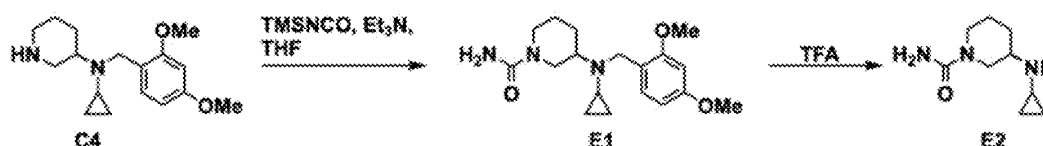
To a mixture of **C4** (4.5 g, 15.5 mmol) and TEA (2.1 mL, 15.5 mmol) in DCM (100 mL) was added 2,5-dioxopyrrolidin-1-yl methylcarbamate (3.2 g, 18.6 mmol) dropwise at 0

°C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was diluted with H₂O (80 mL) and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **D1** (3.4 g, 63%) as white solid. **LC/MS (ESI) *m/z***: 348 (M+H)⁺.

Step 2: Synthesis of D2

A solution of **D1** (3.4 g, 9.7 mmol) in TFA (50 mL) was stirred at 80 °C for 3 hrs under N₂ atmosphere. After completion, the resulting mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (30 mL) and neutralized with NaHCO₃ (aq, sat.) until the pH was adjusted to pH= 8. The resulting mixture was diluted with H₂O (70 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **D2** (1.7 g, 89% yield) as colorless oil. **LC/MS (ESI) *m/z***: 198 (M+H)⁺.

Synthesis of E2



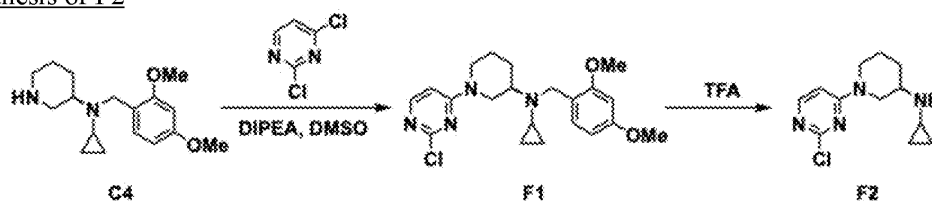
Step 1: Synthesis of E1

To a mixture of **C4** (2 g, 6.8 mmol) and TEA (2.8 mL, 20.6 mmol) in dry THF (40 mL) was added TMSNCO (0.75 g, 7.5 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 16 hrs. Then the mixture was diluted with H₂O (50 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **E1** (1.76 g, 77%) as white solid. **LC/MS (ESI) *m/z***: 334 (M+H)⁺.

Step 2: Synthesis of E2

A solution of **E1** (1.76 g, 5.2 mmol) in TFA (40 mL) was stirred at 80 °C for 3 hrs under N₂ atmosphere. After completion, the resulting mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (30 mL) and neutralized with NaHCO₃ (aq, sat.) until the pH was adjusted to pH=8. The resulting mixture was diluted with H₂O (70 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **E2** (823 mg, 85% yield) as colorless oil. LC/MS (ESI) *m/z*: 184 (M+H)⁺.

Synthesis of F2



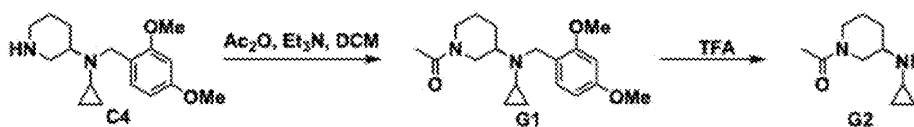
Step 1: Synthesis of F1

To a solution of **C4** (600 mg, 2.06 mmol) in DMSO (12 mL) was added DIEA (667 mg, 5.17 mmol) and 2,4-dichloropyrimidine (367 mg, 2.48 mmol) at room temperature under N₂ atmosphere. The resulting mixture was stirred at 100 °C for 2 hrs. The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~10% EtOAc in PE) to give **F1** (578 mg, 69% yield) as yellow solid. LC/MS (ESI) *m/z*: 403 (M+H)⁺.

Step 2: Synthesis of F2

A solution of **F1** (578 mg, 1.4 mmol) in TFA (10 mL) was stirred at 80°C for 3 hrs. Then the mixture was concentrated under reduced pressure to give crude **F2** (351 mg, 96% yield) which was used in the next step directly without further purification. LC/MS (ESI) *m/z*: 253 (M+H)⁺.

Synthesis of G2



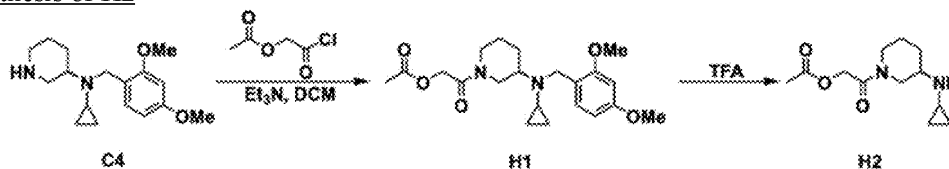
Step 1: Synthesis of G1

To a solution of **C4** (400 mg, 1.38 mmol) in dry DCM (12 mL) were added TEA (418 mg, 4.13 mmol) and acetic anhydride (211 mg, 2.07 mmol) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 30 min. Then the mixture was diluted with H₂O (30 mL) and extracted with DCM (20 mL × 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **2** (440 mg, quant.) as colorless oil which was used in the next step directly without further purification. **LC/MS (ESI) *m/z***: 333 (M+H)⁺.

Step 2: Synthesis of G2

A round-bottom flask was charged with **G1** (440 mg, 1.32 mmol) and TFA (10 mL), the reaction mixture was stirred at 80 °C for 4 hrs. Then the mixture was concentrated under reduced pressure to give crude **G2** (241 mg, quant.) as purple oil which was used in next step directly without further purification. **LC/MS (ESI) *m/z***: 183 (M+H)⁺.

Synthesis of H2

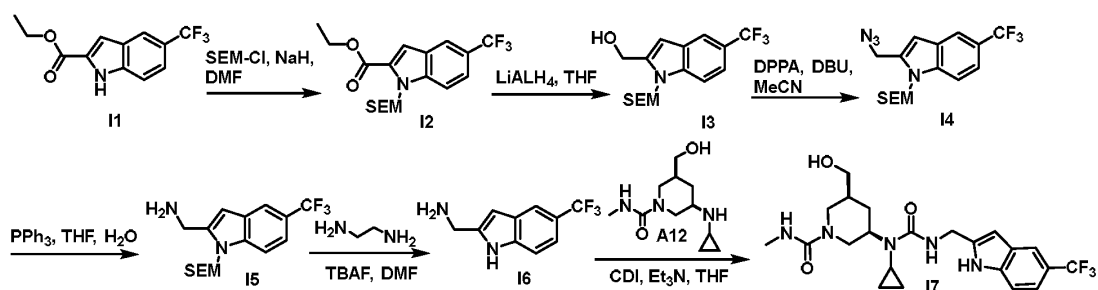


Step 1: Synthesis of H2

To a mixture of **C4** (400 mg, 1.4 mmol) and TEA (212 mg, 2.1 mmol) in dry DCM (12 mL) was added 2-chloro-2-oxoethyl acetate (231 mg, 1.7 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 hr under N₂ atmosphere. Then the mixture was quenched with water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~4% MeOH in DCM) to give **H1** (414 mg, 77% yield) as colorless oil. **LC/MS (ESI) *m/z***: 391 (M+H)⁺.

Step 2: Synthesis of H2

A solution of **H1** (414 mg, 1 mmol) in TFA (10 mL) was stirred at 80 °C for 2 hrs. Then the mixture was concentrated under reduced pressure to give crude **H2** (234 mg, 92% yield) as purple oil which was used in the next step directly without further purification. **LC/MS (ESI)** m/z : 241 (M+H)⁺.

*Syntheses of Select Examples*Synthesis of Example 1**Step 1: Synthesis of I2**

To a solution of **I1** (370 mg, 1.4 mmol) in anhydrous DMF (8 mL) was added NaH (51 mg, 2.1 mmol) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min and then SEMCl (360 mg, 2.1 mmol) was added into the above mixture at 0 °C dropwise. The resulting mixture was allowed to warm to room temperature for 4 hrs. Then the mixture was quenched with saturated NH₄Cl (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~6% EtOAc in PE) to give **I2** (410 mg, 73% yield) as colorless oil.

Step 2: Synthesis of I3

To a solution of **I2** (410 mg, 1.0 mmol) in anhydrous THF (8 mL) was added LiAlH₄ (48 mg, 1.2 mmol) in portions at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 3 hrs. Then the mixture was quenched with H₂O (0.1 mL) followed by the addition of 15% NaOH (0.1 mL) and H₂O (0.3 mL) before it was filtered and rinsed with

EtOAc (20 mL). The filtrate was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~18% EtOAc in PE) to give **I3** (260 mg, 71% yield) as colorless oil. **LC/MS (ESI)** *m/z*: 346 (M+H)⁺.

Step 3: Synthesis of I4

To a solution of **I3** (260 mg, 0.7 mmol) in toluene (8 mL) was added DBU (137 mg, 0.8 mmol) and DPPA (248 mg, 0.8 mmol) at 0 °C. The resulting mixture was stirred at 110 °C for 2 hrs under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were concentrated under reduced pressure to give crude **I4** (210 mg, 75% yield) as yellow oil which was used in the next step directly without further purification.

Step 4: Synthesis of I5

To a solution of **I4** (210 mg, 0.6 mmol) in THF (5 mL) and H₂O (1 mL) was added PPh₃ (223 mg, 0.9 mmol) and the resulting mixture was stirred at room temperature for 18 hrs. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~8% MeOH in DCM) to give **I5** (170 mg, 87% yield) as light-yellow oil. **LC/MS (ESI)** *m/z*: 345 (M+H)⁺.

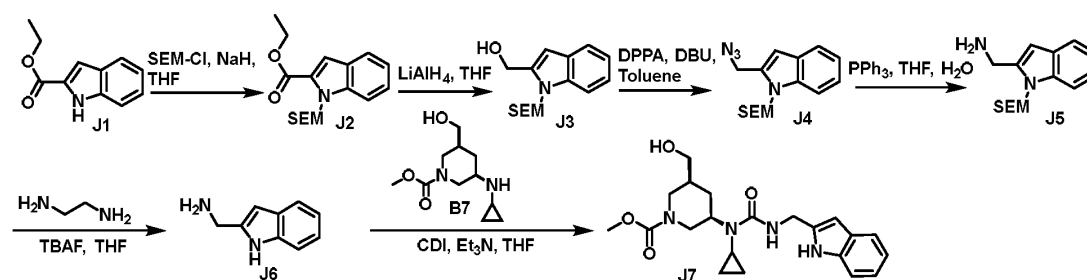
Step 5: Synthesis of I6

To a solution of **I5** (170 mg, 0.49 mmol) in DMF (6 mL) were added ethylenediamine (177 mg, 2.94 mmol) and TBAF (1 N in THF, 0.73 mL, 1.47 mmol). The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give **I6** (83 mg, 79% yield) as colorless oil. **LC/MS (ESI)** *m/z*: 215 (M+H)⁺.

Step 6: Synthesis of I7/Example 1

To a solution of **I6** (83 mg, 0.38 mmol) in anhydrous THF (4 mL) was added CDI (62 mg, 0.38 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give the acyl imidazole (105 mg, 88% yield) as white solid. **LC/MS (ESI) *m/z***: 309 (M+H)⁺. To a solution of acyl imidazole (105 mg, 0.34 mmol) in THF (8 mL) were added TEA (0.22 mL, 1.02 mmol) and **A12** (77 mg, 0.34 mmol). The resulting mixture was stirred at 60 °C for 2 hrs. Then the mixture was diluted with water (30 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give a white solid (63 mg, 52% yield). **LC/MS (ESI) *m/z***: 468 (M+H)⁺. The product was further separated by SFC (Waters Thar 80 preparative SFC; ChiralPak AD, 250×4.6 mm I.D. 5μm; AD_MeOH_DEA_40) to afford **ent-Example 1** and **I7/Example 1** (19 mg, 30% yield, e.e.99%) as white solid. **¹H NMR** (400 MHz, CD₃OD) **¹H NMR** (400 MHz, MeOD) δ 7.80 (s, 1H), 7.51-7.48(m, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.45 (s, 1H), 4.56 (s, 2H), 4.11 (d, J = 12.7 Hz, 1H), 3.94 (d, J = 11.9 Hz, 1H), 3.75 (dd, J = 9.9, 5.7 Hz, 1H), 3.51 – 3.44 (m, 2H), 3.15 (t, J = 12.0 Hz, 1H), 2.73 (s, 3H), 2.58 – 2.52 (m, 1H), 2.48 – 2.40 (m, 1H), 1.89 (dd, J = 23.7, 11.7 Hz, 2H), 1.81 – 1.69 (m, 1H), 0.96 (dd, J = 6.4, 3.1 Hz, 2H), 0.80 (d, J = 4.0 Hz, 2H). **¹⁹F NMR** (377 MHz, CD₃OD) δ -61.60 (s).

Synthesis of Example 2



Step 1: Synthesis of J2

To a solution of **J1** (2 g, 10.5 mmol) in anhydrous THF (60 mL) was added NaH (634 mg, 15.7 mmol) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min and then SEMCl (2.5 g, 15.7 mmol) was added into the above mixture dropwise at 0 °C.

The resulting mixture was stirred at room temperature for 4 hrs. Then the mixture was quenched with saturated NH_4Cl (80 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~6% EtOAc in PE) to give **J2** (3.0 g, 90% yield) as yellow oil.

Step 2: Synthesis of J3

To a solution of **J2** (3.0 g, 19.4 mmol) in anhydrous THF (80 mL) was added LiAlH_4 (428 mg, 23.2 mmol) in portions at 0 °C under N_2 atmosphere. The resulting mixture was stirred at room temperature for 3 hrs. Then the mixture was quenched with H_2O (0.5 mL) followed by the addition of 15% NaOH (0.5 mL) and H_2O (1.5 mL) before it was diluted with EtOAc (100 mL) and filtered. The filtrate was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~18% EtOAc in PE) to give **J3** (2.1 g, 80% yield) as yellow oil. LC/MS (ESI) m/z : 278 (M+H)⁺.

Step 3: Synthesis of J4

To a solution of **J3** (2.1 g, 7.5 mmol) in toluene (50 mL) were added DBU (1.3 g, 9 mmol) and DPPA (2.5 g, 9 mmol). The resulting mixture was stirred at 110 °C for 2 hrs under N_2 atmosphere. Then the mixture was diluted with water (80 mL) and extracted with EtOAc (60 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give crude **J4** (1.8 g, 78% yield) as yellow oil which was used in the next step directly without further purification.

Step 4: Synthesis of J5

To a solution of **J4** (1.8 g, 5.9 mmol) in THF (30 mL) and H_2O (6 mL) was added PPh_3 (1.8 g, 7.0 mmol) and the resulting mixture was stirred at room temperature for 18 hrs. Then the mixture was diluted with H_2O (60 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~8% MeOH in DCM) to give **J5** (1.2 g, 75% yield) as light-yellow oil. LC/MS (ESI) m/z : 277 (M+H)⁺.

Step 5: Synthesis of J6

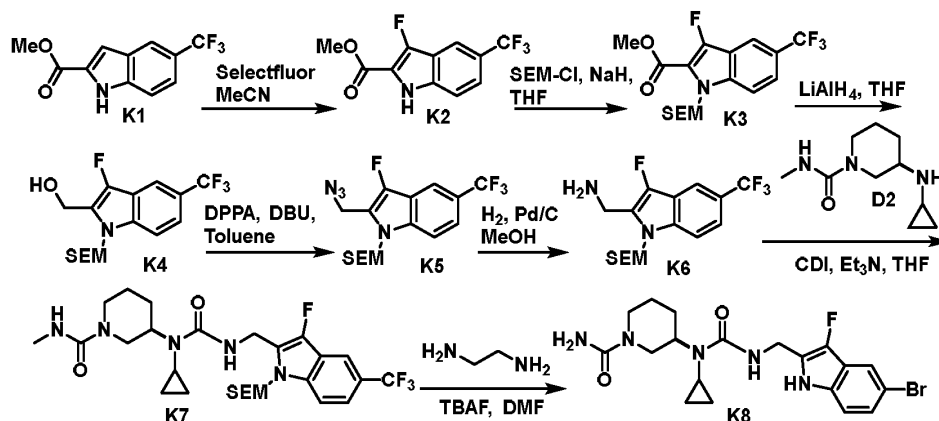
To a solution of **J5** (1.2 g, 4.3 mmol) in DMF (30 mL) was added ethylenediamine (1.5 g, 25.8 mmol) and TBAF (1 N in THF, 1.3 mL, 12.9 mmol) at 0 °C. The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with saturated NH₄Cl solution (80 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with water (80 mL) and brine (80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give **J6** (608 mg, 95% yield) as yellow solid. **LC/MS (ESI) *m/z***: 147 (M+H)⁺.

Step 6: Synthesis of J7/Example 2

To a solution of **J6** (608 mg, 4.1 mmol) in anhydrous THF (15 mL) was added CDI (674 mg, 4.1 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give acyl imidazole (762 mg, 76% yield) as white solid. **LC/MS (ESI) *m/z***: 241 (M+H)⁺. To a mixture of **B7** (50 mg, 0.22 mmol) and TEA (44 mg, 0.44 mmol) in THF (6 mL) was added purified acyl imidazole (53 mg, 0.22 mmol). The resulting mixture was stirred at 60 °C for 3 hrs under N₂ atmosphere. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC to afford the product (34 mg, 39% yield) as white solid, which was further separated by SFC (Waters Thar 80 preparative SFC; ChiralPak C-IG, 250×30 mm I.D. 5μm; AD_MeOH_DEA_40) to afford **ent-Example 2** (9.0 mg, 26% yield, e.e.99%). ¹H NMR (400 MHz, CD₃OD) δ 7.49 - 7.39 (m, 1H), 7.35 - 7.22 (m, 1H), 7.11 - 6.99 (m, 1H), 6.98 - 6.90 (m, 1H), 6.28 (s, 1H), 4.50 (s, 2H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.08 (d, *J* = 10.8 Hz, 1H), 3.78 - 3.62 (m, 4H), 3.53 - 3.45 (m, 1H), 3.42 (d, *J* = 6.6 Hz, 1H), 3.25 - 3.13 (m, 1H), 2.56 - 2.32 (m, 2H), 1.95 - 1.80 (m, 2H), 1.78 - 1.66 (m, 1H), 0.99 - 0.89 (m, 2H), 0.79 - 0.71 (m, 2H); and **Example 2/J7** (10.0 mg, 29% yield, e.e.99%). ¹H NMR (400 MHz, CD₃OD) δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.38 - 7.24 (m, 1H), 7.12 - 7.01 (m, 1H), 6.99 - 6.93 (m, 1H), 6.29 (s, 1H), 4.51 (s, 2H), 4.23 (d, *J* = 11.2 Hz, 1H), 4.09 (d, *J* = 10.0 Hz, 1H), 3.78 - 3.62 (m, 4H), 3.53 - 3.46 (m, 1H), 3.43 (d, *J* = 6.8 Hz, 1H), 3.25 - 3.13 (m, 1H), 2.56

– 2.31 (m, 2H), 1.95 - 1.83 (m, 2H), 1.78 – 1.66 (m, 1H), 1.00 - 0.90 (m, 2H), 0.80 – 0.70 (m, 2H).

Synthesis of Example 3



Step 1: Synthesis of K2

To a solution of **K1** (1.06 g, 4.36 mmol) in MeCN (25 mL) was added Selectfluor (1.85 g, 5.23 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 16 hrs under N₂ atmosphere. Then the mixture was diluted with H₂O (50 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via column chromatography on silica gel (PE: EtOAc= 100: 0 to 100: 8) to give **K2** (301 mg, 26% yield) as white solid. **LC/MS (ESI) *m/z***: 262 (M+H)⁺.

Step 2: Synthesis of K3

To a solution of **K2** (300 mg, 1.15 mmol) in dry THF (10 mL) was added NaH (60 wt%) (69 mg, 1.72 mmol) at 0 °C under N₂ atmosphere, the mixture was stirred at 0 °C for 30 min. Then SEMCl (287 mg, 1.72 mmol) was added into the above mixture dropwise at 0 °C and the resulting mixture was allowed to warm to room temperature for additional 1 hr. Then the mixture was quenched with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL×2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **K3** (449 mg, quant.) as colorless oil which was used in the next step directly without further purification. **LC/MS (ESI) *m/z***: 274 (M-117)⁺.

Step 3: Synthesis of K4

To a solution of **K3** (449 mg, 1.15 mmol) in dry THF (10 mL) was added LiAlH₄ (65 mg, 1.72 mmol) in portions at 0 °C. The resulting mixture was stirred at 0 °C for 1 hr under N₂ atmosphere. Then the mixture was quenched by the addition of H₂O (0.1 mL), 15% NaOH (aq.) (0.1 mL) and H₂O (0.3 mL) at 0 °C and the mixture was stirred at room temperature for 30 min. The suspension was then filtered and rinsed with EtOAc (20 mL). The filtrate was dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (PE: EtOAc= 100: 0 to 100: 10) to give **K4** (260 mg, 62% yield) as colorless oil. **LC/MS (ESI) m/z**: 246 (M-117)⁺.

Step 4: Synthesis of K5

To a solution of **K4** (260 mg, 0.72 mmol) in toluene (8 mL) were added DBU (131 mg, 0.86 mmol) and DPPA (236 mg, 0.86 mmol), the resulting mixture was stirred at 100 °C for 3 hrs under N₂ atmosphere. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL×2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **K5** (275 mg, quant.) which was used in the next step directly without further purification.

Step 5: Synthesis of K6

To a solution of **K5** (275 mg, 0.71 mmol) in MeOH (10 mL) was added Pd/C (200 mg, 10 wt%), under nitrogen atmosphere. The suspension was degassed under vacuum and purged with H₂ several times. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was filtered through a pad of Celite®, the filter cake was washed with MeOH (10 mL). The combined filtrates were concentrated to dryness. The residue was purified by column chromatography on silica gel (DCM: MeOH= 100: 0 to 100: 5) to give **K6** (184 mg, 72% yield) as colorless oil. **LC/MS (ESI) m/z**: 346 (M-16)⁺.

Step 6: Synthesis of K7

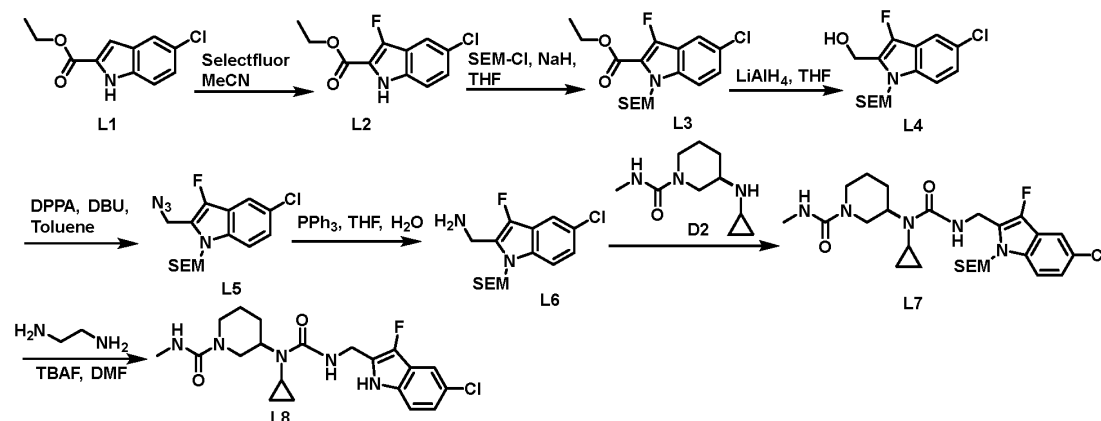
To a solution of **K6** (184 mg, 0.51 mmol) in THF (8 mL) was added CDI (99 mg, 0.61 mmol) at 0 °C, the resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure to give crude acyl imidazole (230 mg, quant.) which was used in the next step directly without further purification. To a solution of **D2** (99 mg, 0.50 mmol) in THF (6 mL) were added TEA (152 mg, 1.50 mmol) and acyl imidazole (230 mg, 0.50 mmol). The resulting mixture was stirred at 55 °C for 16 hrs. Then the mixture

was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL×2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (DCM: MeOH= 100: 0 to 100: 3) to give **K7** (189 mg, 64% yield) as colorless oil. **LC/MS (ESI) *m/z***: 586 (M+H)⁺.

Step 8: Synthesis of **K8/Example 3**

To a solution of **K7** (189 mg, 0.33 mmol) in DMF (5 mL) were added ethylenediamine (119 mg, 1.987 mmol) and TBAF (1.0 mL, 1 mol/L in THF). The resulting mixture was stirred at 80 °C for 1 hr. Then the mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC to give **K8/Example 3** (37.6 mg, 26% yield) as white solid. **LC/MS (ESI) *m/z***: 456 (M+H)⁺. **¹H NMR** (400 MHz, CD₃OD) δ 7.80 (s, 1H), 7.50-7.44 (m, 1H), 7.41-7.35 (m, 1H), 4.58 (s, 2H), 4.02-3.89 (m, 2H), 3.76-3.65 (m, 1H), 3.20-3.10 (m, 1H), 2.73 (s, 3H), 2.71-2.63 (m, 1H), 2.55-2.45 (m, 1H), 2.18-2.06 (m, 1H), 1.97-1.87 (m, 1H), 1.82-1.72 (m, 1H), 1.60-1.44 (m, 1H), 0.98-0.89 (m, 2H), 0.82-0.71 (m, 2H). **¹⁹F NMR** (376 MHz, CD₃OD) δ -61.96 (s), -179.31 (s).

Synthesis of Example 4



Step 1: Synthesis of **L2**

To a solution of **L1** (1 g, 4.5 mmol) in MeCN (30 mL) was added Select Fluor (1.9 g, 5.4 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature

overnight. Then the mixture was quenched with water (40 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~10% EtOAc in PE) to give **L2** (290 mg, 27% yield) as white solid. **LC/MS (ESI) *m/z***: 242 (M+H)⁺.

Step 2: Synthesis of L3

To a solution of **L2** (290 mg, 1.2 mmol) in anhydrous THF (12 mL) was added NaH (72 mg, 1.8 mmol) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min and then SEMCl (300 mg, 1.8 mmol) was added into the above mixture dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was quenched with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **L3** (320 mg, 72% yield) as colorless oil which was used in the next step directly without further purification. **LC/MS (ESI) *m/z***: 372 (M+H)⁺.

Step 3: Synthesis of L4

To a solution of **L3** (320 mg, 0.86 mmol) in anhydrous THF (10 mL) was added LiAlH₄ (48 mg, 1.27 mmol) in portions at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was quenched with H₂O (10 mL) followed by the addition of 15% NaOH (20 mL) and H₂O (10 mL) before it was filtered and rinsed with THF (20 mL). The filtrate was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~15% EtOAc in PE) to give **L4** (270 mg, 95% yield) as colorless oil. **LC/MS (ESI) *m/z***: 330 (M+H)⁺.

Step 4: Synthesis of L5

To a solution of **L4** (270 mg, 0.82 mmol) in toluene (10 mL) were added DBU (129 mg, 0.98 mmol) and DPPA (270 mg, 0.98 mmol). The resulting mixture was stirred at 110 °C for 3 hrs under N₂ atmosphere. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **5**

(220 mg, 76% yield) as yellow oil which was used in next step directly without further purification.

Step 5: Synthesis of L6

To a solution of **L5** (220 mg, 0.62 mmol) in THF (8 mL) and H₂O (2 mL) was added PPh₃ (325 mg, 1.44 mmol) and the resulting mixture was stirred at room temperature overnight. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **L6** (190 mg, 93% yield) as brown oil. **LC/MS (ESI) *m/z***: 312 (M-16)⁺.

Step 6: Synthesis of L7

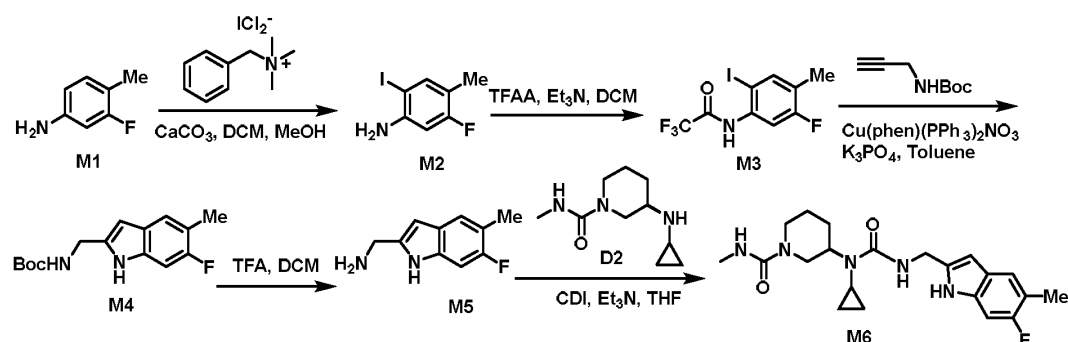
To a solution of **L6** (190 mg, 0.58 mmol) in anhydrous THF (8 mL) was added CDI (103 mg, 0.64 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure to give crude acyl imidazole (212 mg, 86% yield) which was used in next step directly without further purification. **LC/MS (ESI) *m/z***: 423 (M+H)⁺. To a solution of acyl imidazole (80 mg, 0.19 mmol) in anhydrous THF (10 mL) were added TEA (95 mg, 0.94 mmol) and **D2** (37 mg, 0.19 mmol) at 0 °C. The resulting mixture was stirred at 50 °C overnight under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **L7** (92 mg, 87% yield) as colorless oil. **LC/MS (ESI) *m/z***: 552 (M+H)⁺.

Step 8: Synthesis of L8/Example 4

To a solution of **L7** (92 mg, 0.17 mmol) in DMF (5 mL) were added ethylenediamine (64 mg, 1.07 mmol) and TBAF (1 M in THF, 0.51 mL, 0.51 mmol). The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC to give **Example 4/L8** (21

mg, 29% yield) as white solid. **LC/MS (ESI)** m/z : 422 ($M+H$)⁺. **¹H NMR** (400 MHz, CD₃OD) δ 7.42 (d, J = 1.9 Hz, 1H), 7.27 (dd, J = 8.7, 2.4 Hz, 1H), 7.06 (dd, J = 8.7, 2.0 Hz, 1H), 4.54-4.47 (m, 2H), 3.99-3.86 (m, 2H), 3.72-3.61 (m, 1H), 3.13 (t, J = 12.0 Hz, 1H), 2.70 (s, 3H), 2.68-2.60 (m, 1H), 2.51-2.43 (m, 1H), 2.17-2.03 (m, 1H), 1.94-1.83 (m, 1H), 1.81-1.68 (m, 1H), 1.57-1.41 (m, 1H), 0.95-0.85 (m, 2H), 0.78-0.66 (m, 2H). **¹⁹F NMR** (376 MHz, MeOD) δ -179.81 – -180.01 (m).

Synthesis of Example 5



Step 1: Synthesis of M2

To a solution of **M1** (600 mg, 4.79 mmol) in DCM (20 mL) and MeOH (4 mL) was added CaCO₃ (960 mg, 9.58 mmol) and benzyltrimethylammonium dichloroiodate (1827 mg, 5.27 mmol). The resulting mixture was stirred at room temperature for 1 hr. Then the suspension was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was redissolved in DCM (20 mL) and washed successively with 5% NaHSO₄ (20 mL), saturated NaHCO₃ (30 mL), brine (30 mL) and dried over anhydrous MgSO₄. The organic layer was filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 10 % EtOAc in PE) to give **M2** (830 mg, 69% yield) as brown oil. **LC/MS (ESI)** m/z : 252 ($M+H$)⁺.

Step 2: Synthesis of M3

To a mixture of **M2** (630 mg, 2.51 mmol) and TEA (762 mg, 7.53 mmol) in DCM (12 mL) was added TFAA (1739 mg, 8.28 mmol) dropwise at 0 °C and the resulting mixture was stirred at room temperature for 10 min. Then the mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The

residue was purified via flash column chromatography (eluted with 10 % EtOAc in PE) to give **M3** (690 mg, 79% yield) as brown solid. **LC/MS (ESI) m/z : 346 (M-H)⁻**.

Step 3: Synthesis of M4

To a suspension of **M3** (700 mg, 2.02 mmol) and K₃PO₄ (856 mg, 4.03 mmol) in toluene (12 mL) was added tert-butyl prop-2-yn-1-ylcarbamate (470 mg, 3.03 mmol) and Cu(phen)(PPh₃)₂NO₃ (169 mg, 0.2 mmol). The resulting mixture was stirred at 110 °C for 24 hrs under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 10 % EtOAc in PE) to give **M4** (150 mg, 27% yield) as yellow solid. **LC/MS (ESI) m/z : 279 (M+H)⁺**.

Step 4: Synthesis of M5

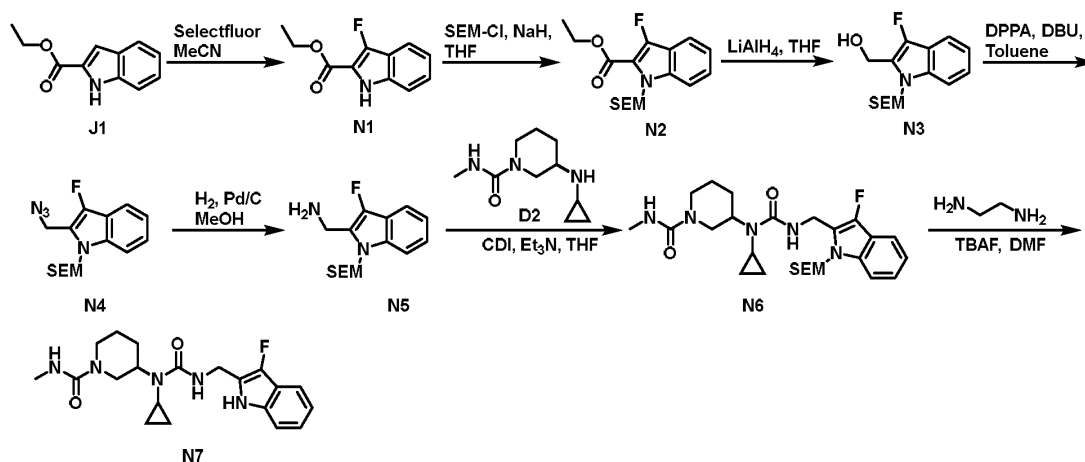
A solution of **M4** (140 mg, 0.5 mmol) in DCM (10 mL) was added TFA (2 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was concentrated under reduced pressure to give crude **M5** (76 mg, quant.) as yellow oil which was used in the next step directly without further purification. **LC/MS (ESI) m/z : 162 (M-16)⁺**.

Step 5: Synthesis of M6/Example 5

To a mixture of **M5** (76 mg, 0.43 mmol) and TEA (86 mg, 0.85 mmol) in THF (10 mL) was added CDI (83 mg, 0.51 mmol) and the resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluted with 70 % EtOAc in PE) to give **acyl imidazole** (82 mg, 71% yield) as white solid. **LC/MS (ESI) m/z : 273 (M+H)⁺**. To a solution of acyl imidazole (82 mg, 0.3 mmol) in THF (10 mL) was added TEA (80 mg, 0.9 mmol) and **D2** (65 mg, 0.33 mmol). The resulting mixture was heated to 60 °C and stirred for 3 hrs. The mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via prep-HPLC to give **Example 5/M6** (29 mg, 24% yield) as white solid. **LC/MS (ESI) m/z : 402 (M+H)⁺**. **¹H NMR**

(400 MHz, CD₃OD) δ 7.23 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 10.7 Hz, 1H), 6.76 (t, J = 5.7 Hz, 1H), 6.19 (s, 1H), 4.45 (d, J = 4.5 Hz, 2H), 4.02 – 3.82 (m, 2H), 3.70 – 3.54 (m, 1H), 3.14 (t, J = 12.0 Hz, 1H), 2.79 – 2.54 (m, 4H), 2.52 – 2.41 (m, 1H), 2.28 (d, J = 1.8 Hz, 3H), 2.17 – 2.00 (m, 1H), 1.93 – 1.85 (m, 1H), 1.80 – 1.70 (m, 1H), 1.61 – 1.42 (m, 1H), 0.96 – 0.88 (m, 2H), 0.80 – 0.56 (m, 2H). ¹⁹F NMR (376 MHz, CD₃OD) δ -127.80 (s).

Synthesis of Example 6



Step 1: Synthesis of N1

To a solution of **J1** (3 g, 15.8 mmol) in MeCN (60 mL) was added Select Fluor (6.73 g, 18.9 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature overnight. Then the mixture was quenched with water (100 mL) and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~10% EtOAc in PE) to give **N1** (760 mg, 23% yield) as white solid. **LC/MS (ESI) m/z** : 208 (M+H)⁺.

Step 2: Synthesis of N2

To a solution of **N1** (660 mg, 3.2 mmol) in anhydrous THF (20 mL) was added NaH (153 mg, 3.8 mmol) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min and then SEMCl (673 mg, 3.8 mmol) was added into the above mixture dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was quenched with saturated NH₄Cl (30 mL, sat. aq.) and extracted with EtOAc (20 mL x 2). The

combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **N2** (860 mg, 80% yield) as colorless oil which was used in the next step directly without further purification. **LC/MS (ESI) *m/z*: 338 (M+H)⁺**.

Step 3: Synthesis of N3

To a solution of **N2** (860 mg, 2.5 mmol) in anhydrous THF (12 mL) was added LiAlH₄ (145 mg, 3.8 mmol) in portions at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was quenched with saturated NH₄Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~15% EtOAc in PE) to give **N3** (740 mg, 98% yield) as colorless oil. **LC/MS (ESI) *m/z*: 296 (M+H)⁺**.

Step 4: Synthesis of N4

To a solution of **N3** (740 mg, 2.5 mmol) in toluene (12 mL) were added DBU (827 mg, 3.0 mmol) and DPPA (457 mg, 3.0 mmol). The resulting mixture was stirred at 110 °C for 3 hrs under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **N4** (710 mg, 88% yield) as yellow oil which was used in the next step directly without further purification.

Step 5: Synthesis of N5

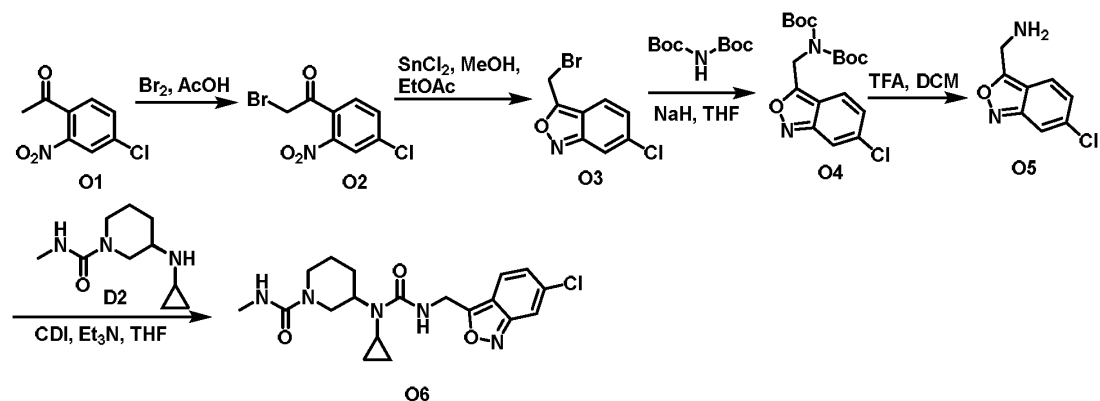
To a solution of **N4** (660 mg, 2.1 mmol) in MeOH (10 mL) was added 10% Pd/C (132 mg) under nitrogen. The suspension was degassed under vacuum and purged with H₂ several times. The resulting mixture was stirred at room temperature for 2 hrs under H₂ atmosphere. Then the mixture was filtered through a pad of Celite®, the filter cake was washed with MeOH (20 mL). The combined filtrates were concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **N5** (520 mg, 86% yield) as brown oil. **LC/MS (ESI) *m/z*: 278 (M-16)⁺**.

Step 6: Synthesis of N6

To a solution of **N5** (300 mg, 1.0 mmol) in anhydrous THF (8 mL) was added CDI (181 mg, 1.1 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min. Then the mixture was concentrated under reduced pressure to give crude acyl imidazole (380 mg, quant.) as light-yellow solid which was used in the next step directly without further purification. **LC/MS (ESI) *m/z***: 389 (M+H)⁺. To a solution of acyl imidazole (380 mg, 0.97 mmol) in anhydrous MeCN (12 mL) was added TEA (492 mg, 4.87 mmol) and **D2** (192 mg, 0.97 mmol). The resulting mixture was stirred at 50 °C overnight under N₂ atmosphere. Then the mixture was quenched with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **N6** (280 mg, 55% yield) as colorless oil. **LC/MS (ESI) *m/z***: 518 (M+H)⁺.

Step 8: Synthesis of **N7/Example 6**

To a solution of **9** (140 mg, 0.27 mmol) in DMF (5 mL) was added ethylenediamine (103 mg, 1.73 mmol) and TBAF (1 M in THF, 0.81 mL, 0.81 mmol) at 0 °C. The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via prep-HPLC to give **N7/Example 6** (18 mg, 12% yield) as white solid. **LC/MS (ESI) *m/z***: 388 (M+H)⁺. **¹H NMR** (400 MHz, CD₃OD) δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 4.54 - 4.47 (m, 2H), 4.01 - 3.93 (m, 1H), 3.92 - 3.85 (m, 1H), 3.73 - 3.62 (m, 1H), 3.13 (t, *J* = 11.9 Hz, 1H), 2.70 (s, 3H), 2.68 - 2.61 (m, 1H), 2.51 - 2.40 (m, 1H), 2.16 - 2.04 (m, 1H), 1.94 - 1.84 (m, 1H), 1.80 - 1.69 (m, 1H), 1.56 - 1.41 (m, 1H), 0.95 - 0.86 (m, 2H), 0.76 - 0.67 (m, 2H). **¹⁹F NMR** (377 MHz, MeOD) δ -180.37 - -180.56 (m).

Synthesis of Example 7**Step 1: Synthesis of O2**

To a solution of **O1** (150 mg, 0.75 mmol) in AcOH (10 mL) was added Br₂ (120 mg, 0.75 mmol). The resulting mixture was stirred at 100 °C for 4 hrs. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified via flash column chromatography (eluted with 0~20% EtOAc in PE) to give **O2** (103 mg, 49% yield) as yellow solid. LC/MS (ESI) *m/z*: 278 (M+H)⁺.

Step 2: Synthesis of O3

To a solution of **O2** (103 mg, 0.37 mmol) in MeOH (5 mL) and EtOAc (5 mL) was added Stannous chloride dihydrate (250 mg, 1.11 mmol). The mixture was stirred at room temperature overnight. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~30% EtOAc in PE) to give **O3** (67 mg, 73% yield) as yellow oil. LC/MS (ESI) *m/z*: 246 (M+H)⁺.

Step 3: Synthesis of O4

To a solution of di-tert-butyl iminodicarbonate (60 mg, 0.33 mmol) in dry THF (10 mL) was added NaH (13 mg, 0.33 mmol) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min. Then a solution of **O3** (67 mg, 0.27 mmol) in 1 mL of THF was added into the above mixture dropwise at 0 °C. The resulting mixture was stirred at room

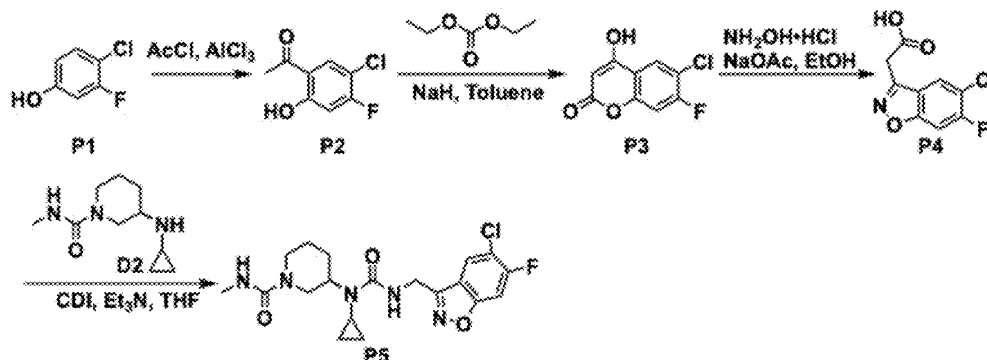
temperature for 2 hrs. Then the mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~50% EtOAc in PE) to give **O4** (83 mg, 81% yield) as yellow oil. **LC/MS (ESI)** m/z : 283 ($\text{M}+\text{H}$)⁺.

Step 4: Synthesis of O5

To a solution of **O4** (83 mg, 0.22 mmol) in DCM (10 mL) was added TFA (2 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was concentrated under reduced pressure to give crude **O5** (32 mg, 80% yield) as purple oil which was used in the next step directly without further purification. **LC/MS (ESI)** m/z : 183 ($\text{M}+\text{H}$)⁺.

Step 5: Synthesis of O6/Example 7

To a mixture of **O5** (32 mg, 0.18 mmol) and TEA (55 mg, 0.54 mmol) in THF (5 mL) was added CDI (29 mg, 0.18 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~15% MeOH in DCM) to give acyl imidazole (35 mg, 70% yield) as white solid. **LC/MS (ESI)** m/z : 277 ($\text{M}+\text{H}$)⁺. To a solution of acyl imidazole (26 mg, 0.13 mmol) in THF (5 mL) was added TEA (30 mg, 0.30 mmol) and **D2** (35 mg, 0.13 mmol). The resulting mixture was stirred at 60 °C for 4 hrs. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC to give **O6/Example 7** (26 mg, 49% yield) as white solid. **LC/MS (ESI)** m/z : 406 ($\text{M}+\text{H}$)⁺. **¹H NMR** (400 MHz, CD_3OD) δ 7.72 (d, J = 0.8 Hz, 1H), 7.55 (s, 1H), 7.35 - 7.26 (m, 1H), 6.98 (d, J = 1.6 Hz, 1H), 4.92 - 4.86 (m, 2H), 3.98 - 3.82 (m, 2H), 3.67 - 3.54 (m, 1H), 3.20 - 3.10 (m, 1H), 2.69 (s, 3H), 2.66 - 2.60 (m, 1H), 2.58 - 2.49 (m, 1H), 2.16 - 2.02 (m, 1H), 1.92 - 1.81 (m, 1H), 1.78 - 1.69 (m, 1H), 1.56 - 1.41 (m, 1H), 1.01 - 0.91 (m, 2H), 0.81 - 0.70 (m, 2H).

Synthesis of Example 8**Step 1: Synthesis of P2**

To a solution of **P1** (1.0 g, 6.8 mmol) in acetyl chloride (1.1 mL, 30.71 mmol) was added AlCl₃ (1.36 g, 10.2 mmol) at 0 °C, the mixture was stirred at room temperature for 1 hr. Then the reaction was stirred at 140 °C for 5 hrs. The mixture was quenched with saturated NH₄Cl solution (50 mL) and extracted with EtOAc (30 mL×2). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 0~5% EtOAc in PE) to give **P2** (1.0 g, 77% yield) as orange solid. **LC/MS (ESI) *m/z***: 187 (M-H)⁻.

Step 2: Synthesis of P3

To a solution of **P2** (1 g, 5.3 mmol) in toluene (25 mL) was added NaH (60 wt%) (1.06 g, 26.5 mmol) and ethyl ethoxymethanoate (1.57 g, 13.2 mmol) at 0 °C, the resulting mixture was stirred at 100 °C for 20 hrs under N₂ atmosphere. Then the mixture was quenched with 1N HCl (aq.) (30 mL) at 0 °C dropwise and extracted with EtOAc (30 mL×2). The combined organic layers were washed with brine (40 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **P3** (370 mg, 32% yield) as white solid which was used in the next step directly without further purification. **LC/MS (ESI) *m/z***: 213 (M-H)⁻.

Step 3: Synthesis of P4

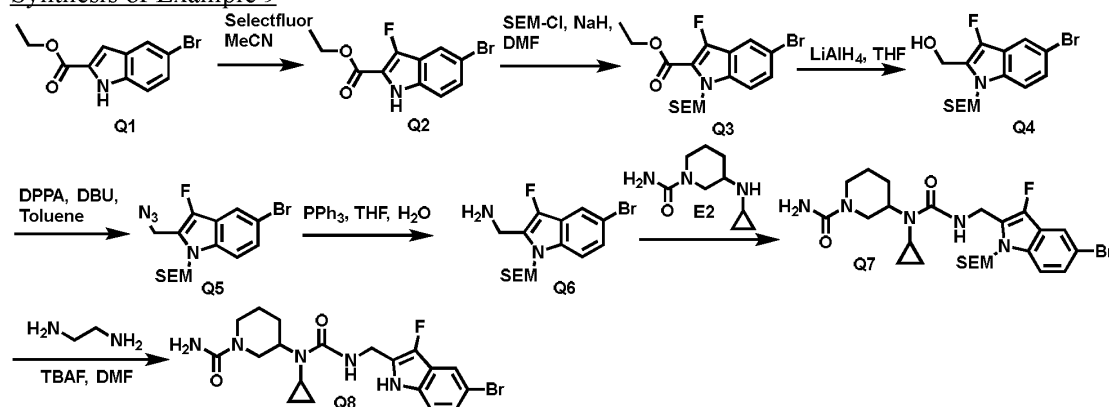
To a solution of **P3** (370 mg, 1.72 mmol) in EtOH (12 mL) were added NaOAc (424 mg, 5.17 mmol) and hydroxylamine hydrochloride (359 mg, 5.17 mmol), the reaction mixture was stirred at 80 °C for 16 hrs. Then the mixture was concentrated under reduced pressure to

dryness. The residue was dissolved in 1N HCl (aq.) (10 mL) and extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **P4** (270 mg, 68% yield) as brown solid. **LC/MS (ESI) *m/z***: 228 (M-H)⁻.

Step 4: Synthesis P5/Example 8

To a solution of **P4** (220 mg, 0.96 mmol) in dry toluene (8 mL) was added TEA (291 mg, 2.88 mmol) and DPPA (316 mg, 1.15 mmol), the reaction mixture was stirred at 120 °C for 1 hr under N₂ atmosphere. Then the mixture was concentrated under reduced pressure to give crude isocyanate (210 mg, 97% yield) as yellow oil which was used in the next step directly without further purification. To a mixture of **D2** (510 mg, 2.25 mmol) and TEA (683 mg, 6.76 mmol) in dry DCM (10 mL) was added a solution of isocyanate (510 mg, 2.25 mmol) in DCM (4 mL) at 0 °C dropwise. The reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with H₂O (20 mL) and extracted with DCM (15 mL $\times$ 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC to give **P5Example 8** (13 mg, 1% yield) as white solid. **LC/MS (ESI) *m/z***: 424 (M+H)⁺. **¹H NMR** (400 MHz, CD₃OD) δ 8.08 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.14 (t, *J* = 5.7 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 2H), 4.01 - 3.80 (m, 2H), 3.66 - 3.54 (m, 1H), 3.19 (t, *J* = 12.0 Hz, 1H), 2.70 (s, 3H), 2.67 - 2.60 (m, 1H), 2.56 - 2.49 (m, 1H), 2.20 - 2.06 (m, 1H), 1.89 (d, *J* = 12.1 Hz, 1H), 1.75 (d, *J* = 13.2 Hz, 1H), 1.57 - 1.43 (m, 1H), 0.99 - 0.85 (m, 2H), 0.80 - 0.65 (m, 2H). **¹⁹F NMR** (376 MHz, CD₃OD) δ -111.81 (d, *J* = 5.4 Hz).

Synthesis of Example 9



Step 1: Synthesis of Q2

To a solution of **Q1** (500 mg, 1.87 mmol) in dry MeCN (16 mL) was added SelectFluor (797 mg, 2.25 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 18 hrs. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~8% EtOAc in PE) to give **Q2** (163 mg, 30% yield) as white solid.

Step 2: Synthesis of Q3

To a solution of **Q2** (163 mg, 0.57 mmol) in anhydrous DMF (4 mL) was added NaH (16 mg, 2.2 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 min and then SEMCl (142 mg, 2.4 mmol) was added into the above mixture dropwise at 0 °C. The resulting mixture was stirred at room temperature for 4 hrs. Then the mixture was quenched with saturated NH₄Cl (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~7% EtOAc in PE) to give **Q3** (223 mg, 94% yield) as colorless oil.

Step 3: Synthesis of Q4

To a solution of **Q3** (223 mg, 0.54 mmol) in anhydrous THF (10 mL) at 0 °C under N₂ atmosphere was added LiAlH₄ (25 mg, 0.65 mmol) in portions. The resulting mixture was stirred at room temperature for 3 hrs. Then the mixture was quenched with H₂O (0.1 mL), 15% NaOH (0.1 mL), and H₂O (0.3 mL). The suspension was then filtered and rinsed with EtOAc (20 mL). The filtrate was dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~16% EtOAc in PE) to give **Q4** (170 mg, 85% yield) as colorless oil. LC/MS (ESI) *m/z*: 374 (M+H)⁺.

Step 4: Synthesis of Q5

To a solution of **Q4** (170 mg, 0.45 mmol) in toluene (10 mL) were added DBU (104 mg, 0.68 mmol) and DPPA (148 mg, 0.54 mmol) at 0 °C. The resulting mixture was stirred at 110 °C for 2 hrs under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and

extracted with EtOAc (20 mL x 2). The combined organic layers were concentrated under reduced pressure to give crude **Q5** (158 mg, 87% yield) which was used in next step directly without further purification.

Step 5: Synthesis of **Q6**

To a solution of **Q5** (158 mg, 0.39 mmol) in THF (8 mL) and H₂O (2 mL) was added PPh₃ (157 mg, 0.59 mmol) and the resulting mixture was stirred at room temperature for 18 hrs. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~8% MeOH in DCM) to give **Q6** (122 mg, 83% yield) as light-yellow oil. **LC/MS (ESI) m/z**: 356 (M-16)⁺.

Step 6: Synthesis of **Q7**

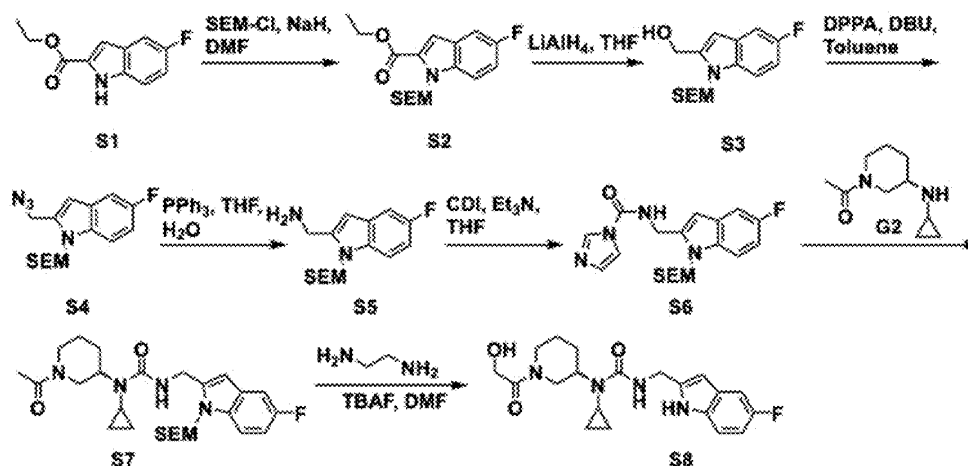
To a solution of **Q6** (60 mg, 0.16 mmol) in anhydrous THF (6 mL) was added CDI (30 mg, 0.19 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give acyl imidazole (58 mg, 77% yield) as white solid. To a solution of acyl imidazole (58 mg, 0.12 mmol) in anhydrous MeCN (6 mL) were added TEA (24 mg, 0.24 mmol) and **D2** (22 mg, 0.12 mmol) at 0 °C. The resulting mixture was stirred at 50 °C for 18 hrs under N₂ atmosphere. Then the mixture was quenched with water (30 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 0~6% MeOH in DCM) to give **Q7** (42 mg, 58% yield) as colorless oil. **LC/MS (ESI) m/z**: 464 (M-117)⁺.

Step 8: Synthesis of **Q8/Example 9**

To a solution of **Q7** (42 mg, 0.07 mmol) in DMF (4 mL) was added ethylenediamine (25 mg, 0.42 mmol) and TBAF (1 N in THF, 0.21 mL, 0.21 mmol) at 0 °C. The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with water (30 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under

reduced pressure. The residue was purified via prep-HPLC to give **Q8/Example 9** (10 mg, 30% yield) as white solid. **LC/MS (ESI) m/z :** 452 ($M+H$)⁺. **1H NMR** (400 MHz, CD₃OD) δ 7.58 (d, J = 1.3 Hz, 1H), 7.26-7.16 (m, 2H), 4.52 (s, 2H), 4.03-3.86 (m, 2H), 3.77-3.64 (m, 1H), 3.22-3.08 (m, 1H), 2.76-2.63 (m, 1H), 2.55-2.44 (m, 1H), 2.21-2.05 (m, 1H), 1.91 (d, J = 12.6 Hz, 1H), 1.77 (d, J = 13.3 Hz, 1H), 1.53 (d, J = 13.1 Hz, 1H), 0.94-0.87 (m, 2H), 0.82-0.69 (m, 2H). **^{19}F NMR** (377 MHz, CD₃OD) δ -179.89 (s).

Synthesis of Example 11



Step 1: Synthesis of S1

To a solution of **S1** (200 mg, 0.96 mmol) in dry DMF (8 mL) was added NaH (77 mg, 1.90 mmol) in portions at 0 °C. The resulting mixture was stirred at 0 °C for 1 hr under N₂ atmosphere and SEMCl (206 mg, 1.24 mmol) was added into the above mixture dropwise. The resulting mixture was stirred at room temperature for 3 hrs under N₂ atmosphere. Then the mixture was quenched with saturated NH₄Cl solution (20 mL) and extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (eluted with 15~20% EtOAc in PE) to give **S2** (270 mg, 83% yield) as light-yellow oil.

Step 2: Synthesis of S3

To a solution of **S2** (270 mg, 0.80 mmol) in dry THF (12 mL) was added LiAlH₄ (60 mg, 1.60 mmol) in portions at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 30 min. Then the mixture was quenched with H₂O (0.1 mL), followed

by the addition of 15% NaOH (0.1 mL) and H₂O (0.3 mL) before it was diluted with EtOAc (20 mL), filtered and rinsed with EtOAc (20 mL). The filtrate was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to dryness. The residue was purified via flash column chromatography (eluted with 20~25% EtOAc in PE) to give **S3** (202 mg, 82% yield) as colorless oil. LC/MS (ESI) *m/z*: 296 (M+H)⁺.

Step 3: Synthesis of S4

To a solution of **S3** (202 mg, 0.68 mmol) in toluene (10 mL) was added DBU (206 mg, 1.36 mmol) and DPPA (226 mg, 0.82 mmol). The resulting mixture was stirred at 110 °C for 4 hrs under N₂ atmosphere. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **S4** (219 mg, quant.) which was used in the next step directly without further purification. LC/MS (ESI) *m/z*: 292 (M-28)⁺.

Step 4: Synthesis of S5

To a solution of crude **S4** (219 mg, 0.68 mmol) in THF/H₂O (6 mL, v/v =5:1) was added PPh₃ (356 mg, 1.36 mmol). The resulting mixture was stirred at 50 °C for 3 hrs under N₂ atmosphere. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude **S5** (201 mg, quant.) which was used in the next step directly without further purification. LC/MS (ESI) *m/z*: 278 (M-16)⁺.

Step 5: Synthesis of S6

To a solution of **S5** (201 mg, 0.68 mmol) in THF (10 mL) was added CDI (111 mg, 0.68 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via flash column chromatography (eluted with 5~10% MeOH in DCM) to give **S6** (102 mg, 39% yield) as light-yellow oil. LC/MS (ESI) *m/z*: 389 (M+H)⁺.

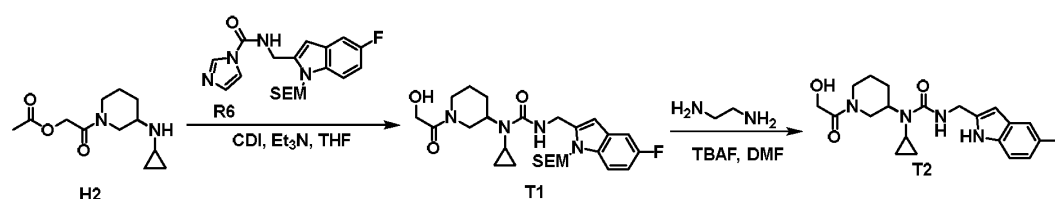
Step 6: Synthesis of S7

To a solution of **G2** (50 mg, 0.27 mmol) in dry THF (10 mL) was added TEA (100 mg, 0.99 mmol) and **S6** (107 mg, 0.27 mmol) at 0 °C, the reaction mixture was stirred at 55 °C for 16 hrs. Then the mixture was diluted with H₂O (20 mL) and extracted with EtOAc (15 mL×2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM: MeOH= 100: 0 to 100: 3) to give **S7** (118 mg, 85% yield) as colorless oil. **LC/MS (ESI)** *m/z*: 503 (M+H)⁺.

Step 2: Synthesis of S8/Example 11

To a solution of **S7** (100 mg, 0.20 mmol) in THF (6 mL) were added ethylenediamine (72 mg, 1.2 mmol) and TBAF (1 mol/L in THF) (0.6 mL), the reaction mixture was stirred at 80 °C for 1 hr. Then the mixture was diluted with H₂O (30 mL) and extracted with EtOAc (15 mL×2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via prep-HPLC to give **S8/Example 11** (20.5 mg, 29% yield) as white solid. **LC/MS (ESI)** *m/z*: 373 (M+H)⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.25 (dd, *J* = 8.8, 4.5 Hz, 1H), 7.10 (dd, *J* = 9.8, 2.4 Hz, 1H), 6.89 - 6.81 (m, 1H), 6.80 - 6.72 (m, 1H), 6.27 (d, *J* = 3.3 Hz, 1H), 4.53 - 4.45 (m, 3H), 3.92 - 3.75 (m, 1.5H), 3.61 - 3.48 (m, 0.5H), 3.35 (s, 0.5H), 3.14 - 2.95 (m, 1H), 2.58 - 2.44 (m, 1.5H), 2.27 - 2.13 (m, 1H), 2.10 (d, *J* = 6.5 Hz, 3H), 1.99 - 1.78 (m, 2H), 1.60 - 1.40 (m, 1H), 0.98 - 0.87 (m, 2H), 0.84 - 0.68 (m, 2H). ¹⁹F NMR (377 MHz, CD₃OD) δ -127.94--128.09 (m).

Synthesis of Example 12



Step 1: Synthesis of T1

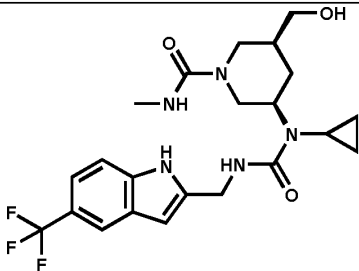
To a solution of **H2** (60 mg, 0.25 mmol) in anhydrous THF (6 mL) were added TEA (50 mg, 0.5 mmol) and **R6** (97 mg, 0.25 mmol) at 0 °C. The resulting mixture was stirred at 50 °C for 18 hrs under N₂ atmosphere. The mixture was diluted with water (30 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue

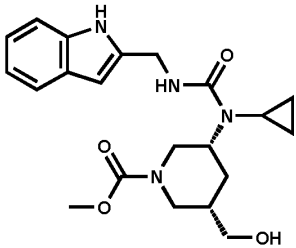
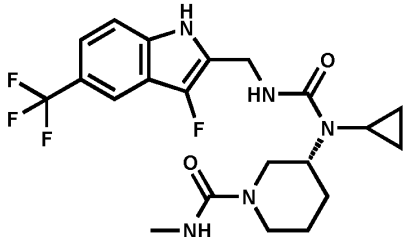
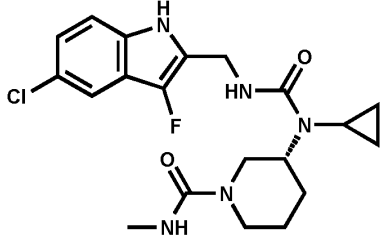
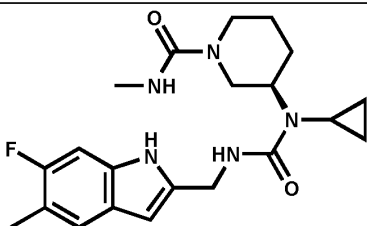
was purified via flash column chromatography (eluted with 0~5% MeOH in DCM) to give **T1** (95 mg, 68% yield) as yellow oil. LC/MS (ESI) m/z : 443 (M-117)⁺.

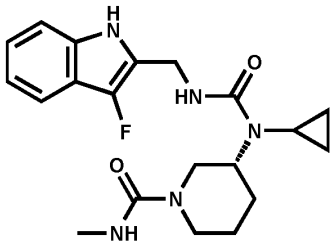
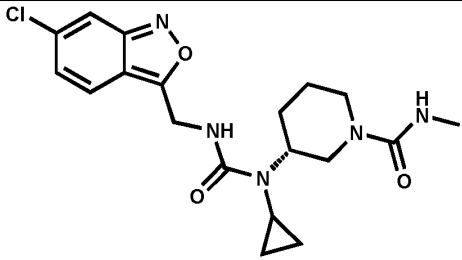
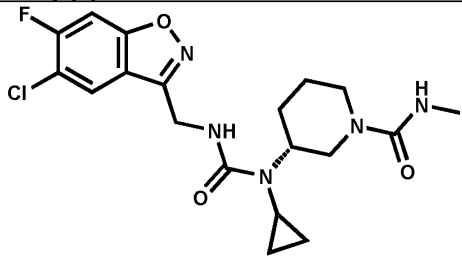
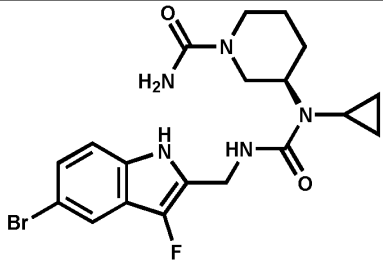
Step 2: Synthesis of T2/Example 12

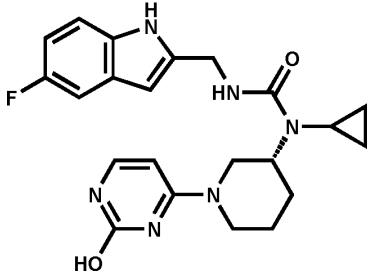
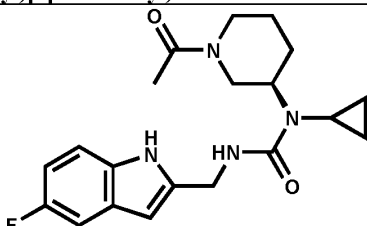
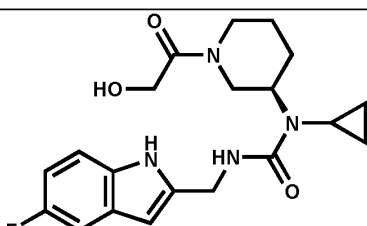
To a solution of **T1** (95 mg, 0.17 mmol) in DMF (5 mL) were added ethylenediamine (60 mg, 1 mmol) and TBAF (1 N in THF, 0.51 ml, 0.51 mmol) at 0 °C. The resulting mixture was stirred at 80 °C for 1 hr under N₂ atmosphere. Then the mixture was diluted with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified via prep-HPLC to give **T2/Example 12** (25 mg, 38% yield) as white solid. LC/MS (ESI) m/z : 389 (M+H)⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.26 (dd, J = 8.8, 4.5 Hz, 1H), 7.11 (dd, J = 9.9, 2.5 Hz, 1H), 6.84 - 6.75 (m, 1H), 6.27 (s, 1H), 4.48 (t, J = 7.8 Hz, 3H), 4.31 (d, J = 15.2 Hz, 0.5H), 4.20 (t, J = 10.1 Hz, 1.5H), 3.80 - 3.55 (m, 2H), 3.25 (d, J = 12.1 Hz, 0.5H), 3.16 (t, J = 11.9 Hz, 0.5H), 2.92 (t, J = 12.0 Hz, 0.5H), 2.60 - 2.45 (m, 1.5H), 2.27 - 2.13 (m, 1H), 2.00 - 1.77 (m, 2H), 1.62 - 1.42 (m, 1H), 0.99 - 0.86 (m, 2H), 0.84 - 0.67 (m, 2H). ¹⁹F NMR (376 MHz, CD₃OD) δ -128.01 (d, J = 14.6 Hz).

The compounds in the table below were prepared according to the methods described above.

Example	Structure	Observed LCMS M/Z	¹ H NMR
Example 1	 (3R,5S)-3-(1-cyclopropyl-3-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)-N-methylpiperidine-1-carboxamide	468.2	¹ H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.51-7.48(m, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.45 (s, 1H), 4.56 (s, 2H), 4.11 (d, J = 12.7 Hz, 1H), 3.94 (d, J = 11.9 Hz, 1H), 3.75 (dd, J = 9.9, 5.7 Hz, 1H), 3.51 - 3.44 (m, 2H), 3.15 (t, J = 12.0 Hz, 1H), 2.73 (s, 3H), 2.58 - 2.52 (m, 1H), 2.48 - 2.40 (m, 1H), 1.89 (dd, J = 23.7, 11.7 Hz, 2H), 1.81 - 1.69 (m, 1H), 0.96 (dd, J = 6.4, 3.1 Hz, 2H), 0.80 (d, J = 4.0 Hz, 2H).

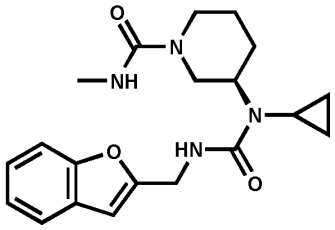
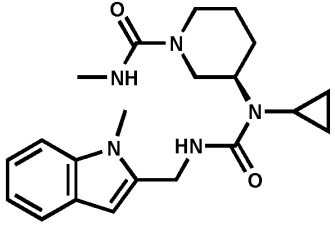
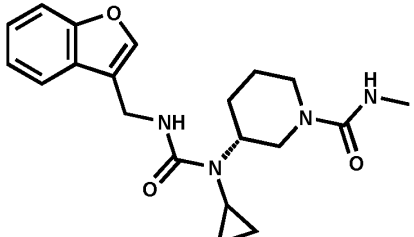
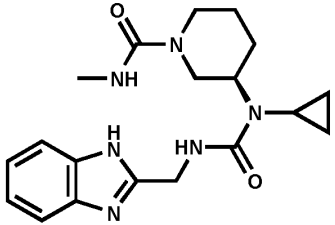
Example 2	 methyl (3R,5S)-3-(3-((1H-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	401.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.45 (d, J = 7.8 Hz, 1H), 7.38 – 7.24 (m, 1H), 7.12 – 7.01 (m, 1H), 6.99 – 6.93 (m, 1H), 6.29 (s, 1H), 4.51 (s, 2H), 4.23 (d, J = 11.2 Hz, 1H), 4.09 (d, J = 10.0 Hz, 1H), 3.72 (d, J = 18.5 Hz, 4H), 3.53 – 3.46 (m, 1H), 3.43 (d, J = 6.8 Hz, 1H), 3.20 (t, J = 11.9 Hz, 1H), 2.49 (d, J = 28.5 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.76 (d, J = 4.9 Hz, 1H), 1.01, 0.90 (m, 2H), 0.76 (s, 2H).
Example 3	 (R)-3-(1-cyclopropyl-3-((3-fluoro-5-(trifluoromethyl)-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	456.2	¹ H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.50 – 7.44 (m, 1H), 7.41 – 7.35 (m, 1H), 4.58 (s, 2H), 4.02 – 3.89 (m, 2H), 3.76 – 3.65 (m, 1H), 3.20 – 3.10 (m, 1H), 2.73 (s, 3H), 2.71 – 2.63 (m, 1H), 2.55 – 2.45 (m, 1H), 2.18 – 2.06 (m, 1H), 1.97 – 1.87 (m, 1H), 1.82 – 1.72 (m, 1H), 1.60 – 1.44 (m, 1H), 0.98 – 0.89 (m, 2H), 0.82 – 0.71 (m, 2H).
Example 4	 (R)-3-(3-((5-chloro-3-fluoro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	422.3	¹ H NMR (400 MHz, MeOD) δ 7.42 (d, J = 1.9 Hz, 1H), 7.27 (dd, J = 8.7, 2.4 Hz, 1H), 7.06 (dd, J = 8.7, 2.0 Hz, 1H), 4.54 – 4.47 (m, 2H), 3.99 – 3.86 (m, 2H), 3.72 – 3.61 (m, 1H), 3.13 (t, J = 12.0 Hz, 1H), 2.70 (s, 3H), 2.68 – 2.60 (m, 1H), 2.51 – 2.43 (m, 1H), 2.17 – 2.03 (m, 1H), 1.94 – 1.83 (m, 1H), 1.81 – 1.68 (m, 1H), 1.57 – 1.41 (m, 1H), 0.95 – 0.85 (m, 2H), 0.78 – 0.66 (m, 2H).
Example 5	 (R)-3-(1-cyclopropyl-3-((6-fluoro-5-methyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	402.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.23 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 10.7 Hz, 1H), 6.76 (t, J = 5.7 Hz, 1H), 6.19 (s, 1H), 4.45 (d, J = 4.5 Hz, 2H), 3.91 (m, 2H), 3.67 (m, 1H), 3.14 (t, J = 12.0 Hz, 1H), 2.79 – 2.54 (m, 4H), 2.52 – 2.41 (m, 1H), 2.28 (d, J = 1.8 Hz, 3H), 2.17 – 2.00 (m, 1H), 1.89 (d, J = 11.8 Hz, 1H), 1.75 (d, J = 13.2 Hz, 1H), 1.61 – 1.42 (m, 1H), 0.95 – 0.90 (m, 2H), 0.80 – 0.56 (m, 2H).

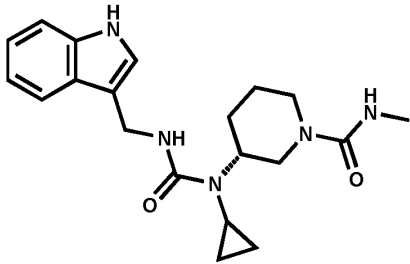
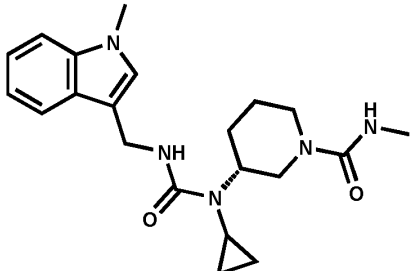
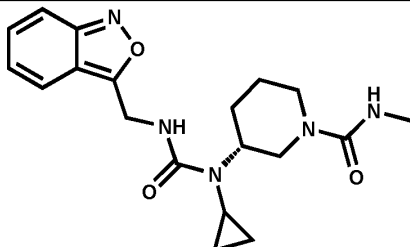
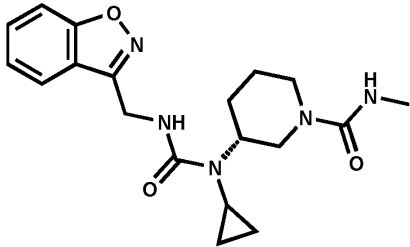
Example 6	 (R)-3-(1-cyclopropyl-3-((3-fluoro-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	388.3	¹ H NMR (400 MHz, MeOD) δ 7.44 (d, J = 7.9 Hz, 1H), 7.28 (dd, J = 8.2, 2.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 4.54 – 4.47 (m, 2H), 4.01 – 3.93 (m, 1H), 3.92 – 3.85 (m, 1H), 3.73 – 3.62 (m, 1H), 3.13 (t, J = 11.9 Hz, 1H), 2.70 (s, 3H), 2.68 – 2.61 (m, 1H), 2.51 – 2.40 (m, 1H), 2.16 – 2.04 (m, 1H), 1.94 – 1.84 (m, 1H), 1.80 – 1.69 (m, 1H), 1.56 – 1.41 (m, 1H), 0.95 – 0.86 (m, 2H), 0.76 – 0.67 (m, 2H).
Example 7	 (R)-3-(3-((6-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.72 (d, J = 0.8 Hz, 1H), 7.55 (s, 1H), 7.35 – 7.26 (m, 1H), 6.98 (d, J = 1.6 Hz, 1H), 4.92 – 4.86 (m, 2H), 3.98 – 3.82 (m, 2H), 3.67 – 3.54 (m, 1H), 3.20 – 3.10 (m, 1H), 2.69 (s, 3H), 2.66 – 2.60 (m, 1H), 2.58 – 2.49 (m, 1H), 2.16 – 2.02 (m, 1H), 1.92 – 1.81 (m, 1H), 1.78 – 1.69 (m, 1H), 1.56 – 1.41 (m, 1H), 1.01 – 0.91 (m, 2H), 0.81 – 0.70 (m, 2H).
Example 8	 (R)-3-(3-((5-chloro-6-fluorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	424.1	¹ H NMR (400 MHz, MeOD) δ 8.08 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.14 (t, J = 5.7 Hz, 1H), 4.75 (d, J = 5.5 Hz, 2H), 4.01 – 3.80 (m, 2H), 3.66 – 3.54 (m, 1H), 3.19 (t, J = 12.0 Hz, 1H), 2.70 (s, 3H), 2.67 – 2.60 (m, 1H), 2.56 – 2.49 (m, 1H), 2.20 – 2.06 (m, 1H), 1.89 (d, J = 12.1 Hz, 1H), 1.75 (d, J = 13.2 Hz, 1H), 1.57 – 1.43 (m, 1H), 0.99 – 0.85 (m, 2H), 0.80 – 0.65 (m, 2H).
Example 9	 (R)-3-(3-((5-bromo-3-fluoro-1H-indol-2-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxamide	454.1	¹ H NMR (400 MHz, MeOD) δ 7.58 (d, J = 1.3 Hz, 1H), 7.26 – 7.16 (m, 2H), 4.52 (s, 2H), 4.03 – 3.86 (m, 2H), 3.77 – 3.64 (m, 1H), 3.22 – 3.08 (m, 1H), 2.76 – 2.63 (m, 1H), 2.55 – 2.44 (m, 1H), 2.21 – 2.05 (m, 1H), 1.91 (d, J = 12.6 Hz, 1H), 1.77 (d, J = 13.3 Hz, 1H), 1.53 (d, J = 13.1 Hz, 1H), 0.94 – 0.87 (m, 2H), 0.82 – 0.69 (m, 2H).

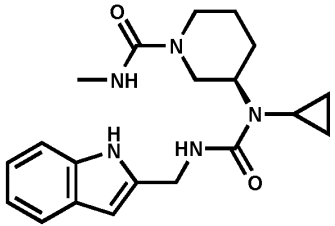
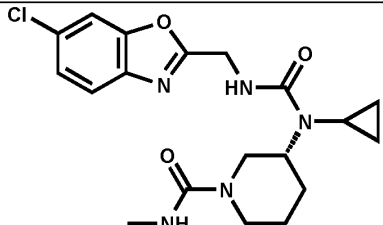
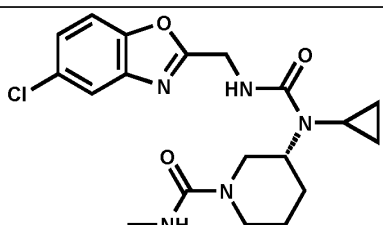
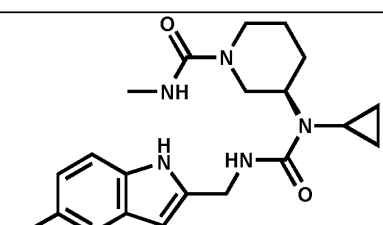
Example 10	 (<i>R</i>)-1-cyclopropyl-3-((5-fluoro-1<i>H</i>-indol-2-yl)methyl)-1-(1-(2-hydroxypyrimidin-4-yl)piperidin-3-yl)urea	425.3	¹ H NMR (400 MHz, MeOD) δ 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.26 (dd, <i>J</i> = 8.8, 4.5 Hz, 1H), 7.10 (dd, <i>J</i> = 9.9, 2.4 Hz, 1H), 6.80 (td, <i>J</i> = 9.3, 2.5 Hz, 1H), 6.27 (s, 1H), 6.18 (d, <i>J</i> = 7.5 Hz, 1H), 4.50 (s, 2H), 4.00 (s, 1H), 3.71 (d, <i>J</i> = 25.9 Hz, 1H), 3.36 (d, <i>J</i> = 12.4 Hz, 2H), 3.04 – 2.66 (m, 1H), 2.54 (s, 1H), 2.26 (tt, <i>J</i> = 12.8, 6.3 Hz, 1H), 1.97 (s, 1H), 1.86 (d, <i>J</i> = 13.6 Hz, 1H), 1.54 (tdd, <i>J</i> = 13.2, 9.3, 4.1 Hz, 1H), 0.94 (s, 2H), 0.78 (s, 2H).
Example 11	 (<i>R</i>)-1-(1-(acetylpiperidin-3-yl)-1-cyclopropyl-3-((5-fluoro-1<i>H</i>-indol-2-yl)methyl)urea	374.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.25 (dd, <i>J</i> = 8.8, 4.5 Hz, 1H), 7.10 (dd, <i>J</i> = 9.8, 2.4 Hz, 1H), 6.89 – 6.81 (m, 1H), 6.80 – 6.72 (m, 1H), 6.27 (d, <i>J</i> = 3.3 Hz, 1H), 4.53 – 4.45 (m, 3H), 3.92 – 3.75 (m, 1.5H), 3.61 – 3.48 (m, 0.5H), 3.35 (s, 0.5H), 3.14 – 2.95 (m, 1H), 2.58 – 2.44 (m, 1.5H), 2.27 – 2.13 (m, 1H), 2.10 (d, <i>J</i> = 6.5 Hz, 3H), 1.99 – 1.78 (m, 2H), 1.60 – 1.40 (m, 1H), 0.98 – 0.87 (m, 2H), 0.84 – 0.68 (m, 2H).
Example 12	 (<i>R</i>)-1-cyclopropyl-3-((5-fluoro-1<i>H</i>-indol-2-yl)methyl)-1-(1-(2-hydroxyacetyl)piperidin-3-yl)urea	389.2	¹ H NMR (400 MHz, MeOD) δ 7.26 (dd, <i>J</i> = 8.8, 4.5 Hz, 1H), 7.11 (dd, <i>J</i> = 9.9, 2.5 Hz, 1H), 6.84 – 6.75 (m, 1H), 6.27 (s, 1H), 4.48 (t, <i>J</i> = 7.8 Hz, 3H), 4.31 (d, <i>J</i> = 15.2 Hz, 1H), 4.20 (t, <i>J</i> = 10.1 Hz, 2H), 3.80 – 3.55 (m, 2H), 3.25 (d, <i>J</i> = 12.1 Hz, 1H), 3.16 (t, <i>J</i> = 11.9 Hz, 1H), 2.92 (t, <i>J</i> = 12.0 Hz, 1H), 2.60 – 2.45 (m, 2H), 2.27 – 2.13 (m, 1H), 2.00 – 1.77 (m, 2H), 1.62 – 1.42 (m, 1H), 0.99 – 0.86 (m, 2H), 0.84 – 0.67 (m, 2H).

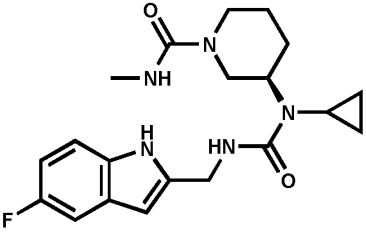
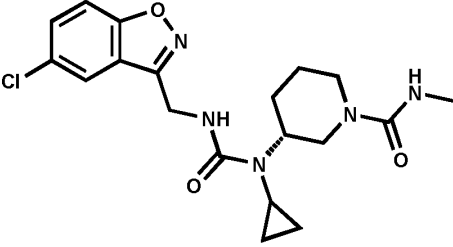
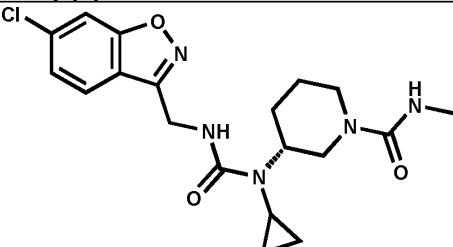
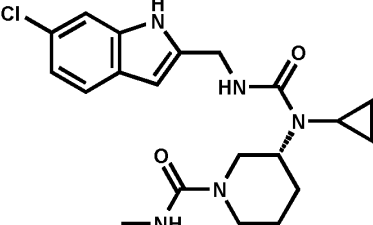
The examples in the table below were prepared according to adaptations of the methods used to prepare Examples 1-9 and 11-12.

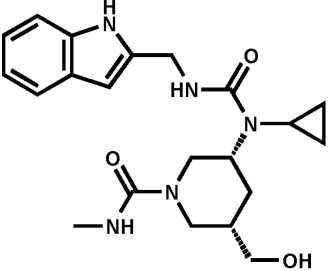
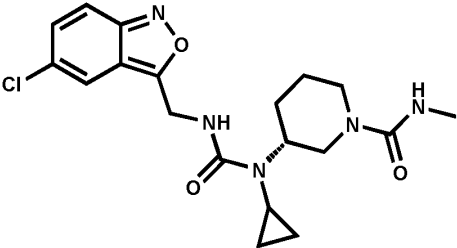
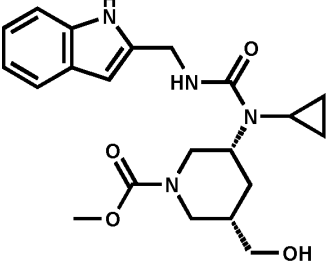
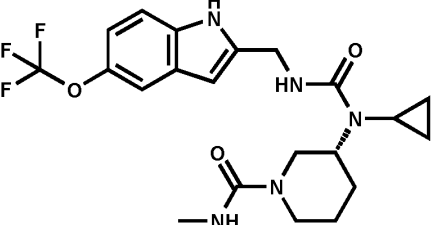
Example	Structure	Observed LCMS M/Z	¹ H NMR
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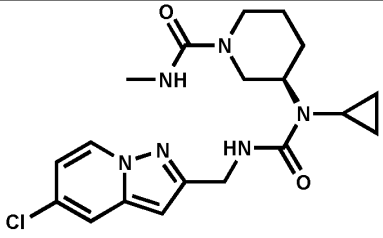
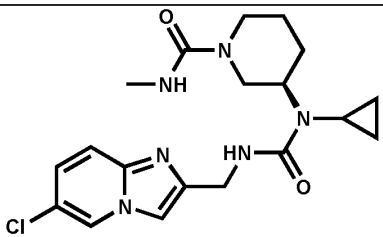
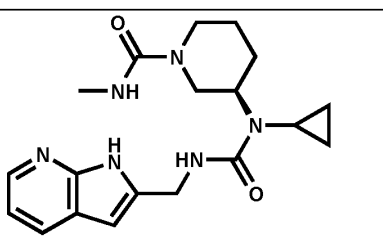
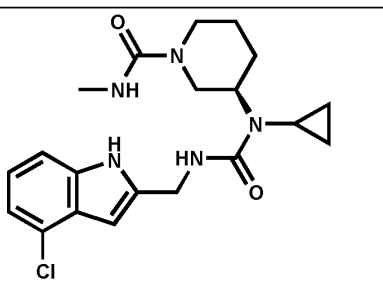
Example 13	 (R)-3-(3-(benzofuran-2-ylmethyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	371.3	¹ H NMR (400 MHz, MeOD) δ 7.55 – 7.46 (m, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.26 – 7.13 (m, 2H), 6.95 (t, J = 5.8 Hz, 1H), 6.59 (s, 1H), 4.57 – 4.45 (m, 2H), 4.02 – 3.93 (m, 1H), 3.92 – 3.83 (m, 1H), 3.70 – 3.57 (m, 1H), 3.15 (t, J = 12.0 Hz, 1H), 2.70 (s, 3H), 2.67 – 2.60 (m, 1H), 2.56 – 2.48 (m, 1H), 2.19 – 2.04 (m, 1H), 1.95 – 1.83 (m, 1H), 1.79 – 1.69 (m, 1H), 1.58 – 1.40 (m, 1H), 1.00 – 0.89 (m, 2H), 0.80 – 0.68 (m, 2H).
Example 14	 (R)-3-(1-cyclopropyl-3-((1-methyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	384.3	¹ H NMR (400 MHz, MeOD) δ 7.46 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.35 (s, 1H), 4.57 (s, 2H), 3.92 (dd, J = 30.9, 12.8 Hz, 2H), 3.73 (s, 3H), 3.64 (tt, J = 11.9, 3.9 Hz, 1H), 3.15 (t, J = 11.9 Hz, 1H), 2.70 (s, 3H), 2.65 (t, J = 13.0 Hz, 1H), 2.51 (td, J = 6.3, 3.3 Hz, 1H), 2.12 (q, J = 12.7 Hz, 1H), 1.89 (d, J = 12.0 Hz, 1H), 1.75 (d, J = 13.5 Hz, 1H), 1.49 (q, J = 12.9 Hz, 1H), 0.91 (d, J = 2.9 Hz, 2H), 0.74 (d, J = 2.6 Hz, 2H).
Example 15	 (R)-3-(3-(benzofuran-3-ylmethyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	371.2	¹ H NMR (400 MHz, MeOD) δ 7.71 – 7.62 (m, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.23 (td, J = 7.5, 0.9 Hz, 1H), 6.76 (t, J = 5.6 Hz, 1H), 4.55 – 4.45 (m, 2H), 3.97 (d, J = 11.8 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.69 – 3.57 (m, 1H), 3.20 – 3.12 (m, 1H), 2.74 – 2.59 (m, 4H), 2.46 (td, J = 6.7, 3.4 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.88 (d, J = 12.1 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.49 (dt, J = 13.1, 4.1 Hz, 1H), 0.87 (td, J = 6.6, 3.5 Hz, 2H), 0.71 – 0.60 (m, 2H).
Example 16	 (R)-3-(3-((1H-benzo[d]imidazol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	371.2	¹ H NMR (400 MHz, MeOD) δ 7.54 (dd, J = 6.0, 3.2 Hz, 2H), 7.23 (dd, J = 6.0, 3.2 Hz, 2H), 4.63 (s, 2H), 3.93 (d, J = 6.9 Hz, 2H), 3.69 (s, 1H), 3.12 (t, J = 12.0 Hz, 1H), 2.72 – 2.62 (m, 4H), 2.61 – 2.54 (m, 1H), 2.11 (dd, J = 12.5, 4.0 Hz, 1H), 1.94 (s, 1H), 1.75 (d, J = 13.4 Hz, 1H), 1.50 (d, J = 13.2 Hz, 1H), 0.96 (dt, J = 6.6, 3.3 Hz, 2H), 0.85 (dd, J = 8.1, 4.0 Hz, 2H).

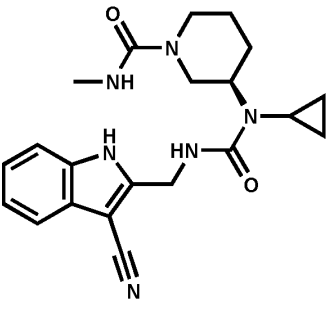
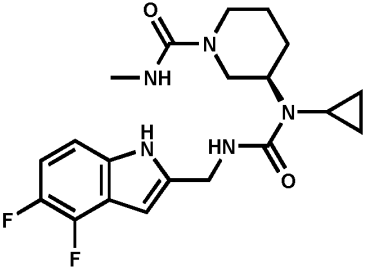
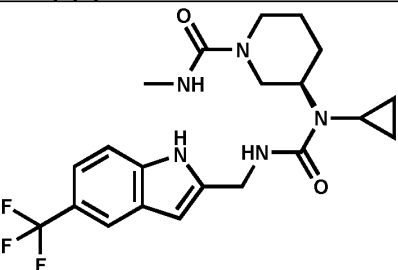
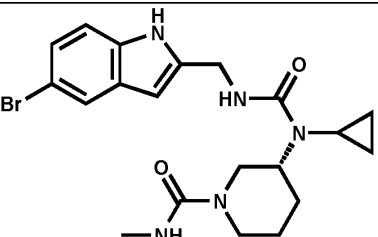
Example 17	 (R)-3-(3-((1H-indol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	370.2	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.40 (t, J = 5.4 Hz, 1H), 6.37 – 6.30(m, 1H), 4.41(d, J=5.4Hz, 2H), 3.95–3.76(m, 2H), 3.56–3.45(m, 1H), 2.97(t, J=11.8Hz, 1H), 2.55(d, J=4.3Hz, 3H), 2.47(d, J=13.3Hz, 1H), 2.40–2.32(m, 1H), 2.03–1.88(m, 1H), 1.72 (d, J = 10.8 Hz, 1H), 1.63 (d, J = 13.0 Hz, 1H), 1.40 – 1.23 (m, 1H), 0.84 – 0.70 (m, 2H), 0.63 – 0.47 (m, 2H).
Example 18	 (R)-3-(1-cyclopropyl-3-((1-methyl-1H-indol-3-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	384.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21 – 7.01 (m, 3H), 4.52 (s, 2H), 3.97 (s, 1H), 3.87 (d, J = 9.9 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 1H), 3.15 (d, J = 11.9 Hz, 1H), 2.73 – 2.63(m, 4H), 2.43(s, 1H), 2.11(d, J=10.9Hz, 1H), 1.89(d, J=15.3Hz, 1H), 1.76(d, J=11.3Hz, 1H), 1.51(d, J=15.4Hz, 1H), 0.80(d, J=7.8Hz, 2H), 0.63(s, 2H).
Example 19	 (R)-3-(3-(benzo[c]isoxazol-3-ylmethyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	372.2	¹ H NMR (400 MHz, MeOD) δ 7.73 – 7.64 (m, 1H), 7.48 (d, J = 9.1 Hz, 1H), 7.35 (dd, J = 9.1, 6.3 Hz, 1H), 7.28 (t, J = 5.8 Hz, 1H), 7.01 (dd, J = 8.8, 6.4 Hz, 1H), 4.96 – 4.87 (m, 2H), 4.00 – 3.90 (m, 1H), 3.90 – 3.76 (m, 1H), 3.66 – 3.54 (m, 1H), 3.19 – 3.10 (m, 1H), 2.69 (s, 3H), 2.67 – 2.59 (m, 1H), 2.57 – 2.49 (m, 1H), 2.16 – 2.02 (m, 1H), 1.93 – 1.81 (m, 1H), 1.79 – 1.66 (m, 1H), 1.55 – 1.41 (m, 1H), 0.98 – 0.89 (m, 2H), 0.79 – 0.69 (m, 2H).
Example 20		372.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.88 (d, J = 8.0 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.41 – 7.33 (m, 1H), 4.82 – 4.73 (m, 2H), 4.02 – 3.84 (m, 2H), 3.69 – 3.58 (m, 1H), 3.22 – 3.10 (m, 1H), 2.70 (s, 3H), 2.69 – 2.60 (m, 1H), 2.57 – 2.50 (m, 1H), 2.18 – 2.06 (m, 1H), 1.90 (d, J = 12.1 Hz, 1H), 1.75 (d, J = 13.5 Hz, 1H),

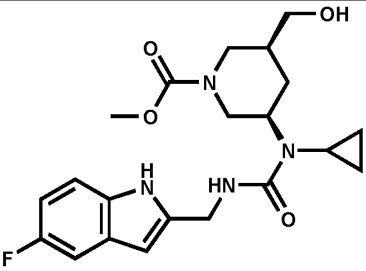
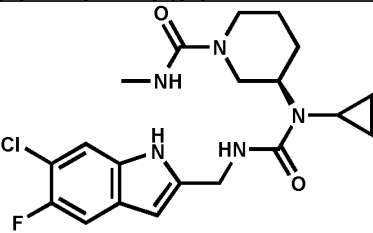
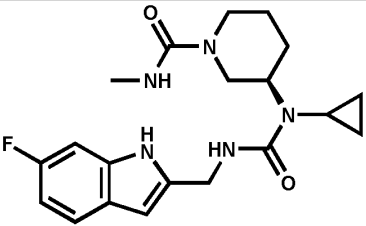
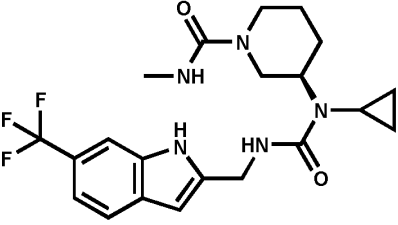
	(R)-3-(3-(benzo[d]isoxazol-3-ylmethyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide		1.59 – 1.44 (m, 1H), 0.97 – 0.89 (m, 2H), 0.79 – 0.69 (m, 2H).
Example 21	 (R)-3-(3-((1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	370.1	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.86 – 10.74 (m, 1H), 7.48 – 7.40 (m, 1H), 7.38 – 7.30 (m, 1H), 7.08 – 6.98 (m, 1H), 6.98 – 6.88 (m, 1H), 6.83 – 6.69 (m, 1H), 6.40 – 6.29 (m, 1H), 6.24 – 6.18 (m, 1H), 4.46 – 4.35 (m, 2H), 3.96 – 3.80 (m, 2H), 3.60 – 3.46 (m, 1H), 3.03 – 2.91 (m, 1H), 2.56 – 2.53 (m, 3H), 2.49 – 2.47 (m, 1H), 2.46 – 2.42 (m, 1H), 2.01 – 1.88 (m, 1H), 1.81 – 1.69 (m, 1H), 1.69 – 1.58 (m, 1H), 1.38 – 1.25 (m, 1H), 0.92 – 0.80 (m, 2H), 0.72 – 0.60 (m, 2H).
Example 22	 (R)-3-(3-((6-chlorobenzo[d]oxazol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, MeOD) δ 7.68 (d, J = 1.7 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.17 (t, J = 5.7 Hz, 1H), 4.64 (d, J = 4.9 Hz, 2H), 3.97 – 3.88 (m, 2H), 3.68 – 3.60 (m, 1H), 3.12 (d, J = 11.7 Hz, 1H), 2.69 (s, 3H), 2.64 – 2.58 (m, 2H), 2.14 – 2.05 (m, 1H), 1.91 (d, J = 11.9 Hz, 1H), 1.74 (d, J = 12.9 Hz, 1H), 1.54 – 1.45 (m, 1H), 0.99 – 0.95 (m, 2H), 0.90 – 0.84 (m, 2H).
Example 23	 (R)-3-(3-((5-chlorobenzo[d]oxazol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.1	¹ H NMR (400 MHz, MeOD) δ 7.66 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.37 (dd, J = 8.7, 2.1 Hz, 1H), 7.19 (t, J = 5.8 Hz, 1H), 4.65 (d, J = 4.4 Hz, 2H), 4.01 – 3.87 (m, 2H), 3.71 – 3.60 (m, 1H), 3.17 – 3.09 (m, 1H), 2.71 – 2.68 (m, 3H), 2.67 – 2.56 (m, 2H), 2.11 (dd, J = 12.5, 4.0 Hz, 1H), 1.92 (d, J = 12.1 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.49 (d, J = 13.1 Hz, 1H), 1.01 – 0.95 (m, 2H), 0.92 – 0.82 (m, 2H).
Example 24		404.0	

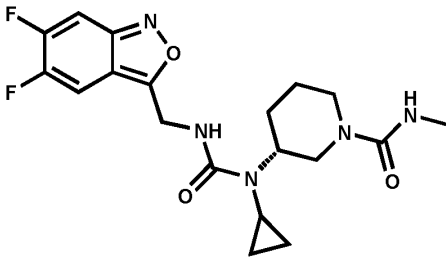
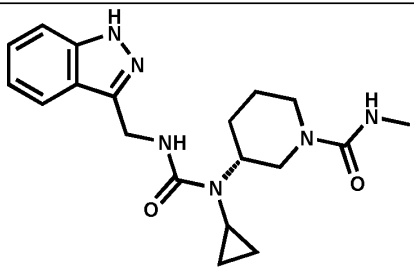
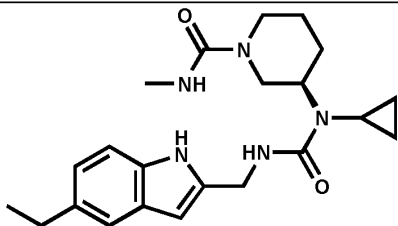
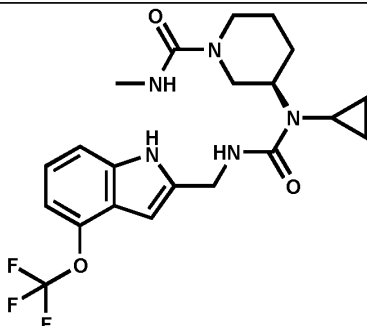
	(R)-3-(3-((5-chloro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide		
Example 25	 (R)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	388.4	¹ H NMR (400 MHz, <i>d</i> -DMSO) δ 10.87 (s, 1H), 7.32 (dd, <i>J</i> = 8.9, 4.8 Hz, 1H), 7.19 (dd, <i>J</i> = 10.0, 2.7 Hz, 1H), 6.83 (td, <i>J</i> = 9.3, 2.6 Hz, 1H), 6.75 (t, <i>J</i> = 9.3 Hz, 1H), 6.32 – 6.31 (m, 1H), 6.21 (s, 1H), 4.39 (d, <i>J</i> = 5.9 Hz, 2H), 3.89 – 3.84 (m, 2H), 3.56 – 3.50 (m, 1H), 2.99 – 2.93 (m, 1H), 2.55 (d, <i>J</i> = 4.3 Hz, 3H), 2.46 – 2.40 (m, 1H), 1.97 – 1.93 (m, 1H), 1.76 – 1.73 (m, 1H), 1.65 – 1.62 (m, 1H), 1.38 – 1.28 (m, 1H), 0.89 – 0.85 (m, 2H), 0.68 – 0.66 (m, 2H).
Example 26	 (R)-3-(3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, MeOD) δ 7.94 (s, 1H), 7.65 – 7.54 (m, 2H), 7.14 (t, <i>J</i> = 5.8 Hz, 1H), 4.79 – 4.71 (m, 2H), 3.99 – 3.86 (m, 2H), 3.65 – 3.56 (m, 1H), 3.24 – 3.13 (m, 1H), 2.70 (s, 3H), 2.68 – 2.60 (m, 1H), 2.56 – 2.49 (m, 1H), 2.20 – 2.08 (m, 1H), 1.94 – 1.84 (m, 1H), 1.79 – 1.70 (m, 1H), 1.56 – 1.41 (m, 1H), 0.96 – 0.87 (m, 2H), 0.80 – 0.70 (m, 2H).
Example 27	 (R)-3-(3-((6-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, MeOD) δ 7.85 (d, <i>J</i> = 8.5 Hz, 1H), 7.72 – 7.65 (m, 1H), 7.38 (dd, <i>J</i> = 8.5, 1.5 Hz, 1H), 7.12 (t, <i>J</i> = 5.8 Hz, 1H), 4.81 – 4.72 (m, 2H), 4.02 – 3.85 (m, 2H), 3.69 – 3.56 (m, 1H), 3.16 (t, <i>J</i> = 11.9 Hz, 1H), 2.69 (d, <i>J</i> = 7.0 Hz, 3H), 2.68 – 2.60 (m, 1H), 2.56 – 2.47 (m, 1H), 2.18 – 2.03 (m, 1H), 1.88 (d, <i>J</i> = 11.9 Hz, 1H), 1.75 (d, <i>J</i> = 13.4 Hz, 1H), 1.56 – 1.41 (m, 1H), 0.97 – 0.86 (m, 2H), 0.81 – 0.67 (m, 2H).
Example 28		404.2	¹ H NMR (400 MHz, MeOD) δ 7.39 (d, <i>J</i> = 8.4 Hz, 1H), 7.31 (d, <i>J</i> = 1.7 Hz, 1H), 6.93 (dd, <i>J</i> = 8.4, 1.9 Hz, 1H), 6.28 (s, 1H), 4.48 (s, 2H), 4.00 – 3.86 (m, 2H), 3.71 – 3.61 (m, 1H), 3.19 – 3.09 (m, 1H), 2.72 – 2.61 (m, 4H), 2.54 – 2.46 (m, 1H), 2.19 – 2.04 (m, 1H), 1.96 – 1.84 (m, 1H), 1.76 (d, <i>J</i> = 13.4 Hz, 1H),

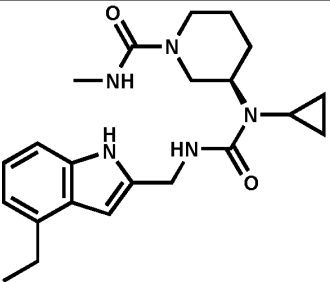
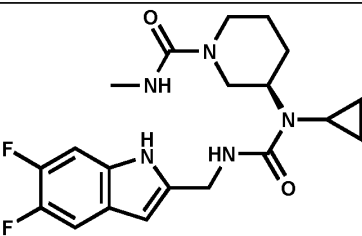
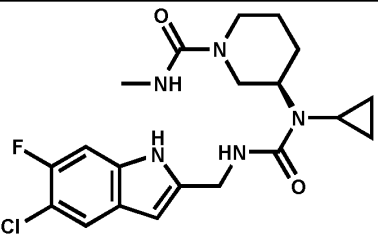
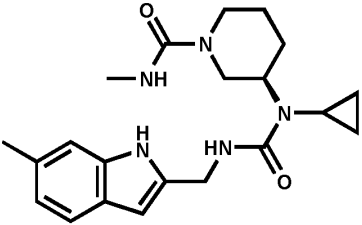
	(R)-3-(3-((6-chloro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide		1.56 – 1.42 (m, 1H), 0.97 – 0.86 (m, 2H), 0.82 – 0.70 (m, 2H).
Example 29 (cis)	 (3R,5S)-3-(3-((1H-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)-N-methylpiperidine-1-carboxamide	400.3	¹ H NMR (400 MHz, MeOD) δ 7.39 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 6.93 (dd, J = 8.4, 1.9 Hz, 1H), 6.28 (s, 1H), 4.48 (s, 2H), 4.00 – 3.86 (m, 2H), 3.71 – 3.61 (m, 1H), 3.19 – 3.09 (m, 1H), 2.72 – 2.61 (m, 4H), 2.54 – 2.46 (m, 1H), 2.19 – 2.04 (m, 1H), 1.96 – 1.84 (m, 1H), 1.76 (d, J = 13.4 Hz, 1H), 1.56 – 1.42 (m, 1H), 0.97 – 0.86 (m, 2H), 0.82 – 0.70 (m, 2H).
Example 30	 (R)-3-(3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, DMSO) δ 7.86 (s, 1H), 7.65 (d, J = 9.4 Hz, 1H), 7.36 (dd, J = 9.4, 1.7 Hz, 1H), 7.25 (t, J = 5.8 Hz, 1H), 6.35 (d, J = 4.4 Hz, 1H), 4.78 (d, J = 5.7 Hz, 2H), 3.84 (t, J = 14.3 Hz, 2H), 3.44 (dd, J = 15.6, 7.8 Hz, 1H), 2.97 (t, J = 11.8 Hz, 1H), 2.54 (d, J = 4.3 Hz, 3H), 2.46 (dd, J = 8.5, 5.0 Hz, 2H), 1.93 (td, J = 12.4, 3.9 Hz, 1H), 1.67 (dd, J = 41.2, 11.8 Hz, 2H), 1.32 (q, J = 13.1 Hz, 1H), 0.89 (d, J = 4.0 Hz, 2H), 0.63 (s, 2H).
Example 31 (cis)	 methyl (3R,5S)-3-(3-((1H-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	401.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.45 (d, J = 7.8 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.10 – 7.00 (m, 1H), 6.99 – 6.91 (m, 1H), 6.28 (s, 1H), 4.50 (d, J = 5.6 Hz, 2H), 4.22 (d, J = 10.2 Hz, 1H), 4.07 (s, 1H), 3.69 (s, 4H), 3.55 – 3.45 (m, 1H), 3.41 (s, 1H), 3.19 (t, J = 11.9 Hz, 1H), 2.51 (s, 2H), 1.94 – 1.80 (m, 2H), 1.75 (d, J = 4.8 Hz, 1H), 0.97 – 0.87 (m, 2H), 0.75 (s, 2H).
Example 32	 (R)-3-(1-cyclopropyl-3-((5-(trifluoromethoxy)-1H-indol-2-yl)methyl)-1-ureido)-N-methylpiperidine-1-carboxamide	454.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.10 (s, 1H), 7.49 – 7.37 (m, 2H), 7.04 – 6.94 (m, 1H), 6.90 – 6.78 (m, 1H), 6.38 – 6.32 (m, 1H), 6.30 – 6.27 (m, 1H), 4.40 (d, J = 5.7 Hz, 2H), 3.95 – 3.78 (m, 2H), 3.62 – 3.47 (m, 1H), 2.96 (t, J = 11.8 Hz, 1H), 2.54 (d, J = 4.2 Hz, 3H), 2.49 – 2.39 (m, 2H), 2.01 – 1.89 (m, 1H), 1.80 – 1.71 (m, 1H), 1.68 – 1.58 (m, 1H), 1.38 – 1.25 (m, 1H), 0.94 –

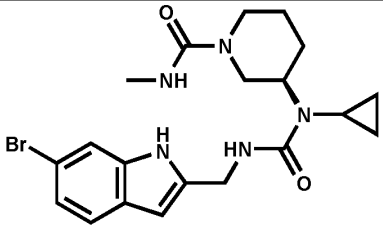
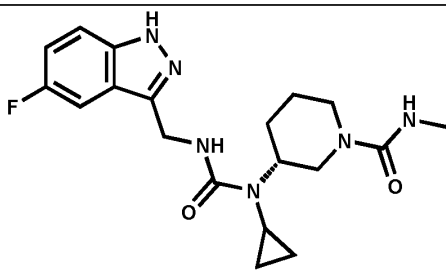
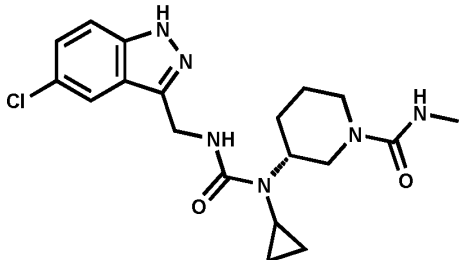
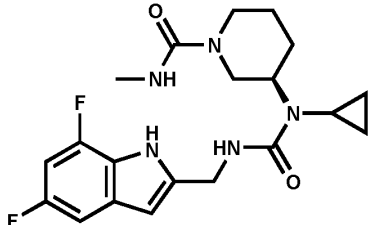
	yl)methylureido)- <i>N</i> -methylpiperidine-1-carboxamide		0.84 (m, 2H), 0.72 – 0.63 (m, 2H).
Example 33	 (<i>R</i>)-3-(3-((5-chloropyrazolo[1,5-<i>a</i>]pyridin-2-yl)methyl)-1-cyclopropylureido)-<i>N</i>-methylpiperidine-1-carboxamide	405.2	¹ H NMR (400 MHz, MeOD) δ 8.46 – 8.37 (m, 1H), 7.62 (s, 1H), 6.93 (t, <i>J</i> = 5.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.4, 2.2 Hz, 1H), 6.46 (s, 1H), 4.58 – 4.51 (m, 2H), 4.00 – 3.86 (m, 2H), 3.70 – 3.60 (m, 1H), 3.18 – 3.09 (m, 1H), 2.70 (s, 3H), 2.68 – 2.60 (m, 1H), 2.56 – 2.49 (m, 1H), 2.18 – 2.06 (m, 1H), 1.94 – 1.86 (m, 1H), 1.79 – 1.71 (m, 1H), 1.55 – 1.42 (m, 1H), 0.98 – 0.91 (m, 2H), 0.82 – 0.73 (m, 2H).
Example 34	 (<i>R</i>)-3-(3-((6-chloroimidazo[1,2-<i>a</i>]pyridin-2-yl)methyl)-1-cyclopropylureido)-<i>N</i>-methylpiperidine-1-carboxamide	405.1	¹ H NMR (400 MHz, MeOD) δ 8.57 (dd, <i>J</i> = 1.9, 0.7 Hz, 1H), 7.71 (s, 1H), 7.49 (d, <i>J</i> = 9.6 Hz, 1H), 7.30 (dd, <i>J</i> = 9.6, 2.0 Hz, 1H), 4.50 (s, 2H), 3.91 (ddd, <i>J</i> = 14.0, 12.6, 7.0 Hz, 2H), 3.70 – 3.58 (m, 1H), 3.20 – 3.09 (m, 1H), 2.73 – 2.59 (m, 4H), 2.56 – 2.49 (m, 1H), 2.11 (dd, <i>J</i> = 12.5, 4.0 Hz, 1H), 1.89 (d, <i>J</i> = 11.8 Hz, 1H), 1.75 (d, <i>J</i> = 13.1 Hz, 1H), 1.56 – 1.41 (m, 1H), 0.99 – 0.89 (m, 2H), 0.85 – 0.74 (m, 2H).
Example 35	 (<i>R</i>)-3-(3-((1<i>H</i>-pyrrolo[2,3-<i>b</i>]pyridin-2-yl)methyl)-1-cyclopropylureido)-<i>N</i>-methylpiperidine-1-carboxamide	371.3	¹ H NMR (400 MHz, MeOD) δ 8.12 – 8.09 (m, 1H), 7.92 – 7.88 (m, 1H), 7.08 – 7.03 (m, 1H), 6.33 (s, 1H), 4.53 (s, 2H), 3.98 – 3.87 (m, 2H), 3.65 (t, <i>J</i> = 11.8 Hz, 1H), 3.16 (d, <i>J</i> = 12.2 Hz, 1H), 2.70 (s, 3H), 2.66 (s, 1H), 2.55 – 2.50 (m, 1H), 2.18 – 2.09 (m, 1H), 1.90 (d, <i>J</i> = 10.5 Hz, 1H), 1.75 (d, <i>J</i> = 13.7 Hz, 1H), 1.50 (d, <i>J</i> = 13.0 Hz, 1H), 0.97 – 0.92 (m, 2H), 0.77 (d, <i>J</i> = 3.8 Hz, 2H).
Example 36	 (<i>R</i>)-3-(3-((4-chloro-1<i>H</i>-indol-2-yl)methyl)-1-cyclopropylureido)-<i>N</i>-methylpiperidine-1-carboxamide	404.2	¹ H NMR (400 MHz, MeOD) δ 7.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.36 (s, 1H), 4.51 (s, 2H), 4.01 – 3.88 (m, 2H), 3.72 – 3.63 (m, 1H), 3.14 (d, <i>J</i> = 11.5 Hz, 1H), 2.70 (s, 3H), 2.68 – 2.61 (m, 1H), 2.54 – 2.48 (m, 1H), 2.17 – 2.07 (m, 1H), 1.91 (d, <i>J</i> = 14.2 Hz, 1H), 1.76 (d, <i>J</i> = 13.3 Hz, 1H), 1.56 – 1.45 (m, 1H), 0.96 – 0.90 (m, 2H), 0.77 (d, <i>J</i> = 2.9 Hz, 2H).

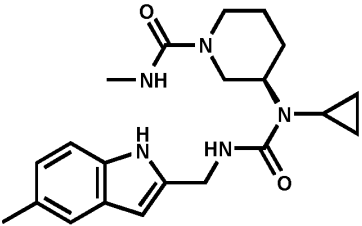
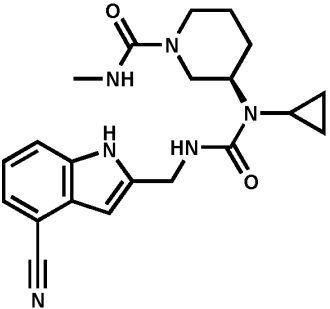
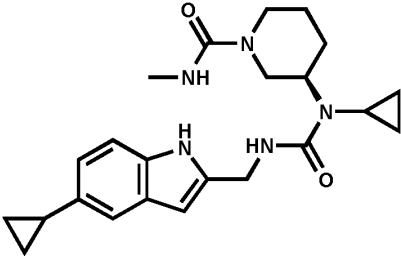
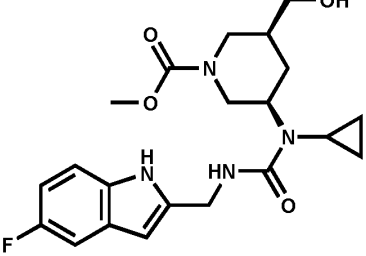
Example 37	 (R)-3-(3-((3-cyano-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	395.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.60 – 7.51 (m, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.30 – 7.08 (m, 3H), 4.68 (d, J = 5.5 Hz, 2H), 4.03 – 3.88 (m, 2H), 3.76 – 3.64 (m, 1H), 3.21 – 3.07 (m, 1H), 2.71 (s, 3H), 2.68 – 2.55 (m, 2H), 2.18 – 2.05 (m, 1H), 1.95 (d, J = 10.1 Hz, 1H), 1.75 (d, J = 13.4 Hz, 1H), 1.57 – 1.43 (m, 1H), 0.99 – 0.92 (m, 2H), 0.90 – 0.80 (m, 2H).
Example 38	 (R)-3-(1-cyclopropyl-3-((4,5-difluoro-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	406.3	¹ H NMR (400 MHz, MeOD) δ 6.95 – 6.91 (m, 1H), 6.91 – 6.86 (m, 1H), 6.37 (s, 1H), 4.52 – 4.44 (m, 2H), 3.99 – 3.86 (m, 2H), 3.71 – 3.63 (m, 1H), 3.18 – 3.11 (m, 1H), 2.70 (s, 3H), 2.69 – 2.62 (m, 1H), 2.55 – 2.47 (m, 1H), 2.19 – 2.05 (m, 1H), 1.94 – 1.87 (m, 1H), 1.80 – 1.72 (m, 1H), 1.58 – 1.44 (m, 1H), 0.98 – 0.90 (m, 2H), 0.81 – 0.73 (m, 2H).
Example 39	 (R)-3-(1-cyclopropyl-3-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	438.3	¹ H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 6.89 (t, J = 5.6 Hz, 1H), 6.42 (s, 1H), 4.54 (d, J = 4.0 Hz, 2H), 4.01 – 3.87 (m, 2H), 3.67 (tt, J = 11.7, 3.9 Hz, 1H), 3.15 (t, J = 11.9 Hz, 1H), 2.70 (s, 3H), 2.69 – 2.61 (m, 1H), 2.55 – 2.48 (m, 1H), 2.12 (qd, J = 12.7, 4.2 Hz, 1H), 1.91 (d, J = 10.8 Hz, 1H), 1.76 (d, J = 13.4 Hz, 1H), 1.50 (dtd, J = 13.1, 9.0, 4.1 Hz, 1H), 0.93 (dd, J = 6.4, 3.3 Hz, 2H), 0.81 – 0.72 (m, 2H).
Example 40	 (R)-3-(3-((5-bromo-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	450.2	¹ H NMR (400 MHz, MeOD) δ 7.60 – 7.55 (m, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.13 (dd, J = 8.6, 1.9 Hz, 1H), 6.26 (s, 1H), 4.49 (s, 2H), 3.92 (ddd, J = 13.1, 12.5, 7.5 Hz, 2H), 3.72 – 3.62 (m, 1H), 3.20 – 3.11 (m, 1H), 2.71 (s, 3H), 2.64 (dd, J = 13.0, 2.6 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.12 (dd, J = 12.6, 3.9 Hz, 1H), 1.91 (d, J = 10.9 Hz, 1H), 1.76 (d, J = 13.2 Hz, 1H), 1.50 (d, J = 13.2 Hz, 1H), 0.97 –

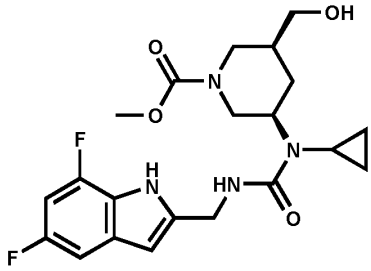
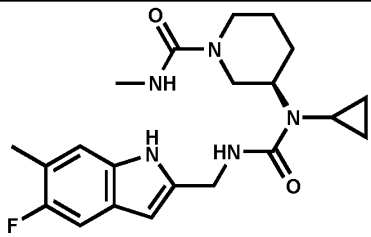
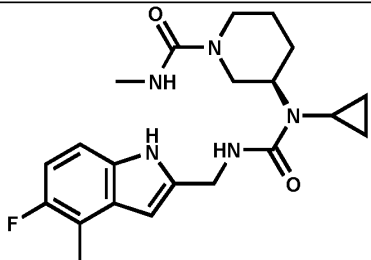
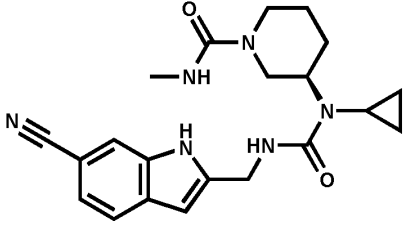
			0.87 (m, 2H), 0.77 (dd, J = 6.6, 3.1 Hz, 2H).
Example 41 (cis)	 methyl (3R,5S)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)piperidine-1-carboxylate	419.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 7.22 (m, 1H), 7.13 – 7.07 (m, 1H), 6.83 – 6.77 (m, 1H), 6.27 (s, 1H), 4.49 (s, 2H), 4.22 (d, J = 10.6 Hz, 1H), 4.08 (d, J = 7.1 Hz, 1H), 3.71 (d, J = 20.8 Hz, 4H), 3.53 – 3.45 (m, 1H), 3.41 (s, 1H), 3.18 (t, J = 12.0 Hz, 1H), 2.48 (d, J = 25.2 Hz, 2H), 1.87 (t, J = 10.0 Hz, 2H), 1.75 (s, 1H), 0.96 – 0.87 (m, 2H), 0.75 (s, 2H).
Example 42	 (R)-3-(3-((6-chloro-5-fluoro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	422.2	¹ H NMR (400 MHz, MeOD) δ 7.40 – 7.33 (m, 1H), 7.25 (d, J = 10.1 Hz, 1H), 6.86 (t, J = 5.6 Hz, 1H), 6.28 (s, 1H), 4.52 – 4.44 (m, 2H), 3.98 – 3.87 (m, 2H), 3.72 – 3.61 (m, 1H), 3.18 – 3.11 (m, 1H), 2.70 (s, 3H), 2.68 – 2.61 (m, 1H), 2.55 – 2.45 (m, 1H), 2.19 – 2.06 (m, 1H), 1.93 – 1.85 (m, 1H), 1.79 – 1.71 (m, 1H), 1.54 – 1.42 (m, 1H), 0.97 – 0.88 (m, 2H), 0.81 – 0.72 (m, 2H).
Example 43	 (R)-3-(1-cyclopropyl-3-((6-fluoro-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	388.3	¹ H NMR (400 MHz, MeOD) δ 7.38 (dd, J = 8.6, 5.4 Hz, 1H), 7.01 (dd, J = 9.9, 1.8 Hz, 1H), 6.74 (td, J = 9.9, 2.3 Hz, 1H), 6.27 (s, 1H), 4.47 (s, 2H), 4.02 – 3.83 (m, 2H), 3.67 (ddd, J = 11.8, 7.9, 4.1 Hz, 1H), 3.15 (t, J = 12.0 Hz, 1H), 2.76 – 2.61 (m, 4H), 2.54 – 2.40 (m, 1H), 2.11 (dd, J = 12.5, 4.0 Hz, 1H), 1.90 (d, J = 11.6 Hz, 1H), 1.75 (d, J = 13.3 Hz, 1H), 1.60 – 1.41 (m, 1H), 0.91 (dd, J = 6.2, 3.5 Hz, 2H), 0.80 – 0.67 (m, 2H).
Example 44	 (R)-3-(1-cyclopropyl-3-((6-(trifluoromethyl)-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	438.2	¹ H NMR (400 MHz, MeOD) δ 7.64 – 7.56 (m, 2H), 7.23 – 7.19 (m, 1H), 6.39 (s, 1H), 4.54 (s, 2H), 3.99 – 3.88 (m, 2H), 3.72 – 3.62 (m, 1H), 3.18 – 3.09 (m, 1H), 2.70 (s, 3H), 2.68 – 2.61 (m, 1H), 2.55 – 2.49 (m, 1H), 2.18 – 2.07 (m, 1H), 1.91 (d, J = 13.5 Hz, 1H), 1.76 (d, J = 13.3 Hz, 1H), 1.57 – 1.43 (m, 1H), 0.96 – 0.88 (m, 2H), 0.81 – 0.73 (m, 2H).

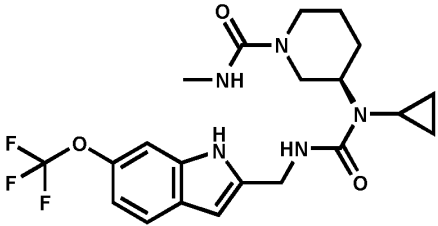
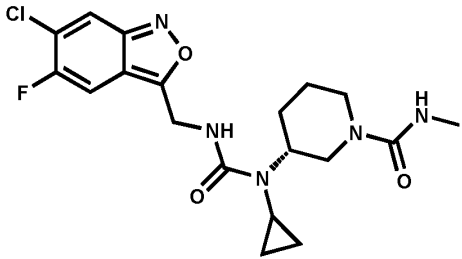
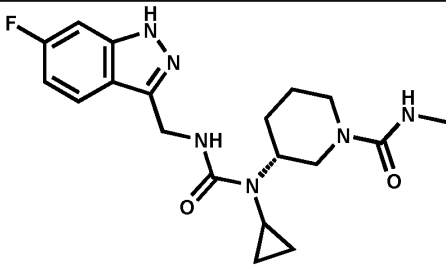
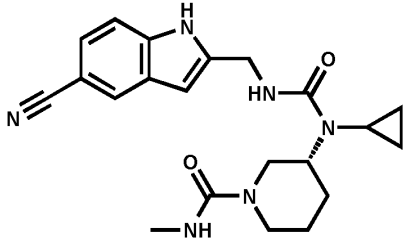
Example 45	 (R)-3-(1-cyclopropyl-3-((5,6-difluorobenzo[c]isoxazol-3-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	408.2	¹ H NMR (400 MHz, MeOD) δ 7.60 – 7.48 (m, 1H), 7.37 (dd, J = 10.2, 6.9 Hz, 1H), 4.83 (s, 2H), 3.90 (dd, J = 29.3, 12.3 Hz, 2H), 3.65 – 3.52 (m, 1H), 3.14 (dd, J = 14.7, 9.3 Hz, 1H), 2.72 – 2.58 (m, 4H), 2.52 (td, J = 6.7, 3.4 Hz, 1H), 2.10 (dd, J = 12.5, 4.0 Hz, 1H), 1.86 (d, J = 11.6 Hz, 1H), 1.74 (d, J = 13.4 Hz, 1H), 1.57 – 1.39 (m, 1H), 1.01 – 0.86 (m, 2H), 0.74 (d, J = 4.2 Hz, 2H).
Example 46	 (R)-3-(3-((1H-indazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	371.1	
Example 47	 (R)-3-(1-cyclopropyl-3-((5-ethyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	398.3	¹ H NMR (400 MHz, MeOD) δ 7.26 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.92 (dd, J = 8.3, 1.5 Hz, 1H), 6.21 (s, 1H), 4.48 (s, 2H), 4.05 – 3.84 (m, 2H), 3.72 – 3.61 (m, 1H), 3.19 – 3.07 (m, 1H), 2.71 (s, 3H), 2.70 – 2.61 (m, 3H), 2.53 – 2.44 (m, 1H), 2.12 (dd, J = 12.5, 4.0 Hz, 1H), 1.91 (d, J = 10.9 Hz, 1H), 1.76 (d, J = 13.1 Hz, 1H), 1.59 – 1.43 (m, 1H), 1.24 (t, J = 7.6 Hz, 3H), 0.98 – 0.86 (m, 2H), 0.76 (dd, J = 6.5, 3.2 Hz, 2H).
Example 48	 (R)-3-(1-cyclopropyl-3-((4-(trifluoromethoxy)-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	454.3	¹ H NMR (400 MHz, MeOD) δ 7.31 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 7.7 Hz, 2H), 6.36 (s, 1H), 4.52 (d, J = 5.0 Hz, 2H), 3.92 (ddd, J = 13.1, 12.5, 7.6 Hz, 2H), 3.67 (tt, J = 11.7, 3.9 Hz, 1H), 3.16 (t, J = 11.9 Hz, 1H), 2.70 (s, 3H), 2.64 (dd, J = 13.1, 2.5 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.12 (qd, J = 12.7, 4.1 Hz, 1H), 1.91 (d, J = 12.0 Hz, 1H), 1.75 (d, J = 13.4 Hz, 1H), 1.50 (dtd, J = 13.2, 9.1, 4.1 Hz,

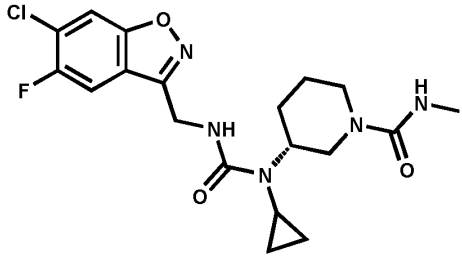
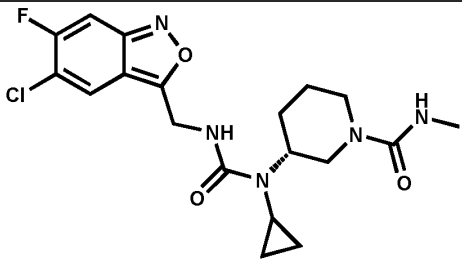
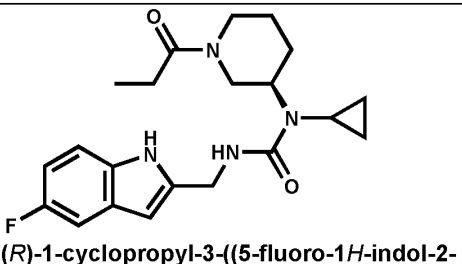
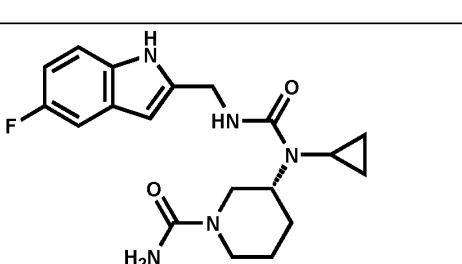
	yl)methylureido)- <i>N</i> -methylpiperidine-1-carboxamide		1H), 0.92 (dd, J = 6.3, 3.5 Hz, 2H), 0.77 (d, J = 3.2 Hz, 2H).
Example 49	 (<i>R</i>)-3-(1-cyclopropyl-3-((4-ethyl-1<i>H</i>-indol-2-yl)methyl)ureido)-<i>N</i>-methylpiperidine-1-carboxamide	398.2	¹ H NMR (400 MHz, MeOD) δ 7.14 (d, J = 8.1 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.78 (d, J = 7.1 Hz, 1H), 6.34 (s, 1H), 4.51 (d, J = 4.3 Hz, 2H), 3.92 (ddd, J = 14.2, 12.6, 7.4 Hz, 2H), 3.67 (ddd, J = 15.6, 7.9, 4.0 Hz, 1H), 3.15 (t, J = 12.0 Hz, 1H), 2.85 (q, J = 7.6 Hz, 2H), 2.70 (d, J = 5.6 Hz, 3H), 2.64 (dd, J = 13.0, 2.4 Hz, 1H), 2.49 (dd, J = 6.5, 2.8 Hz, 1H), 2.12 (qd, J = 12.6, 4.1 Hz, 1H), 1.90 (d, J = 11.0 Hz, 1H), 1.75 (d, J = 13.2 Hz, 1H), 1.56 – 1.45 (m, 1H), 1.30 (t, J = 7.6 Hz, 3H), 0.91 (dd, J = 6.2, 3.4 Hz, 2H), 0.75 (d, J = 3.5 Hz, 2H).
Example 51	 (<i>R</i>)-3-(1-cyclopropyl-3-((5,6-difluoro-1<i>H</i>-indol-2-yl)methyl)ureido)-<i>N</i>-methylpiperidine-1-carboxamide	406.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.24 (dd, J = 11.2, 7.9 Hz, 1H), 7.16 (dd, J = 11.2, 6.8 Hz, 1H), 6.27 (s, 1H), 4.47 (s, 2H), 4.02 – 3.84 (m, 2H), 3.73 – 3.55 (m, 1H), 3.21 – 3.06 (m, 1H), 2.71 (s, 3H), 2.70 – 2.61 (m, 1H), 2.54 – 2.46 (m, 1H), 2.18 – 2.07 (m, 1H), 1.94 – 1.87 (m, 1H), 1.83 – 1.69 (m, 1H), 1.59 – 1.43 (m, 1H), 0.96 – 0.89 (m, 2H), 0.80 – 0.71 (m, 2H).
Example 52	 (<i>R</i>)-3-(3-((5-chloro-6-fluoro-1<i>H</i>-indol-2-yl)methyl)-1-cyclopropylureido)-<i>N</i>-methylpiperidine-1-carboxamide	422.2	¹ H NMR (400 MHz, MeOD) δ 7.53 – 7.42 (m, 1H), 7.17 (d, J = 10.0 Hz, 1H), 6.84 (s, 1H), 6.26 (s, 1H), 4.50 – 4.44 (m, 2H), 3.99 – 3.88 (m, 2H), 3.72 – 3.62 (m, 1H), 3.18 – 3.11 (m, 1H), 2.71 (s, 3H), 2.67 – 2.61 (m, 1H), 2.54 – 2.46 (m, 1H), 2.18 – 2.06 (m, 1H), 1.95 – 1.86 (m, 1H), 1.79 – 1.70 (m, 1H), 1.56 – 1.43 (m, 1H), 0.95 – 0.88 (m, 2H), 0.79 – 0.72 (m, 2H).
Example 53	 (<i>R</i>)-3-(1-cyclopropyl-3-((6-methyl-1<i>H</i>-indol-2-yl)methyl)ureido)-<i>N</i>-methylpiperidine-1-carboxamide	384.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.32 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 6.86 – 6.79 (m, 1H), 6.22 (s, 1H), 4.48 (d, J = 5.6 Hz, 2H), 4.02 – 3.85 (m, 2H), 3.73 – 3.62 (m, 1H), 3.20 – 3.10 (m, 1H), 2.74 – 2.70 (m, 3H), 2.69 – 2.61 (m, 1H), 2.54 – 2.46 (m, 1H), 2.40 (s, 3H), 2.18 – 2.05 (m, 1H), 1.91 (d, J = 12.7 Hz, 1H), 1.76 (d, J = 13.1 Hz, 1H), 1.58 –

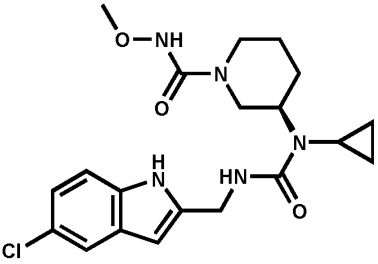
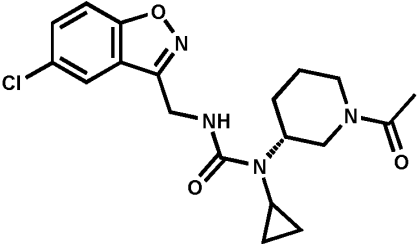
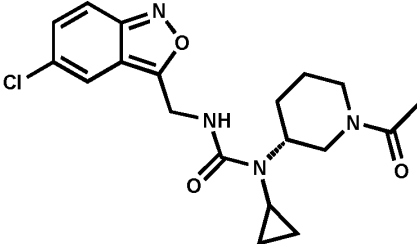
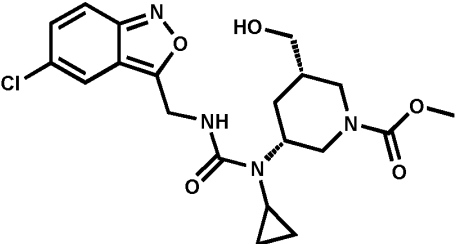
			1.45 (m, 1H), 0.98 – 0.88 (m, 2H), 0.81 – 0.69 (m, 2H).
Example 54	 (R)-3-(3-((6-bromo-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	450.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.48 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.11 – 7.04 (m, 1H), 6.29 (s, 1H), 4.49 (d, J = 4.4 Hz, 2H), 4.00 – 3.87 (m, 2H), 3.72 – 3.62 (m, 1H), 3.20 – 3.11 (m, 1H), 2.71 (s, 3H), 2.70 – 2.63 (m, 1H), 2.54 – 2.48 (m, 1H), 2.18 – 2.06 (m, 1H), 1.91 (d, J = 11.4 Hz, 1H), 1.76 (d, J = 13.5 Hz, 1H), 1.57 – 1.47 (m, 1H), 0.97 – 0.89 (m, 2H), 0.80 – 0.73 (m, 2H).
Example 55	 (R)-3-(1-cyclopropyl-3-((5-fluoro-1H-indazol-3-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	389.3	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.53 – 7.43 (m, 2H), 7.25 – 7.12 (m, 1H), 6.85 (t, J = 5.8 Hz, 1H), 4.76 – 4.68 (m, 2H), 4.03 – 3.93 (m, 1H), 3.93 – 3.84 (m, 1H), 3.73 – 3.58 (m, 1H), 3.23 – 3.13 (m, 1H), 2.70 (s, 3H), 2.67 – 2.61 (m, 1H), 2.56 – 2.46 (m, 1H), 2.21 – 2.07 (m, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.71 (m, 1H), 1.57 – 1.43 (m, 1H), 0.95 – 0.84 (m, 2H), 0.77 – 0.64 (m, 2H).
Example 56	 (R)-3-(3-((5-chloro-1H-indazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	405.3	
Example 57	 (R)-3-(1-cyclopropyl-3-((5,7-difluoro-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	406.1	¹ H NMR (400 MHz, MeOD) δ 6.97 (dd, J = 9.4, 2.1 Hz, 1H), 6.85 (t, J = 5.8 Hz, 1H), 6.71 – 6.60 (m, 1H), 6.34 (d, J = 3.3 Hz, 1H), 4.50 (d, J = 5.4 Hz, 2H), 3.93 (dd, J = 26.2, 12.7 Hz, 2H), 3.72 – 3.58 (m, 1H), 3.19 – 3.11 (m, 1H), 2.73 – 2.60 (m, 4H), 2.55 – 2.46 (m, 1H), 2.10 (td, J = 12.6, 4.0 Hz, 1H), 1.90 (d, J = 11.7 Hz, 1H), 1.75 (d, J = 13.2 Hz, 1H), 1.58 – 1.42 (m, 1H), 0.93 (dd, J = 6.2, 3.3 Hz, 2H), 0.77 (d, J = 3.8 Hz, 2H).

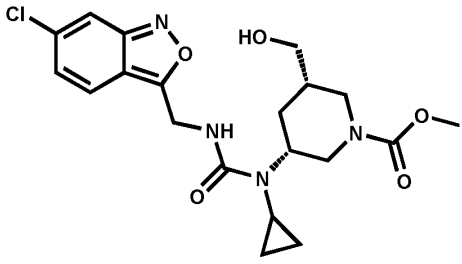
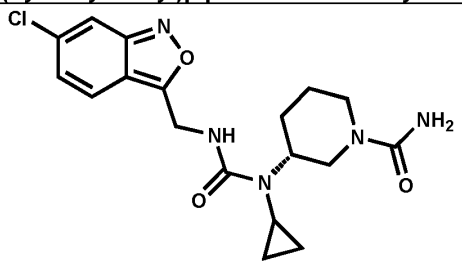
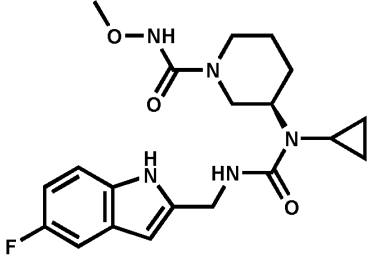
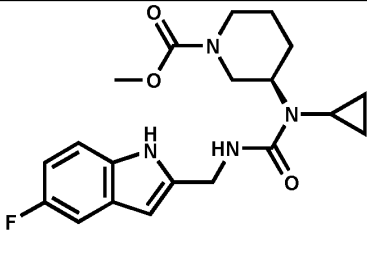
Example 58	 (R)-3-(1-cyclopropyl-3-((5-methyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	384.3	¹ H NMR (400 MHz, MeOD) δ 7.23 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 6.89 – 6.85 (m, 1H), 6.19 (s, 1H), 4.48 (d, J = 4.0 Hz, 2H), 4.00 – 3.87 (m, 2H), 3.72 – 3.62 (m, 1H), 3.18 – 3.12 (m, 1H), 2.71 (s, 3H), 2.69 – 2.61 (m, 1H), 2.53 – 2.46 (m, 1H), 2.37 (s, 3H), 2.13 – 2.01 (m, 1H), 1.90 (d, J = 11.1 Hz, 1H), 1.75 (d, J = 12.8 Hz, 1H), 1.56 – 1.44 (m, 1H), 0.94 – 0.88 (m, 2H), 0.78 – 0.70 (m, 2H).
Example 59	 (R)-3-(3-((4-cyano-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	395.2	¹ H NMR (400 MHz, MeOD) δ 7.63 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 5.6 Hz, 1H), 6.46 (s, 1H), 4.57 (d, J = 4.8 Hz, 2H), 3.93 (dd, J = 24.2, 13.0 Hz, 2H), 3.72 – 3.61 (m, 1H), 3.19 – 3.11 (m, 1H), 2.71 – 2.61 (m, 4H), 2.56 – 2.49 (m, 1H), 2.19 – 2.05 (m, 1H), 1.91 (d, J = 11.4 Hz, 1H), 1.76 (d, J = 13.0 Hz, 1H), 1.57 – 1.41 (m, 1H), 0.98 – 0.88 (m, 2H), 0.78 (d, J = 3.1 Hz, 2H).
Example 60	 (R)-3-(1-cyclopropyl-3-((5-cyclopropyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	410.3	¹ H NMR (400 MHz, MeOD) δ 7.18 (d, J = 8.2 Hz, 2H), 6.82 (dd, J = 8.5, 1.4 Hz, 1H), 6.19 (s, 1H), 4.47 (s, 2H), 4.01 – 3.85 (m, 2H), 3.66 (dd, J = 9.7, 5.9 Hz, 1H), 3.20 – 3.11 (m, 1H), 2.71 (s, 3H), 2.69 – 2.62 (m, 1H), 2.53 – 2.45 (m, 1H), 2.12 (dd, J = 12.5, 4.0 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.76 (d, J = 13.3 Hz, 1H), 1.57 – 1.45 (m, 1H), 0.94 – 0.85 (m, 4H), 0.79 – 0.71 (m, 2H), 0.66 – 0.59 (m, 2H).
Example 61	 methyl (3R,5S)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)piperidine-1-carboxylate	419.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.33 – 7.22 (m, 1H), 7.16 – 7.05 (m, 1H), 6.88 – 6.75 (m, 1H), 6.27 (s, 1H), 4.49 (s, 2H), 4.22 (d, J = 10.4 Hz, 1H), 4.09 (d, J = 11.0 Hz, 1H), 3.71 (d, J = 15.0 Hz, 4H), 3.52 – 3.46 (m, 1H), 3.42 (d, J = 6.4 Hz, 1H), 3.19 (t, J = 12.0 Hz, 1H), 2.49 (d, J = 28.1 Hz, 2H), 1.88 (t, J = 10.0 Hz, 2H), 1.75 (s, 1H), 0.98 – 0.87 (m, 2H), 0.76 (s, 2H).

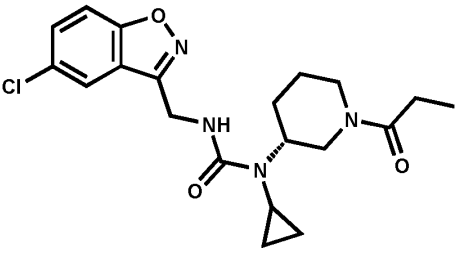
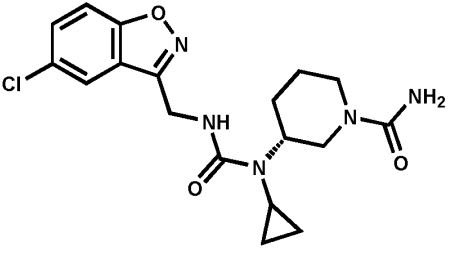
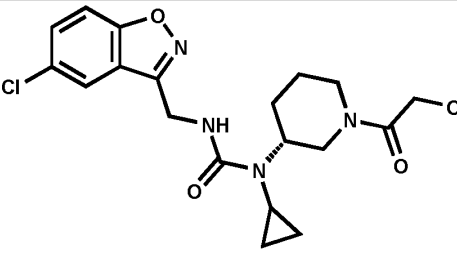
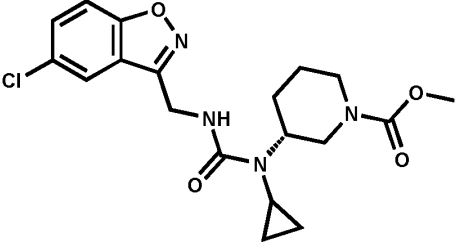
Example 62 (cis)	 methyl (3R,5S)-3-(1-cyclopropyl-3-((5,7-difluoro-1H-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)piperidine-1-carboxylate	437.1	¹ H NMR (400 MHz, MeOD) δ 6.98 (dd, J = 9.4, 2.1 Hz, 1H), 6.84 (s, 1H), 6.71 – 6.61 (m, 1H), 6.34 (d, J = 3.3 Hz, 1H), 4.50 (d, J = 5.6 Hz, 2H), 4.20 (s, 1H), 4.06 (s, 1H), 3.68 (s, 4H), 3.46 (dt, J = 23.7, 11.9 Hz, 2H), 3.18 (t, J = 11.3 Hz, 1H), 2.48 (d, J = 34.8 Hz, 2H), 1.87 (t, J = 10.0 Hz, 2H), 1.73 (s, 1H), 0.93 (d, J = 2.8 Hz, 2H), 0.76 (s, 2H).
Example 63	 (R)-3-(1-cyclopropyl-3-((5-fluoro-6-methyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	402.2	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.11 (d, J = 6.5 Hz, 1H), 7.04 (d, J = 10.7 Hz, 1H), 6.82 – 6.74 (m, 1H), 6.21 (d, J = 0.9 Hz, 1H), 4.51 – 4.42 (m, 2H), 4.02 – 3.85 (m, 2H), 3.75 – 3.60 (m, 1H), 3.20 – 3.08 (m, 1H), 2.71 (s, 3H), 2.69 – 2.60 (m, 1H), 2.54 – 2.44 (m, 1H), 2.30 (d, J = 2.1, 0.8 Hz, 3H), 2.17 – 2.05 (m, 1H), 1.95 – 1.85 (m, 1H), 1.81 – 1.70 (m, 1H), 1.60 – 1.43 (m, 1H), 0.97 – 0.86 (m, 2H), 0.79 – 0.70 (m, 2H).
Example 64	 (R)-3-(1-cyclopropyl-3-((5-fluoro-4-methyl-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	402.2	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.13 – 7.05 (m, 1H), 6.81 – 6.75 (m, 1H), 6.34 – 6.28 (m, 1H), 4.54 – 4.46 (m, 2H), 4.02 – 3.86 (m, 2H), 3.74 – 3.61 (m, 1H), 3.19 – 3.09 (m, 1H), 2.71 (s, 3H), 2.68 – 2.59 (m, 1H), 2.54 – 2.45 (m, 1H), 2.36 (d, J = 1.8 Hz, 3H), 2.16 – 2.05 (m, 1H), 1.96 – 1.85 (m, 1H), 1.81 – 1.71 (m, 1H), 1.58 – 1.44 (m, 1H), 0.98 – 0.86 (m, 2H), 0.81 – 0.70 (m, 2H).
Example 65	 (R)-3-(3-((6-cyano-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	395.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.28 – 7.20 (m, 1H), 6.42 (s, 1H), 4.56 (d, J = 4.4 Hz, 2H), 3.94 (t, J = 14.7 Hz, 2H), 3.72 – 3.62 (m, 1H), 3.22 – 3.10 (m, 1H), 2.71 (s, 3H), 2.69 – 2.61 (m, 1H), 2.56 – 2.49 (m, 1H), 2.18 – 2.06 (m, 1H), 1.91 (d, J = 11.6 Hz, 1H), 1.76 (d, J = 12.9 Hz, 1H), 1.56 – 1.45 (m, 1H), 0.97 – 0.90 (m, 2H), 0.82 – 0.74 (m, 2H).

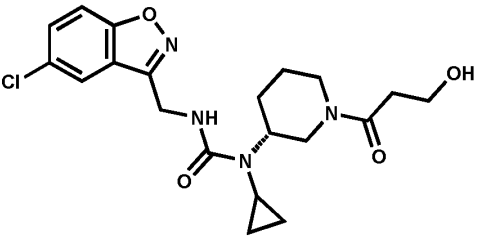
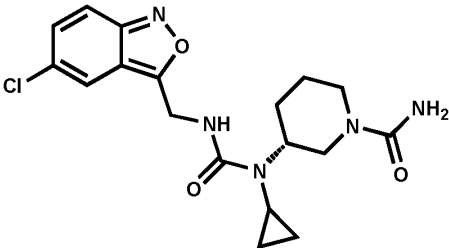
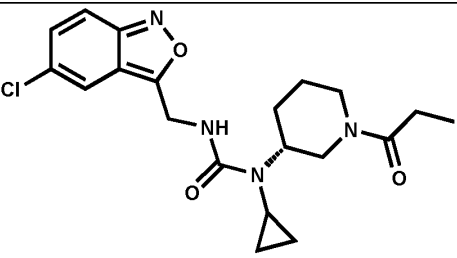
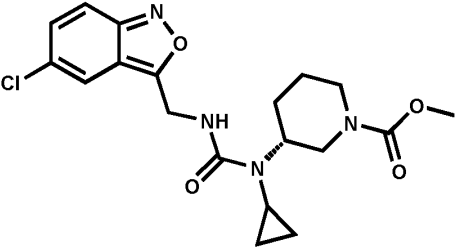
Example 66	 (R)-3-(1-cyclopropyl-3-((6-(trifluoromethoxy)-1H-indol-2-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	454.2	¹ H NMR (400 MHz, MeOD) δ 7.47 (d, J = 8.6 Hz, 1H), 7.23 (s, 1H), 6.88 (d, J = 9.4 Hz, 1H), 6.33 (s, 1H), 4.50 (s, 2H), 3.98 – 3.88 (m, 2H), 3.70 – 3.63 (m, 1H), 3.18 – 3.13 (m, 1H), 2.71 (s, 3H), 2.67 – 2.62 (m, 1H), 2.52 – 2.48 (m, 1H), 2.16 – 2.08 (m, 1H), 1.91 (d, J = 11.2 Hz, 1H), 1.76 (d, J = 13.1 Hz, 1H), 1.56 – 1.47 (m, 1H), 0.95 – 0.90 (m, 2H), 0.78 – 0.74 (m, 2H).
Example 67	 (R)-3-(3-((6-chloro-5-fluorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	424.1	¹ H NMR (400 MHz, MeOD) δ 7.77 (d, J = 6.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.28 (s, 1H), 4.83 (s, 2H), 3.96 – 3.84 (m, 2H), 3.63 – 3.55 (m, 1H), 3.14 (t, J = 12.0 Hz, 1H), 2.69 (s, 3H), 2.64 (d, J = 2.6 Hz, 1H), 2.56 – 2.50 (m, 1H), 2.10 (dd, J = 12.6, 4.0 Hz, 1H), 1.86 (d, J = 12.5 Hz, 1H), 1.74 (d, J = 13.4 Hz, 1H), 1.54 – 1.43 (m, 1H), 0.98 – 0.91 (m, 2H), 0.74 (d, J = 4.0 Hz, 2H).
Example 68	 (R)-3-(1-cyclopropyl-3-((6-fluoro-1H-indazol-3-yl)methyl)ureido)-N-methylpiperidine-1-carboxamide	389.4	¹ H NMR (400 MHz, CD ₃ OD) δ 7.87 – 7.73 (m, 1H), 7.15 (dd, J = 9.4, 1.9 Hz, 1H), 6.98 – 6.89 (m, 1H), 6.85 (t, J = 5.5 Hz, 1H), 4.72 (d, J = 1.3 Hz, 2H), 3.96 (d, J = 12.8 Hz, 1H), 3.89 (d, J = 12.5 Hz, 1H), 3.70 – 3.58 (m, 1H), 3.15 (t, J = 12.0 Hz, 1H), 2.70 (s, 3H), 2.70 – 2.59 (m, 1H), 2.54 – 2.43 (m, 1H), 2.19 – 2.05 (m, 1H), 1.89 (d, J = 11.3 Hz, 1H), 1.75 (d, J = 13.3 Hz, 1H), 1.57 – 1.42 (m, 1H), 0.93 – 0.83 (m, 2H), 0.75 – 0.66 (m, 2H).
Example 69	 (R)-3-(3-((5-cyano-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	395.2	¹ H NMR (400 MHz, MeOD) δ 7.89 (d, J = 0.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 8.4, 1.5 Hz, 1H), 6.43 (s, 1H), 4.53 (s, 2H), 4.00 – 3.85 (m, 2H), 3.73 – 3.59 (m, 1H), 3.20 – 3.08 (m, 1H), 2.74 – 2.63 (m, 4H), 2.56 – 2.46 (m, 1H), 2.18 – 2.06 (m, 1H), 1.91 (d, J = 11.9 Hz, 1H), 1.76 (d, J = 13.2 Hz, 1H), 1.50 (d, J = 13.1 Hz, 1H), 0.97 – 0.88 (m, 2H), 0.82 – 0.73 (m, 2H).

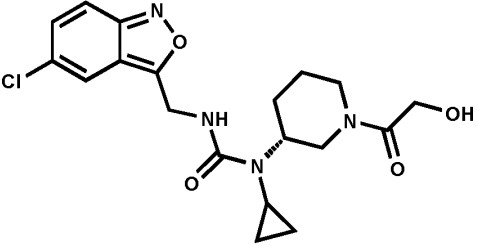
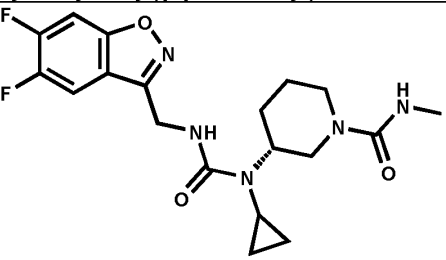
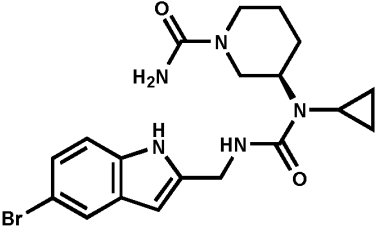
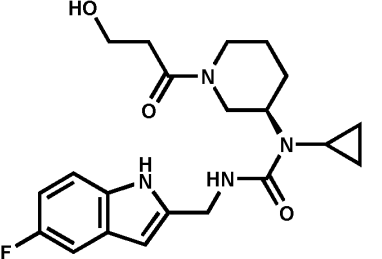
Example 70	 (R)-3-(3-((6-chloro-5-fluorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	424.1	¹ H NMR (400 MHz, MeOD) δ 7.89 – 7.83 (m, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.13 (t, J = 5.8 Hz, 1H), 4.76 – 4.71 (m, 2H), 3.98 – 3.87 (m, 2H), 3.67 – 3.57 (m, 1H), 3.21 – 3.13 (m, 1H), 2.70 (s, 3H), 2.69 – 2.61 (m, 1H), 2.55 – 2.50 (m, 1H), 2.18 – 2.06 (m, 1H), 1.91 – 1.84 (m, 1H), 1.78 – 1.71 (m, 1H), 1.56 – 1.44 (m, 1H), 0.95 – 0.89 (m, 2H), 0.78 – 0.70 (m, 2H).
Example 71	 (R)-3-(3-((5-chloro-6-fluorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-N-methylpiperidine-1-carboxamide	424.1	¹ H NMR (400 MHz, MeOD) δ 7.95 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 9.4 Hz, 1H), 4.85 – 4.84 (m, 2H), 3.89 (ddd, J = 14.0, 12.6, 7.7 Hz, 2H), 3.59 (tt, J = 11.8, 4.0 Hz, 1H), 3.19 – 3.10 (m, 1H), 2.71 – 2.59 (m, 4H), 2.56 – 2.49 (m, 1H), 2.11 (qd, J = 12.6, 4.1 Hz, 1H), 1.87 (d, J = 12.0 Hz, 1H), 1.74 (d, J = 13.0 Hz, 1H), 1.54 – 1.42 (m, 1H), 0.98 – 0.91 (m, 2H), 0.75 (dd, J = 7.7, 3.3 Hz, 2H).
Example 73	 (R)-1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)-1-(1-propionylpiperidin-3-yl)urea	387.2	¹ H NMR (400 MHz, MeOD) δ 7.28 – 7.22 (m, 1H), 7.13 – 7.07 (m, 1H), 6.80 (t, J = 9.2 Hz, 1H), 6.27 (d, J = 3.8 Hz, 1H), 4.49 (d, J = 6.6 Hz, 3H), 3.89 (d, J = 12.7 Hz, 1H), 3.79 (s, 1H), 3.51 (d, J = 26.5 Hz, 1H), 3.09 (d, J = 11.8 Hz, 1H), 2.97 (t, J = 12.6 Hz, 1H), 2.57 – 2.44 (m, 2H), 2.44 – 2.34 (m, 2H), 2.24 – 2.13 (m, 1H), 1.83 (s, 2H), 1.57 – 1.43 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H), 0.97 – 0.89 (m, 2H), 0.76 (d, J = 29.1 Hz, 2H).
Example 74	 (R)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)piperidine-1-carboxamide	374.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.29 – 7.23 (m, 1H), 7.14 – 7.07 (m, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.82 – 6.76 (m, 1H), 6.27 (s, 1H), 4.49 (d, J = 4.4 Hz, 2H), 4.02 – 3.88 (m, 2H), 3.77 – 3.63 (m, 1H), 3.25 – 3.14 (m, 1H), 2.69 (td, J = 13.0, 2.4 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.20 – 2.06 (m, 1H), 1.91 (d, J = 11.1 Hz, 1H), 1.77 (d, J = 13.1 Hz, 1H), 1.59 – 1.46 (m, 1H), 0.98 – 0.88 (m, 2H), 0.81 – 0.72 (m, 2H).

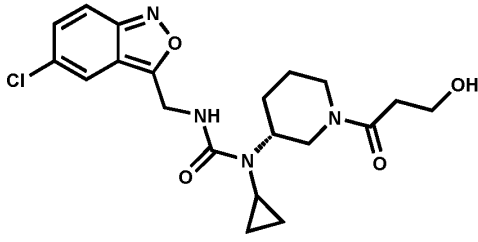
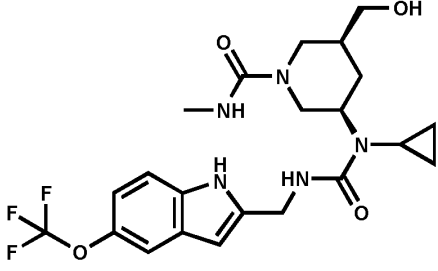
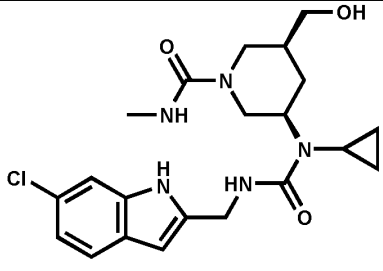
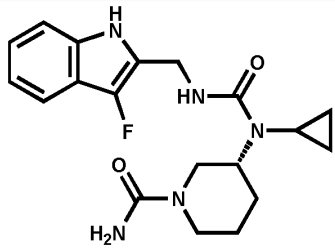
Example 75	 (R)-3-(3-((5-chloro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-N-methoxypiperidine-1-carboxamide	420.4	¹ H NMR (400 MHz, CD ₃ OD) δ 7.42 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.00 (dd, J = 8.6, 2.0 Hz, 1H), 6.86 - 6.83 (m, 1H), 6.26 (s, 1H), 4.50 (d, J = 4.6 Hz, 2H), 3.99 - 3.79 (m, 2H), 3.76 - 3.53 (m, 4H), 3.22 - 3.05 (m, 1H), 2.76 - 2.60 (m, 1H), 2.59 - 2.46 (m, 1H), 2.25 - 2.05 (m, 1H), 1.98 - 1.83 (m, 1H), 1.84 - 1.66 (m, 1H), 1.65 - 1.43 (m, 1H), 0.99 - 0.84 (m, 2H), 0.83 - 0.66 (m, 2H).
Example 76	 (R)-1-(1-(1-acetylpiperidin-3-yl)-3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylurea	391.1	
Example 78	 (R)-1-(1-(1-acetylpiperidin-3-yl)-3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylurea	391.2	
Example 80	 methyl (3R,5S)-3-(3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	437.2	¹ H NMR (400 MHz, MeOD) δ 7.74 (d, J = 0.9 Hz, 1H), 7.53 (d, J = 9.5 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 4.86 (s, 2H), 4.21 (d, J = 11.5 Hz, 1H), 4.03 (s, 1H), 3.67 (s, 4H), 3.46 (dd, J = 11.1, 5.1 Hz, 1H), 3.38 (s, 1H), 3.19 (t, J = 11.9 Hz, 1H), 2.49 (d, J = 48.2 Hz, 2H), 1.86 (t, J = 9.4 Hz, 2H), 1.73 (s, 1H), 1.02 - 0.88 (m, 2H), 0.74 (s, 2H).

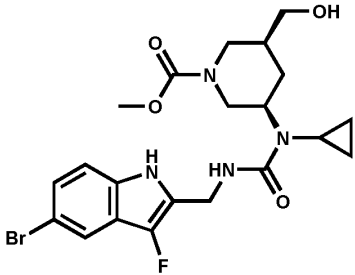
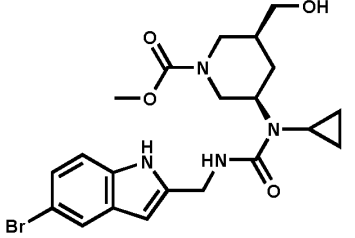
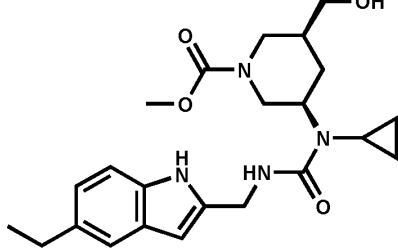
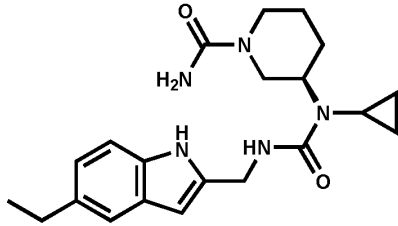
Example 81	 methyl (3R,5S)-3-(3-((6-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	437.1	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.72 (dd, J = 9.2, 0.9 Hz, 1H), 7.59 – 7.52 (m, 1H), 6.98 (dd, J = 9.2, 1.6 Hz, 1H), 4.87 (s, 2H), 4.26 – 4.12 (m, 1H), 4.12 – 3.97 (m, 1H), 3.67 (s, 4H), 3.49 – 3.43 (m, 1H), 3.42 – 3.33 (m, 1H), 3.24 – 3.11 (m, 1H), 2.61 – 2.50 (m, 1H), 2.50 – 2.33 (m, 1H), 1.91 – 1.79 (m, 2H), 1.77 – 1.64 (m, 1H), 1.02 – 0.90 (m, 2H), 0.82 – 0.68 (m, 2H).
Example 82	 (R)-3-(3-((6-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxamide	392.1	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.72 (dd, J = 9.2, 0.8 Hz, 1H), 7.59 – 7.53 (m, 1H), 6.98 (dd, J = 9.3, 1.6 Hz, 1H), 4.88 (d, J = 1.4 Hz, 2H), 4.03 – 3.85 (m, 2H), 3.70 – 3.56 (m, 1H), 3.24 – 3.13 (m, 1H), 2.75 – 2.61 (m, 1H), 2.60 – 2.49 (m, 1H), 2.17 – 2.04 (m, 1H), 1.93 – 1.82 (m, 1H), 1.81 – 1.68 (m, 1H), 1.61 – 1.43 (m, 1H), 1.06 – 0.88 (m, 2H), 0.83 – 0.67 (m, 2H).
Example 83	 (R)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-N-methoxypiperidine-1-carboxamide	404.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.25 (dd, J = 8.8, 4.5 Hz, 1H), 7.10 (dd, J = 9.8, 2.4 Hz, 1H), 6.89 – 6.72 (m, 2H), 6.27 (s, 1H), 4.49 (d, J = 3.9 Hz, 2H), 3.99 – 3.78 (m, 2H), 3.74 – 3.64 (m, 1H), 3.62 (s, 3H), 3.21 – 3.07 (m, 1H), 2.73 – 2.60 (m, 1H), 2.56 – 2.43 (m, 1H), 2.22 – 2.01 (m, 1H), 1.99 – 1.85 (m, 1H), 1.80 – 1.69 (m, 1H), 1.61 – 1.43 (m, 1H), 0.99 – 0.85 (m, 2H), 0.82 – 0.63 (m, 2H).
Example 84	 methyl (R)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)piperidine-1-carboxylate	389.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.30 – 7.21 (m, 1H), 7.15 – 7.05 (m, 1H), 6.84 – 6.79 (m, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.27 (s, 1H), 4.49 (d, J = 5.2 Hz, 2H), 4.06 (d, J = 9.3 Hz, 2H), 3.68 (s, 4H), 3.21 (t, J = 11.9 Hz, 1H), 2.69 (s, 1H), 2.50 (s, 1H), 2.21 – 2.05 (m, 1H), 1.89 (d, J = 12.3 Hz, 1H), 1.77 (d, J = 13.2 Hz, 1H), 1.57 – 1.42 (m, 1H), 0.97 – 0.87 (m, 2H), 0.75 (s, 2H).

Example 85	 (R)-3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-propionylpiperidin-3-yl)urea	405.2	¹ H NMR (400 MHz, MeOD) δ 7.93 (d, J = 8.4 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.21 – 7.07 (m, 1H), 4.76 (d, J = 4.4 Hz, 2H), 4.54 – 4.47 (m, 1H), 3.94 – 3.85 (m, 1H), 3.82 – 3.73 (m, 1H), 3.55 – 3.44 (m, 1H), 3.35 – 3.31 (m, 1H), 3.13 (t, J = 11.8 Hz, 1H), 2.98 (t, J = 13.0 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.46 – 2.35 (m, 2H), 2.29 – 2.14 (m, 1H), 1.99 – 1.78 (m, 2H), 1.59 – 1.40 (m, 1H), 1.11 (s, 3H), 0.99 – 0.88 (m, 2H), 0.83 – 0.63 (m, 2H).
Example 86	 (R)-3-3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxamide	392.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 – 7.91 (m, 1H), 7.65 – 7.54 (m, 2H), 4.78 – 4.74 (m, 2H), 4.03 – 3.85 (m, 2H), 3.70 – 3.58 (m, 1H), 3.29 – 3.20 (m, 1H), 2.75 – 2.64 (m, 1H), 2.58 – 2.48 (m, 1H), 2.23 – 2.08 (m, 1H), 1.90 (d, J = 12.4 Hz, 1H), 1.77 (d, J = 13.4 Hz, 1H), 1.59 – 1.46 (m, 1H), 0.98 – 0.88 (m, 2H), 0.80 – 0.68 (m, 2H).
Example 87	 (R)-3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-(2-hydroxyacetyl)piperidin-3-yl)urea	407.1	¹ H NMR (400 MHz, MeOD) δ 7.94 (d, J = 3.0 Hz, 1H), 7.66 – 7.55 (m, 2H), 7.15 (d, J = 15.0 Hz, 1H), 4.81 – 4.70 (m, 2H), 4.47 (d, J = 12.3 Hz, 1H), 4.32 – 4.14 (m, 2H), 3.78 – 3.63 (m, 2H), 3.59 – 3.46 (m, 1H), 3.33 (d, J = 10.5 Hz, 1H), 3.21 (t, J = 11.9 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.62 – 2.48 (m, 2H), 2.31 – 2.14 (m, 1H), 2.00 – 1.76 (m, 2H), 1.60 – 1.43 (m, 1H), 0.93 (dd, J = 16.0, 6.8 Hz, 2H), 0.82 – 0.61 (m, 2H).
Example 88	 methyl (R)-3-3-((5-chlorobenzo[d]isoxazol-3-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxylate	407.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.97 – 7.90 (m, 1H), 7.65 – 7.55 (m, 2H), 4.75 (s, 2H), 4.05 (d, J = 10.6 Hz, 2H), 3.67 (s, 4H), 3.23 (d, J = 12.1 Hz, 1H), 2.69 (s, 1H), 2.53 (s, 1H), 2.21 – 2.07 (m, 1H), 1.88 (d, J = 12.7 Hz, 1H), 1.77 (d, J = 12.8 Hz, 1H), 1.52 (t, J = 13.0 Hz, 1H), 0.97 – 0.89 (m, 2H), 0.71 (s, 2H).

Example 89	 (R)-3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-(3-hydroxypropanoyl)piperidin-3-yl)urea	421.2	¹ H NMR (400 MHz, MeOD) δ 7.94 (d, J = 6.1 Hz, 1H), 7.62 – 7.52 (m, 2H), 4.78 – 4.71 (m, 2H), 4.56 – 4.47 (m, 1H), 3.94 (d, J = 12.7 Hz, 1H), 3.82 (t, J = 6.3 Hz, 2H), 3.76 – 3.70 (m, 0.5H), 3.56 – 3.45 (m, 0.5H), 3.40 – 3.34 (m, 0.5H), 3.16 (t, J = 11.8 Hz, 0.5H), 3.03 – 2.95 (m, 0.5H), 2.72 – 2.64 (m, 0.5H), 2.64 – 2.50 (m, 3H), 2.23 (pd, J = 12.6, 4.0 Hz, 1H), 1.99 – 1.77 (m, 2H), 1.58 – 1.38 (m, 1H), 0.93 (ddd, J = 18.8, 8.9, 5.8 Hz, 2H), 0.75 (tdd, J = 11.8, 7.2, 5.1 Hz, 2H).
Example 90	 (R)-3-(3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxamide	392.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.76 (d, J = 0.9 Hz, 1H), 7.53 (d, J = 9.5 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 4.86 (s, 2H), 4.00 – 3.85 (m, 2H), 3.67 – 3.56 (m, 1H), 3.26 – 3.16 (m, 1H), 2.73 – 2.63 (m, 1H), 2.59 – 2.51 (m, 1H), 2.20 – 2.06 (m, 1H), 1.89 (d, J = 11.2 Hz, 1H), 1.75 (d, J = 13.5 Hz, 1H), 1.60 – 1.46 (m, 1H), 0.99 – 0.92 (m, 2H), 0.81 – 0.71 (m, 2H).
Example 91	 (R)-3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-propionylpiperidin-3-yl)urea	405.2	¹ H NMR (400 MHz, MeOD) δ 7.75 (d, J = 8.3 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.32 – 7.28 (m, 1H), 4.90 – 4.85 (m, 2H), 4.50 (d, J = 10.9 Hz, 1H), 3.86 (t, J = 14.9 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.47 (t, J = 11.8 Hz, 1H), 3.26 (s, 1H), 3.10 (t, J = 11.8 Hz, 1H), 2.96 (t, J = 12.0 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.54 – 2.46 (m, 1H), 2.44 – 2.33 (m, 2H), 2.18 (dt, J = 21.4, 6.2 Hz, 1H), 1.99 – 1.75 (m, 2H), 1.56 – 1.40 (m, 1H), 1.13 – 1.06 (m, 3H), 1.01 – 0.89 (m, 2H), 0.84 – 0.64 (m, 2H).
Example 92		407.1	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 (s, 1H), 7.53 (d, J = 9.5 Hz, 1H), 7.38 – 7.23 (m, 1H), 4.89 (s, 2H), 4.02 (s, 2H), 3.64 (d, J = 23.3 Hz, 4H), 3.22 (t, J = 11.9 Hz, 1H), 2.68 (s, 1H), 2.54 (s, 1H), 2.20 – 2.06 (m, 1H), 1.87 (d, J = 12.2 Hz, 1H), 1.75 (d, J = 12.9 Hz, 1H), 1.49 (q, J = 13.3

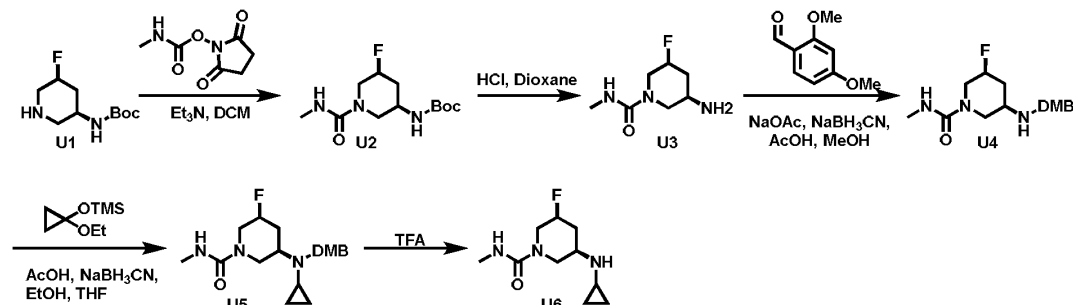
	methyl (<i>R</i>)-3-(3-((5-chlorobenzo[<i>c</i>]isoxazol-3-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxylate		Hz, 1H), 1.01 – 0.90 (m, 2H), 0.73 (s, 2H).
Example 93	 (<i>R</i>)-3-((5-chlorobenzo[<i>c</i>]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-(2-hydroxyacetyl)piperidin-3-yl)urea	407.1	¹ H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.54 (d, <i>J</i> = 9.4 Hz, 1H), 7.36 – 7.25 (m, 2H), 4.85 – 4.83 (m, 2H), 4.44 (d, <i>J</i> = 6.0 Hz, 1H), 4.30 – 4.12 (m, 2H), 3.76 – 3.46 (m, 2H), 3.27 (s, 1H), 3.16 (t, <i>J</i> = 12.0 Hz, 1H), 2.98 – 2.83 (m, 1H), 2.63 – 2.46 (m, 2H), 2.28 – 2.11 (m, 1H), 2.01 – 1.74 (m, 2H), 1.60 – 1.41 (m, 1H), 1.02 – 0.88 (m, 2H), 0.85 – 0.63 (m, 2H).
Example 94	 (<i>R</i>)-3-(1-cyclopropyl-3-((5,6-difluorobenzo[<i>d</i>]isoxazol-3-yl)methyl)ureido)-<i>N</i>-methylpiperidine-1-carboxamide	408.2	¹ H NMR (400 MHz, MeOD) δ 7.86 – 7.74 (m, 1H), 7.69 – 7.58 (m, 1H), 7.12 (t, <i>J</i> = 5.9 Hz, 1H), 4.77 – 4.70 (m, 2H), 4.00 – 3.85 (m, 2H), 3.67 – 3.57 (m, 1H), 3.23 – 3.11 (m, 1H), 2.70 (s, 3H), 2.68 – 2.60 (m, 1H), 2.55 – 2.48 (m, 1H), 2.19 – 2.05 (m, 1H), 1.95 – 1.84 (m, 1H), 1.80 – 1.70 (m, 1H), 1.58 – 1.43 (m, 1H), 0.97 – 0.87 (m, 2H), 0.78 – 0.68 (m, 2H).
Example 97	 (<i>R</i>)-3-(3-((5-bromo-1<i>H</i>-indol-2-yl)methyl)-1-cyclopropylureido)piperidine-1-carboxamide	436.1	
Example 98	 (<i>R</i>)-1-cyclopropyl-3-((5-fluoro-1<i>H</i>-indol-2-yl)methyl)-1-(1-(3-hydroxypropanoyl)piperidin-3-yl)urea	403.3	¹ H NMR (400 MHz, MeOD) δ 7.28 – 7.19 (m, 1H), 7.10 (d, <i>J</i> = 9.7 Hz, 1H), 6.80 (t, <i>J</i> = 9.2 Hz, 1H), 6.27 (d, <i>J</i> = 2.5 Hz, 1H), 4.49 (d, <i>J</i> = 6.4 Hz, 3H), 3.95 (d, <i>J</i> = 13.3 Hz, 1H), 3.82 (t, <i>J</i> = 6.3 Hz, 3H), 3.64 – 3.42 (m, 1H), 3.16 – 2.97 (m, 1H), 2.72 – 2.56 (m, 2H), 2.56 – 2.39 (m, 2H), 2.20 (d, <i>J</i> = 12.1 Hz, 1H), 1.98 – 1.77 (m, 2H), 1.58 – 1.41 (m, 1H), 0.99 – 0.85 (m, 2H), 0.76 (d, <i>J</i> = 17.0 Hz, 2H).

Example 99	 (R)-3-((5-chlorobenzo[c]isoxazol-3-yl)methyl)-1-cyclopropyl-1-(1-(3-hydroxypropanoyl)piperidin-3-yl)urea	421.2	¹ H NMR (400 MHz, CDCl ₃) δ 7.64 (s, 1H), 7.53 – 7.48 (m, 1H), 7.24 – 7.18 (m, 1H), 6.00 – 5.88 (m, 1H), 4.89 (t, J = 5.6 Hz, 2H), 4.65 – 4.51 (m, 1H), 3.94 – 3.83 (m, 2H), 3.81 – 3.72 (m, 2H), 3.56 – 3.39 (m, 1H), 3.24 – 3.15 (m, 1H), 2.99 – 2.92 (m, 1H), 2.68 – 2.60 (m, 1H), 2.56 – 2.41 (m, 3H), 2.35 – 2.24 (m, 1H), 2.18 – 2.09 (m, 1H), 1.98 – 1.77 (m, 2H), 1.53 – 1.45 (m, 1H), 1.00 – 0.89 (m, 2H), 0.87 – 0.67 (m, 2H).
Example 100	 (3R,5S)-3-(1-cyclopropyl-3-((5-(trifluoromethoxy)-1H-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)-N-methylpiperidine-1-carboxamide	484.2	¹ H NMR (400 MHz, CD ₃ OD) δ 7.34 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.0 Hz, 1H), 6.34 (s, 1H), 4.51 (s, 2H), 4.08 (d, J = 11.5 Hz, 1H), 3.92 (d, J = 12.6 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.49 – 3.39 (m, 2H), 3.13 (t, J = 12.0 Hz, 1H), 2.71 (s, 3H), 2.55 – 2.47 (m, 1H), 2.47 – 2.38 (m, 1H), 1.97 – 1.80 (m, 2H), 1.78 – 1.67 (m, 1H), 0.99 – 0.88 (m, 2H), 0.77 (d, J = 3.9 Hz, 2H).
Example 101	 (3R,5S)-3-(3-((6-chloro-1H-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)-N-methylpiperidine-1-carboxamide	456.4	¹ H NMR (400 MHz, MeOD) δ 7.40 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 6.94 (dd, J = 8.4, 1.9 Hz, 1H), 6.29 (s, 1H), 4.49 (s, 2H), 4.08 (d, J = 10.3 Hz, 1H), 3.91 (d, J = 12.4 Hz, 1H), 3.80 – 3.68 (m, 1H), 3.52 – 3.42 (m, 2H), 3.13 (t, J = 12.0 Hz, 1H), 2.71 (s, 3H), 2.55 – 2.48 (m, 1H), 2.47 – 2.37 (m, 1H), 1.95 – 1.81 (m, 2H), 1.73 (dd, J = 10.8, 5.3 Hz, 1H), 0.92 (dd, J = 6.3, 3.2 Hz, 2H), 0.77 (d, J = 4.0 Hz, 2H).
Example 102	 (R)-3-(1-cyclopropyl-3-((3-fluoro-1H-indol-2-yl)methyl)ureido)piperidine-1-carboxamide	374.3	¹ H NMR (400 MHz, MeOD) δ 7.44 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 6.9 Hz, 1H), 4.52 (s, 2H), 3.92 (d, J = 13.2 Hz, 2H), 3.68 (d, J = 11.6 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.68 (t, J = 13.2 Hz, 1H), 2.48 (s, 1H), 2.19 – 2.02 (m, 1H), 1.89 (s, 1H), 1.75 (s, 1H), 1.53 (d, J = 12.9 Hz, 1H), 0.94 – 0.80 (m, 2H), 0.75 (d, J = 3.8 Hz, 2H).

Example 103	 methyl (3<i>R</i>,5<i>S</i>)-3-(3-((5-bromo-3-fluoro-1<i>H</i>-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	497.1	¹ H NMR (400 MHz, MeOD) δ 7.58 (d, <i>J</i> = 1.3 Hz, 1H), 7.26 – 7.15 (m, 2H), 4.52 (s, 2H), 4.21 (d, <i>J</i> = 11.5 Hz, 1H), 4.07 (d, <i>J</i> = 10.9 Hz, 1H), 3.68 (s, 4H), 3.51 – 3.38 (m, 2H), 3.17 (t, <i>J</i> = 12.0 Hz, 1H), 2.49 (s, 2H), 1.92 – 1.69 (m, 3H), 0.96 – 0.86 (m, 2H), 0.74 (s, 2H).
Example 104	 methyl (3<i>R</i>,5<i>S</i>)-3-(3-((5-bromo-1<i>H</i>-indol-2-yl)methyl)-1-cyclopropylureido)-5-(hydroxymethyl)piperidine-1-carboxylate	479.2	¹ H NMR (400 MHz, MeOD) δ 7.58 (d, <i>J</i> = 1.8 Hz, 1H), 7.23 (d, <i>J</i> = 8.6 Hz, 1H), 7.13 (dd, <i>J</i> = 8.6, 1.9 Hz, 1H), 6.83 (s, 1H), 6.26 (s, 1H), 4.49 (d, <i>J</i> = 5.2 Hz, 2H), 4.21 (d, <i>J</i> = 11.8 Hz, 1H), 4.06 (s, 1H), 3.68 (s, 4H), 3.51 – 3.37 (m, 2H), 3.18 (t, <i>J</i> = 12.0 Hz, 1H), 2.51 (s, 2H), 1.91 – 1.68 (m, 3H), 0.96 – 0.89 (m, 2H), 0.82 – 0.68 (m, 2H).
Example 105	 methyl (3<i>R</i>,5<i>S</i>)-3-(1-cyclopropyl-3-((5-ethyl-1<i>H</i>-indol-2-yl)methyl)ureido)-5-(hydroxymethyl)piperidine-1-carboxylate	429.3	¹ H NMR (400 MHz, MeOD) δ 7.14 (s, 1H), 7.09 (d, <i>J</i> = 8.3 Hz, 1H), 6.79 (dd, <i>J</i> = 8.3, 1.5 Hz, 1H), 6.62 (t, <i>J</i> = 5.5 Hz, 1H), 6.10 (s, 1H), 4.36 (d, <i>J</i> = 4.8 Hz, 2H), 4.09 (d, <i>J</i> = 11.4 Hz, 1H), 3.96 (d, <i>J</i> = 9.8 Hz, 1H), 3.68–3.58 (m, 1H), 3.57 (s, 3H), 3.36 (dd, <i>J</i> = 11.0, 5.3 Hz, 1H), 3.30 (d, <i>J</i> = 6.2 Hz, 1H), 3.06 (t, <i>J</i> = 12.0 Hz, 1H), 2.55 (q, <i>J</i> = 7.6 Hz, 2H), 2.38 (s, 2H), 1.75 (t, <i>J</i> = 10.2 Hz, 2H), 1.63 (d, <i>J</i> = 4.9 Hz, 1H), 1.12 (t, <i>J</i> = 7.6 Hz, 3H), 0.82 – 0.75 (m, 2H), 0.62 (s, 2H).
Example 106	 (<i>R</i>)-3-(1-cyclopropyl-3-((5-ethyl-1<i>H</i>-indol-2-yl)methyl)ureido)piperidine-1-carboxamide	384.3	¹ H NMR (400 MHz, MeOD) δ 7.33 (s, 1H), 7.29 (d, <i>J</i> = 8.3 Hz, 1H), 6.99 (dd, <i>J</i> = 8.3, 1.5 Hz, 1H), 6.82 (t, <i>J</i> = 5.7 Hz, 1H), 6.29 (s, 1H), 4.56 (d, <i>J</i> = 4.5 Hz, 2H), 4.09 – 3.96 (m, 2H), 3.77 (tt, <i>J</i> = 11.8, 3.9 Hz, 1H), 3.27 (t, <i>J</i> = 12.0 Hz, 1H), 2.80 – 2.71 (m, 3H), 2.60 – 2.54 (m, 1H), 2.20 (qd, <i>J</i> = 12.6, 4.1 Hz, 1H), 1.98 (d, <i>J</i> = 11.9 Hz, 1H), 1.84 (d, <i>J</i> = 13.2 Hz, 1H), 1.60 (qt, <i>J</i> = 12.9, 4.0 Hz, 1H), 1.31 (t, <i>J</i> = 7.6 Hz, 3H), 1.02 – 0.96 (m, 2H), 0.86 – 0.80 (m, 2H).

Synthesis of Additional Common Intermediates

Synthesis of U6

**Step 1: Synthesis of U2**

To a solution of **U1** (2.5 g, 9.84 mmol) in DCM (50 mL) were added TEA (3 g, 29.52 mmol) and 2,5-dioxopyrrolidin-1-yl methylcarbamate (1.9 g, 11.04 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was diluted with water (150 mL) and extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~8% MeOH in DCM) to give **U2** (2.62 g, 96% yield) as colorless oil. **LC/MS (ESI) *m/z*: 276 (M+H)⁺**.

Step 2: Synthesis of U3

To a solution of **U2** (2.62 g, 9.54 mmol) in DCM (50 mL) was added TFA (10 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was concentrated to dryness under reduced pressure to give crude **U3** (1.66 g, 99% yield) as yellow oil which was used in the next step directly without further purification. **LC/MS (ESI) *m/z*: 176 (M+H)⁺**.

Step 3: Synthesis of U4

To a mixture of **U3** (1.66 g, 9.47 mmol) and 2,4-dimethoxybenzaldehyde (1.65 g, 9.95 mmol) in MeOH (60 mL) were added NaOAc (2.33 g, 28.42 mmol) and AcOH (0.5 mL). The mixture was stirred at room temperature for 1 hr. Then the reaction mixture was cooled down to 0 °C and NaBH₃CN (1.79 g, 28.42 mmol) was added into the above mixture in portions. The resulting mixture was stirred at room temperature for another 4 hrs. After completion, the

reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (60 mL) and basified with saturated NaHCO_3 solution to adjust pH=8. Then the mixture was extracted with DCM (60 mL x 2). The combined organic layers were washed with brine (120 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **U4** (2.67 g, 87% yield) as yellow oil. **LC/MS (ESI) m/z : 326 (M+H)⁺**.

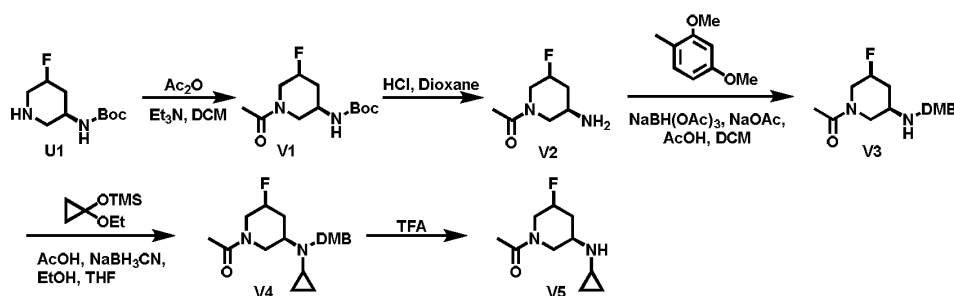
Step 4: Synthesis of U5

To a mixture of **U4** (2.67 g, 8.21 mmol) and AcOH (4.7 mL, 82.1 mmol) in EtOH (30 mL) and THF (60 mL) was added (1-ethoxycyclopropoxy)trimethylsilane (4.95 mL, 24.62 mmol) and NaBH_3CN (1.55 g, 24.62 mmol). The resulting mixture was stirred at 80 °C for 6 hrs under N_2 atmosphere. Then the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (80 mL) and basified with saturated $\text{NaHCO}_3(\text{aq.})$ to adjust pH=8. Then the mixture was extracted with DCM (60 mL x 2), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~3% MeOH in DCM) to give **U5** (2.6 g, 87% yield) as yellow oil. **LC/MS (ESI) m/z : 366 (M+H)⁺**.

Step 5: Synthesis of U6

A solution of **U5** (2.6 g, 7.12 mmol) in TFA (30 mL) was stirred at 80 °C for 4 hrs under N_2 atmosphere. Then the mixture was cooled and concentrated to dryness under reduced pressure to give crude **U6** (1.53 g, 99% yield) as purple oil which was used in the next step directly without further purification. **LC/MS (ESI) m/z : 216 (M+H)⁺**.

Synthesis of V5



Step 1: Synthesis of V1

To a solution of **U1** (50.5 g, 231.6 mmol) in DCM (900 mL) was added TEA (46.7 g, 463.2 mmol) and acetic anhydride (28.3 g, 277.9 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at room temperature for 2 hrs. Then the mixture was diluted with water (1200 mL) and extracted with DCM (500 mL x 2). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~8% MeOH in DCM) to give **V1** (55.0 g, 91% yield) as white solid. **LC/MS (ESI) m/z**: 261 (M+H)⁺.

Step 2: Synthesis of V2

A solution of **V1** (55.0 g, 211.5 mmol) in HCl/dioxane (700 mL, 4 M) was stirred at room temperature for 2 hrs under N₂ atmosphere. Then the mixture was concentrated to dryness under reduced pressure to give crude **V2** (33.8 g, 99% yield) as white solid which was used in the next step directly without further purification. **LC/MS (ESI) m/z**: 161 (M+H)⁺.

Step 3: Synthesis of V3

To a mixture of **V2** (33.8 g, 211.2 mmol) and 2,4-dimethoxybenzaldehyde (35.0 g, 221.2 mmol) in DCM (1200 mL) was added NaOAc (51.9 g, 633.6 mmol) and AcOH (38.0 g, 633.6 mmol). The mixture was stirred at room temperature for 1 hr. Then the reaction mixture was cooled down to 0 °C and NaBH(OAc)₃ (89.5 g, 422.4 mmol) was added into the above mixture in portions. The resulting mixture was stirred at room temperature for 2 hrs. After completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (600 mL) and basified with saturated NaHCO₃ solution to adjust pH=8. Then the mixture was extracted with DCM (1000 mL x 5). The combined organic layers were washed with brine (1200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **V3** (55.6 g, 85% yield) as yellow oil. **LC/MS (ESI) m/z**: 311 (M+H)⁺.

Step 4: Synthesis of V4

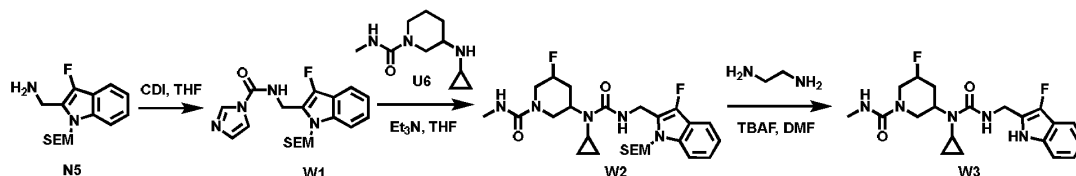
To a mixture of **V3** (55.6 g, 179.3 mmol) and AcOH (107.6 g, 1793 mmol) in EtOH (400 mL) and THF (1600 mL) was added (1-ethoxycyclopropoxy)trimethylsilane (93.6 g, 537.9

mmol) and NaBH_3CN (22.5 g, 35.8 mmol). The resulting mixture was stirred at 80 °C for 6 hrs under N_2 atmosphere. Then the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (1000 mL) and basified with saturated $\text{NaHCO}_3(\text{aq.})$ to adjust pH=8. Then the mixture was extracted with DCM (1000 mL x 4), the combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **V4** (58.4 g, 93.1% yield) as yellow oil. **LC/MS (ESI) m/z : 351 ($\text{M}+\text{H}$)⁺**.

Step 5: Synthesis of V5

A solution of **V4** (58.4 g, 166.8 mmol) in TFA (500 mL) was stirred at 80 °C for 4 hrs under N_2 atmosphere. Then the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in DCM (1000 mL) and basified with saturated $\text{NaHCO}_3(\text{aq.})$ to adjust pH=8. Then the mixture was extracted with DCM (1000 mL x 6), the combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **V5** (29.2 g, 87% yield) as yellow oil. **LC/MS (ESI) m/z : 201 ($\text{M}+\text{H}$)⁺**.

Synthesis of W2/Example 107



Step 1: Synthesis of W1

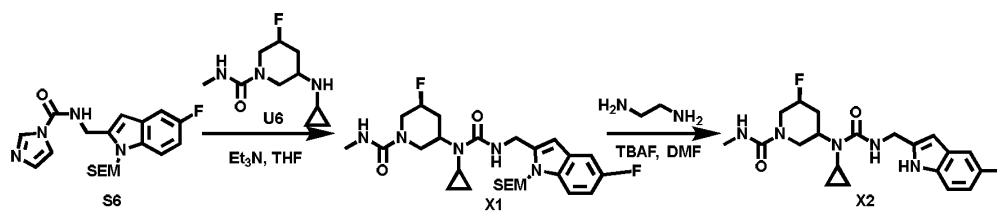
To a solution of **N5** (48.8 g, 166 mmol) in THF (800 mL) was added CDI (29.6 g, 182.6 mmol) in portions at 0 °C under N_2 atmosphere. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was diluted with water (700 mL) and extracted with EtOAc (600 mL x 3). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~72% EtOAc in PE) to give **W1** (52 g, 80.7% yield) as yellow oil. **LC/MS (ESI) m/z : 389 ($\text{M}+\text{H}$)⁺**.

Step 2: Synthesis of W2

To a mixture of **U6** (52 g, 134 mmol) and TEA (27.1 g, 268 mmol) in THF (900 mL) was added **W1** (28.8 g, 134 mmol) at 0 °C. The resulting mixture was stirred at 50 °C for 16 hrs under N₂ atmosphere. Then the mixture was diluted with H₂O (800 mL) and extracted with EtOAc (800 mL×2). The combined organic layers were washed with brine (800 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~90% EtOAc in PE) to give **W2** (43.9 g, 61% yield) as yellow oil. **LC/MS (ESI) m/z**: 418 (M+H-118)⁺.

Step 3: Synthesis of W3/Example 107

To a solution of **W2** (43.9 g, 82 mmol) in DMF (800 mL) was added ethane-1,2-diamine (29.5 g, 492 mmol) and a solution of TBAF in THF (246 mL, 1 M). The resulting mixture was stirred at 80 °C for 2 hrs under N₂ atmosphere. Then the mixture was diluted with EtOAc (1.5 L) and washed with H₂O (600 mL x 8). The organic layer was separated, washed with brine (1 L), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified via prep-HPLC (C18, H₂O/MeCN (10-40%)/0.1% NH₄HCO₃) to give **Example 107** (18.2 g, 54% yield) as Pale-yellow solid. **LC/MS (ESI) m/z**: 406 (M+H)⁺. **¹H NMR** (400 MHz, MeOD) δ 7.45 (d, J = 7.9 Hz, 1H), 7.28 (dd, J = 8.2, 2.5 Hz, 1H), 7.14 – 7.07 (m, 1H), 7.02 (dd, J = 11.1, 3.9 Hz, 1H), 4.57 – 4.36 (m, 3H), 4.34 – 4.25 (m, 1H), 3.88 – 3.67 (m, 2H), 3.21 – 3.09 (m, 1H), 2.73 – 2.63 (m, 4H), 2.56 – 2.45 (m, 1H), 2.40 – 2.18 (m, 2H), 0.92 (d, J = 6.0 Hz, 2H), 0.83 – 0.69 (m, 2H). **¹⁹F NMR** (376 MHz, MeOD) δ -180.46 (s), -182.15 (s).

Synthesis of X2/Example 108**Step 1: Synthesis of X1**

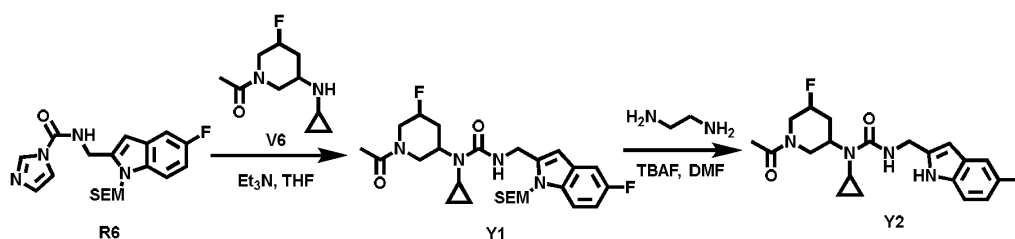
To a solution of **U6** (1.53 g, 7.08 mmol) in THF (50 mL) was added TEA (2.7 ml, 19.3 mmol) dropwise and **S6** (2.5 g, 6.44 mmol) at 0 °C, the resulting mixture was stirred at 60 °C for 16 hrs under N₂ atmosphere. Then the mixture was diluted with water (100 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine

(120 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with 0~50% EtOAc in PE) to give **X1** (3.2 g, 93% yield) as yellow solid. **LC/MS (ESI) m/z** : 418 ($\text{M}+\text{H}-118$)⁺.

Step 2: Synthesis of X2/Example 108

To a solution of **X1** (3.2 g, 5.97 mmol) in DMF (50 mL) was added ethylenediamine (2.4 mL, 35.84 mmol) and TBAF (4.68 g, 17.92 mmol). The resulting mixture was stirred at 80 °C for 3 hrs under N_2 atmosphere. Then the mixture was diluted with water (100 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with saturated NH_4Cl solution (100 mL x 3) and brine (100 mL x 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **Example 108** (1.1 g, 45% yield) as white solid. **LC/MS (ESI) m/z** : 406 ($\text{M}+\text{H}$)⁺. **^1H NMR** (400 MHz, MeOD) δ 7.25 (dd, $J = 8.8, 4.5$ Hz, 1H), 7.10 (dd, $J = 9.9, 2.5$ Hz, 1H), 6.84 – 6.76 (m, 1H), 6.27 (s, 1H), 4.57 – 4.45 (m, 3H), 4.40 (dd, $J = 10.4, 5.2$ Hz, 1H), 4.29 (dd, $J = 12.5, 2.0$ Hz, 1H), 3.84 (dd, $J = 12.8, 1.5$ Hz, 1H), 3.77 – 3.66 (m, 1H), 3.15 (dd, $J = 12.5, 11.5$ Hz, 1H), 2.74 – 2.61 (m, 4H), 2.55 – 2.48 (m, 1H), 2.31 (dd, $J = 14.3, 8.0$ Hz, 2H), 0.93 (d, $J = 5.8$ Hz, 2H), 0.78 (d, $J = 3.5$ Hz, 2H). **^{19}F NMR** (377 MHz, MeOD) δ -127.96 (s), -182.11 (s).

Synthesis of Y2/Example 109



Step 1: Synthesis of Y1

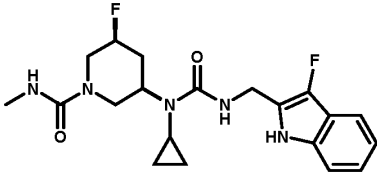
To a solution of **V6** (29.2 g, 146.0 mmol) in THF (800 mL) was added TEA (29.4 g, 292.0 mmol) and **R6** (56.6 g, 146.0 mmol) and the resulting mixture was stirred at 60 °C for 16 hrs under N_2 atmosphere. Then the mixture was diluted with water (700 mL) and extracted with EtOAc (600 mL x 3). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The

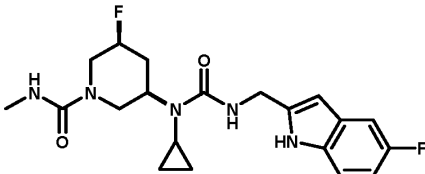
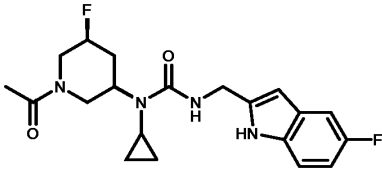
residue was purified by column chromatography on silica gel (eluted with 0~77% EtOAc in PE) to give **Y1** (56.7 g, 74.7% yield) as yellow solid. **LC/MS (ESI)** m/z : 403 ($M+H-118$)⁺.

Step 2: Synthesis of Y2/Example 109

To a solution of **Y1** (56.7 g, 109.0 mmol) in DMF (1000 mL) was added ethylenediamine (39.2 g, 654.2 mmol) and TBAF (85.3 g, 327.1 mmol). The resulting mixture was stirred at 80 °C for 4 hrs under N₂ atmosphere. Then the mixture was diluted with water (3000 mL) and extracted with EtOAc (2000 mL) twice. The combined organic layers were washed with brine (700 mL x 6), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel (eluted with 0~5% MeOH in DCM) to give **Example 109** (20.2 g, 47.5% yield) as white solid. **LC/MS (ESI)** m/z : 391 ($M+H$)⁺. **¹H NMR** (400 MHz, MeOD) δ 7.28 - 7.20 (m, 1H), 7.10 (dd, J = 9.9, 2.5 Hz, 1H), 6.84 - 6.75 (m, 1H), 6.27 (s, 1H), 4.79 - 4.71 (m, 0.6H), 4.67 - 4.33 (m, 3.7H), 4.17 - 4.08 (m, 0.4H), 3.90 - 3.76 (m, 1H), 3.66 - 3.54 (m, 0.5H), 3.13 - 2.98 (m, 1H), 2.60 - 2.47 (m, 1.7H), 2.45 - 2.23 (m, 2H), 2.15 - 2.10 (m, 3H), 1.00 - 0.89 (m, 2H), 0.86 - 0.69 (m, 2H). **¹⁹F NMR** (377 MHz, MeOD) δ -127.01 - -128.90 (m), -181.97 (d, J = 8.8 Hz), -182.43 (d, J = 8.6 Hz).

The compounds in the table below were prepared according to the methods described above.

Example	Structure	Observed LCMS M/Z	¹ H NMR
Example 107	 (3<i>R</i>,5<i>S</i>)-3-(1-cyclopropyl-3-((3-fluoro-1<i>H</i>-indol-2-yl)methyl)ureido)-5-fluoro-<i>N</i>-methylpiperidine-1-carboxamide	406.3	¹ H NMR (400 MHz, MeOD) δ 7.45 (d, J = 7.9 Hz, 1H), 7.28 (dd, J = 8.2, 2.5 Hz, 1H), 7.14 - 7.07 (m, 1H), 7.02 (dd, J = 11.1, 3.9 Hz, 1H), 4.57 - 4.36 (m, 3H), 4.34 - 4.25 (m, 1H), 3.88 - 3.67 (m, 2H), 3.21 - 3.09 (m, 1H), 2.73 - 2.63 (m, 4H), 2.56 - 2.45 (m, 1H), 2.40 - 2.18 (m, 2H), 0.92 (d, J = 6.0 Hz, 2H), 0.83 - 0.69 (m, 2H). ¹⁹ F NMR (376 MHz, MeOD) δ -180.46 (s), -182.15 (s).
Example 108		406.3	¹ H NMR (400 MHz, MeOD) δ 7.25 (dd, J = 8.8, 4.5 Hz, 1H), 7.10 (dd, J = 9.9, 2.5 Hz, 1H), 6.84 - 6.76 (m, 1H),

	 (3R,5S)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-5-fluoro-N-methylpiperidine-1-carboxamide		6.27 (s, 1H), 4.57 – 4.45 (m, 3H), 4.40 (dd, $J = 10.4, 5.2$ Hz, 1H), 4.29 (dd, $J = 12.5, 2.0$ Hz, 1H), 3.84 (dd, $J = 12.8, 1.5$ Hz, 1H), 3.77 – 3.66 (m, 1H), 3.15 (dd, $J = 12.5, 11.5$ Hz, 1H), 2.74 – 2.61 (m, 4H), 2.55 – 2.48 (m, 1H), 2.31 (dd, $J = 14.3, 8.0$ Hz, 2H), 0.93 (d, $J = 5.8$ Hz, 2H), 0.78 (d, $J = 3.5$ Hz, 2H). ¹⁹ F NMR (377 MHz, MeOD) δ -127.96 (s), -182.11 (s).
Example 109	 1-((3R,5S)-1-acetyl-5-fluoropiperidin-3-yl)-1-cyclopropyl-3-((3-fluoro-1H-indol-2-yl)methyl)urea	391.3	¹ H NMR (400 MHz, MeOD) δ 7.28 - 7.20 (m, 1H), 7.10 (dd, $J = 9.9, 2.5$ Hz, 1H), 6.84 - 6.75 (m, 1H), 6.27 (s, 1H), 4.79 - 4.71 (m, 0.6H), 4.67 - 4.33 (m, 3.7H), 4.17 - 4.08 (m, 0.4H), 3.90 - 3.76 (m, 1H), 3.66 - 3.54 (m, 0.5H), 3.13 - 2.98 (m, 1H), 2.60 - 2.47 (m, 1.7H), 2.45 - 2.23 (m, 2H), 2.15 - 2.10 (m, 3H), 1.00 - 0.89 (m, 2H), 0.86 - 0.69 (m, 2H). ¹⁹ F NMR (377 MHz, MeOD) δ -127.01 - -128.90 (m), -181.97 (d, $J = 8.8$ Hz), -182.43 (d, $J = 8.6$ Hz).

INCORPORATION BY REFERENCE

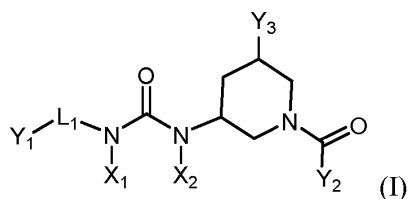
All of the U.S. patents and U.S. and PCT patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of Formula (I):



wherein:

L₁ is -alkyl-;

X₁ and X₂ are independently selected from -H and cycloalkyl; provided that X₁ and X₂ are not both -H;

Y₁ is an optionally substituted 5,6-fused bicyclic heteroaryl;

Y₂ is selected from -NH(Y₂'), -OY₂'', alkyl, and hydroxyalkyl;

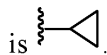
Y₂' is selected from -H, alkyl, and -O-alkyl;

Y₂'' is alkyl; and

Y₃ is selected from -H, hydroxyalkyl, and halogen;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein one of X₁ and X₂ is -H; and the other of X₁ and X₂

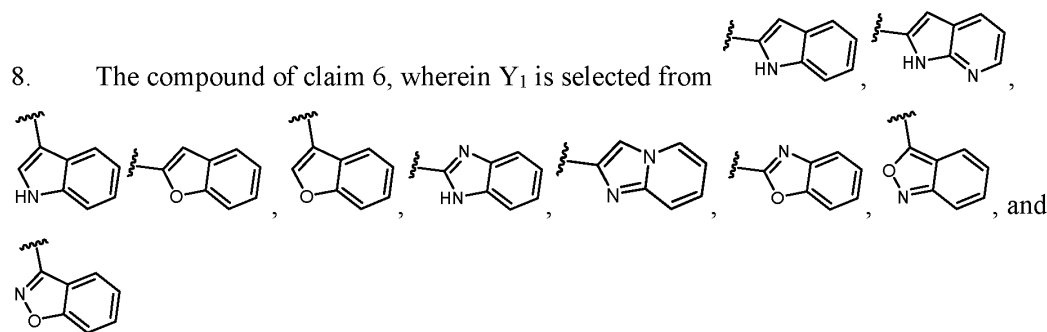
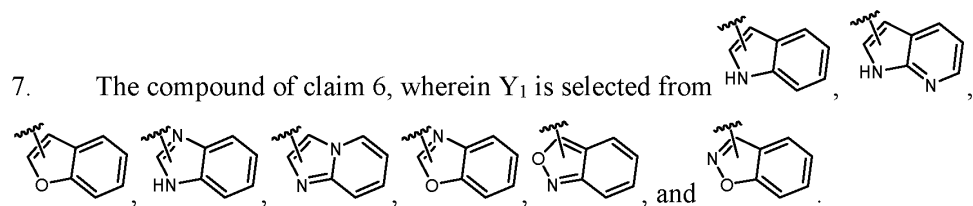


3. The compound of claim 2, wherein X₁ is -H; and X₂ is

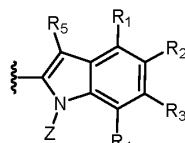
4. The compound of any one of claims 1-3, wherein L₁ is -C₁-C₄ alkyl-.

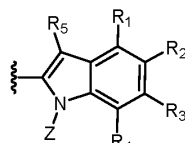
5. The compound of claim 4, wherein L₁ is -CH₂-.

6. The compound of any one of claims 1-5, wherein Y₁ is an unsubstituted 5,6-fused bicyclic heteroaryl.



9. The compound of any one of claims 1-5, wherein Y₁ is a substituted 5,6-fused bicyclic heteroaryl.

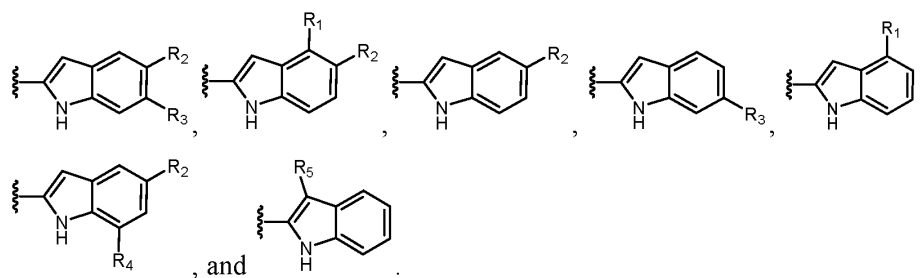


10. The compound of claim 9, wherein Y₁ is ; and each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, alkyl, alkoxy, cycloalkyl, halogen, -OH, -CN, -CF₃, -OCHF₂, and -OCF₃; and Z is H or alkyl; provided that at least one of R₁, R₂, R₃, R₄, R₅, and Z is not -H.

11. The compound of claim 10, wherein each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, alkyl, cycloalkyl, halogen, -CN, -CF₃, and -OCF₃; and Z is -H; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

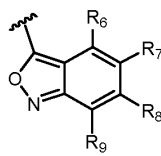
12. The compound of claim 11, wherein each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, -Cl, -Br, -F, -CH₃, , -CF₃, and -OCF₃; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

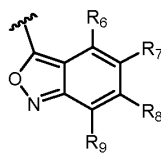
13. The compound of any one of claims 10-12, wherein Y₁ is selected from



14. The compound of claim 13, wherein each of R_1 , R_2 , R_3 , R_4 , and R_5 is a halogen.

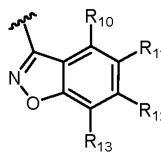
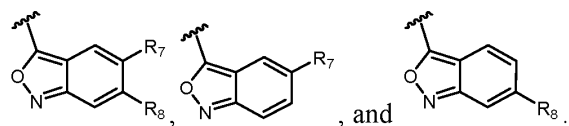
15. The compound of claim 14, wherein each of R_1 , R_2 , R_3 , R_4 , and R_5 is $-F$.

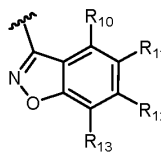


16. The compound of claim 9, wherein Y_1 is ; and each occurrence of R_6 , R_7 , R_8 , and R_9 is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

17. The compound of claim 16, wherein each occurrence of R_6 , R_7 , R_8 , and R_9 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

18. The compound of claim 16 or 17, wherein Y_1 is selected from

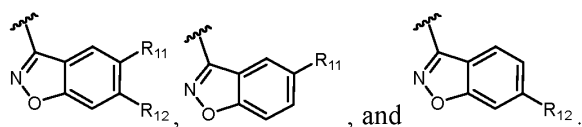


19. The compound of claim 9, wherein Y_1 is ; and

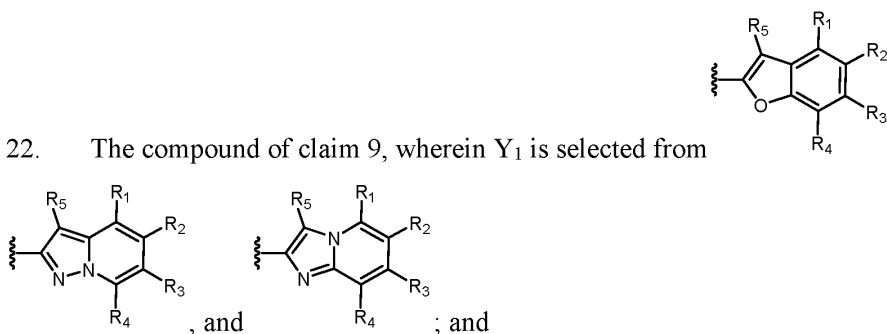
each occurrence of R_{10} , R_{11} , R_{12} , and R_{13} is independently selected from $-H$, alkyl, alkoxy, cycloalkyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

20. The compound of claim 19, wherein each occurrence of R_{10} , R_{11} , R_{12} , and R_{13} is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_6 , R_7 , R_8 , and R_9 is not $-H$.

21. The compound of claim 19 or 20, wherein Y_1 is selected from



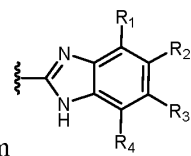
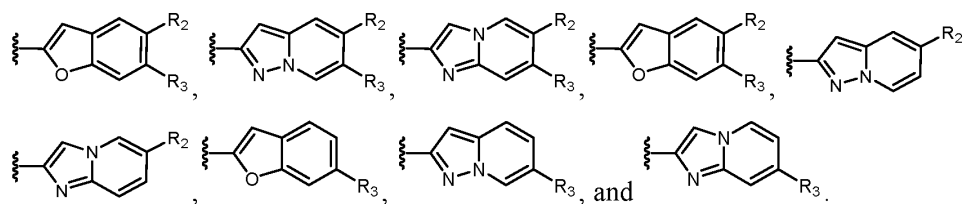
22. The compound of claim 9, wherein Y_1 is selected from



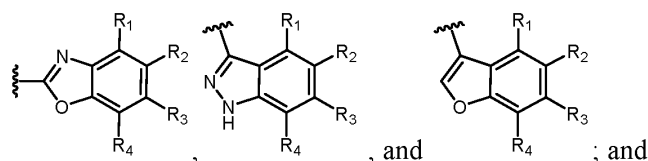
each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, halogen, alkyl, alkoxy, cyclopropyl, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

23. The compound of claim 22, wherein each occurrence of R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , R_4 , and R_5 is not $-H$.

24. The compound of claim 22 or 23, wherein Y_1 is selected from



25. The compound of claim 9, wherein Y_1 is selected from

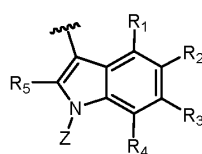
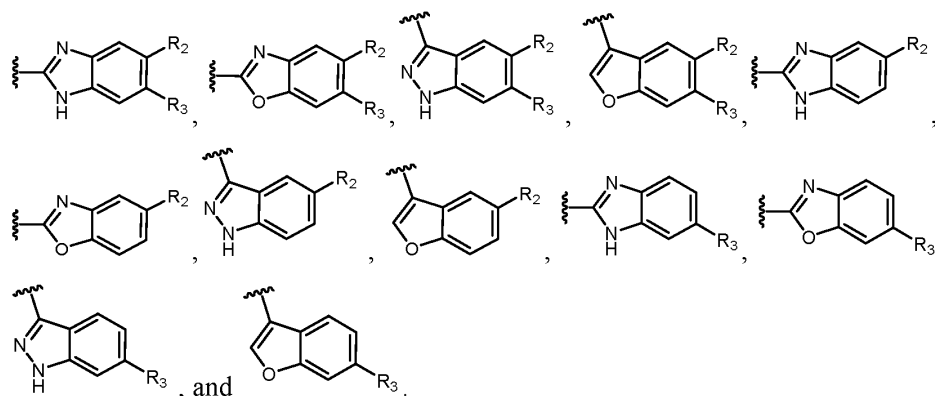


each occurrence of R_1 , R_2 , R_3 , and R_4 is independently selected from $-H$, alkyl, alkoxy, cyclopropyl, halogen, $-OH$, $-CN$, $-CF_3$, $-OCHF_2$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , and R_4 is not $-H$.

26. The compound of claim 25, wherein each occurrence of R_1 , R_2 , R_3 , and R_4 is

independently selected from $-H$, $-Cl$, $-Br$, $-F$, $-CH_3$, , $-CF_3$, and $-OCF_3$; provided that at least one of R_1 , R_2 , R_3 , and R_4 is not $-H$.

27. The compound of claim 25 or 26, wherein Y_1 is selected from



28. The compound of claim 9, wherein Y_1 is

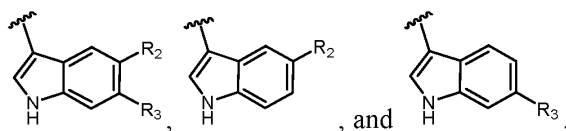
each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, alkyl, alkoxy, cycloalkyl, halogen, -OH, -CN, -CF₃, -OCHF₂, and -OCF₃; and

Z is H or alkyl; provided that at least one of R₁, R₂, R₃, R₄, R₅, and Z is not -H.

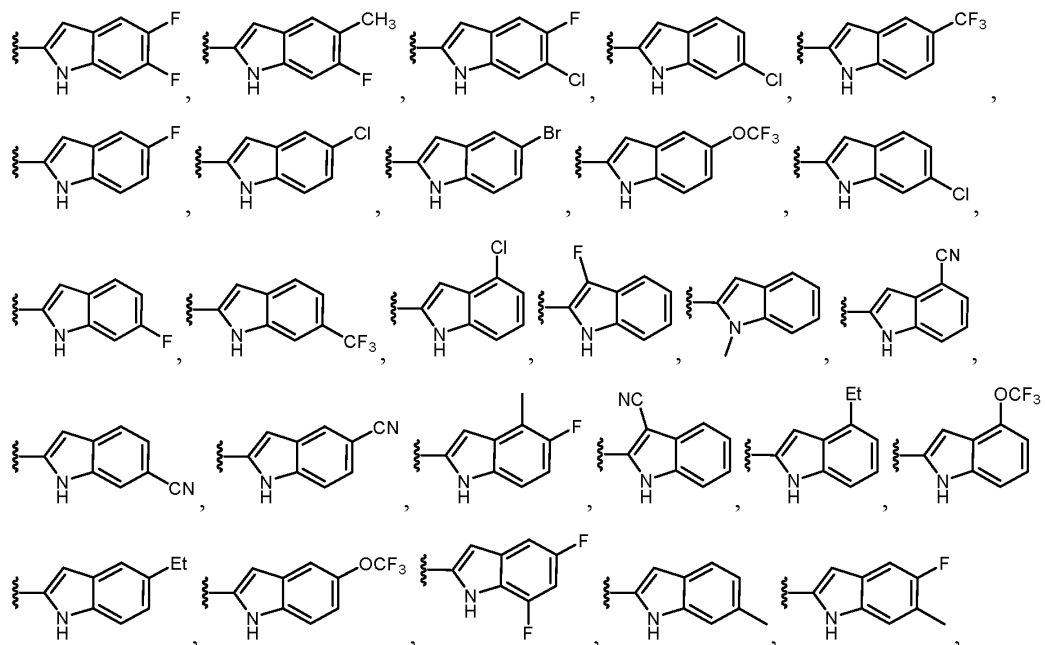
29. The compound of claim 28, wherein each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, alkyl, cycloalkyl, halogen, -OH, -CN, -CF₃, -OCHF₂, and -OCF₃; and Z is -H; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

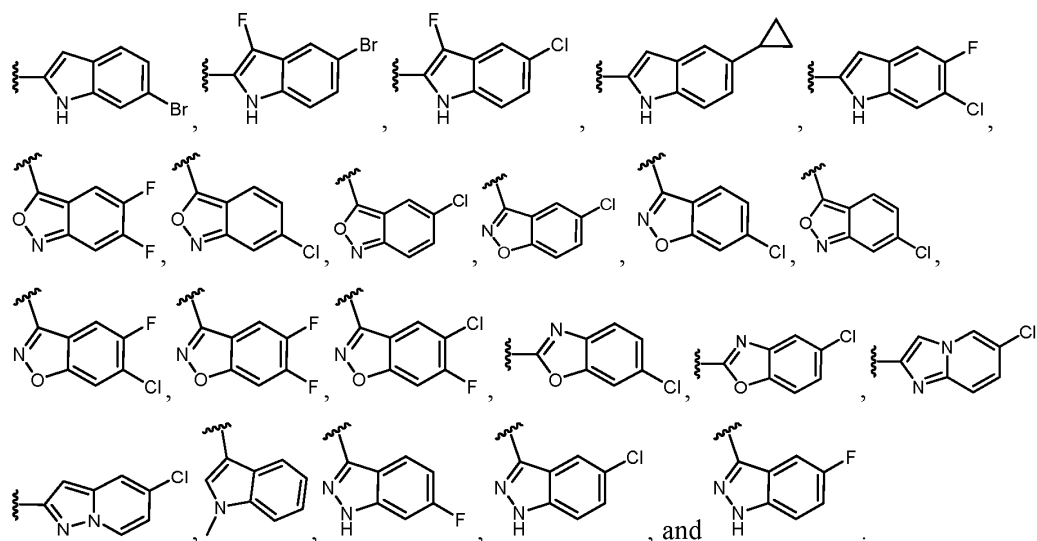
30. The compound of claim 29, wherein each occurrence of R₁, R₂, R₃, R₄, and R₅ is independently selected from -H, -Cl, -Br, -F, -CH₃, , -CF₃, and -OCF₃; and Z is -H; provided that at least one of R₁, R₂, R₃, R₄, and R₅ is not -H.

31. The compound of any one of claims 28-30, wherein Y₁ is selected from

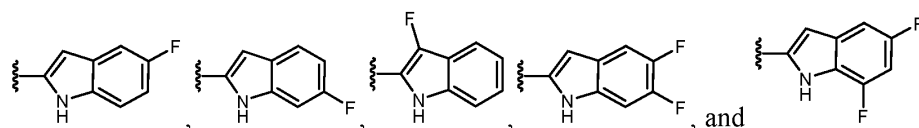


32. The compound of any one of claims 9-31, wherein Y₁ is selected from





33. The compound of any one of claims 13-15, wherein Y_1 is selected from



34. The compound of any one of claims 1-33, wherein Y_2 is $-NH(Y_2')$.

35. The compound of claim 34, wherein Y_2' is C_1 - C_4 alkyl.

36. The compound of claim 35, wherein Y_2' is $-CH_3$.

37. The compound of claim 34, wherein Y_2' is $-H$.

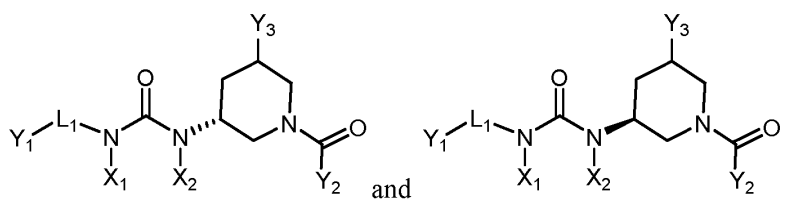
38. The compound of claim 34, wherein Y_2' is $-O$ -alkyl.

39. The compound of claim 38, wherein Y_2' is $-O$ -(C_1 - C_4 alkyl).

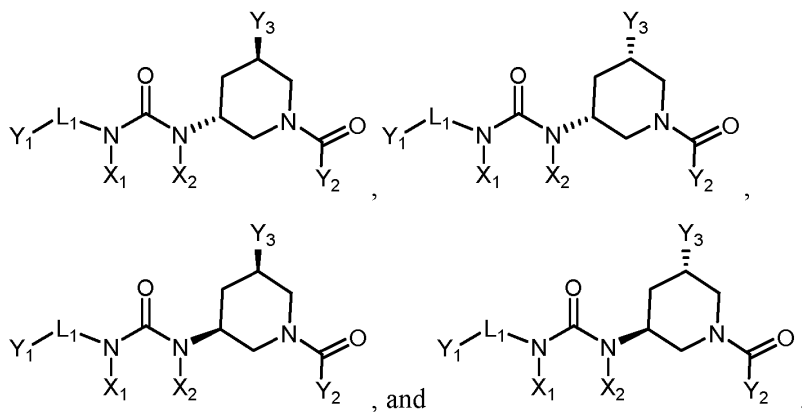
40. The compound of claim 39, wherein Y_2' is $-OCH_3$.

41. The compound of any one of claims 1-33, wherein Y_2 is $-OY_2''$.

42. The compound of claim 41, wherein Y_2'' is C_1 - C_4 alkyl.
43. The compound of claim 42, wherein Y_2'' is $-CH_3$.
44. The compound of any one of claims 1-33, wherein Y_2 is alkyl.
45. The compound of claim 44, wherein Y_2 is C_1 - C_4 alkyl.
46. The compound of claim 45, wherein Y_2 is selected from $-CH_3$ or $-CH_2CH_3$.
47. The compound of any one of claims 1-33, wherein Y_2 is hydroxyalkyl.
48. The compound of claim 47, wherein Y_2 is $(C_1$ - C_4 alkyl)-OH.
49. The compound of claim 48, wherein Y_2 is selected from $-CH_2OH$, $-CH_2CH_2OH$, and $-CH_2CH_2CH_2OH$.
50. The compound of any one of claims 1-49, wherein Y_3 is $-H$.
51. The compound of any one of claims 1-49, wherein Y_3 is hydroxyalkyl.
52. The compound of claim 51, wherein Y_3 is $(C_1$ - C_4 alkyl)-OH.
53. The compound of claim 52, wherein Y_3 is $-CH_2OH$.
54. The compound of any one of claims 1-49, wherein Y_3 is halogen.
55. The compound of claim 54, wherein Y_3 is $-F$.
56. The compound of claim 1 having the structure selected from:



57. The compound of claim 30 having the structure selected from:



58. The compound of claim 1, 56, or 57, wherein:

L₁ is -alkyl-;

X₁ and X₂ are independently selected from -H and cyclopropyl; provided that X₁ and X₂ are not both -H;

Y₁ is an optionally substituted indolyl;

Y₂ is -NH(Y₂')

Y₂' is alkyl; and

Y₃ is -H or halogen;

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, 56, or 57, wherein:

L₁ is -alkyl-;

X₁ and X₂ are independently selected from -H and cyclopropyl; provided that X₁ and X₂ are not both -H;

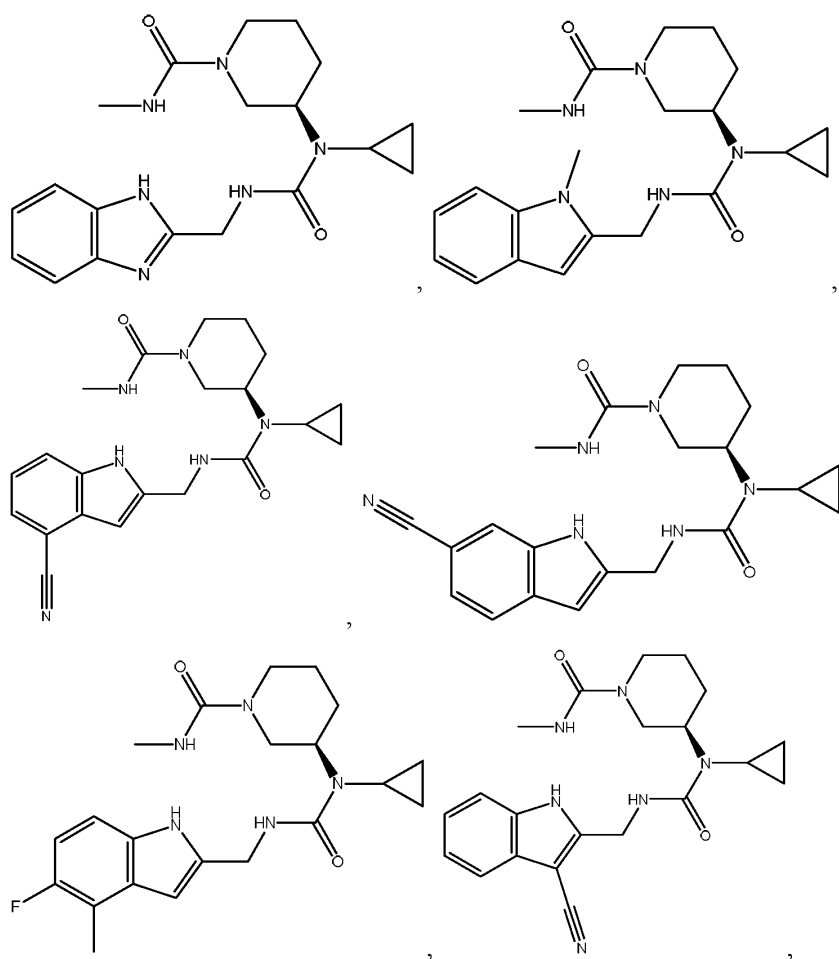
Y₁ is an optionally substituted indolyl;

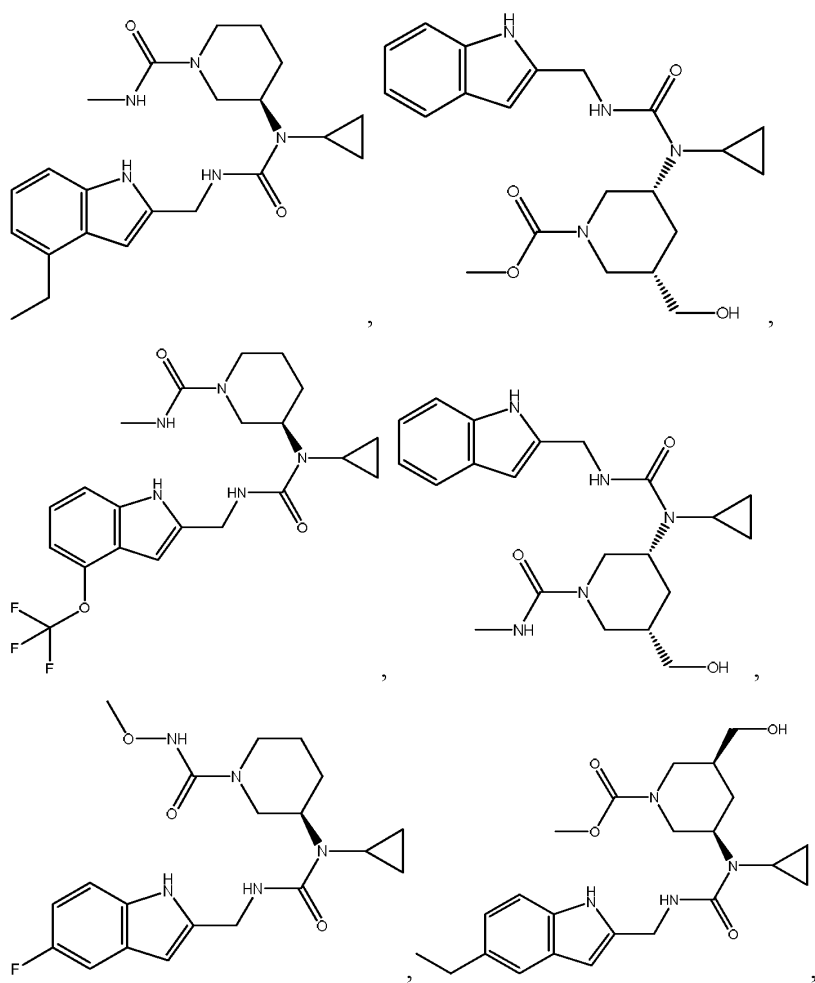
Y₂ is alkyl; and

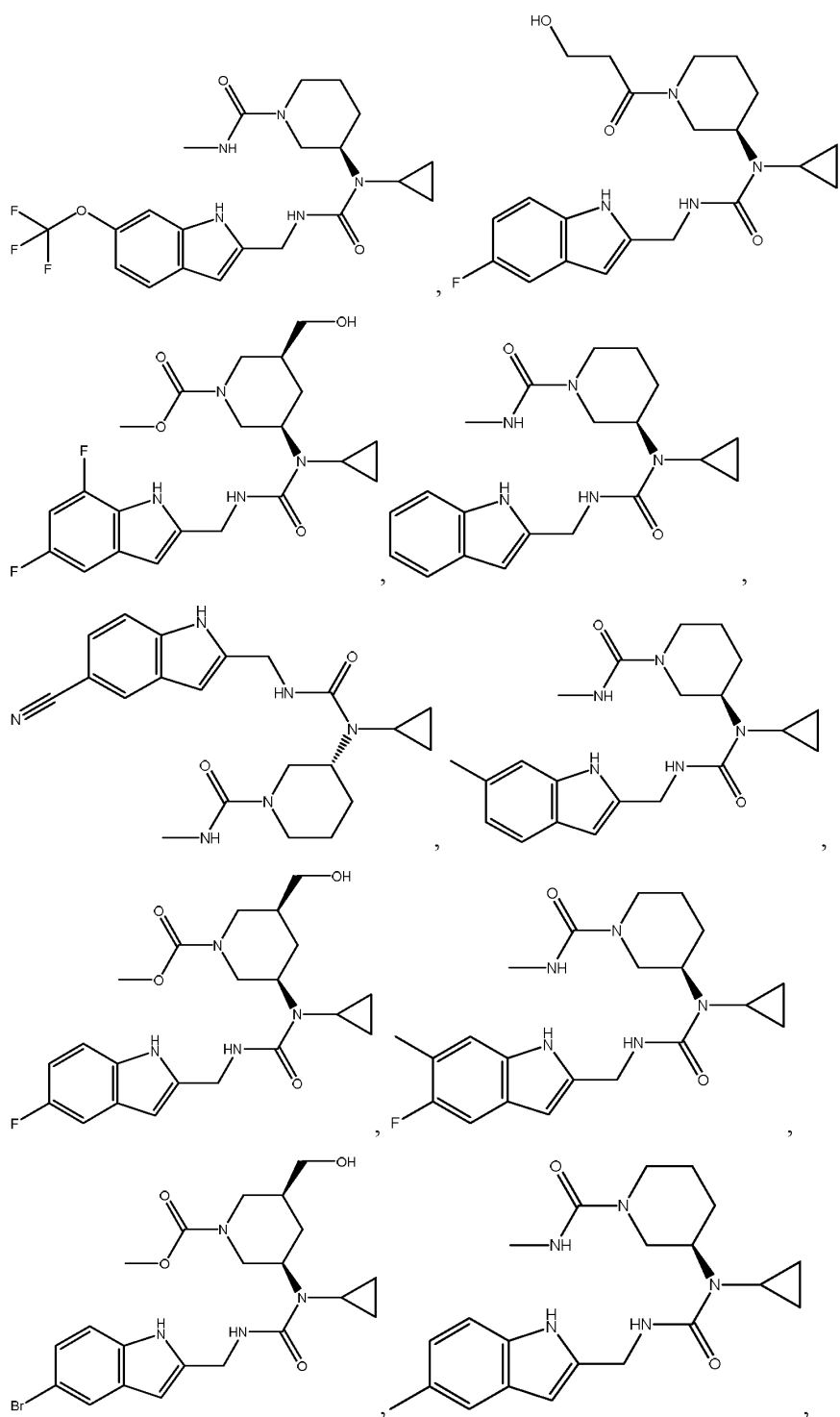
Y₃ is -H or halogen;

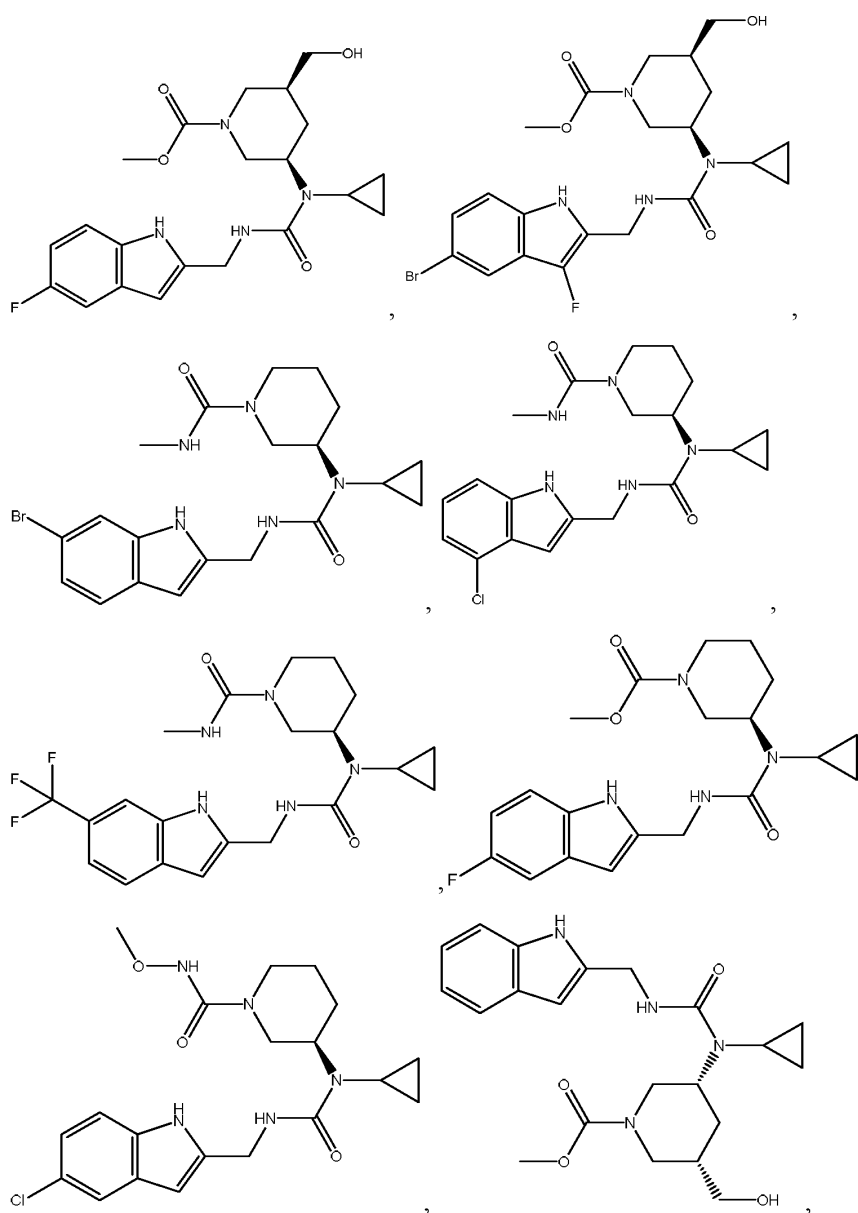
or a pharmaceutically acceptable salt thereof.

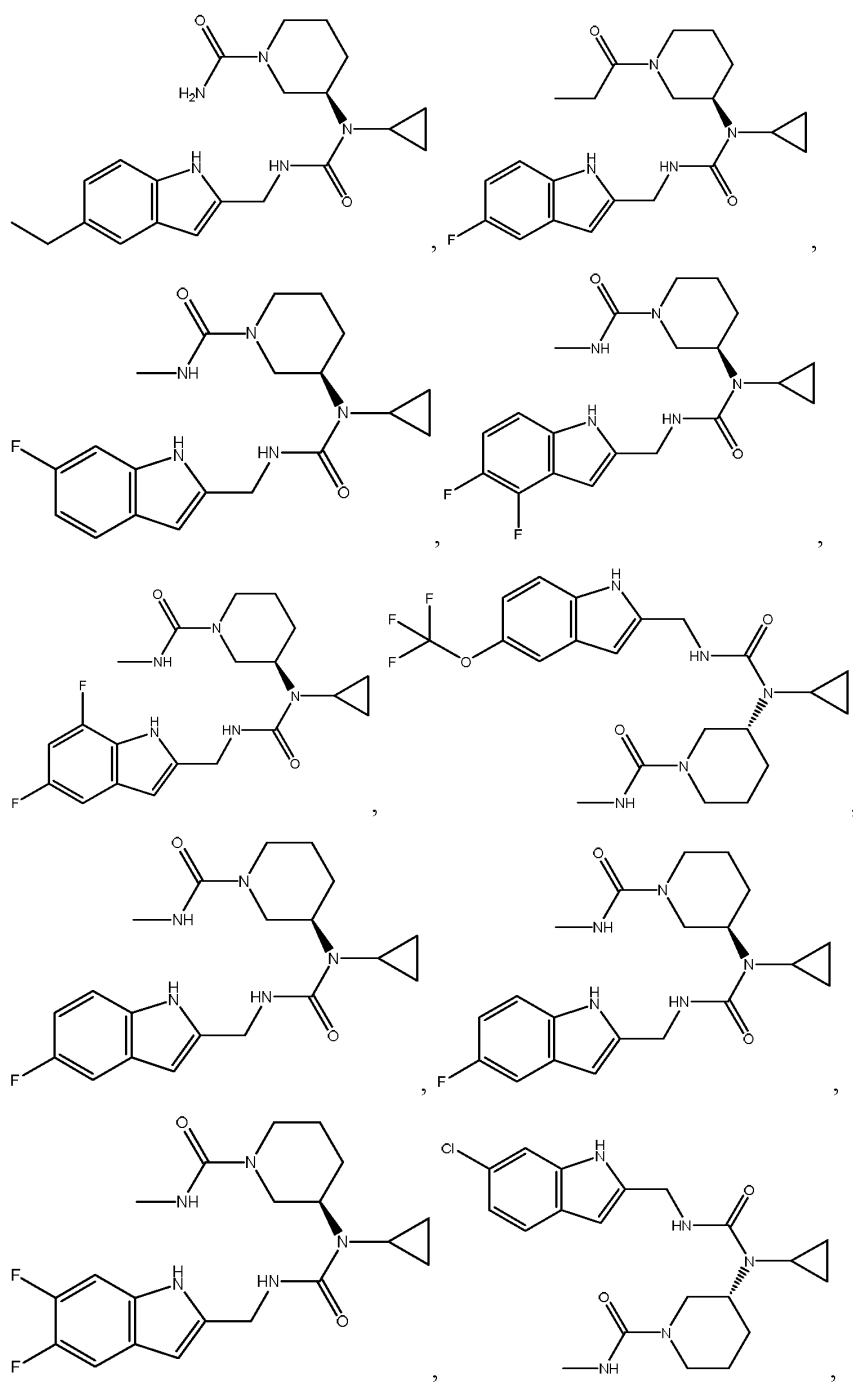
60. The compound of claim 58 or 59, wherein Y₃ is halogen.
61. The compound of claim 60, wherein Y₃ is -F.
62. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure selected from:

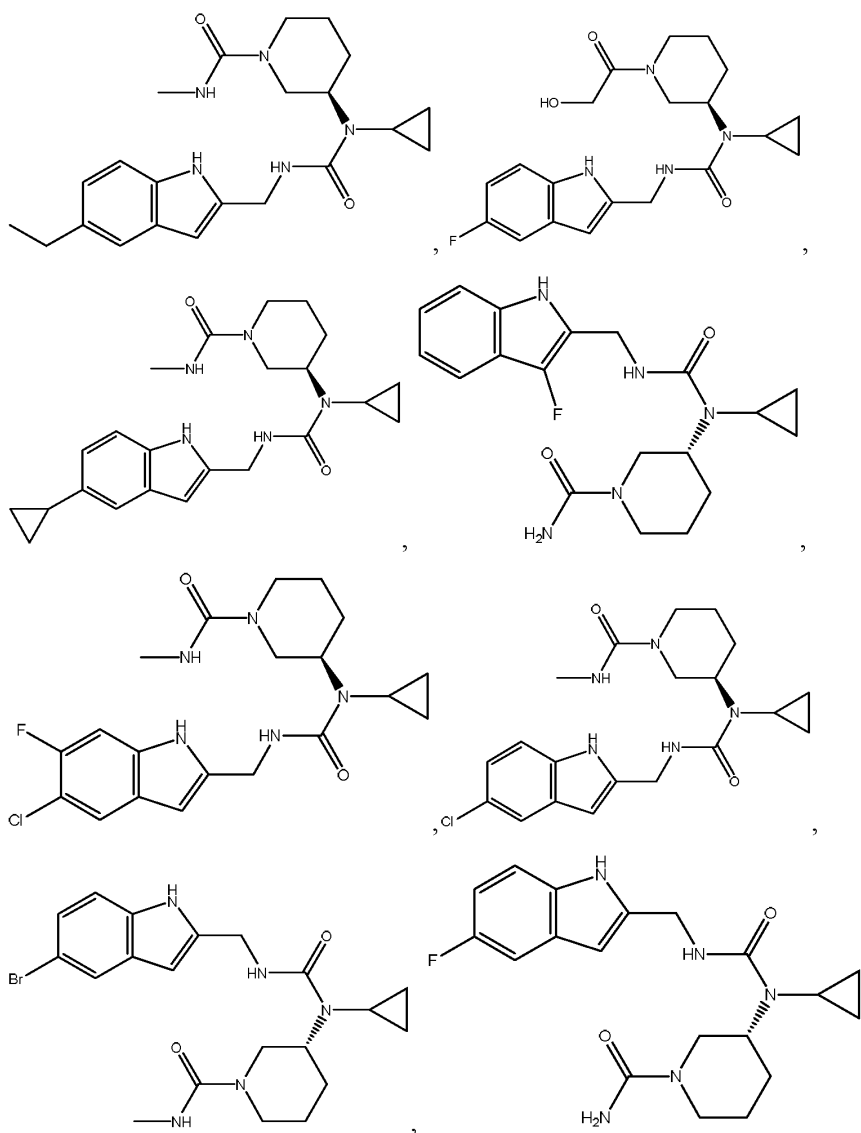


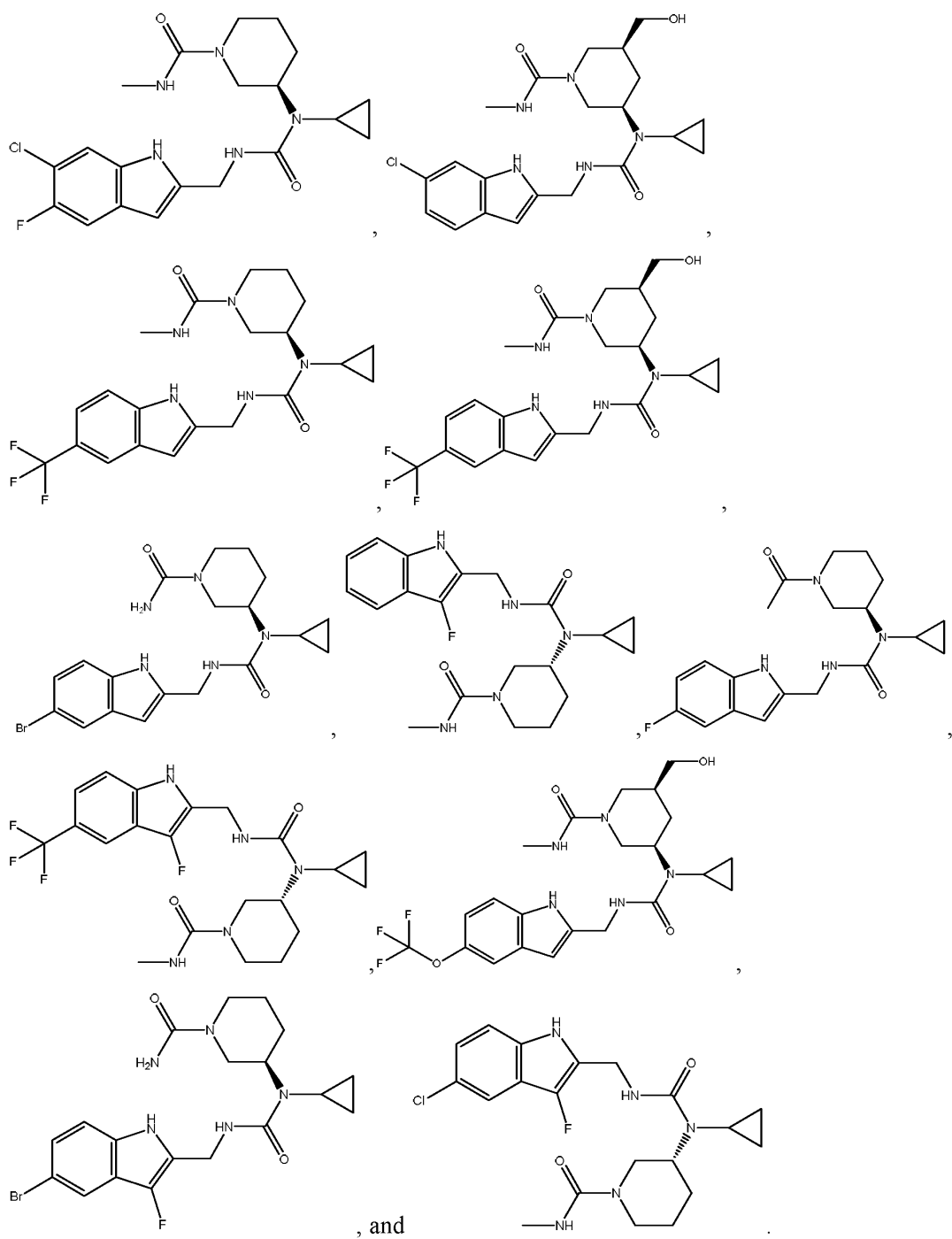




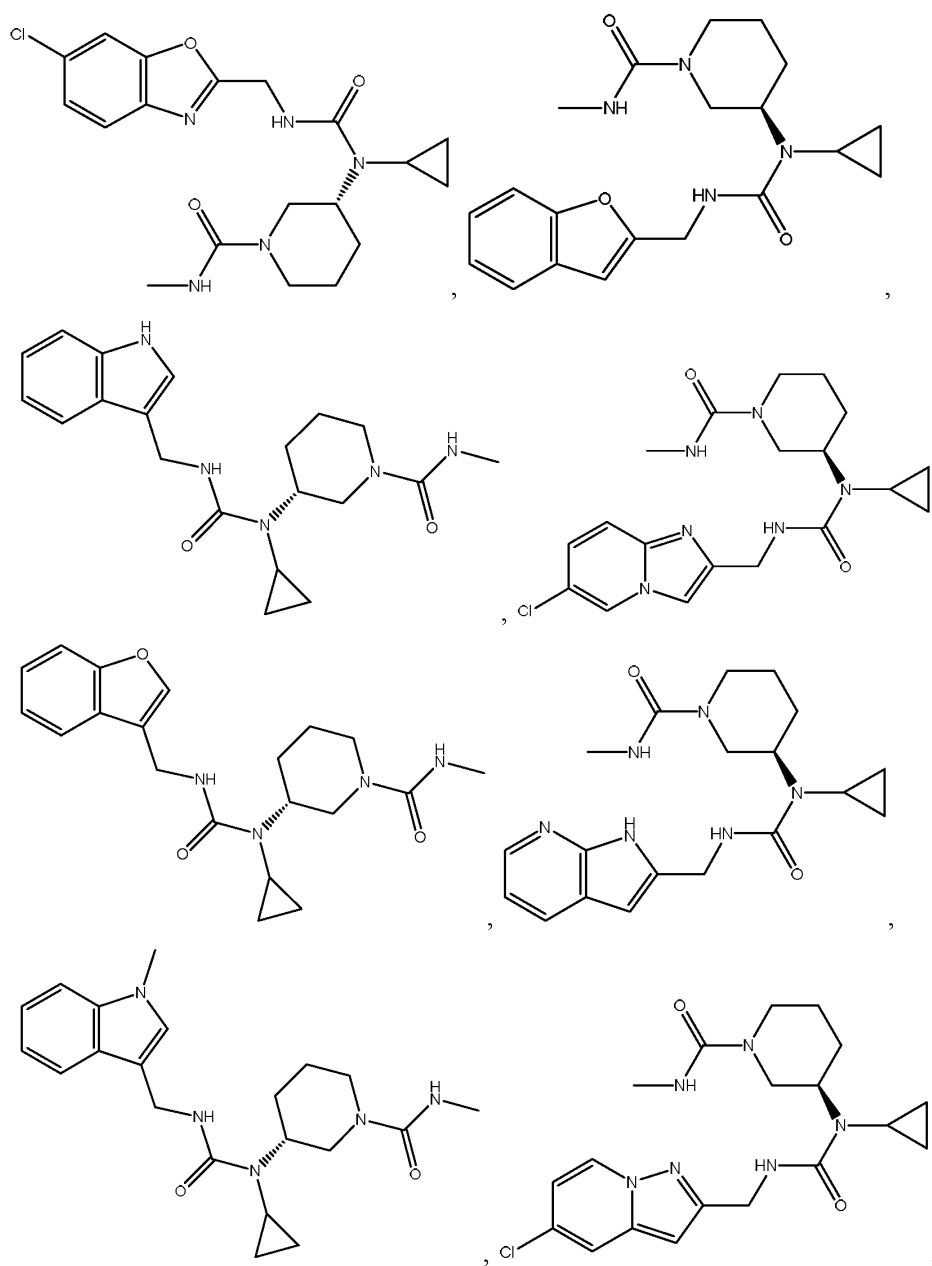


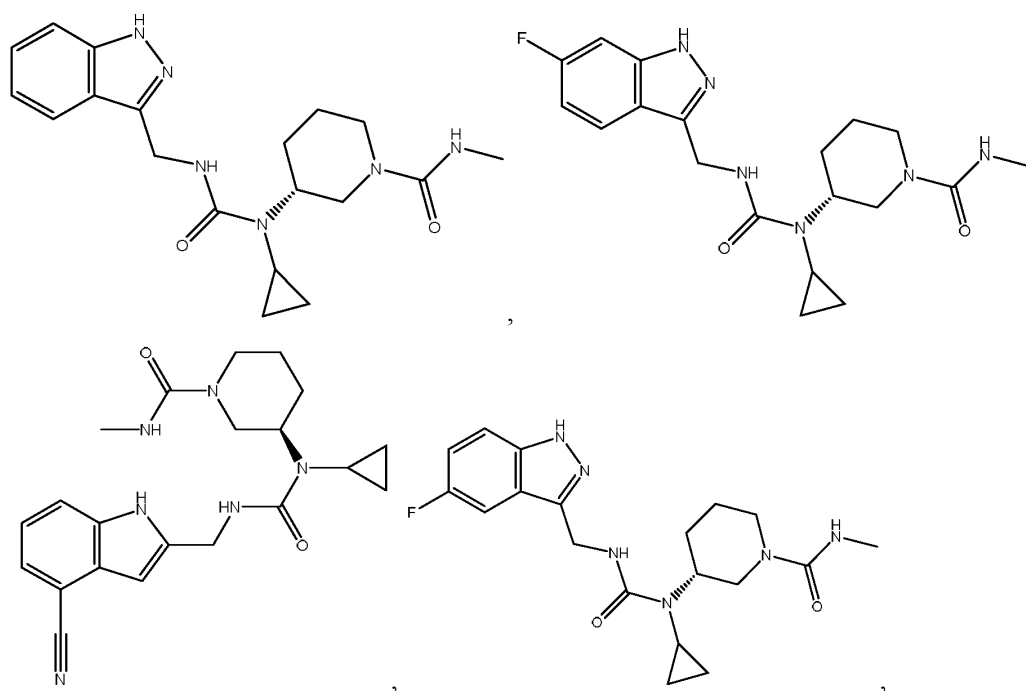


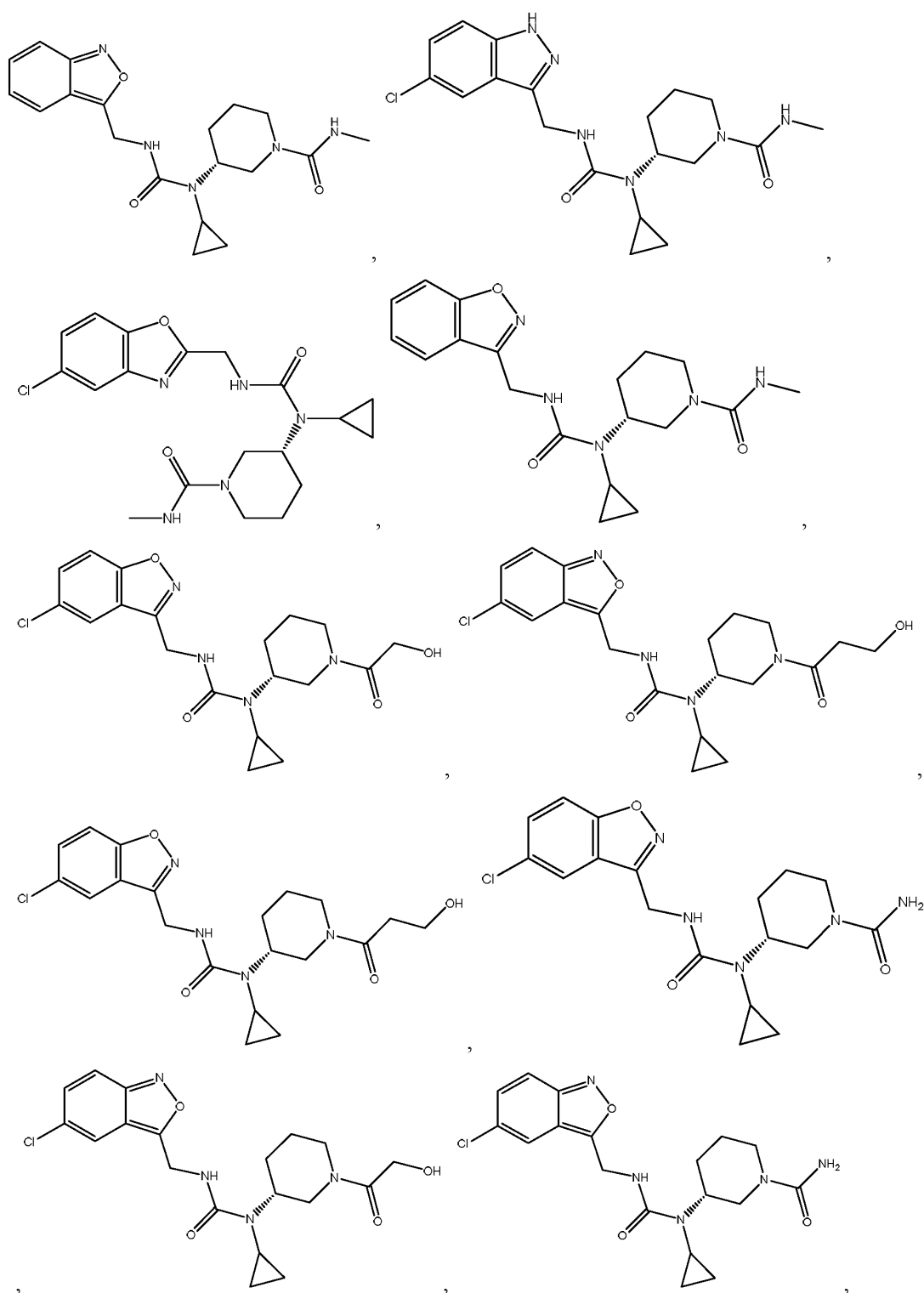


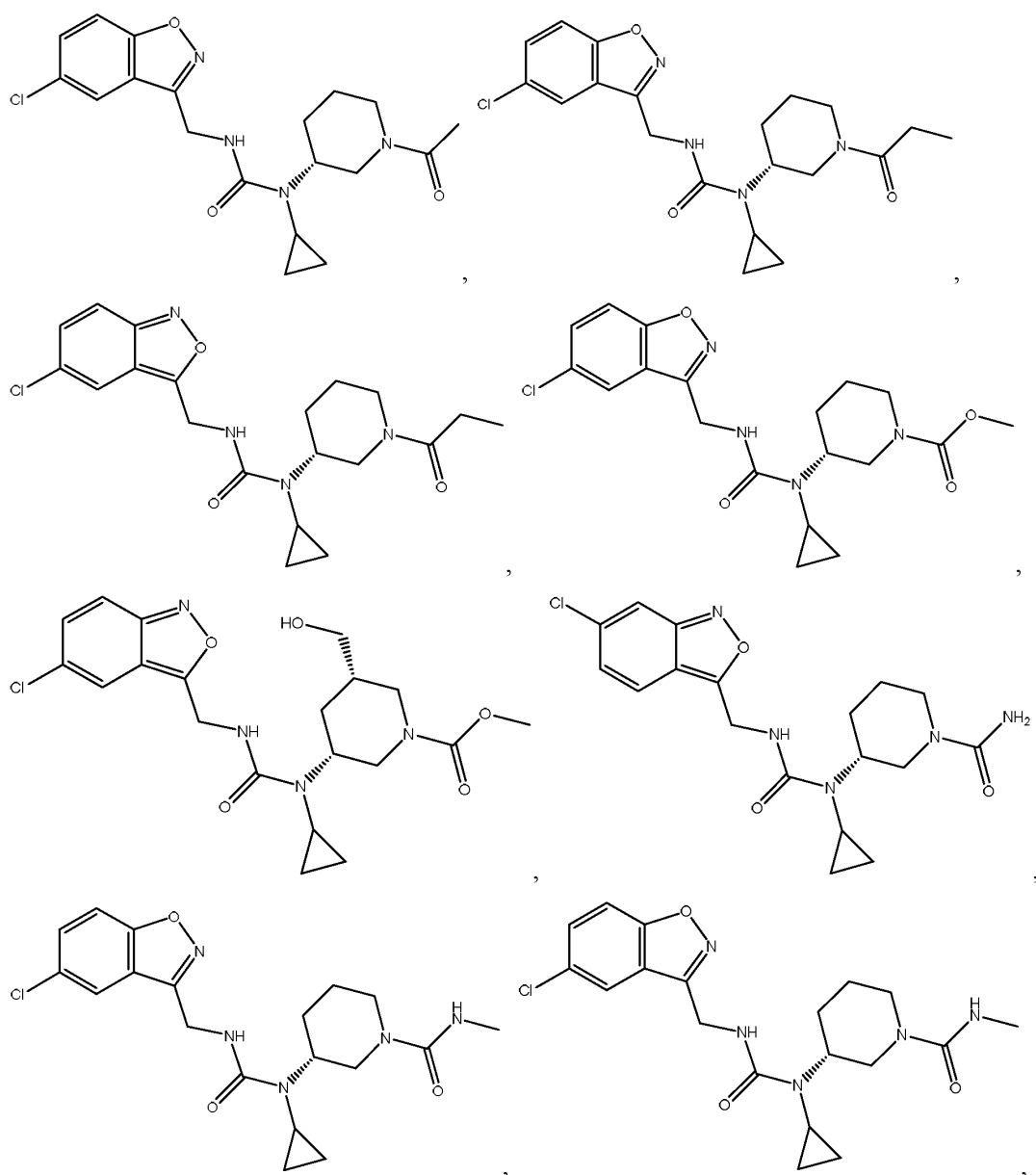


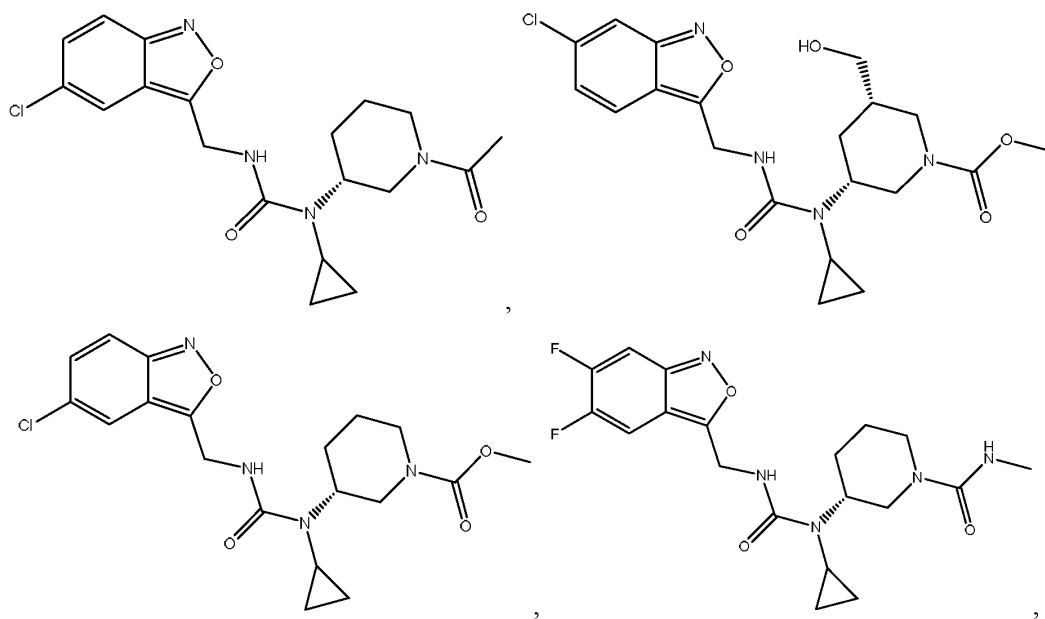
- 124 -

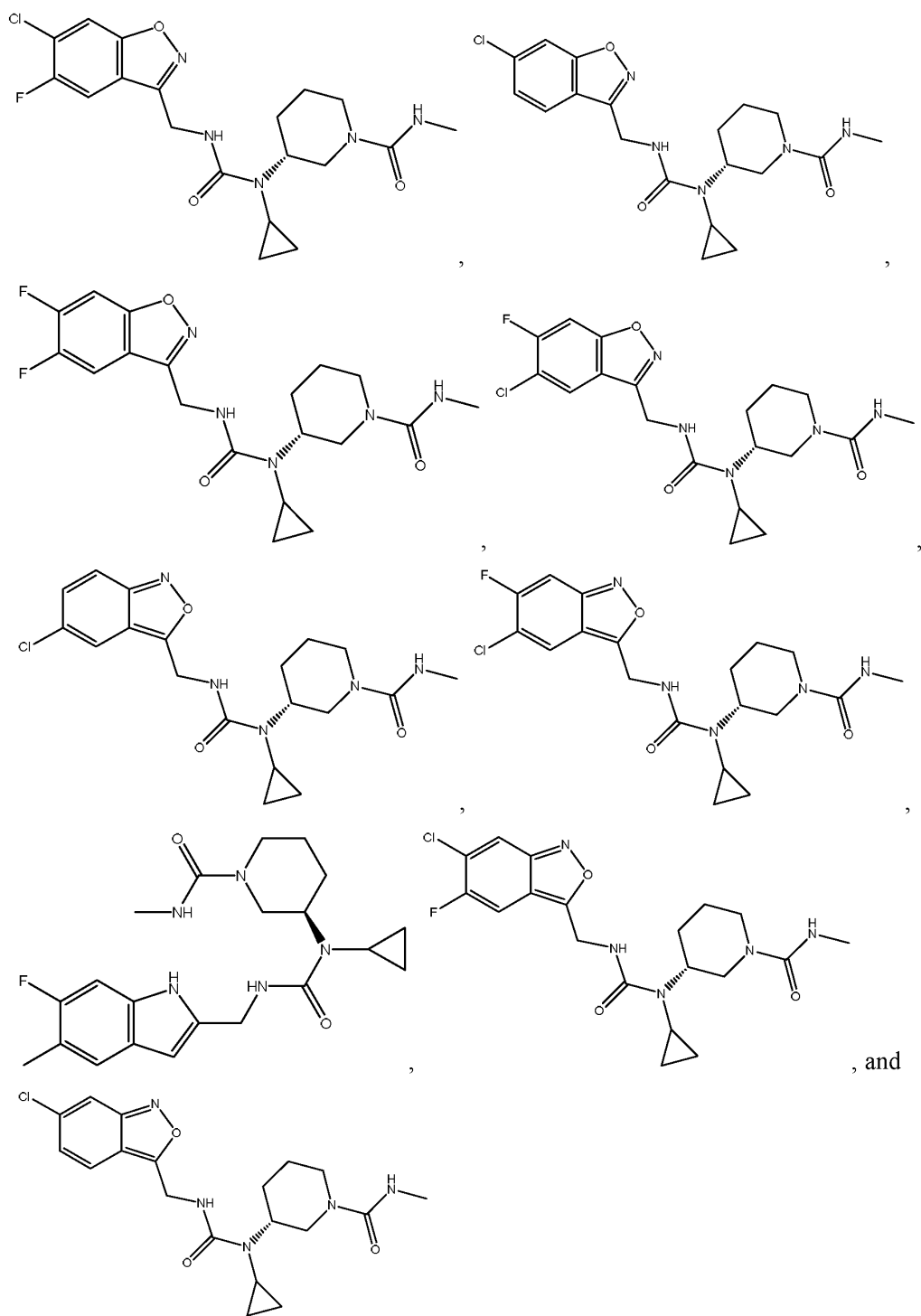




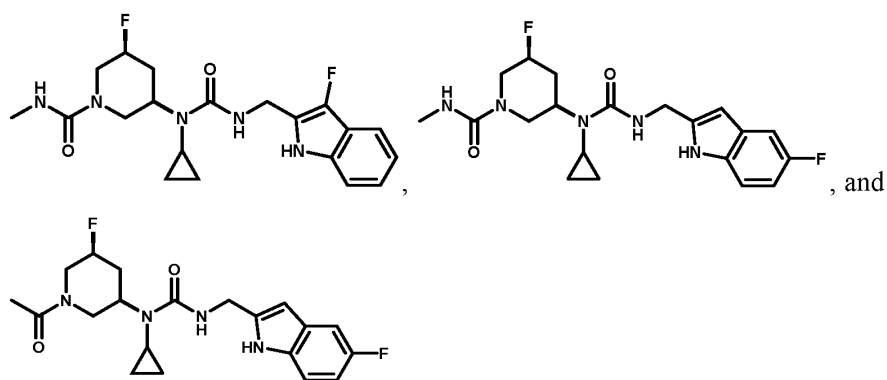








64. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure selected from:



65. A pharmaceutical composition, comprising a compound of any one of claims 1-64; and a pharmaceutical acceptable excipient.
66. A method of treating or preventing a disease or disorder associated with a genetic defect in phenylalanine hydroxylase, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
67. A method of treating or preventing phenylketonuria, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
68. A method of treating or preventing hyperphenylalaninemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
69. The method of any one of claims 66-68, wherein the compound reduces systemic phenylalanine levels in the subject.
70. A method of treating or preventing tyrosinemia (Type I, II, or III), comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
71. The method of claim 70, wherein the compound reduces systemic tyrosine levels in the subject.

72. A method of treating or preventing nonketotic hyperglycinemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
73. The method of claim 72, wherein the compound reduces systemic glycine levels in the subject.
74. A method of treating or preventing isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
75. A method of treating or preventing diabetes, chronic kidney disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, metabolic syndrome, obesity related disorders, or neurodevelopmental and autism-spectrum disorders, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-64.
76. The method of any one of claims 66-75, wherein the compound inhibits SLC6A19 in the subject.