

SPIRO DERIVATIVES AS M4 ACTIVATORS/MODULATORS AND USES THEREOF

FIELD

[0001] The present disclosure generally relates to novel pyridine azaspiro compounds which are agonists/activators/modulators of the muscarinic M4 receptor and are useful in the treatment of M4-mediated diseases and disorders, but not limited to schizophrenia, Alzheimer's disease, dementia related psychosis, dementia with Lewy Bodies, Parkinson's disease and related memory and executive dysfunction, bipolar, agitation, and psychosis associated therewith.

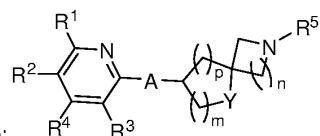
BACKGROUND

[0002] Patients with Schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, depression, and various other neurological/neurodegenerative diseases frequently suffer from behavioral and cognitive impairments resulting in debilitating disruption to their daily lives. Over the years, many pharmacological treatments have been discovered that provide some improvement in behavior and cognitive function. However, the improvement is modest at best, and as is often the case, the underlying dose-limiting adverse effects associated with these treatments, including extrapyramidal and metabolic side-effects, lead to partial responsiveness, and non-compliance.

[0003] The muscarinic acetylcholine receptor (mAChR) is a viable mechanism for treating such diseases. There are five mAChR subtypes (M1-M5) that have been identified and are part of the G protein-coupled receptor (GPCR) superfamily. These subtypes are distributed widely throughout the periphery and the central nervous system (CNS), with the M1 and M4 subtypes being predominantly expressed in the CNS. The M4 agonist HTL0016878 being developed for the treatment of major symptoms of Alzheimer's Disease entered into a Phase 2 clinical study.

[0004] Thus, a need exists for agonists of the muscarinic M4 receptors to treat M4-mediated diseases and disorders such as Parkinson's Disease, Schizophrenia, Alzheimer's Disease and others described herein.

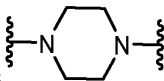
SUMMARY

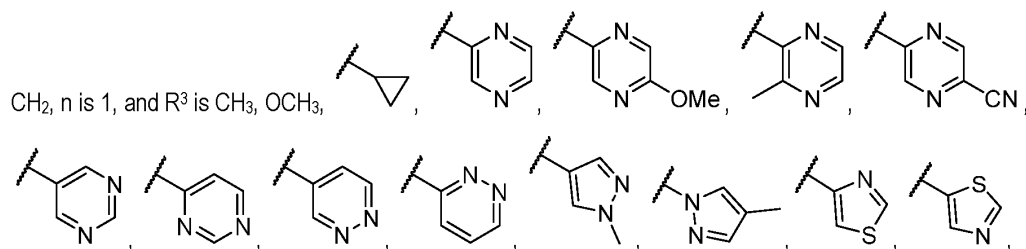


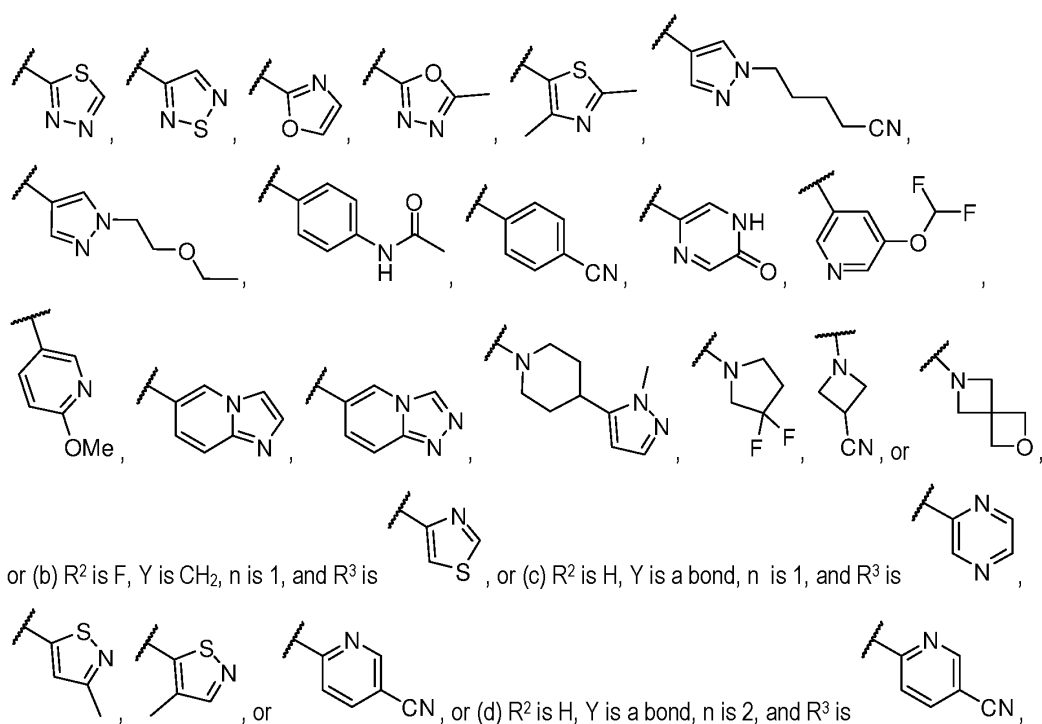
[0005] Provided herein are compounds having a structure of Formula (I): (I), or an *N*-oxide thereof, or a pharmaceutically acceptable salt of the compound or the *N*-oxide thereof, wherein: A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and optionally substituted with 1 to 3 R^A; each R^A is independently C₁₋₃alkyl, halogen, =O, OH, C₁₋₃hydroxyalkyl, or C₁₋₃haloalkyl; Y is a bond, S, O, CH₂, CHF, CF₂, or C(OH)H; m is 1 or 2; n is 1 or 2; p is 1 or 2; R¹ is H, halogen, CN, OH, NO₂, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle or -[O]₀₋₁-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀-

$1-C_{3-6}$ cycloalkyl, $-[O]_{0-1}-C_{6-10}$ aryl, $-[O]_{0-1}-4-8$ membered heterocycle, $-[O]_{0-1}-5-10$ membered heteroaryl, $-NH-C_{3-6}$ cycloalkyl, $-NH-C_{6-10}$ aryl, $-NH-4-8$ membered heterocycle, $-NH-5-10$ membered heteroaryl, $-N(C_{1-6}alkyl)-C_{3-6}$ cycloalkyl, $-N(C_{1-6}alkyl)-C_{6-10}$ aryl, $-N(C_{1-6}alkyl)-4-8$ membered heterocycle, or $-N(C_{1-6}alkyl)-5-10$ membered heteroaryl, R^1 is substituted with 0, 1, 2, or 3 substituents independently selected from halogen, CN, OH, $=O$, SO_2 , and $C_{1-3}alkyl$; R^2 is H, halogen, CN, OH, $-N(R^6)(R^7)$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkoxy$, $C_{2-6}heteroalkyl$, $C_{3-6}cycloalkyl$, or 4-8 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S; R^3 is halogen, $C_{0-6}alkylene-CN$, OH, $-N(R^6)(R^7)$, $C_{1-6}alkyl$, $C_{2-6}heteroalkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $C_{1-6}alkylene-O-C_{1-6}alkyl$, $C_{1-6}alkylene-NHC(O)C_{1-6}alkyl$, $C_{1-6}alkylene-C(O)NHC_{1-6}alkyl$, $C_{0-6}alkylene-Cyc$, $O-C_{0-6}alkylene-Cyc$, $NH-Cyc$, $N(C_{1-6}alkyl)-Cyc$, or $C(O)Cyc$; Cyc is C_{3-12} cycloalkyl, $C_{3-6}heterocycloalkyl$, $C_{5-12}spirocycloalkyl$, $C_{5-12}heterospirocycloalkyl$, $C_{6-10}aryl$, 3-12 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents; each R^{3a} is independently selected from halogen, CN, OH, $=O$, $=N(C_{1-6}alkyl)$, SO_2 , $C_{1-6}alkyl$, $C_{2-10}alkene$, $C_{1-6}hydroxyalkyl$, $C_{1-6}haloalkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkoxy$, $C_{1-6}alkylene-O-C_{1-6}alkyl$, $C_{0-6}alkylene-C(O)C_{1-6}alkyl$, $C_{0-6}alkylene-NH_2$, $C_{0-6}alkylene-NH(C_{1-6}alkyl)$, $C_{0-6}alkylene-N(C_{1-6}alkyl)_2$, $-S-C_{1-6}alkyl$, $C_{0-6}alkylene-SO_2C_{1-6}alkyl$, $C_{0-6}alkylene-C(O)NH_2$, $C_{0-6}alkylene-C(O)NH(C_{1-6}alkyl)$, $C_{0-6}alkylene-C(O)N(C_{1-6}alkyl)_2$, $C_{0-6}alkylene-NHC(O)C_{1-6}alkyl$, $C_{0-6}alkylene-COOH$, $C_{0-6}alkylene-CO_2C_{1-6}alkyl$, $C_{0-6}alkylene-C_{3-6}cycloalkyl$, and $C_{0-6}alkylene-3-6$ membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S; R^4 is H, halogen, CN, OH, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, or $C_{1-6}alkoxy$; R^5 is $-CO_2-Z$, or a bioisostere thereof; each R^6 and R^7 is independently H, $C_{1-6}alkyl$, $C(O)-C_{1-6}alkyl$, spiro or bicyclic C_{8-14} cycloalkyl, 8-14 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R^6 or R^7 is other than H, it is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, CN, $=O$, SO_2 , OH, $C_{0-6}alkylene-NH_2$, $C_{0-6}alkylene-NH(C_{1-6}alkyl)$, $C_{0-6}alkylene-N(C_{1-6}alkyl)_2$, $C_{0-6}alkylene-SO_2C_{1-6}alkyl$, $C_{1-6}alkyl$ and $C_{1-6}alkoxy$, or

R^6 and R^7 , together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N, O, and S; and Z is $C_{1-7}alkyl$, $C_{1-7}haloalkyl$, $C_{3-6}cycloalkyl$, or $C_{2-6}alkyne$, and Z is substituted with 0, 1, 2, or 3 $C_{1-6}alkoxy$ or $C_{3-6}cycloalkyl$; with the

proviso that when R^1 and R^4 are each H, m and p are each 1, and A is , and (a) R^2 is H, Y is





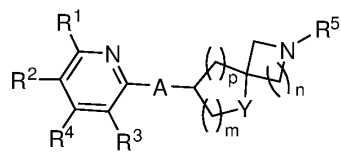
then R⁵ is not CO₂CH₂CH₃ or CO₂CH(CH₃)₃. In some embodiments, one or more H, including but not limited to those present in any R¹, R², R³, and/or R⁴ groups, can be replaced with a D.

[0006] Further provided herein are pharmaceutical compositions comprising the compounds as disclosed herein. Also provided are methods of treating an M4-mediated (or M4-associated) disease or disorder associated with aberrant M4 receptor activity in a subject, comprising administering to the subject a therapeutically effective amount of a compound as disclosed herein.

[0007] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compounds and methods disclosed herein are susceptible of cases in various forms, the description hereafter includes specific cases with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific cases described herein.

DETAILED DESCRIPTION

[0008] Provided herein are compounds that have a structure of Formula (I):



(I), or a pharmaceutically acceptable

salt thereof. Also provided herein are compounds that act on M4 receptors. The compounds described herein can be used to treat M4-mediated or M4-associated diseases.

Chemical Definitions

[0009] As used herein, the term "alkyl" refers to straight chained and branched saturated hydrocarbon groups containing one to thirty carbon atoms, for example, one to twenty carbon atoms, or one to ten carbon atoms. The term C_n means the alkyl group has "n" carbon atoms. For example, C₆alkyl refers to an alkyl group that has 6 carbon atoms. C₁₋₇alkyl refers to an alkyl group having a number of carbon atoms encompassing the entire range (i.e., 1 to 7 carbon atoms), as well as all subgroups (e.g., 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Nonlimiting examples of alkyl groups include, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl (2-methylpropyl), and t-butyl (1,1-dimethylethyl). Unless otherwise indicated, an alkyl group can be an unsubstituted alkyl group or a substituted alkyl group.

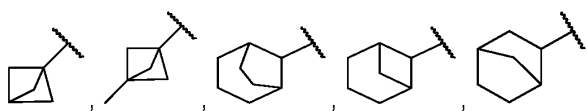
[0010] As used herein, the term "alkylene" refers to a bivalent saturated aliphatic radical. The term C_n means the alkylene group has "n" carbon atoms, e.g., a C₁alkylene is CH₂. For example, C₁₋₆alkylene refers to an alkylene group having a number of carbon atoms encompassing the entire range, as well as all subgroups, as previously described for "alkyl" groups. A C₀alkylene indicates a direct bond (i.e., no alkylene linker).

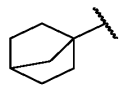
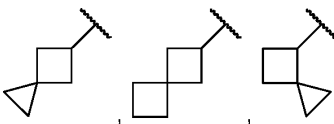
[0011] As used herein, the term "alkene" or "alkenyl" is defined identically as "alkyl" except for containing at least one carbon-carbon double bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkenyl group has "n" carbon atoms. For example, C₄alkenyl refers to an alkenyl group that has 4 carbon atoms. C₂₋₇alkenyl refers to an alkenyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (e.g., 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, and butenyl. Unless otherwise indicated, an alkenyl group can be an unsubstituted alkenyl group or a substituted alkenyl group. Unless otherwise indicated, an alkenyl group can be a cis-alkenyl or trans-alkenyl.

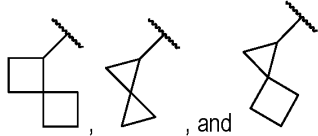
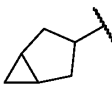
[0012] As used herein, the term "alkyne" or "alkynyl" is defined identically as "alkyl" except for containing at least one carbon-carbon triple bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkynyl group has "n" carbon atoms. For example, C₄alkynyl refers to an alkynyl group that has 4 carbon atoms. C₂₋₇alkynyl refers to an alkynyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (e.g., 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, and butynyl. Unless otherwise indicated, an alkynyl group can be an unsubstituted alkynyl group or a substituted alkynyl group.

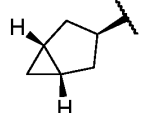
[0013] As used herein, the term "cycloalkyl" specifically refers to a non-aromatic ring in which each atom of the ring is carbon, i.e., a carbocycle, and can be monocyclic, bicyclic, bridged, fused or spirocyclic. The term C_n means the cycloalkyl group has "n" ring carbon atoms. For example, C₅ cycloalkyl refers to a cycloalkyl group that has 5 ring carbon atoms in the ring. C₃₋₁₂ cycloalkyl refers to cycloalkyl groups having a number of ring carbon atoms encompassing the entire range (i.e., 3 to 12 carbon atoms), as well as all subgroups (e.g., 4-8, 3-7,

4-7, 3-6, 4-6, 3-5, 4-5, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 carbon atoms). Nonlimiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Non limiting

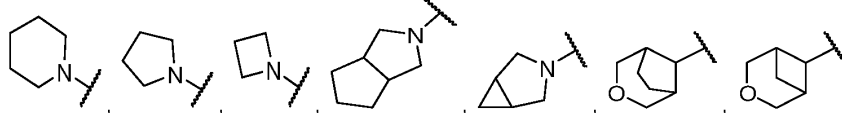
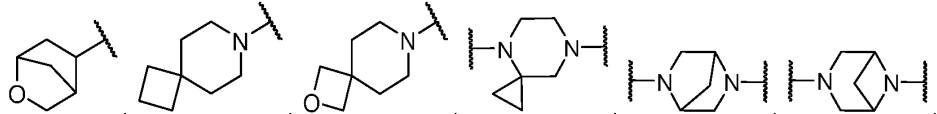
examples of bridged cycloalkyl groups include .

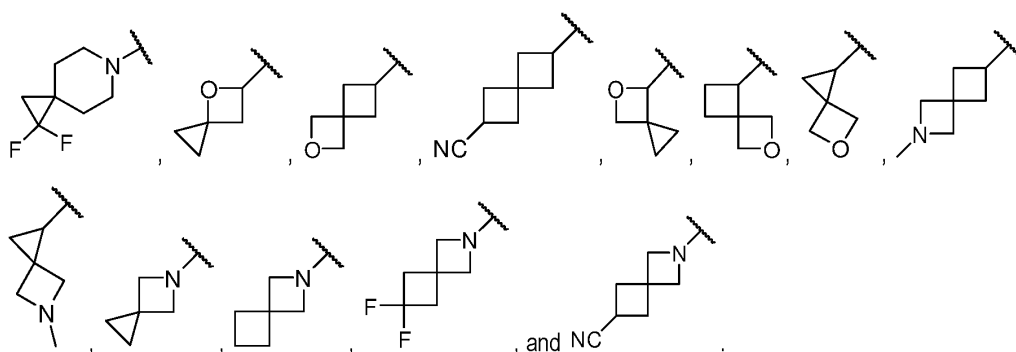
and . Non limiting examples of spirocycloalkyl groups include .

, and . A non-limiting example of a fused cycloalkyl is  (e.g.,

). Unless otherwise indicated, a cycloalkyl group can be an unsubstituted cycloalkyl group or a substituted cycloalkyl group.

[0014] As used herein, the term “heterocycle” is defined similarly as cycloalkyl, except the ring contains one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur. Additionally, heterocycles of the disclosure can be monocyclic, bicyclic, bridged, fused or spirocyclic. For example, a heterocycle can be a monocyclic, bicyclic, bridged, fused, or spirocyclic 3-12 membered ring having 1 or 2 or 3 heteroatoms selected from N, O, and S. As another example, a heterocycle can be a 5-12 or 8-10 membered bicyclic, bridged, fused, or spirocyclic group having 1 or 2 or 3 ring heteroatoms selected from N, O, and S in the bicyclic ring. Nonlimiting examples of heterocycle groups include piperidine, piperazine, tetrahydrofuran, tetrahydropyran, dihydrofuran, morpholine, oxazepane, thiazole, pyrrole, and pyridine. Non limiting examples of heterocycle

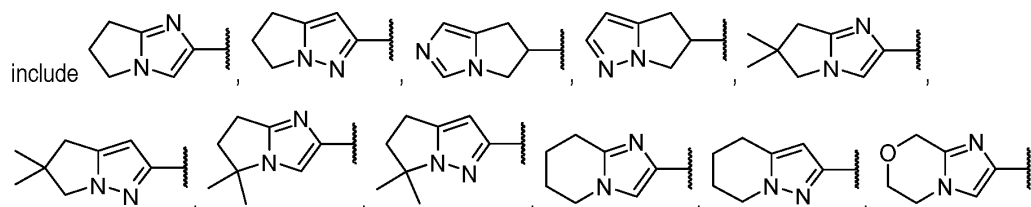
groups include , .

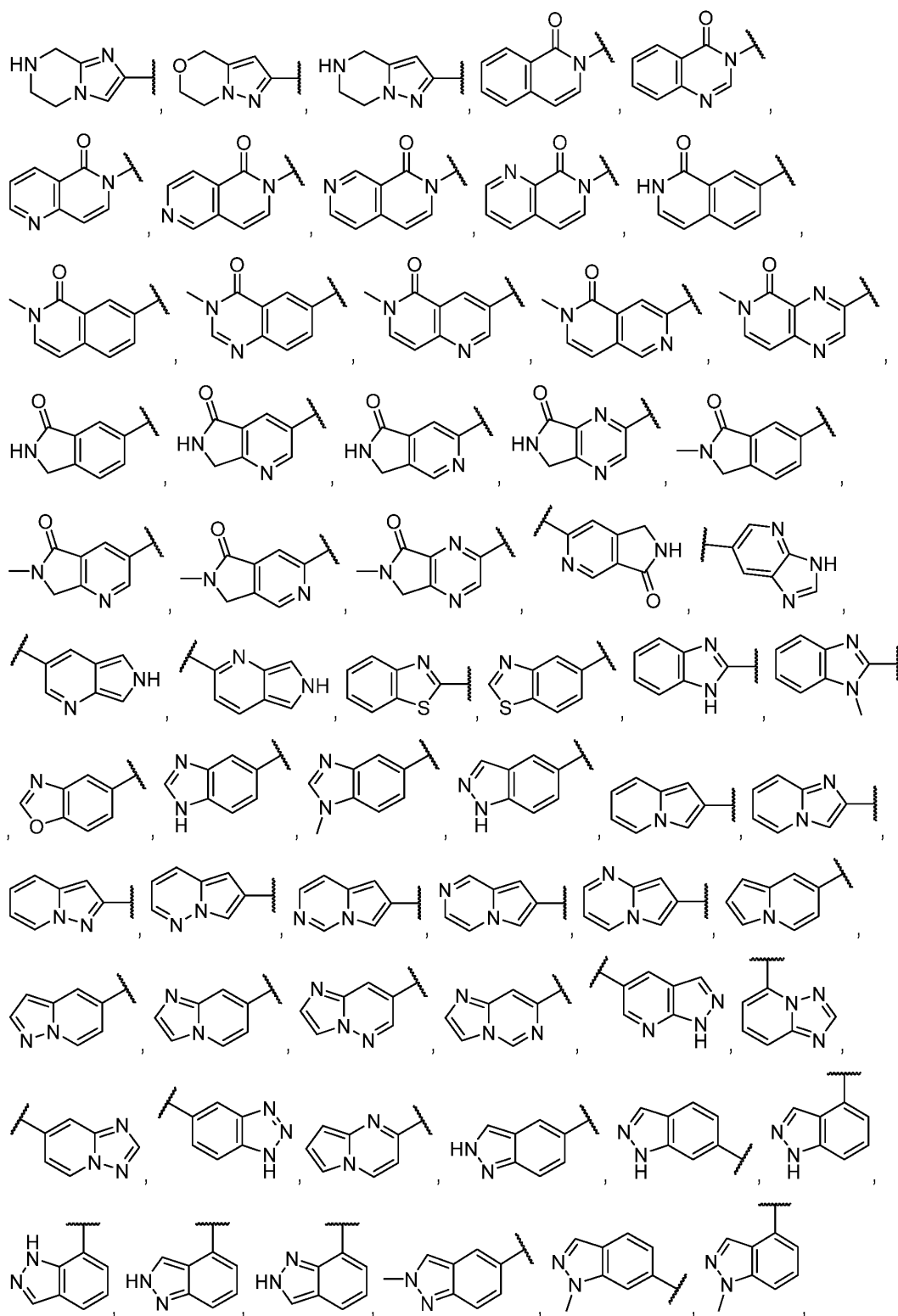


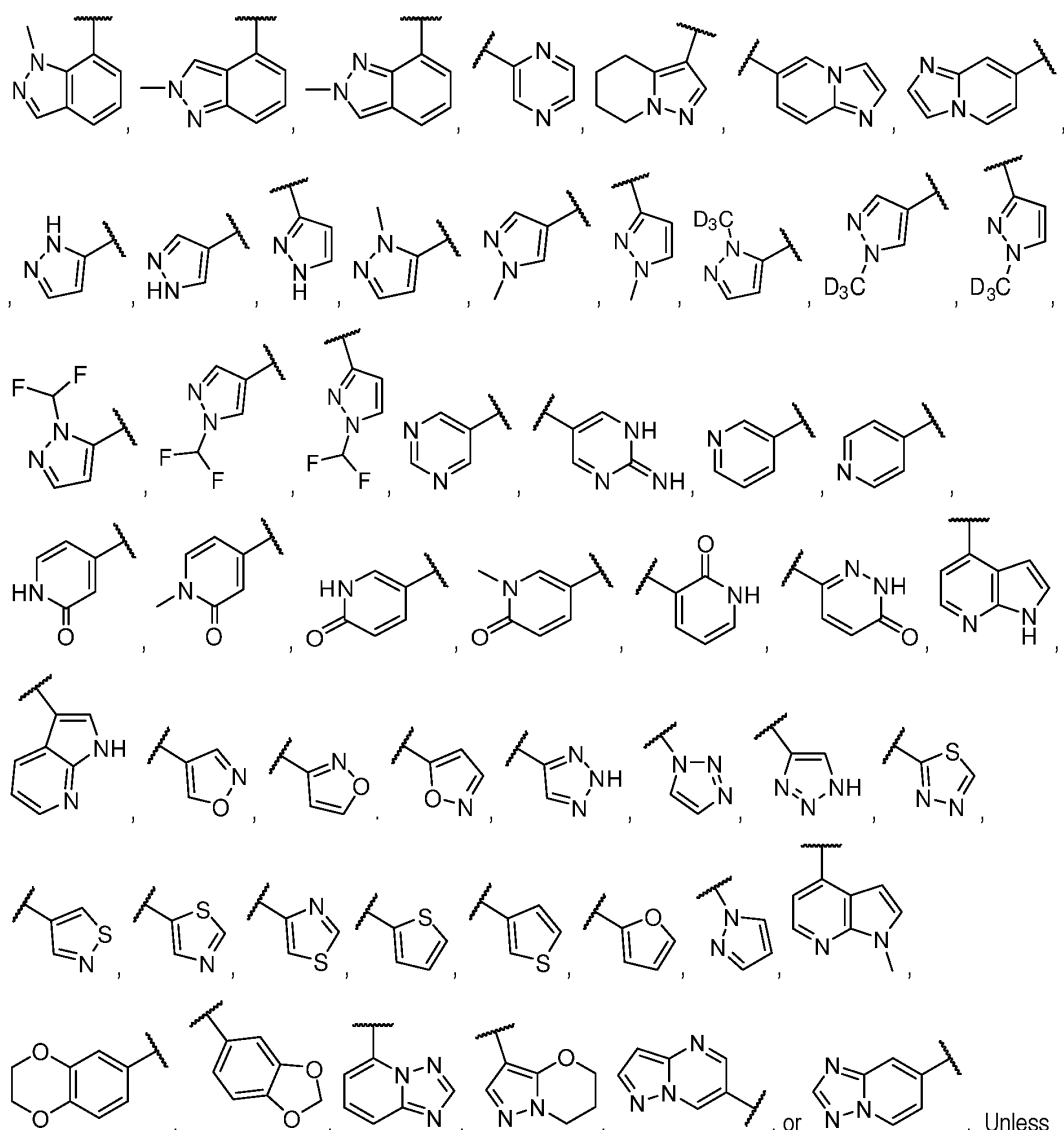
[0015] Cycloalkyl and heterocycle groups can be saturated or partially unsaturated ring systems (e.g., having double or triple bonds), but the groups are not aromatic. Cycloalkyl and heterocycle groups can be optionally substituted with, for example, one to three groups, independently selected alkyl, alkoxy, alkylene, OH, C₀₋₆alkylene-C(O)NH₂, NH₂, =O, SO₂, aryl, haloalkyl, haloalkoxy, C₀₋₆alkylene-C(O)-alkyl, C₀₋₆alkylene-SO₂alkyl, halogen, OH, NHC₁₋₃alkylene-aryl, OC₁₋₃alkylene-aryl, C₁₋₃alkylene-aryl, and C₀₋₆alkylene-C₃₋₆heterocycle having 1-3 heteroatoms selected from N, O, and S. Other contemplated substitutions are discussed in detail elsewhere in this disclosure.

[0016] As used herein, the term “aryl” refers to an aromatic ring in which each atom of the ring is carbon, and can be monocyclic or polycyclic (e.g., fused bicyclic and fused tricyclic) carbocyclic aromatic ring systems. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, phenanthrenyl, biphenylenyl, indanyl, indenyl, anthracenyl, fluorenyl, tetralinyl. Unless otherwise indicated, an aryl group can be an unsubstituted aryl group or a substituted aryl group.

[0017] As used herein, the term “heteroaryl” refers to an aromatic heterocycle, and can be monocyclic or polycyclic (e.g., fused bicyclic and fused tricyclic) aromatic ring systems, wherein one to four (e.g., one to three) ring atoms are selected from oxygen, nitrogen, and sulfur, and the remaining ring atoms are carbon, said ring system being joined to the remainder of the molecule by any of the ring atoms. Nonlimiting examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, tetrazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, furanyl, thienyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzimidazolyl, benzofuranyl, benzothiazolyl, triazinyl, triazolyl, purinyl, pyrazinyl, purinyl, indolinyl, phthalziny, indazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, naphthyridinyl, pyridopyridinyl, indolyl, 3H-indolyl, pteridinyl, and quinoxalinyl. Nonlimiting examples of heteroaryl groups







Unless otherwise indicated, a heteroaryl group can be an unsubstituted heteroaryl group or a substituted heteroaryl group.

[0018] As used herein, the term “hydroxy” or “hydroxyl” refers to an “—OH” group. Accordingly, a “hydroxyalkyl” refers to an alkyl group substituted with one or more —OH groups.

[0019] As used herein, the term “alkoxy” or “alkoxyl” refers to a “—O-alkyl” group.

[0020] As used herein, the term “halogen” is defined as fluoro, chloro, bromo, and iodo. Accordingly, a “haloalkyl” refers to an alkyl group substituted with one or more halogen atoms. In some cases, the haloalkyl group is a perhaloalkyl, i.e., all hydrogen atoms of the alkyl group have been substituted with a halogen. Some non-limiting examples of haloalkyl groups include CF₃, CHF₂, CH₂F, CCl₃, CH₂Cl, and CH₂CF₃. Similarly, a “haloalkoxy” refers to an alkoxy group that is substituted with one or more halogen atoms, e.g., OCF₃. And

"haloalkyl" refers to an alkyl group where one or more of the hydrogen atoms have been substituted with one or more halogen.

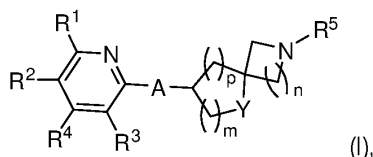
[0021] As used herein, the term "heteroalkyl" refers to an alkyl chain interrupted with one or more heteroatoms selected from N, O, and S and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the heteroalkyl group has "n" carbon atoms. For example, C₆heteroalkyl refers to an alkyl group that has 6 carbon atoms and the carbon chain is interrupted with one or more heteroatoms. C₂₋₆heteroalkyl refers to an alkyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 6 carbon atoms), as well as all subgroups (e.g., 2-5, 3-6, 3-5, 4-6, 2, 3, 4, 5, and 6 carbon atoms). The number of heteroatoms in the heteroalkyl chain can be, e.g., 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 or 2. Specific numbers of heteroatoms contemplated include 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 heteroatoms.

[0022] As used herein, the term "bioisostere" refers to a molecule resulting from the exchange of an atom or of a group of atoms with an alternative, broadly similar, atom or group of atoms. For example, an ester group can be replaced by one of the following bioisosteres for the ester, including, without limitation, acylsulfonamides (CO—NRSO₂R), hydroxamic acids (CONROH), hydroxamates (CONROR), tetrazoles, hydroxyisoxazoles, isoxazol-3-ones, and sulfonamides (SO₂NR₂), where each R may independently represent hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclialkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0023] A "substituted" functional group (e.g., a substituted alkyl, cycloalkyl, aryl, or heteroaryl) is a functional group having at least one hydrogen radical that is substituted with a non-hydrogen radical (i.e., a substituent). Examples of non-hydrogen radicals (or substituents) include, but are not limited to, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, ether, aryl, O-alkylene aryl, N-alkylene aryl, alkylene aryl, heteroaryl, heterocycle, hydroxy, hydroxyalkyl, haloalkoxy, amido, =O, SO₂, alkoxy, ester, thioester, acyl, carboxyl, cyano, nitro, amino, sulfhydryl, and halogen. When a substituted alkyl group includes more than one non-hydrogen radical, the substituents can be bound to the same carbon or two or more different carbon atoms.

Compounds of the Disclosure

[0024] Disclosed herein are compounds having a structure of Formula (I):



or an *N*-oxide thereof, or a pharmaceutically acceptable salt of the compound or the *N*-oxide thereof,

wherein:

A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and optionally substituted with 1 to 3 R^A;

each R^A is independently C₁₋₃alkyl, halogen, =O, OH, C₁₋₃hydroxyalkyl, or C₁₋₃haloalkyl ;

Y is a bond, S, O, CH₂, CHF, CF₂, or C(OH)H;

m is 1 or 2;

n is 1 or 2;

p is 1 or 2;

R¹ is H, halogen, CN, OH, NO₂, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle or -[O]₀₋₁-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle, -[O]₀₋₁-5-10 membered heteroaryl, -NH-C₃₋₆cycloalkyl, -NH-C₆₋₁₀aryl, -NH-4-8 membered heterocycle, -NH-5-10 membered heteroaryl, -N(C₁₋₆alkyl)-C₃₋₆cycloalkyl, -N(C₁₋₆alkyl)-C₆₋₁₀aryl, -N(C₁₋₆alkyl)-4-8 membered heterocycle, or -N(C₁₋₆alkyl)-5-10 membered heteroaryl, R¹ is substituted with 0, 1, 2, or 3 substituents independently selected from halogen, CN, OH, =O, SO₂, and C₁₋₃alkyl,

R² is H, halogen, CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₂₋₆heteroalkyl, C₃₋₆cycloalkyl, or 4-8 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S;

R³ is halogen, C₀₋₆alkylene-CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-C(O)NHC₁₋₆alkyl, C₀₋₆alkylene-Cyc, O-C₀₋₆alkylene-Cyc, NH-Cyc, N(C₁₋₆alkyl)-Cyc, or C(O)Cyc;

Cyc is C₃₋₁₂cycloalkyl, C₃₋₆heterocycloalkyl, C₅₋₁₂spirocycloalkyl, C₅₋₁₂heterospirocycloalkyl, C₆₋₁₀aryl, 4-12 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents;

each R^{3a} is independently selected from halogen, CN, OH, =O, =N(C₁₋₆alkyl), SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₀₋₆alkylene-C(O)C₁₋₆alkyl, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₀₋₆alkylene-C(O)NH₂, C₀₋₆alkylene-C(O)NH(C₁₋₆alkyl), C₀₋₆alkylene-C(O)N(C₁₋₆alkyl)₂, C₀₋₆alkylene-NHC(O)C₁₋₆alkyl, C₀₋₆alkylene-COOH, C₀₋₆alkylene-CO₂C₁₋₆alkyl, C₀₋₆alkylene-C₃₋₆cycloalkyl, and C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S;

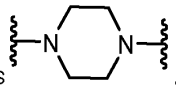
R⁴ is H, halogen, CN, C₁₋₆alkyl, OH, or C₁₋₆alkoxy;

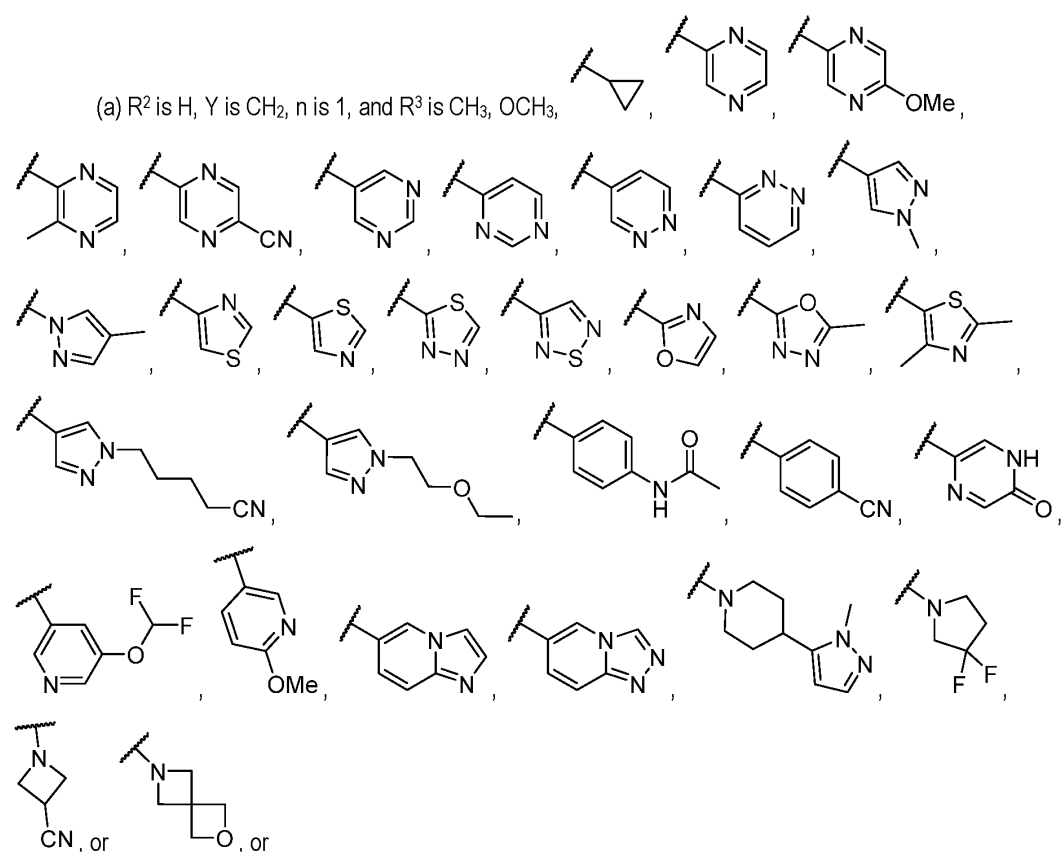
R⁵ is -CO₂-Z, or a bioisostere thereof;

each R⁶ and R⁷ is independently H, C₁₋₆alkyl, C(O)-C₁₋₆alkyl, spiro or bicyclic C₈₋₁₄cycloalkyl, 8-14 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R⁶ or R⁷ is other than H, it is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, CN, =O, SO₂, OH, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₁₋₆alkyl and C₁₋₆alkoxy, or

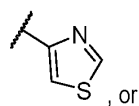
R⁶ and R⁷, together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N, O, and S; and

Z is C₁₋₇alkyl, C₁₋₇haloalkyl, C₃₋₆cycloalkyl, or C₂₋₆alkyne, and Z is substituted with 0, 1, 2, or 3 C₁₋₆alkoxy or C₃₋₆cycloalkyl;

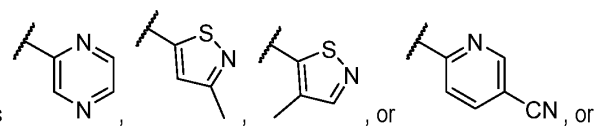
with the proviso that when R¹ and R⁴ are each H, m and p are each 1, and A is , and



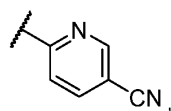
(b) R² is F, Y is CH₂, n is 1, and R³ is



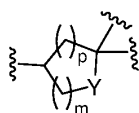
(c) R² is H, Y is a bond, n is 1, and R³ is

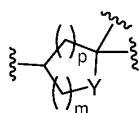


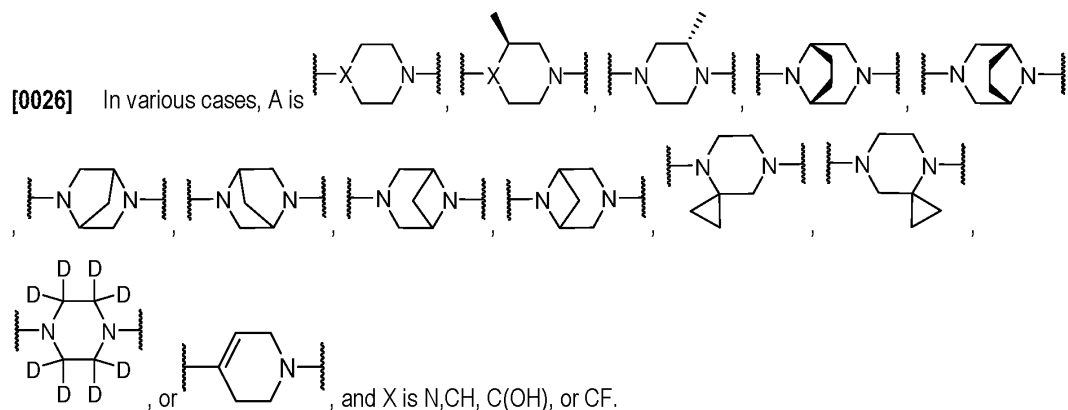
(d) R² is H, Y is a bond, n is 2, and R³ is



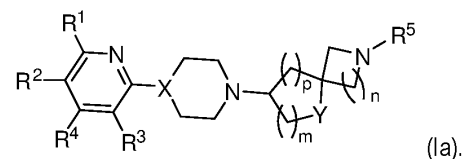
then R⁵ is not CO₂CH₂CH₃ or CO₂CH(CH₃)₃. In some embodiments, one or more H, including but not limited to those present in any R¹, R², R³, and/or R⁴ groups, can be replaced with a D.



[0025] In various cases, the ring comprising the Y substituent, , is optionally substituted somewhere on the ring with a C₁₋₃alkyl, halogen, C₁₋₃haloalkyl, OH, or CN. In some cases, the ring comprising the Y substituent is substituted with a methyl, fluoro, CF₃, OH, or CN.

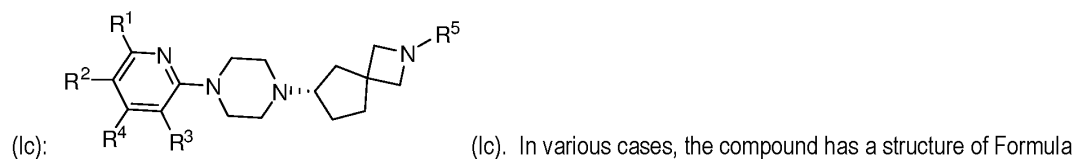
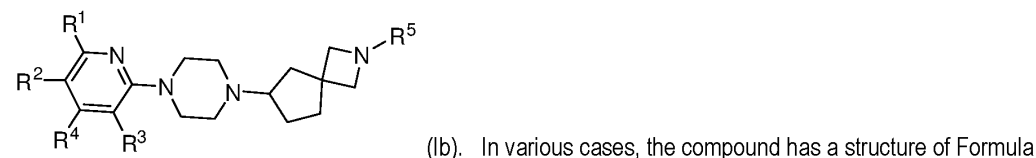


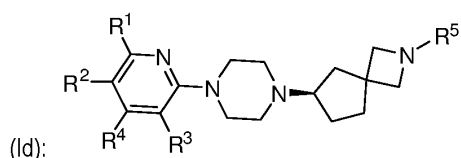
[0027] In some cases, the compound has a structure of Formula (Ia):



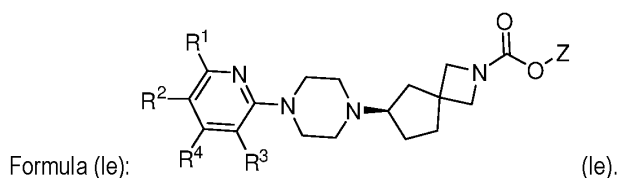
[0028] In various cases, Y is CH₂, CHF, CF₂, or C(OH)H. In some cases, Y is CH₂. In some cases, m is 1. In some cases, n is 1. In some cases, p is 1.

[0029] In various cases, the compound has a structure of Formula (Ib):



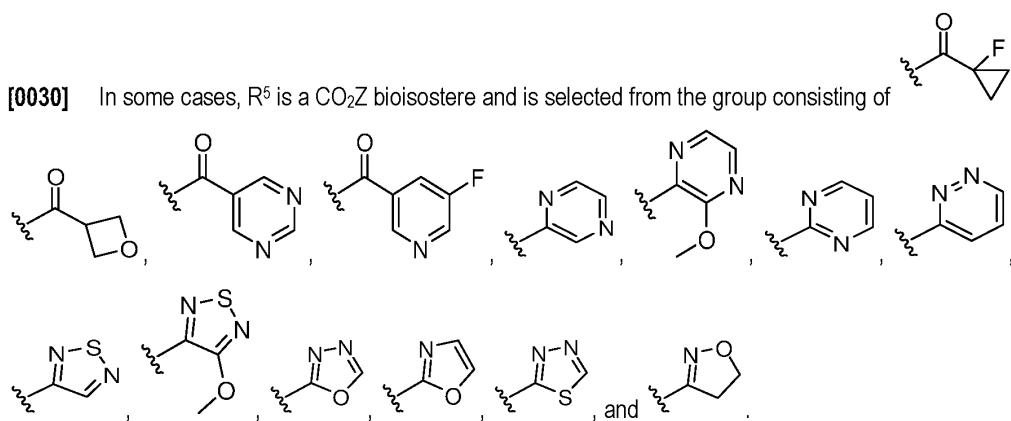


(Id). In various cases, the compound has a structure of

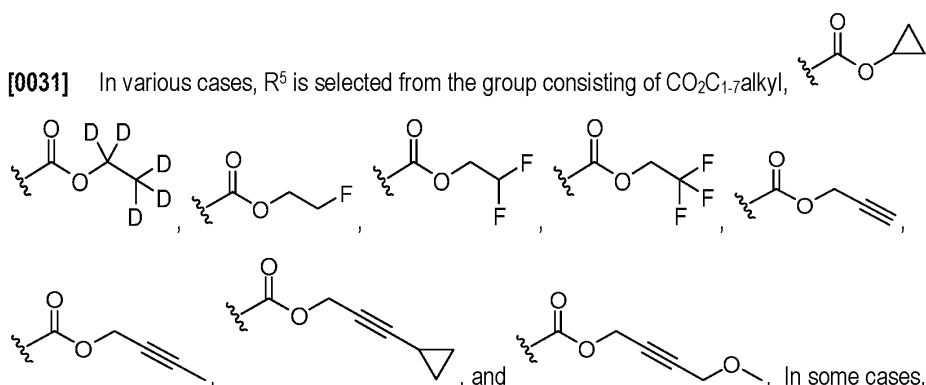


(le).

[0030] In some cases, R⁵ is a CO₂Z bioisostere and is selected from the group consisting of



[0031] In various cases, R⁵ is selected from the group consisting of CO₂C₁₋₇alkyl,


$$\text{CO}_2\text{CH}_2\text{CH}_3.$$

[0032] In various cases, R¹ is H, halogen, CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, or C₁₋₆alkoxy. In some cases, R¹ is H or halogen.

[0033] In various cases, R² is H, halogen, CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, or C₁₋₆haloalkoxy. In some cases, wherein R² is H, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, or C₁₋₆haloalkoxy. In some cases, R² is H or halogen.

[0034] In various cases, each R⁶ and R⁷ are independently H, C₁₋₆alkyl, or C(O)-C₁₋₆alkyl. In some cases, each R⁶ and R⁷ are independently H or C₁₋₆alkyl. In some cases, at least one R⁶ and R⁷, together with the

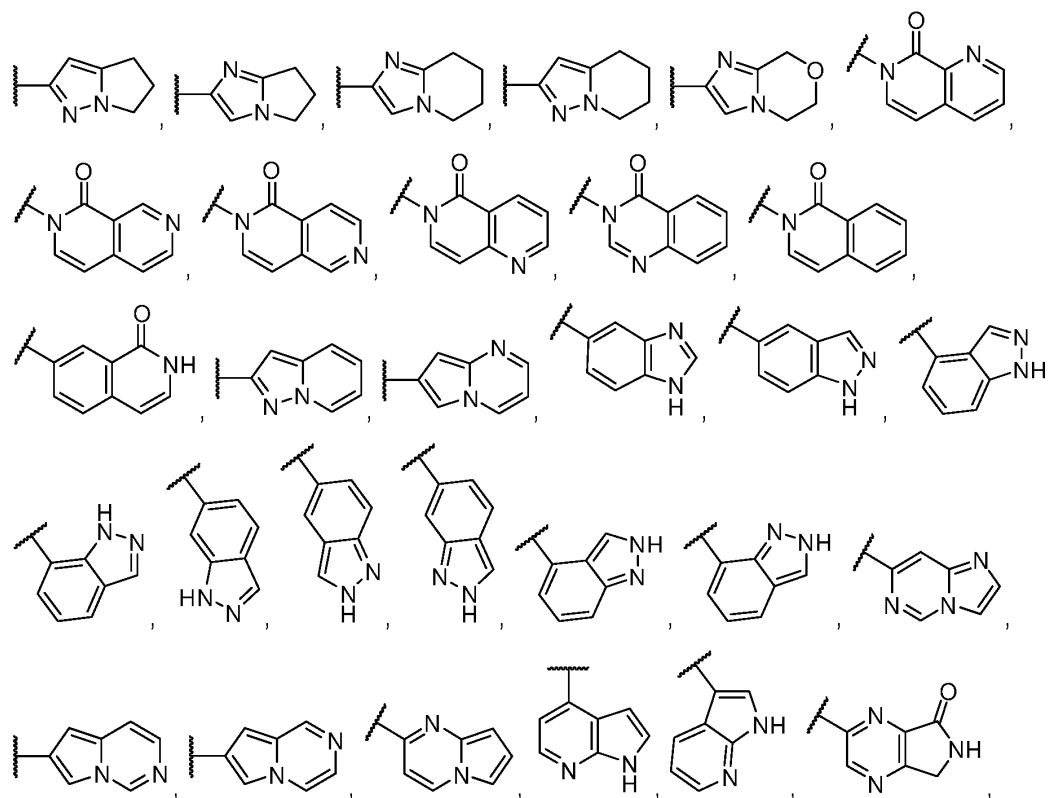
nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N and O.

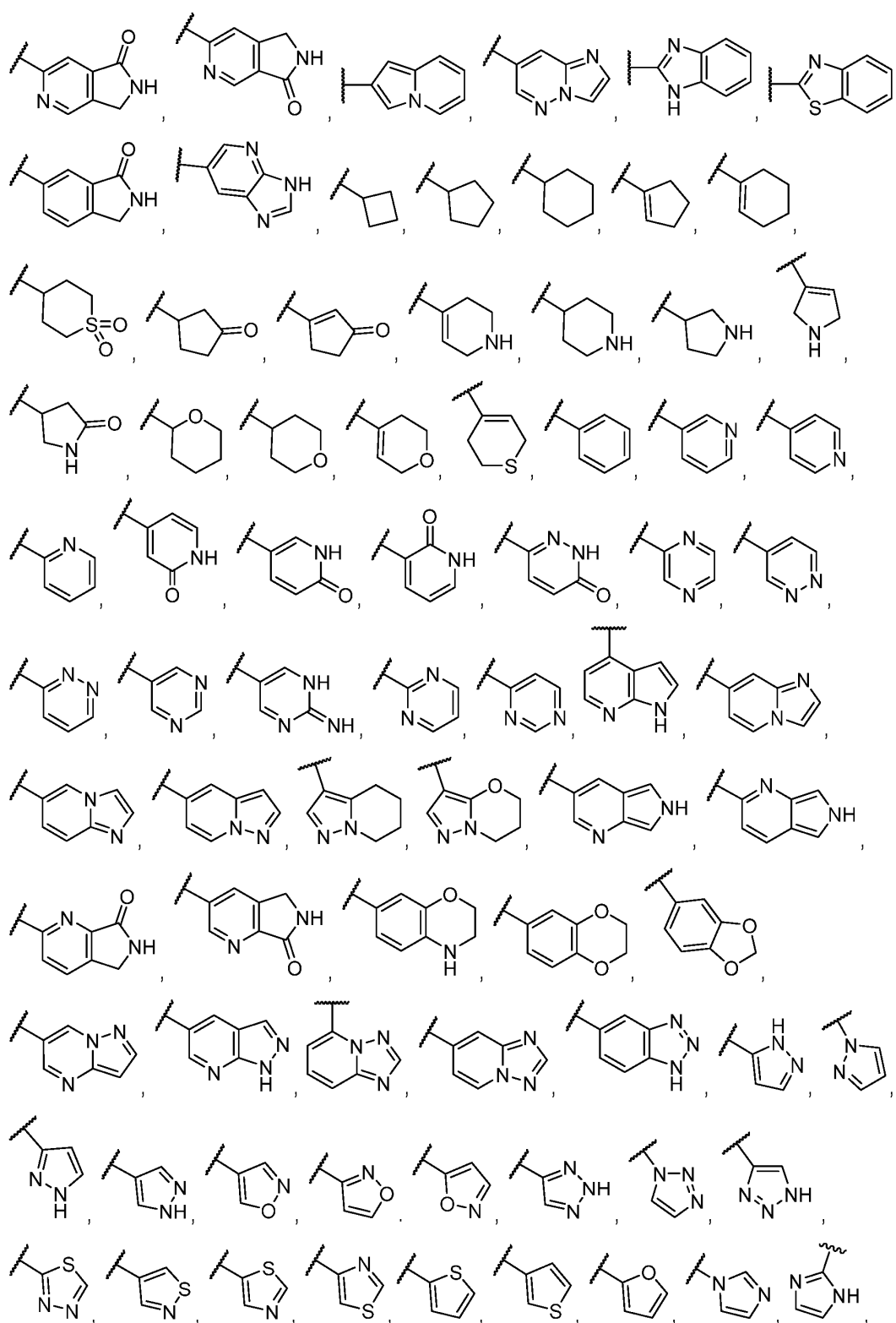
[0035] In various cases, R⁴ is H or halogen.

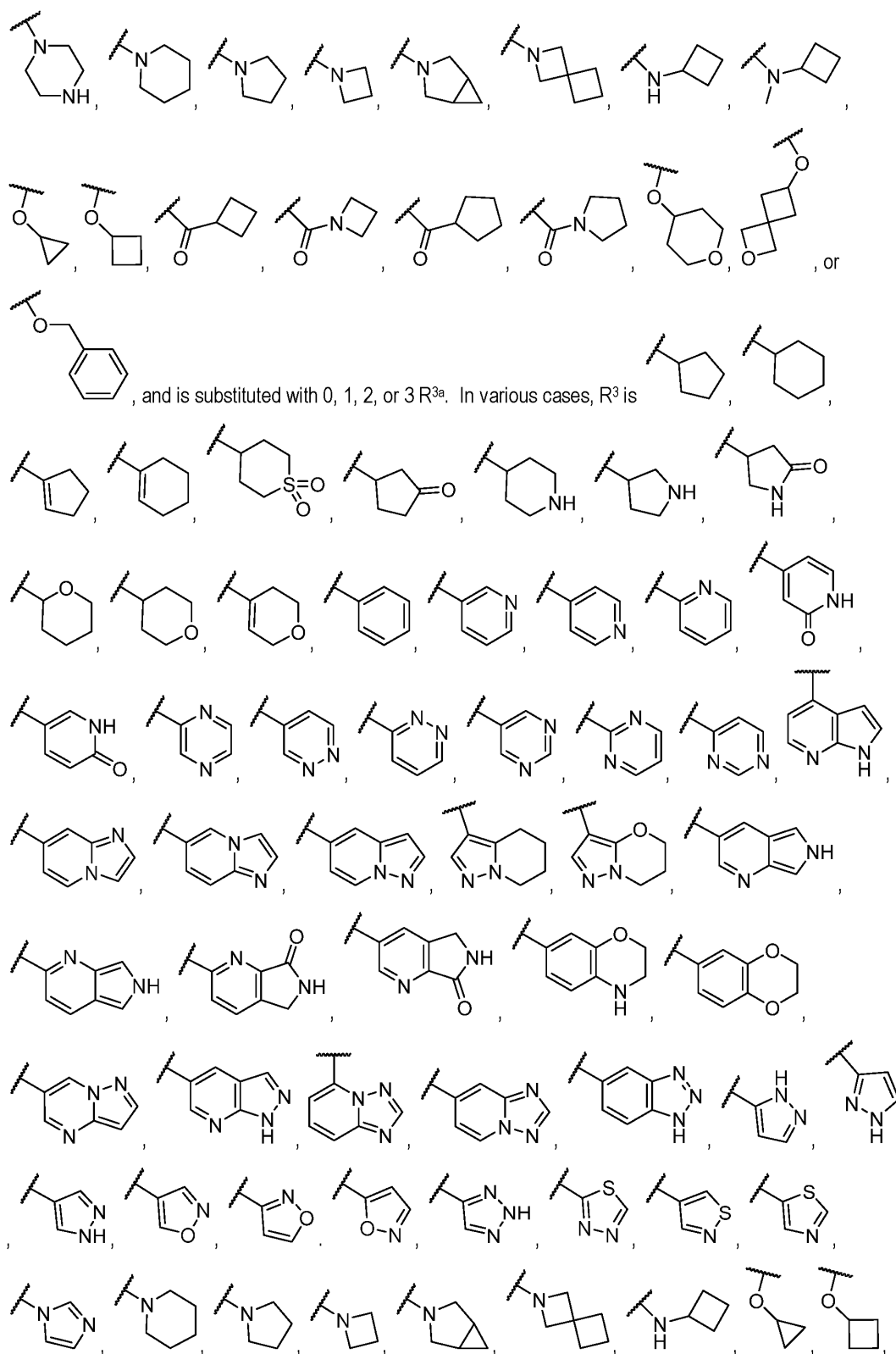
[0036] In various cases, at least one of R^1 , R^2 , and R^4 is halogen. In some cases, at least one of R^1 , R^2 , and R^4 is F.

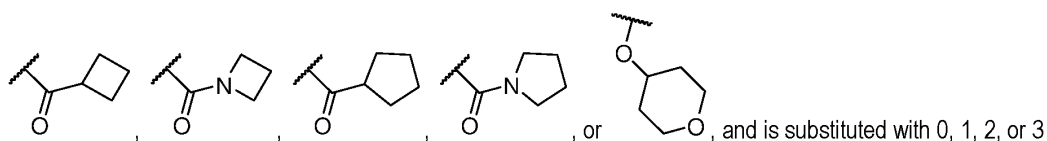
[0037] In various cases, R³ is C₀₋₆alkylene-Cyc, O-C₀₋₆alkylene-Cyc, NH-Cyc, N(C₁₋₆alkyl)-Cyc, or C(O)Cyc, where Cyc is C₃₋₆cycloalkyl, C₆₋₁₀aryl, 4-8 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents. In various cases, R³ is C₀₋₆alkylene-Cyc, O-C₀₋₆alkylene-Cyc, NH-Cyc, N(C₁₋₆alkyl)-Cyc, or C(O)Cyc, where Cyc is C₃₋₁₂cycloalkyl, C₆₋₁₀aryl, 4-12 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents. In various cases, R³ is -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle, or -[O]₀₋₁-5-10 membered heteroaryl, and is

optionally substituted with 1, 2, or 3 R^{3a}. In some cases, R³ is









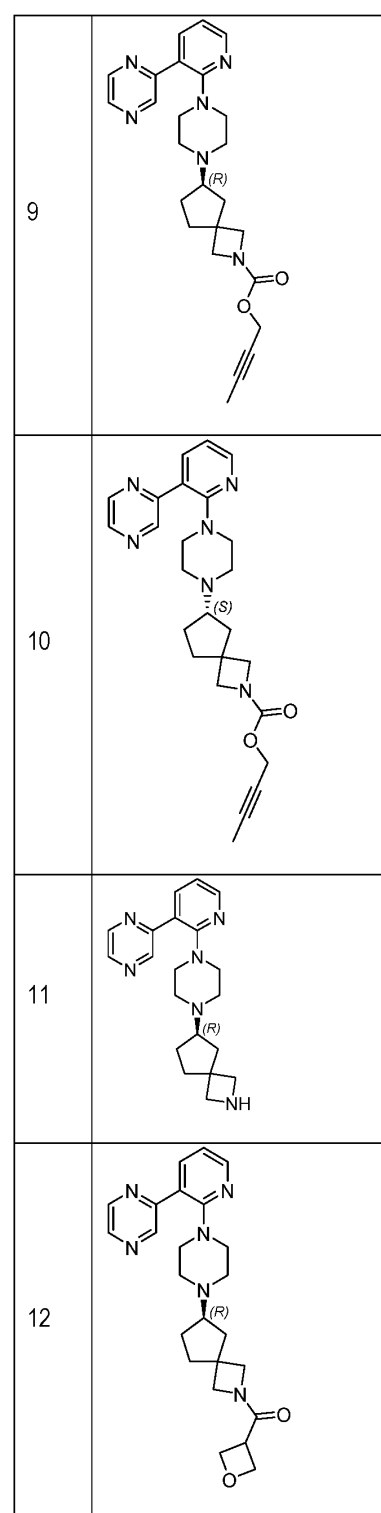
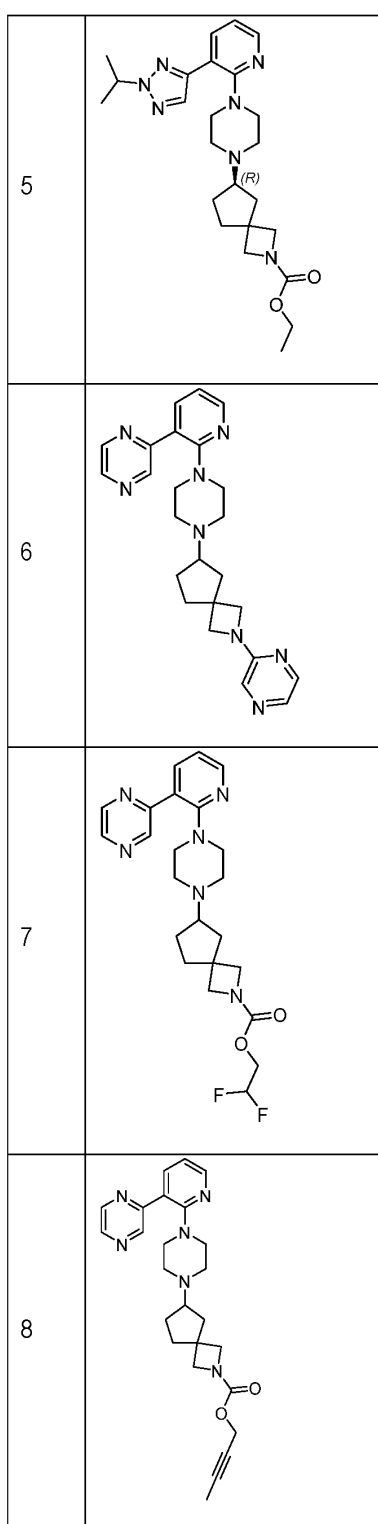
R^{3a} . In some cases, R^3 is unsubstituted. In various cases, R^3 is substituted with 1 or 2 R^{3a} . In some cases, R^3 is substituted with 1 R^{3a} . In some cases, at least one R^{3a} is halogen, CN, OH, =O, SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, C₁₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, or C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S. In some cases, at least one R^{3a} is CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, CF₃, CH₂CH₂F, CH₂CHF₂, CH₂OH, C(CH₃)₂OH, CH₂OCH₃, CH₂CH₂OCH₃, CH₂OCH₂CH₃, F, CN, =O, SO₂, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCHF₂, CH₂OCH₃, CH₂OCF₃, SCH₃,

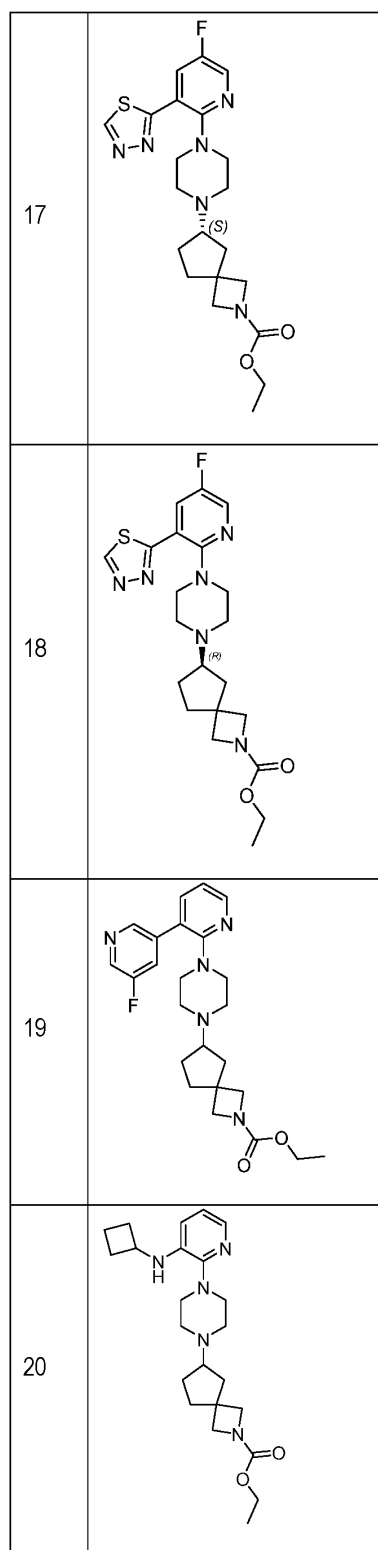
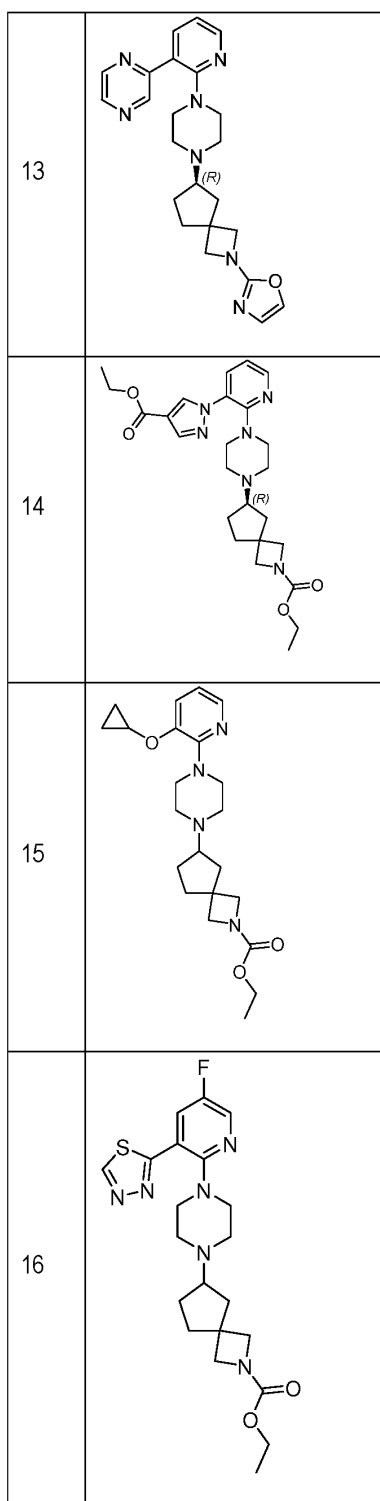
N(CH₃)₂, NHCOCH₃, CD₃, , or . In various case, at least one R^{3a} is CH₃, CH₂CH₃, F, CN, OH, OCH₃, CF₃, CH₂OH, or OCHF₂.

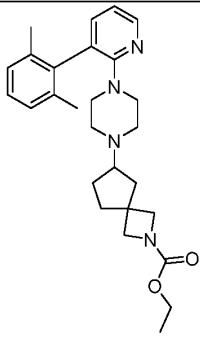
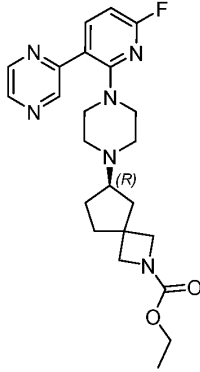
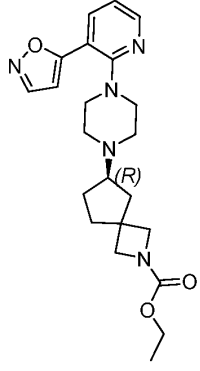
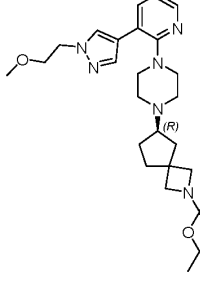
[0038] Some specific examples of compounds (or pharmaceutically acceptable salts thereof) disclosed herein are shown in Table A.

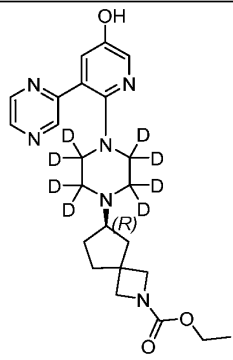
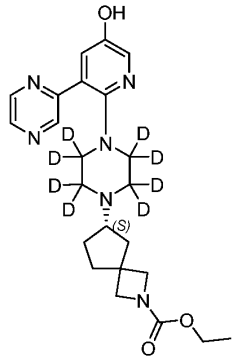
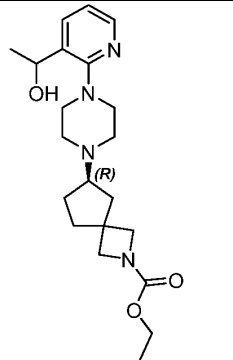
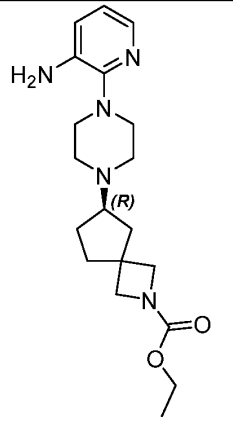
Table A

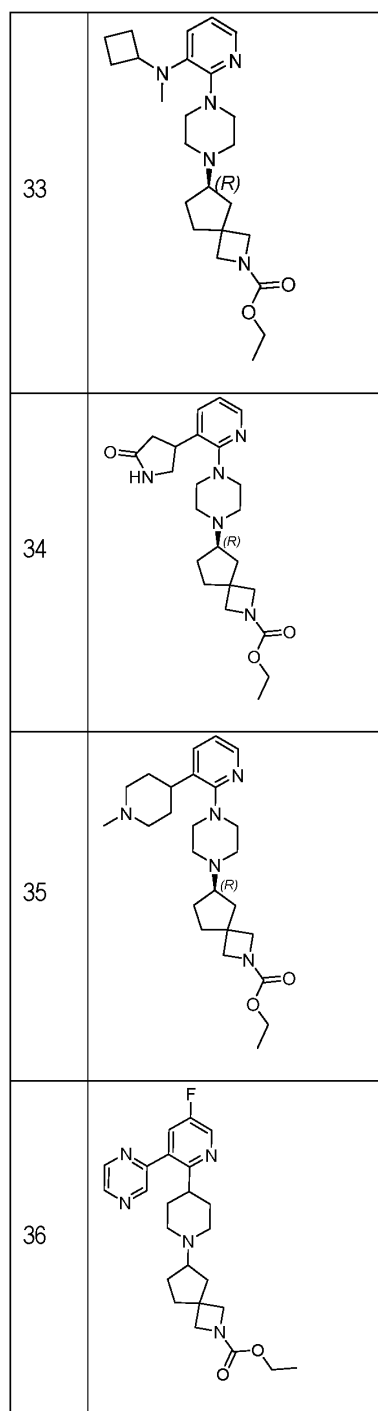
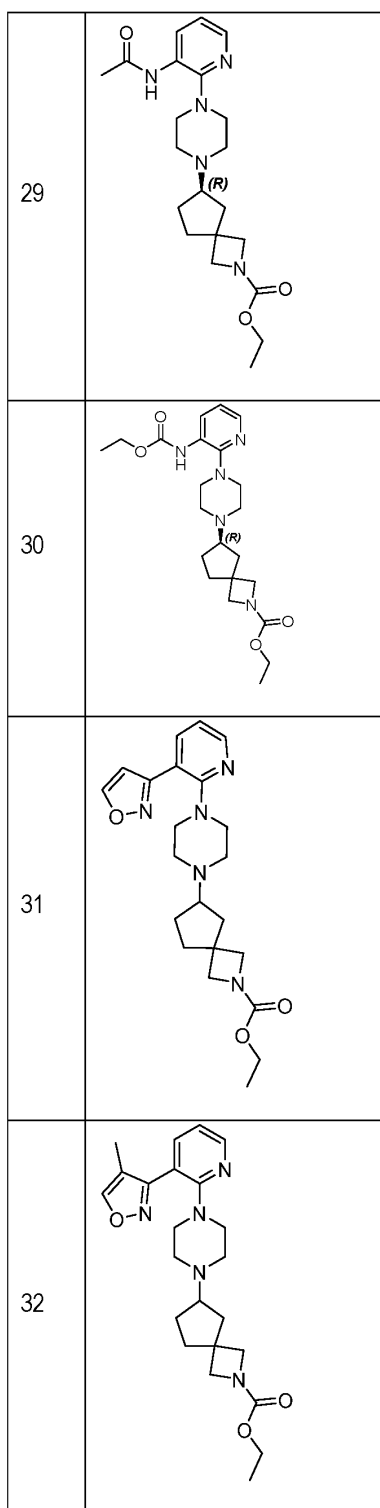
Ex.	Structure
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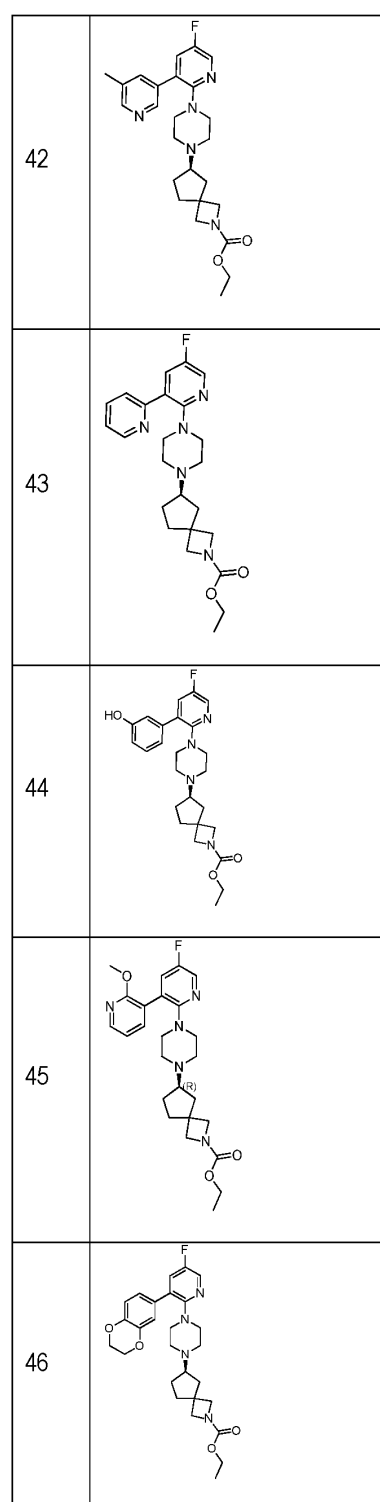
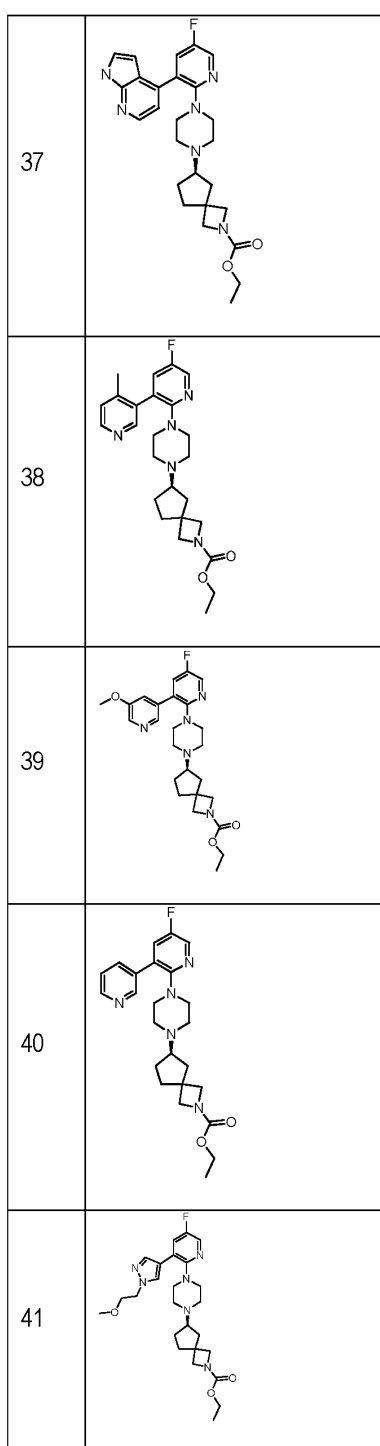


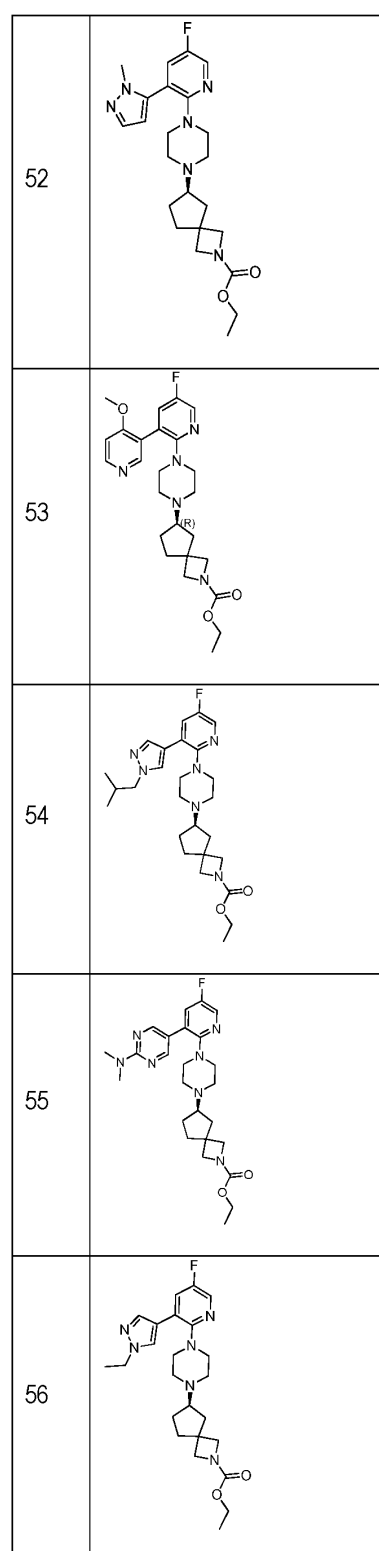
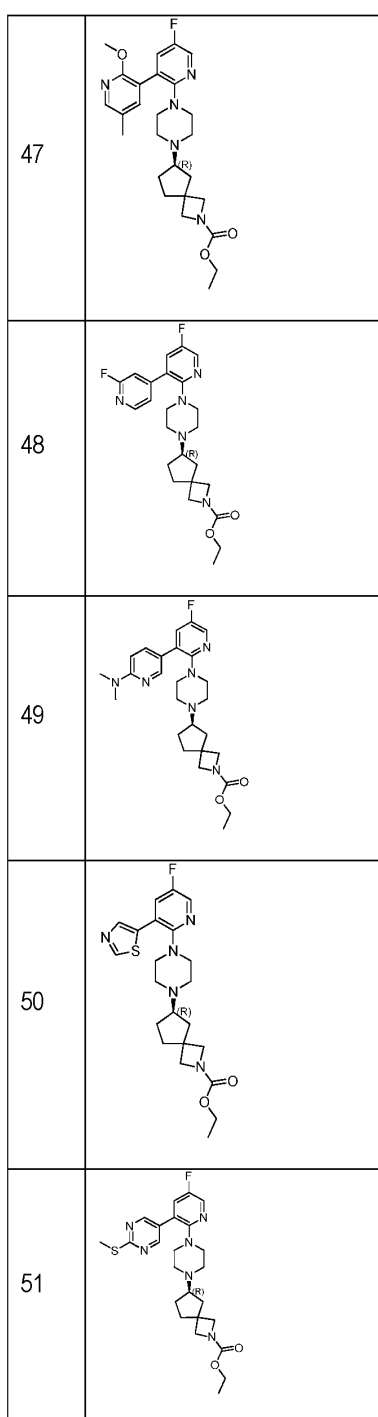


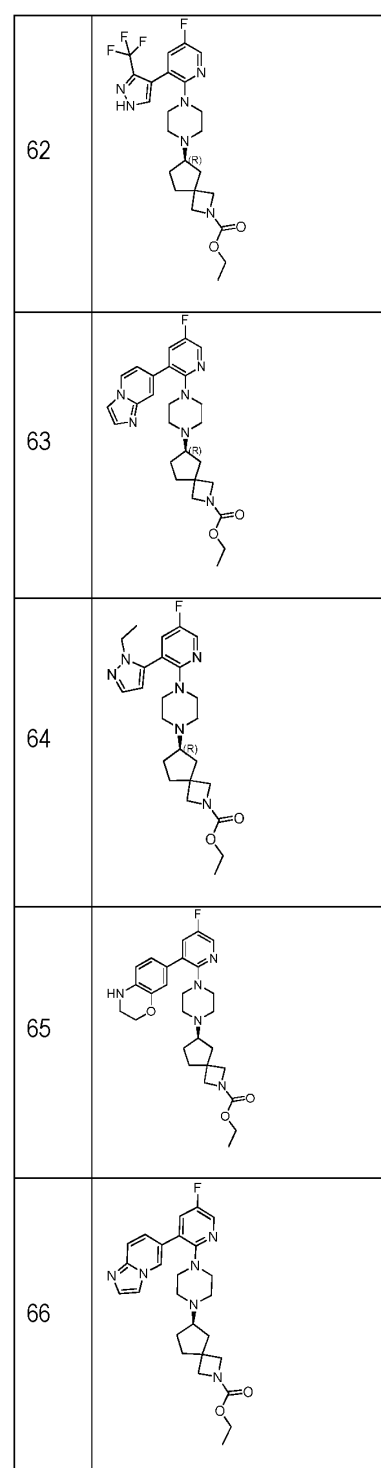
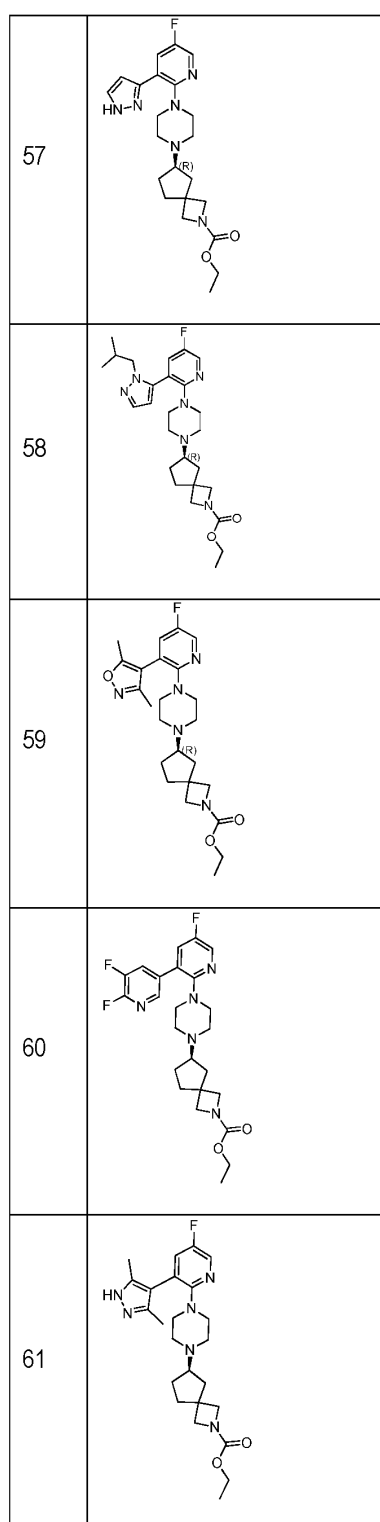
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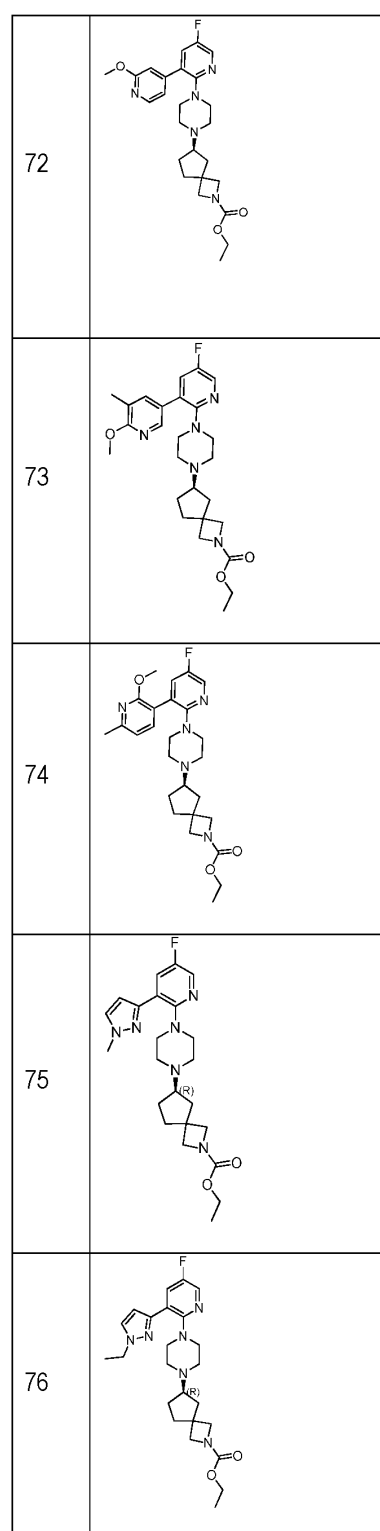
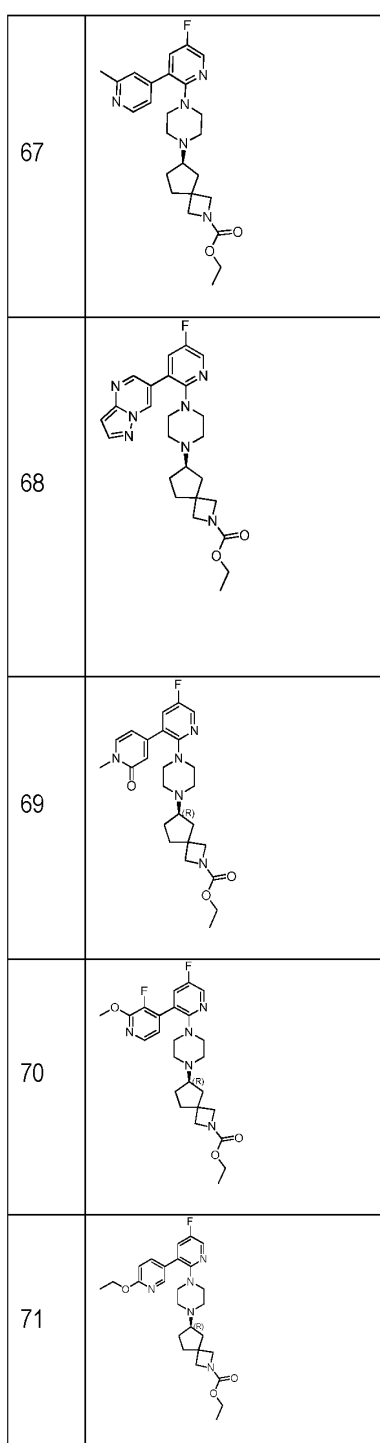
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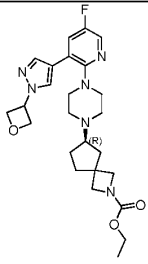
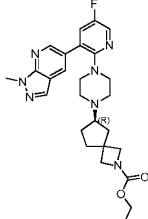
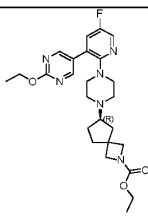
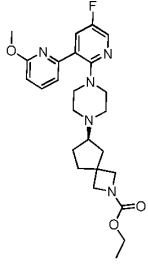
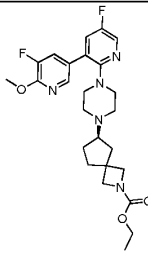


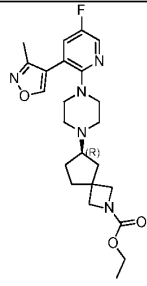
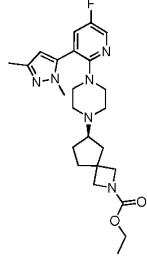
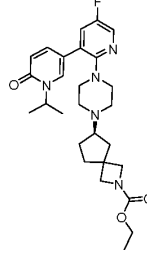
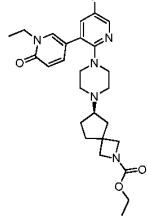
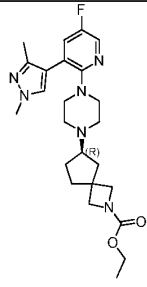


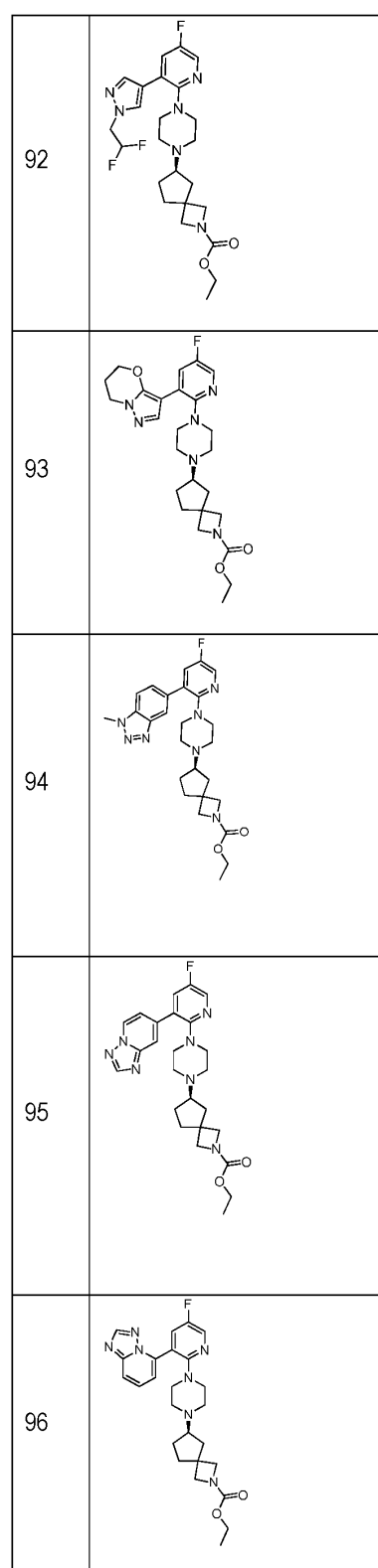
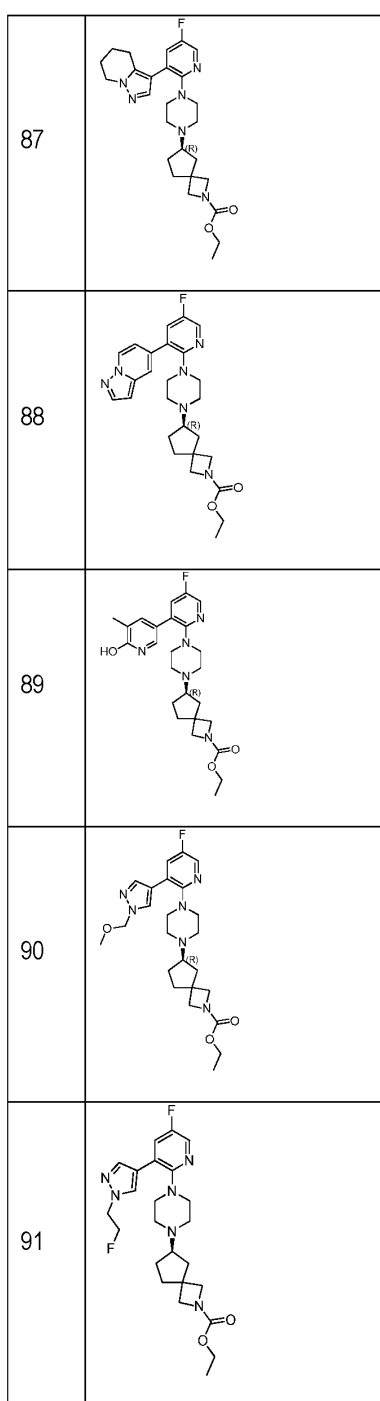


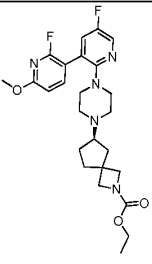
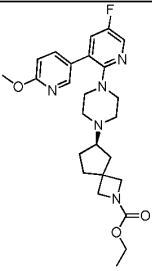
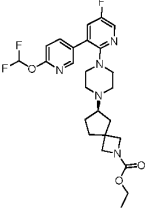
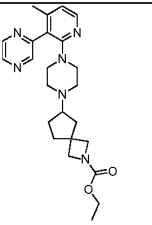
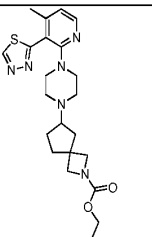
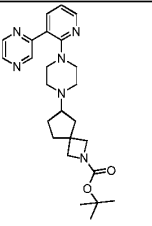


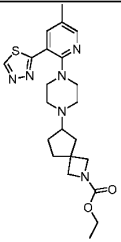
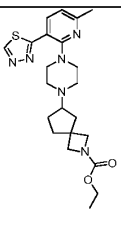
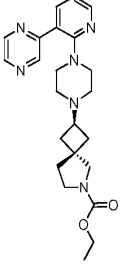
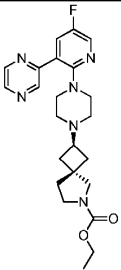
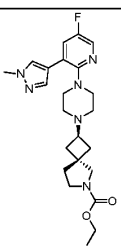
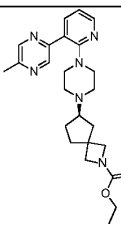


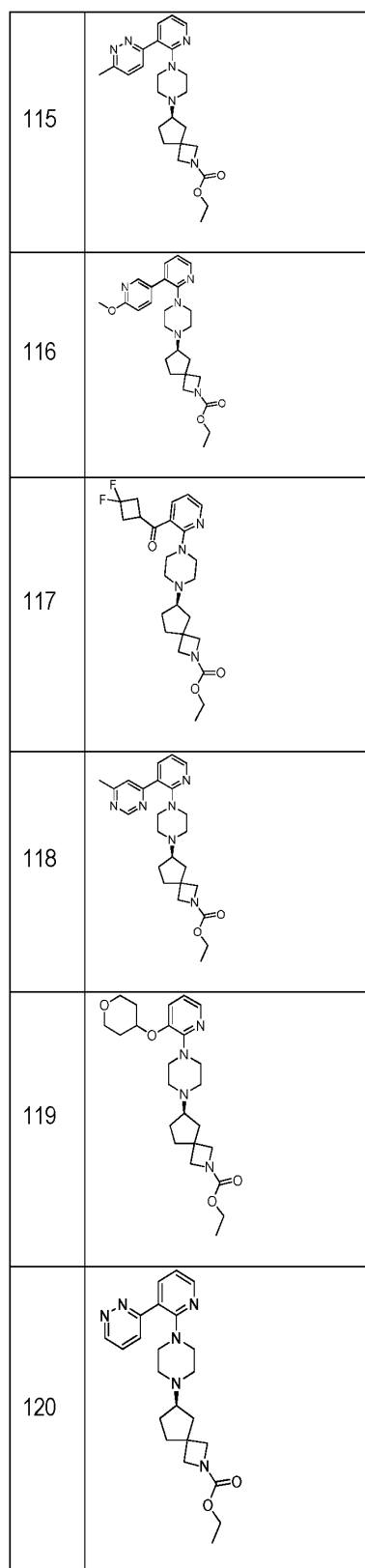
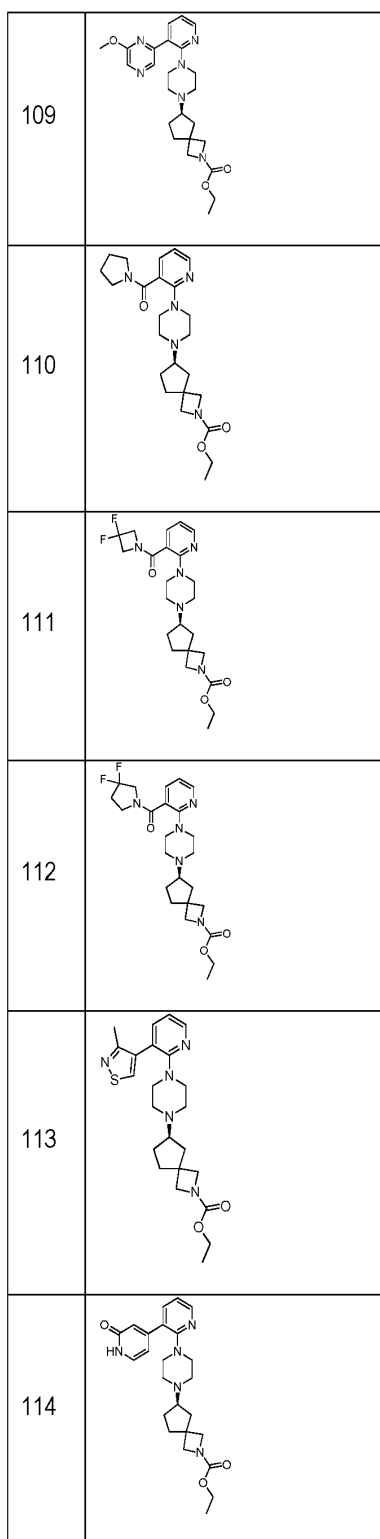
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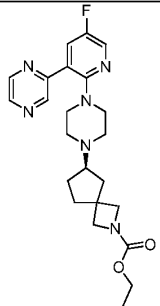
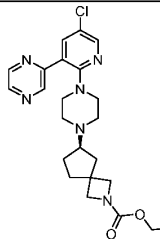
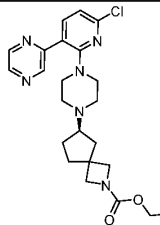
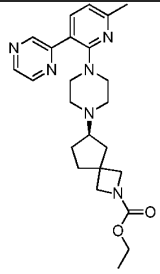
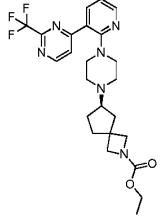
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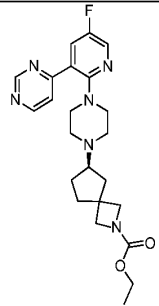
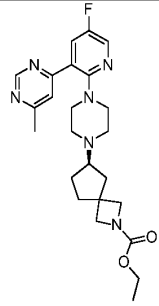
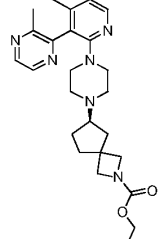
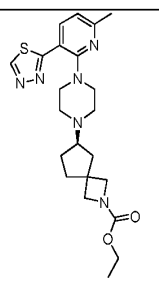
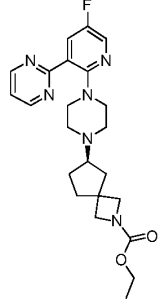


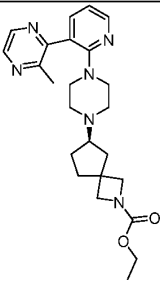
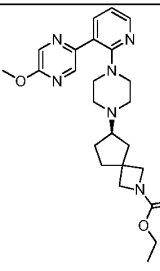
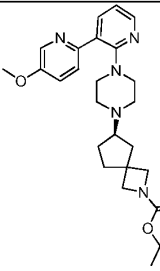
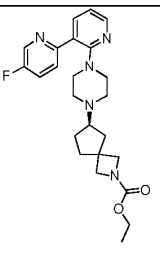
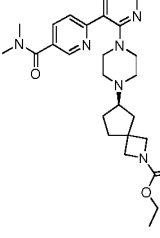
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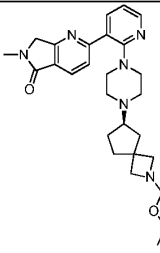
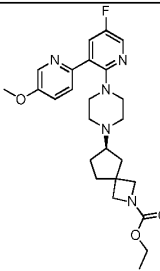
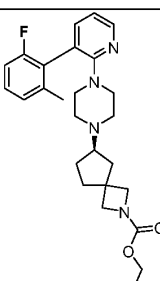
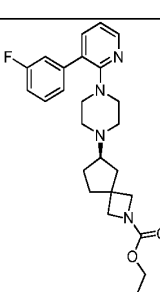
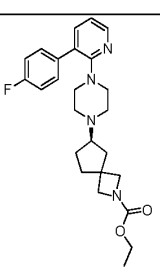
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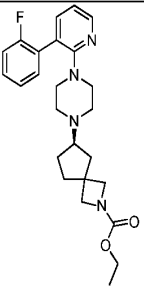
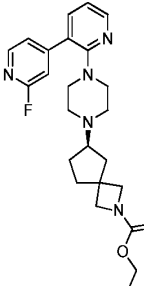
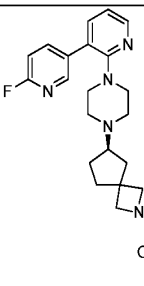
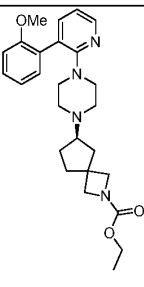
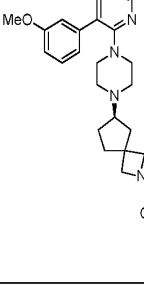


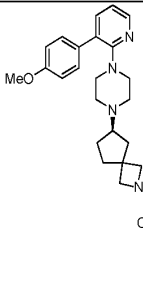
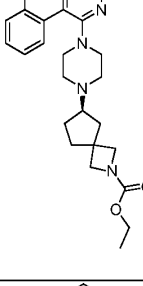
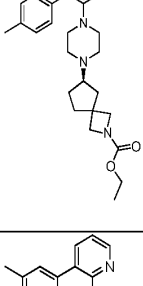
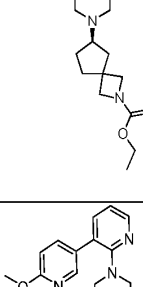
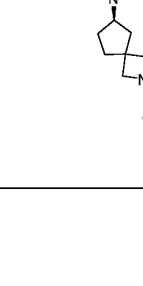
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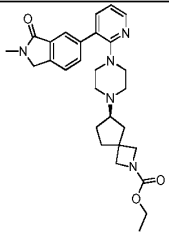
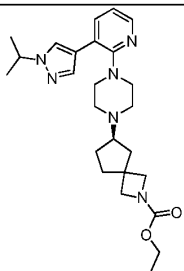
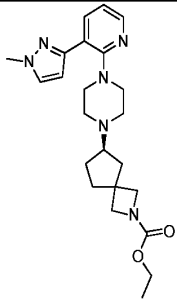
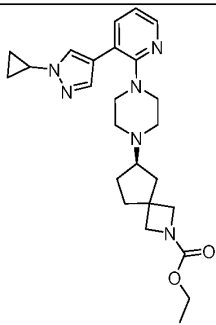
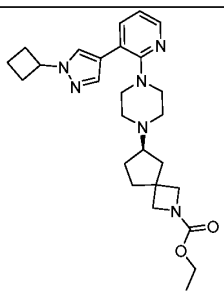
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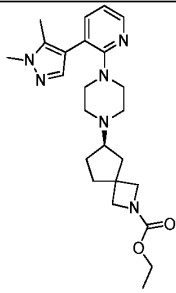
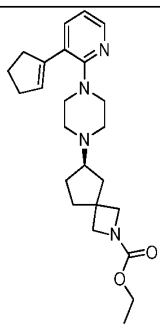
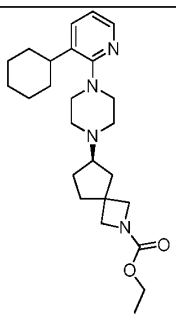
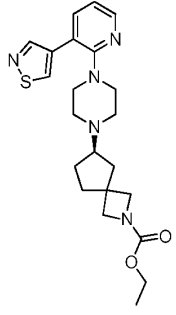
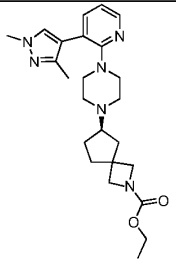
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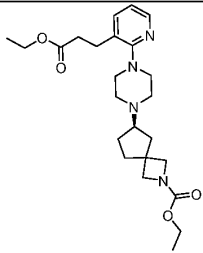
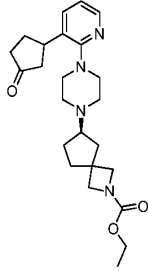
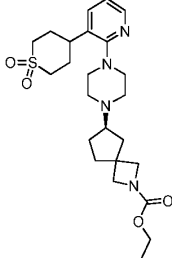
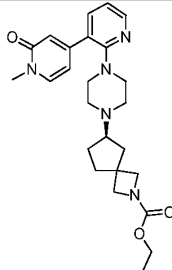
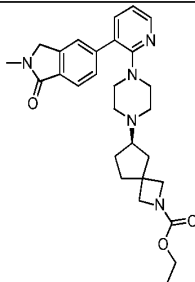
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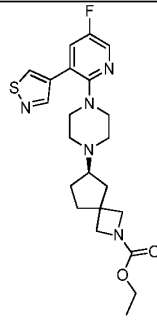
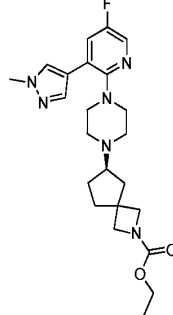
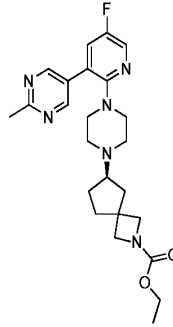
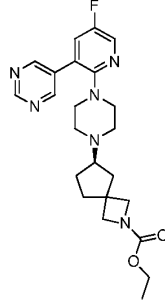
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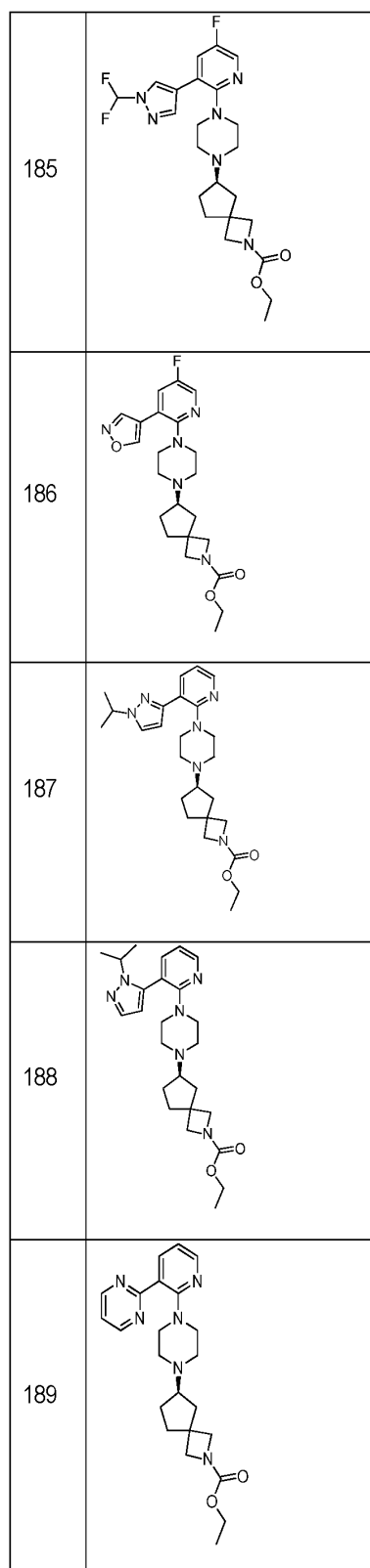
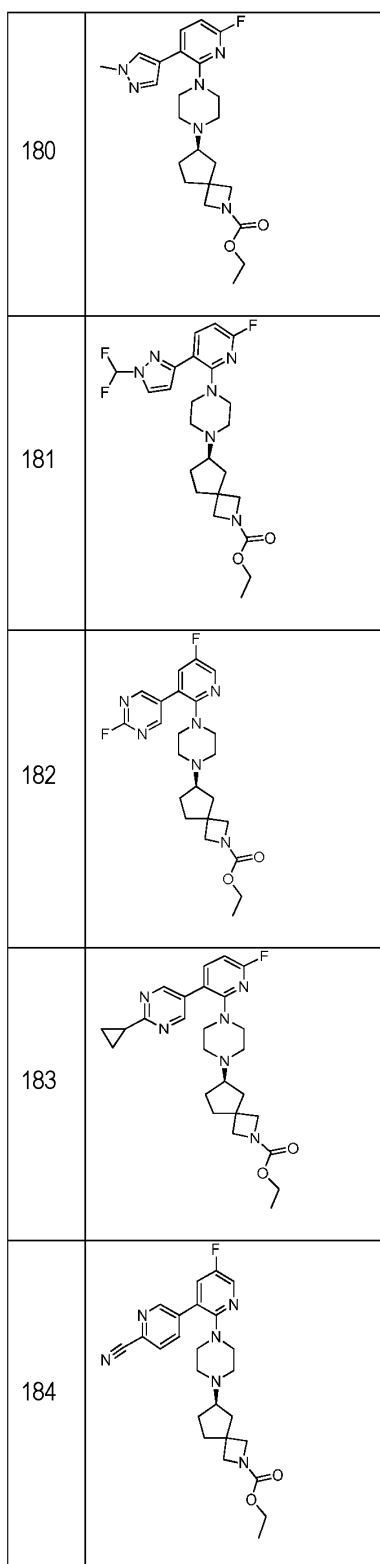
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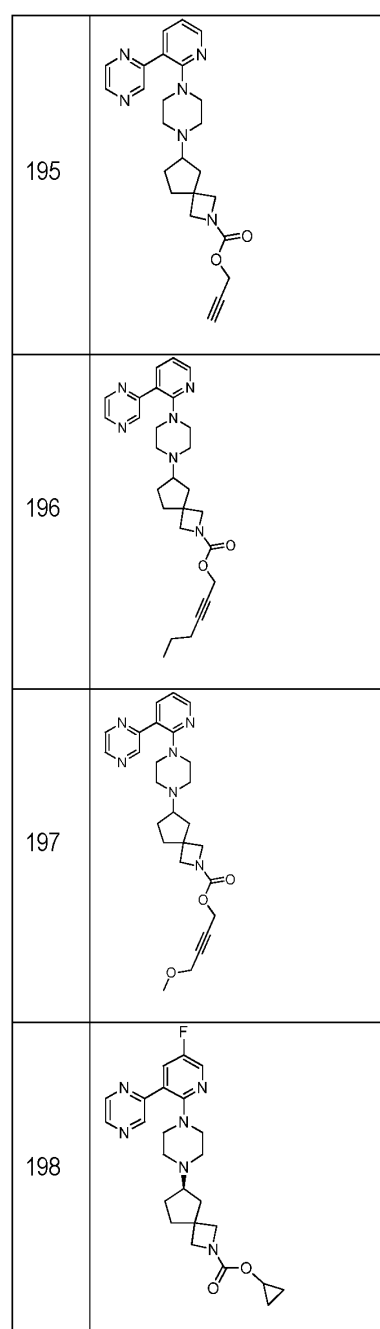
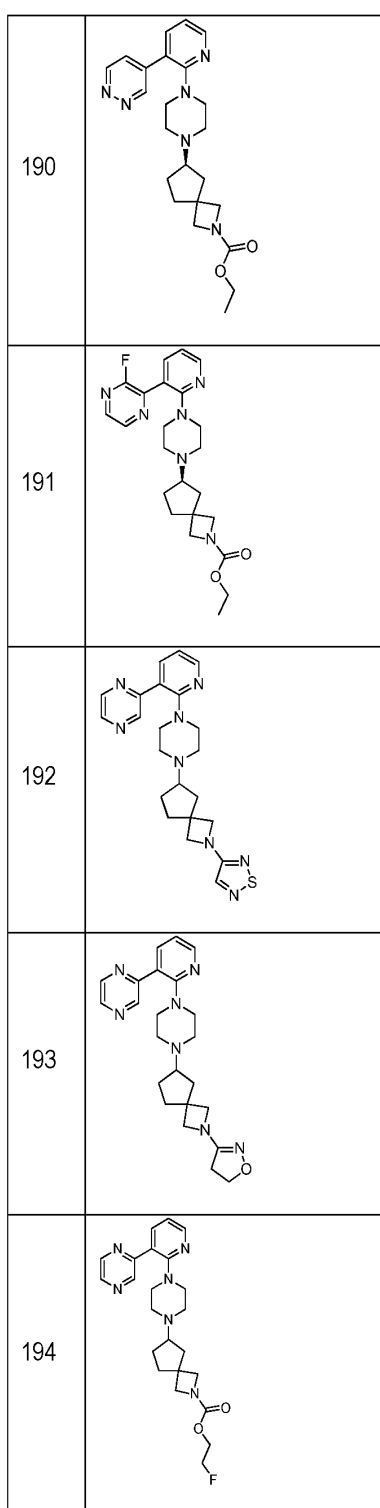
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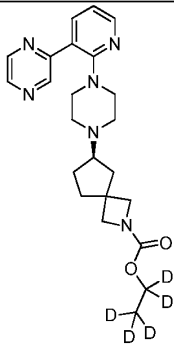
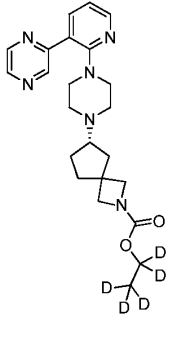
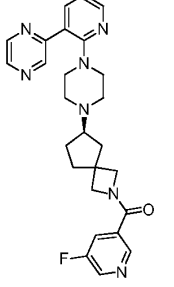
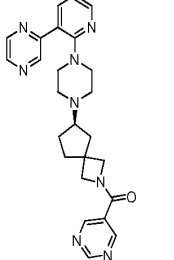
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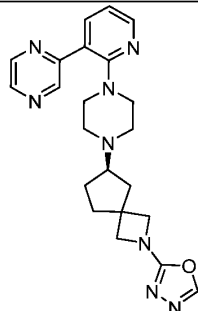
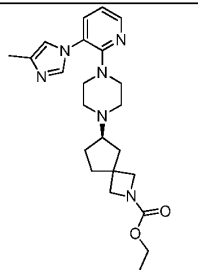
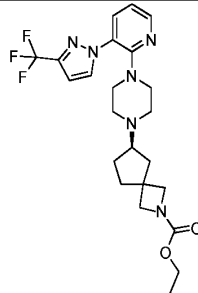
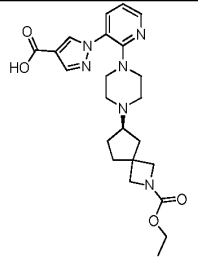
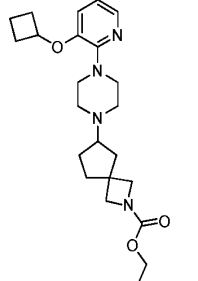
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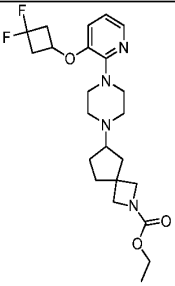
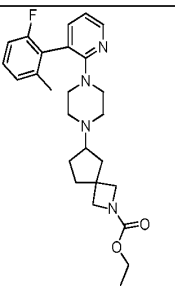
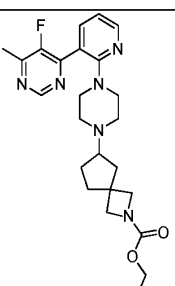
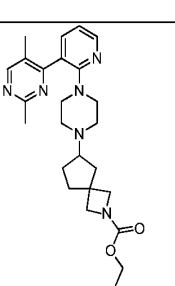
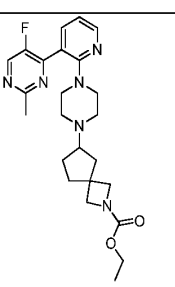
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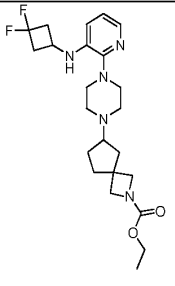
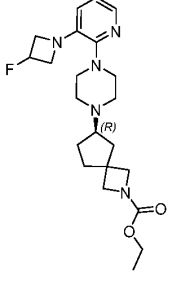
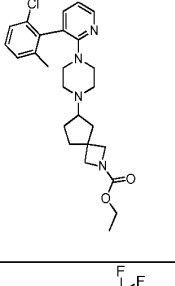
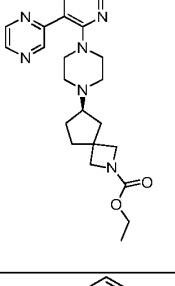
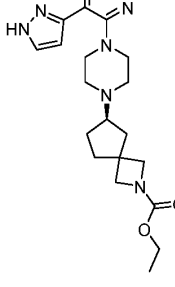


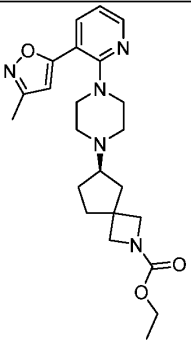
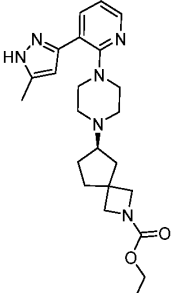
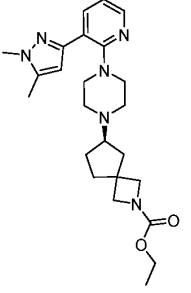
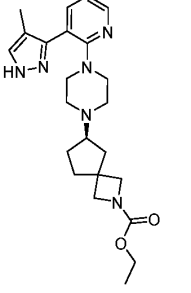


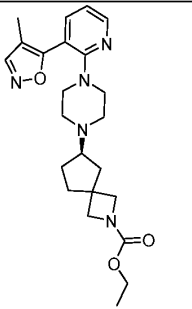
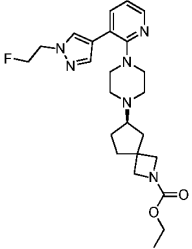
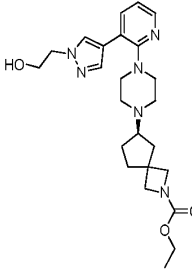
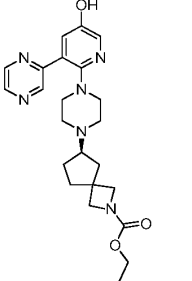
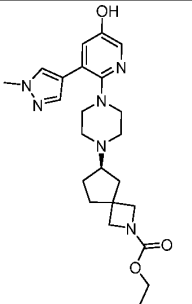
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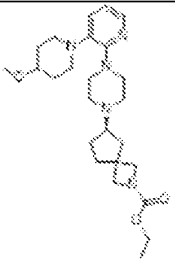
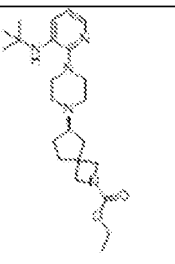
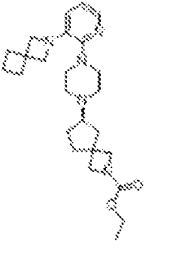
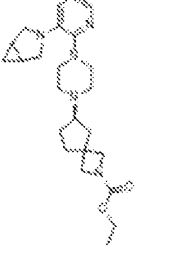
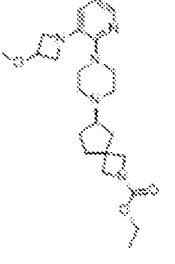
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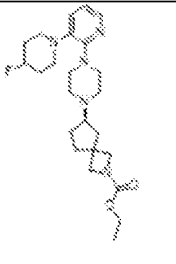
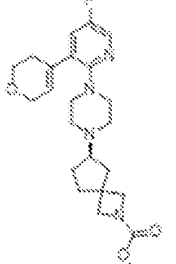
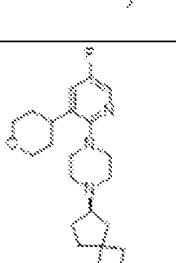
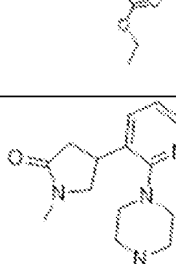
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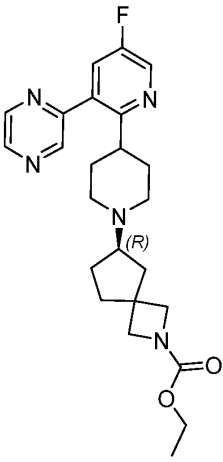
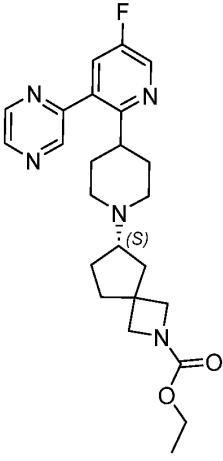
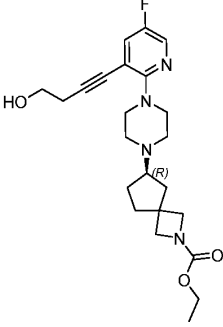
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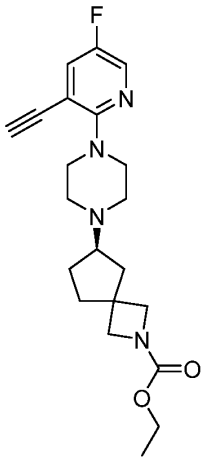
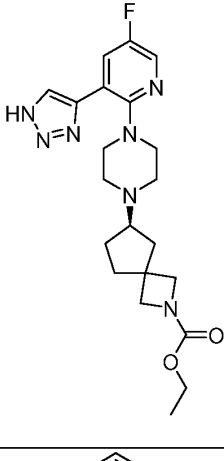
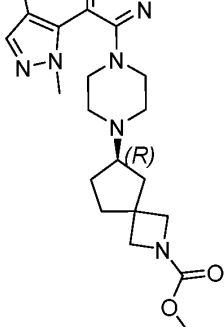
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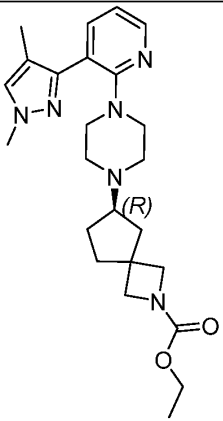
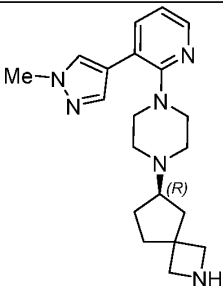
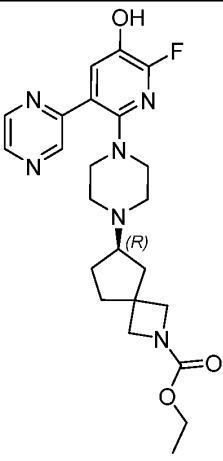
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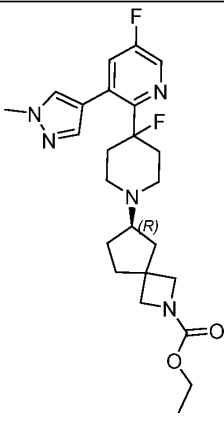
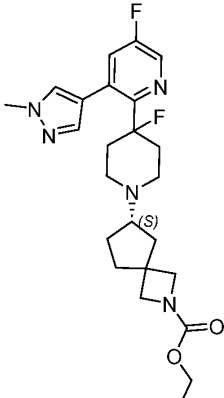
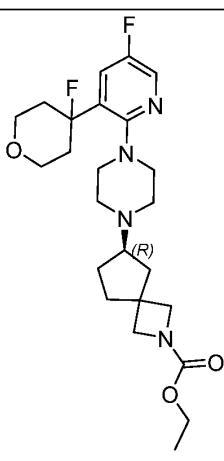
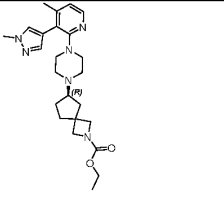
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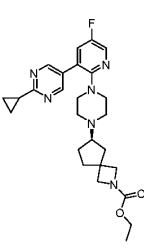
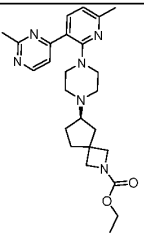
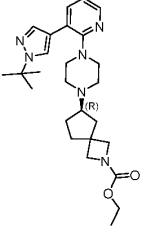
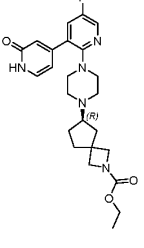
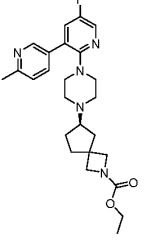
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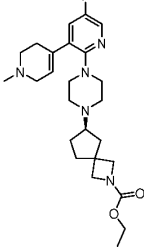
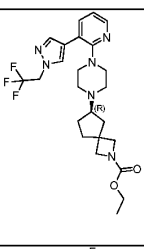
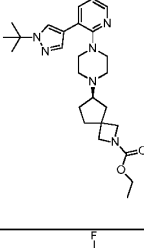
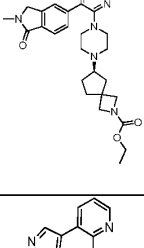
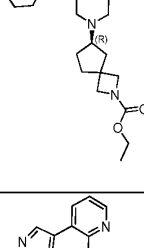
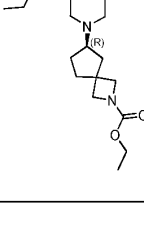
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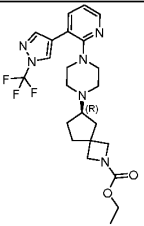
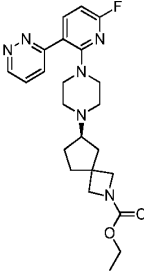
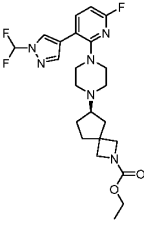
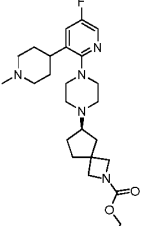
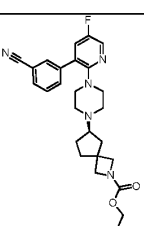
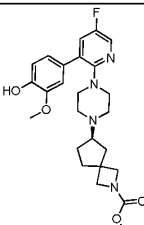
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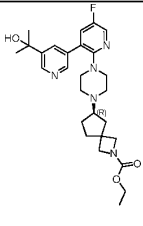
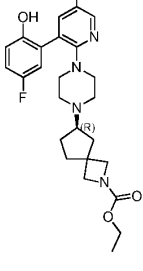
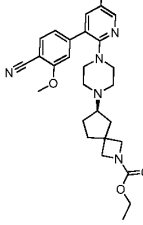
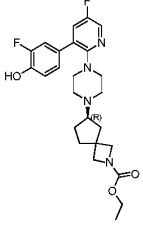
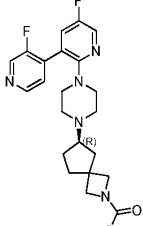
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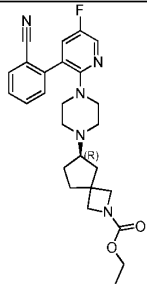
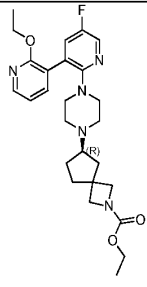
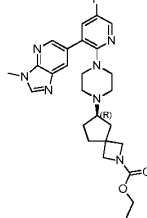
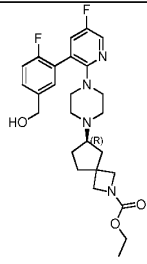
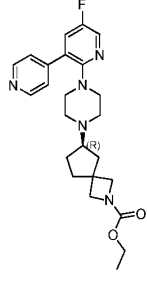
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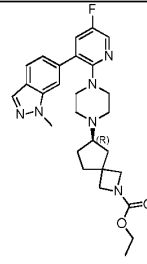
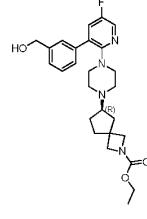
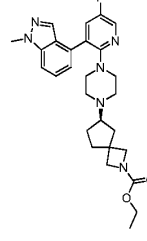
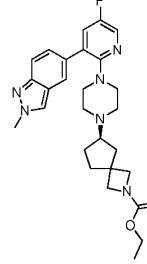
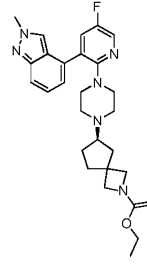
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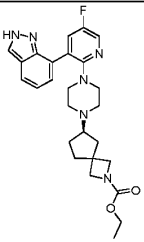
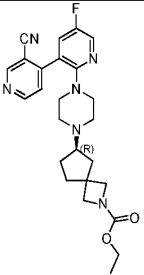
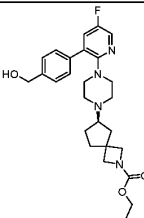
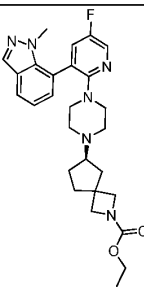
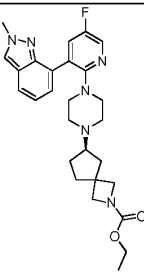
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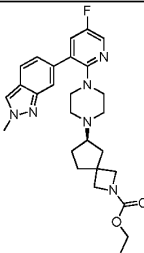
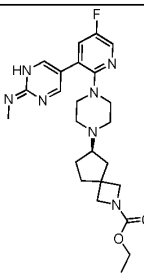
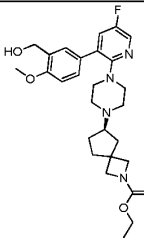
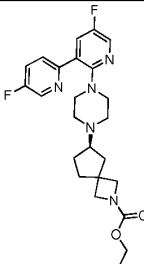
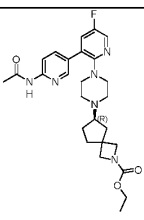
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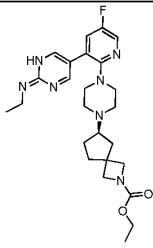
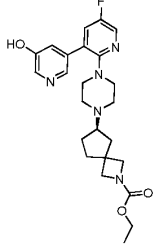
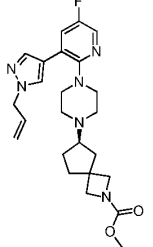
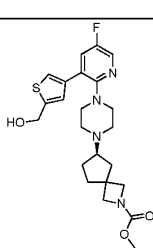
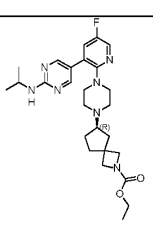
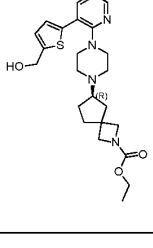
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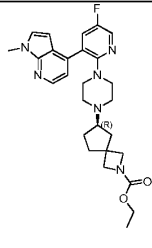
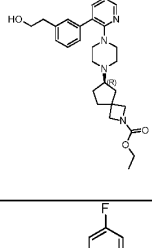
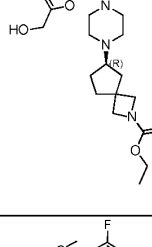
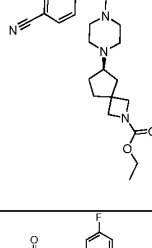
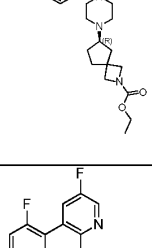
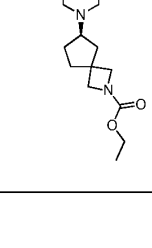
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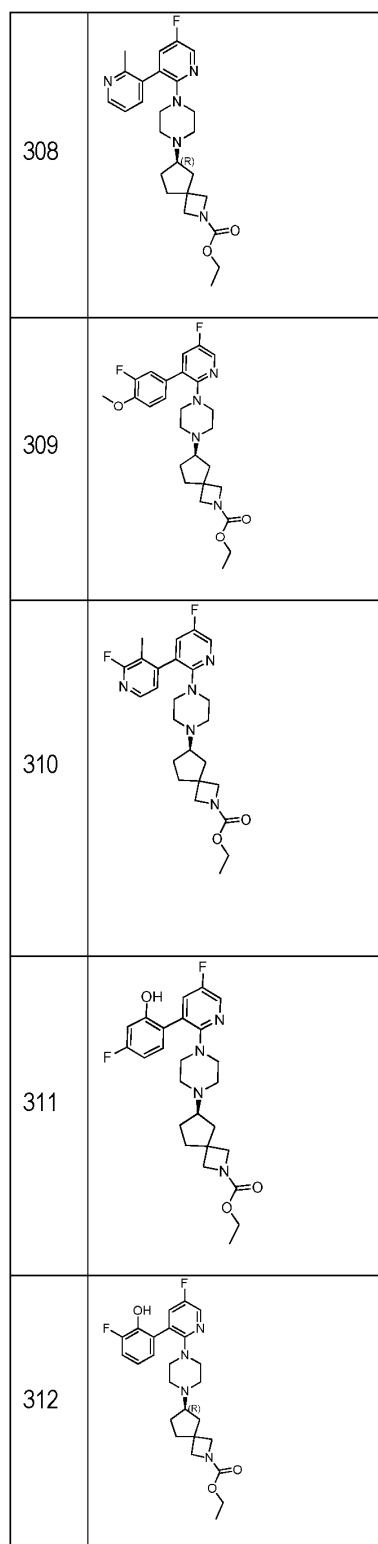
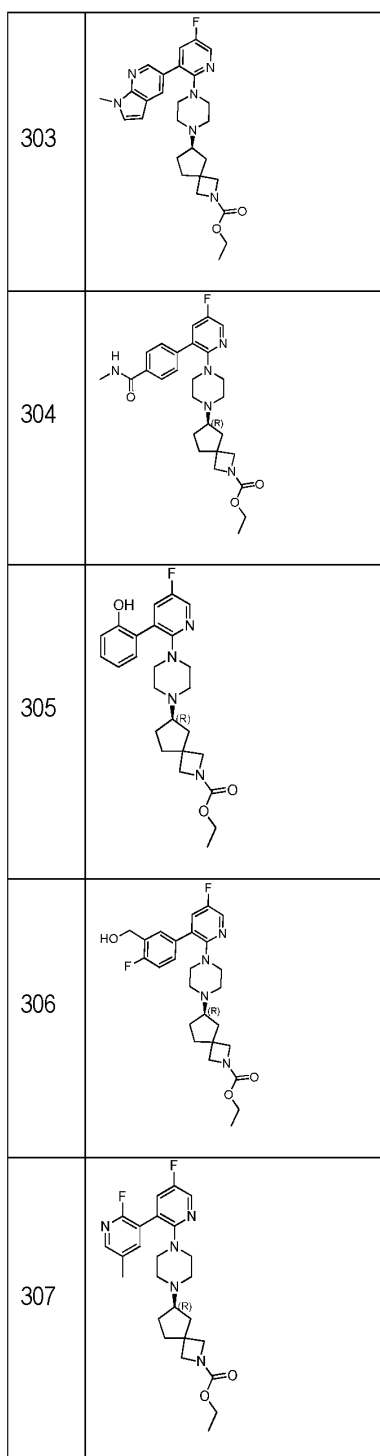
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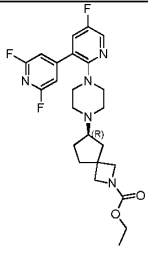
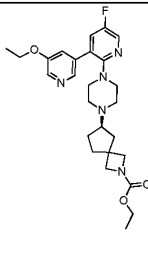
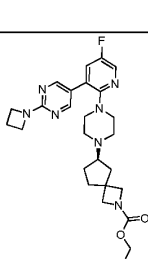
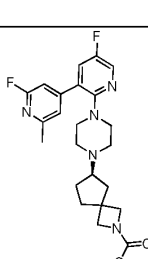
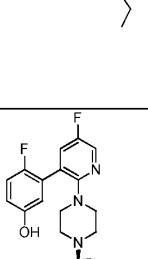
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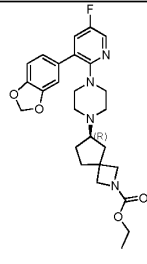
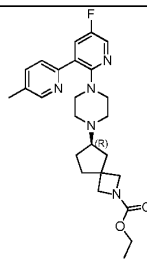
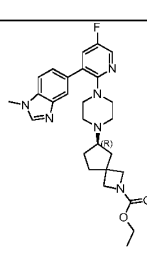
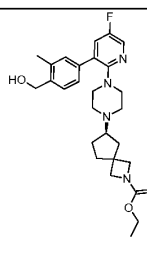
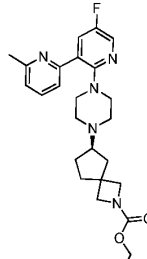
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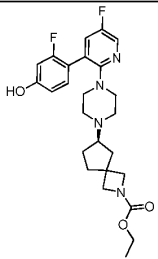
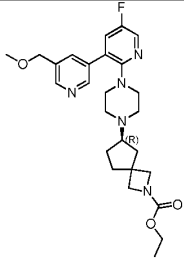
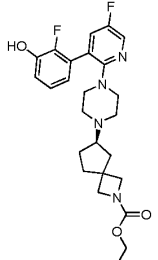
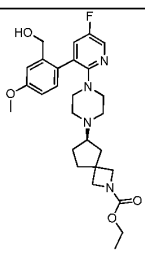
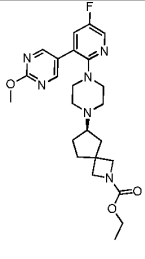
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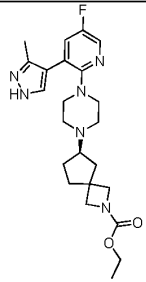
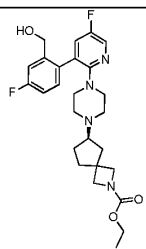
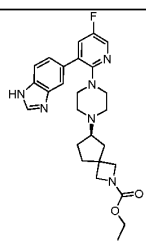
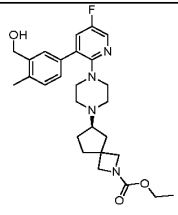
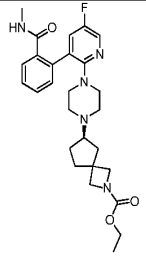
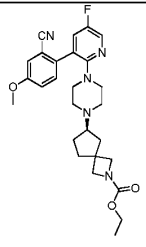
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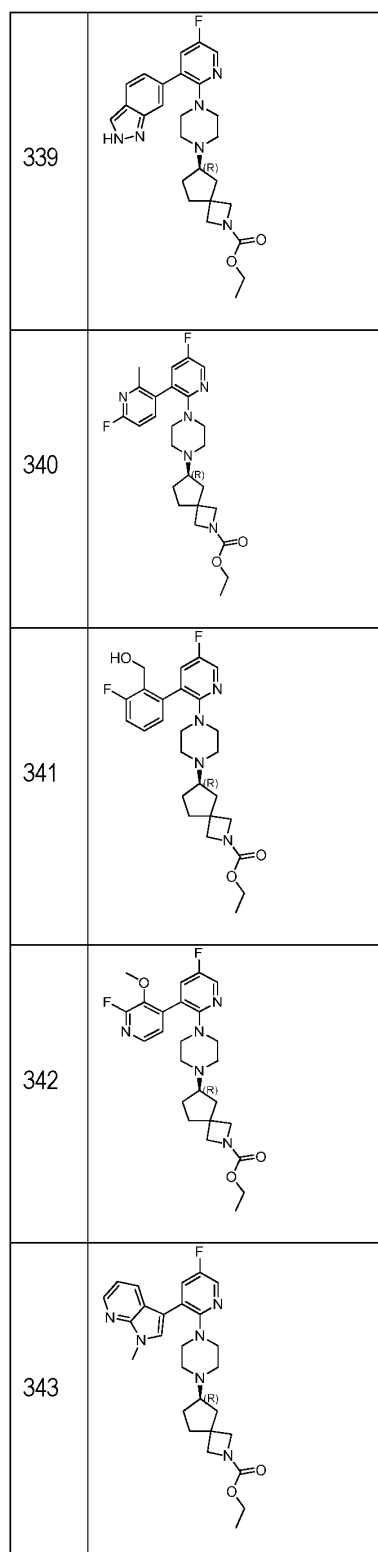
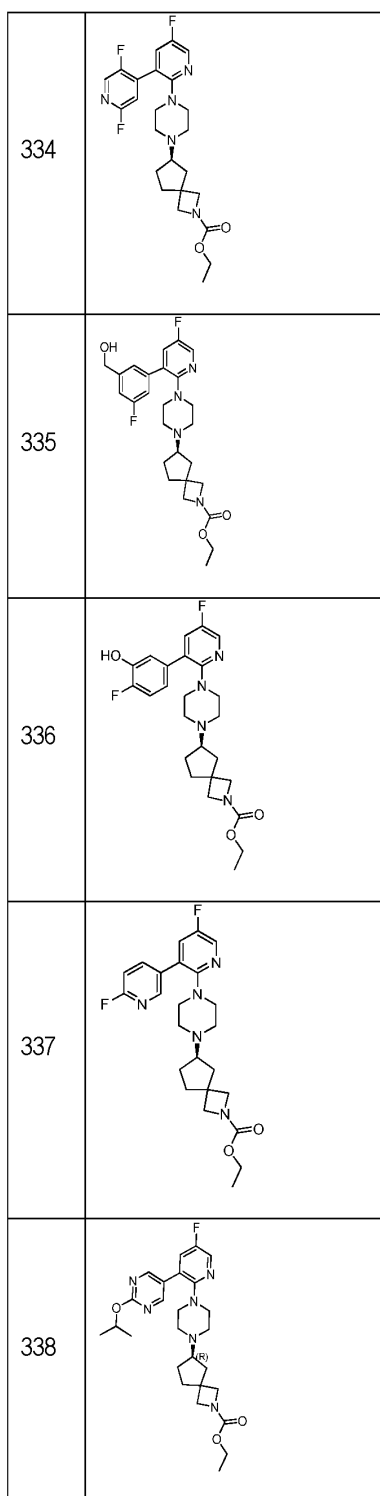


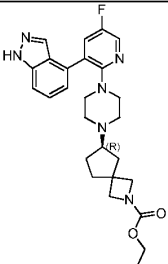
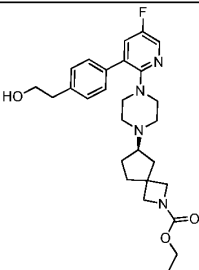
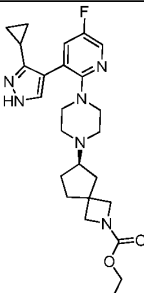
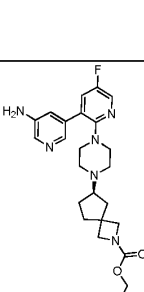
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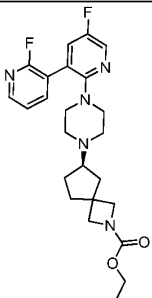
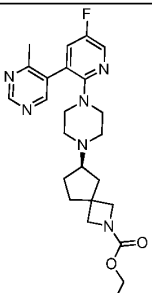
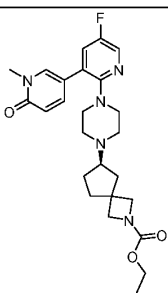
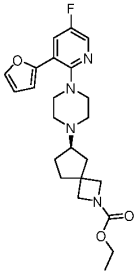
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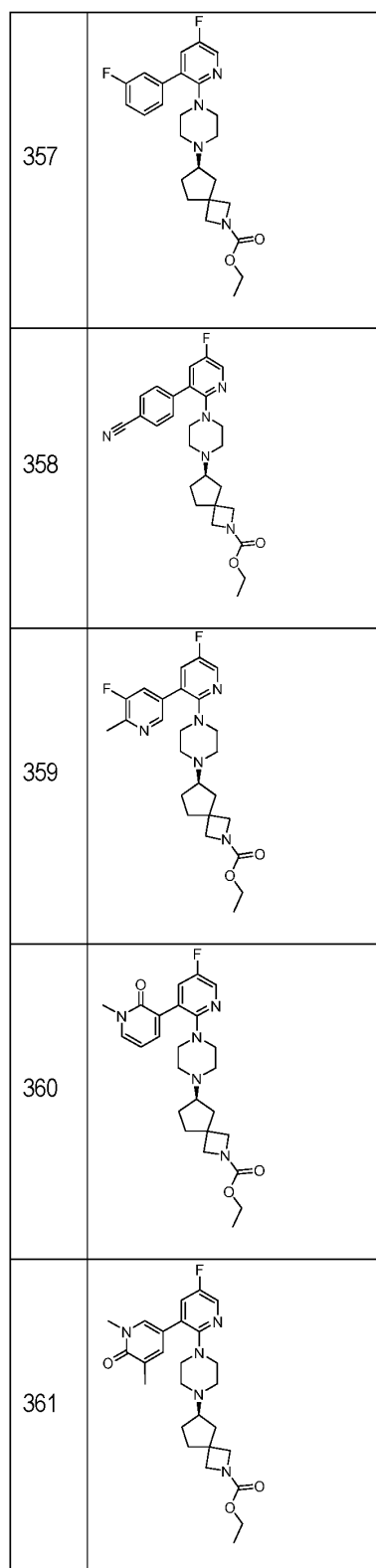
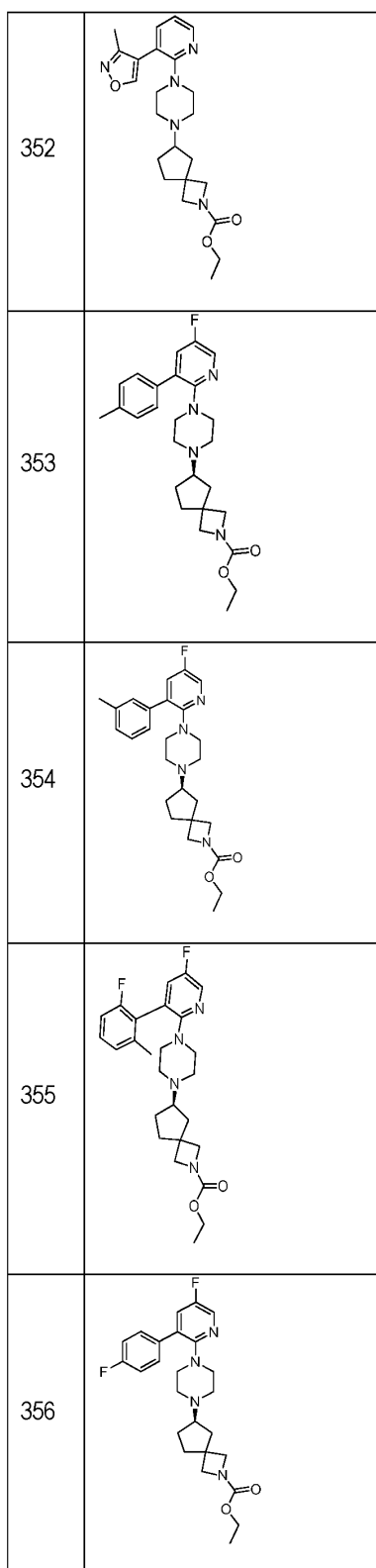
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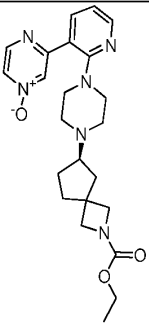
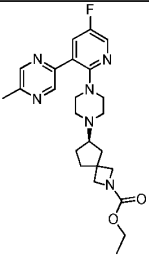
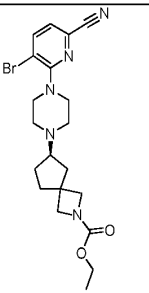
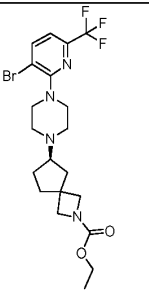
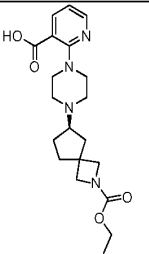
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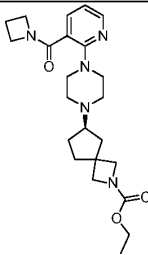
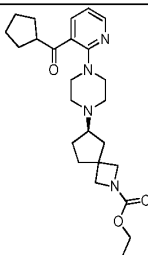
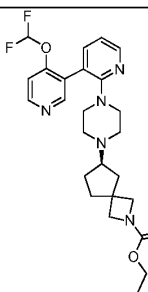
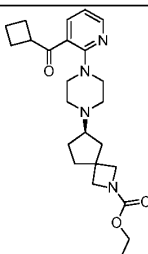
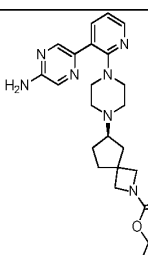
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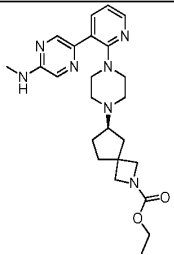
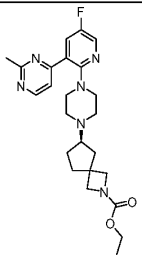
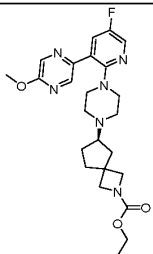
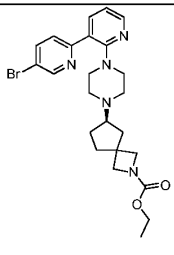
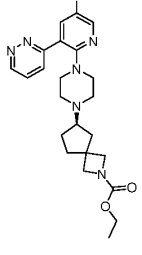


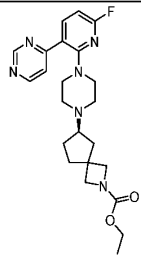
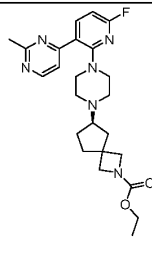
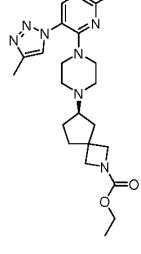
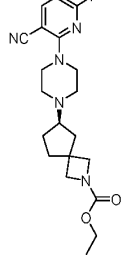
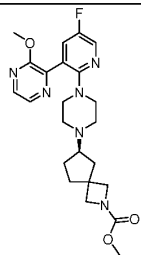
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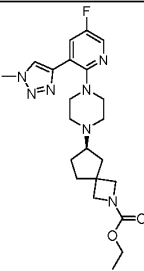
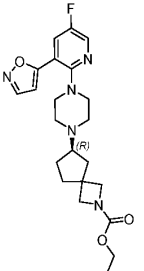
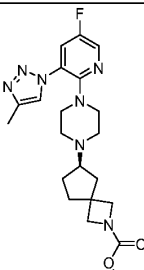
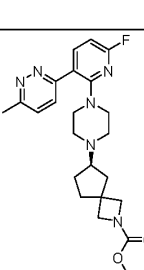
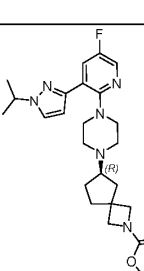
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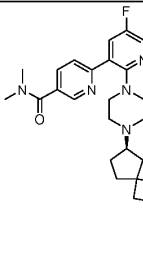
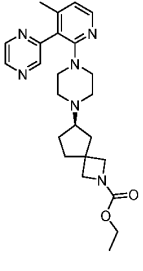
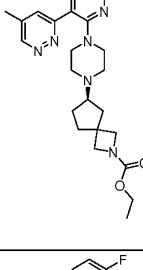
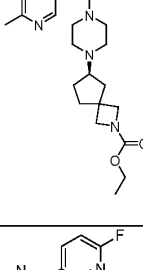
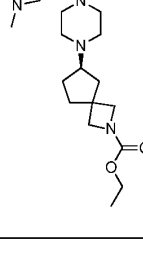
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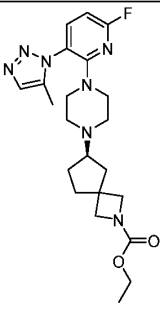
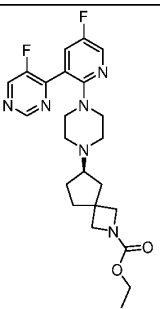
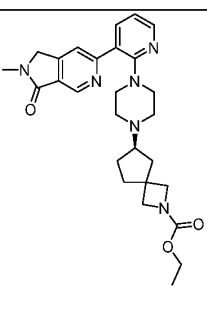
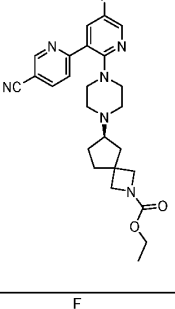
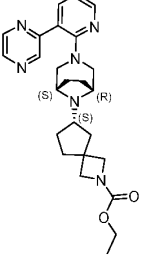
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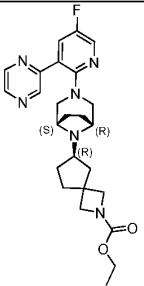
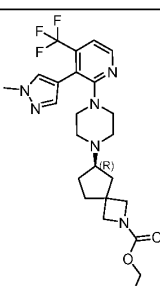
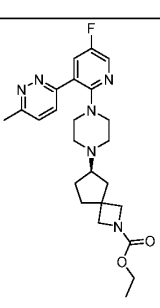
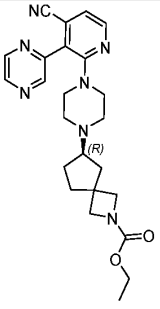
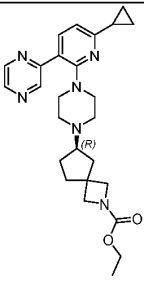
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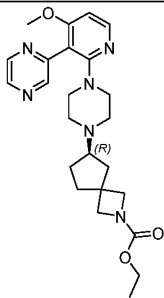
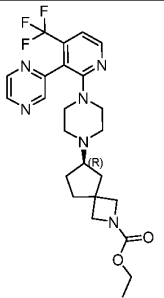
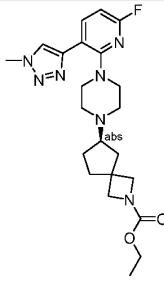
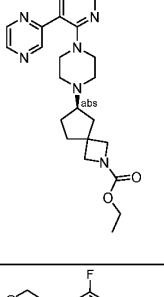
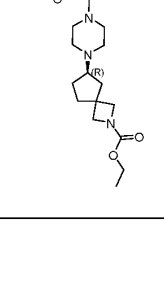
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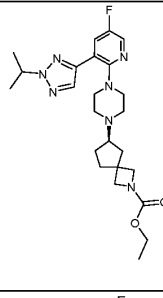
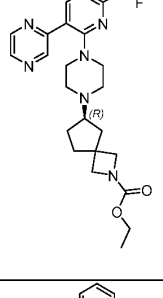
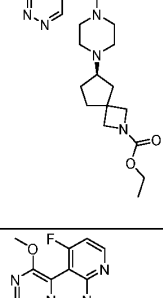
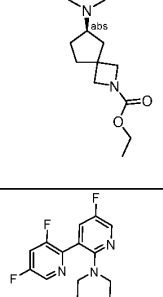
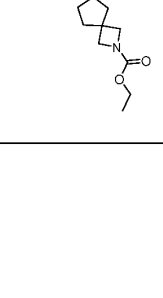
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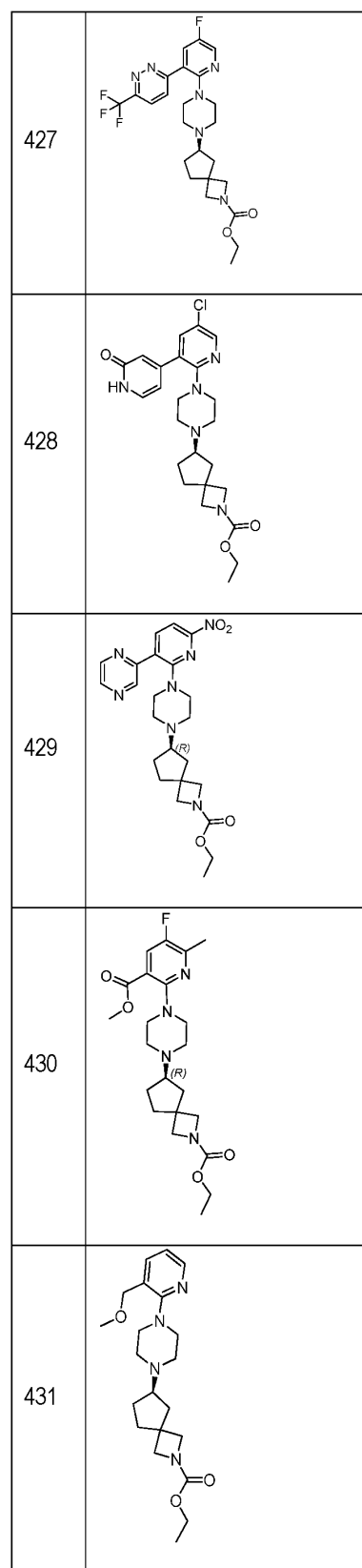
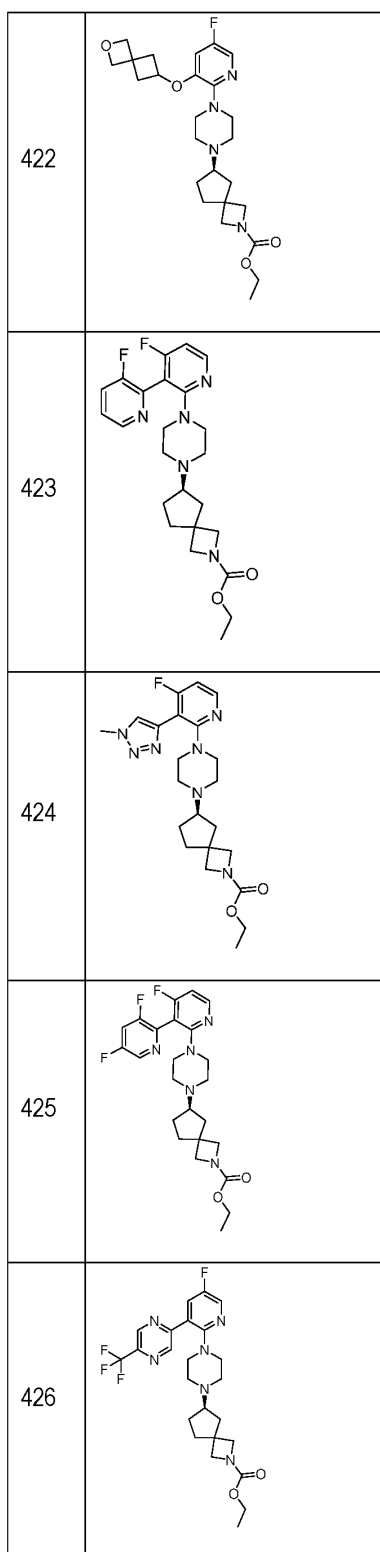
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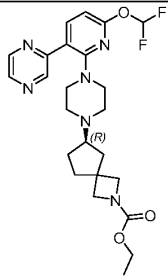
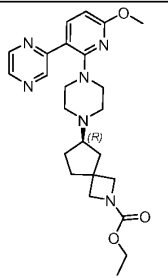
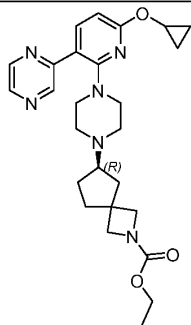
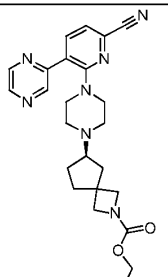
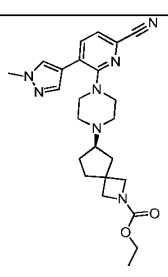
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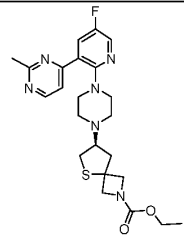
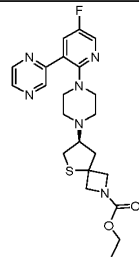
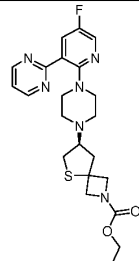
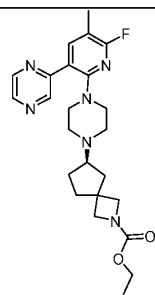
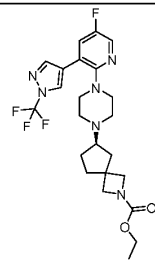
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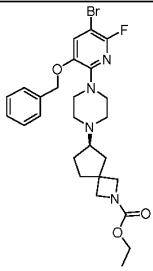
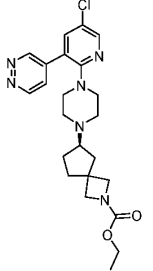
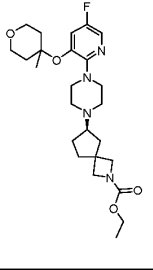
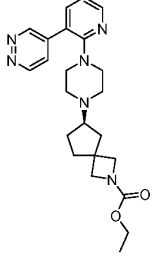
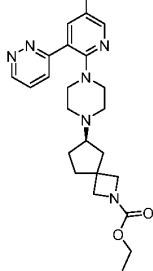
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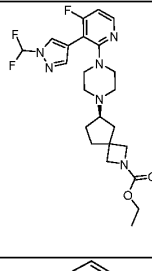
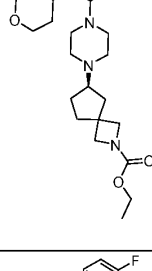
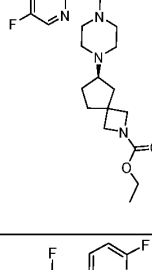
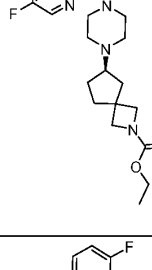
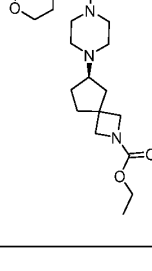
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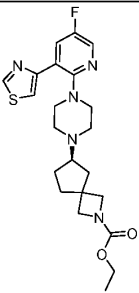
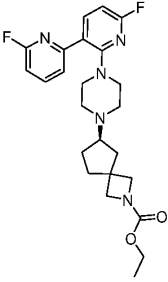
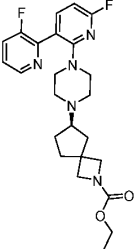
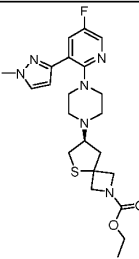
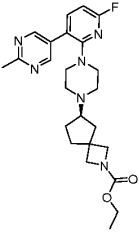


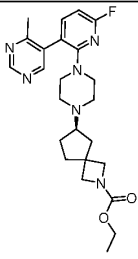
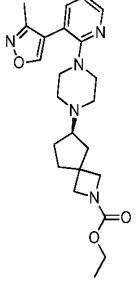
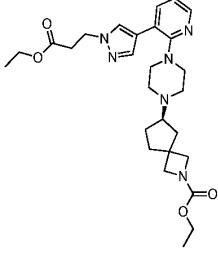
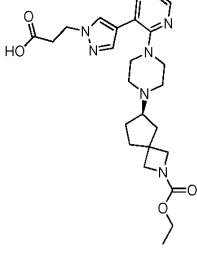
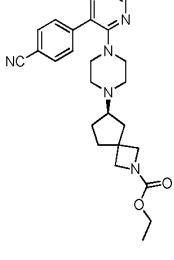
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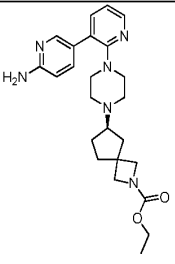
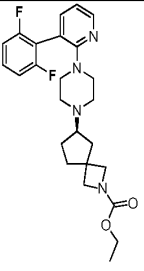
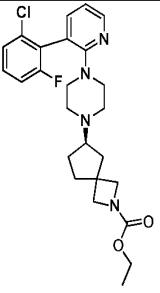
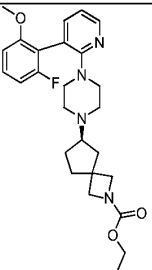
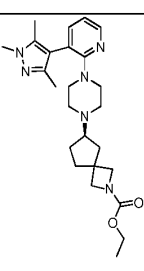
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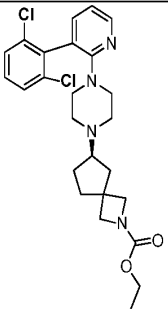
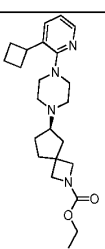
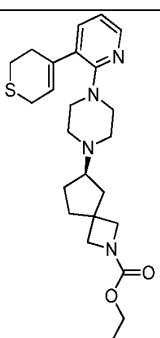
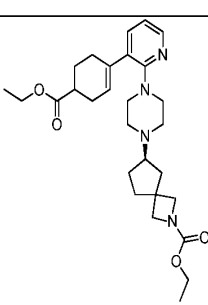
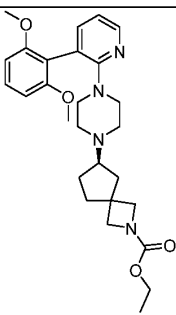
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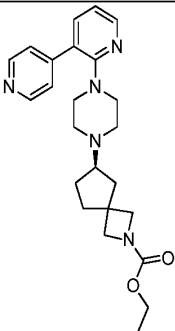
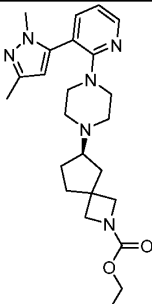
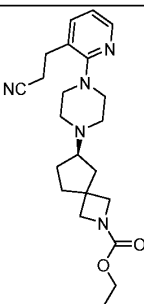
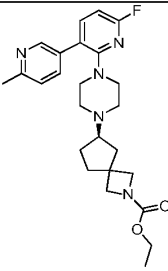
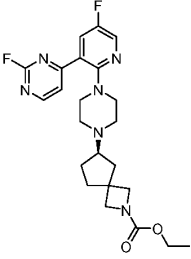
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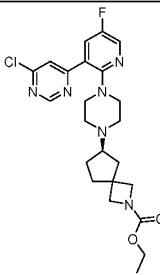
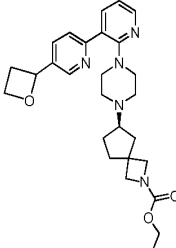
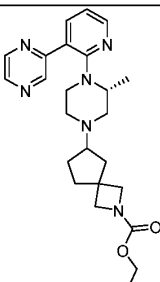
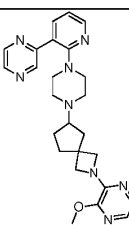
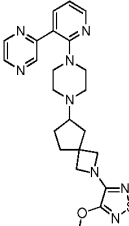
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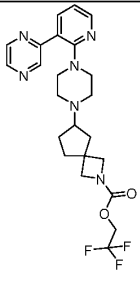
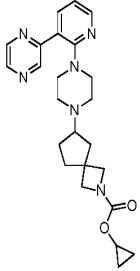
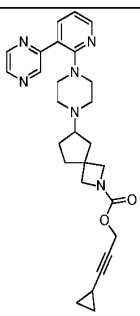
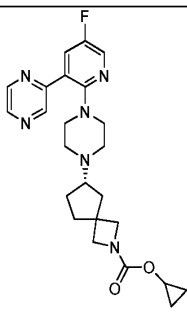
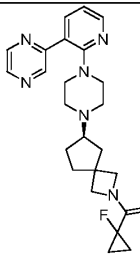
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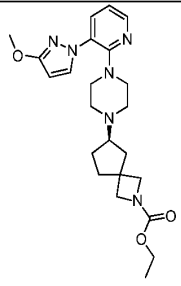
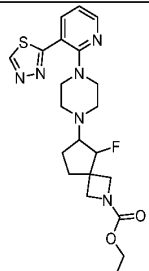
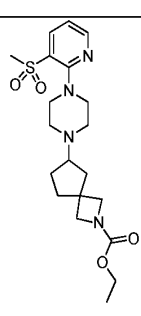
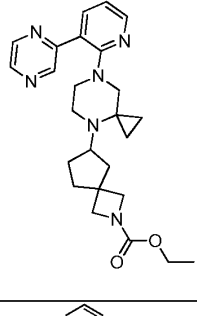
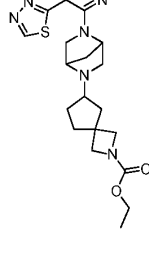
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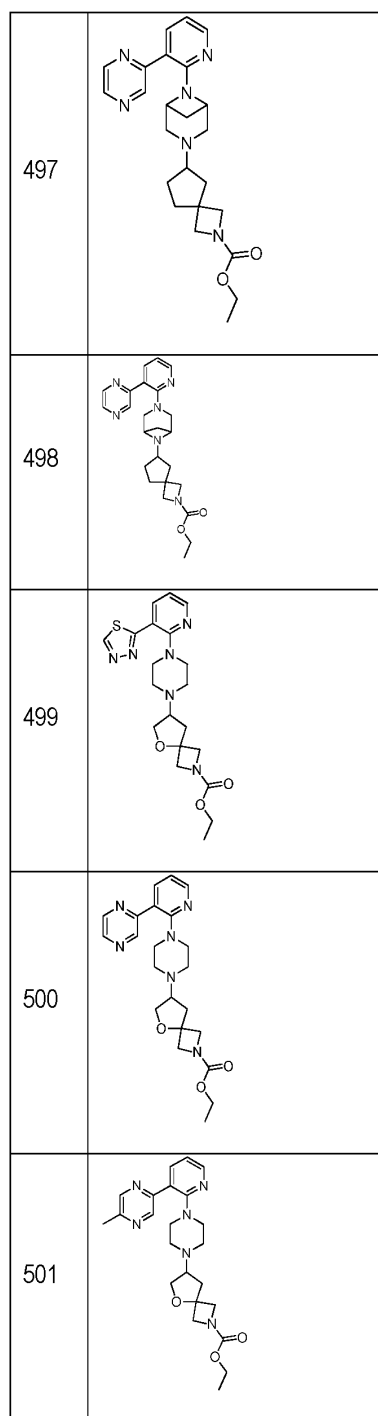
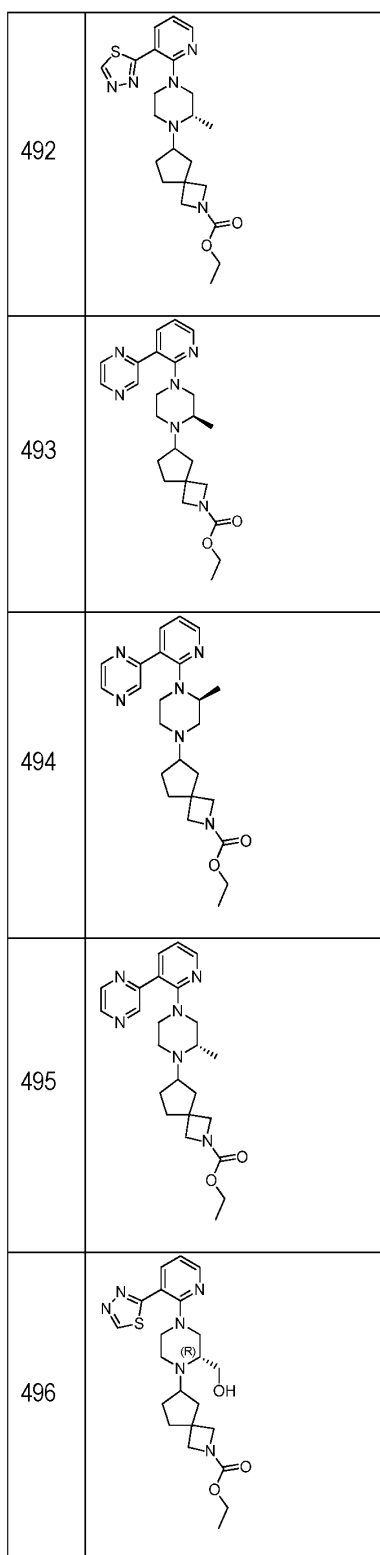
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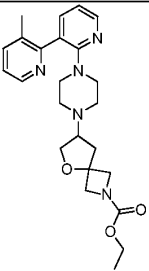
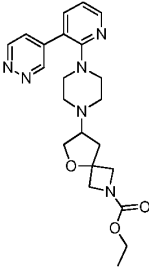
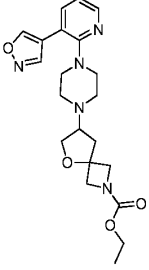
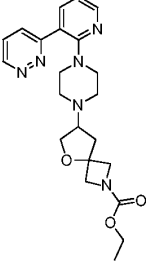
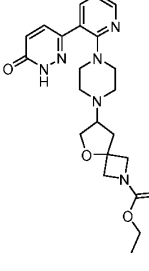
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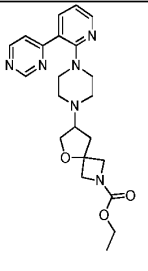
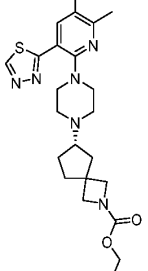
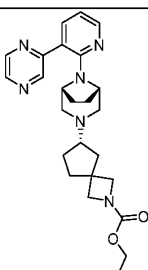
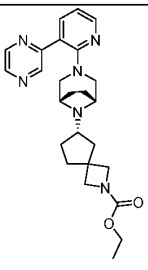
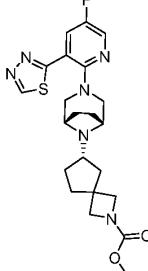
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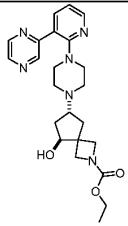
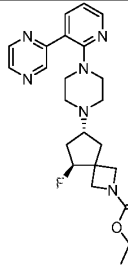
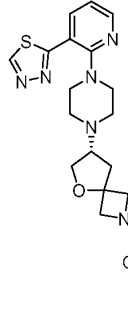
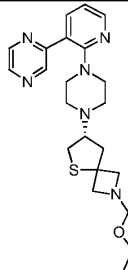
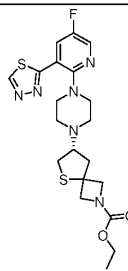
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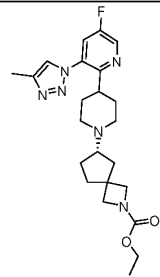
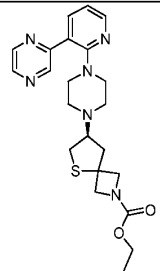
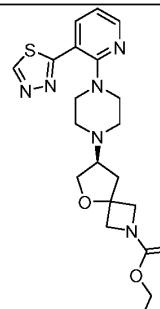
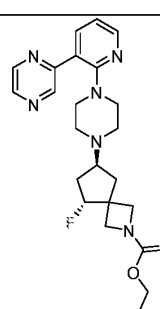
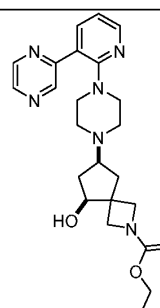
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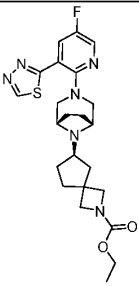
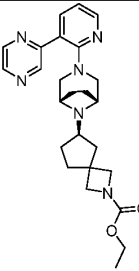
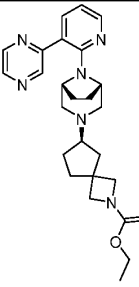
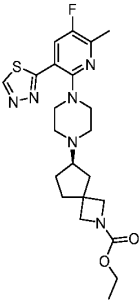
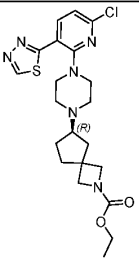


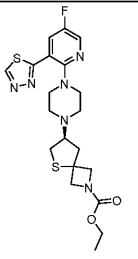
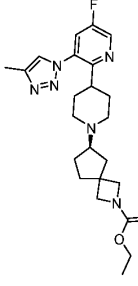
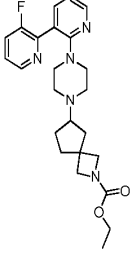
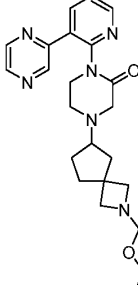
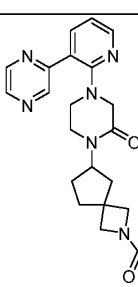
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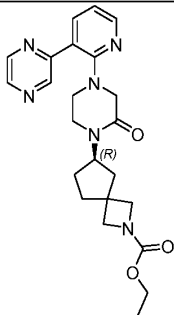
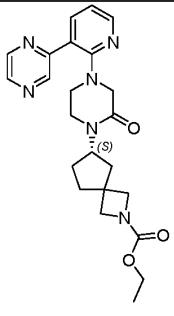
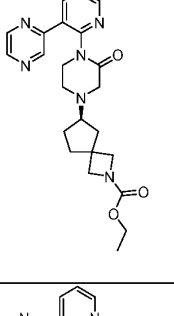
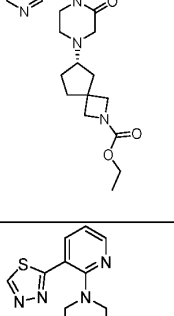
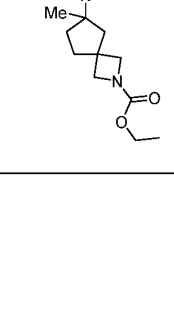
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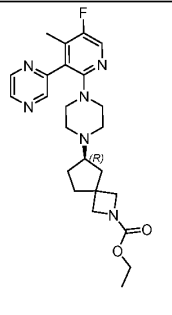
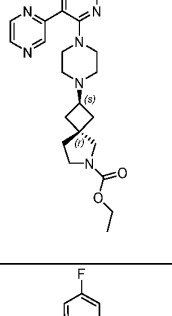
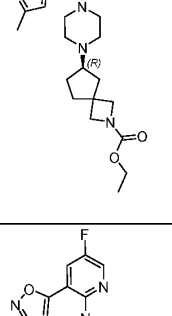
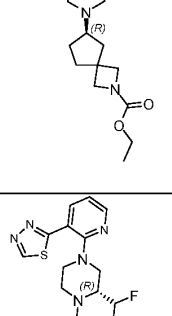
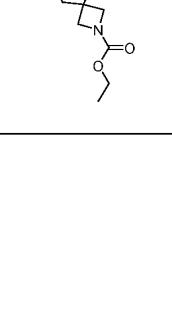
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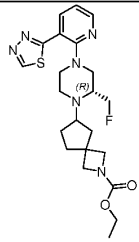
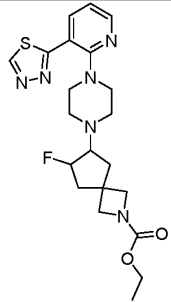
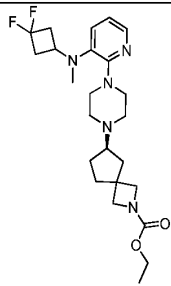
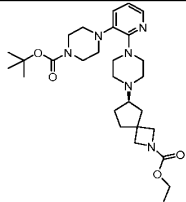
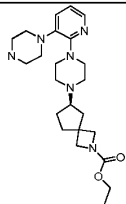
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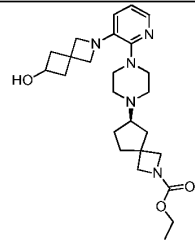
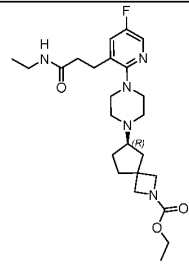
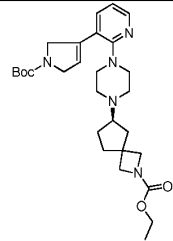
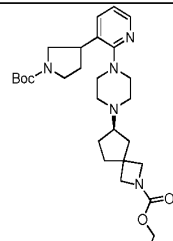
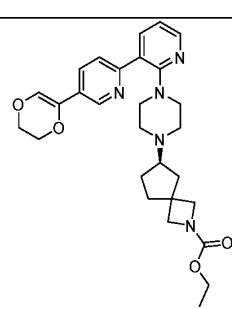
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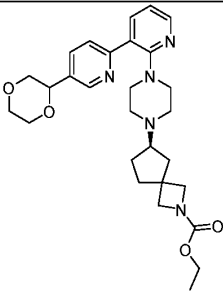
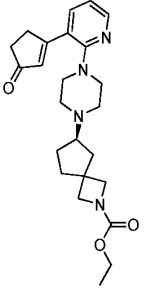
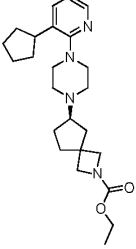
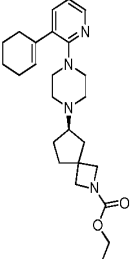
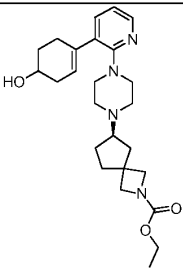
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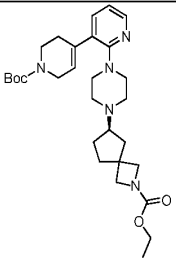
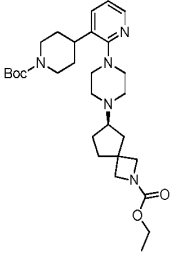
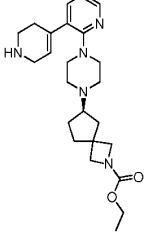
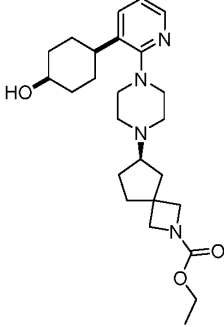
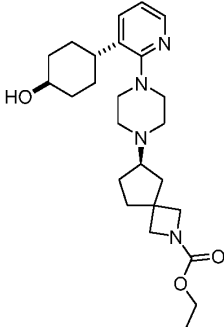
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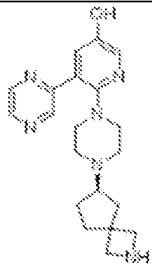
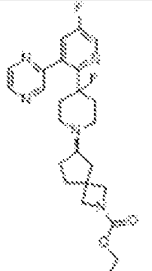
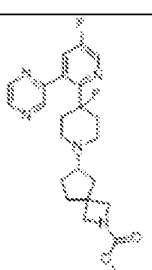
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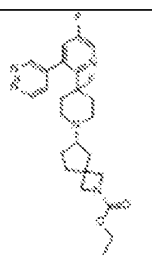
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[0039] The present disclosure also includes all pharmaceutically acceptable isotopically labeled compounds, which are identical to those recited herein, wherein one or more atoms are replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Examples of isotopes suitable for inclusion in the compounds of the present disclosure include, but are not limited to, isotopes of hydrogen, such as ^2H , ^3H ; carbon, such as ^{11}C , ^{13}C , and ^{14}C ; chlorine, such as ^{36}Cl ; fluorine, such as ^{18}F ; iodine, such as ^{123}I and ^{125}I ; nitrogen, such as ^{13}N and ^{15}N ; oxygen, such as ^{15}O , ^{17}O , and ^{18}O ; phosphorus, such as ^{32}P ; and sulfur, such as ^{35}S . Isotopically-labeled compounds may include combinations of two or more of the above, same or different, isotopes. Certain isotopically-labeled compounds of the present disclosure, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies (e.g., assays). The radioactive isotopes tritium, i.e., ^3H or "T", and carbon-14, i.e., ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e., ^2H , or "D", may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Substitution with positron-emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in positron emission tomography (PET) studies for examining substrate receptor occupancy. Isotopically labeled compounds of the present disclosure can generally be prepared by conventional

techniques known to those skilled in the art or by processes analogous to those described in the accompanying Schemes and/or in the Examples and Preparations using an appropriate isotopically labeled reagent in place of the non-labeled reagent previously employed. Pharmaceutically acceptable solvates in accordance with the disclosure include those wherein the solvent of crystallization may be isotopically substituted, e.g., D₂O, acetone-*d*₆, or DMSO-*d*₆.

[0040] The chemical structures having one or more stereocenters depicted with dashed and bold wedged bonds (i.e.,  and ) are meant to indicate absolute stereochemistry of the stereocenter(s) present in the chemical structure. Bonds symbolized by a simple line do not indicate a stereo-preference. Bonds symbolized by dashed or bold straight bonds (i.e.,  and ) are meant to indicate a relative stereochemistry of the stereocenter(s) present in the chemical structure. Unless otherwise indicated to the contrary, chemical structures that include one or more stereocenters which are illustrated herein without indicating absolute or relative stereochemistry, encompass all possible stereoisomeric forms of the compound (e.g., diastereomers, enantiomers) and mixtures thereof. Structures with a single bold or dashed wedged line, and at least one additional simple line, encompass a single enantiomeric series of all possible diastereomers. Similarly, the chemical structures having alkenyl groups are meant to encompass both cis and trans orientations, or when substituted, E- and Z-isomers of the chemical structure.

Pharmaceutically Acceptable Salts and Co-crystals

[0041] As used herein, the term "pharmaceutically acceptable salt" refers to salts of a compound which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue side effects, such as, toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[0042] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, which is incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. These salts can be prepared *in situ* during the final isolation and purification of the compounds.

[0043] As used herein, "Formula (I)", "Formula (Ia)", "Formula (Ib)", "Formula (Ic)", "Formula (Id)", and "Formula (Ie)", are also defined to include all forms of the compounds of the disclosure including, but not limited to, hydrates, solvates, isomers (including for example rotational stereoisomers), crystalline and non-crystalline forms, isomorphs, polymorphs, metabolites, prodrugs thereof. For example, the compounds disclosed herein, or pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on

humidity and drying conditions. In such cases, non-stoichiometry will be the norm. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present disclosure.

[0044] The compounds of the disclosure may exist as clathrates or other complexes (e.g., co-crystals). Included within the scope of the disclosure are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the compounds of the disclosure containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. Pharm. Sci., 64 (8), 1269-1288 by Halebian (August 1975). Co-crystals are typically defined as crystalline complexes of neutral molecular constituents that are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together; see O. Almarsson and M. J. Zaworotko, Chem. Commun. 2004, 17, 1889-1896. For a general review of multi-component complexes, see J. K. Halebian, J. Pharm. Sci. 1975, 64, 1269-1288.

[0045] In some cases, the compounds of the present disclosure may exist in and/or be isolated as atropisomers (e.g., one or more atropenantiomers). Those skilled in the art would recognize that atropisomerism may exist in a compound that has two or more aromatic rings (for example, two aromatic rings linked through a single bond). See e.g., Freedman, T. B. et al., Absolute Configuration Determination of Chiral Molecules in the Solution State Using Vibrational Circular Dichroism. Chirality 2003, 15, 743-758; and Bringmann, G. et al., Atroposelective Synthesis of Axially Chiral Biaryl Compounds. Angew. Chem., Int. Ed. 2005, 44, 5384-5427.

[0046] When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

[0047] The compounds of the present disclosure may also exist as an N-oxide thereof, or a pharmaceutically acceptable salt of the compound or N-oxide.

[0048] As it is known to the person skilled in the art, amine compounds (i.e., those comprising one or more nitrogen atoms), for example tertiary amines, can form N-oxides (also known as amine oxides or amine N-oxides). Generally, an N-oxide has the formula of $R_3N^+-O^-$ wherein the parent amine R_3N can be for example, a tertiary amine (for example, each R is independently alkyl, arylalkyl, aryl, heteroaryl, or the like), a heterocyclic or heteroaromatic amine (for example, R_3N together forms 1-alkylpiperidine, 1-alkylpyrrolidine, 1-benzylpyrrolidine, or pyridine). For instance, an imine nitrogen, especially heterocyclic or heteroaromatic imine nitrogen, or pyridine-type nitrogen (=N-) atom, such as a nitrogen atom in pyridine, pyridazine, or pyrazine, can be N-oxidized to form the N-oxide comprising the $\equiv N^+-O^-$ group. Thus, a compound according to the present disclosure comprising one or more nitrogen atoms (e.g., an imine nitrogen atom) may be capable of forming an N-oxide thereof (e.g.,

mono-N-oxides, bis-N-oxides or multi-N-oxides, or mixtures thereof depending on the number of nitrogen atoms suitable to form stable N-oxides).

[0049] As used herein, the term "N-oxide(s)" refer to all possible, and in particular all stable, N-oxide forms of the amine compounds (e.g., compounds comprising one or more imine nitrogen atoms) described herein, such as mono-N-oxides (including different isomers when more than one nitrogen atom of an amine compound can form a mono-N-oxide) or multi-N-oxides (e.g., bis-N-oxides), or mixtures thereof in any ratio.

[0050] As noted above, the compounds of the disclosure (or N-oxides thereof) may exist in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

[0051] Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of the present disclosure with an acid whose anion, or a base whose cation, is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the methods of the present disclosure because of their greater aqueous solubility relative to the parent compound.

[0052] Suitable pharmaceutically acceptable acid addition salts of the compounds of the present disclosure when possible include those derived from inorganic acids, such as, but not limited to, hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, meta-phosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include but are not limited to aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

[0053] Specific examples of suitable organic acids include but are not limited to acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylamino-sulfonate, algenic acid, β -hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalene-sulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, and undecanoate.

[0054] Furthermore, where the compounds of the disclosure carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In another embodiment, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

[0055] Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanol- amine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen- containing groups may be quaternized with agents such as lower alkyl (C1-Cs) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others.

[0056] In some cases, hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts, or sequifumarate.

[0057] For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of the disclosure are known to one of skill in the art.

[0058] Other acids and bases, although not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid or base addition salts.

[0059] It should be understood that a compound disclosed herein can be present as a mixture/combination of different pharmaceutically acceptable salts. Also contemplated are mixtures/combinations of compounds in free form and pharmaceutically acceptable salts.

[0060] Compounds of the disclosure may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long-range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from apparent solid to a material with liquid properties occurs, which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

[0061] The compounds of the disclosure may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as -COO'Na*, -COOK*, or -SO₃s'Na*) or non-ionic (such as -N"N*(CH₃)₃) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

[0062] The disclosure also relates to prodrugs of the compounds of the present disclosure. Thus certain derivatives of compounds of the disclosure which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of Formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs". Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

[0063] Prodrugs in accordance with the disclosure can, for example, be produced by replacing appropriate functionalities present in the compounds of the disclosure with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985), or in Prodrugs: Challenges and Reward, 2007 edition, edited by Valentino Stella, Ronald Borchardt, Michael Hageman, Reza Oliyai, Hans Maag, Jefferson Tilley, pages 134-175 (Springer, 2007).

[0064] Moreover, certain compounds of the disclosure may themselves act as prodrugs of other compounds of the disclosure. This disclosure also encompasses compounds of the disclosure containing protective groups. One skilled in the art will also appreciate that compounds of the disclosure can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry", edited by J. W. F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T. W. Greene and P. G. M. Wuts, Wiley- Interscience (1999).

[0065] Also included within the scope of the disclosure are metabolites of compounds of the disclosure, that is, compounds formed in vivo upon administration of the drug.

Pharmaceutical Formulations

[0066] Also provided herein are pharmaceutical formulations that include an effective amount of compounds of the disclosure and one or more pharmaceutically acceptable excipients. As used herein, the term "formulation" is used interchangeable with "composition."

[0067] An "effective amount" includes a "therapeutically effective amount" and a "prophylactically effective amount." The term "therapeutically effective amount" refers to an amount effective in treating and/or ameliorating a disease or condition in a subject. The term "prophylactically effective amount" refers to an amount effective in preventing and/or substantially lessening the chances of a disease or condition in a subject. As used herein, the terms "patient" and "subject" may be used interchangeably and mean animals, such as dogs, cats, cows, horses, and sheep (i.e., non-human animals) and humans. Particular patients or subjects are mammals (e.g., humans). The terms "patient" and "subject" include males and females.

[0068] As used herein, the term "excipient" means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices.

[0069] The compounds of the disclosure can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds can be administered all at once, as for example, by a bolus injection, multiple times, e.g., by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compound can be varied over time.

[0070] The compounds disclosed herein and other pharmaceutically active compounds, if desired, can be administered to a subject or patient by any suitable route, e.g., orally, topically, rectally, parenterally, (for example, subcutaneous injections, intravenous, intramuscular, intrasternal, and intrathecal injection or infusion techniques), or as a buccal, inhalation, or nasal spray. The administration can be to provide a systemic effect (e.g., eneteral or parenteral). All methods that can be used by those skilled in the art to administer a pharmaceutically active agent are contemplated. In some cases, the disclosed formulations can be administered orally or topically.

[0071] Suitable oral compositions or formulations in accordance with the disclosure include without limitation tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, syrups or elixirs. Compositions or formulations suitable for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions.

[0072] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0073] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. The pharmaceutical composition may provide immediate or modified or extended release of the compound(s), individually or in total. Examples of pharmaceutical compositions includes, but is not limited to immediate release dosage forms, modified release dosage forms, and extended-release dosage forms.

[0074] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0075] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0076] The pharmaceutical compositions and formulations described herein may also be administered topically or transdermally, especially when the target of treatment includes areas or organs readily accessible by

topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract, e.g., can be effected in a rectal suppository formulation or in a suitable enema formulation. Dosage forms for topical or transdermal administration of a compound described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, suppositories, or patches.

[0077] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment, cream, lotion, or gel, containing the active component suspended or dissolved in one or more carriers, and any needed preservatives or buffers as may be required. Carriers for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0078] Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0079] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0080] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0081] In order to prolong the effect of a compound described herein, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline

form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Depot injection formulations are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0082] Compositions for rectal or vaginal administration are specifically suppositories which can be prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0083] Sterile injectable forms of the compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0084] The pharmaceutical compositions may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0085] The compounds for use in the methods of the disclosure can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be

for a single daily dose or one of multiple daily doses (e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose.

[0086] For oral administration, the compositions may be provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion.

Methods of Treatment

[0087] The compounds disclosed herein can act on the M4 receptor. The muscarinic acetylcholine receptor M4 (also known as muscarinic 4 or CHRM4) is a protein in humans that is encoded for the CHRM4 gene. M4 receptors are predominantly expressed in the brain. Key regions of the brain where M4 receptor expression occurs are the striatum, cortex, and hippocampus with the highest expression occurring in the striatum (approx. 46%) where M4 is the major muscarinic subtype. M4 is sporadically expressed in the periphery (e.g., testis, skin and colon).

[0088] M4 receptors are coupled to G_{q/i} proteins and function as inhibitory autoreceptors in the striatum and midbrain (Zhang et. al; "Multiple Muscarinic Acetylcholine Receptor Subtypes Modulate Striatal Dopamine Release, as Studied with M1–M5 Muscarinic Receptor Knock-Out Mice"; Journal of Neuroscience 1 August 2002, 22 (15) 6347-6352; Tzavara. et. al.; "M₄ muscarinic receptors regulate the dynamics of cholinergic and dopaminergic neurotransmission: relevance to the pathophysiology and treatment of related central nervous system pathologies"; The FASEB Journal, 2004; 18: 1410-1412), and as postsynaptic modulatory receptors in the striatum, neocortex and hippocampus (Levey et. al; Identification and localization of muscarinic acetylcholine receptor proteins in brain with subtype-specific antibodies; Journal of Neuroscience 1 October 1991, 11 (10) 3218-3226; Gil, et al; "Muscarinic receptor subtypes in human iris-ciliary body measured by immunoprecipitation." Investigative ophthalmology & visual science 38.7 (1997): 1434-1442). M4 receptors are also found presynaptically on glutamatergic synapses from cortex to striatum (Pancani, T., et al., "Allosteric activation of M4 improve behavioral and physiological alterations in early symptomatic YAC128 mice", Proceedings of the National Academy of the Sciences of the United States of America, 2015 Nov. 10; 112(45):14078-83), and on hippocampal glutamate neurons where presynaptic M4 modulates glutamate release. The highest expression of M4 receptors is found in the striatum, M4 receptors also possess a regulatory effect on dopaminergic neurotransmission and are coexpressed with D1 dopamine receptors in a subset of striatal medium spiny neurons which contain GABA as a major neurotransmitter (Bernard, et al; "Phenotypical characterization of the rat striatal neurons expressing muscarinic receptor genes"; Journal of Neuroscience 1 September 1992, 12 (9) 3591-3600; Di Chiara, et. al; "Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions; Trends in Neurosciences; Volume 17, Issue 6, 1994, Pages 228-233; ince,

et.al; "Differential expression of D1 and D2 dopamine and m4 muscarinic acetylcholine receptor proteins in identified striatonigral neurons"; Synapse, (1997) 27: 357-366).

[0089] It has been hypothesized that administration of a selective M4 agonist would provide antipsychotic activity for the treatment of schizophrenia (Felder et al. "Elucidating the Role of Muscarinic Receptors in Psychosis", Life Sci. 68:2605-2613, 2001). This belief was further supported by studies that demonstrated M4 receptors modulate the dynamics of dopaminergic and cholinergic neurotransmission and that a state of dopamine hyperfunctions results with a loss of M4 function (Tzavara et al., 2004).

[0090] The compounds of the present disclosure may also be useful for treating/alleviating the neuropsychiatric symptoms (i.e., behavioral symptoms) associated with Alzheimer's Disease and Schizophrenia (Foster et. al., "Activation of M1 and M4 muscarinic receptors as potential treatments for Alzheimer's disease and schizophrenia", Neuropsychiatric Disease and Treatment; Volume 2014.10, pp. 183-191). These behavioral symptoms include, but are not limited to, agitation, vocal outburst, compulsiveness, anxiety, irritability, combativeness, disorientation, illusion, delusion, hallucination, suspiciousness, apathy, depression, disinhibition, aberrant motor and obsessive-compulsive behaviors, as well as sleep disorders (Dillon, Carol, et. al. "Behavioral symptoms related to cognitive impairment", Neuropsychiatric Disease and Treatment; 2013:9 1443-1455). By treating/alleviating the above-mentioned behavioral symptoms, it is believed that the compounds of the present disclosure will also enhance cognition.

[0091] In view of the above, the compounds of the present disclosure may be useful for the treatment of schizophrenia and Alzheimer's Disease. The compounds of the present disclosure may also be useful for the treatment of Parkinson's Disease, Huntington's Disease, addiction, substance abuse disorder, depression and epilepsy. The compounds of the present disclosure may also be useful for Alzheimer's disease psychosis.

[0092] It is believed the M4 selective activators of the present disclosure may also have a wide range of other therapeutic applications for the treatment of conditions or diseases of the central nervous system which include neurologic, neurodegenerative and/or psychiatric disorders. Neurologic, neurodegenerative and/or psychiatric disorders include but are not limited to, (1) mood [affective] disorders; (2) neurotic, stress-related and somatoform disorders including anxiety disorders; (3) disorders comprising the symptom of cognitive deficiency in a mammal, including a human; (4) disorders comprising attention deficits, executive function deficits (working memory deficits), dysfunction of impulse control, extrapyramidal symptoms, disorders that are based on a malfunction of basal ganglia, hippocampus and prefrontal cortex; (5) behavioral and emotional disorders with onset usually occurring in childhood and adolescence; (6) disorders of psychological development; (7) systemic atrophies primarily affecting the central nervous system; (8) extrapyramidal and movement disorders; (9) behavioral syndromes associated with physiological disturbances and physical factors; (10) disorders of adult personality and behavior; (11) schizophrenia and other psychotic disorders; (12) mental and behavioral disorders due to psychoactive substance use; (13) sexual dysfunction comprising excessive sexual drive; (14) mental

retardation; (15) factitious disorders, e.g., acute hallucinatory mania; (16) episodic and paroxysmal disorders, epilepsy; (17) narcolepsy; (18) dementia, and (19) amyotrophic lateral sclerosis.

[0093] Examples of mood (affective) disorders that can be treated according to the present disclosure include, but are not limited to, bipolar disorder, hypomania (manic and mixed form), bipolar disorder II; depressive disorders such as single depressive episode or recurrent major depressive disorder, chronic depression, psychotic depression, minor depressive disorder, depressive disorder with postpartum onset, depressive disorders with psychotic symptoms; persistent mood [affective] disorders such as cyclothymia, dysthymia, euthymia; premenstrual syndrome (PMS) and premenstrual dysphoric disorder.

[0094] Examples of neurotic, stress-related and somatoform disorders that can be treated according to the present disclosure include, but are not limited to, anxiety disorders, social anxiety disorder, general anxiety disorder, panic disorder with or without agoraphobia, specific phobia, social phobia, chronic anxiety disorders; obsessive compulsive disorder; reaction to severe stress and adjustment disorders, such as post-traumatic stress disorder (PTSD), acute stress disorder, other neurotic disorders such as depersonalization-derealization syndrome.

[0095] The phrase "cognitive deficiency" as used herein and "disorders comprising the symptom of cognitive deficiency" refers to a subnormal functioning or a suboptimal functioning in one or more cognitive aspects such as memory, intellect, learning and logic ability, or attention and executive function (working memory) in a particular individual comparative to other individuals within the same general age population.

[0096] Examples of "disorders comprising the symptom of cognitive deficiency" that can be treated according to the present disclosure include, but are not limited to, cognitive deficits primarily but not exclusively related to amnesia, psychosis (schizophrenia), Parkinson's disease, Alzheimer's Disease, multi-infarct dementia, senile dementia, Lewis body dementia, stroke, frontotemporal dementia, progressive supranuclear palsy, Huntington's disease, HIV disease (HIV-associated dementia), cerebral trauma and drug abuse; mild cognitive disorder ADHD, Asperger's syndrome, and age-associated memory impairment; cognitive decline or delirium post-operative or in association with intensive care therapy.

[0097] Examples of disorders usually first diagnosed in infancy, childhood and adolescence that can be treated according to the present disclosure include, but are not limited to, hyperkinetic disorders including disturbance of activity and attention, attention deficit/hyperactivity disorder (ADHD), hyperkinetic conduct disorder; attention deficit disorder (ADD); conduct disorders, including but not limited to depressive conduct disorder; tic disorders including transient tic disorder, chronic motor or vocal tic disorder, combined vocal and multiple motor tic disorder (Gilles de la Tourette's syndrome), substance-induced tic disorders; autistic disorders; Batten disease, excessive masturbation, nail-biting, nose-picking and thumb-sucking.

[0098] Examples of disorders of psychological development that can be treated according to the present disclosure include, but are not limited to pervasive developmental disorders, including but not limited to Asperger's syndrome and Rett syndrome, autistic disorders, childhood autism and overactive disorder associated

with mental retardation and stereotyped movements, specific developmental disorder of motor function, specific developmental disorders of scholastic skills.

[0099] Examples of systemic atrophies primarily affecting the central nervous system that can be treated according to the present disclosure include, but are not limited to, multiple sclerosis systemic atrophies primarily affecting the basal ganglia including Huntington's disease, and amyotrophic lateral sclerosis.

[0100] Examples of extrapyramidal and movement disorders with malfunction and/or degeneration of basal ganglia that can be treated according to the present disclosure include, but are not limited to, Huntington's disease; Parkinson's disease; second Parkinsonism such as postencephalitic Parkinsonism; Parkinsonism comprised in other disorders; Niemann-Pick disease, Lewy body disease; degenerative diseases of the basal ganglia; other extrapyramidal and movement disorders including tremor, essential tremor and drug-induced tremor, myoclonus, chorea and drug-induced chorea, drug-induced tics and tics of organic origin, drug-induced acute dystonia, drug-induced tardive dyskinesia, muscular spasms and disorders associated with muscular spasticity or weakness including tremors; mental deficiency (including spasticity, Down syndrome and fragile X syndrome), L-dopa-induced dyskinesia; restless leg syndrome and Stiff-man syndrome.

[0101] Further examples of movement disorders with malfunction and/or degeneration of basal ganglia that can be treated according to the present disclosure include, but are not limited to, dystonia including but not limited to focal dystonia, multiple-focal or segmental dystonia, torsion dystonia, hemispheric, generalized and tardive dystonia (induced by psychopharmacological drugs). Focal dystonia include cervical dystonia (torticollis), blepharospasm (cramp of the eyelid), appendicular dystonia (cramp in the extremities, like the writer's cramp), or mandibular dystonia and spasmodic dysphonia (cramp of the vocal cord); neuroleptic-induced movement disorders including but not limited to neuroleptic malignant syndrome (NMS), neuroleptic-induced Parkinsonism, neuroleptic-induced early onset or acute dyskinesia, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia, and neuroleptic-induced tremor.

[0102] Examples of behavioral syndromes associated with physiological disturbances and physical factors according to the present disclosure include, but are not limited to, nonorganic sleep disorders, including but not limited to nonorganic hypersomnia, nonorganic disorder of the sleep-wake schedule (circadian rhythm sleep disorder), insomnia, parasomnia and sleep deprivation; mental and behavioral disorders associated with the puerperium including postnatal and postpartum depression; eating disorders, including but not limited to anorexia nervosa, bulimia nervosa, binge eating disorder, hyperphagia, obesity, compulsive eating disorders and pagophagia.

[0103] Examples of disorders of adult personality and behavior that can be treated according to the present disclosure include, but are not limited to, personality disorders, including but not limited to emotionally unstable, borderline, obsessive-compulsive, anankastic, dependent and passive-aggressive personality disorder; habit and impulse disorders (impulse-control disorder) including intermittent explosive disorder, pathological gambling,

pathological fire-setting (pyromania), pathological stealing (kleptomania), trichotillomania; Munchausen syndrome.

[0104] Examples of schizophrenia and other psychotic disorders that can be treated according to the present disclosure include, but are not limited to, continuous or episodic schizophrenia of different types (for instance paranoid, hebephrenic, catatonic, undifferentiated, residual, and schizophreniform disorders); schizotypal disorders (such as borderline, latent, prepsychotic, prodromal, pseudoneurotic pseudopsychopathic schizophrenia and schizotypal personality disorder); persistent delusional disorders; acute, transient and persistent psychotic disorders; induced delusional disorders; schizoaffective disorders of different type (for instance manic depressive or mixed type); puerperal psychosis and other and unspecified nonorganic psychosis such as social withdrawal in schizophrenia.

[0105] Examples of mental and behavioral disorders due to psychoactive substance use that can be treated according to the present disclosure include, but are not limited to, mental and behavioral disorders due to use of alcohol, opioids, cannabinoids, sedatives or hypnotics, cocaine; mental and behavioral disorders due to the use of other stimulants including caffeine, mental and behavioral disorders due to drug dependence and abuse (e.g., narcotic dependence, alcoholism, amphetamine and methamphetamine dependence, opioid dependence, cocaine addiction, nicotine dependence, and drug withdrawal syndrome, and relapse prevention), use of hallucinogens, tobacco (nicotine), volatile solvents and mental and behavioral disorders due to multiple drug use and use of other psychoactive substances including the following subtype symptoms: harmful use, dependence syndrome, withdrawal state, and withdrawal state with delirium.

[0106] Examples of dementia that can be treated according to the present disclosure include, but are not limited to, vascular dementia, dementia due to Creutzfeld-Jacob disease, HIV, head trauma, Parkinson's, Huntington's, Pick's disease, dementia of the Alzheimer's type.

[0107] Schizophrenia or psychosis for which the compounds of the disclosure may be useful includes one or more of the following conditions: schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anesthesia, amphetamine and other psychostimulants and cocaine) psychosis/psychotic disorder, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's Disease and post-traumatic stress syndrome), including both the positive and the negative symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (associated with Alzheimer's Disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic disorders, or age related cognitive decline.

[0108] In addition to the central nervous system disorders mentioned above, the compounds of the present disclosure may be used to treat other M4-mediated (or M4-associated) disorders such as, but not limited to, addiction (e.g., substance addiction such as addiction to opioids, cocaine, or alcohol), pain (e.g., acute pain, inflammatory pain, and neuropathic pain), and a sleep disorder (such as those related to REM sleep regulation, for example, those related to REM sleep onset). Additional M4-mediated (or M4-associated) disorders or conditions that may be treated by the compounds of the disclosure include, dry mouth, a cognitive disorder (e.g., mild cognitive impairment), dyskinesia, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, urinary incontinence, glaucoma, Trisomy 21 (Down Syndrome), cerebral amyloid angiopathy, dementia (e.g. degenerative dementia), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes, autism, and atherosclerosis. See e.g., US Patent No. 8,664,234.

[0109] Potential sleep disorders for which the compounds of the foregoing of the disclosure may be useful include: enhancing sleep quality; improving sleep quality; augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e., stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; insomnia; hypersomnia; narcolepsy; interrupted sleep; sleep apnea; wakefulness; nocturnal myoclonus; REM sleep interruptions; jet-lag; shift workers' sleep disturbances; dyssomnias; night terror; insomnias associated with depression, emotional/mood disorders, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules; conditions due to drugs which cause reductions in REM sleep as a side effect; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; and conditions which result from a diminished quality of sleep.

[0110] Pain disorders for which the compounds of the disclosure may be useful include neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, phantom limb pain, root avulsions, painful diabetic neuropathy, painful traumatic mononeuropathy, painful polyneuropathy); central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system); postsurgical pain syndromes (e.g., postmastectomy syndrome, postthoracotomy syndrome, stump pain); bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia); perioperative

pain (general surgery, gynecological), chronic pain, dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g., osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout), headache, migraine and cluster headache, headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization.

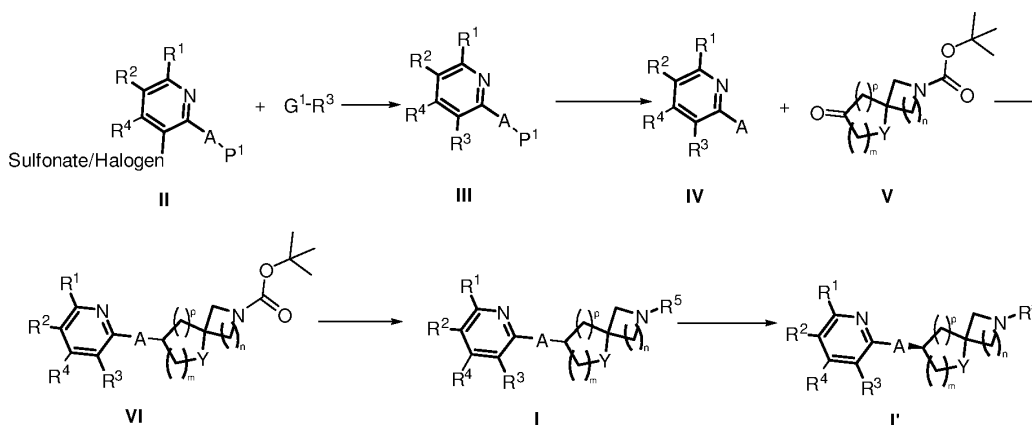
[0111] The compounds of the disclosure may be used to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g., alcohol, opioids, and cocaine.

[0112] In various cases, the M4-mediated (or M4-associated) disease or disorder can be selected from the group consisting of Alzheimer's disease, schizophrenia or psychosis, pain, addiction, a sleep disorder, a cognitive disorder (e.g., mild cognitive impairment), Parkinson's disease, Parkinson's disease-levodopa-induced dyskinesia, Huntington's disease, dyskinesia, dry mouth, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, urinary incontinence, glaucoma, Trisomy 21 (Down syndrome), cerebral amyloid angiopathy, dementia, hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes, autism, and atherosclerosis. In some cases, the M4-mediated (or M4-associated) disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain, addiction, Parkinson's disease, Parkinson's disease-levodopa-induced dyskinesia, and a sleep disorder.

Synthesis of the Compounds of the Disclosure

[0113] The compounds of the disclosure can be synthesized by any methods known in the art. For example, the compounds of the disclosure can be synthesized according to any of Schemes 1-6.

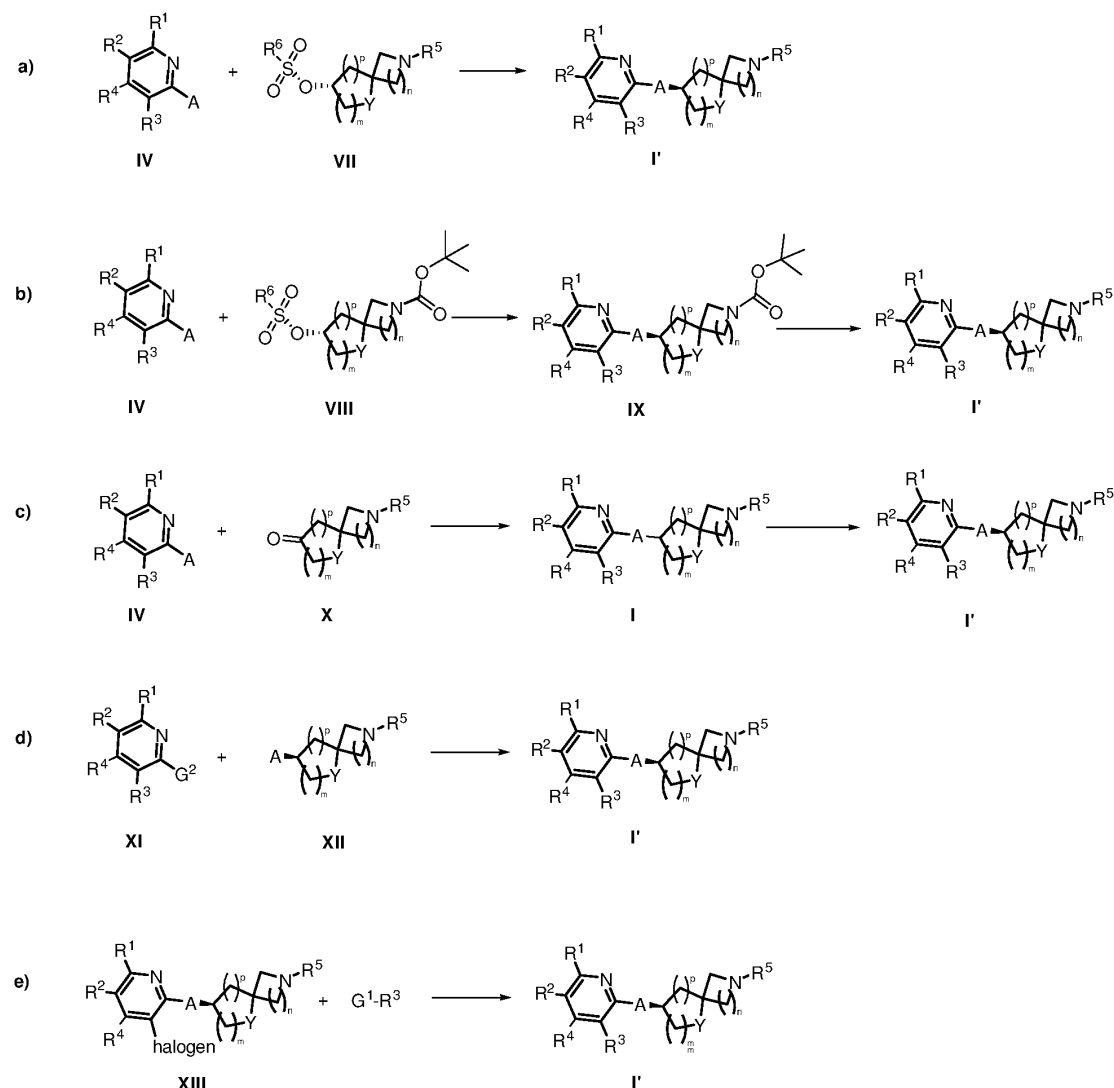
Scheme 1



[0114] Scheme 1 refers to one synthetic sequence for the preparation of compounds of Formula I and I'. According to Scheme 1, compound II can be coupled to a heteroaryl, aryl, alkenyl, heterocycloalkyl, cycloalkyl, spiroheteroalkyl, spiroalkyl, alkyl and heteroalkyl boronic acids, boronate esters or potassium trifluoroborates via the Suzuki-Miyaura coupling reaction. The scope of the reaction types is not restricted to the Suzuki-Miyaura, but

includes the Stille, Negishi, Hiyama, and decarboxylative coupling; the Sonogashira coupling with alkyne/silyl alkynes; and a nucleophilic aromatic substitutions (S_NAr) of amines and alcohols, wherein the R^1 , R^2 , R^3 , R^4 and A substituents should be represented by the same moieties as desired in the final product or protected variation thereof, to produce compound **III** via a coupling reaction or a S_NAr reaction with G^1-R^3 whereas G^1 is a boronic acid/ester/trifluoroborate, stannane, magnesium, zinc, carboxylic acid, carboxylate; or whereas G^1-R^3 is an alcohol/amine; or a terminal alkyne/silyl alkyne, using a standard selection of metal source, ligand, and base, in a standard solvent/cosolvent, but not limited to DMF, acetonitrile, 1,4-dioxane, THF, pyridine, toluene, ethanol, n-butanol, t-butanol. Examples of the Pd/ligand/base combination in coupling reaction include but are not limited to tetrakis(triphenylphosphine)palladium(0) plus sodium carbonate and tris(dibenzylideneacetone)dipalladium(0) plus dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl plus potassium carbonate. In a S_NAr reaction, examples of bases include, but are not limited to triethylamine, *N,N*-diisopropylethylamine, K_2CO_3 , Cs_2CO_3 , K_3PO_4 , $K_3PO_4 \cdot H_2O$, $tBuOK$, and NaH . Removal of protecting group P^1 results in compound **IV**. Protecting group P^1 in this case refers to groups well known to those skilled in the art for an amine protection. For example, P^1 may be a *tert*-butoxycarbonyl (Boc), which can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM). Alternatively P^1 may be one of many other protecting groups suitable for amines, including carboxybenzyl (Cbz) or benzoyl (Bz) group and can be cleaved under standard conditions known to those skilled in the art. Compounds **IV** can be coupled with compound **V**, wherein m , n and p are independently represented by an integer selected from 1 or 2, to produce racemic compounds **VI** using a standard reductive amination procedure, for example but not limited to, a combination of sodium cyanoborohydride and titanium(IV) ethoxide or sodium triacetoxyborohydride in a suitable solvent, followed by a treatment with R^5 to install the carbamates or carbamate bioisosteres, wherein the R^5 should be represented by the same moieties as desired in the final product or protected variation thereof in dichloromethane or other appropriate solvents, to produce compounds of Formula I as a racemic mixture. Chiral separation of the racemic mixture, for example, a chiral chromatographic method such as a chiral HPLC or a chiral supercritical fluid chromatography (SFC), can produce enantiomerically pure compounds of Formula I'.

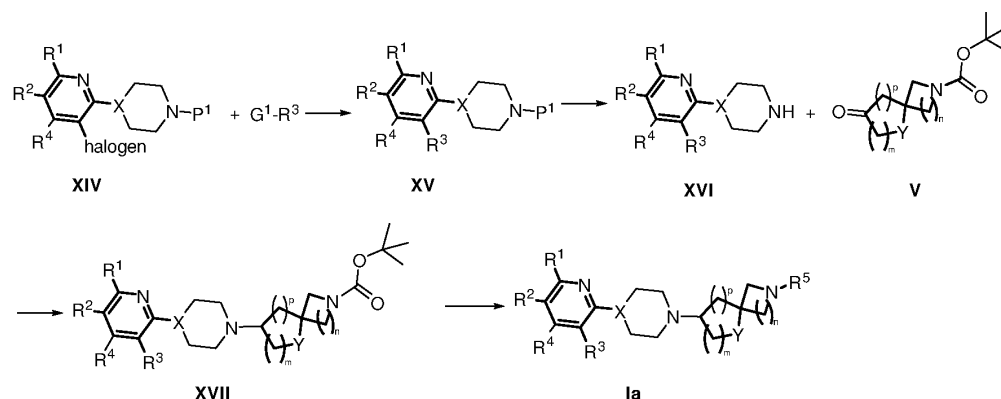
Scheme 2



[0115] Scheme 2 refers to alternative synthetic routes for the preparation of compounds of Formula I and I'. Referring to Scheme 2a, compound IV, wherein the R¹, R², R³, R⁴ and A substituents of Formula IV should be represented by the same moieties as desired in the final product or protected variation thereof, can displace the sulfonate of enantiomerically pure compound VII, wherein the R⁵ of Formula VII should be represented by the same moieties as desired in the final product or protected variation thereof, where R⁶ is an aryl, an alkyl, a fluoroaryl or a fluoroalkyl substituent, for example 4-methylphenyl, methyl, nonafluorobutyl; and m, n and p are independently represented by an integer selected from 1 or 2, and Y should be represented by the same moieties as desired in the final product in the presence of a base such as potassium carbonate or potassium phosphate tribasic in an appropriate solvent, including but not limited to MeCN, DMSO, DMF, or THF. Referring to Scheme 2b, compound IV, wherein the R¹, R², R³, R⁴ and A should be represented by the same moieties as

desired in the final product or protected variation thereof, can similarly displace the aryl alkyl/fluoroalkyl sulfonate on chiral compound **VIII**, where R^6 is an aryl, an alkyl, a fluoroaryl or a fluoroalkyl substituent, for example 4-methylphenyl, methyl, nonafluorobutyl; and m, n and p are independently represented by an integer selected from 1 or 2, and Y should be represented by the same moieties as desired in the final product to produce compound **IX**. Removal of the Boc group, which can be cleaved via acidic conditions in an appropriate solvent, including but not limited to trifluoroacetic acid in dichloromethane (DCM), followed by treatment with R^5 to install the carbamate or carbamate bioisosteres, wherein the R^5 should be represented by the same moieties as desired in the final product or protected variation thereof, to produce compounds of Formula **I'** as a single enantiomer. Alternately, as shown in Scheme 2c, compound **IV**, wherein the R^1 , R^2 , R^3 , R^4 and A substituents of Formula **IV** should be represented by the same moieties as desired in the final product or protected variation thereof, can be coupled to compound **X**, wherein the R^5 of Formula **X** should be represented by the same moieties as desired in the final product or protected variation thereof, m, n and p are independently represented by an integer selected from 1 or 2, and Y should be represented by the same moieties as desired in the final product to produce compounds of the general Formula **I** as a racemic mixture using a standard reductive amination procedure, for example but not limited to, a combination of sodium cyanoborohydride and titanium(IV) ethoxide or sodium triacetoxyborohydride in a suitable solvent. Chiral separation of the racemate of Formula **I** can be accomplished by a chiral HPLC or a chiral SFC to provide compounds of Formula **I'** as a single enantiomer. In Scheme 2d, compound **XI**, wherein the R^1 , R^2 , R^3 and R^4 should be represented by the same moieties as desired in the final product or protected variation thereof, where G^2 is a sulfonate, or halogen, can be coupled to enantiomerically pure compound **XII**, wherein the A and R^5 of Formula **XII** should be represented by the same moieties as desired in the final product or protected variation thereof, m, n and p are independently represented by an integer selected from 1 or 2, and Y should be represented by the same moieties as desired in the final product to produce compounds of the Formula **I'** using a standard coupling procedure, for example but not limited to Suzuki-Miyaura coupling or Buchwald-Hartwig coupling reactions as well as a S_NAr reaction of amines. In addition, referring to Scheme 2e, enantiomerically pure compound **XIII**, can be coupled to a heteroaryl, aryl, alkenyl, heterocycloalkyl, cycloalkyl, spiroheteroalkyl, spiroalkyl, alkyl and heteroalkyl boronic acids, boronate esters or potassium trifluoroborates via Suzuki-Miyaura coupling reaction. The scope of the reaction types is not restricted to Suzuki-Miyaura, but includes Stille, Negishi, Hiyama, and decarboxylative coupling; Sonogashira coupling with alkyne/silyl alkynes; and nucleophilic aromatic substitutions (S_NAr) of amines and alcohols, to generate the Formula **I'** as a single enantiomer, wherein the R^1 , R^2 , R^3 , R^4 , R^5 and A substituents should be represented by the same moieties as desired in the final product or protected variation thereof, m, n and p are independently represented by an integer selected from 1 or 2, and Y should be represented by the same moieties as desired in the final product.

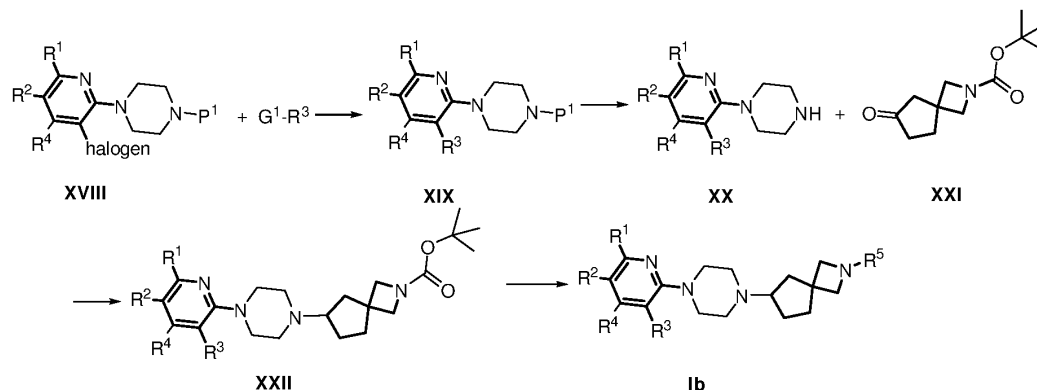
Scheme 3



[0116] Scheme 3 refers to one synthetic sequence for the preparation of compounds of Formula **Ia**. According to Scheme 3, compound **XIV** can be coupled to a heteroaryl, aryl, alkenyl, heterocycloalkyl, cycloalkyl, spiroheteroalkyl, spiroalkyl, alkyl and heteroalkyl boronic acids, boronate esters or potassium trifluoroborates via the Suzuki-Miyaura coupling reaction. The scope of the reaction types is not restricted to the Suzuki-Miyaura, but includes the Stille, Negishi, Hiyama, and decarboxylative coupling; the Sonogashira coupling with alkyne/silyl alkynes; and a nucleophilic aromatic substitutions (S_NAr) of amines and alcohols, and to produce compound **XV**, wherein the R^1 , R^2 , R^3 and R^4 substituents, and X should be represented by the same moieties as desired in the final product or protected variation thereof, via a coupling reaction or a S_NAr reaction, using a standard selection of metal source, ligand, and base, in a standard solvent, for example but not limited to DMF, acetonitrile, 1,4-dioxane, THF, pyridine, toluene, ethanol, n-butanol, t-butanol. Examples of the Pd/ligand/base combination in coupling reaction include but are not limited to tetrakis(triphenylphosphine)palladium(0) plus potassium carbonate and tris(dibenzylideneacetone)dipalladium(0) plus dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl plus potassium carbonate. In a S_NAr reaction, examples of bases include but are not limited to triethylamine, *N,N*-diisopropylethylamine, K_2CO_3 , CS_2CO_3 , K_3PO_4 , *t*-BuOK, and NaH. Removal of protecting group P^1 results in compound **XVI**. Protecting group P^1 in this case refers to groups well known to those skilled in the art for an amine protection. For example, P^1 may be a *tert*-butoxycarbonyl (Boc), which can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM). Alternatively P^1 may be one of many other protecting groups suitable for amines, including carboxybenzyl (Cbz) or benzoyl (Bz) group and can be cleaved under standard conditions known to those skilled in the art. Compounds **XVI**, can be coupled to compound **V**, wherein m , n and p are independently represented by an integer selected from 1 or 2; and X and Y should be represented by the same moieties as desired in the final product to produce racemic compounds **XVII** using a standard reductive amination procedure, for example but not limited to, a combination of sodium cyanoborohydride and titanium(IV) ethoxide or sodium triacetoxyborohydride in a suitable solvent, followed by deprotection of Boc-protecting group and treatment with R^5 to install the carbamates or carbamate bioisosteres, wherein the R^5 should be represented

by the same moieties as desired in the final product or protected variation thereof, to produce compounds of Formula **1a**.

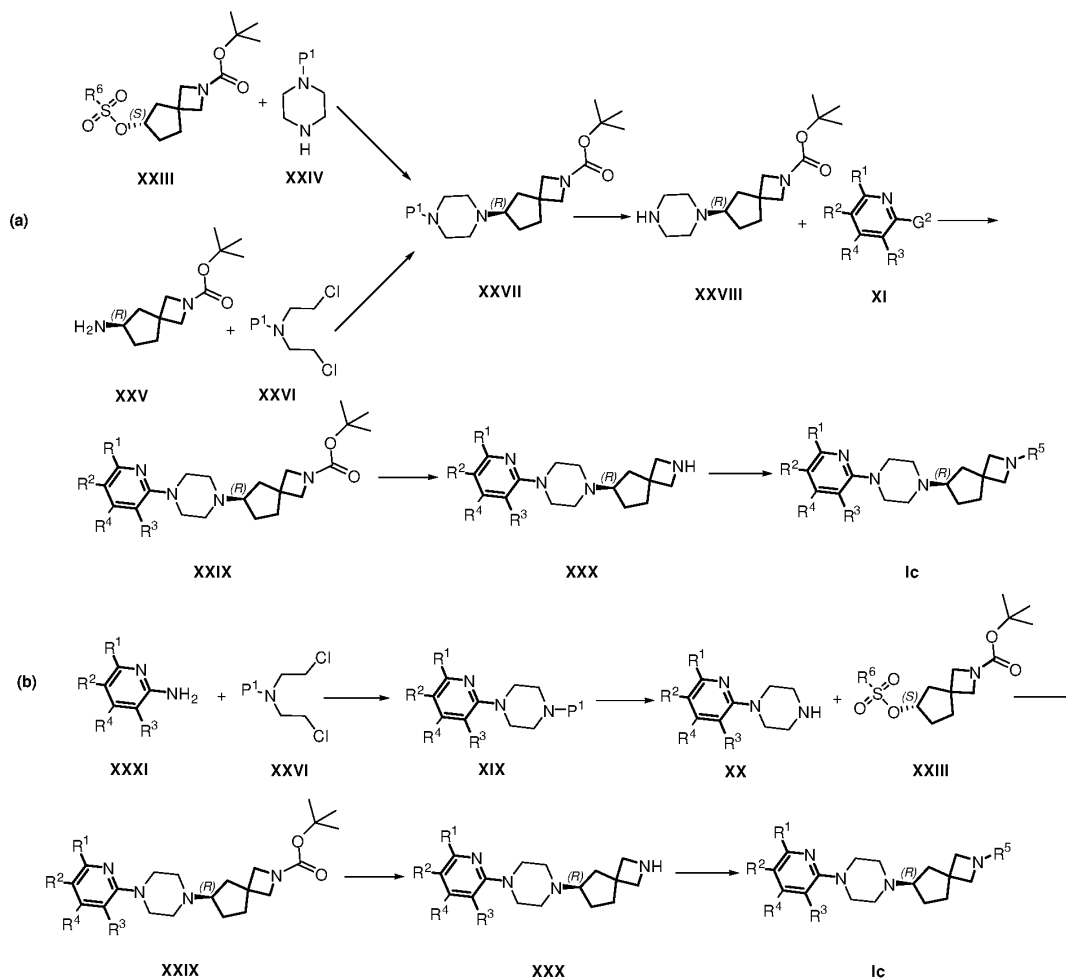
Scheme 4



[0117] Scheme 4 refers to one synthetic sequence for the preparation of compounds of Formula **1b**. Referring to Scheme 4, compound **XVIII** can be coupled to a heteroaryl, aryl, alkenyl, heterocycloalkyl, cycloalkyl, spiroheteroalkyl, spiroalkyl, alkyl and heteroalkyl boronic acids, boronate esters or potassium trifluoroborates via the Suzuki-Miyaura coupling reaction. The scope of the reaction types is not restricted to the Suzuki-Miyaura, but includes the Stille, Negishi, Hiyama, and decarboxylative coupling; the Sonogashira coupling with alkyne/silyl alkynes; and nucleophilic aromatic substitutions (S_NAr) of amines and alcohols, and to produce compound **XIX**, wherein the R^1 , R^2 , R^3 , and R^4 substituents should be represented by the same moieties as desired in the final product or protected variation thereof, via a coupling reaction or a S_NAr reaction, using a standard selection of metal source, ligand, and base, in a standard solvent, for example but not limited to DMF, acetonitrile, 1,4-dioxane, THF, pyridine, toluene, ethanol, n-butanol, t-butanol. Examples of the Pd/ligand/base combination in coupling reaction include but are not limited to tetrakis(triphenylphosphine)palladium(0) plus sodium carbonate and tris(dibenzylideneacetone)dipalladium(0) plus dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl plus potassium carbonate. In a S_NAr reaction, examples of bases include but are not limited to triethylamine, N,N-diisopropylethylamine, K_2CO_3 , Cs_2CO_3 , K_3PO_4 , $tBuOK$, and NaH. Removal of protecting group P^1 results in compound **XX**. Protecting group P^1 in this case refers to groups well known to those skilled in the art for amine protection. For example, P^1 may be a *tert*-butoxycarbonyl (Boc), which can be cleaved via an acidic condition in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM). Alternatively P^1 may be one of many other protecting groups suitable for amines, including carboxybenzyl (Cbz) or benzoyl (Bz) group and can be cleaved under standard conditions known to those skilled in the art. Compounds **XX**, can be coupled to compound **XXI** to produce racemic compounds **XXII** using a standard reductive amination procedure, for example but not limited to, a combination of sodium cyanoborohydride and titanium(IV) ethoxide or sodium triacetoxyborohydride in a suitable solvent, followed by deprotection of the Boc group and treatment with R^5 to install the carbamates or carbamate bioisosteres, wherein

the R⁵ should be represented by the same moieties as desired in the final product or protected variation thereof in dichloromethane or other appropriate solvents, to produce compounds of Formula **1b**.

Scheme 5

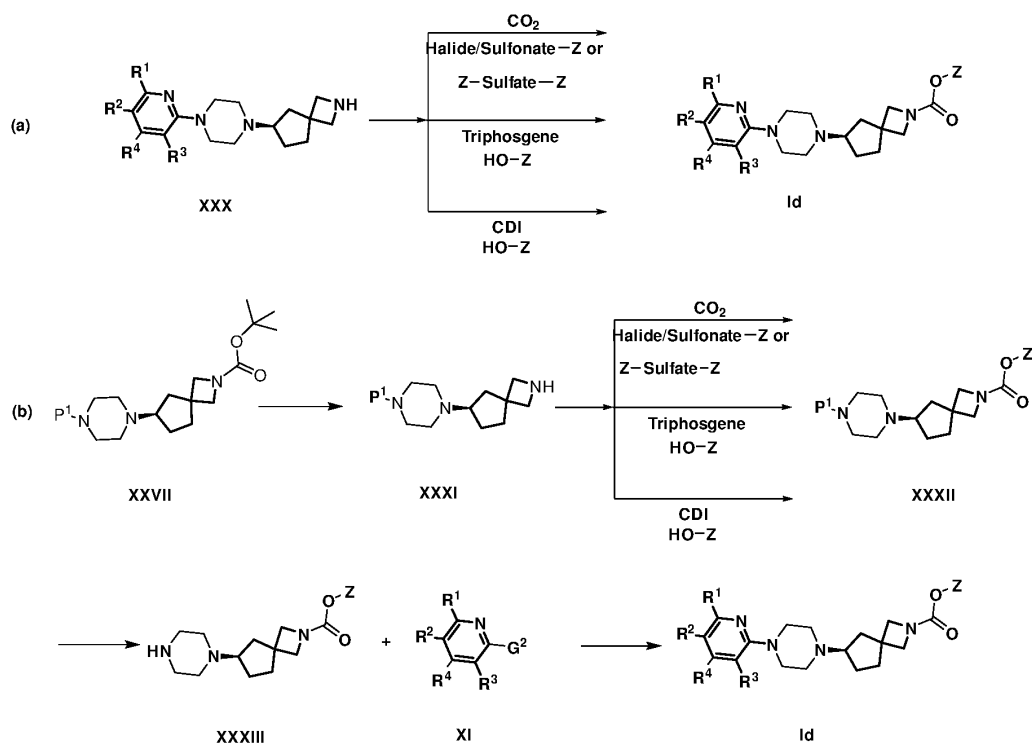


[0118] Scheme 5 refers to alternative synthetic routes for the preparation of compounds of Formula **1c**.

Referring to Scheme 5a, compound **XXVII**, can be prepared via two synthetic methods, one is that enantiomerically pure compound **XXIII**, wherein the R⁶ of Formula **XXIII** should be represented by an aryl, an alkyl, a fluoroaryl, or a fluoroalkyl substituent, for example 4-methylphenyl, methyl or nonafluorobutyl can be coupled with **XXIV** in the presence of a base such as potassium carbonate or potassium phosphate tribasic in an appropriate solvent, including but not limited to MeCN, DMSO, DMF, or THF. Alternatively, compound **XXVII** can be prepared by the double S_N2 reaction of the enantiomerically pure amine **XXV** and a dichloro **XXVI**. Removal of protecting group P¹ results in compound **XXVIII**. Protecting group P¹ in this case refers to groups well known to those skilled in the art for amine protection. For example, P¹ may be a carboxybenzyl (Cbz), which can be cleaved via H₂ gas conditions in an appropriate solvent, including but not limited to treatment with a solution of wet 10% Pd/C in methanol (MeOH). Alternatively P¹ may be one of many other protecting groups suitable for

amines, including benzyl (Bn) or benzoyl (Bz) groups and can be cleaved under standard conditions known to those skilled in the art. Compound **XXVIII** can be coupled to compound **XI**, wherein the R^1 , R^2 , R^3 and R^4 should be represented by the same moieties as desired in the final product or protected variation thereof, where G^2 is a sulfonate, or a halogen, to produce compounds of compound **XXIX** using a standard C-N coupling procedure, for example but not limited to Buchwald-Hartwig coupling reactions or a S_NAr reaction of amines where appropriate. Subsequently, the *tert*-butoxycarbonyl (Boc) of compound **XXIX** can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM), to provide enantiomeric compound **XXX**, followed by a treatment with R^5 to install the carbamates or carbamate bioisosteres, wherein the R^5 should be represented by the same moieties as desired in the final product or protected variation thereof in dichloromethane or other appropriate solvents, to produce compounds of Formula **1c**. Alternately, as shown in Scheme 5b, compound **XXXI**, wherein the R^1 , R^2 , R^3 and R^4 should be represented by the same moieties as desired in the final product or protected variation thereof, can be coupled to **XXVI** through the double S_N2 reaction, to produce the cyclized compound **XIX**. Removal of protecting group P^1 results in compound **XX**. Protecting group P^1 in this case refers to groups well known to those skilled in the art for an amine protection. For example, P^1 may be a *tert*-butoxycarbonyl (Boc), which can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM). Alternatively P^1 may be one of many other protecting groups suitable for amines, including carboxybenzyl (Cbz) or benzoyl (Bz) group and can be cleaved under standard conditions known to those skilled in the art. Compound **XX** can displace a sulfonate of enantiomerically pure compound **XXIII**, where R^6 is an aryl, an alkyl, a fluoroaryl, or a fluoroalkyl substituent, for example 4-methylphenyl, methyl, nonafluorobutyl; for example 4-methylphenyl or methyl in the presence of a base such as potassium carbonate in an appropriate solvent, including but not limited to DMSO, DMF, or THF, to generate compound **XXIX**. Subsequently, the *tert*-butoxycarbonyl (Boc) of compound **XXIX** can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM), to provide enantiomeric compound **XXX**, further followed by treatment with R^5 to install the carbamates or carbamate bioisosteres, wherein the R^5 should be represented by the same moieties as desired in the final product or protected variation thereof in dichloromethane or other appropriate solvents, to produce compounds of Formula **1c**.

Scheme 6

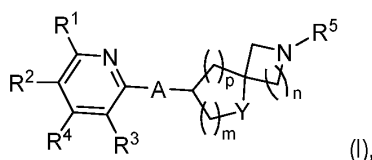


[0119] Scheme 6 refers to the synthetic sequences for the preparation of compounds of Formula **Id**. Referring to Scheme 6a, compound **XXX**, wherein the R^1 , R^2 , R^3 and R^4 substituents of Formula **XXX** should be represented by the same moieties as desired in the final product or protected variation thereof, can be followed by treatment with CO_2 gas, a base such as DBU, and a Halide/Sulfonate-Z or a Z-sulfate-Z, wherein the Z should be represented by the same moieties as desired in the final product or protected variation thereof, in DMF or other appropriate solvents, to produce compounds of Formula **Id**. The alternative synthetic routes for the preparation of Formula **Id**, is to use triphosgene and ZOH, in an appropriate solvent such as DCM and a base such as pyridine wherein the Z should be represented by the same moieties as desired in the final product or protected variation thereof, to react with compound **XXX** for synthesizing the carbamates of Formula **Id**. Another alternative method for the preparation of Formula **Id**, is to use CDI instead of triphosgene and ZOH wherein the Z should be represented by the same moieties as desired in the final product or protected variation thereof, to react with compound **XXX** for synthesizing the carbamates of Formula **Id**. In Scheme 6b, the tert-butoxycarbonyl (Boc) of compound **XXVII** can be cleaved via acidic conditions in an appropriate solvent, including but not limited to treatment with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM), to provide enantiomeric compound **XXXI**, then followed by three reaction approaches to afford compound **XXXII**, wherein the Z should be represented by the same moieties as desired in the final product or protected variation thereof. These three methods are: 1) treatment with CO_2 gas, a base such as DBU, and Z-sulfate-Z, or Halide/Sulfonate-Z, in an appropriate solvent such as DMF; 2) using triphosgene and ZOH, in an appropriate solvent such as DCM and a

base such as pyridine; 3) using CDI and ZOH in an appropriate solvent such as THF. Removal of protecting group P¹ results in compound **XXXIII**. Protecting group P¹ in this case refers to groups well known to those skilled in the art for amine protection. For example, P¹ may be a carboxybenzyl (Cbz), which can be cleaved via H₂ gas conditions in an appropriate solvent, including but not limited to treatment with a solution of wet 10% Pd/C in methanol (MeOH). Alternatively P¹ may be one of many other protecting groups suitable for amines, including benzyl (Bn) or benzoyl (Bz) group and can be cleaved under standard conditions known to those skilled in the art. Compound **XXXIII** can be coupled to compound **XI**, wherein the R¹, R², R³ and R⁴ should be represented by the same moieties as desired in the final product or protected variation thereof, where G² is a sulfonate, or a halogen, to produce compounds of Formula **Id** using a standard C-N coupling procedure, for example but not limited to Buchwald-Hartwig coupling reactions and a S_NAr reaction of amines where appropriate.

Embodiments of the Disclosure

1. A compound having a structure of Formula (I):



or an *N*-oxide thereof, or a pharmaceutically acceptable salt of the compound or the *N*-oxide thereof, wherein:

A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and is substituted with 0, 1, 2, or 3 R^A;

each R^A is independently C₁₋₃alkyl, halogen, =O, OH, C₁₋₃hydroxyalkyl, or C₁₋₃haloalkyl;

Y is a bond, S, O, CH₂, CHF, CF₂, or C(OH)H;

m is 1 or 2;

n is 1 or 2;

p is 1 or 2;

R¹ is H, halogen, CN, OH, NO₂, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle or -[O]₀₋₁-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle, -[O]₀₋₁-5-10 membered heteroaryl, -NH-C₃₋₆cycloalkyl, -NH-C₆₋₁₀aryl, -NH-4-8 membered heterocycle, -NH-5-10 membered heteroaryl, -N(C₁₋₆alkyl)-C₃₋₆cycloalkyl, -N(C₁₋₆alkyl)-C₆₋₁₀aryl, -N(C₁₋₆alkyl)-4-8 membered heterocycle, or -N(C₁₋₆alkyl)-5-10 membered heteroaryl, R¹ is substituted with 0, 1, 2, or 3 substituents independently selected from halogen, CN, OH, =O, SO₂, and C₁₋₃alkyl;

R² is H, halogen, CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₂₋₆heteroalkyl, C₃₋₆cycloalkyl, or 4-8 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S;

R³ is halogen, C₀₋₆alkylene-CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-C(O)NHC₁₋₆alkyl, C₀₋₆alkylene-Cyc, O-C₀₋₆alkylene-Cyc, NH-Cyc, N(C₁₋₆alkyl)-Cyc, or C(O)Cyc;

Cyc is C₃₋₁₂cycloalkyl, C₃₋₆heterocycloalkyl, C₅₋₁₂spirocycloalkyl, C₅₋₁₂heterospirocycloalkyl, C₆₋₁₀aryl, 4-12 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents;

each R^{3a} is independently selected from halogen, CN, OH, =O, =N(C₁₋₆alkyl), SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₀₋₆alkylene-C(O)C₁₋₆alkyl, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₀₋₆alkylene-C(O)NH₂, C₀₋₆alkylene-C(O)NH(C₁₋₆alkyl), C₀₋₆alkylene-C(O)N(C₁₋₆alkyl)₂, C₀₋₆alkylene-NHC(O)C₁₋₆alkyl, C₀₋₆alkylene-COOH, C₀₋₆alkylene-CO₂C₁₋₆alkyl, C₀₋₆alkylene-C₃₋₆cycloalkyl, and C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S;

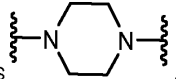
R⁴ is H, halogen, CN, OH, C₁₋₆alkyl, C₁₋₆-haloalkyl, or C₁₋₆alkoxy;

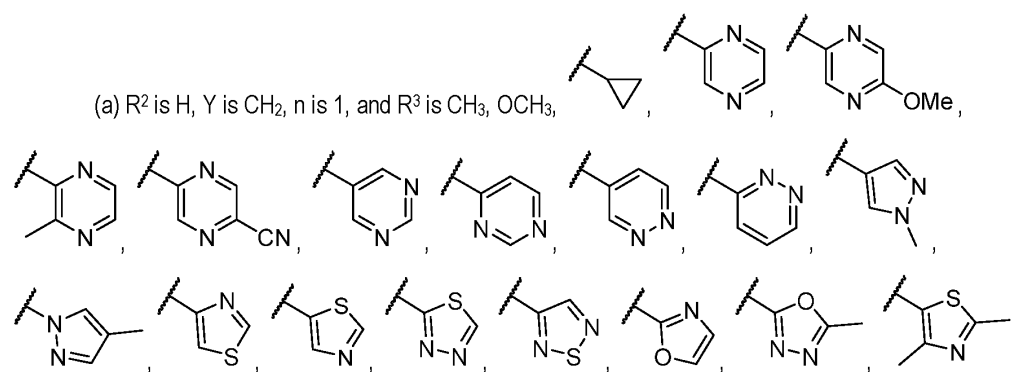
R⁵ is -CO₂-Z, or a bioisostere thereof;

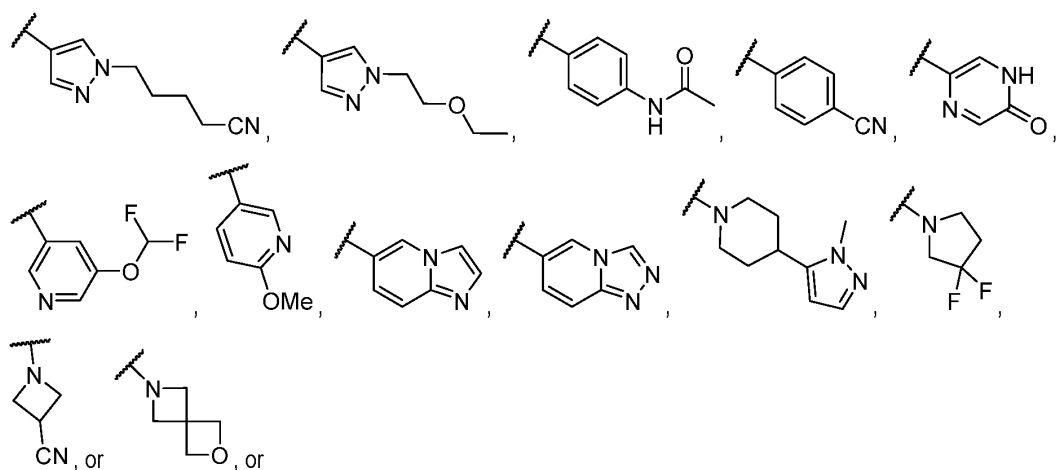
each R⁶ and R⁷ is independently H, C₁₋₆alkyl, C(O)-C₁₋₆alkyl, spiro or bicyclic C₈₋₁₄cycloalkyl, 8-14 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R⁶ or R⁷ is other than H, it is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, CN, =O, SO₂, OH, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₁₋₆alkyl and C₁₋₆alkoxy, or

R⁶ and R⁷, together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N, O, and S; and

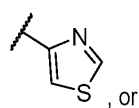
Z is C₁₋₇alkyl, C₁₋₇haloalkyl, C₃₋₆cycloalkyl, or C₂₋₆alkyne, and Z is optionally substituted with C₁₋₆alkoxy or C₃₋₆cycloalkyl;

with the proviso that when R¹ and R⁴ are each H, m and p are each 1, and A is , and

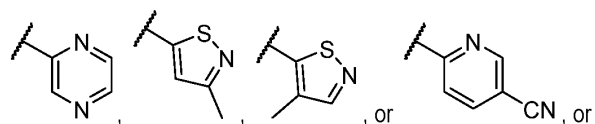




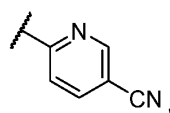
(b) R² is F, Y is CH₂, n is 1, and R³ is



(c) R² is H, Y is a bond, n is 1, and R³ is

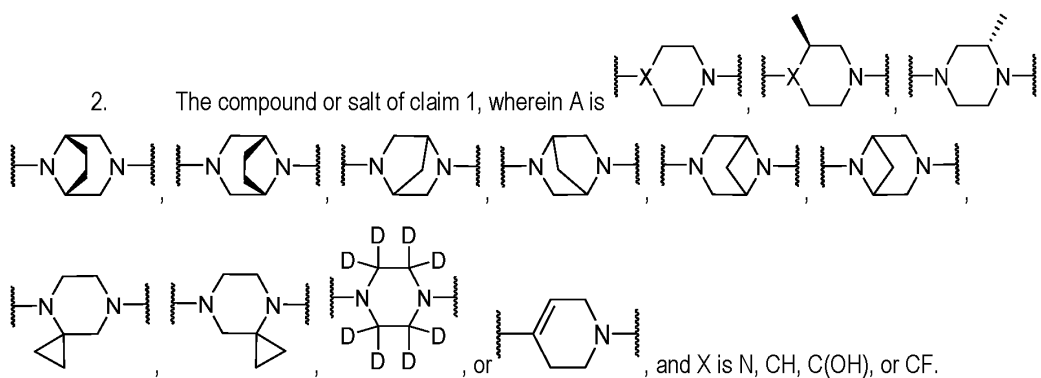


(d) R² is H, Y is a bond, n is 2, and R³ is

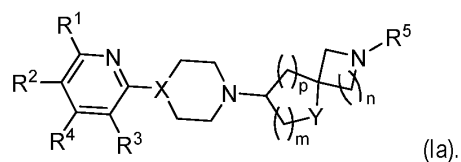


then R⁵ is not CO₂CH₂CH₃ or CO₂CH(CH₃)₃.

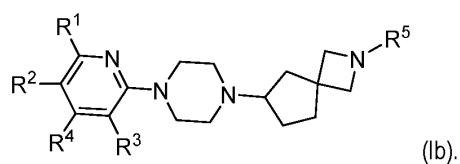
2. The compound or salt of claim 1, wherein A is



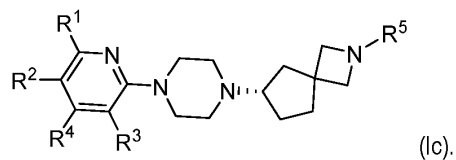
3. The compound or salt of embodiment 2, having a structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



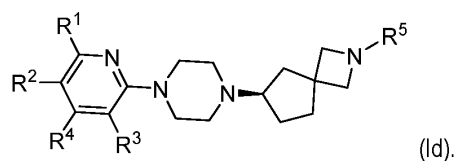
4. The compound or salt of any one of embodiments 1 to 3, wherein Y is CH₂, CHF, CF₂, or C(OH)H.
5. The compound or salt of embodiment 4, wherein Y is CH₂.
6. The compound or salt of any one of embodiments 1 to 5, wherein m is 1.
7. The compound or salt of any one of embodiments 1 to 6, wherein n is 1.
8. The compound or salt of any one of embodiments 1 to 7, wherein p is 1.
9. The compound or salt of embodiment 1, having a structure of Formula (lb):



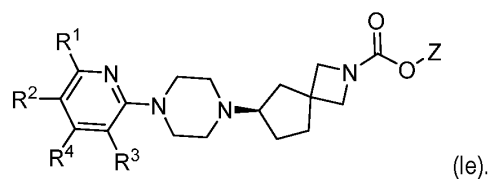
10. The compound or salt of embodiment 9, having a structure of Formula (lc):



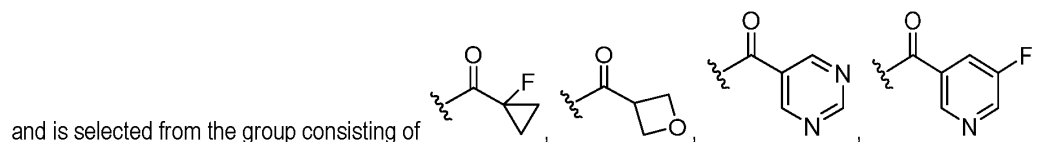
11. The compound or salt of embodiment 9, having a structure of Formula (ld):

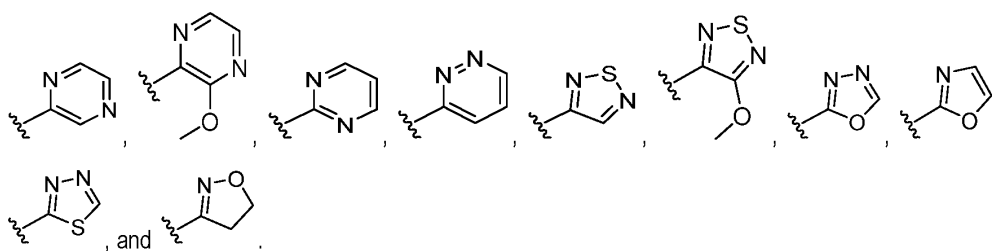


12. The compound or salt of embodiment 1, having a structure of Formula (le), or a pharmaceutically acceptable salt thereof:

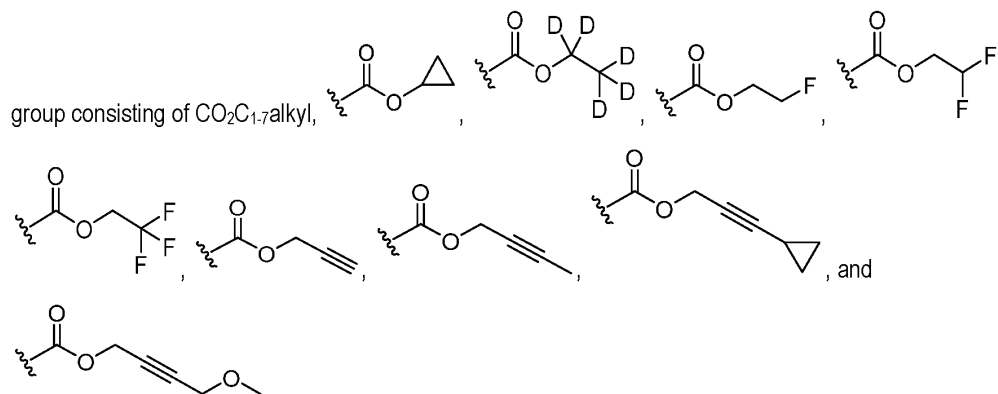


13. The compound or salt of any one of embodiments 1 to 11, wherein R⁵ is a CO₂Z bioisostere





14. The compound or salt of any one of embodiments 1 to 12, wherein R^5 is selected from the



15. The compound or salt of embodiment 14, wherein R^5 is $\text{CO}_2\text{CH}_2\text{CH}_3$.

16. The compound or salt of any one of embodiments 1 to 15, wherein R^1 is H, halogen, CN, OH, $\text{N}(\text{R}^6)(\text{R}^7)$, $\text{C}_{1-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkoxy}$.

17. The compound or salt of embodiment 16, wherein R^1 is H or halogen.

18. The compound or salt of any one of embodiments 1 to 17, wherein R^2 is H, halogen, CN, OH, $\text{N}(\text{R}^6)(\text{R}^7)$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{haloalkyl}$, $\text{C}_{1-6}\text{alkoxy}$, or $\text{C}_{1-6}\text{haloalkoxy}$.

19. The compound or salt of embodiment 18, wherein R^2 is H, halogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkoxy}$, $\text{C}_{1-6}\text{haloalkyl}$, or $\text{C}_{1-6}\text{haloalkoxy}$.

20. The compound or salt of embodiment 19, wherein R^2 is H or halogen.

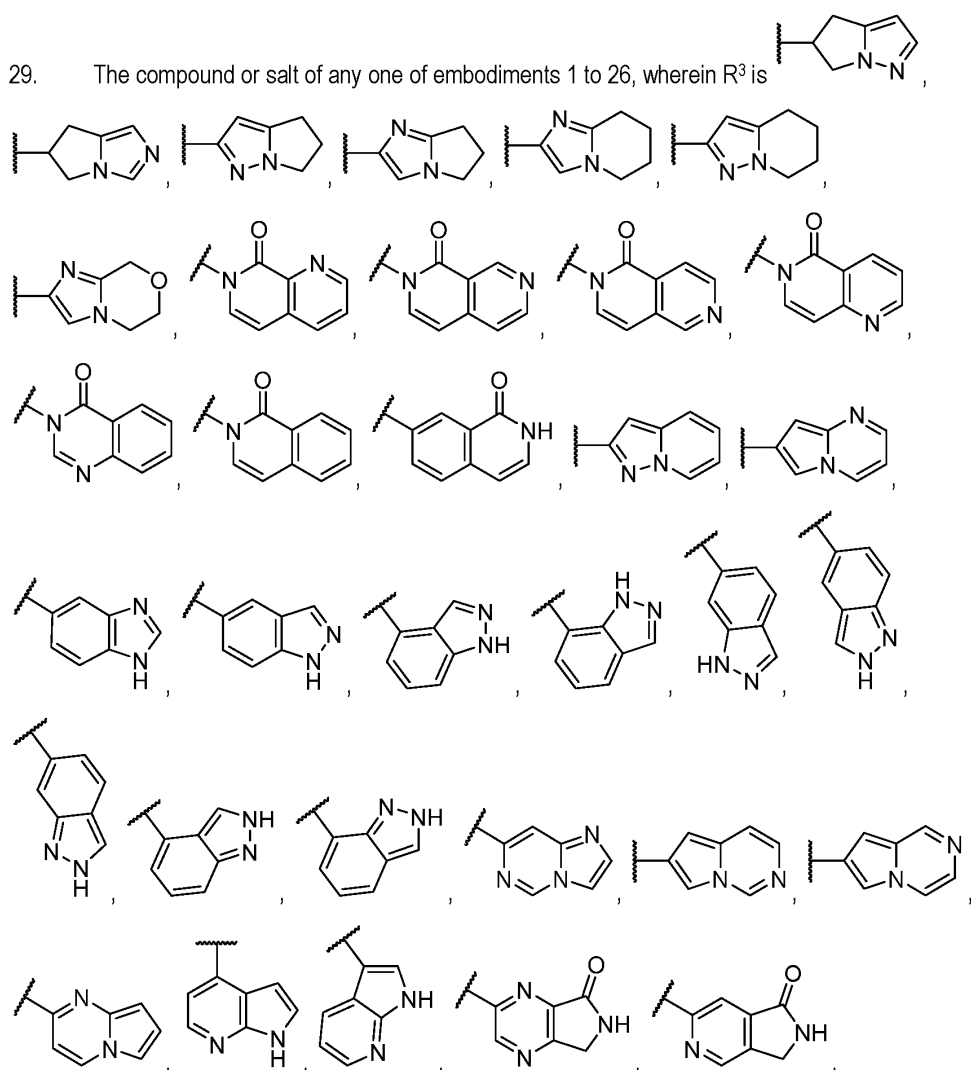
21. The compound or salt of any one of embodiments 1 to 20, wherein each R^6 and R^7 are independently H, $\text{C}_{1-6}\text{alkyl}$, or $\text{C}(\text{O})\text{-C}_{1-6}\text{alkyl}$.

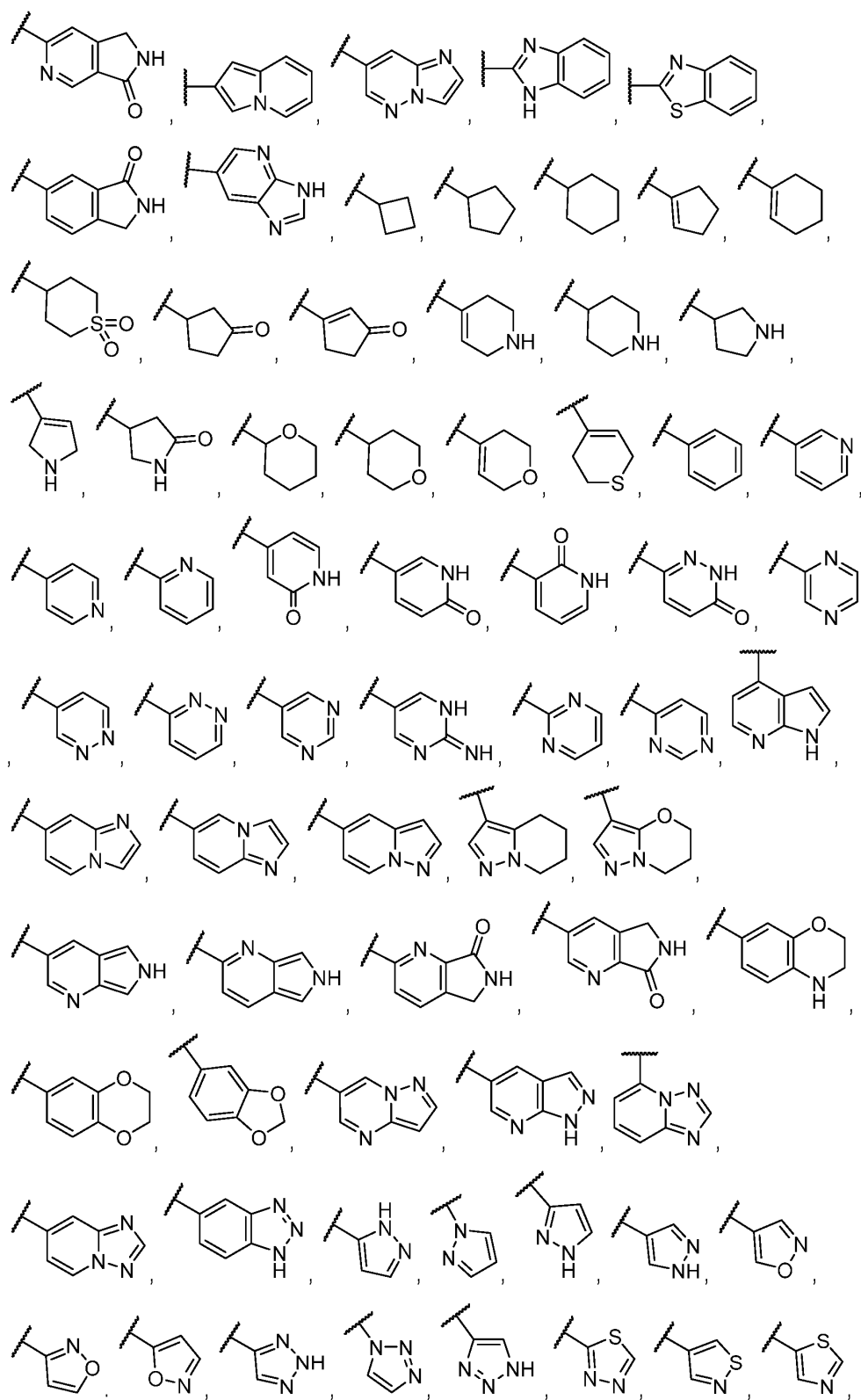
22. The compound or salt of embodiment 21, wherein each R^6 and R^7 are independently H or $\text{C}_{1-6}\text{alkyl}$.

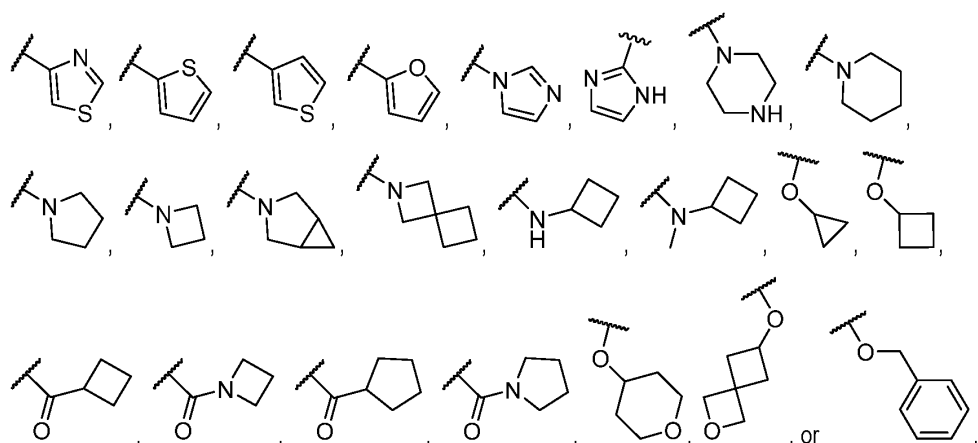
23. The compound or salt of any one of embodiments 1 to 20, wherein at least one R^6 and R^7 , together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N and O.

24. The compound or salt of any one of embodiments 1 to 23, wherein R^4 is H or halogen.

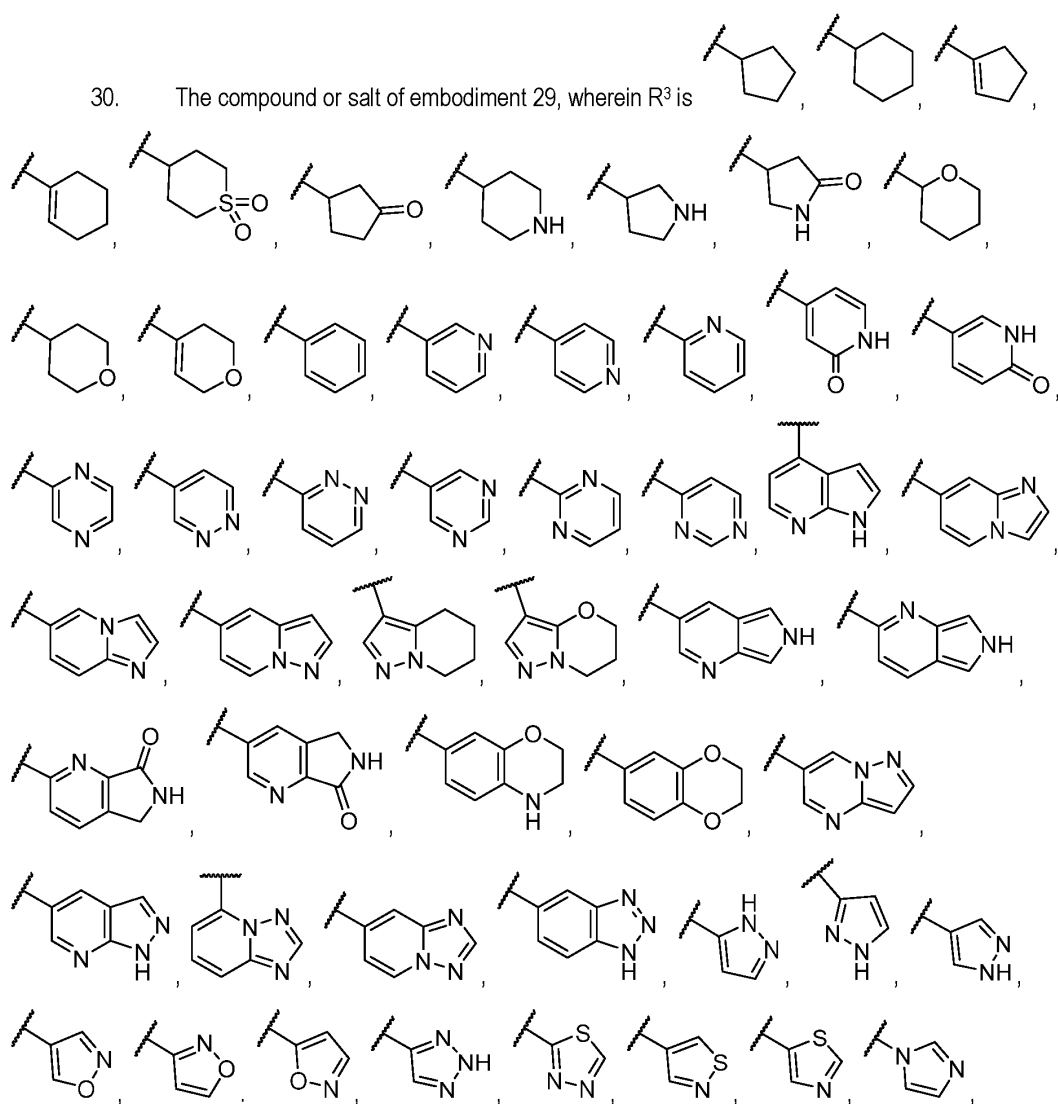
25. The compound or salt of any one of embodiments 1 to 24, wherein at least one of R¹, R², and R⁴ is halogen.
26. The compound or salt of any one of embodiments 1 to 25, wherein at least one of R¹, R², and R⁴ is F.
27. The compound or salt of any one of embodiments 1 to 26, wherein R³ is -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle, or -[O]₀₋₁-5-10 membered heteroaryl, and R³ is substituted with 0, 1, 2, or 3 R^{3a}.
28. The compound or salt of embodiment 27, wherein R³ is C₃₋₆ cycloalkyl, 5-10 membered heteroaryl, or 4-8 membered heterocycle, and R³ is substituted with 0, 1, 2, or 3 R^{3a}.

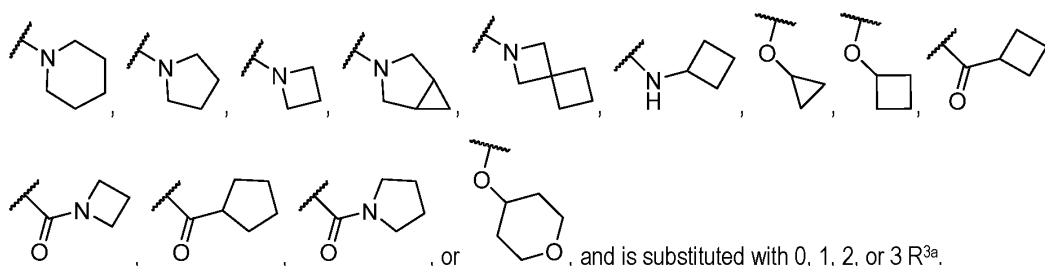






and is substituted with 0, 1, 2, or 3 R^{3a}.





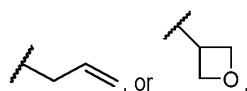
31. The compound or salt of any one of embodiments 1 to 30, wherein R³ is unsubstituted.

32. The compound or salt of any one of embodiments 1 to 30, wherein R³ is substituted with 1 or 2 R^{3a}.

33. The compound or salt of embodiment 32, wherein R³ is substituted with 1 R^{3a}.

34. The compound or salt of any one of embodiments 1 to 30, 32 and 33, wherein at least one R^{3a} is halogen, CN, OH, =O, SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, C₁₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, or C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S.

35. The compound or salt of embodiment 34, wherein at least one R^{3a} is CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, CF₃, CH₂CH₂F, CH₂CHF₂, CH₂OH, C(CH₃)₂OH, CH₂OCH₃, CH₂CH₂OCH₃, CH₂OCH₂CH₃, F, CN, =O, SO₂, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCHF₂, CH₂OCH₃, CH₂OCF₃, SCH₃, N(CH₃)₂, NHCOCH₃, CD₃,



36. The compound or salt of embodiment 35, wherein at least one R^{3a} is CH₃, CH₂CH₃, F, CN, OH, OCH₃, CF₃, CH₂OH, or OCHF₂.

37. A compound, or pharmaceutically acceptable salt thereof, as recited in Table A.

38. The salt of embodiment 37, wherein the salt selected from HCl, HCl·H₂O, maleate, and maleate·H₂O.

39. A pharmaceutical formulation comprising a therapeutically effective amount of the compound or salt of any one of embodiments 1 to 38, and a pharmaceutically acceptable excipient.

40. A method for treating an M4-mediated (or M4-associated) disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of the compound or salt of any one of embodiments 1 to 38.

41. The method of embodiment 40, wherein the M4-mediated (or M4-associated) disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia or psychosis, pain, addiction, a sleep disorder, a cognitive disorder (e.g., mild cognitive impairment), Parkinson's disease,

Parkinson's disease-levodopa-induced dyskinesia, Huntington's disease, dyskinesia, dry mouth, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, urinary incontinence, glaucoma, Trisomy 21 (Down syndrome), cerebral amyloid angiopathy, Alzheimer's disease psychosis, dementia-related psychosis, bipolar, hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes, autism, and atherosclerosis

42. The method of embodiment 41, wherein the M4-mediated (or M4-associated) disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain, addiction, Parkinson's disease, Parkinson's disease-levodopa-induced dyskinesia, and sleep disorder.

EXAMPLES

[0120] The following examples are provided for illustration and are not intended to limit the scope of the disclosure.

[0121] As used throughout these examples, common organic abbreviations are defined as follows:

Abbreviation	Chemical
Ac	Acetyl
AcOH	Acetic Acid
ACN or MeCN	Acetonitrile
Bn	Benzyl
Bz	Benzoyl
BOC or Boc	tert-Butoxycarbonyl
br	broad
Cbz	carboxybenzyl
CDI	carbonyldiimidazole
Cmpd	Compound
d	Doublet
DAST	(diethylamino)sulfur trifluoride
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DIBAL-H	Diisobutylaluminum hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMA	dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc or EA	Ethyl acetate
ESI	electrospray ionization
EtOH	Ethanol
FLIPR	fluorescence imaging plate reader
GPCR	G-protein coupled receptor
h	hours
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBSS	Hanks' balanced salt solution
HPLC	high performance liquid chromatography

Abbreviation	Chemical
Hz	hertz
IPA	propan-2-ol
L	liter
LCMS	liquid chromatography mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
mAChR	muscarinic acetylcholine receptor
mCBPA	meta-Chloroperoxybenzoic acid
MeOH	Methanol
min	minute(s)
MTBE	methyl tert-butyl ether
NCS	<i>N</i> -chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
PE	Petroleum ether
ppm	Parts per million
py	Pyridine
QC	Quality control
rt	Room temperature
Rt	Retention Time
s	singlet
SFC	Supercritical Fluid Chromatography
t	triplet
TEA or NEt ₃	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TR-FRET	time-resolved fluorescence resonance energy transfer
XantPhos	(9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)

Abbreviation	Chemical
XPhos	dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

[0122] Inert atmosphere (nitrogen or argon) was generally required, particularly in cases where oxygen- or moisture-sensitive reagents such as dry Pd/C, intermediates, and/or inert conditions were employed. Commercial solvents and reagents were generally used without further purification. Anhydrous solvents were employed where appropriate, generally from WuXi-EHS, which the following QC specifications for water were attained: a) <50 ppm for N,N-dimethylformamide; b) <100 ppm for dichloromethane, toluene, and tetrahydrofuran; c) <200 ppm for methanol, ethanol, 1,4-dioxane and diisopropylamine. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing. Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS) and high-performance liquid chromatography (HPLC). ¹H NMR spectra were recorded at 400 MHz on a Bruker instrument. Chemical shifts (δ) for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm) referenced to residual peaks from the deuterated solvents employed. In addition, chiral separations were carried out to separate enantiomers of certain compounds of the invention by supercritical fluid chromatography (SFC). In some examples, the separated enantiomers are designated as Peak 1 and Peak 2, according to their order of elution. Based upon the potency, the chirality may be implemented as (R) or (S)-isomer. Reactions proceeding through detectable intermediates were generally followed by LCMS and allowed to proceed to full conversion prior to addition of subsequent reagents.

[0123] For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. Microwave-mediate reactions were performed in Biotage Initiator microwave reactors for some compounds. In general, reactions were monitored by thin-layer chromatography or mass spectrometry, and subjected to work-up when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate R_f or retention times. All starting materials in these Preparations and Examples are either commercially available or can be prepared by methods known in the art or as described herein.

[0124] LCMC Method 1: Instrument: SHIMADZU LC20-MS2010; Mobile Phase: 1.5mL/4L TFA in water (solvent A) and 0.75mL/4L TFA in ACN (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.5 mL/min; Column: MERCK, RP-18e 25-2 mm; Wavelength: UV 220 nm & 254 nm; Column temperature: 50 °C; MS ionization: ESI.

[0125] LCMC Method 2: Instrument: SHIMADZU LC20-MS2020; Mobile Phase: 0.8 mL/4L NH₃·H₂O in water (solvent A) and ACN (solvent B), using the elution gradient 10%-80% (solvent B) over 6 minutes and holding at 80% for 0.5 minutes at a flow rate of 0.8 mL/min; Column: Titank C18, 5 μm, 2.1×50 mm; Wavelength: UV 220 nm & 254 nm; Column temperature: 50 °C; MS ionization: ESI.

[0126] LCMC Method 3: Instrument: SHIMADZU LCMS-2020; Mobile phase: Ramp from 5% ACN (0.01875% TFA) in water (0.0375% TFA) to 95% ACN in water in 0.60 min, flow rate is set at 2.0 mL/min; then hold at 95% ACN for 0.18 minutes, flow rate is set at 2.0 mL/min; return back to 5% ACN in water and hold for 0.02 min, Flow rate is set at 2.0 mL/min; Column: Kinetex® EVO C18 2.1×30 mm, 5 μ m. Column temperature: 50°C.

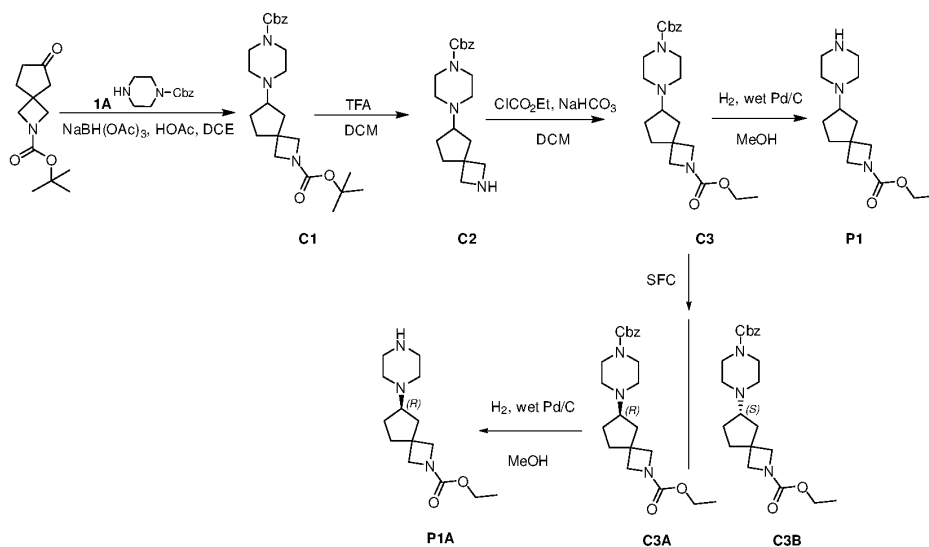
[0127] HPLC Method 1: Instrument: SHIMADZU LC20-MS2020; Mobile Phase: 0.2 mL/1L $\text{NH}_3 \cdot \text{H}_2\text{O}$ in water (solvent A) and ACN (solvent B), using the elution gradient 10%-80% (solvent B) over 6 minutes and holding at 80% for 2 minutes at a flow rate of 0.8 mL/min; Column: Titank C18, 5 μ m, 2.1×50 mm; Wavelength: UV 220 nm, 215 nm & 254 nm; Column temperature: 50°C.

[0128] HPLC Method 2: Instrument: SHIMADZU LC-20AD; Mobile phase: Ramp from 10% ACN (0.018%TFA) in water (0.037%TFA) to 80% ACN in water in 3.00 min, flow rate is set at 1.5 mL/min; then hold at 80% ACN for 0.70 minutes, flow rate is set at 1.5 mL/min; return back to 10% ACN in water and hold for 0.30 min, flow rate is set at 2.0 mL/min; Column: Kinetex C18 LC Column 4.6×50 mm, 5 μ m. Wavelength: UV 220 nm & 254 nm. Column temperature: 50°C.

[0129] SFC Method 1: Instrument: CAS-SH-ANA-SFC-G (Agilent 1260 with DAD detector); Column: ChiralPak AD-3 150×4.6 mm I.D., 3 μ m; Mobile phase: A: CO_2 B: Methanol (0.05% DEA) Isocratic: 40% B; Flow rate: 2.5 mL/min Column temp.: 40 °C; Back pressure: 100 bar.

[0130] SFC Method 2: Instrument: CAS-SH-ANA-SFC-L (Waters UPCC with PDA Detector); Column: Chiralcel OD-3 150×4.6mm I.D., 3 μ m; Mobile phase: A: CO_2 B: methanol (0.05% DEA) Gradient: from 5% to 40% of B in 4 min and from 40% to 5% of B in 0.2 min, then hold 5% of B for 1.8 min; Flow rate: 2.5 mL/min; Column temp.: 35 °C; Back pressure: 1500 psi.

Ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (**P1**), and ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (**P1A**)



[0131] *Step 1. Synthesis of tert-butyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (C1):* To a mixture of tert-butyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (**1A**, commercially available, 100 g, 444 mmol), benzyl piperazine-1-carboxylate (commercially available, 117 g, 532 mmol) and 4Å molecular sieve (67.5 g) in DCE (2.30 L) was added CH₃COOH (13.2 g, 221 mmol) at 25 °C. The mixture was stirred at 25 °C for 60 min, then NaBH(OAc)₃ (235 g, 1.10 mol) was added in portions and stirred at 25 °C for 15 hours. The mixture was poured into saturated aqueous NaHCO₃ (1.70 L), stirred for 10 min and separated. The aqueous phase was extracted with DCM (3 × 800 mL). The combined organic phase was washed with brine (1.20 L), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum at 50 °C. The crude product was triturated with petroleum ether (1.80 L) at 25 °C for 60 min. The suspension was filtered off and filter cake was dried in vacuum at 50 °C to afford tert-butyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 7.36-7.33 (m, 5H), 5.12 (s, 2H), 3.86-3.75 (m, 2H), 3.74 - 3.67 (m, 2H), 3.53 (t, *J* = 4.8 Hz, 4H), 2.57 (t, *J* = 8.0 Hz, 1H), 2.43 (s, 4H), 2.09 (dd, *J* = 6.8, 12.4 Hz, 1H), 1.96-1.78 (m, 3H), 1.70 (dd, *J* = 9.6, 12.4 Hz, 1H), 1.60-1.49 (m, 1H), 1.43 (s, 9H).

[0132] *Step 2. Synthesis of benzyl 4-(2-azaspiro[3.4]octan-6-yl)piperazine-1-carboxylate (C2):* To a solution of tert-butyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (170 g, 381 mmol) in DCM (800 mL) was added TFA (286 g, 2.51 mol). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under a reduced pressure at 50 °C to give benzyl 4-(2-azaspiro[3.4]octan-6-yl)piperazine-1-carboxylate (340 g, crude, TFA salt), which was used directly in the next step without further purification. **¹H NMR (DMSO-d₆ 400 MHz)** δ_H = 7.47-7.30 (m, 5H), 5.17-5.05(m, 2H), 4.25-4.05 (m, 2H), 3.98-3.71 (m, 4H), 3.65-3.53 (m, 1H), 3.51-3.35 (m, 2H), 3.20 (d, *J* = 5.2 Hz, 2H), 3.09-2.86 (m, 2H), 2.35 (dd, *J* = 8.4, 13.6 Hz, 1H), 2.10-1.96 (m, 3H), 1.85 (dd, *J* = 6.0, 8.4Hz, 1H), 1.79-1.69 m, 1H). **LCMS [M+H]⁺** 330.

[0133] *Step 3. Synthesis of ethyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (C3):* To a mixture of benzyl 4-(2-azaspiro[3.4]octan-6-yl)piperazine-1-carboxylate (220 g, 496 mmol, TFA salt) in DCM (1.50 L) and H₂O (750 mL) was added NaHCO₃ (541 g, 6.45 mol) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min and ethyl carbonochloridate (178 g, 1.64 mol) was added dropwise at 25 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was poured into water (500 mL) and stirred for 30 min at 25 °C, and the phases were separated. The aqueous phase was extracted with DCM (2× 600 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford ethyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 7.41-7.27 (m, 5H), 5.12 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.90-3.79 (m, 2H), 3.79-3.73 (m, 2H), 3.50 (t, *J* = 4.8 Hz, 4H), 2.60-2.49 (m, 1H), 2.40 (s, 4H), 2.08 (dd, *J* = 7.2, 12.8 Hz, 1H), 1.93-1.81 (m, 3H), 1.68 (dd, *J* = 9.6, 12.8 Hz, 1H), 1.58-1.46 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).

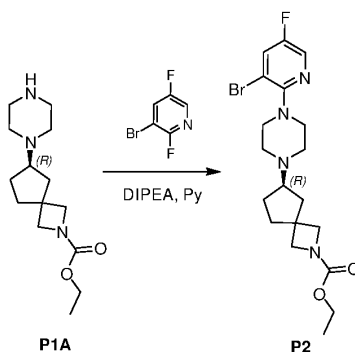
[0134] *Step 4. Synthesis of ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (P1):* To a solution of ethyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (800 mg, 1.99 mmol) in EtOH (10.0 mL) was added wet Pd/C (80.0 mg, 10% by wt.) under a N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ gas several times. The mixture was stirred under H₂ gas (40 psi) at 50 °C for

16 hours. The reaction mixture was filtered and the filtrate was concentrated to afford ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate, which was used for the next step directly. ¹H NMR (CDCl₃ 400 MHz) δ_H = 4.09 (q, *J* = 7.2 Hz, 2H), 3.90-3.70 (m, 4H), 2.98-2.82 (m, 3H), 2.65-2.35 (m, 5H), 2.12-2.05 (m, 1H), 1.95-1.75 (m, 4H), 1.73-1.62 (m, 1H), 1.55-1.46 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H).

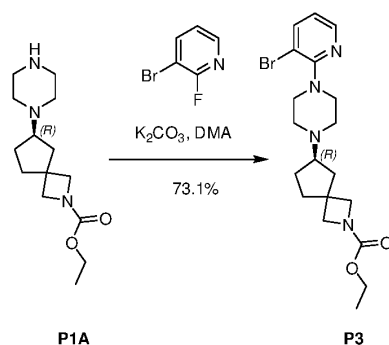
[0135] *Step 5. Synthesis of ethyl (6R)-6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (C3A) and ethyl (6S)-6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (C3B):* A racemic mixture of ethyl 6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (430 g, 1.07 mol) was purified by SFC (column: DAICEL CHIRALCEL OJ (250mm*50mm, 10μm); mobile phase: [0.1% NH₃H₂O MeOH]; B%: 20%-20%, min) to give ethyl (6R)-6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate and ethyl (6S)-6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate, purity 95.9%. LCMS [M+H]⁺ 402.

[0136] *Step 6. Synthesis of ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (P1A):* To a solution of ethyl (6R)-6-(4-benzyloxycarbonylpiperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (120 g, 299 mmol) in MeOH (1200 mL) was added wet 10% Pd/C (15.0 g) at 20 °C. The suspension was degassed under a vacuum and purged with H₂ gas several times. The mixture was stirred under H₂ gas (15 psi) at 25 °C for 16 hours. The reaction mixture was filtered and washed with MeOH (2 x 1,000 mL). The filter was concentrated to give ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ_H = 4.08 (q, *J* = 7.2 Hz, 2H), 3.92-3.71 (m, 4H), 2.88 (t, *J* = 5.2 Hz, 4H), 2.58-2.33 (m, 5H), 2.15-2.03 (m, 1H), 1.97-1.75 (m, 3H), 1.71-1.63 (m, 1H), 1.57-1.43 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). LCMS [M+H]⁺ 268.

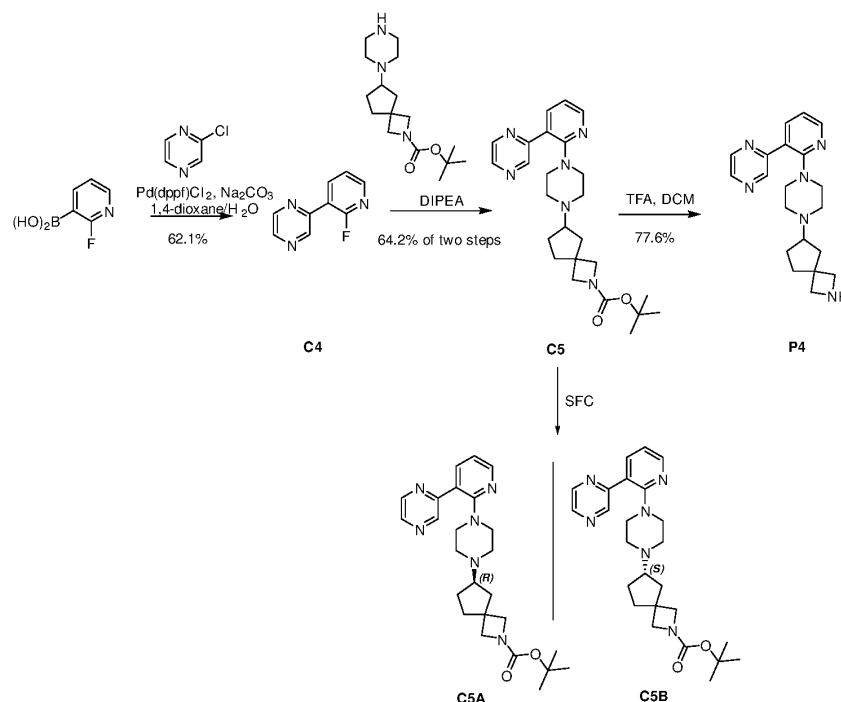
Ethyl (6R)-6-[4-(3-bromo-5-fluoro-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (P2)



[0137] A mixture of ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (1.27 g, 4.75 mmol), 3-bromo-2,5-difluoro-pyridine (921 mg, 4.75 mmol) and DIPEA (14.0 mL, 80.2 mmol) in pyridine (10.0 mL) was degassed and purged with N₂ gas for three times and stirred at 120 °C for 12 hours under a N₂ gas atmosphere. The reaction mixture was concentrated under reduced pressure to remove volatile reagents. The residue was purified by silica gel flash chromatography (Eluent of 0~10% MeOH/DCM) to give ethyl (6R)-6-[4-(3-bromo-5-fluoro-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. LCMS *m/z* [M+H]⁺ 443.

Ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (P3)

[0138] To a mixture of 3-bromo-2-fluoro-pyridine (1.65 g, 9.35 mmol) and ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (2.50 g, 9.35 mmol) in DMA (25.0 mL) was added K_2CO_3 (2.58 g, 18.7 mmol) in one portion at 20 °C. The mixture was heated to 140 °C and stirred for 12 hours. The mixture was cooled to 20 °C and concentrated under a reduced pressure at 50 °C. Water (50 mL) was added into the leftover residue and extracted DCM (4 × 50 mL). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure at 50 °C. The residue was purified by silica gel chromatography (Eluent of 0~5% MeOH/DCM) to afford ethyl (6R)-6-[4-(3-bromo-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **$^1\text{H NMR}$ (CDCl_3 400 MHz)** δ_{H} = 8.22 (dd, J = 1.6 Hz, 4.8Hz, 1H), 8.77 (dd, J = 1.6 Hz, 8.0Hz, 1H), 6.76 (dd, J = 4.8 Hz, 7.6Hz, 1H), 5.30 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.95-3.74 (m, 4H), 3.43-3.27 (m, 4H), 2.68-2.60 (m, 4H), 2.14 (dd, J = 7.2 Hz, 12.8Hz, 1H), 1.99-1.88 (m, 2H), 1.88-1.71 (m, 2H), 1.60-1.52 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 423, 425.

6-(4-(3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane (P4)

[0139] Step 1: Synthesis of 2-(2-fluoropyridin-3-yl)pyrazine (**C4**): To a mixture of 2-chloropyrazine (1.56 mL, 17.5 mmol), (2-fluoro-3-pyridyl)boronic acid (2.46 g, 17.5 mmol) and Na₂CO₃ (5.55 g, 52.4 mmol) in 1,4-dioxane (30.0 mL) and H₂O (6.00 mL) was added Pd(dppf)Cl₂ (1.28 g, 1.75 mmol) in one portion at 20 °C and degassed under N₂ gas for several times. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was concentrated under a reduced pressure. The residue was diluted with EtOAc (100 mL), the organic layer was washed with water (2×50 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~30% EtOAc /petroleum ether) to give 2-(2-fluoro-3-pyridyl)pyrazine. **LCMS** [M+H]⁺ 176.

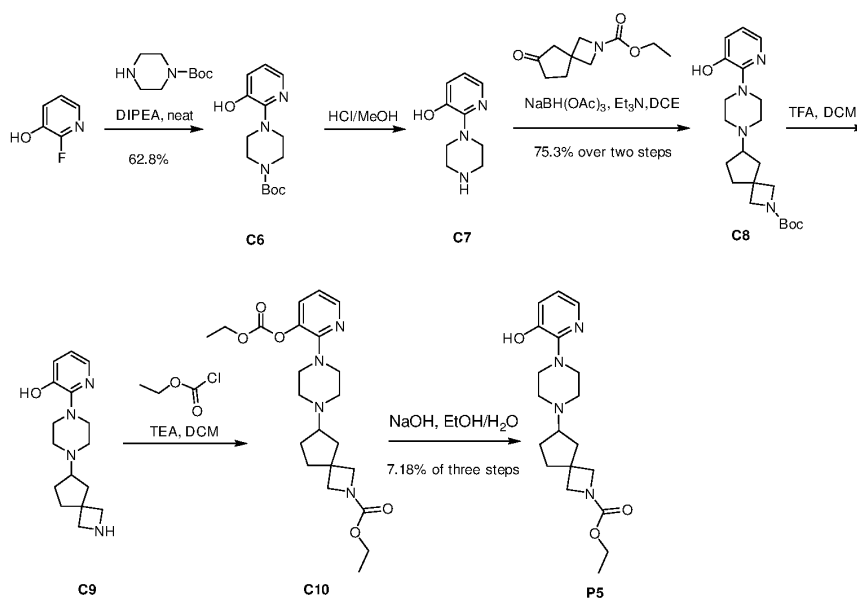
[0140] Step 2: Synthesis of tert-butyl 6-(4-(3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2- azaspiro[3.4]octane-2- carboxylate (**C5**): A solution of 2-(2-fluoro-3-pyridyl)pyrazine (3.26 g, 18.6 mmol) and tert-butyl 6-pipera-zin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (5.50 g, 18.6 mmol) in DIPEA (10.0 mL) was stirred at 140 °C for 16 hours. The mixture was concentrated under a reduced pressure to give a residue. The residue was diluted with DCM (200 mL) and washed with water (2 ×100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (Eluent of 0~10% MeOH/DCM) to give tert-butyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2- azaspiro[3.4]octane-2-carboxylate, and purified by prep-HPLC (column: Phenomenex Gemini-NX 80×40 mm×3 um; mobile phase: [water (0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 35%-65%, 8 min) to give tert-butyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 9.24 (s, 1H), 8.65 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.86 (dd, J = 1.6 Hz, 7.2 Hz,

1H), 7.01 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 3.82-3.68 (m, 4H), 3.15 (s, 4H), 2.60-2.39 (m, 5H), 2.06 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.93-1.75 (m, 3H), 1.66-1.57 (m, 1H), 1.56-1.47 (m, 1H), 1.42 (s, 9H). **LCMS** $[M+H]^+$ 451.

[0141] *Step 3: Synthesis of tert-butyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (C5A) and tert-butyl (6S)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (C5B):* tert-Butyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (2.68 g, 5.95 mmol) was purified by a prep-SFC. The sample was purified by a SFC (column: DAICEL CHIRALCEL OD (250 mm $\times$ 50 mm, 10 μ m); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ ETOH]; B%: 30%-30%, 7 min) to give **Peak 1** of tert-butyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (1.18 g, 2.61 mmol, 43.8% yield, 99.5% purity) as an off-white solid and **Peak 2** of tert-butyl (6S)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1: LCMS** $[M+H]^+$ 451. **Peak 2: LCMS** $[M+H]^+$ 451.

[0142] *Step 4: Synthesis of 6-[4-(3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl]-2-azaspiro[3.4]octane (P4):* To a solution of tert-butyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (6.30 g, 14.0 mmol) in DCM (30.0 mL) was added TFA (19.6 mL, 264 mmol). The mixture was stirred at 20 $^\circ\text{C}$ for 5 hours. The mixture was adjusted to pH = 9 with 10% aqueous NaOH, and then diluted with DCM (50 mL). The aqueous phase was extracted with DCM (2 $\times$ 30 mL). The combined organic layer dried over anhydrous Na_2SO_4 and filtered. The organic layer was concentrated under a reduced pressure to give 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane. **$^1\text{H NMR}$ (CDCl_3 , 400 MHz)** δ_{H} = 9.23 (d, $J = 1.2$ Hz, 1H), 8.73-8.57 (m, 1H), 8.46 (d, $J = 2.0$ Hz, 1H), 8.39-8.27 (m, 1H), 7.86 (d, $J = 7.2$ Hz, 1H), 7.08-6.92 (m, 1H), 3.72-3.38 (m, 2H), 3.21-3.00 (m, 7H), 2.45 (d, $J = 2.4$ Hz, 5H), 2.24-2.15 (m, 1H), 2.10-2.02 (m, 1H), 1.96-1.88 (m, 1H), 1.77-1.68 (m, 1H), 1.65-1.54 (m, 1H), 1.48-1.36 (m, 1H). **LCMS** $[M+H]^+$ 351.

Ethyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (P5)



[0143] Step 1: Synthesis of tert-butyl 4-(3-hydroxypyridin-2-yl)piperazine-1-carboxylate (**C6**): A mixture of 2-fluoropyridin-3-ol (2.00 g, 17.7 mmol), tert-butyl piperazine-1-carboxylate (6.59 g, 35.4 mmol), DIPEA (9.24 mL, 53.1 mmol) was degassed and purged with N₂ gas for three times. Then the mixture was heated to 140 °C and stirred at 140 °C for 16 hours under an atmosphere of N₂ gas. The reaction mixture was concentrated under a reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~20% EtOAc /petroleum ether) to give tert-butyl 4-(3-hydroxy-2-pyridyl)piperazine-1-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δH = 7.96 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.22 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.03 (dd, *J* = 4.8 Hz, 8.0 Hz, 1H), 3.67-3.59 (m, 4H), 3.09-2.98 (m, 4H), 1.50 (s, 9H). **LCMS [M+H]⁺ 280.**

[0144] Step 2: Synthesis of 2-(piperazin-1-yl)pyridin-3-ol (**C7**): To a solution of tert-butyl 4-(3-hydroxy-2-pyridyl)piperazine-1-carboxylate (3.00 g, 10.7 mmol) in MeOH (10.0 mL) was added HCl/MeOH (4 M, 15.0 mL). The mixture was stirred at 20 °C for 1.5 hours. The reaction mixture was concentrated under a reduced pressure to give to a crude 2-(piperazin-1-yl)pyridin-3-ol. **LCMS [M+H]⁺ 180.**

[0145] Step 3: Synthesis of tert-butyl 6-(4-(3-hydroxypyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4] octane-2-carboxylate (**C8**): To a solution of 2-piperazin-1-ylpyridin-3-ol (1.90 g, 10.6 mmol, HCl salt) in DCE (20.0 mL) was added ethyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (2.09 g, 10.6 mmol), NaBH(OAc)₃ (2.70 g, 12.7 mmol) and CH₃COOH (318 mg, 5.30 mmol) and Et₃N (4.43 mL, 31.8 mmol). The mixture was stirred at 25 °C for 16 hours. The reaction mixture was added saturated aqueous NaHCO₃ (20 mL) and separated. The aqueous was extracted with EtOAc (3×150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (Eluent of 0~10% MeOH/DCM) to give tert-butyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4] octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δH = 7.95 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.19 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.99 (dd, *J* = 3.2 Hz, 4.4 Hz, 1H), 3.89-3.80 (m, 2H), 3.79-3.74 (m, 2H), 3.13 (t, *J* = 4.8 Hz, 4H), 2.77-2.60 (m, 5H), 2.20-2.10 (m, 1H), 2.00-1.75 (m, 4H), 1.65-1.55 (m, 1H), 1.46 (s, 9H). **LCMS [M+H]⁺ 389.**

[0146] Step 4: Synthesis of 2-(4-(2-azaspiro[3.4]octan-6-yl)piperazin-1-yl)pyridin-3-ol (**C9**): To a solution of tert-butyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4] octane-2-carboxylate (2.00 g, 5.15 mmol) in DCM (50.0 mL) was added TFA (5.72 mL, 77.2 mmol). The mixture was stirred at 20 °C for 16 hours. The reaction mixture was concentrated under a reduced pressure to give 2-[4-(2-azaspiro[3.4]octan-6-yl)piperazin-1-yl]pyridin-3-ol. **LCMS [M+H]⁺ 289.**

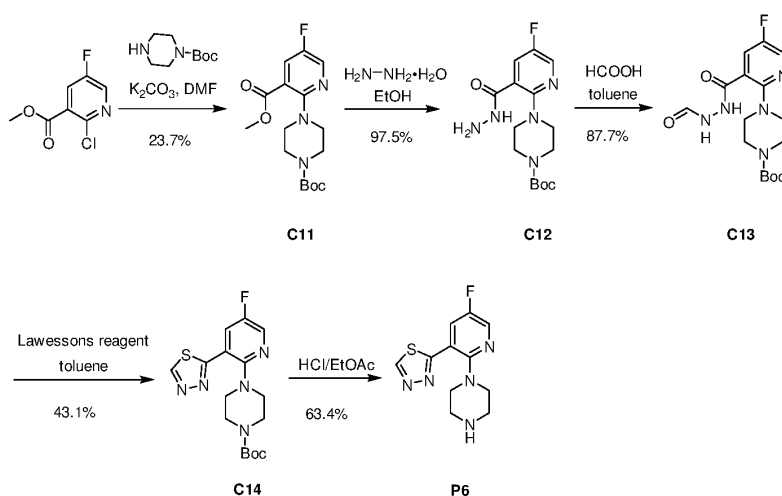
[0147] Step 5: Synthesis of ethyl 6-(4-(3-((ethoxycarbonyl)oxy)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C10**): To a solution of 2-[4-(2-azaspiro[3.4]octan-6-yl)piperazin-1-yl]pyridin-3-ol (1.60 g, 5.55 mmol) in DCM (10.0 mL) was added Et₃N (1.68 g, 16.6 mmol) and ethyl carbonochloridate (2.80 g, 25.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by an addition of water (10 mL) at 0 °C and then diluted with DCM (5 mL). The mixture was extracted with DCM (3×10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced

pressure to give ethyl 6-[4-(3-ethoxycarbonyloxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate.

LCMS [M+H]⁺ 433.

[0148] Step 6: Synthesis of ethyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (P5): A mixture of ethyl 6-[4-(3-ethoxycarbonyloxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (2.50 g, 5.78 mmol) and NaOH (1.20 g, 30.0 mmol) in EtOH (20.0 mL) and H₂O (10.0 mL) was heated to 60 °C and stirred at 60 °C for 16 hours. The mixture was cooled to 25 °C and concentrated in a vacuum. Then DCM (200 mL) was added to the mixture and filtered. Then filtrate was concentrated under a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~10% MeOH/DCM) to give ethyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. LCMS [M+H]⁺ 361.

2-(5-fluoro-2-piperazin-1-yl-3-pyridyl)-1,3,4-thiadiazole (P6)



[0149] Step 1: Synthesis of tert-butyl 4-(5-fluoro-3-methoxycarbonyl-2-pyridyl)piperazine-1-carboxylate (**C11**):

A mixture of methyl 2-chloro-5-fluoropyridine-3-carboxylate (1.50 g, 7.91 mmol), tert-butyl piperazine-1-carboxylate (1.77 g, 9.50 mmol) and K₂CO₃ (2.19 g, 15.8 mmol) in DMF (15.0 mL) was degassed and purged with a N₂ gas for several times at 25 °C. Then the mixture was heated to 120 °C and stirred at 120 °C for 12 hours under an atmosphere of N₂ gas. The mixture was poured into H₂O (50 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with H₂O (100 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a vacuum to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~7% EtOAc /petroleum ether) to give tert-butyl 4-(5-fluoro-3-methoxycarbonyl-2-pyridyl)piperazine-1-carboxylate. LCMS [M+H]⁺ 340.

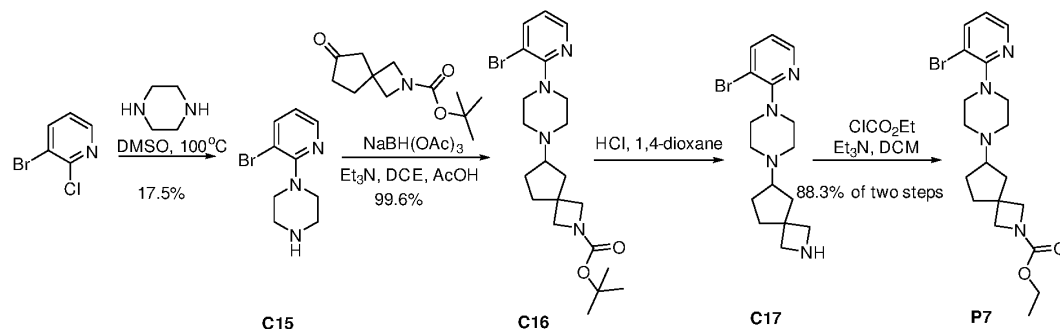
[0150] Step 2: Synthesis of tert-butyl 4-[5-fluoro-3-(hydrazinecarbonyl)-2-pyridyl]piperazine-1-carboxylate (**C12**): To a solution of tert-butyl 4-(5-fluoro-3-methoxycarbonyl-2-pyridyl)piperazine-1-carboxylate (1.81 g, 5.33 mmol) in EtOH (18.0 mL) was added NH₂NH₂·H₂O (4.71 g, 80.0 mmol, 85.0% purity) at 25 °C. Then the mixture was heated to 80 °C and stirred at 80 °C for 16 hours. The mixture was concentrated under a vacuum to give a residue. The residue was purified by triturated with EtOAc /petroleum ether (1/1, 15 mL) at 25 °C, and filtered.

The filtrate was concentrated under a reduced pressure to give tert-butyl 4-[5-fluoro-3-(hydrazinecarbonyl)-2-pyridyl]piperazine-1-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 10.10 (br s, 1H), 8.25 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 3.66-3.56 (m, 4H), 3.13-3.02 (m, 4H), 1.51-1.45 (m, 9H). **LCMS** [M+H]⁺ 340.

[0151] Step 3: Synthesis of tert-butyl 4-[5-fluoro-3-(formamidocarbamoyl)-2-pyridyl]piperazine-1-carboxylate (**C13**): To a solution of tert-butyl 4-[5-fluoro-3-(hydrazinecarbonyl)-2-pyridyl]piperazine-1-carboxylate (1.30 g, 3.83 mmol) in toluene (26.0 mL) was added HCO₂H (1.88 g, 38.3 mmol, 98% purity) at 25 °C under a N₂ gas atmosphere. Then the mixture was heated to 50 °C and stirred at 50 °C for 1 hour. The mixture was adjusted to pH = 8 with saturated aqueous NaHCO₃. The mixture was extracted with EtOAc (3×50 mL). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~35% EtOAc /petroleum ether) to give tert-butyl 4-[5-fluoro-3-(formamidocarbamoyl)-2-pyridyl]piperazine-1-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 13.15 (br d, J = 7.2 Hz, 1H), 9.04 (br d, J = 6.4 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.29-8.11 (m, 2H), 3.76 (br s, 4H), 3.08 (br s, 4H), 1.48 (s, 9H). **LCMS** [M+H]⁺ 368.

[0152] Step 4: Synthesis of tert-butyl 4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazine-1-carboxylate (**C14**): To a solution of tert-butyl 4-[5-fluoro-3-(formamidocarbamoyl)-2-pyridyl]piperazine-1-carboxylate (1.00 g, 2.72 mmol) in toluene (50.0 mL) was added Lawesson's reagent (1.32 g, 3.27 mmol) at 25 °C under a N₂ gas atmosphere. Then the mixture was heated to 90 °C and stirred at 90 °C for 16 hours. The mixture was added saturated aqueous NaHCO₃ (60 mL) and stirred for 5 minutes. The mixture was extracted with EtOAc (3×50 mL). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~25% EtOAc /petroleum ether) to give the tert-butyl 4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazine-1-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 9.28-9.13 (m, 1H), 8.39 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 8.34 (d, J = 2.8 Hz, 1H), 3.67-3.58 (m, 4H), 3.09-2.96 (m, 4H), 1.48 (s, 9H). **LCMS** [M+H]⁺ 366.

[0153] Step 5: Synthesis of 2-(5-fluoro-2-piperazin-1-yl-3-pyridyl)-1,3,4-thiadiazole (**P6**): To a solution of tert-butyl 4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazine-1-carboxylate (100 mg, 274 μ mol) in DCM (3.00 mL) was added HCl/EtOAc (4.00 M, 2.00 mL) at 25 °C under nitrogen gas atmosphere. Then the mixture was stirred at 25 °C for 12 hours. The mixture was adjusted to pH = 8 with saturated aqueous NaHCO₃ and extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrate under vacuum to give a solid. The 2-(5-fluoro-2-piperazin-1-yl-3-pyridyl)-1,3,4-thiadiazole and used in the next step without further purification. **LCMS** [M+H]⁺ 266.

Ethyl 6-(4-(3-bromopyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (P7)

[0154] Step 1: Synthesis of 1-(3-bromopyridin-2-yl)piperazine (**C15**): A mixture of 3-bromo-2-chloropyridine (1.00 g, 5.20 mmol) and piperazine (537 mg, 6.24 mmol) in DMSO (20.0 mL) was stirred at 100 °C for 16 hours. The mixture was worked up with another same scale together. The residue was poured into water (150 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~30% EtOAc / MeOH) to afford 1-(3-bromo-2-pyridyl)piperazine. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.23 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.79 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 6.78 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 3.35-3.27 (m, 4H), 3.10-3.01 (m, 4H). **LCMS** [M+H]⁺ 242, 244.

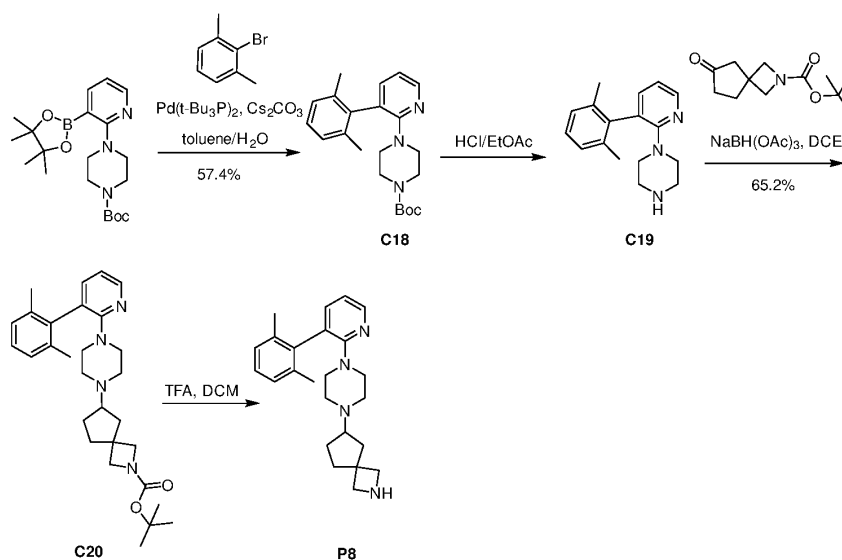
[0155] Step 2: Synthesis of tert-butyl 6-(4-(3-bromopyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]-octane-2-carboxylate (**C16**): To a mixture of tert-butyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (409 mg, 1.82 mmol) and 1-(3-bromo-2-pyridyl)piperazine (550 mg, 1.82 mmol) in DCE (10.0 mL) was added HOAc (0.100 mL) and NaBH(OAc)₃ (1.16 g, 5.45 mmol) in one portion. The mixture was stirred at 20 °C for 16 hours. The residue was poured into saturated aqueous NaHCO₃ (50 mL). The aqueous phase was extracted with DCM (3 × 30 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~15% MeOH/DCM) to afford tert-butyl 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]-octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.23 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.78 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 6.77 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 3.89-3.83 (m, 1H), 3.83-3.78 (m, 1H), 3.77-3.71 (m, 2H), 3.39 (br s, 4H), 2.65 (br s, 5H), 2.20-2.10 (m, 1H), 1.99-1.81 (m, 3H), 1.79-1.70 (m, 1H), 1.45 (s, 9H). **LCMS** [M+H]⁺ 451, 453.

[0156] Step 3: Synthesis of 6-(4-(3-bromopyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane (**C17**): A mixture of tert-butyl 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]-octane-2-carboxylate (850 mg, 1.88 mmol) in 1,4-dioxane (10.0 mL) was added HCl/1,4-dioxane (4 M, 4.00 mL) in one portion at 20 °C for 1 hour. The mixture was concentrated to give 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane, which was used for the next step directly.

[0157] Step 4: Synthesis of ethyl 6-(4-(3-bromopyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**P7**): To a mixture of 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (1.00 g, 2.85

mmol, HCl salt) and Et₃N (1.44 g, 14.2 mmol) in DCM (10.0 mL) was added ethyl carbonochloridate (970 mg, 8.94 mmol) in one portion at 0 °C under a nitrogen atmosphere. The mixture was stirred at 20 °C for 2 hours. The residue was poured into water (50 mL). The aqueous phase was extracted with DCM (3 × 30 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~20% MeOH/DCM) to afford ethyl 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.23 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.78 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 6.77 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 4.16-4.10 (m, 2H), 3.94-3.89 (m, 1H), 3.88-3.83 (m, 1H), 3.83-3.77 (m, 2H), 3.38 (br s, 4H), 2.64 (br s, 5H), 2.20-2.10 (m, 1H), 1.99-1.90 (m, 2H), 1.89-1.73 (m, 2H), 1.61-1.54 (m, 1H), 1.30-1.24 (m, 3H). **LCMS** [M+H]⁺ 423, 425.

6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]-octane (P8)



[0158] Step 1: Synthesis of tert-butyl 4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazine-1-carboxylate (**C18**): A mixture of tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-piperazine-1-carboxylate (200 mg, 514 μmol), 2-bromo-1,3-dimethylbenzene (114 mg, 617 μmol), Pd(t-Bu₃P)₂ (26.3 mg, 51.4 μmol), Cs₂CO₃ (502 mg, 1.54 mmol), toluene (4.50 mL), and H₂O (0.500 mL) was added in a sealed tube in the glovebox under N₂ gas, then was heated to 80 °C and stirred for 16 hours at 80 °C. Then the mixture was cooled to 25 °C and concentrated in vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~8% EtOAc /petroleum ether) to give tert-butyl 4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazine-1-carboxylate. **LCMS** [M+H]⁺ 368.

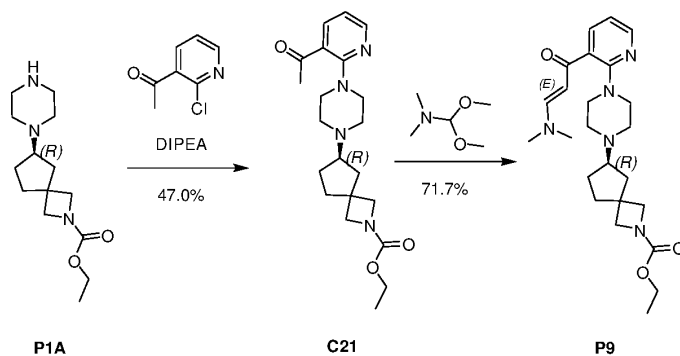
[0159] Step 2: Synthesis of 1-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazine (**C19**): A mixture of tert-butyl 4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazine-1-carboxylate (110 mg, 299 μmol) in EtOAc (5.00 mL) and then HCl/EtOAc (4 M, 3.00 mL) was added to the mixture at 20 °C. The mixture was stirred at 20 °C for 4 hours. The

mixture was concentrated in a vacuum and was used as is in the next step without further purification. **LCMS** [M+H]⁺ 268.

[0160] Step 3: Synthesis of tert-butyl 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C20**): A mixture of 1-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazine (90.0 mg, 296 μ mol, HCl salt) and Et₃N (150 mg, 1.48 mmol) in DCE (5.00 mL) was stirred at 20 °C for 10 min. Then tert-butyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (66.7 mg, 296 μ mol) was added to the mixture and stirred at 20 °C for 20 min. Then AcOH (12.8 mg, 214 μ mol) and NaBH(OAc)₃ (188 mg, 889 μ mol) were added into the mixture at 20 °C and stirred at 20 °C for 16 hours. Then an aqueous solution of NaHCO₃ (10%, 25 mL) was added to the mixture and the mixture was extracted with DCM (50 mL $\times$ 2), dried over anhydrous Na₂SO₄. The combined organic phase was concentrated under a vacuum. The residue was purified by silica gel flash chromatography (Eluent of 0~3% MeOH/DCM) to afford tert-butyl 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** [M+H]⁺ 477.

[0161] Step 4: Synthesis of 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane (**P8**): tert-Butyl 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (95.0 mg, 199 μ mol) was dissolved in DCM (5.00 mL) to obtain a clear solution. Then TFA (0.250 mL, 3.39 mmol) was added to the mixture and stirred for 2 hours at 20 °C. The mixture was concentrated in a vacuum and was used in the next step without further purification. **LCMS** [M+H]⁺ 377.

Ethyl (6R)-6-[4-[3-[(E)-3-(dimethylamino)prop-2-enyl]-2-pyridyl]-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**P9**)

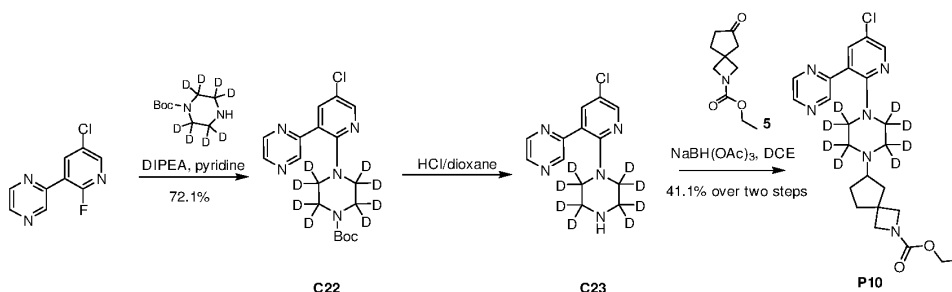


[0162] Step 1: Synthesis of ethyl 6-[4-(3-acetyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C21**): To a solution of ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (300 mg, 1.12 mmol) in DIPEA (10.0 mL) was added 1-(2-chloro-3-pyridyl)ethanone (175 mg, 1.12 mmol) in one portion at 20 °C. The mixture was heated to 130 °C and stirred for 16 hours. The mixture was cooled to 20 °C. The mixture was added water (20 mL), DCM (10 mL) and stirred for 5 min, and separated. The aqueous phase was extracted with DCM (2 $\times$ 10 mL). The combined organic phase was concentrated under a reduced pressure at 50 °C. The residue was purified by silica gel flash chromatography (Eluent of 0~5% MeOH/DCM) to afford ethyl 6-[4-(3-acetyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃, 400 MHz) δ _H = 8.29 (dd, *J* = 2.0 Hz,

4.8 Hz, 1H), 7.72 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.83 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92 - 3.74 (m, 4H), 3.42-3.30 (m, 4H), 2.70-2.45 (m, 8H), 2.15-2.10 (m, 1H), 1.98-1.80 (m, 3H), 1.77-1.69 (m, 1H), 1.55-1.53 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). **LCMS** $[M+H]^+$ 387.

[0163] Step 2: Synthesis of ethyl (6R)-6-[4-[3-[(E)-3-(dimethylamino)prop-2-enoyl]-2-pyridyl]-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**P9**): A mixture of ethyl (6R)-6-[4-(3-acetyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (120 mg, 310 μ mol) and 1,1-dimethoxy-N,N-dimethyl-methanamine (1.20 mL, 9.03 mmol) was heated to 100 °C and stirred for 16 hours at 100 °C. The mixture was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~8% MeOH/DCM) to give ethyl (6R)-6-[4-[3-[(E)-3-(dimethylamino)prop-2-enoyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** $[M+H]^+$ 442.

Ethyl 6-[4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate(**P10**)

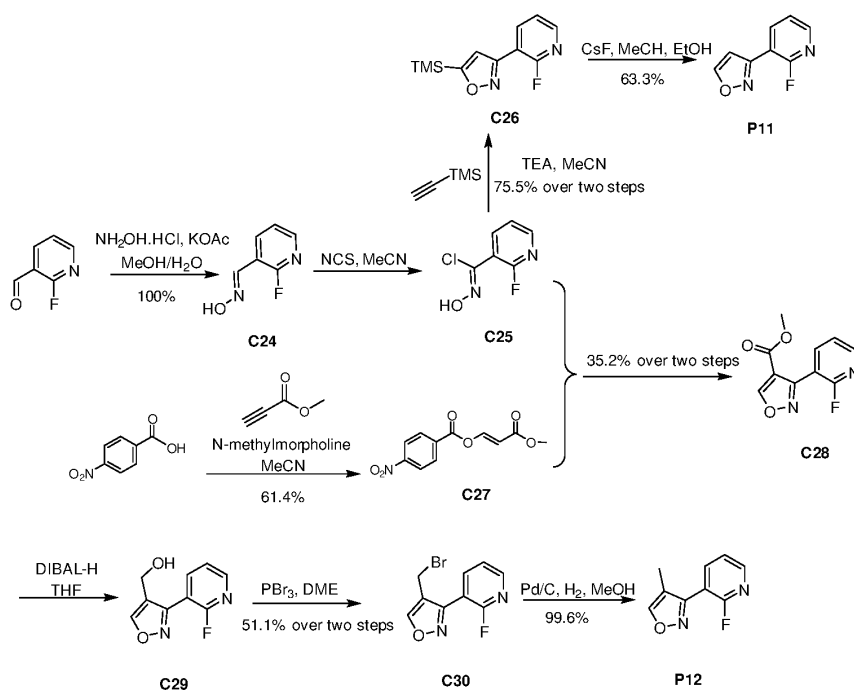


[0164] Step 1: Synthesis of tert-butyl 4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine-1-carboxylate (**C22**): A mixture of 2-(5-chloro-2-fluoro-3-pyridyl)pyrazine (450 mg, 2.15 mmol) and tert-butyl 2,2,3,3,5,5,6,6-octadeuteriopiperazine-1-carboxylate (417 mg, 2.15 mmol) in pyridine (10.0 mL) and DIPEA (10.0 mL) was heated to 130 °C and stirred at 130 °C for 12 hours. The reaction mixture was poured into water (50 mL) at 20 °C, then extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under a reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~70% EtOAc /petroleum ether) to afford tert-butyl 4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine-1-carboxylate. **LCMS** $[M+H]^+$ 384.

[0165] Step 2: Synthesis of 1-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine (**C23**): To a solution of tert-butyl 4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine-1-carboxylate (600 mg, 1.56 mmol) in 1,4-dioxane (10.0 mL) was added HCl/EtOAc (4 M, 4.00 mL) in one portion at 20 °C. The mixture was stirred at 20 °C for 1 hour. The mixture was concentrated under reduced pressure to give 1-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine. The product was used for next step directly without further purification. **LCMS** $[M+H]^+$ 284.

[0166] Step 3: Synthesis of ethyl 6-[4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**P10**): To a solution of 1-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazine (440 mg, 1.55 mmol) and ethyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (367 mg, 1.86 mmol) in DCE (5.00 mL) was added HOAc (9.31 mg, 155 μ mol) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 30 min, then NaBH(OAc)₃ (986 mg, 4.65 mmol) was added at 0 °C. The mixture was warmed to 20 °C and stirred at 20 °C for 16 hours. The reaction mixture was poured into water (50 mL) at 20 °C, then extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~30% of MeOH in DCM) to give ethyl 6-[4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** [M+H]⁺ 465.

3-(2-fluoropyridin-3-yl)isoxazole (**P11**) and 3-(2-fluoropyridin-3-yl)-4-methylisoxazole (**P12**)



[0167] Step 1: Synthesis of (E)-2-fluoronicotinaldehyde oxime (**C24**): To a solution of 2-fluoropyridine-3-carbaldehyde (1.00 g, 7.99 mmol) in MeOH (2.00 mL) was added a solution of NH₂OH·HCl (833 mg, 12.0 mmol) and KOAc (1.18 g, 12.0 mmol) in H₂O (7.00 mL). The mixture was stirred at 15 °C for 4 hours. The mixture was concentrated under reduced pressure to remove MeOH. Then the residue was added saturated aqueous Na₂CO₃ (50 mL) and extracted with DCM (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (eluent of 0~20% EtOAc /petroleum ether) to give (3E)-2-fluoropyridine-3-carbaldehyde oxime. **LCMS** [M+H]⁺ 141.

[0168] Step 2: Synthesis of (Z)-2-fluoro-N-hydroxynicotinimidoyl chloride (**C25**): (3E)-2-Fluoropyridine-3-carbaldehyde oxime (900 mg, 6.42 mmol) was dissolved in MeCN (15.0 mL). Then, a solution of NCS (1.03 g, 7.71 mmol) in MeCN (15.0 mL) was slowly added dropwise at 15 °C. After the addition, the reaction mixture was stirred at 15 °C for 3 hours. The mixture was used in the next step without work up.

[0169] Step 3: Synthesis of 3-(2-fluoropyridin-3-yl)-5-(trimethylsilyl)isoxazole (**C26**): To a solution of (3Z)-2-fluoro-N-hydroxy-pyridine-3-carboximidoyl chloride (1.10 g, 6.30 mmol) and ethynyl(trimethyl)silane (1.05 mL, 7.56 mmol) in MeCN (30.0 mL) was added TEA (965 μ L, 6.93 mmol) and the reaction mixture was stirred at 15 °C for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~30% EtOAc /petroleum ether) to give [3-(2-fluoro-3- pyridyl)isoxazol-5-yl]-trimethyl-silane. ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.60-8.41 (m, 1H), 8.30-8.25 (m, 1H), 7.32-7.28 (m, 1H), 6.91-6.88 (m, 1H), 0.38 (m, 9H). ¹⁹F NMR (CDCl₃ 400 MHz) δ_{F} = -68.19. LCMS [M+H]⁺ 237.

[0170] Step 4: Synthesis of 3-(2-fluoropyridin-3-yl)isoxazole (**P11**): To a solution of [3-(2-fluoro-3-pyridyl)isoxazol-5-yl]-trimethyl-silane (100 mg, 423 μ mol) in EtOH (1.00 mL) and MeCN (3.00 mL) was added CsF (46.8 μ L, 1.27 mmol). The reaction was stirred at 20 °C for 2 hours. The mixture was concentrated under a reduced pressure. The residue was diluted with DCM (30 mL) and washed with water (20 mL). The organic phase was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~50% EtOAc /petroleum ether) to give 3-(2-fluoro-3- pyridyl)-isoxazole. LCMS [M+H]⁺ 165.

[0171] Step 5: Synthesis of (E)-3-methoxy-3-oxoprop-1-en-1-yl 4-nitrobenzoate (**C27**): 4-Nitrobenzoic acid (3.00 g, 17.9 mmol) and methyl prop-2-ynoate (1.64 mL, 19.7 mmol) were dissolved in MeCN (30.0 mL) and N-methylmorpholine (990 μ L, 8.98 mmol) was added. Then the mixture was stirred at 40 °C for 16 hours. The mixture was concentrated under a reduced pressure to remove MeCN. The residue was stirred in MTBE (100 mL) for 30 min at 20 °C, then the mixture was filtered. The collected filter cake was dried under a reduced pressure to give [(E)-3-methoxy-3-oxo-prop-1-enyl] 4-nitrobenzoate. ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.52 (d, *J* = 12.8 Hz, 1H), 8.37-8.30 (m, 4H), 5.98 (d, *J* = 12.4 Hz, 1H), 3.80 (s, 3H).

[0172] Step 6: Synthesis of methyl 3-(2-fluoropyridin-3-yl)isoxazole-4-carboxylate (**C28**): To a solution of (3Z)-2-fluoro-N-hydroxy-pyridine-3-carboximidoyl chloride (1.25 g, 7.16 mmol) in MeCN was added a solution of [(E)-3-methoxy-3-oxo-prop-1-enyl] 4-nitrobenzoate (1.05 mL, 7.88 mmol) in DCM (20.0 mL). Then TEA (1.10 mL, 7.88 mmol) was added in one portion. The mixture was stirred at 15 °C for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~30% EtOAc /petroleum ether) to give methyl 3-(2-fluoro-3-pyridyl)isoxazole-4-carboxylate. LCMS [M+H]⁺ 223.

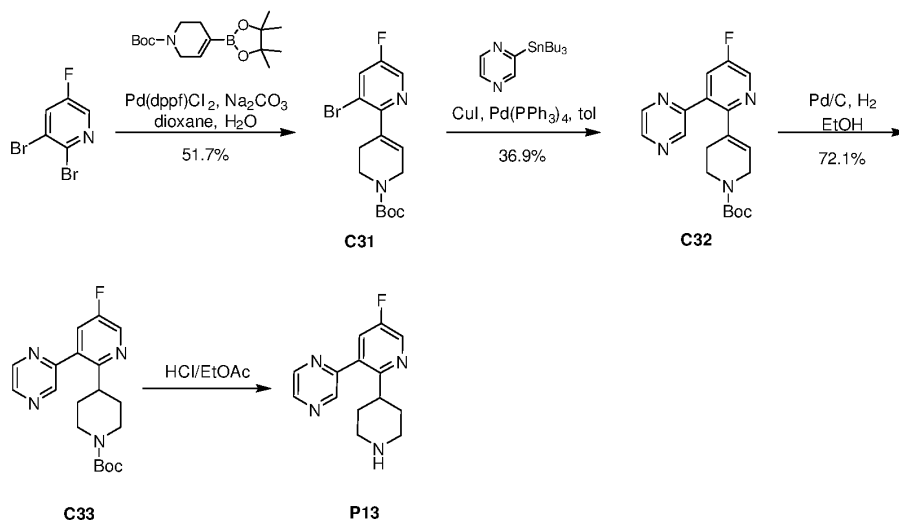
[0173] Step 7: Synthesis of (3-(2-fluoropyridin-3-yl)isoxazol-4-yl)methanol (**C29**): A solution of methyl 3-(2-fluoro-3-pyridyl)isoxazole-4-carboxylate (690 mg, 3.11 mmol) in THF (20.0 mL) was cooled to -30 °C in a dry-ice bath. Then DIBAL-H in toluene (1 M, 12.4 mL) was added dropwise and the mixture was stirred at -30 °C for 3 hours. The reaction mixture was quenched by an addition of saturated aqueous NaHCO₃ (20 mL) at -30 °C to 20 °C. Then the mixture was diluted with EtOAc (20 mL) and extracted with EtOAc (2 $\times$ 10 mL). The combined

organic layer was washed with water (20 mL), dried over Na₂SO₄, filtered and concentrated under a reduced pressure to give [3-(2-fluoro-3-pyridyl)isoxazol-4-yl]methanol, which was used to the next step without further purification. ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.60-8.53 (m, 1H), 8.41-8.31 (m, 1H), 8.16-8.10 (m, 1H), 7.37-7.34 (m, 1H), 4.71-4.65 (m, 2H). ¹⁹F NMR (CDCl₃ 400 MHz) δ_{F} = -67.89.

[0174] Step 8: Synthesis of 4-(bromomethyl)-3-(2-fluoropyridin-3-yl)isoxazole (**C30**): To solution of [3-(2-fluoro-3-pyridyl)isoxazol-4-yl]methanol (348 mg, 1.79 mmol) in DME (6.00 mL) was added dropwise PBr₃ (1.21 g, 4.48 mmol) at 0 °C. Then this mixture was stirred at 20 °C for 6 hours. The mixture was cooled to 0 °C and neutralized with saturated aqueous NaHCO₃ to pH=7.0. To this mixture DCM (20 mL) and H₂O (10 mL) were added, stirred and separated. The aqueous layer was extracted with DCM (20 mL). The combined organic layer was dried over anhydrous MgSO₄, filtered and concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~30% EtOAc /petroleum ether) to give 4-(bromomethyl)-3-(2-fluoro-3-pyridyl)isoxazole. LCMS [M+H]⁺ 257, 259.

[0175] Step 9: Synthesis of 3-(2-fluoropyridin-3-yl)-4-methylisoxazole (**P12**): A mixture of 4-(bromomethyl)-3-(2-fluoro-3-pyridyl)isoxazole (100 mg, 389 μ mol) and 10% wet Pd/C (50.0 mg) in MeOH (4.00 mL). The mixture was degassed and purged with H₂ gas for three times. The mixture was stirred at 20 °C for 5 hours under H₂ gas (15 psi). The mixture was filtered and concentrated under a reduced pressure to give 3-(2-fluoro-3-pyridyl)-4-methyl-isoxazole, which was used in the next step without further purification. LCMS [M+H]⁺ 179.

2-(5-fluoro-2-(piperidin-4-yl)pyridin-3-yl)pyrazine (**P13**)



[0176] Step 1: Synthesis of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (**C31**): A mixture of 2,3-dibromo-5-fluoro-pyridine (500 mg, 1.96 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (606 mg, 1.96 mmol), Na₂CO₃ (415 mg, 3.92 mmol) in 1,4-dioxane (10.0 mL) and H₂O (2.00 mL) was added Pd(dppf)Cl₂ 226 mg, 196 μ mol at 20 °C. Then the mixture was purged with N₂ for 3 times at 20 °C. The mixture was stirred at 100 °C for 16 hours under N₂. The mixture

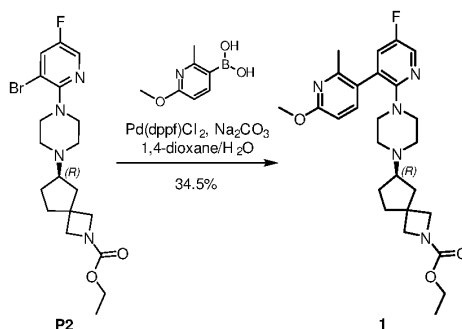
was concentrated under a reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of 0~30% EtOAc /Petroleum ether) to give tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.40 (d, *J* = 2.4 Hz, 1H), 7.68 (dd, *J* = 2.4 Hz, 7.6 Hz, 1H), 5.98 (br s, 1H), 4.13-4.07 (m, 2H), 3.69-3.61 (m, 2H), 2.57-2.50 (m, 2H), 1.49 (s, 9H). **LCMS** [M+H]⁺ 304.

[0177] Step 2: Synthesis of tert-butyl 4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (**C32**): A mixture of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (280 mg, 783 μ mol), tributyl(pyrazin-2-yl)stannane (289 mg, 783 μ mol), Pd(PPh₃)₄ (90.6 mg, 78.4 μ mol), CuI (14.9 mg, 78.4 μ mol) in toluene (3.00 mL) was degassed and purged with N₂ gas for 3 times at 20 °C. Then the mixture was heated to 110 °C and stirred at 110 °C for 16 hours under a N₂ atmosphere. The filtrate was concentrated under a reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~50% EtOAc /Petroleum ether) to give tert-butyl 4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate. **LCMS** [M+H]⁺ 257.

[0178] Step 3: Synthesis of tert-butyl 4-(5-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperidine-1-carboxylate (**C33**): A mixture of tert-butyl 4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (124 mg, 347 μ mol), wet Pd/C (50.0 mg, 10% wt.) in EtOH (5.00 mL) was degassed and purged with H₂ gas for 3 times, and then the mixture was stirred at 50 °C for 24 hours under H₂ gas (40 psi). The mixture was filtered and the filtrate was concentrated under a reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~30% EtOAc /Petroleum ether) to give tert-butyl 4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)piperidine-1-carboxylate. **LCMS** [M+H]⁺ 259.

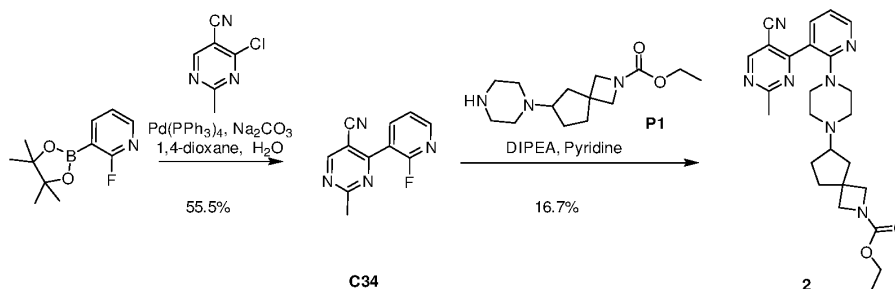
[0179] Step 4: Synthesis of 2-(5-fluoro-2-(piperidin-4-yl)pyridin-3-yl)pyrazine (**P13**): A mixture of tert-butyl 4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)piperidine-1-carboxylate (90.0 mg, 251 μ mol) and HCl/1,4-dioxane (5.00 mL, 4M) was stirred at 20 °C for 2 hours under N₂. The mixture was concentrated under reduced pressure to give 2-[5-fluoro-2-(4-piperidinyl)-3-pyridyl]pyrazine, which was used directly in the next without further purification. **LCMS** [M+H]⁺ 259.

Example 1: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(6-methoxy-2-methyl-3-pyridyl)-2-pyridyl]-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**1**)



[0180] Step 1: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(6-methoxy-2-methyl-3-pyridyl)-2-pyridyl]-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**1**): A mixture of ethyl (6R)-6-[4-(3-bromo-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (40.0 mg, 90.6 μ mol), (6-methoxy-2-methyl-3-pyridyl)boronic acid (22.7 mg, 136 μ mol), Pd(dppf)Cl₂ (6.63 mg, 9.06 μ mol), Na₂CO₃ (28.8 mg, 272 μ mol) in 1,4-dioxane (2.00 mL) and H₂O (0.500 mL) was degassed and purged with N₂ gas for 3 times. The mixture was stirred at 90 °C for 2 hours under a N₂ gas atmosphere. The reaction mixture was concentrated under a reduced pressure to remove the solvent to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150×25mm 10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 53%-83%, 9min) to give ethyl (6R)-6-[4-[5-fluoro-3-(6-methoxy-2-methyl-3-pyridyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ _H = 8.11 (d, *J* = 2.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 3.88-3.78 (m, 2H), 3.74 (s, 2H), 3.03 (br s, 4H), 2.49 (br s, 1H), 2.34 (s, 7H), 2.06 (br dd, *J* = 6.8 Hz, 12.4 Hz, 1H), 1.95-1.74 (m, 4H), 1.56-1.46 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). ¹⁹F NMR (CDCl₃ 400 MHz) δ _F = -138.654. LCMS [M+H]⁺ 484.

Example 2: Synthesis of ethyl 6-(4-(3-(5-cyano-2-methylpyrimidin-4-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**2**)

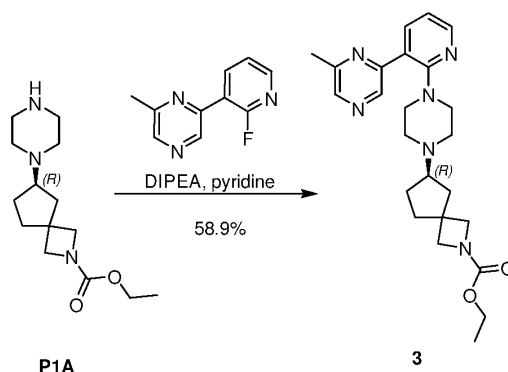


[0181] Step 1: Synthesis of 4-(2-fluoro-3-pyridyl)-2-methyl-pyrimidine-5-carbonitrile (**C34**): To a mixture of 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (435 mg, 1.95 mmol), 4-chloro-2-methyl-pyrimidine-5-carbonitrile (200 mg, 1.30 mmol) and Na₂CO₃ (414 mg, 3.91 mmol) in 1,4-dioxane (4.00 mL) and H₂O (0.50 mL) was added Pd(PPh₃)₄ (150 mg, 130 μ mol) in one portion at 20 °C. The mixture was degassed under a vacuum and purged with N₂ gas several times. The mixture was heated to 90 °C and stirred for 16 hours at 90 °C. The reaction mixture was cooled to 20 °C and DCM (20 mL) was added. The mixture was washed with brine (20 mL). The organic layer was separated and dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~10% EtOAc /petroleum ether) to give 4-(2-fluoro-3-pyridyl)-2-methyl-pyrimidine-5-carbonitrile. LCMS [M+H]⁺ 215.

[0182] Step 2: Synthesis of ethyl 6-[4-[3-(5-cyano-2-methyl-pyrimidin-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**2**): To a mixture of 4-(2-fluoro-3-pyridyl)-2-methyl-pyrimidine-5-carbonitrile (130 mg, 607 μ mol), ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (194 mg, 728 μ mol) was added DIPEA (3.00 mL) and pyridine (3.00 mL) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was heated to 90 °C and stirred for 16 hours. The reaction mixture was concentrated in vacuum to give the crude

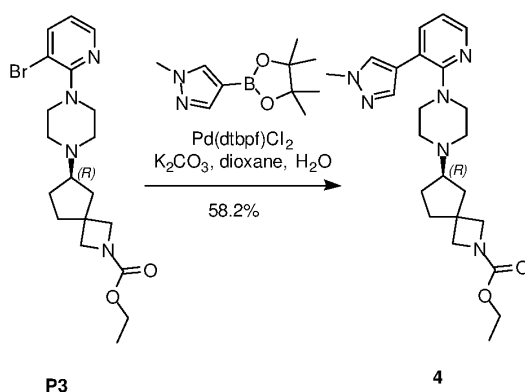
as a brown oil. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80×40mm×3um; mobile phase: [water (0.05% NH₃H₂O + 10mM NH₄HCO₃)-ACN]; B%: 26%-56%, 8 min) to give ethyl 6-[4-[3-(5-cyano-2-methyl-pyrimidin-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ_{H} = 8.91 (s, 1H), 8.43 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.75 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.03 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.90-3.82 (m, 2H), 3.81-3.75 (m, 2H), 3.22-3.13 (m, 4H), 2.89 (s, 3H), 2.62-2.52 (m, 1H), 2.50-2.39 (m, 4H), 2.14-2.06 (m, 1H), 1.97-1.77 (m, 3H), 1.73-1.68 (m, 1H), 1.57-1.48 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 462.

Example 3: Synthesis of ethyl (6R)-6-[4-[3-(6-methylpyrazin-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (3)



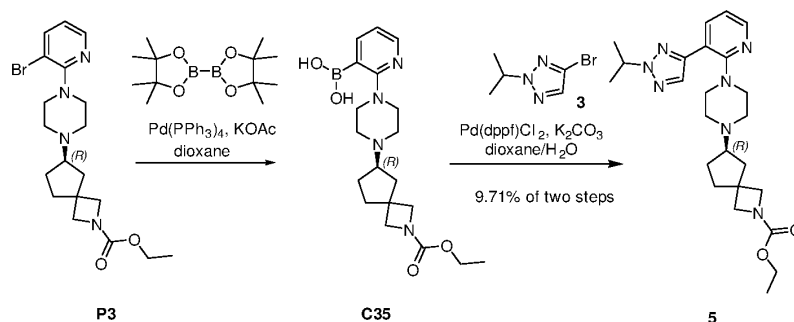
[0183] Synthesis of ethyl (6R)-6-[4-[3-(6-methylpyrazin-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (3): A mixture of 2-(2-fluoro-3-pyridyl)-6-methyl-pyrazine (50.0 mg, 264 μ mol), ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (70.7 mg, 264 μ mol), DIPEA (1.00 mL) and pyridine (1.00 mL) was heated to 130 °C and stirred for 16 hours at 130 °C. The reaction mixture was concentrated in a vacuum to give the crude as a brown oil. The residue was purified by prep-HPLC (column: Boston Prime C18 150×30mm×5um; mobile phase: [water (0.05% NH₃H₂O + 10mM NH₄HCO₃)-ACN]; B%: 40%-70%, 7 min) to give ethyl (6R)-6-[4-[3-(6-methylpyrazin-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ_{H} = 9.03 (s, 1H), 8.36 (s, 1H), 8.31 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.87 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.00 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.90-3.80 (m, 2H), 3.79-3.74 (m, 2H), 3.16 (t, J = 4.8 Hz, 4H), 2.64 (s, 3H), 2.60-2.38 (m, 5H), 2.12-2.04 (m, 1H), 1.96-1.78 (m, 3H), 1.73-1.65 (m, 1H), 1.57-1.46 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 437.

Example 4: Synthesis of ethyl (6R)-6-[4-[3-(1-methylpyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**4**)



[0184] Synthesis of ethyl (6R)-6-[4-[3-(1-methylpyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**4**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 118 μ mol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (24.6 mg, 118 μ mol) in 1,4-dioxane (2.00 mL) and H₂O (400 μ L) was added PdCl₂(dtbpf) (7.70 mg, 11.8 μ mol) and K₂CO₃ (32.7 mg, 236 μ mol) in one portion at 20 °C. Then the mixture was degassed under vacuum and purged with N₂ gas several times. The reaction mixture was heated to 100 °C and stirred at 100 °C for 16 hours under a nitrogen gas atmosphere. The mixture was concentrated under a reduced pressure at 50 °C. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80×40mm×3 μ m; mobile phase: [water(0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 26%-50%, 8 min) to give ethyl (6R)-6-[4-[3-(1-methylpyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ _H = 8.17 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.87 (s, 1H), 7.75 (s, 1H), 7.52 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 6.89 (dd, *J* = 5.2 Hz, 7.6 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.98-3.94 (m, 3H), 3.92-3.75 (m, 4H), 3.28-3.02 (m, 4H), 2.74-2.31 (m, 5H), 2.16-2.08 (m, 1H), 1.98-1.77 (m, 3H), 1.76-1.66 (m, 1H), 1.58-1.47 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 425.

Example 5: Synthesis of ethyl (6R)-6-[4-[3-(2-isopropyltriazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**5**)

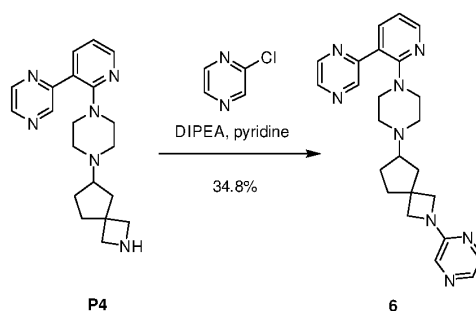


[0185] Step 1: Synthesis of (R)-2-(4-(2-(ethoxycarbonyl)-2-azaspiro[3.4]octan-6-yl)piperidin-1-yl)pyridin-3-yl)boronic acid (**C35**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-

carboxylate (100 mg, 236 μmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (112 mg, 472 μmol) in 1,4-dioxane (5.00 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (27.3 mg, 23.6 μmol) and KOAc (46.4 mg, 472 μmol) in one portion at 25 °C. Then the mixture was degassed under vacuum and purged with N_2 gas several times. The reaction mixture was heated to 100 °C and stirred at 100 °C for 16 hours under a nitrogen gas atmosphere. The reaction mixture was cooled to 25 °C. The reaction mixture was used directly in the next step without further purification.

[0186] Step 2: Synthesis of ethyl (6R)-6-[4-[3-(2-isopropyltriazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**5**): A mixture of [2-[4-[(6R)-2-ethoxycarbonyl-2-azaspiro[3.4]octan-6-yl]piperazin-1-yl]-3-pyridyl]boronic acid (91.7 mg, 236 μmol) in 1,4-dioxane was added 4-bromo-2-isopropyltriazole (49.4 mg, 260 μmol), H_2O (500 μL), $\text{Pd}(\text{dppf})\text{Cl}_2$ (17.3 mg, 23.62 μmol) and K_2CO_3 (65.3 mg, 472 μmol) at 25 °C. Then the mixture was degassed under a vacuum and purged with N_2 gas several times. The reaction mixture was heated to 100 °C and stirred at 100 °C for 12 hours under a nitrogen gas atmosphere. The mixture was cooled to 25 °C and added DCM (5 mL) and filtered. The filtrate was concentrated under a reduced pressure at 50 °C. The residue was purified by silica gel flash chromatography (eluent of 0~10% MeOH/DCM) to afford a crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 $\times$ 30 mm $\times$ 5 μm ; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$)-ACN]; B%: 45%-75%, 7 min) to give ethyl (6R)-6-[4-[3-(2-isopropyltriazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. $^1\text{H NMR}$ (CDCl_3 400 MHz) δ_{H} = 8.26 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.10 (s, 1H), 7.97 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.96 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.90-4.83 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.90-3.75 (m, 4H), 3.19-3.12 (m, 4H), 2.61-2.50 (m, 5H), 2.15-2.08 (m, 1H), 1.96-1.79 (m, 3H), 1.76-1.68 (m, 1H), 1.65-1.61 (m, 6H), 1.56-1.52 (m, 1H), 1.24 (m, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 454.

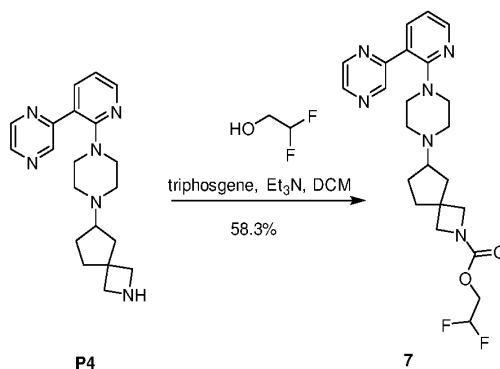
Example 6: Synthesis of 2-pyrazin-2-yl-6-[4-(3-pyrazin-2-yl-2-pyridyl) piperazin-1-yl] -2-azaspiro[3.4]octane (6**)**



[0187] Synthesis of 2-(pyrazin-2-yl)-6-[4-(3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl]-2-azaspiro[3.4]octane (**6**): A solution of 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (50.0 mg, 143 μmol) and 2-chloropyrazine (15.3 μL , 171 μmol) in DIPEA (2.50 mL, 14.3 mmol) and pyridine (1.25 mL, 15.5 mmol) was stirred at 100 °C for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 $\times$ 30mm $\times$ 5 μm ; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$)-ACN]; B%: 23%-53%, 7 min) to give 2-pyrazin-2-yl-6-[4-(3-pyrazin-2-yl-2-pyridyl) piperazin-1-yl] -2-

azaspiro[3.4]octane. ¹H NMR (CDCl₃ 400 MHz) δ_H = 9.25 (d, *J* = 1.2 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 8.33 (dd, *J* = 2.0 Hz, 4.8 Hz, 1H), 8.04-7.89 (m, 1H), 7.87 (dd, *J* = 2.0 Hz, 3.6 Hz, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.75 (s, 1H), 7.02 (dd, *J* = 5.2 Hz, 7.6 Hz, 1H), 4.00-3.90 (m, 4H), 3.17 (t, *J* = 4.0 Hz, 4H), 2.63-2.57 (m, 1H), 2.48 (d, *J* = 4.0 Hz, 4H), 2.18 (dd, *J* = 7.2 Hz, 12.8 Hz, 1H), 2.04-2.00 (m, 1H), 1.96-1.87 (m, 2H), 1.78 (dd, *J* = 9.6 Hz, 12.8 Hz, 1H), 1.57-1.50 (m, 1H). LCMS [M+H]⁺ 429.

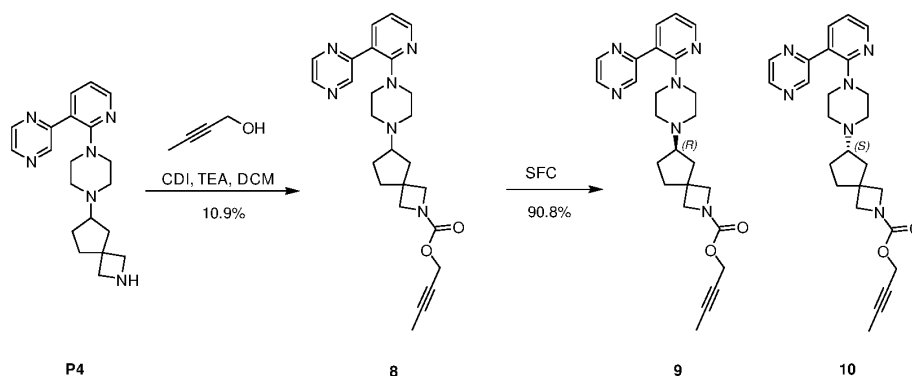
Example 7: Synthesis of 2,2-difluoroethyl 6-[4-(3-pyrazin-2-yl-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (7)



[0188] Synthesis of 2,2-difluoroethyl 6-(4-(3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**7**): A solution of 2,2-difluoroethanol (719 uL, 12.2 mmol), bis(trichloromethyl) carbonate (1.22 g, 4.11 mmol) and DMF (93.8 uL, 1.22 mmol) in DCM (6.00 mL) was cooled to 0 °C. Et₃N (1.70 mL, 12.2 mmol) was added and stirred at 20 °C for 3 hours. Then a solution of 6-[4-(3-pyrazin-2-yl-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]octane (100 mg, 285 umol) and Et₃N (119 uL, 856 umol) in DCM (4.00 mL) was added. The mixture was stirred at 20 °C for 2 hours. The mixture was diluted with DCM (20 mL) and washed with saturated aqueous Na₂CO₃ (20 mL), brine (20 mL), then dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The crude product was purified by prep-HPLC (column: Boston Prime C18 150×30 mm×5 um; mobile phase: [water (0.05% NH₃H₂O + 10mM NH₄HCO₃)- CAN]; B%: 35%-65%, 7 min) to give 2,2-difluoroethyl 6-[4-(3-pyrazin-2-yl-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ_H = 9.23 (s, 1H), 8.67 (dd, *J* = 2.8 Hz, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.33 (dd, *J* = 2.0 Hz, 5.2 Hz, 1H), 7.87 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.02 (dd, *J* = 4.8 Hz, 7.2 Hz, 1H), 6.06-5.77 (m, 1H), 4.26-4.18 (m, 2H), 3.92-3.81 (m, 4H), 3.16 (t, *J* = 4.8 Hz, 4H), 2.55-2.45 (m, 5H), 2.08 (dd, *J* = 4.8 Hz, 7.2 Hz, 1H), 1.95-1.79 (m, 3H), 1.72-1.67 (m, 1H), 1.53-1.49 (m, 1H). ¹⁹F NMR (CDCl₃ 400 MHz) δ_F = -126.01. LCMS [M+H]⁺ 459.

Examples 8, 9 and 10: Synthesis of but-2-ynyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**8**), but-2-ynyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-

azaspiro[3.4]-octane-2-carboxylate (**9**), and but-2-ynyl (6S)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro-[3.4]octane-2-carboxylate (**10**)

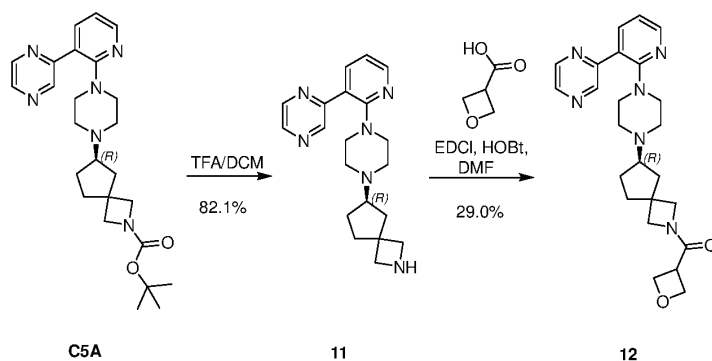


[0189] Step 1: Synthesis of but-2-ynyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**8**): A solution of but-2-yn-1-ol (21.0 mg, 300 μ mol) and CDI (48.6 mg, 300 μ mol) in DCM (2.00 mL) was stirred at 20 °C for 1 hour. Then Et₃N (36.4 mg, 360 μ mol) and 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (105 mg, 300 μ mol) in DCM (1.00 mL) was added. Then the mixture was stirred at 20 °C for 16 hours. The mixture was diluted with DCM (40 mL), washed with saturated aqueous NaHCO₃ (20 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under a reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75×30mm×3 μ m; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; B%: 37%-67%, 7 min) to give but-2-ynyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 9.24 (d, J = 1.2 Hz, 1H), 8.65 (dd, J = 1.6 Hz, 2.4 Hz, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.87 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.01 (dd, J = 5.2 Hz, 7.6 Hz, 1H), 4.65-4.60 (m, 2H), 3.93-3.82 (m, 2H), 3.80 (s, 2H), 3.15 (t, J = 4.8 Hz, 4H), 2.61-2.50 (m, 1H), 2.50-2.40 (m, 3H), 2.49-2.40 (m, 1H), 2.12-2.04 (m, 1H), 1.95-1.78 (m, 6H), 1.71-1.66 (m, 1H), 1.54-1.45 (m, 1H). LCMS [M+H]⁺ 447.

[0190] Step 2: Synthesis of but-2-ynyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**9**) and but-2-ynyl (6S)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**10**): But-2-ynyl 6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (500 mg, 1.12 mmol) was purified by SFC (column: Phenomenex-Cellulose-2 (250mm×30mm, 10 μ m); mobile phase: [0.1% NH₃H₂O EtOH]; B%: 40%-40%, min) to give **Peak 1** of but-2-ynyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate and **Peak 2** of but-2-ynyl (6S)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1**: ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 9.23 (br s, 1H), 8.65 (br s, 1H), 8.48 (br s, 1H), 8.33 (br d, J = 5.2 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.05-6.97 (m, 1H), 4.62 (br s, 2H), 3.94-3.73 (m, 4H), 3.16 (br s, 4H), 2.65-2.35 (m 5H), 2.07 (br s, 1H), 1.96-1.75 (m, 6H), 1.67 (br s, 1H), 1.53-1.44 (m, 1H). LCMS [M+H]⁺ 447. **Peak 2**: ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 9.23 (br s, 1H), 8.66 (br s, 1H), 8.48 (br s, 1H), 8.33 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.87 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.07-6.97 (m,

1H), 4.62 (d, $J = 2.8$ Hz, 2H), 3.94-3.75 (m, 4H), 3.16 (br s, 4H), 2.46 (br s, 5H), 2.08 (br s, 1H), 1.99-1.74 (m, 6H), 1.68 (br s, 1H), 1.53-1.44 (m, 1H). **LCMS** $[M+H]^+$ 447.

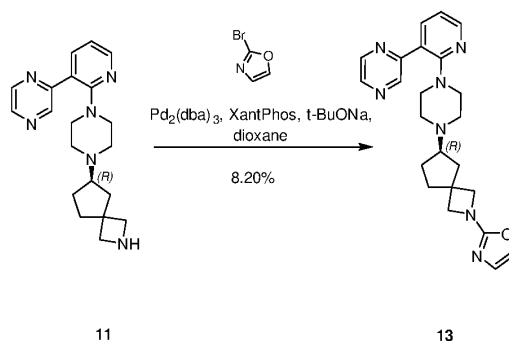
Examples 11 and 12: Synthesis of (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (**11**) and oxetan-3-yl-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]methanone (**12**)



[0191] Step 1: Synthesis of (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (**11**): To a solution of tert-butyl (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (200 mg, 444 μ mol) in DCM (4.00 mL) was added TFA (1.00 mL, 13.5 mmol) and the mixture was stirred at 20 °C for 2 hours. The mixture was adjusted to pH = 9 with 10% aqueous NaOH. The mixture was extracted with DCM (2 x 50 mL). The combined organic layer dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under a reduced pressure to give (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane. **¹H NMR (CDCl₃, 400 MHz)** δ_{H} = 9.24 (d, $J = 1.2$ Hz, 1H), 8.65 (s, 1H), 8.47 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.86 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.00 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 3.74-3.30 (m, 4H), 3.15 (d, $J = 4.4$ Hz, 4H), 2.46 (s, 5H), 2.07-1.69 (m, 4H), 1.61 (dd, $J = 10.0, 12.4$ Hz, 1H), 1.50-1.36 (m, 1H). **LCMS** $[M+H]^+$ 351.

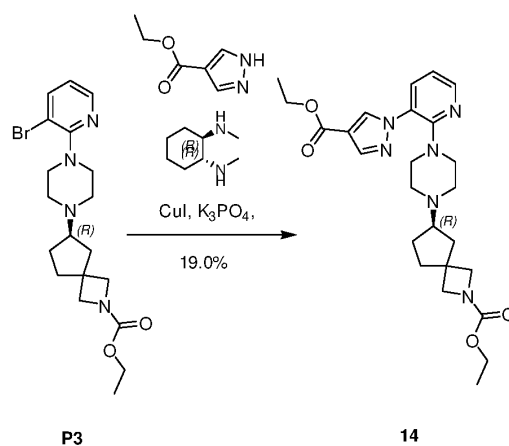
[0192] Step 2: Synthesis of oxetan-3-yl-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]methanone (**12**): A mixture of oxetane-3-carboxylic acid (8.74 mg, 85.6 μ mol), EDCI (24.62 mg, 128.40 μ mol), HOBT (3.47 mg, 25.7 μ mol) and DIPEA (45.0 μ L, 257 μ mol) in DMF (1.00 mL) was stirred at 20 °C for 0.5 hour. Then (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (30.0 mg, 85.6 μ mol) was added into the mixture and the mixture was stirred at 20 °C for 16 hours. The mixture was purified by prep-HPLC (column: Welch Xtimate C18 150x30 mmx5 μ m; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O} + \text{NH}_4\text{HCO}_3$)-ACN]; B%: 13%-43%, 9 min) to give oxetan-3-yl-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]methanone. **¹H NMR (CDCl₃, 400 MHz)** δ_{H} = 9.24 (s, 1H), 8.66 (s, 1H), 8.48 (br s, 1H), 8.33 (d, $J = 3.2$ Hz, 1H), 7.88 (d, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 4.0$ Hz, 1H), 4.94-4.84 (m, 2H), 4.72 (dd, $J = 6.4, 8.0$ Hz, 2H), 3.95-3.73 (m, 5H), 3.16 (br s, 4H), 2.67-2.32 (m, 5H), 2.17-1.99 (m, 1H), 1.97-1.78 (m, 3H), 1.75-1.66 (m, 1H), 1.54-1.43 (m, 1H). **LCMS** $[M+H]^+$ 435.

Example 13: Synthesis of ethyl 2-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]oxazole (13)



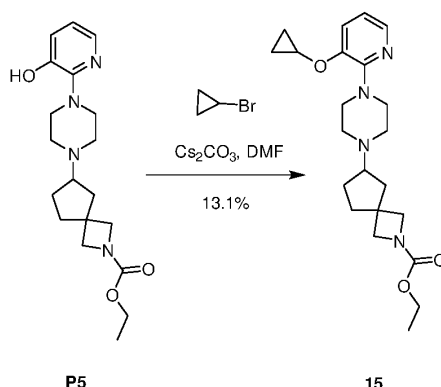
[0193] Synthesis of ethyl 2-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]oxazole (**13**): To a solution of (6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane (96.0 mg, 274 μmol) and 2-bromooxazole (48.6 mg, 329 μmol) in 1,4-dioxane (2.00 mL) was added t-BuONa (79.0 mg, 822 μmol), XantPhos (19.0 mg, 32.8 μmol) and $\text{Pd}_2(\text{dba})_3$ (25.1 mg, 27.4 μmol) at 20 °C. The mixture was degassed under a vacuum and purged with N_2 gas several times. Then the mixture was stirred at 90 °C for 16 hours. The mixture was cooled to 20 °C. The reaction mixture was filtered and the filter cake was washed with THF (15 mL). Then the filtrate was concentrated under a reduced pressure to give a crude product. The crude product was purified by prep HPLC (column: Welch Xtimate C18 150×30 mm×5 μm ; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}$ + NH_4HCO_3)-ACN]; B%: 25%-55%, 25 min) to give 2-[(6R)-6-[4-(3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octan-2-yl]oxazole. ^1H NMR (CDCl_3 400 MHz) δ_{H} = 9.24 (s, 1H), 8.67-8.62 (m, 1H), 8.47 (d, J = 2.8 Hz, 1H), 8.33 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.87 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.19 (s, 1H), 7.01 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.78 (s, 1H), 4.01-3.93 (m, 2H), 3.93-3.88 (m, 2H), 3.17 (s, 4H), 2.60-2.43 (m, 5H), 2.16 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 2.02-1.95 (m, 1H), 1.92-1.84 (m, 2H), 1.74 (d, J = 10.8 Hz, 1H), 1.52 (s, 1H). LCMS $[\text{M}+\text{H}]^+$ 418.

Example 14: Synthesis of 6R)-6-[4-[3-(4-ethoxycarbonylpyrazol-1-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (14)



[0194] Synthesis of ethyl (6R)-6-[4-[3-(4-ethoxycarbonylpyrazol-1-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**14**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 118 μ mol), ethyl 1H-pyrazole-4-carboxylate (24.8 mg, 177 μ mol) and (1R,2R)-N₁,N₂-dimethylcyclohexane-1,2-diamine (3.36 mg, 23.6 μ mol) in DMF (1.00 mL) was added CuI (2.25 mg, 11.8 μ mol) and K₃PO₄ (75.2 mg, 354 μ mol) in one portion at 20 °C. Then the mixture was degassed under a vacuum and purged with N₂ gas several times. The reaction mixture was heated to 130 °C and stirred at 130 °C for 16 hours under a nitrogen gas atmosphere. The mixture was cooled to 25 °C, DCM (3.00 mL) was added and filtered. The filtrate was concentrated under a reduced pressure at 50 °C. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80×40 mm×3 μ m; mobile phase: [water (0.05% NH₃H₂O)-ACN]; B%: 32%-62%, 8 min) to give ethyl (6R)-6-[4-[3-(4-ethoxycarbonylpyrazol-1-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ _H = 8.50 (s, 1H), 8.29 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 8.10 (s, 1H), 7.72 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 6.97 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.88-3.72 (m, 4H), 3.05-2.94 (m, 4H), 2.58-2.39 (m, 5H), 2.09 (dd, *J* = 6.8 Hz, 12.8 Hz, 1H), 1.94-1.77 (m, 3H), 1.68 (dd, *J* = 9.6 Hz, 12.8 Hz, 1H), 1.52-1.47 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). LCMS [M+H]⁺ 483.

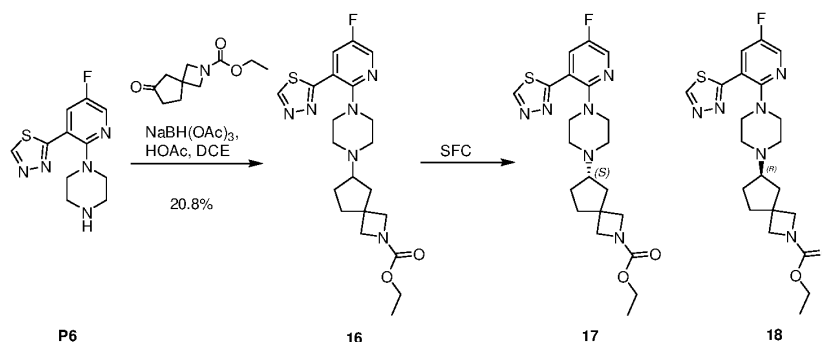
Example 15: Synthesis of ethyl 6-[4-[3-(cyclopropoxy)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**15**)



[0195] Synthesis of ethyl 6-[4-[3-(cyclopropoxy)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**15**): A mixture of ethyl 6-[4-(3-hydroxy-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (80.0 mg, 222 μ mol), bromocyclopropane (269 mg, 2.22 mmol, 178 μ L) and Cs₂CO₃ (217 mg, 666 μ mol) in DMA (3.00 mL) was heated to 130 °C and stirred at 130 °C for 14 hours. The mixture was cooled to 20 °C and DCM (20.0 mL) was added to the mixture, filtered and concentrated under a vacuum to give the crude product (100 mg). The crude product was purified by pre-HPLC (column: Phenomenex Gemini-NX 80×40 mm×3 μ m; mobile phase: [water (0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 35%-61%, 8 min). Then the fractions containing the product were combined and concentrated under a vacuum and freeze-dried to afford ethyl 6-[4-[3-(cyclopropoxy)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ _H = 7.88 (dd, *J* = 1.2 Hz, 5.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 6.83 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H),

3.95-3.87 (m, 1H), 3.86-3.82 (m, 1H), 3.81-3.75 (m, 2H), 3.74-3.68 (m, 1H), 3.60-3.16 (m, 4H), 2.81-2.41 (m, 5H), 2.20-2.09 (m, 1H), 2.02-1.88 (m, 2H), 1.87-1.65 (m, 2H), 1.62-1.58 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.85-0.75 (m, 4H). **LCMS** $[M+H]^+$ 401.

Examples 16, 17 and 18: Synthesis of ethyl 6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**16**), ethyl (6S)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**17**) and ethyl (6R)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**18**)

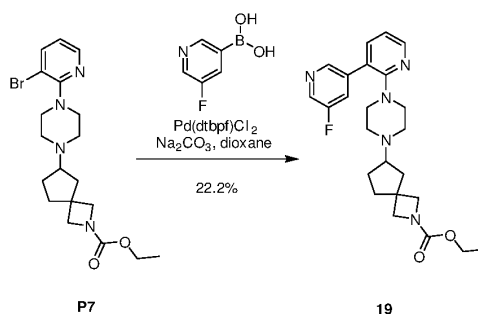


[0196] Step 1: Synthesis of ethyl 6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**16**): A mixture of 2-(5-fluoro-2-piperazin-1-yl-3-pyridyl)-1,3,4-thiadiazole (60.0 mg, 226 μ mol) and ethyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (37.2 mg, 188 μ mol) in DCE (2.00 mL) was stirred at 20 °C for 1 hour. Then AcOH (5.66 mg, 94.2 μ mol) and $\text{NaBH}(\text{OAc})_3$ (120 mg, 565 μ mol) was added to the reaction mixture. The mixture was stirred at 20 °C for 16 hours. The mixture was poured onto saturated aqueous NaHCO_3 (30 mL) and stirred for 5 min. The mixture was extracted with DCM (3×30 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in a vacuum to give a residue. The residue was purified by silica gel flash chromatography (Eluent of 0–3% MeOH/DCM) to give a crude. The crude was purified by prep-HPLC (column: Phenomenex C18 80 × 40 mm × 3 μ m; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}$)-ACN]; B%: 36%–66%, 8 min) to give ethyl 6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **^1H NMR (CDCl₃ 400 MHz)** $\delta_{\text{H}} = 9.21$ (s, 1H), 8.33 (br d, $J = 2.0$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.97–3.82 (m, 2H), 3.79 (s, 2H), 3.11 (br s, 4H), 2.66 (br s, 5H), 2.15 (br s, 1H), 2.03–1.83 (m, 3H), 1.76 (br s, 1H), 1.64–1.58 (m, 1H), 1.24 (t, $J = 6.8$ Hz, 3H). **^{19}F NMR (CDCl₃ 400 MHz)** $\delta_{\text{F}} = -132.678$. **LCMS** $[M+H]^+$ 447.

[0197] Step 2: Synthesis of ethyl (6S)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**17**) and ethyl (6R)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**18**): Ethyl 6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (150 mg, 336 μ mol) was purified by SFC (column: DAICEL CHIRALCEL OD-H (250mm×30mm,5 μ m); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ EtOH]; B%: 30%–30%, min) to give **Peak 1** of ethyl (6S)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate, and **Peak 2** of ethyl (6R)-6-[4-[5-fluoro-3-(1,3,4-thiadiazol-2-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-

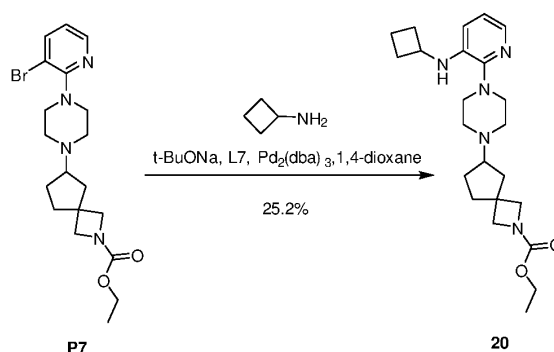
carboxylate. **Peak 1:** $^1\text{H NMR}$ (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.21$ (s, 1H), 8.33 (d, $J = 2.0$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.75 (m, 4H), 3.10 (s, 4H), 2.65 (s, 5H), 2.13 (br s, 1H), 2.01-1.78 (m, 3H), 1.74 (s, 2H), 1.24 (t, $J = 7.2$ Hz, 3H). $^{19}\text{F NMR}$ (CDCl_3 400 MHz) $\delta_{\text{F}} = -132.66$. **LCMS** $[\text{M}+\text{H}]^+ 447$. **Peak 2:** $^1\text{H NMR}$ (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.21$ (s, 1H), 8.33 (d, $J = 2.0$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.75 (m, 4H), 3.10 (s, 4H), 2.65 (s, 5H), 2.13 (br s, 1H), 2.01-1.78 (m, 3H), 1.74 (s, 2H), 1.24 (t, $J = 7.2$ Hz, 3H). $^{19}\text{F NMR}$ (CDCl_3 400 MHz) $\delta_{\text{F}} = -132.66$. **LCMS** $[\text{M}+\text{H}]^+ 447$.

Example 19: Synthesis of ethyl 6-(4-(5'-fluoro-[3,3'-bipyridin]-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (19)



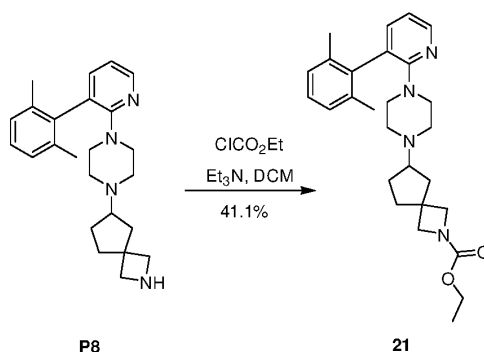
[0198] Synthesis of ethyl 6-(4-(5'-fluoro-[3,3'-bipyridin]-2-yl)piperazin-1-yl)-2-azaspiro-[3.4]octane-2-carboxylate (**19**): To a mixture of ethyl 6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 118 μmol), (5-fluoro-3-pyridyl)boronic acid (33.3 mg, 236 μmol) and Na_2CO_3 (37.6 mg, 354 μmol) in 1,4-dioxane (4.00 mL) and H_2O (1.00 mL) was added [1,1'-bis(di-tert-butylphosphino)ferrocene] dichloropalladium(II) (7.70 mg, 11.8 μmol) in one portion at 20 °C under a nitrogen gas atmosphere. Then the mixture was degassed under a vacuum and purged with N_2 gas several times. The mixture was stirred at 80 °C for 16 hours. The reaction mixture was concentrated. The crude product was purified by prep-HPLC (Column: Phenomenex Gemini-NX 80×40mm× μm . Condition: water (0.05% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)-ACN. Begin B: 26; End B: 56. Gradient Time (min): 8. 100%B Hold Time(min): 3. Flow Rate (ml/min): 30) to afford ethyl 6-[4-[3-(5-fluoro-3-pyridyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. $^1\text{H NMR}$ (CDCl_3 400 MHz) $\delta_{\text{H}} = 8.66$ (s, 1H), 8.45 (d, $J = 2.4$ Hz, 1H), 8.31 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.73 (br d, $J = 9.6$ Hz, 1H), 7.49 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 6.99 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.86 (m, 1H), 3.86-3.80 (m, 1H), 3.80-3.74 (m, 2H), 3.20-3.10 (m, 4H), 2.65-2.34 (m, 5H), 2.10 (br dd, $J = 7.2$ Hz, 12.4 Hz, 1H), 1.97-1.78 (m, 3H), 1.74-1.65 (m, 1H), 1.55-1.45 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+ 440$.

Example 20: Synthesis of ethyl 6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro-[3.4]octane-2-carboxylate (**20**)



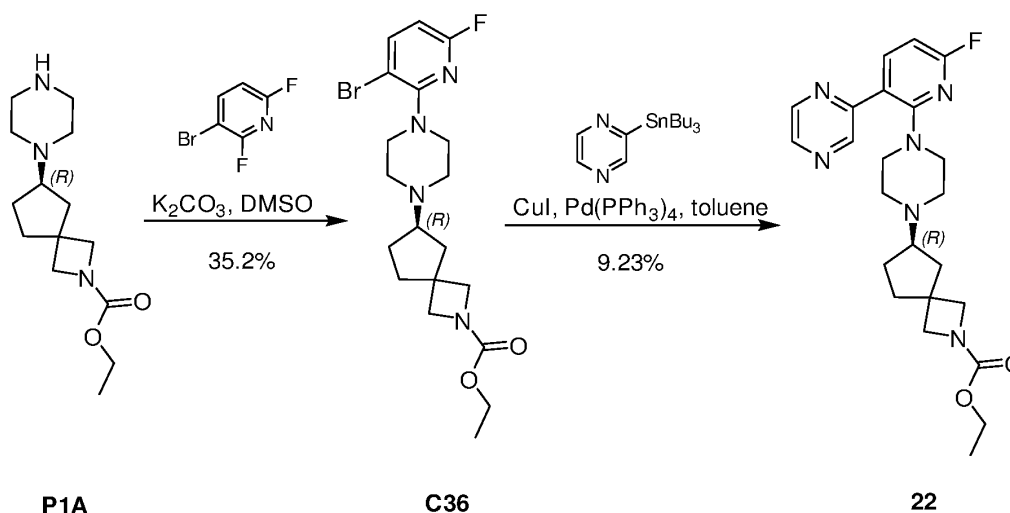
[0199] Synthesis of ethyl 6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro-[3.4]octane-2-carboxylate (**20**): A mixture of ethyl 6-[4-[3-(2-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 118 μmol), cyclobutanamine (42.0 mg, 590 μmol), t-BuONa (34.1 mg, 354 μmol), 2-[bis(3,5-trifluoromethylphenyl)phosphino]-3,6-dimethoxy-2,6-dimethylamino-1,1-biphenyl (L7, 8.93 mg, 11.8 μmol) and $\text{Pd}_2(\text{dba})_3$ (10.8 mg, 11.8 μmol) in 1,4-dioxane (3.00 mL). The mixture was degassed under a vacuum and purged with N_2 gas for several times. Then the mixture was heated to 100 $^\circ\text{C}$ and stirred at 100 $^\circ\text{C}$ for 16 hours. The mixture was cooled to 20 $^\circ\text{C}$ and DCM (5 mL) was added to the mixture, filtered and concentrated in vacuum to give a crude product. The crude product was purified by pre-HPLC (column: Phenomenex Gemini-NX 80 $\times$ 40mm $\times$ 3 μm ; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)-ACN]; B%: 48%-72%, 8 min). Then the fractions containing the product were combined and concentrated in vacuum and freeze-dried to obtain ethyl 6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **$^1\text{H NMR}$ (CDCl_3 , 400 MHz)** δ_{H} = 7.70 (d, J = 0.4 Hz, 1H), 6.86 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.33-4.21 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.95-3.89 (m, 1H), 3.89-3.82 (m, 2H), 3.82-3.76 (m, 2H), 3.33-3.29 (m, 4H), 3.28-2.50 (m, 4H), 2.50-2.35 (m, 2H), 2.21-2.09 (m, 1H), 1.99-1.90 (m, 2H), 1.90-1.72 (m, 6H), 1.68-1.60 (m, 2H), 1.24 (t, J = 6.8 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 414.

Example 21: Synthesis of ethyl 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro-[3.4]octane-2-carboxylate (**21**)



[0200] Synthesis of ethyl 6-[4-[3-(2, 6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro- [3.4]octane-2-carboxylate (**21**): A mixture of 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane (75.0 mg, 199 μ mol, TFA salt), TEA (60.5 mg, 598 μ mol) in DCM (5.00 mL) at 0-5 °C. Then ethyl carbonochloridate (340 mg, 3.13 mmol) was added dropwise into the mixture at 0-5 °C. Then the mixture was warmed to 20 °C and stirred at 20 °C for 5 hours. The reaction was quenched with aqueous NaHCO₃ (10%, 25 mL) slowly and then extracted with DCM (50 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a vacuum. The residue was purified by pre-HPLC (column: Phenomenex Gemini-NX 80×40mm×3 μ m; mobile phase: [water (0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 53%-77%, 8 min) to give ethyl 6-[4-[3-(2,6-dimethylphenyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_{H} = 8.26 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.23 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.19-7.14 (m, 1H), 7.13-7.08 (m, 2H), 6.87 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.08 (q, J = 3.2 Hz, 2H), 3.87-3.77 (m, 2H), 3.76-3.69 (m, 2H), 3.18-3.06 (m, 4H), 2.54-2.33 (m, 1H), 2.31-2.16 (m, 4H), 2.08 (s, 6H), 2.04-1.99 (m, 1H), 1.91-1.75 (m, 3H), 1.69-1.61 (m, 1H), 1.53-1.42 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 449.

Example 22: Synthesis of ethyl (6R)-6-[4-(6-fluoro-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**22**)

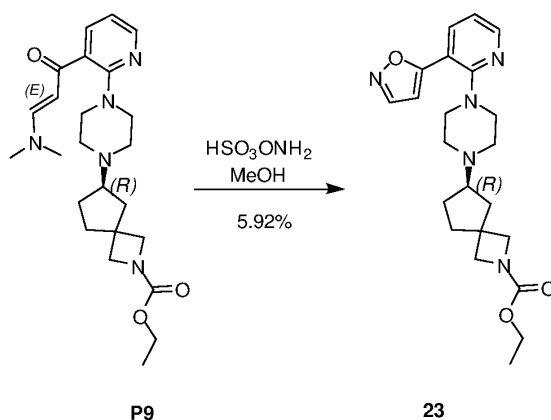


[0201] Step 1: Synthesis of ethyl (6R)-6-[4-(3-bromo-6-fluoro-2-pyridyl)]piperazin-1-yl]-2- azaspiro[3.4]octane-2-carboxylate (**C36**): To a solution of 3-bromo-2,6-difluoro-pyridine (100 mg, 516 μ mol) in DMSO (3.00 mL) and K₂CO₃ (214 mg, 1.55 mmol) was added ethyl (6R)-6-piperazin-1-yl]-2-azaspiro[3.4]octane- 2-carboxylate (152 mg, 567 μ mol) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was degassed and purged with N₂ gas for several times. The mixture was stirred at 20 °C for 16 hours. The reaction mixture was poured into water (100 mL) at 20 °C, then extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under a reduced pressure to give the residue. The residue was purified by silica gel flash chromatography (eluent of 0~100% EtOAc /petroleum ether) to afford

ethyl (6R)-6-[4-(3-bromo-6-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** $[M+H]^+$ 441, 443.

[0202] Step 2: Synthesis of ethyl (6R)-6-[4-(6-fluoro-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**22**): To a solution of ethyl (6R)-6-[4-(3-bromo-6-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 227 μ mol) in toluene (3.00 mL), $Pd(PPh_3)_4$ (26.2 mg, 22.7 μ mol) and CuI (14.9 mg, 78.4 μ mol) in toluene (3.00 mL) was added tributyl(pyrazin-2-yl)stannane (100 mg, 272 μ mol) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was heated to 110 °C and stirred at 110 °C for 12 hours. The reaction mixture was poured onto water (100 mL) at 20 °C, then extracted with EtOAc (3×100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under a reduced pressure. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150×25mm×5 μ m; mobile phase: [water ($NH_3H_2O+NH_4HCO_3$)-ACN]; B%: 45%-75%, 7 min) to give ethyl (6R)-6-[4-(6-fluoro-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **1H NMR ($CDCl_3$ 400 MHz)** δ_H = 9.11 (d, J = 1.2 Hz, 1H), 8.76-8.61 (m, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.94 (t, J = 8.0 Hz, 1H), 6.56 (dd, J = 3.2 Hz, 8.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.90-3.69 (m, 4H), 3.30-3.05 (m, 4H), 2.73-2.32 (m, 5H), 2.07 (dd, J = 7.2, 12.4 Hz, 1H), 1.95-1.76 (m, 3H), 1.67-1.61 (m, 1H), 1.51 (s, 1H), 1.22 (t, J = 7.2 Hz, 3H). **^{19}F NMR ($CDCl_3$ 400 MHz)** δ_F = -67.666. **LCMS** $[M+H]^+$ 441.

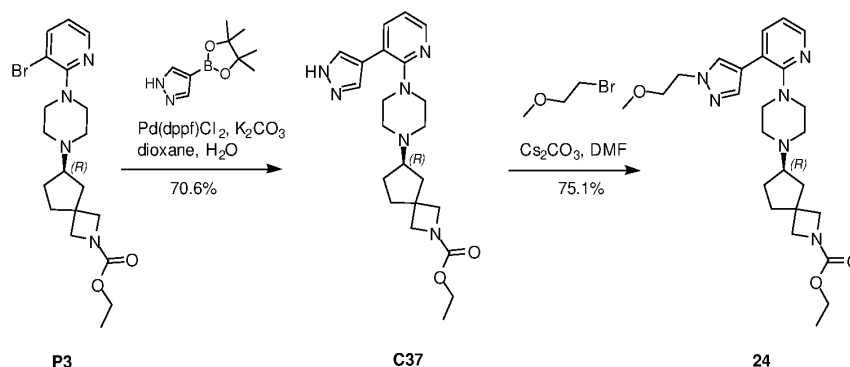
Example 23: Synthesis of ethyl (6R)-6-[4-(3-isoxazol-5-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**23**)



[0203] Synthesis of ethyl (6R)-6-[4-(3-isoxazol-5-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**23**): A mixture of ethyl (6R)-6-[4-[(E)-3-(dimethylamino)prop-2-en-1-yl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 226 μ mol) in anhydrous MeOH (2.00 mL) was cooled to 0-5 °C under an ice-water bath, then a solution of amino hydrogen sulfate (28.2 mg, 249 μ mol) in anhydrous MeOH (1.00 mL) was added dropwise at 0-5 °C. Then the mixture was allowed to warm to 20 °C and stirred for 20 hours at 20 °C. The reaction mixture was concentrated under a reduced pressure. The residue was added saturated aqueous NH_4Cl (10 mL), extracted with DCM (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure to give the

residue as a brown oil. The residue was purified by prep-HPLC (column: Xtimate C18 100×30 mm×3 μm; mobile phase: [water (0.225%FA)-ACN]; B%: 5%-35%, 8 min) to give ethyl (6R)-6-[4-(3-isoxazol-5-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.41-8.30 (m, 2H), 8.02 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.01 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 6.81 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.97-3.73 (m, 4H), 3.24 (br s, 4H), 2.59 (br s, 5H), 2.16 (br dd, *J* = 6.8 Hz, 12.4 Hz, 1H), 2.03-1.82 (m, 3H), 1.80-1.70 (br s, 1H), 1.57-1.49 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 412.

Example 24: Synthesis of ethyl (6R)-6-[4-[3-[1-(2-methoxyethyl)pyrazol-4-yl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (24)

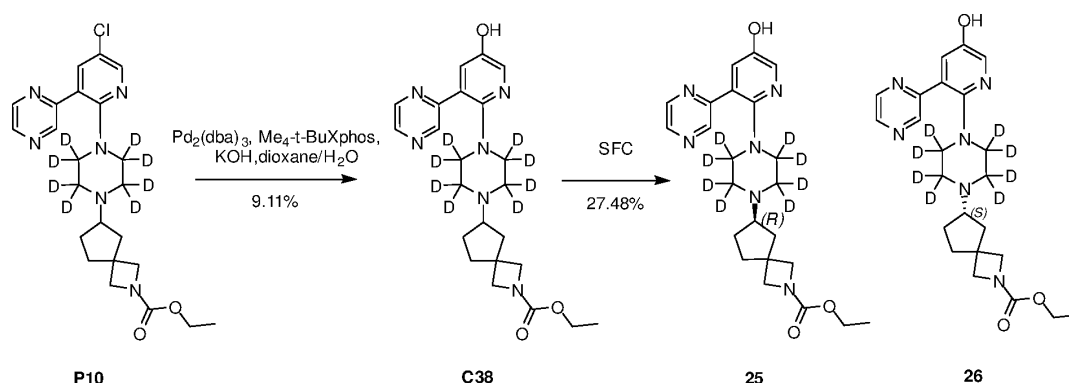


[0204] Step 1: Synthesis of ethyl (6R)-6-[4-[3-(1H-pyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C37**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (300 mg, 709 μmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (208 mg, 709 μmol), K₂CO₃ (196 mg, 1.42 mmol) in 1,4-dioxane (5.00 mL) and water (1.00 mL) was added Pd(dppf)Cl₂ (51.9 mg, 70.9 μmol) in one portion under a nitrogen gas atmosphere. The mixture was degassed under vacuum and purged with N₂ gas several times. Then the mixture was stirred for 4 hours at 100 °C. The reaction mixture was filtered and the filter cake was washed with DCM (3 × 15 mL). Then the filtrate was concentrated under a reduced pressure to give a crude product. The crude product was purified by silica gel flash chromatography (eluent of 0~5% MeOH/DCM) to give ethyl (6R)-6-[4-[3-(1H-pyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** [M+H]⁺ 411.

[0205] Step 2: Synthesis of ethyl (6R)-6-[4-[3-[1-(2-methoxyethyl)pyrazol-4-yl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**24**): A mixture of ethyl (6R)-6-[4-[3-(1H-pyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (40 mg, 97.4 μmol), 1-bromo-2-methoxyethane (16.2 mg, 117 μmol), Cs₂CO₃ (63.5 mg, 195 μmol) in DMF (2.00 mL) was stirred at 85 °C for 12 hours under a N₂ gas atmosphere. The reaction mixture was filtered and the filtrate was concentrated under a reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: Welch Xtimate C18 150×30 mm×5 μm; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; B%: 27%-57%, 7 min) to give ethyl (6R)-6-[4-[3-[1-(2-methoxyethyl)pyrazol-4-yl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.16 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.55 (dd, *J* = 2.0, 7.6 Hz, 1H), 6.90 (dd, *J*

= 4.8 Hz, 7.2 Hz, 1H), 4.32 (t, J = 5.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.81 (m, 2H), 3.80-3.75 (m, 4H), 3.36 (s, 3H), 3.17 (s, 4H), 2.54 (s, 5H), 2.11 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.96-1.81 (m, 3H), 1.73 (s, 1H), 1.67 (s, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** $[M+H]^+$ 469.

Examples 25 and 26: Synthesis of ethyl (6R)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**25**) and ethyl (6S)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**26**)

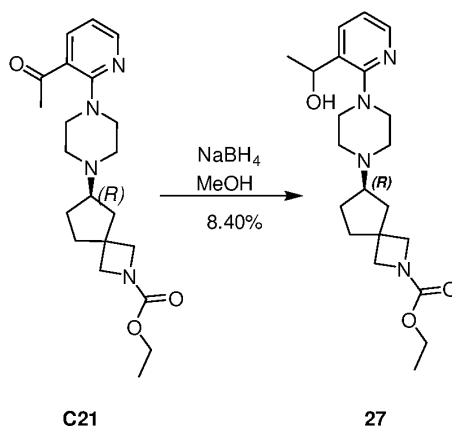


[0206] Step 1: Synthesis of ethyl 6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C38**): To a solution of ethyl 6-[4-(5-chloro-3-pyrazin-2-yl-2-pyridyl)-2,2,3,3,5,5,6,6-octadeuterio-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (400 mg, 860 μ mol) in 1,4-dioxane (4.00 mL) was added a solution of KOH (145 mg, 2.58 mmol) in water (4.00 mL) in one portion at 20 °C under a nitrogen gas atmosphere. Then di-tert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]-phosphane (Me_4t -BuXphos, 82.7 mg, 172 μ mol) and tris(dibenzylideneacetone)dipalladium (39.4 mg, 43.0 μ mol) was added in one portion at 20 °C. The mixture was degassed and purged with N_2 gas for several times at 25 °C. The mixture was heated to 100 °C and stirred at 100 °C for 12 hours. The reaction mixture was poured onto water (20 mL) at 20 °C, then extracted with EtOAc (3 $\times$ 15 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~20% of MeOH in DCM) to afford ethyl 6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** $[M+H]^+$ 447.

[0207] Step 2: Synthesis of ethyl (6R)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**25**) and ethyl (6S)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**26**): Ethyl 6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate was purified by SFC (column: DAICEL CHIRALCEL OD-H (250mm $\times$ 30 mm, 5 μ m); mobile phase: [0.1% $NH_3 \cdot H_2O$ MeOH]; B%: 30%-30%, min) to give ethyl (6R)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (13.3 mg, 28.2 μ mol, 25.2% yield, 94.7% purity) as a yellow solid and ethyl (6S)-6-[2,2,3,3,5,5,6,6-octadeuterio-4-(5-hydroxy-3-pyrazin-2-yl-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate.

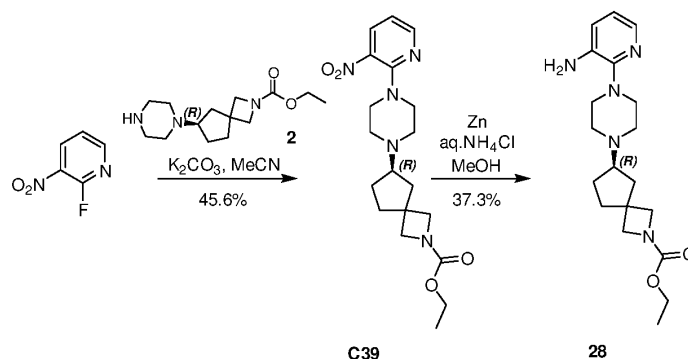
pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1:** $^1\text{H NMR}$ (CDCl_3 400 MHz) δ_{H} = 9.40-9.30 (m, 1H), 8.72-8.56 (m, 1H), 8.48 (d, J = 2.6 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.65-7.41 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.59 (m, 4H), 2.60 (s, 1H), 2.09 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.98-1.66 (m, 4H), 1.56 (s, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 447. **Peak 2:** $^1\text{H NMR}$ (CDCl_3 400 MHz) δ_{H} = 9.40-9.30 (m, 1H), 8.72-8.56 (m, 1H), 8.48 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.65-7.41 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.59 (m, 4H), 2.60 (s, 1H), 2.09 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.98-1.66 (m, 4H), 1.56 (s, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 447.

Example 27: Synthesis of (6R)-ethyl 6-(4-(3-(1-hydroxyethyl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (27)



[0208] Synthesis of (6R)-ethyl 6-(4-(3-(1-hydroxyethyl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**27**): To a mixture of ethyl (6R)-6-[4-(3-acetyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 259 μmol) in MeOH (5.00 mL) was added NaBH_4 (11.7 mg, 310 μmol) and stirred at 25 °C for 16 hours. The mixture was added more NaBH_4 (11.7 mg, 310 μmol) and heated to 40 °C, then the mixture reaction was stirred at 40 °C for 1 hour. The mixture was added water (20 mL) and extracted with EtOAc (2 $\times$ 20 mL). The combined organic phase was washed with brine (2 $\times$ 20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: Phenomenex Gemini-NX 80 $\times$ 30 mm $\times$ 3 μm , mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 9 min) to afford ethyl (6R)-6-[4-[3-(1-hydroxyethyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. $^1\text{H NMR}$ (CDCl_3 400 MHz) δ_{H} = 8.29 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.61-7.56 (m, 1H), 7.06 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 5.07 (q, J = 6.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.82 (m, 2H), 3.82-3.76 (m, 2H), 3.30-3.04 (m, 4H), 2.67 (br s, 5H), 2.17-2.09 (m, 1H), 1.95-1.70 (m, 5H), 1.54 (d, J = 4.8 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 389.

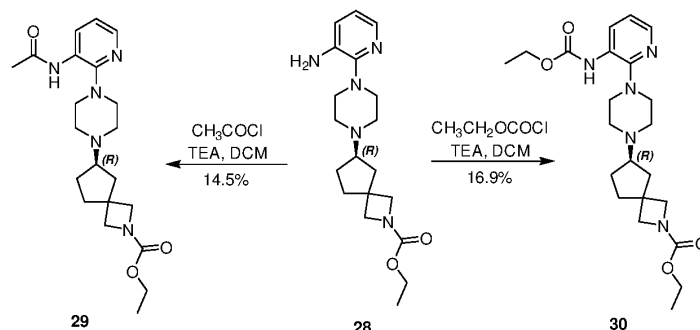
Example 28: Synthesis of ethyl (6R)-6-[4-(3-amino-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]-octane-2-carboxylate (**28**)



[0209] Step 1: Synthesis of ethyl (6R)-6-[4-(3-nitro-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]- octane-2-carboxylate (**C39**): To a solution of 2-fluoro-3-nitro-pyridine (300 mg, 2.11 mmol) and ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (677 mg, 2.53 mmol) in MeCN (5.00 mL) was added K_2CO_3 (875 mg, 6.33 mmol) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was stirred at 80 °C for 12 hours. The reaction mixture was added water (20 mL) at 25 °C, then extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under a reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (eluent 0–20% of MeOH in DCM) to afford ethyl (6R)-6-[4-(3-nitro-2-pyridyl) piperazin-1-yl]-2-azaspiro[3.4]- octane-2-carboxylate. **LCMS** $[M+H]^+$ 390.

[0210] Step 2: Synthesis of ethyl (6R)-6-[4-(3-amino-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]- octane-2-carboxylate (**28**): To a solution of ethyl (6R)-6-[4-(3-nitro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane- 2-carboxylate (500 mg, 1.28 mmol) in MeOH (10.0 mL) was added Zn (1.67 g, 25.6 mmol) and saturated aqueous NH_4Cl (10.0 mL) under a nitrogen gas atmosphere. The mixture was stirred at 25 °C for 16 hours. The residue was filtered and the filtrate was extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure to give a black oil (360 mg). 320 mg of the black oil was used in the next step without further purification. 40.0 mg of the black oil was purified by prep-HPLC (Column: Phenomenex Gemini-NX 80×30 mm×3 μm ; Condition: water (10 mM NH_4HCO_3)-ACN; Begin B: 27; End B: 57; Gradient Time(min): 9; 100%B Hold Time(min): 1.5; Flow Rate (ml/min): 30; Injections: 2) to give ethyl (6R)-6-[4-(3-amino-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **1H NMR ($CDCl_3$, 400 MHz)** δ_H = 7.75 (br d, J = 4.4 Hz, 1H), 6.95 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.88–6.81 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.06–3.96 (m, 1H), 3.94–3.87 (m, 1H), 3.80–3.75 (m, 2H), 3.74–3.49 (m, 4H), 3.48–2.61 (m, 6H), 2.44–1.73 (m, 6H), 1.70–1.61 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** $[M+H]^+$ 360.

Examples 29 and 30: Synthesis of ethyl (6R)-6-[4-(3-acetamido-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**29**) and ethyl (6R)-6-[4-[3-(ethoxycarbonylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**30**)

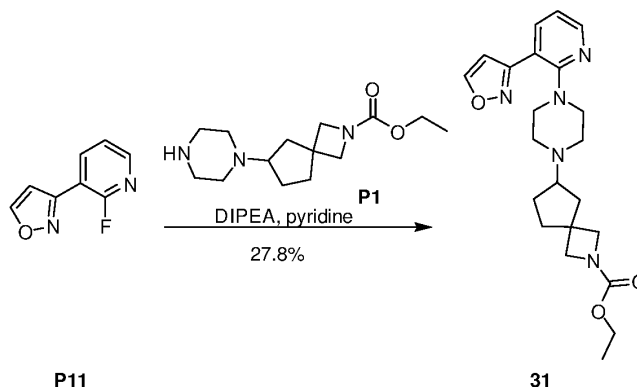


[0211] Step to the left: Synthesis of ethyl (6R)-6-[4-(3-acetamido-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**29**): To a solution of ethyl (6R)-6-[4-(3-amino-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 139 μ mol) and TEA (42.2 mg, 417 μ mol) in DCM (3.00 mL) was added CH_3COCl (13.1 mg, 167 μ mol) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was stirred at 20 °C for 16 hours. The residue was poured onto water (10 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (3 $\times$ 10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure. The residue was purified by prep-HPLC (Column: Phenomenex Gemini-NX 80 $\times$ 30 mm $\times$ 3 μ m; Condition: water (10 mM NH_4HCO_3)-ACN; Begin B: 23; End B: 53; Gradient Time (min): 9; 100%B Hold Time (min): 1.5; Flow Rate (ml/min): 30; Injections: 3) to give ethyl (6R)-6-[4-(3-acetamido-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **^1H NMR (CDCl_3 400 MHz)** δ_{H} = 8.53 (br d, J = 7.2 Hz, 1H), 8.10-8.02 (m, 1H), 7.94-7.56 (m, 1H), 7.07-7.00 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.00-3.83 (m, 2H), 3.82-3.74 (m, 2H), 3.65-3.05 (m, 4H), 3.04-2.28 (m, 5H), 2.23 (s, 3H), 2.20-2.11 (m, 1H), 2.08-1.67 (m, 4H), 1.66-1.60 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 402.

[0212] Step to the right: Synthesis of ethyl (6R)-6-[4-[3-(ethoxycarbonylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**30**): To a solution of ethyl (6R)-6-[4-(3-amino-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 139 μ mol) and TEA (42.2 mg, 417 μ mol) in DCM (3.00 mL) was added ethyl chloroformate (0.160 g, 1.47 mmol) in one portion at 20 °C under a nitrogen gas atmosphere. The mixture was stirred at 20 °C for 16 hours. LCMS showed the starting material was remained. Thus, more ethyl chloroformate (0.530 g, 4.88 mmol) was added at 20 °C. The mixture was stirred at 20 °C for another 4 hours. The mixture was poured onto water (10 mL). The aqueous phase was extracted with EtOAc (3 $\times$ 10 mL). The combined organic phase was washed with brine (20.0 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure. The residue was further purification by prep-HPLC (Column: Phenomenex Gemini-NX 80 $\times$ 30 mm $\times$ 3 μ m; Condition: water (10 mM NH_4HCO_3)-ACN; Begin B: 32; End B: 62; Gradient Time(min): 9; 100%B Hold Time(min): 1.5; Flow Rate(ml/min): 30; Injections: 3) to give ethyl (6R)-6-[4-[3-(ethoxycarbonylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **^1H NMR (CDCl_3 400**

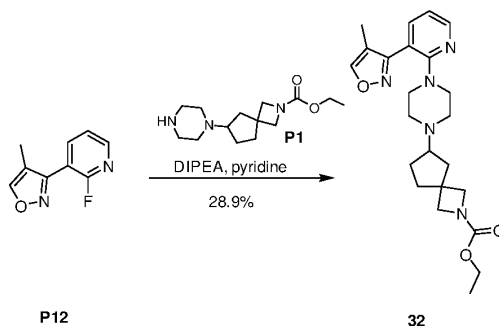
MHz) δ_{H} = 8.40-8.20 (m, 1H), 8.02 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.26-7.17 (m, 1H), 7.02 (dd, J = 5.2 Hz, 8.0 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.69 (m, 4H), 3.07 (br t, J = 4.8 Hz, 4H), 2.80-2.40 (m, 5H), 2.14 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.99-1.81 (m, 3H), 1.81-1.76 (m, 1H), 1.65-1.53 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** $[M+H]^+$ 432.

Example 31: Synthesis of ethyl 6-(4-(3-(isoxazol-3-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (31)



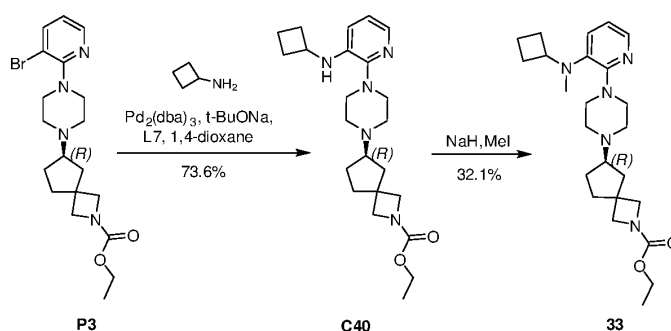
[0213] Synthesis of ethyl 6-(4-(3-(isoxazol-3-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**31**): A solution of ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (70.0 mg, 262 μmol) and 3-(2-fluoro-3-pyridyl)isoxazole (43.0 mg, 262 μmol) in DIPEA (500 μL) and pyridine (250 μL) was stirred at 100 °C for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by prep-HPLC (column: Boston Prime C18 150×30 mm×5 μm ; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)-ACN]; B%: 40%-70%, 7 min) to give ethyl 6-[4-(3-isoxazol-3-yl-2-pyridyl)-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **^1H NMR** (CDCl_3 , 400 MHz) δ_{H} = 8.46 (d, J = 1.6 Hz, 1H), 8.33 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.88 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.95 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.90-3.75 (m, 4H), 3.18 (t, J = 4.8 Hz, 4H), 2.63-2.41 (m, 5H), 2.15-2.06 (m, 1H), 1.95-1.78 (m, 3H), 1.72-1.67 (m, 1H), 1.57-1.46 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). **LCMS** $[M+H]^+$ 412.

Example 32: Synthesis of ethyl 6-(4-(3-(4-methylisoxazol-3-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (32)



[0214] Synthesis of ethyl 6-(4-(3-(4-methylisoxazol-3-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**32**): A solution of ethyl 6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 374 μ mol) and 3-(2-fluoro-3-pyridyl)-4-methyl-isoxazole (66.6 mg, 374 μ mol) in DIPEA (700 μ L) and pyridine (350 μ L) was stirred at 100 °C for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by a prep-HPLC (column: Phenomenex Gemini-NX 80 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 32%-62%, 9 min) to give ethyl 6-[4-(3-(4-methylisoxazol-3-yl)-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ _H = 8.34 (dd, *J* = 2.0 Hz, 4.8 Hz, 1H), 8.27-8.23 (m, 1H), 7.60 (dd, *J* = 2.0 Hz, 7.6 Hz, 1H), 6.92 (dd, *J* = 4.8 Hz, 7.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.90 - 3.72 (m, 4H), 3.31-3.10 (m, 4H), 2.57-2.29 (m, 5H), 2.12-2.03 (m, 1H), 2.00-1.96 (m, 3H), 1.94-1.78 (m, 3H), 1.74-1.65 (m, 1H), 1.57-1.45 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). LCMS [M+H]⁺ 426.

Example 33: Synthesis of ethyl (6R)-6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (33**)**

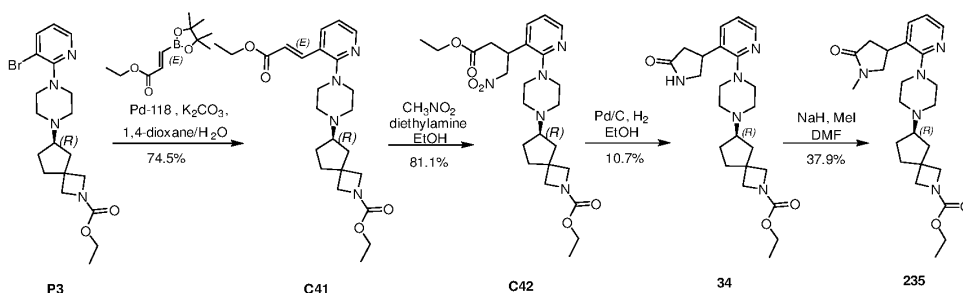


[0215] Synthesis of ethyl (6R)-6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C40**): A mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 118 μ mol), cyclobutanamine (84.0 mg, 1.18 mmol), t-BuONa (34.1 mg, 354 μ mol), 2-[bis(3,5-trifluoromethylphenyl)phosphino]-3,6-dimethoxy-2,6-dimethylamino-1,1-biphenyl (L7, 8.93 mg, 11.8 μ mol) and Pd₂(dba)₃ (10.8 mg, 11.8 μ mol) in 1,4-dioxane (2.50 mL). The mixture was degassed under a vacuum and purged with N₂ gas for several times. Then the mixture was heated to 100 °C and stirred at 100 °C for 10 hours. The mixture was cooled to 20 °C and DCM (20 mL) was added to the mixture, and filtered. The filtrate was concentrated under a vacuum. The residue was purified by silica gel flash chromatography (eluent of 0~3.2% MeOH/DCM) to afford ethyl (6R)-6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. LCMS [M+H]⁺ 414.

[0216] Step 2: Synthesis of ethyl (6R)-6-[4-[3-(cyclobutyl(methyl)amino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**33**): A mixture of ethyl (6R)-6-[4-[3-(cyclobutylamino)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (40.0 mg, 96.7 μ mol), NaH (19.3 mg, 484 μ mol, 60% purity) in DMF (0.500 mL). The mixture was degassed under a vacuum and purged with N₂ gas for several times. The mixture was stirred at 0 °C for 0.5 hour. Then a solution of MeI (16.5 mg, 116 μ mol) in DMF (0.500 mL) was added dropwise into the mixture. The mixture was stirred at 0 °C for 1.5 hours. H₂O (5 mL) was added to the mixture, filtered and

concentrated under a vacuum to give a crude product. The crude was purified by pre-HPLC (column: Phenomenex Gemini-NX 80×40 mm×3 μ m; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$)-ACN]; B%: 50%-80%, 8 min). Then the fraction was concentrated under a vacuum and freeze-dried to obtain ethyl (6R)-6-[4-[3-[cyclobutyl-(methyl)amino]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. $^1\text{H NMR}$ (MeOD 400 MHz) δ_{H} = 7.80 (dd, J = 1.2 Hz, 4.8 Hz, 1H), 7.10 (dd, J = 1.2 Hz, 7.6 Hz, 1H), 6.85 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.95-3.75 (m, 5H), 3.66-3.39 (m, 4H), 2.75-2.60 (m, 8H), 2.28-2.15 (m, 3H), 2.03-1.85 (m, 5H), 1.83-1.70 (m, 3H), 1.64-1.55 (m, 1H), 1.24 (t, J = 6.8 Hz, 3H). LCMS $[\text{M}+\text{H}]^+$ 428.

Examples 34 and 235: Synthesis of ethyl (6R)-6-[4-[3-(5-oxopyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (34) and ethyl (6R)-6-[4-[3-(1-methyl-5-oxo-pyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (235)



[0217] Step 1: Synthesis of ethyl (6R)-6-[4-[3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-2-pyridyl]-piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C41**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (500 mg, 1.18 mmol), ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (320 mg, 1.42 mmol), [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (Pd-118, 76.9 mg, 118 μ mol) and K_2CO_3 (326 mg, 2.36 mmol) in H_2O (2.00 mL) and 1,4-dioxane (10.0 mL). The mixture was degassed under a reduced pressure and purged with N_2 gas for several times. The reaction mixture was stirred at 85 $^\circ\text{C}$ for 16 hours. The mixture was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~5% MeOH/DCM) to afford ethyl (6R)-6-[4-[3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. LCMS $[\text{M}+\text{H}]^+$ 443.

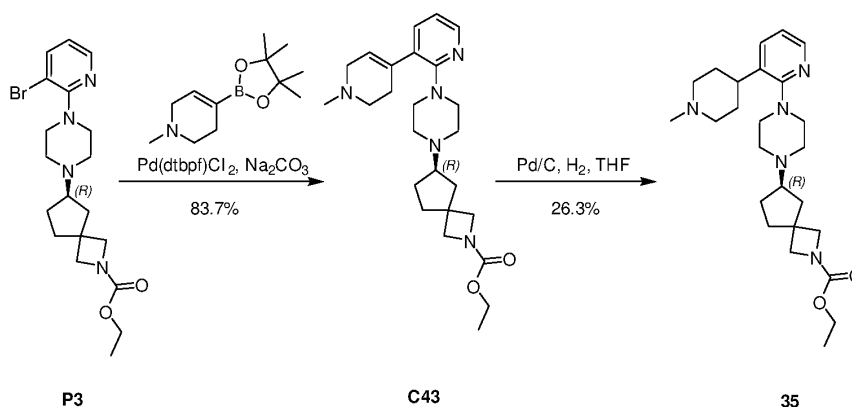
[0218] Step 2: Synthesis of ethyl (6R)-6-[4-[3-[3-ethoxy-1-(nitromethyl)-3-oxo-propyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C42**): To a mixture of ethyl (6R)-6-[4-[3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (300 mg, 678 μ mol) in CH_3NO_2 (1.50 mL, 27.8 mmol) was added DBU (206 mg, 1.36 mmol) dropwise at 0 $^\circ\text{C}$. Then the mixture was stirred at 20 $^\circ\text{C}$ for 12 hours. The mixture was concentrated under a reduced pressure. The residue was purified by silica gel flash chromatography (eluent of 0~10% MeOH/DCM) to afford ethyl (6R)-6-[4-[3-[3-ethoxy-1-(nitromethyl)-3-oxo-propyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. LCMS $[\text{M}+\text{H}]^+$ 504.

[0219] Step 3: Synthesis of ethyl (6R)-6-[4-[3-(5-oxopyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**34**): To a mixture of ethyl (6R)-6-[4-[3-[3-ethoxy-1-(nitromethyl)-3-oxo-propyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (160 mg, 318 μ mol) in EtOH (8.00 mL) was added

10% wet Pd/C (30 mg) at 20 °C under a N₂ gas atmosphere. Then the mixture was degassed under a reduced pressure and purged with H₂ gas for several times. Then the mixture was stirred at 60 °C for 24 hours under a H₂ gas pressure (50 psi). The residue was purified by silica gel flash chromatography (eluent of 0~15% MeOH/DCM) and prep-HPLC (column: Boston Prime C18 150×30 mm×5 μm; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; B%: 20%-50%, 7 min) to give ethyl (6R)-6-[4-[3-(5-oxopyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ_H = 8.24 (dd, *J* = 2.0 Hz, 4.8 Hz, 1H), 7.59 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.00 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 5.97 (s, 1H), 4.15-3.99 (m, 3H), 3.93-3.76 (m, 5H), 3.32 (dd, *J* = 6.8 Hz, 9.6 Hz, 1H), 3.19-3.02 (m, 4H), 2.83-2.74 (m, 1H), 2.73-2.52 (m, 5H), 2.40 (dd, *J* = 8.0 Hz, 16.8 Hz, 1H), 2.13 (dd, *J* = 7.2 Hz, 12.8 Hz, 1H), 2.02-1.76 (m, 4H), 1.65-1.56 (m, 1H), 1.23 (t, *J* = 6.8 Hz, 3H). **LCMS [M+H]⁺ 428.**

[0220] Step 4: Synthesis of ethyl (6R)-6-[4-[3-(1-methyl-5-oxo-pyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**235**): To a mixture of ethyl (6R)-6-[4-[3-(5-oxopyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (50.0 mg, 117 μmol) in DMF (1.50 mL) was added NaH (14.0 mg, 351 μmol, 60% purity) at 0 °C and stirred at 0 °C for 30 minutes under N₂ gas. Then CH₃I (16.6 mg, 117 μmol) was added to the mixture at 0 °C and the reaction was warmed to 20 °C, stirred at 20 °C for 1 hour. Then, H₂O (5 mL) was added to mixture dropwise, the mixture was extracted with DCM (3 × 5 mL), and the concentrated under reduced pressure to provide a crude material. The crude material was purified by prep-HPLC (column: Welch Xtimate C18 150×30mm×5μm; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; B%: 30%-60%, 7 min) to afford ethyl (6R)-6-[4-[3-(1-methyl-5-oxo-pyrrolidin-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ_H = 8.24 (dd, *J* = 2.0 Hz, 4.8 Hz, 1H), 7.52 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.00 (dd, *J* = 4.4 Hz, 7.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.94-3.76 (m, 6H), 3.30 (dd, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.25-2.95 (m, 4H), 2.93-2.82 (m, 4H), 2.81-2.50 (m, 5H), 2.45 (dd, *J* = 6.4 Hz, 16.8 Hz, 1H), 2.21-2.10 (m, 1H), 1.99-1.64 (m, 5H), 1.24 (t, *J* = 7.2 Hz, 3H). **LCMS [M+H]⁺ 442.**

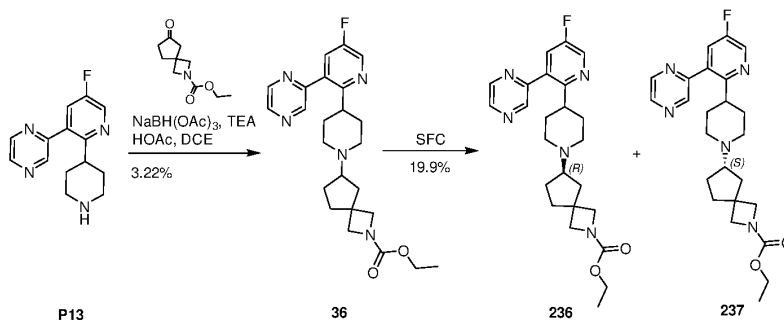
Example 35: Synthesis of (R)-ethyl 6-(4-(3-(1-methylpiperidin-4-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**35**)



[0221] Step 1: Synthesis of (R)-ethyl 6-(4-(1'-methyl-1',2',3',6'-tetrahydro- [3,4'-bipyridin]-2-yl)- piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C43**): To a mixture of ethyl (6R)-6-[4-(3-bromo-2-pyridyl)]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 236 μmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (105 mg, 472 μmol) and Na_2CO_3 (75.1 mg, 709 μmol) in 1,4-dioxane (4.00 mL) and H_2O (1.00 mL) was added ditert-butyl(cyclopentyl)phosphane; dichloropalladium;iron ($\text{Pd}(\text{dtbpf})\text{Cl}_2$, 15.4 mg, 23.6 μmol) in one portion at 20°C under a N_2 gas atmosphere. Then the mixture was degassed under vacuum and purged with N_2 gas several times. The mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated. The residue was purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) to afford ethyl (6R)-6-[4-[3-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-2-pyridyl]]piperazin-1-yl]-2-azaspiro-[3.4]octane-2-carboxylate. **LCMS** $[\text{M}+\text{H}]^+$ 440.

[0222] Step 2: Synthesis of (R)-ethyl 6-(4-(3-(1-methylpiperidin-4-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**35**): To a solution of ethyl (6R)-6-[4-[3-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-2-pyridyl]]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 227 μmol) in THF (5.00 mL) was added Pd/C (wet) (10.0 mg, 10.0% purity) under a N_2 gas atmosphere. The suspension was degassed and purged with H_2 gas for 3 times. The mixture was stirred under H_2 gas (15 psi) at 20°C for 16 hours. The reaction mixture was filtered and the filter was concentrated. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 $\times$ 30mm $\times$ 5 μm ; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}$ + NH_4HCO_3)-ACN]; B%: 32%-62%, 7 min) to afford ethyl (6R)-6-[4-[3-(1-methyl-4-piperidyl)-2-pyridyl]]piperazin-1-yl]-2- azaspiro[3.4]octane-2-carboxylate. **^1H NMR (CDCl_3 400 MHz)** δ_{H} = 8.17 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.51 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.94 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.94-3.84 (m, 2H), 3.84-3.78 (m, 2H), 3.12 (t, J = 4.8 Hz, 4H), 3.02 (br d, J = 11.2 Hz, 2H), 2.87-2.76 (m, 1H), 2.63 (br s, 5H), 2.36 (s, 3H), 2.16 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 2.11-2.02 (m, 2H), 2.00-1.90 (m, 2H), 1.86 (br dd, J = 5.2 Hz, 13.6 Hz, 1H), 1.80-1.69 (m, 5H), 1.64-1.55 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). **LCMS** $[\text{M}+\text{H}]^+$ 442.

Examples 36, 236, and 237: Synthesis of ethyl 6-(4-(5-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperidin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**36**), ethyl (6R)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**236**) and ethyl (6S)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**237**)

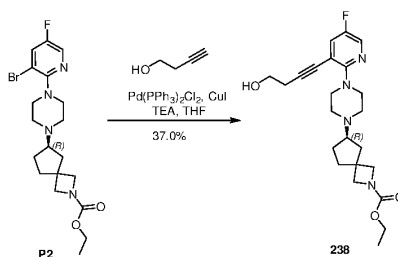


[0223] Step 1: Synthesis of ethyl 6-(4-(5-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperidin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**36**): A mixture of 2-[5-fluoro-2-(4-piperidyl)-3-pyridyl]pyrazine (90.0 mg, 348

umol) and ethyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (75.6 mg, 383 umol) in DCE (2.00 mL) was added TEA (176 mg, 1.74 mmol) and the mixture was stirred at 20 °C for 2 hours. Then NaBH(OAc)₃ (221 mg, 1.05 mmol) and HOAc (20.9 mg, 348 umol) were added at 20 °C. The mixture was stirred at 20°C for 18 hours under a N₂ gas atmosphere. The mixture was concentrated under a reduced pressure. The residue was purified by prep-HPLC (column: Welch Xtimate C18 100×40 mm×3 um; mobile phase: [water (TFA)-ACN]; B%: 5%-35%, 8 min) to give ethyl 6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.63 (s, 1H), 8.80-8.75 (m, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 2.8 Hz, 1H), 7.79 (dd, *J* = 2.8 Hz, 9.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.97-3.83 (m, 4H), 3.65 (br d, *J* = 12.0 Hz, 2H), 3.58-3.53 (m, 1H), 3.04-2.94 (m, 2H), 2.48-2.40 (m, 1H), 2.35-1.98 (m, 9H), 1.85-1.76 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). **¹⁹F NMR (CDCl₃ 400 MHz)** δ_F = -77.130, -131.279. **LCMS [M+H]⁺ 440.**

[0224] Step 2: Synthesis of ethyl (6R)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**236**) and ethyl (6S)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**237**): The ethyl 6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 228 μmol) was purified by SFC (column: DAICEL CHIRALPAK IG (250mm×30mm, 10μm); mobile phase: [CO₂-MeOH (0.1% NH₃H₂O)]; B%: 55%-55%, 9 min) to give ethyl (6R)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1, ¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.73-8.68 (m, 2H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.53 (d, *J* = 2.8 Hz, 1H), 7.42 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.94-3.78 (m, 2H), 3.78-3.72 (m, 2H), 3.15-2.98 (m, 2H), 2.92-2.75 (m, 1H), 2.67-2.41 (m, 1H), 2.17-2.02 (m, 3H), 2.00-1.65 (m, 9H), 1.23 (t, *J* = 7.2 Hz, 3H). **LCMS [M+H]⁺ 440.** And ethyl (6S)-6-[4-(5-fluoro-3-pyrazin-2-yl-2-pyridyl)-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 2, ¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.71 (s, 2H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 3.2 Hz, 1H), 7.48-7.35 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.94-3.79 (m, 2H), 3.76 (s, 2H), 3.31-2.71 (m, 3H), 2.70-2.42 (m, 1H), 2.30-2.05 (m, 3H), 2.03-1.64 (m, 9H), 1.23 (t, *J* = 7.2 Hz, 3H). **LCMS [M+H]⁺ 440.**

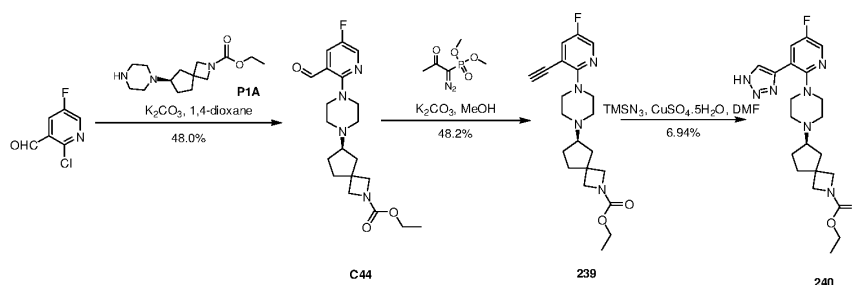
Example 37: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxybut-1-ynyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (238**)**



[0225] Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxybut-1-ynyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**238**): To a mixture of ethyl (6R)-6-[4-(3-bromo-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 227 umol), but-but-3-yn-1-ol (31.8 mg, 453 umol, 34.3 uL), CuI (4.32 mg, 22.7 umol) and TEA (45.7 mg, 453 umol) in toluene (2.00 mL) and H₂O (1.00 mL) was added Pd(PPh₃)₂Cl₂ (15.9 mg, 22.7 umol) at 20°C. Then, the mixture was degassed under vacuum and purged with N₂

gas several times. The reaction mixture was heated to 110 °C and stirred at 110 °C for 12 hours under a N₂ gas atmosphere. The mixture was cooled to 20 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of 0~10%, MeOH/DCM) and further purified by prep-HPLC (column: Welch Xtimate C18 150×25mm×5um; mobile phase: [water (NH₃H₂O)-ACN]; B%: 22%-52%, 8 min) to afford ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxybut-1-ynyl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.03 (d, *J* = 3.2 Hz, 1H), 7.35 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.92-3.76 (m, 6H), 3.50 (br s, 4H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.62 (br s, 5H), 2.14 (dd, *J* = 6.8 Hz, 12.0 Hz, 1H), 2.02-1.71 (m, 5H), 1.24 (t, *J* = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 431.

Example 38: Synthesis of ethyl (6R)-6-[4-(3-ethynyl-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (239) and ethyl (6R)-6-[4-[5-fluoro-3-(1H-triazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (240)



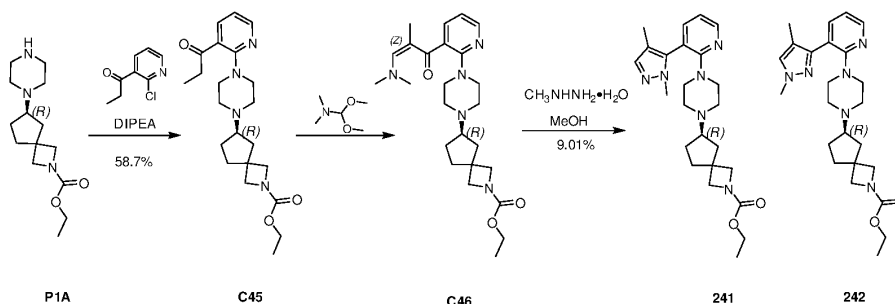
[0226] Step 1: Synthesis of (R)-ethyl 6-(4-(5-fluoro-3-formylpyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C44**): A mixture of 2-chloro-5-fluoro-pyridine-3-carbaldehyde (1.00 g, 6.27 mmol) and K₂CO₃ (866 mg, 6.27 mmol) was stirred in 1,4-dioxane (40.0 mL). Then, ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (2.18 g, 8.15 mmol) was added and the mixture was stirred at 20 °C for 16 hours. The mixture was diluted with EtOAc (100 mL), filtered, concentrated, and purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) to give (R)-ethyl 6-(4-(5-fluoro-3-formylpyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** [M+H]⁺ 391.

[0227] Step 2: Synthesis of (R)-ethyl 6-(4-(3-ethynyl-5-fluoropyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**239**): A mixture of ethyl (6R)-6-[4-(5-fluoro-3-formyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 256 μmol) and K₂CO₃ (70.8 mg, 512 μmol) was stirred in MeOH (3.00 mL). Then, a solution of 1-diazo-1-dimethoxyphosphorylpropan-2-one (54.1 mg, 281 μmol) in MeOH (3.00 mL) was added and the mixture was stirred at 25 °C for 5 hours. The mixture was diluted with water (3 mL) and concentrated. Water (5 mL) was added to the resulting residue again, and the aqueous phase was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by prep-HPLC (column: Waters xbridge 150 × 25mm 10 μm; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 36%-66%, 8 min) to give ethyl (6R)-6-[4-(3-ethynyl-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.09 (d, *J* = 2.8 Hz, 1H), 7.45 (dd, *J* = 3.2 Hz, 8.0 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.95-3.90 (m, 1H), 3.89-3.85 (m, 1H), 3.84-3.78

(m, 2H), 3.62-3.52 (m, 4H), 3.51 (s, 1H), 2.75-2.55 (m, 5H), 2.17 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 2.03-1.91 (m, 2H), 1.91-1.84 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.62 (m, 1H), 1.26 (t, $J = 6.8$ Hz, 3H). **LCMS** $[M+H]^+$ 387.

[0228] Step 3: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(1H-triazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**240**): A mixture of ethyl (6R)-6-[4-(3-ethynyl-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (48.0 mg, 124 μ mol), $TMSN_3$ (71.5 mg, 621 μ mol), $CuSO_4 \cdot 5H_2O$ (3.10 mg, 12.4 μ mol) and sodium ascorbate (4.92 mg, 24.8 μ mol) in *t*-BuOH (4.00 mL) and H_2O (1.00 mL) was degassed and purged with N_2 gas 3 times. Then, the mixture was stirred at 80 °C for 18 hours under N_2 gas. The mixture was quenched with water (10 mL) and extracted with EtOAc (20 mL $\times$ 3), the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC (column: Welch Ultimate C18 150 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (FA)-ACN]; B%: 6%-36%, 10 min) to give ethyl (6R)-6-[4-[5-fluoro-3-(1H-triazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **1H NMR ($CDCl_3$, 400 MHz)** $\delta_H = 8.23$ (br s, 1H), 8.18-8.09 (m, 1H), 7.90-7.80 (m, 1H), 4.10 (q, $J = 6.8$ Hz, 2H), 3.97-3.74 (m, 4H), 3.35-3.18 (m, 4H), 3.00-2.72 (m, 5H), 2.26-2.14 (m, 1H), 2.10-1.74 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H). **LCMS** $[M+H]^+$ 430.

Example 39: Synthesis of ethyl (6R)-6-[4-[3-(1,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (241**) and ethyl (6R)-6-[4-[3-(2,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**242**)**

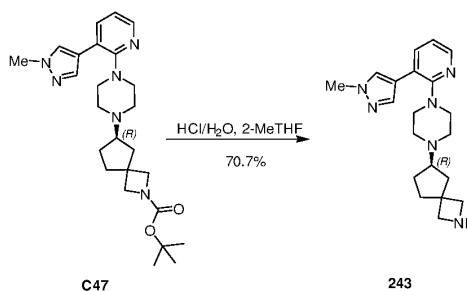


[0229] Step 1: Synthesis of (R)-ethyl 6-(4-(3-propionylpyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C45**): A solution of 1-(2-chloro-3-pyridyl)propan-1-one (500 mg, 2.95 mmol) in DIPEA (1.50 mL) and pyridine (0.500 mL) was mixed with ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (828 mg, 3.10 mmol) in one portion at 20 °C under N_2 gas. The mixture was heated to 130 °C and stirred at 130 °C for 12 h. Then, the reaction mixture was poured into aqueous HCl (2M, 30 mL) at 20 °C, extracted with EtOAc (3 $\times$ 30 mL) and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Eluent 0~10% of MeOH in DCM) to afford ethyl (6R)-6-[4-(3-propionyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **1H NMR ($CDCl_3$, 400 MHz)** $\delta_H = 8.27$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.63 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 6.82 (dd, $J = 5.6$ Hz, 7.2 Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.93-3.71 (m, 4H), 3.34 (br t, $J = 4.8$ Hz, 4H), 2.96 (q, $J = 7.2$ Hz, 2H), 2.65-2.53 (m, 5H), 2.12 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 2.00-1.80 (m, 3H), 1.79-1.67 (m, 1H), 1.55-1.50 (m, 1H), 1.23 (t, $J = 7.6$ Hz, 3H), 1.16 (t, $J = 7.2$ Hz, 3H). **LCMS** $[M+H]^+$ 401.

[0230] Step 2: Synthesis of (R,Z)-ethyl 6-(4-(3-(3-(dimethylamino)-2-methylacryloyl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C46**): A solution of ethyl (6R)-6-[4-(3-propanoyl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 250 μ mol) in MeCN (2.00 mL) was mixed with 1,1-dimethoxy-N,N-dimethyl-methanamine (149 mg, 1.25 mmol) in one portion at 20 °C under N₂ gas. The mixture was heated to 115 °C and stirred at 115 °C for 30 hours. The reaction mixture was concentrated to give ethyl (6R)-6-[4-[3-[(Z)-3-(dimethylamino)-2-methyl-prop-2-enoyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. The crude product was used for next step directly without further purification. **LCMS** [M+H]⁺ 456.

[0231] Step 3: Synthesis of Ethyl (6R)-6-[4-[3-(1,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**241**) and ethyl (6R)-6-[4-[3-(2,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**242**): To a solution of ethyl (6R)-6-[4-[3-[(Z)-3-(dimethylamino)-2-methyl-prop-2-enoyl]-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (400 mg, 878 μ mol) in MeOH (5.00 mL) was added methylhydrazine;hydrate (2.77 g, 17.3 mmol) in one portion at 20 °C under N₂ gas. The mixture was heated to 70 °C and stirred at 70 °C for 12 hours. The reaction mixture was poured into water (20.0 mL) at 25 °C, then extracted with EtOAc (3 $\times$ 15 mL). The combined organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under a reduced pressure to provide a residue. The residue was purified by flash silica gel chromatography (Eluent 0~10% of MeOH in DCM) to afford a mixture of products. The crude products were purified by SFC ([0.1% NH₃H₂O EtOH]; B%: 30%-30%, 9 min) to give ethyl (6R)-6-[4-[3-(1,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1, ¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.31 (dd, J = 2.0, 4.8 Hz, 1H), 7.43-7.26 (m, 2H), 6.91 (dd, J = 5.2, 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.96-3.51 (m, 7H), 3.13 (br s, 4H), 2.80-2.14 (m, 5H), 2.13-2.04 (m, 1H), 1.97 (s, 3H), 1.94-1.73 (m, 4H), 1.56-1.47 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 439. And ethyl (6R)-6-[4-[3-(2,4-dimethylpyrazol-3-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 2, ¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.22 (dd, J = 2.0, 5.2 Hz, 1H), 7.52 (dd, J = 2.0, 7.2 Hz, 1H), 7.17 (s, 1H), 6.83 (dd, J = 4.8, 7.6 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.90-3.64 (m, 7H), 3.16 (t, J = 4.8 Hz, 4H), 2.54-2.30 (m, 5H), 2.10-2.02 (m, 1H), 1.97 (s, 3H), 1.96-1.94 (m, 1H), 1.90-1.80 (m, 2H), 1.72-1.60 (m, 1H), 1.56-1.44 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H). **LCMS** [M+H]⁺ 439.

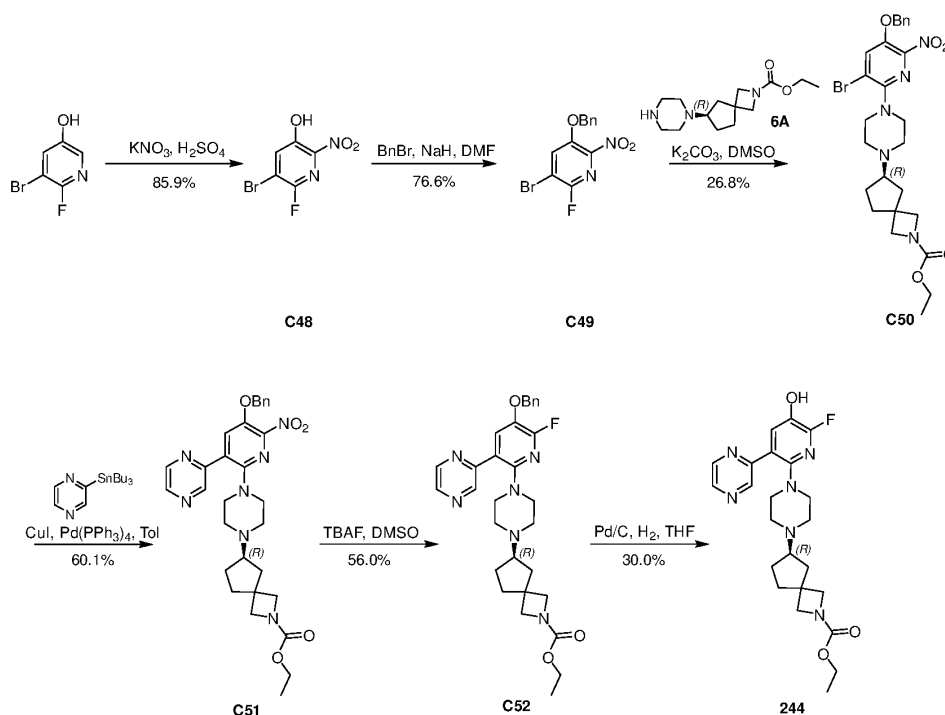
Example 40: Synthesis of 6(R)-(4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane hydrochloride (243**)**



[0232] Step 1: Synthesis of (R)-6-(4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane hydrochloride (**243**): To a solution of tert-butyl (6R)-6-[4-[3-(1-methylpyrazol-4-yl)-2-

pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (250 mg, 552 μmol) in 2-MeTHF (2.00 mL) was added HCl/H₂O (6 M in H₂O, 0.900 mL) in one portion at 20 °C. The mixture was stirred at 20 °C for 3 hours. The reaction mixture was extracted with EtOAc (3 $\times$ 5 mL). The aqueous phase was concentrated under a reduced pressure. The residue was freeze-dried to afford (6R)-6-[4-[3-(1-methylpyrazol-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane. ¹H NMR (Methonal-*d*₄ 400 MHz) δ_{H} = 8.37 (s, 1H), 8.35-8.20 (m, 2H), 8.08 (s, 1H), 7.53 (dd, *J* = 6.4 Hz, 7.6 Hz, 1H), 4.35-3.77 (m, 10H), 3.75-3.57 (m, 4H), 3.55-3.37 (m, 2H), 2.63 (dd, *J* = 8.4 Hz, 13.6 Hz, 1H), 2.40-2.21 (m, 3H), 2.12-1.92 (m, 2H). LCMS [M+H]⁺ 353.

Example 41: Synthesis of ethyl (R)-6-(4-(6-fluoro-5-hydroxy-3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (244)



[0233] Step 1: Synthesis of 5-bromo-6-fluoro-2-nitropyridin-3-ol (**C48**): An aliquot of concentrated H₂SO₄ (13.0 mL) and KNO₃ (470 mg, 4.65 mmol) was mixed in one portion at room temperature and stirred at room temperature for 30 min. Then, 5-bromo-6-fluoro-pyridin-3-ol (500 mg, 2.60 mmol) was added in one portion and the mixture was stirred at room temperature for 16 h. The mixture was poured into ice-water (50 mL) slowly and extracted with EtOAc (3 $\times$ 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure to give 5-bromo-6-fluoro-2-nitropyridin-3-ol. ¹H NMR (CDCl₃ 400 MHz) δ_{H} = 10.21 (s, 1H), 8.00 (d, *J* = 6.4 Hz, 1H).

[0234] Step 2: Synthesis of 3-(benzyloxy)-5-bromo-6-fluoro-2-nitropyridine (**C49**): To a solution of 5-bromo-6-fluoro-2-nitropyridin-3-ol (530 mg, 2.24 mmol) in DMF (5.00 mL), was added NaH (134 mg, 3.35 mmol, 60% purity) in one portion at 0 °C under N₂ gas and stirred at 0 °C for 30 min. Next, BnBr (765 mg, 4.47 mmol) was

added in one portion at 0 °C, then the mixture was warmed to room temperature and stirred at room temperature for 16 hours. The reaction mixture was poured into water (30 mL), then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~20% EtOAc /Petroleum ether) to afford 5-benzyloxy-3-bromo-2-fluoro-6-nitro-pyridine. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 7.86 (d, J = 6.4 Hz, 1H), 7.48-7.31 (m, 5H), 5.25 (s, 2H). **LCMS** m/z [M+H]⁺ 327, 329.

[0235] Step 3: Synthesis of ethyl (R)-6-(4-(5-(benzyloxy)-3-bromo-6-nitropyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C50**): A solution of 5-benzyloxy-3-bromo-2-fluoro-6-nitro-pyridine (500 mg, 1.53 mmol) in DMSO (20.0 mL) was mixed with ethyl (6R)-6-piperazin-1-yl-2-azaspiro[3.4]octane-2-carboxylate (409 mg, 1.53 mmol) and K₂CO₃ (634 mg, 4.59 mmol) in one portion. The mixture was stirred at room temperature for 12 hours. Then, the mixture was poured into water (30 mL), extracted with EtOAc (3 × 20 mL), and washed with brine (50 mL). Next, the mixture was dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) to give ethyl (6R)-6-[4-(5-benzyloxy-3-bromo-6-nitro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** m/z [M+H]⁺ 574, 576.

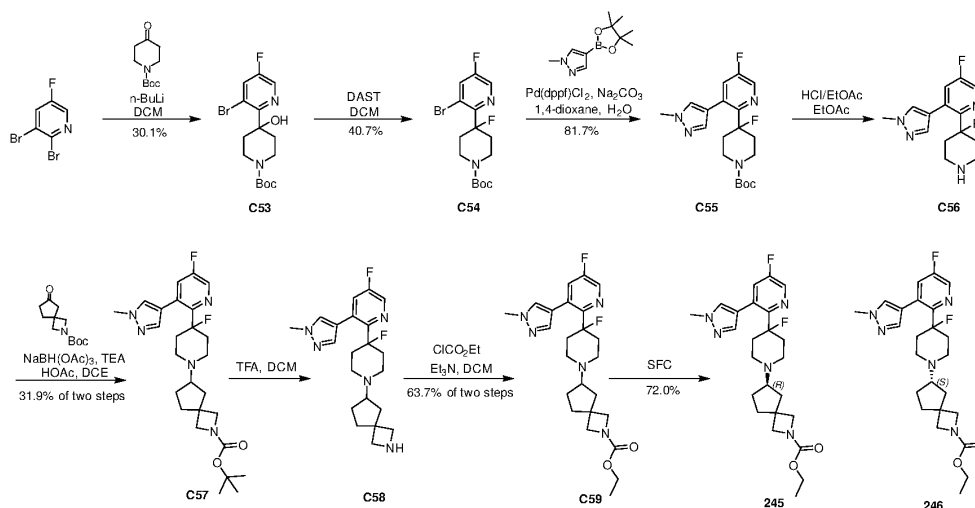
[0236] Step 4: Synthesis of ethyl (R)-6-(4-(5-(benzyloxy)-6-nitro-3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C51**): A solution of ethyl (6R)-6-[4-(5-benzyloxy-3-bromo-6-nitro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (250 mg, 435 μmol) and tributyl(pyrazin-2-yl)stannane (193 mg, 522 μmol) in toluene (10.0 mL) was mixed with CuI (8.29 mg, 43.5 μmol) and Pd(PPh₃)₄ (25.1 mg, 21.8 μmol) in one portion. The mixture was degassed under vacuum and purged with N₂ gas 3 times and stirred at 110 °C for 16 hours. Then, the reaction mixture was filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) to give ethyl (6R)-6-[4-(5-benzyloxy-6-nitro-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** m/z [M+H]⁺ 574.

[0237] Step 5: Synthesis of ethyl (R)-6-(4-(5-(benzyloxy)-6-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**C52**): To a solution of ethyl (6R)-6-[4-(5-benzyloxy-6-nitro-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (80.0 mg, 139 μmol) in DMSO (2.00 mL) was added a solution of TBAF in THF (1 M, 1.00 mL) in one portion. The mixture was stirred at room temperature for 16 h. The mixture was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water (2 × 20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~12% MeOH/DCM) to give ethyl (6R)-6-[4-(5-benzyloxy-6-fluoro-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** m/z [M+H]⁺ 547.

[0238] Step 6: Synthesis of ethyl (R)-6-(4-(6-fluoro-5-hydroxy-3-(pyrazin-2-yl)pyridin-2-yl)piperazin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (**244**): To a solution of ethyl (6R)-6-[4-(5-benzyloxy-6-fluoro-3-pyrazin-2-yl-2-

pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (70.0 mg, 128.06 μ mol) in THF (10.0 mL) was added dry Pd/C (20 mg, 10% w/w) in one portion. The mixture was degassed and purged with a H₂ gas for 3 times. The mixture was stirred under H₂ gas (40 psi) at 30 °C for 16 hours. The reaction mixture was filtered and concentrated to provide a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) and further purified by prep-HPLC (column: Phenomenex C18, 80 × 40 mm × 3 μ m; mobile phase: [water (NH₃H₂O + NH₄HCO₃)-ACN]; gradient: 19%-49% B, over 8 min) to give ethyl (6R)-6-[4-(6-fluoro-5-hydroxy-3-pyrazin-2-yl-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. ¹H NMR (CD₃CN 400 MHz) δ _H = 9.27 (d, J = 1.6 Hz, 1H), 8.62 (dd, J = 1.6 Hz, 2.4 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 10.8 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 3.82-3.61 (m, 4H), 2.92 (t, J = 4.8 Hz, 4H), 2.61-2.38 (m, 5H), 2.06-2.01 (m, 1H), 1.88-1.76 (m, 3H), 1.62 (dd, J = 9.2 Hz, 12.8 Hz, 1H), 1.50-1.38 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H). ¹⁹F NMR (CD₃CN 400 MHz) δ _F = -89.28. LCMS m/z [M+H]⁺ 457.

Example 42: Synthesis of ethyl (R)-6-(4-fluoro-4-(5-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperidin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (245) and ethyl (S)-6-(4-fluoro-4-(5-fluoro-3-(pyrazin-2-yl)pyridin-2-yl)piperidin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate (246)



[0239] Step 1: Synthesis of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-hydroxy-piperidine-1-carboxylate (**C53**): A mixture of 2,3-dibromo-5-fluoropyridine (3.50 g, 13.7 mmol) in DCM (35.0 mL) was mixed with n-BuLi in n-hexane (2.5 M, 6.09 mL) at -70 °C under N₂ gas and stirred at -70 °C for 10 min. Then, a solution of tert-butyl 4-oxopiperidine-1-carboxylate (2.19 g, 11.0 mmol) in DCM (20.0 mL) was added dropwise to the mixture at -70 °C and the mixture was stirred at -70 °C for 1 hour. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution (50 mL) and extracted with DCM (3 × 20 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by flash silica gel chromatography (Eluent of 0~13% EtOAc /Petroleum ether) to afford tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-hydroxy-piperidine-1-carboxylate. ¹H NMR (CDCl₃ 400 MHz) δ _H = 8.39 (d, J = 2.4 Hz, 1H), 7.75 (dd, J = 2.4 Hz, 7.2 Hz, 1H), 4.21-3.97 (m, 2H), 3.45-3.15 (m, 2H), 2.85-2.73 (m, 2H), 1.49 (s, 9H), 1.45-1.36 (m, 2H). LCMS m/z [M+H-100]⁺ 275, 277.

[0240] Step 2: Synthesis of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-fluoro-piperidine-1- carboxylate (**C54**): A mixture of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-hydroxy-piperidine-1-carboxylate (700 mg, 1.87 mmol) in DCM (7.00 mL) was mixed with DAST (756 mg, 4.69 mmol) at 0 °C and stirred at 25 °C for 12 hours. The mixture was added into a saturated aqueous NaHCO₃ solution (50 mL) and extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in a vacuum. The residue was purified by flash silica gel chromatography (Eluent of 0~7% EtOAc /Petroleum ether) to afford tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-fluoro-piperidine-1-carboxylate. **LCMS** m/z [M+H-56]⁺ 321, 323.

[0241] Step 3: Synthesis of tert-butyl 4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]- piperidine-1- carboxylate (**C55**): A mixture of tert-butyl 4-(3-bromo-5-fluoro-2-pyridyl)-4-fluoro-piperidine-1-carboxylate (340 mg, 901 μmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (225 mg, 1.08 mmol) in 1,4-dioxane (5.00 mL) and H₂O (0.700 mL) was mixed with Pd(dppf)Cl₂ (66.0 mg, 90.1 μmol) and Na₂CO₃ (191 mg, 1.80 mmol). The mixture was degassed under vacuum and purged with N₂ gas 3 times and stirred at 100 °C for 12 hours. The mixture was concentrated and purified by flash silica gel chromatography (Eluent of 0~49% EtOAc /Petroleum ether) to afford tert-butyl 4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]piperidine-1- carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.33 (d, J = 2.8 Hz, 1H), 7.56-7.54 (m, 1H), 7.52 (d, J = 3.2 Hz, 1H), 7.30 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 4.02-3.86 (m, 5H), 3.34-3.04 (m, 2H), 2.11-2.00 (m, 4H), 1.45 (s, 9H). **¹⁹F NMR (CDCl₃ 400 MHz)** δ_F = -129.12, -150.16. **LCMS** m/z [M+H-56]⁺ 323.

[0242] Step 4: Synthesis of 5-fluoro-2-(4-fluoro-4-piperidyl)-3-(1-methylpyrazol-4-yl)pyridine (**C56**): A mixture of tert-butyl 4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]piperidine-1- carboxylate (390 mg, 1.03 mmol) in EtOAc (1.00 mL) was mixed with HCl/EtOAc (4 M, 5.00 mL) and stirred at 20 °C for 1 hour. The mixture was concentrated to afford 5-fluoro-2-(4-fluoro-4-piperidyl)-3-(1-methylpyrazol-4-yl)pyridine, which was used to next step without purification. **LCMS** m/z [M+H]⁺ 279.

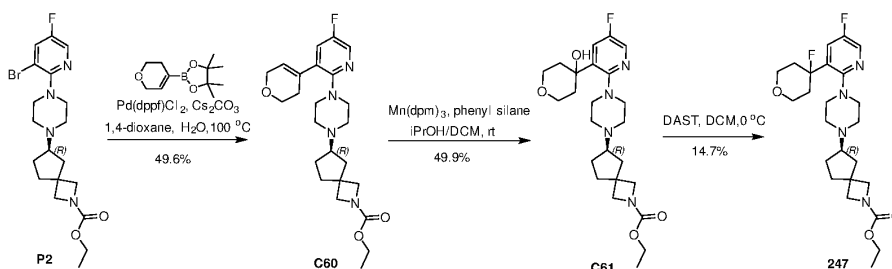
[0243] Step 5: Synthesis of tert-butyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2- azaspiro[3.4]octane-2-carboxylate (**C57**): A mixture of 5-fluoro-2-(4-fluoro-4-piperidyl)-3-(1-methylpyrazol-4-yl)pyridine (324 mg, 1.03 mmol, HCl) in DCE (10.0 mL) was mixed with TEA (521 mg, 5.15 mmol) and tert-butyl 6-oxo-2-azaspiro[3.4]octane-2-carboxylate (255 mg, 1.13 mmol). The mixture was stirred at 25 °C for 1 hour, then NaBH(OAc)₃ (654.48 mg, 3.09 mmol) and AcOH (30.9 mg, 515 μmol) were added and the mixture was stirred for 12 hours at 25 °C. The reaction mixture was mixed with saturated aqueous NaHCO₃ solution (50 mL) and extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to provide a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~5% MeOH/DCM) to afford tert-butyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃ 400 MHz)** δ_H = 8.33 (d, J = 2.8 Hz, 1H), 7.57-7.49 (m, 2H), 7.29 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 3.96 (s, 3H), 3.85-3.68 (m, 4H), 2.84-2.72 (m, 2H), 2.64-2.52 (m, 1H), 2.40-2.06 (m, 7H), 1.96-1.63 (m, 4H), 1.55-1.50 (m, 1H), 1.43 (s, 9H). **LCMS** m/z [M+H]⁺ 488.

[0244] Step 6: Synthesis of 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane (**C58**): A mixture of tert-butyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (200 mg, 410 μ mol) in DCM (2.00 mL) was mixed with TFA (614 mg, 5.38 mmol) and stirred at 20 °C for 12 hours. The mixture was concentrated to provide 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane, which was used for the next step without further purification. **LCMS** m/z [M+H]⁺ 388.

[0245] Step 7: Synthesis of ethyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**C59**): A mixture of 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane (205 mg, 409 μ mol, TFA), TEA (124 mg, 1.23 mmol) in DCM (3.00 mL) at 0 °C was mixed with ethyl carbonochloridate (160 mg, 1.47 mmol), added dropwise at 0 °C. Then, the mixture was warmed to 20 °C and stirred at 20 °C for 4 hours. The reaction was quenched slowly with a saturated aqueous NaHCO₃ solution (10 mL) and then extracted with DCM (3 $\times$ 5 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography (Eluent of 0~7% MeOH/DCM) to give ethyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** m/z [M+H]⁺ 460.

[0246] Step 8: Synthesis of ethyl (6R)-6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**245**) and ethyl (6S)-6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate (**246**): The ethyl 6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm $\times$ 30 mm, 10 μ m); mobile phase: [CO₂-EtOH (0.1% NH₃H₂O)]; B%: 20%, isocratic elution mode) to afford ethyl (6R)-6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 1:** ¹H NMR (CDCl₃ 400 MHz) δ_H = 8.32 (d, J = 2.4 Hz, 1H), 7.57-7.50 (m, 2H), 7.29 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.91-3.72 (m, 4H), 2.92-2.73 (m, 2H), 2.69-2.55 (m, 1H), 2.47-2.01 (m, 7H), 1.98-1.67 (m, 4H), 1.64-1.48 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). ¹⁹F NMR (CDCl₃ 400 MHz) δ_F = -75.75, -129.31. **LCMS** m/z [M+H]⁺ 460. And of ethyl (6S)-6-[4-fluoro-4-[5-fluoro-3-(1-methylpyrazol-4-yl)-2-pyridyl]-1-piperidyl]-2-azaspiro[3.4]octane-2-carboxylate. **Peak 2:** ¹H NMR (CDCl₃ 400 MHz) δ_H = 8.32 (d, J = 2.8 Hz, 1H), 7.59-7.48 (m, 2H), 7.29 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.96 (s, 3H), 3.91-3.72 (m, 4H), 2.86-2.72 (m, 2H), 2.66-2.54 (m, 1H), 2.42-2.02 (m, 7H), 1.96-1.72 (m, 1H), 1.96-1.72 (m, 3H), 1.60-1.47 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). ¹⁹F NMR (CDCl₃ 400 MHz) δ_F = -75.76, -129.40. **LCMS** m/z [M+H]⁺ 460.

Example 43: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(4-fluorotetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (247**)**



[0247] Step 1: Synthesis of ethyl (6R)-6-[4-[3-(3,6-dihydro-2H-pyran-4-yl)-5-fluoro-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C60**): A mixture of ethyl (6R)-6-[4-(3-bromo-5-fluoro-2-pyridyl)piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (230 mg, 521 μ mol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (132 mg, 628 μ mol), Cs_2CO_3 (340 mg, 1.04 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (77.0 mg, 105 μ mol) in 1,4-dioxane (8.00 mL) and H_2O (2.00 mL) was degassed and purged with N_2 gas 3 times. Then, the mixture was stirred at 100 °C for 3 hours under N_2 gas. The mixture was concentrated to provide a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~10% MeOH/DCM) to give ethyl (6R)-6-[4-[3-(3,6-dihydro-2H-pyran-4-yl)-5-fluoro-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **^1H NMR (DMSO- d_6 400 MHz)** δ_{H} = 8.11 (d, J = 3.2 Hz, 1H), 7.39 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 6.03 (br s, 1H), 4.21 (br d, J = 2.4 Hz, 2H), 3.98 (q, J = 7.2 Hz, 2H), 3.81-3.77 (m, 2H), 3.77-3.63 (m, 4H), 3.10 (br s, 4H), 2.48-2.43 (m, 7H), 2.08-2.00 (m, 1H), 1.83-1.72 (m, 3H), 1.66-1.59 (m, 1H), 1.48-1.40 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). **LCMS** m/z $[\text{M}+\text{H}]^+$ 445.

[0248] Step 2: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxytetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**C61**): To a mixture of ethyl (6R)-6-[4-[3-(3,6-dihydro-2H-pyran-4-yl)-5-fluoro-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (100 mg, 224 μ mol), tris[(Z)-1-tert-butyl-4,4-dimethyl-3-oxo-pent-1-en-1-yl]manganese (40.8 mg, 67.4 μ mol) in *i*-PrOH (10.0 mL) was added phenylsilane (97.3 mg, 899 μ mol) in DCE (4.00 mL) at 0 °C. Then, the mixture was stirred at room temperature for 16 hours under O_2 gas (15 psi). The mixture was concentrated to provide a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~8% MeOH/DCM) to give ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxytetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **LCMS** m/z $[\text{M}+\text{H}]^+$ 463.

[0249] Step 3: Synthesis of ethyl (6R)-6-[4-[5-fluoro-3-(4-fluorotetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (**247**): A mixture of ethyl (6R)-6-[4-[5-fluoro-3-(4-hydroxytetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate (95.0 mg, 205 μ mol) in DCM (10.0 mL) was degassed and purged with N_2 gas 3 times. Then, DAST (170 mg, 1.06 mmol) in DCM (3.00 mL) was added dropwise to the mixture at 0 °C and the mixture was stirred at 0 °C for 2 hours under N_2 gas. The pH was adjusted to 7~8 with a saturated aqueous NaHCO_3 solution, then the organic layer was washed with H_2O (2×10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to provide a residue. The residue was purified by

prep-HPLC (column: Waters Xbridge, 150 × 25mm × 5um; mobile phase: [water (NH₃H₂O)-ACN]; gradient: 36% - 66% B, over 10 min), lyophilized to give ethyl (6R)-6-[4-[5-fluoro-3-(4-fluorotetrahydropyran-4-yl)-2-pyridyl]piperazin-1-yl]-2-azaspiro[3.4]octane-2-carboxylate. **¹H NMR (CDCl₃, 400 MHz)** δ_H = 8.24 (d, J = 2.8 Hz, 1H), 7.62 (dd, J = 2.8 Hz, 9.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.96-3.91 (m, 2H), 3.91-3.87 (m, 2H), 3.87-3.82 (m, 2H), 3.80 (s, 2H), 2.96 (br s, 4H), 2.81-2.70 (m, 1H), 2.68-2.63 (m, 2H), 2.62-2.54 (m, 2H), 2.18-2.07 (m, 2H), 1.98-1.89 (m, 2H), 1.88-1.79 (m, 2H), 1.79-1.72 (m, 2H), 1.71-1.51 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H). **LCMS m/z** [M+H]⁺ 465.

[0250] Using the methodologies described above for Examples 1-36 and analogous starting materials as noted in the table 1, Examples 37-234 were synthesized. Table 1 also showed specific methods employed, as well as characterization data for these Examples. Peak 1 or Peak 2 denotes the order of elution on a chiral HPLC/SFC.

Table 1

Example	Prepared Like	LCMS and/or ¹ H NMR
37	Example 1	LCMS m/z [M+H] ⁺ 479.
38	Example 1	LCMS m/z [M+H] ⁺ 454.
39	Example 1	LCMS m/z [M+H] ⁺ 470.
40	Example 1	LCMS m/z [M+H] ⁺ 440.
41	Example 1	LCMS m/z [M+H] ⁺ 487.
42	Example 1	LCMS m/z [M+H] ⁺ 454.
43	Example 1	LCMS m/z [M+H] ⁺ 440.
44	Example 1	¹H NMR (CDCl₃, 400 MHz) δ _H = 8.04 (d, J = 2.8 Hz, 1H), 7.30 - 7.27 (m, 2H), 7.16 (s, 1H), 7.02 - 6.98 (m, 1H), 6.85 (dd, J = 2.1, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93 - 3.80 (m, 2H), 3.75 (s, 2H), 3.28 (br s, 4H), 3.04 - 2.98 (m, 1H), 2.84 (br d, J = 1.2 Hz, 4H), 2.19 - 2.12 (m, 1H), 2.10 - 1.77 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
45	Example 1	LCMS m/z [M+H] ⁺ 470.
46	Example 1	¹H NMR (CDCl₃, 400 MHz) δ _H = 8.03 (d, J = 2.8 Hz, 1H), 7.21 (dd, J = 2.8, 8.8 Hz, 1H), 7.12 - 7.07 (m, 2H), 6.90 (br d, J = 8.8 Hz, 1H), 4.31 (s, 4H), 4.09 (q, J = 7.2 Hz, 2H), 3.90 - 3.72 (m, 4H), 3.20 - 2.96 (m, 4H), 2.59 - 2.33 (m, 5H), 2.10 (br dd, J = 6.4, 12.4 Hz, 1H), 1.98 - 1.81 (m, 3H), 1.75 - 1.68 (m, 1H), 1.48 - 1.39 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 497.
47	Example 1	¹H NMR (CDCl₃, 400 MHz) δ _H = 8.08 (d, J = 2.8 Hz, 1H), 7.99 (s, 1H), 7.59 (br s, 1H), 7.31 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.82 (br s, 2H), 3.75 (s, 2H), 3.02 (br s, 4H), 2.51-2.41 (m, 1H), 2.38-2.21 (m, 7H), 2.13-2.00 (m, 1H), 1.94-1.76 (m, 3H), 1.70-1.61 (m, 1H), 1.52-1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 484.
48	Example 1	LCMS m/z [M+H] ⁺ 458.
49	Example 1	LCMS m/z [M+H] ⁺ 483.
50	Example 1	LCMS m/z [M+H] ⁺ 446.
51	Example 1	LCMS m/z [M+H] ⁺ 487.
52	Example 1	¹H NMR (CDCl₃, 400 MHz) δ _H = 8.18 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.28 - 7.27 (m, 1H), 7.29 (m, 1H), 7.25 (s, 1H), 6.30 (d, J = 2.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.87 - 3.72 (m, 7H), 3.06 (m, 4H), 2.61 - 2.31 (m, 5H), 2.14 - 2.04 (m, 1H), 1.93 - 1.77 (m, 3H), 1.73 - 1.63 (m, 1H), 1.51 - 1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 443.
53	Example 1	LCMS m/z [M+H] ⁺ 470.

54	Example 1	LCMS m/z [M+H] ⁺ 485.
55	Example 1	LCMS m/z [M+H] ⁺ 484.
56	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.01 (d, J = 2.8 Hz, 1H), 7.89 (d, J = 6.4 Hz, 2H), 7.33 (dd, J = 2.8, 8.8 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.92 - 3.82 (m, 2H), 3.78 (s, 2H), 3.11 (br s, 4H), 2.73 - 2.39 (m, 5H), 2.12 (br dd, J = 6.8, 12.0 Hz, 1H), 2.01 - 1.68 (m, 5H), 1.54 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 457.
57	Example 1	LCMS m/z [M+H] ⁺ 429.
58	Example 1	LCMS m/z [M+H] ⁺ 485.
59	Example 1	LCMS m/z [M+H] ⁺ 458.
60	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.17 (dd, J = 2.3, 4.8 Hz, 2H), 7.97 (br t, J = 9.2 Hz, 1H), 7.30 - 7.26 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90 - 3.73 (m, 4H), 3.04 (br s, 4H), 2.62 - 2.31 (m, 5H), 2.14 - 2.05 (m, 1H), 1.96 - 1.78 (m, 3H), 1.74 - 1.63 (m, 1H), 1.53 - 1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 476.
61	Example 1	LCMS m/z [M+H] ⁺ 457.
62	Example 1	LCMS m/z [M+H] ⁺ 497.
63	Example 1	LCMS m/z [M+H] ⁺ 479.
64	Example 1	LCMS m/z [M+H] ⁺ 457.
65	Example 1	LCMS m/z [M+H] ⁺ 496.
66	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.33 (s, 1H), 8.15 (d, J = 2.8 Hz, 1H), 7.78 (br d, J = 9.2 Hz, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.51 (dd, J = 1.6, 8.0 Hz, 1H), 7.34 (dd, J = 2.8, 8.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.01 - 3.84 (m, 2H), 3.75 (s, 2H), 3.49 (br s, 4H), 3.09 - 2.91 (m, 5H), 2.35 - 2.27 (m, 1H), 2.22 (br d, J = 8.0 Hz, 1H), 2.11 (br d, J = 9.6 Hz, 2H), 2.03 - 1.95 (m, 1H), 1.90 - 1.79 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
67	Example 1	LCMS m/z [M+H] ⁺ 454.
68	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.91 (d, J = 1.6 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 2.8, 8.0 Hz, 2H), 7.35 (dd, J = 2.8, 8.0 Hz, 1H), 6.76 (d, J = 1.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90 - 3.78 (m, 2H), 3.75 (s, 1H), 3.73 - 3.72 (m, 1H), 3.11 (br s, 4H), 2.59 - 2.36 (m, 5H), 2.10 - 2.01 (m, 1H), 1.83 (br s, 3H), 1.72 - 1.63 (m, 1H), 1.53 - 1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 480.
69	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.12 (d, J = 2.8 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.28 (br d, J = 3.2 Hz, 1H), 6.73 (s, 1H), 6.52 (br d, J = 6.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91 - 3.81 (m, 2H), 3.76 (s, 2H), 3.59 (s, 3H), 3.20 (br s, 4H), 2.52 (br s, 5H), 2.11 (br dd, J = 7.2 Hz, 12.4 Hz, 1H), 2.01 - 1.74 (m, 5H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 470.
70	Example 1	LCMS m/z [M+H] ⁺ 488.
71	Example 1	LCMS m/z [M+H] ⁺ 484.
72	Example 1	LCMS m/z [M+H] ⁺ 470.
73	Example 1	LCMS m/z [M+H] ⁺ 484.
74	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.06 (d, J = 3.2 Hz, 1H), 7.63 (br d, J = 7.6 Hz, 1H), 7.31 (dd, J = 3.0, 8.8 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.08 (d, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.87 (br s, 1H), 3.84 - 3.80 (m, 1H), 3.75 (s, 2H), 3.09 (br d, J = 2.4 Hz, 4H), 2.62 - 2.22 (m, 8H), 2.13 - 2.04 (m, 1H), 2.00 - 1.66 (m, 5H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 484.
75	Example 1	LCMS m/z [M+H] ⁺ 443.
76	Example 1	LCMS m/z [M+H] ⁺ 457.
77	Example 1	LCMS m/z [M+H] ⁺ 485.
78	Example 1	LCMS m/z [M+H] ⁺ 494.
79	Example 1	LCMS m/z [M+H] ⁺ 485.
80	Example 1	LCMS m/z [M+H] ⁺ 470.
81	Example 1	LCMS m/z [M+H] ⁺ 488.

82	Example 1	LCMS m/z [M+H] ⁺ 444.
83	Example 1	LCMS m/z [M+H] ⁺ 457.
84	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 8.08 (d, J = 2.0 Hz, 1H), 7.64 - 7.55 (m, 2H), 7.20 - 7.16 (m, 1H), 6.64 (d, J = 9.2 Hz, 1H), 5.32 (s, 1H), 4.09 (d, J = 7.2 Hz, 2H), 3.93 (d, J = 6.4 Hz, 1H), 3.86 (s, 1H), 3.77 (s, 2H), 3.40 - 3.06 (m, 4H), 2.81 - 2.35 (m, 5H), 2.14 (d, J = 2.0 Hz, 1H), 2.04 - 1.91 (m, 2H), 1.85 (dd, J = 6.8, 12.4 Hz, 2H), 1.58 (d, J = 2.8 Hz, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 498.
85	Example 1	LCMS m/z [M+H] ⁺ 484.
86	Example 1	LCMS m/z [M+H] ⁺ 457.
87	Example 1	LCMS m/z [M+H] ⁺ 483.
88	Example 1	LCMS m/z [M+H] ⁺ 479.
89	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 12.14-11.67 (m, 1H), 8.08 (d, J = 2.8 Hz, 1H), 7.71 (br s, 1H), 7.51 (br s, 1H), 7.19 (br dd, J = 2.4 Hz, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.95-3.81 (m, 2H), 3.77 (s, 2H), 3.38-2.92 (m, 4H), 2.70-2.30 (m, 4H), 2.22 (s, 3H), 2.18-2.08 (m, 1H), 2.06-1.65 (m, 5H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 470.
90	Example 1	LCMS m/z [M+H] ⁺ 473.
91	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 8.02 (d, J = 3.2 Hz, 1H), 8.00 (s, 1H), 7.92 (s, 1H), 7.34 (dd, J = 2.8, 8.8 Hz, 1H), 4.86 (t, J = 4.8 Hz, 1H), 4.74 (t, J = 4.8 Hz, 1H), 4.50 (t, J = 4.8 Hz, 1H), 4.43 (t, J = 4.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.82 (m, 2H), 3.81-3.76 (m, 2H), 3.13 (br s, 4H), 2.58 (br s, 5H), 2.13 (dd, J = 6.8, 12.4 Hz, 1H), 1.96-1.81 (m, 3H), 1.76 (s, 1H), 1.56-1.49 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 475.
92	Example 1	LCMS m/z [M+H] ⁺ 493.
93	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 8.63 (d, J = 7.2 Hz, 1H), 8.40 (s, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.93 (s, 1H), 7.44 (br d, J = 6.8 Hz, 1H), 7.37 (dd, J = 2.8, 8.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.90 - 3.79 (m, 2H), 3.75 (s, 2H), 3.16 (br s, 4H), 2.61 - 2.37 (m, 4H), 2.08 (br dd, J = 6.4, 12.0 Hz, 1H), 1.97 - 1.58 (m, 9H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 485.
94	Example 1	LCMS m/z [M+H] ⁺ 494.
95	Example 1	LCMS m/z [M+H] ⁺ 480.
96	Example 1	LCMS m/z [M+H] ⁺ 480.
97	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 8.23 (s, 1H), 8.12 (d, J = 2.8 Hz, 1H), 7.80 (br d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.33 (dd, J = 2.8, 8.4 Hz, 1H), 4.36 (s, 3H), 4.08 (d, J = 7.2 Hz, 2H), 3.90 - 3.85 (m, 1H), 3.82 (s, 1H), 3.74 (s, 2H), 3.14 (br s, 4H), 2.63 - 2.40 (m, 4H), 2.11 - 2.03 (m, 1H), 1.80 (br dd, J = 6.4, 12.4 Hz, 5H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 488.
98	Example 1	LCMS m/z [M+H] ⁺ 470.
99	Example 1	LCMS m/z [M+H] ⁺ 506.
100	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 8.89 (s, 2H), 8.49 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 4.8 Hz, 1H), 6.86 (d, J = 5.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.81 (dd, J = 8.4 Hz, 19.6 Hz, 2H), 3.76-3.70 (m, 2H), 3.00 (t, J = 4.8 Hz, 4H), 2.48-2.39 (m, 1H), 2.33-2.17 (m, 4H), 2.82 (s, 3H), 2.02 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.91-1.74 (m, 3H), 1.67- 1.59 (m, 1H), 1.50-1.41 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 437.
101	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 9.28 (s, 1H), 8.24 (d, J = 5.2 Hz, 1H), 6.89 (d, J = 4.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.88-3.73 (m, 4H), 3.03-3.16 (m, 4H), 2.54-2.33 (m, 5H), 2.30 (s, 3H), 2.09-2.02 (m, 1H), 1.93-1.76 (m, 3H), 1.69-1.62 (m, 1H), 1.53-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 443.
102	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ_H = 9.24 (s, 1H), 8.65 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.86 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.01 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 3.82-3.68 (m, 4H), 3.15 (s, 4H), 2.60-2.39 (m,

		5H), 2.06 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.93-1.75 (m, 3H), 1.66-1.57 (m, 1H), 1.56-1.47 (m, 1H), 1.42 (s, 9H). LCMS m/z $[M+H]^+$ 451.
103	Example 2	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.17$ (s, 1H), 8.34 (d, $J = 2.0$ Hz, 1H), 8.28 (d, $J = 1.6$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.76 (m, 4H), 3.16-3.07 (m, 4H), 2.70-2.55 (m, 5H), 2.36 (s, 3H), 2.12 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 1.98-1.82 (m, 3H), 1.77-1.70 (m, 1H), 1.56-1.52 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.
104	Example 2	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.14$ (s, 1H), 8.34 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.76 (m, 4H), 3.21-3.08 (m, 4H), 2.71-2.53 (m, 5H), 2.52 (s, 3H), 2.12 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 2.01-1.79 (m, 3H), 1.78-1.67 (m, 1H), 1.58-1.51 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.
105	Example 2	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.22$ (s, 1H), 8.67-8.62 (m, 1H), 8.47 (s, 1H), 8.33 (dd, $J = 2.0$, 4.8 Hz, 1H), 7.87 (dd, $J = 1.6$, 7.6 Hz, 1H), 7.05-6.94 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.45-3.08 (m, 8H), 2.72 (s, 1H), 2.33 (s, 4H), 2.09-1.96 (m, 2H), 1.94-1.79 (m, 4H), 1.28-1.19 (m, 3H). LCMS m/z $[M+H]^+$ 423.
106	Example 2	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.36$ (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.19 (d, $J = 2.8$ Hz, 1H), 7.72 (dd, $J = 2.8$, 8.4 Hz, 1H), 4.17-4.08 (m, 2H), 3.40-3.27 (m, 4H), 3.10 (s, 4H), 2.72 (s, 1H), 2.34 (s, 4H), 2.08 (s, 2H), 1.90-1.75 (m, 4H), 1.26 (q, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
107	Example 2	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.01$ (d, $J = 2.8$ Hz, 1H), 7.91-7.79 (m, 2H), 7.31 (br d, $J = 8.8$ Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.96 (s, 3H), 3.35 (s, 5H), 3.09 (br s, 4H), 2.73 (br s, 1H), 2.39 (br s, 4H), 2.10 (br s, 1H), 1.84 (br s, 3H), 1.32-1.22 (m, 4H). LCMS m/z $[M+H]^+$ 443.
108	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.15$ (s, 1H), 8.54 (s, 1H), 8.31 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.85 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.99 (dd, $J = 5.2$ Hz, 7.6 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.80 (m, 4H), 3.79-3.74 (m, 2H), 3.16 (t, $J = 4.8$ Hz, 4H), 2.62 (s, 3H), 2.60-2.38 (m, 5H), 2.12-2.04 (m, 1H), 1.96-1.78 (m, 3H), 1.73-1.65 (m, 1H), 1.57-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
109	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.83$ (s, 1H), 8.30 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.13 (s, 1H), 7.92 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.99 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 4.04 (s, 3H), 3.92-3.81 (m, 2H), 3.80-3.74 (m, 2H), 3.35-3.15 (m, 4H), 2.74-2.35 (m, 5H), 2.18-2.05 (m, 1H), 2.00-1.73 (m, 4H), 1.64-1.45 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 453.
110	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.22$ (d, $J = 4.8$ Hz, 1H), 7.52 (d, $J = 7.2$ Hz, 1H), 6.82-6.76 (m, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.92-3.72 (m, 4H), 3.65-3.54 (m, 2H), 3.53-3.29 (m, 6H), 2.61-2.42 (m, 5H), 2.11 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.99-1.83 (m, 7H), 1.76-1.68 (m, 1H), 1.61-1.48 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 442.
111	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.29$ (dd, $J = 2.0$ Hz, 5.2 Hz, 1H), 7.70 (dd, $J = 2.0$ Hz, 7.2 Hz, 1H), 6.86 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.51-4.33 (m, 4H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.76 (m, 4H), 3.49-3.30 (m, 4H), 2.70-2.44 (m, 5H), 2.17-2.10 (m, 1H), 1.99-1.78 (m, 3H), 1.77-1.69 (m, 1H), 1.57-1.51 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 464.
112	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.31$ -8.26 (m, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 6.88-6.82 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.98-3.73 (m, 6H), 3.49-3.32 (m, 4H), 2.63-2.30 (m, 7H), 2.12 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 2.02-1.78 (m, 3H), 1.76-1.68 (m, 1H), 1.67-1.61 (m, 2H), 1.60-1.50 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 478.
113	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.54$ (s, 1H), 8.29 (d, $J = 3.2$ Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 1H), 6.94-6.89 (m, 1H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.88-3.73 (m, 4H), 3.12-3.06 (m, 4H), 2.52-2.32 (m, 8H), 2.07 (dd, $J = 7.2$, 12.4 Hz, 1H),

		1.93-1.78 (m, 3H), 1.69-1.62 (m, 1H), 1.51-1.43 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 442.
114	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 12.71$ (s, 1H), 8.27 (dd, $J = 1.6$ Hz, 4.4 Hz, 1H), 7.50 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.40 (d, $J = 6.8$ Hz, 1H), 6.94 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 6.73 (s, 1H), 6.63 (d, $J = 6.0$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.95-3.81 (m, 2H), 3.80-3.73 (m, 2H), 3.54-3.11 (m, 4H), 2.90-2.34 (m, 5H), 2.19-2.09 (m, 1H), 2.04-1.83 (m, 4H), 1.79-1.72 (m, 1H), 1.22 (t, $J = 7.6$ Hz, 3H). LCMS m/z $[M+H]^+$ 438.
115	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.31$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.04-7.89 (m, 2H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.92-3.78 (m, 2H), 3.78-3.69 (m, 2H), 3.16 (br s, 4H), 2.75 (s, 3H), 2.59-2.44 (m, 5H), 2.07-2.05 (m, 1H), 1.97-1.60 (m, 5H), 1.21 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
116	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.31$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 2H), 7.95 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.05-6.89 (m, 2H), 4.17 (s, 3H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.90-3.79 (m, 2H), 3.78-3.70 (m, 2H), 3.13 (br s, 4H), 2.57-2.47 (m, 1H), 2.42 (br s, 4H), 2.10-2.05 (m, 1H), 1.94-1.76 (m, 4H), 1.56-1.42 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 453.
117	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.31$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.69 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.84 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.03-3.92 (m, 1H), 3.91-3.74 (m, 4H), 3.41-3.26 (m, 4H), 2.90-2.66 (m, 4H), 2.64-2.48 (m, 5H), 2.12 (dd, $J = 7.2$ Hz, 12.3 Hz, 1H), 1.99-1.78 (m, 3H), 1.77-1.67 (m, 1H), 1.58-1.51 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 463.
118	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.15$ (d, $J = 0.8$ Hz, 1H), 8.30 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.94 (dd, $J = 2.0$ Hz, 7.2 Hz, 1H), 7.82 (s, 1H), 6.97 (dd, $J = 6.0$ Hz, 10.8 Hz, 1H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.90-3.71 (m, 4H), 3.30-3.09 (m, 4H), 2.62-2.33 (m, 8H), 2.18-2.02 (m, 1H), 1.98-1.77 (m, 3H), 1.73-1.66 (m, 1H), 1.56-1.46 (m, 1H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
119	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 7.90$ (dd, $J = 1.6$, 4.8 Hz, 1H), 7.06 (dd, $J = 1.6$, 8.0 Hz, 1H), 6.78 (dd, $J = 4.8$, 8.0 Hz, 1H), 4.55-4.45 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 4.02-3.93 (m, 2H), 3.92-3.76 (m, 4H), 3.63-3.55 (m, 2H), 3.50-3.40 (m, 4H), 2.65-2.55 (m, 5H), 2.16 (dd, $J = 7.6$, 13.2 Hz, 1H), 2.04-1.92 (m, 4H), 1.88-1.75 (m, 4H), 1.26-1.21 (m, 4H). LCMS m/z $[M+H]^+$ 445.
120	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.15$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 8.33 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 8.05-7.95 (m, 2H), 7.52 (dd, $J = 4.8$ Hz, 8.8 Hz, 1H), 7.07 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.92-3.77 (m, 2H), 3.75 (s, 2H), 3.32 (t, $J = 4.8$ Hz, 4H), 2.86-2.78 (m, 1H), 2.76-2.62 (m, 4H), 2.20-2.10 (m, 1H), 2.01-1.85 (m, 3H), 1.85-1.74 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 423.
121	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.38$ (s, 1H), 8.70-8.62 (m, 1H), 8.51 (d, $J = 2.8$ Hz, 1H), 8.19 (d, $J = 3.2$ Hz, 1H), 7.73 (dd, $J = 3.2$, 8.8 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.79 (m, 2H), 3.76 (s, 2H), 3.10 (br s, 4H), 2.66-2.34 (m, 5H), 2.08 (br dd, $J = 6.8$, 12.4 Hz, 1H), 1.96-1.78 (m, 3H), 1.74-1.62 (m, 1H), 1.53-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
122	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.25$ (d, $J = 1.2$ Hz, 1H), 8.68-8.65 (m, 1H), 8.51 (d, $J = 2.4$ Hz, 1H), 8.25 (d, $J = 2.8$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.90-3.80 (m, 2H), 3.77 (s, 2H), 3.16 (br s, 4H), 2.64-2.42 (m, 5H), 2.13-2.05 (m, 1H), 1.97-1.85 (m, 2H), 1.83-1.61 (m, 3H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 457.
123	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.13$ (d, $J = 1.2$ Hz, 1H), 8.67-8.63 (m, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 4.13-4.06 (m, 2H), 3.91-3.80 (m, 2H), 3.77 (s, 2H), 3.22 (br s, 4H), 2.65-2.41

		(m, 5H), 2.13-2.02 (m, 1H), 1.98-1.85 (m, 3H), 1.83-1.68 (m, 2H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 457.
124	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.22$ (s, 1H), 8.70-8.53 (m, 1H), 8.43 (d, $J = 4$ Hz, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 6.85 (d, $J = 7.6$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.79 (m, 2H), 3.76 (s, 2H), 3.25-3.04 (m, 4H), 2.63-2.35 (m, 8H), 2.13-2.02 (m, 1H), 1.93-1.74 (m, 3H), 1.73-1.63 (m, 1H), 1.53-1.43 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
125	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.86$ (d, $J = 5.2$ Hz, 1H), 8.35 (dd, $J = 2.0, 4.8$ Hz, 1H), 8.24-8.17 (m, 1H), 8.13 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.08-7.01 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.71 (m, 4H), 3.42-2.98 (m, 4H), 2.77-2.29 (m, 5H), 2.19-2.04 (m, 1H), 2.00-1.82 (m, 3H), 1.72-1.57 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 491.
126	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.29$ (d, $J = 1.2$ Hz, 1H), 8.76 (d, $J = 5.2$ Hz, 1H), 8.18 (d, $J = 2.8$ Hz, 1H), 8.13-8.07 (m, 1H), 7.89-7.81 (m, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.91-3.76 (m, 4H), 3.34-3.06 (m, 4H), 2.73-2.42 (m, 5H), 2.16-2.08 (m, 1H), 2.01-1.91 (m, 2H), 1.88-1.84 (m, 1H), 1.83-1.67 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
127	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.16$ (s, 1H), 8.17 (d, $J = 2.8$ Hz, 1H), 7.99 (s, 1H), 7.81 (dd, $J = 3.2$ Hz, 8.8 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.89-3.75 (m, 4H), 3.18-3.05 (m, 4H), 2.61-2.42 (m, 8H), 2.14-2.05 (m, 1H), 1.97-1.79 (m, 3H), 1.72-1.65 (m, 1H), 1.55-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
128	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.53$ (d, $J = 8.0$ Hz, 1H), 8.24 (d, $J = 4.8$ Hz, 1H), 6.96 (d, $J = 5.2$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.05-3.73 (m, 4H), 3.90-3.00 (m, 4H), 2.60-2.40 (m, 1H), 2.27 (s, 3H), 2.25-1.90 (m, 8H), 1.88-1.17 (m, 4H), 1.55-1.45 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 451.
129	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.50$ (s, 1H), 8.32 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.00-3.80 (m, 4H), 3.85-3.73 (m, 4H), 3.70-2.90 (m, 5H), 2.53 (s, 3H), 2.40-2.33 (m, 1H), 2.15-1.85 (m, 4H), 1.80-1.65 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.
130	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.88$ (d, $J = 4.8$ Hz, 1H), 8.19 (d, $J = 3.2$ Hz, 1H), 7.81 (d, $J = 6.8$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.00-3.80 (m, 4H), 3.28 (br s, 4H), 2.56 (br s, 5H), 2.20-2.10 (m, 1H), 2.05-1.80 (m, 4H), 1.60-1.50 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
131	Example 3	1H NMR (CDCl₃ 400MHz) $\delta_H = 8.48$ (dd, $J = 2.4$ Hz, 16.4 Hz, 2H), 8.35 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.56 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.99 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.88-3.82 (m, 1H), 3.82-3.77 (m, 1H), 3.77-3.70 (m, 2H), 3.27-2.88 (m, 4H), 2.56-2.39 (m, 4H), 2.38-2.19 (m, 4H), 2.12-2.01 (m, 1H), 1.94-1.74 (m, 3H), 1.70-1.62 (m, 1H), 1.54-1.41 (m, 1H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
132	Example 3	1H NMR (CDCl₃ 400MHz) $\delta_H = 8.76$ (s, 1H), 8.31 (d, $J = 1.2$ Hz, 1H), 8.28 (dd, $J = 2.0$ Hz, 5.2 Hz, 1H), 7.80 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.98 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 4.03 (s, 3H), 3.90-3.84 (m, 1H), 3.84-3.79 (m, 1H), 3.79-3.74 (m, 2H), 3.26-3.03 (m, 4H), 2.67-2.36 (m, 5H), 2.14-2.05 (m, 1H), 1.97-1.78 (m, 3H), 1.75-1.63 (m, 1H), 1.55-1.47 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 453.
133	Example 3	1H NMR (CDCl₃ 400MHz) $\delta_H = 8.38$ (s, 1H), 8.28-8.21 (m, 1H), 7.90-7.73 (m, 2H), 7.25-7.20 (m, 1H), 7.00-6.90 (m, 1H), 4.15-4.00 (m, 2H), 3.94-3.89 (m, 3H), 3.88-3.79 (m, 2H), 3.76 (s, 2H), 3.14 (s, 4H), 2.51 (s, 1H), 2.43 (s, 4H), 2.13-2.04 (m, 1H), 1.97-1.75 (m, 4H), 1.51 (s, 1H), 1.30-1.13 (m, 3H). LCMS m/z $[M+H]^+$ 452.

134	Example 3	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.54 (d, J = 2.4 Hz, 1H), 8.30-8.23 (m, 1H), 7.93 (dd, J = 4.4 Hz, 8.4 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.43 (dt, J = 2.4 Hz, 8.4 Hz, 1H), 6.95 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.79 (m, 2H), 3.78-3.72 (m, 2H), 3.12 (s, 4H), 2.53-2.47 (m, 1H), 2.42 (s, 4H), 2.08 (dd, J = 6.8, 12.4 Hz, 1H), 1.95-1.86 (m, 2H), 1.79 (d, J = 7.2 Hz, 1H), 1.71-1.62 (m, 1H), 1.57-1.42 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 440.
135	Example 3	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.77 (d, J = 1.6 Hz, 1H), 8.28 (dd, J = 1.6, 4.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 2.0, 7.6 Hz, 1H), 7.80 (dd, J = 2.2, 8.0 Hz, 1H), 6.97 (dd, J = 5.2, 10.0 Hz, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.89-3.80 (m, 2H), 3.79-3.74 (m, 2H), 3.22-3.04 (m, 10H), 2.57-2.33 (m, 5H), 2.08 (dd, J = 6.8, 12.4 Hz, 1H), 1.95-1.78 (m, 3H), 1.72-1.66 (m, 1H), 1.52 (s, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 493.
136	Example 3	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.31 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.14- 8.09 (m, 1H), 8.04-7.99 (m, 1H), 7.87 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.99 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.51 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.89-3.85 (m, 1H), 3.84-3.80 (m, 1H), 3.80-3.74 (m, 2H), 3.27 (s, 3H), 3.21-3.10 (m, 4H), 2.58-2.49 (m, 1H), 2.47-2.35 (m, 4H), 2.08 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 1.95-1.79 (m, 3H), 1.75-1.59 (m, 1H), 1.56-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H).. LCMS m/z [M+H] ⁺ 491.
137	Example 3	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.38 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 3.2 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 3.2 Hz, 8.8 Hz, 1H), 7.24 (d, J = 3.2 Hz, 1H), 4.110 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.88-3.80 (m, 2H), 3.79-3.73 (m, 2H), 3.20-2.97 (m, 4H), 2.55-2.49 (m, 1H), 2.48-2.36 (m, 4H), 2.08 (dd, J = 7.2 Hz, 12.4 Hz, 1H), 1.94-1.79 (m, 3H), 1.68 (dd, J = 10.0 Hz, 12.4 Hz, 1H), 1.54-1.46 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 470.
138	Example 4	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.28 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.39-7.32 (m, 1H), 7.25-7.20 (m, 1H), 7.6 (d, J = 7.2 Hz, 1H), 7.03-6.95 (m, 1H), 6.93-6.86 (m, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.92-3.78 (m, 2H), 3.77-3.70 (m, 2H), 3.26-2.96 (m, 4H), 2.72-2.18 (m, 5H), 2.14 (s, 3H), 2.09-1.99 (m, 1H), 1.94-1.61 (m, 4H), 1.52-1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
139	Example 4	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.24 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.47-7.42 (m, 1H), 7.42-7.31 (m, 3H), 7.09-6.97 (m, 1H), 6.91 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91- 3.72 (m, 4H), 3.20-3.05 (m, 4H), 2.60-2.46 (m, 1H), 2.45-2.30 (m, 4H), 2.14-2.03 (m, 1H), 1.97-1.77 (m, 3H), 1.71-1.64 (m, 1H), 1.59-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 439.
140	Example 4	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.23 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.61-7.52 (m, 2H), 7.42 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.16-7.07 (m, 2H), 6.92 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.73 (m, 4H), 3.12 (br s, 4H), 2.59-2.30 (m, 5H), 2.17-2.02 (m, 1H), 1.99-1.76 (m, 3H), 1.75-1.62 (m, 1H), 1.55-1.42 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 439.
141	Example 4	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.25 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.52-7.43 (m, 2H), 7.36-7.28 (m, 1H), 7.22-7.11 (m, 2H), 6.88 (dd, J = 4.2 Hz, 7.8 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.78 (m, 2H), 3.77-3.71 (m, 2H), 3.20-3.09 (m, 4H), 2.54-2.43 (m, 1H), 2.43-2.28 (m, 4H), 2.11-2.02 (m, 1H), 1.93-1.79 (m, 3H), 1.72-1.64 (m, 1H), 1.58-1.46 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 439.
142	Example 4	¹ H NMR (CDCl ₃ 400MHz) δ _H = 8.29 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.26 (d, J = 5.2 Hz, 1H), 7.49 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.45-7.40 (m, 1H), 7.18 (s, 1H), 6.96 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.92-3.80 (m, 2H), 3.79- 3.73 (m, 2H), 3.36-3.06 (m, 4H), 2.72-2.29 (m, 5H), 2.15-2.07 (m,

		1H), 1.98-1.78 (m, 4H), 1.64-1.50 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 440$.
143	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.41$ (d, $J = 2.4$ Hz, 1H), 8.28 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.12-8.02 (m, 1H), 7.44 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.04-6.93 (m, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.79 (m, 2H), 3.79-3.73 (m, 2H), 3.17-3.02 (m, 4H), 2.59-2.47 (m, 1H), 2.46-2.27 (m, 4H), 2.12-2.04 (m, 1H), 1.95-1.77 (m, 3H), 1.73-1.66 (m, 1H), 1.57-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 440$.
144	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.22$ (d, $J = 3.2$ Hz, 1H), 7.45 (d, $J = 6.0$ Hz, 1H), 7.37-7.29 (m, 2H), 7.03-6.96 (m, 2H), 6.86 (s, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.90-3.76 (m, 5H), 3.75-3.70 (m, 2H), 3.12 (br s, 4H), 2.81-2.13 (m, 5H), 2.08-2.03 (m, 1H), 1.90-1.60 (m, 4H), 1.54-1.41 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 451$.
145	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.22$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.45 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 5.2$ Hz, 2H), 6.92-6.84 (m, 2H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.88-3.79 (m, 5H), 3.76 (d, $J = 2.0$ Hz, 2H), 3.14 (br s, 4H), 2.61-2.20 (m, 5H), 2.12-2.05 (m, 1H), 1.97-1.75 (m, 3H), 1.73-1.60 (m, 1H), 1.55-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 451$.
146	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.19$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.42 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.97-6.93 (m, 2H), 6.89 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.93-3.78 (m, 5H), 3.76 (d, $J = 1.6$ Hz, 2H), 3.12 (br s, 4H), 2.83-2.19 (m, 5H), 2.13-2.04 (m, 1H), 1.95-1.76 (m, 3H), 1.68 (d, $J = 10.0$ Hz, 1H), 1.55-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 451$.
147	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.26$ (dd, $J = 1.6$ Hz, 5.2 Hz, 1H), 7.35 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.29-7.26 (m, 2H), 7.25 (d, $J = 4.0$ Hz, 2H), 6.89 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.90-3.80 (m, 2H), 3.78-3.72 (m, 2H), 3.16 (br s, 4H), 2.56-2.32 (m, 5H), 2.20 (s, 3H), 2.12-2.03 (m, 1H), 1.96-1.72 (m, 4H), 1.57 (s, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 435$.
148	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.19$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 3H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.95-6.87 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.73 (m, 4H), 3.25 (s, 4H), 2.80-2.30 (m, 8H), 2.12 (s, 1H), 2.00-1.73 (m, 4H), 1.55-1.51 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 435$.
149	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.09$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.32 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.26-7.12 (m, 3H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.76 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 3.97 (q, $J = 6.8$ Hz, 2H), 3.76-3.67 (m, 2H), 3.67-3.61 (m, 2H), 3.01 (s, 4H), 2.45-2.34 (m, 1H), 2.27 (br s, 7H), 1.96 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.82-1.65 (m, 3H), 1.59-1.52 (m, 1H), 1.48-1.31 (m, 1H), 1.11 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 435$.
150	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.32$ (d, $J = 2.0$ Hz, 1H), 8.24 (dd, $J = 2.0$, 5.2 Hz, 1H), 7.88 (dd, $J = 2.0$, 8.8 Hz, 1H), 7.44 (dd, $J = 1.6$, 7.6 Hz, 1H), 6.96 (dd, $J = 4.8$, 7.4 Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.00 (s, 3H), 3.92-3.88 (m, 1H), 3.84-3.82 (m, 1H), 3.76 (s, 2H), 3.20 (br s, 4H), 2.48 (br s, 5H), 2.12 (br dd, $J = 7.2$, 12.4 Hz, 1H), 2.00-1.68 (m, 5H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 452$.
151	Example 4	1H NMR (CDCl₃, 400MHz) $\delta_H = 8.30$ -8.21 (m, 1H), 8.01 (s, 1H), 7.81 (br d, $J = 7.6$ Hz, 1H), 7.47 (br d, $J = 8.0$ Hz, 2H), 6.93 (dd, $J = 5.2$, 7.6 Hz, 1H), 4.43 (s, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.88-3.71 (m, 4H), 3.24 (s, 3H), 3.11 (br s, 4H), 2.55-2.42 (m, 1H), 2.36 (br s, 4H), 2.05 (br dd, $J = 7.2$, 12.4 Hz, 1H), 1.93-1.74 (m, 3H), 1.68-1.61 (m, 1H), 1.52-1.43 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 490$.

152	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.16 (d, <i>J</i> = 4.0 Hz, 1H), 7.89-7.82 (m, 2H), 7.54 (d, <i>J</i> = 7.2 Hz, 1H), 6.90 (dd, <i>J</i> = 5.2 Hz, 7.2 Hz, 1H), 4.59-4.51 (m, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.91-3.75 (m, 4H), 3.27-3.06 (m, 4H), 2.66-2.40 (m, 5H), 2.16-2.07 (m, 1H), 1.99-1.78 (m, 3H), 1.77-1.68 (m, 1H), 1.67-1.62 (m, 1H), 1.55 (d, <i>J</i> = 6.8 Hz, 6H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 453.
153	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.21 (dd, <i>J</i> = 2.0 Hz, 4.8 Hz, 1H), 7.87 (dd, <i>J</i> = 1.6 Hz, 7.2 Hz, 1H), 7.37 (d, <i>J</i> = 2.0 Hz, 1H), 6.90 (dd, <i>J</i> = 4.8 Hz, 7.2 Hz, 1H), 6.75 (s, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.95 (s, 3H), 3.91-3.74 (m, 4H), 3.22-3.08 (m, 4H), 2.68-2.37 (m, 5H), 2.16-2.07 (m, 1H), 1.99-1.77 (m, 3H), 1.76-1.66 (m, 1H), 1.59-1.51 (m, 1H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 425.
154	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.16 (dd, <i>J</i> = 2.0 Hz, 5.2 Hz, 1H), 7.85 (s, 2H), 7.52 (dd, <i>J</i> = 2.0 Hz, 7.2 Hz, 1H), 6.89 (dd, <i>J</i> = 5.2 Hz, 7.6 Hz, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.91-3.76 (m, 4H), 3.67-3.61 (m, 1H), 3.24-3.09 (m, 4H), 2.66-2.40 (m, 5H), 2.15-2.09 (m, 1H), 1.97-1.81 (m, 3H), 1.76-1.69 (m, 1H), 1.57-1.53 (m, 1H), 1.24 (t, <i>J</i> = 7.2 Hz, 3H), 1.19-1.13 (m, 2H), 1.12-1.04 (m, 2H). LCMS <i>m/z</i> [M+H] ⁺ 451.
155	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.16 (dd, <i>J</i> = 2.0 Hz, 5.2 Hz, 1H), 7.91-7.84 (s, 2H), 7.54 (dd, <i>J</i> = 1.6 Hz, 7.2 Hz, 1H), 6.90 (dd, <i>J</i> = 4.8 Hz, 7.6 Hz, 1H), 4.85-4.75 (m, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.92-3.75 (m, 4H), 3.28-3.08 (m, 4H), 2.68-2.39 (m, 9H), 2.15-2.08 (m, 1H), 1.98-1.89 (m, 3H), 1.88-1.78 (m, 2H), 1.77-1.70 (m, 1H), 1.63-1.55 (m, 1H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 465.
156	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.19 (dd, <i>J</i> = 2.0 Hz, 4.8 Hz, 1H), 7.58 (s, 1H), 7.34 (dd, <i>J</i> = 2.0 Hz, 7.2 Hz, 1H), 6.87 (dd, <i>J</i> = 5.2 Hz, 8.2 Hz, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.90-3.80 (m, 5H), 3.79-3.73 (m, 2H), 3.29-3.00 (m, 4H), 2.61-2.30 (m, 5H), 2.25 (s, 3H), 2.13-2.05 (m, 1H), 1.96-1.68 (m, 4H), 1.57-1.46 (m, 1H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 439.
157	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.08 (dd, <i>J</i> = 1.6 Hz, 4.8 Hz, 1H), 7.53 (dd, <i>J</i> = 2.0 Hz, 7.6 Hz, 1H), 6.93 (dd, <i>J</i> = 4.8 Hz, 7.6 Hz, 1H), 6.18-6.14 (m, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.96-3.76 (m, 4H), 3.36-3.31 (m, 4H), 3.02-2.76 (m, 5H), 2.75-2.67 (m, 2H), 2.54-2.47 (m, 2H), 2.31-2.24 (m, 1H), 2.11-1.76 (m, 6H), 1.68-1.58 (m, 1H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 411.
158	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.14 (dd, <i>J</i> = 1.6 Hz, 4.4 Hz, 1H), 7.46 (dd, <i>J</i> = 2.0 Hz, 7.6 Hz, 1H), 6.91 (dd, <i>J</i> = 4.8 Hz, 7.6 Hz, 1H), 4.10 (q, <i>J</i> = 7.2 Hz, 2H), 3.93-3.76 (m, 4H), 3.18-3.06 (m, 4H), 2.86-2.75 (m, 1H), 2.73-2.51 (m, 5H), 2.15 (dd, <i>J</i> = 7.2 Hz, 12.8 Hz, 1H), 2.01-1.91 (m, 2H), 1.90-1.82 (m, 3H), 1.81-1.72 (m, 4H), 1.61-1.53 (m, 1H), 1.45-1.33 (m, 4H), 1.33-1.27 (m, 1H), 1.24 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 427.
159	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.82 (s, 1H), 8.74 (s, 1H), 8.20 (dd, <i>J</i> = 2.0 Hz, 7.2 Hz, 1H), 7.48 (dd, <i>J</i> = 1.6 Hz, 7.2 Hz, 1H), 6.88 (dd, <i>J</i> = 4.8 Hz, 7.2 Hz, 1H), 4.03 (q, <i>J</i> = 7.2 Hz, 2H), 3.83-3.67 (m, 4H), 3.10-2.98 (m, 4H), 2.55-2.30 (m, 5H), 2.06-1.95 (m, 1H), 1.91-1.71 (m, 3H), 1.67-1.58 (m, 1H), 1.49-1.40 (m, 1H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 428.
160	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.19 (dd, <i>J</i> = 2.0 Hz, 5.2 Hz, 1H), 7.45 (s, 1H), 7.36 (dd, <i>J</i> = 1.6 Hz, 7.2 Hz, 1H), 6.86 (dd, <i>J</i> = 5.2 Hz, 7.2 Hz, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.93-3.80 (m, 5H), 3.80-3.73 (m, 2H), 3.33-2.98 (m, 4H), 2.81-2.29 (m, 5H), 2.26 (s, 3H), 2.15-2.05 (m, 1H), 1.99-1.68 (m, 4H), 1.55-1.49 (m, 1H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 439.
161	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ_{H} = 8.18 (dd, <i>J</i> = 1.6 Hz, 4.8 Hz, 1H), 7.98 (s, 2H), 7.57 (dd, <i>J</i> = 2.0 Hz, 7.6 Hz, 1H), 6.92 (dd, <i>J</i> = 5.2 Hz, 7.2 Hz, 1H), 4.09 (q, <i>J</i> = 7.2 Hz, 2H), 3.98-3.81 (m, 2H), 3.80-3.73 (m, 2H), 3.46-3.04 (m, 4H), 2.90-2.29 (m, 5H), 2.22-2.07 (m, 1H), 1.99-1.74 (m, 4H), 1.48-1.86 (m, 1H), 1.23 (t, <i>J</i> = 6.8 Hz, 3H). LCMS <i>m/z</i> [M+H] ⁺ 411.

162	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.16 (dd, J = 2.00 Hz, 4.8 Hz, 1H), 7.84 (s, 1H), 7.78 (s, 1H), 7.52 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.89 (dd, J = 4.4 Hz, 7.2 Hz, 1H), 4.16 (d, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.91-3.86 (m, 1H), 3.84-3.76 (m, 3H), 3.15 (br, 4H), 2.91-2.83 (m, 1H), 2.65-2.42 (m, 5H), 2.15-2.07 (m, 3H), 2.02-1.80 (m, 7H), 1.76-1.67 (m, 1H), 1.58-1.47 (m, 1H), 1.23 (q, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
163	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.17 (dd, J = 2.00 Hz, 5.2 Hz, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 7.54 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.90 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.01 (q, J = 7.6 Hz, 2H), 3.94-3.76 (m, 6H), 3.17 (br, 4H), 2.52 (br, 5H), 2.10 (dd, J = 6.4 Hz, 12.4 Hz, 1H), 1.95-1.81 (m, 3H), 1.74-1.68 (m, 1H), 1.65-1.45 (m, 1H), 1.24 (q, J = 7.2 Hz, 3H), 1.0 (s, 9H). LCMS m/z [M+H] ⁺ 481.
164	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.71 (d, J = 2.0 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.29 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.97 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.01-6.95 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.88-3.74 (m, 4H), 3.27-3.02 (m, 4H), 2.70-2.31 (m, 5H), 2.15-2.04 (m, 1H), 1.96-1.79 (m, 3H), 1.74-1.63 (m, 1H), 1.53-1.49 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 456.
165	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.16 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.49 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.94 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.98-3.69 (m, 4H), 3.20 (d, J = 11.6 Hz, 2H), 3.14-3.06 (m, 4H), 3.01-2.88 (m, 1H), 2.79-2.70 (m, 2H), 2.70-2.51 (m, 5H), 2.14 (dd, J = 7.2 Hz, 12.4 Hz, 1H), 1.98-1.82 (m, 5H), 1.79-1.71 (m, 3H), 1.62-1.59 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 428.
166	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.17 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.86 (d, J = 18.4 Hz, 2H), 7.52 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.89 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 5.56-5.44 (m, 1H), 5.15-5.04 (m, 4H), 4.10 (q, J = 6.8 Hz, 2H), 3.92-3.74 (m, 4H), 3.17 (br s, 4H), 2.53 (br s, 5H), 2.12 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.99-1.79 (m, 3H), 1.77-1.67 (m, 1H), 1.57 (br, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 467.
167	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.17 (d, J = 3.2 Hz, 1H), 7.55 (d, J = 6.0 Hz, 1H), 6.94 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.82 (m, 2H), 3.79 (s, 2H), 3.60-3.38 (m, 2H), 3.27-3.06 (m, 6H), 2.84-2.75 (m, 1H), 2.63 (br s, 5H), 2.70-2.55 (m, 1H), 2.30-2.25 (m, 1H), 2.22-1.90 (m, 3H), 1.88-1.71 (m, 2H), 1.58-1.56 (m, 1H), 1.26-1.22 (m, 3H). LCMS m/z [M+H] ⁺ 414.
168	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.14 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.72 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.95 (dd, J = 4.8 Hz, 8.0 Hz, 1H), 4.50-4.41 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.75 (m, 4H), 3.43-3.27 (m, 1H), 3.17-3.08 (m, 4H), 2.73-2.53 (m, 5H), 2.51-2.40 (m, 1H), 2.27-2.02 (m, 2H), 1.98-1.77 (m, 8H), 1.76-1.70 (m, 1H), 1.57-1.49 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 429.
169	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.14 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.43 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 6.90 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.76 (m, 4H), 3.11 (t, J = 4.8 Hz, 4H), 2.88-2.75 (m, 1H), 2.73 (s, 1H), 2.63 (br s, 5H), 2.29 (d, J = 10.0 Hz, 2H), 2.14 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.99-1.74 (m, 6H), 1.70-1.62 (m, 4H), 1.57 (s, 1H), 1.33-1.20 (m, 6H). LCMS m/z [M+H] ⁺ 499.
170	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.16 (d, J = 3.2 Hz, 1H), 7.47 (d, J = 6.0 Hz, 1H), 6.98-6.92 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.98-3.77 (m, 4H), 3.22 (br s, 4H), 3.06-2.71 (m, 7H), 2.33 (d, J = 11.2 Hz, 2H), 2.18 (d, J = 7.2 Hz, 2H), 1.87-1.83 (m, 6H), 1.72-1.57 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 471.
171	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.12 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.36 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.83 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.12-3.98 (m, 4H),

		3.87-3.75 (m, 2H), 3.75-3.68 (m, 2H), 3.08 (br t, $J = 4.8$ Hz, 4H), 2.92-2.84 (m, 2H), 2.66-2.49 (m, 7H), 2.07 (dd, $J = 7.2$ Hz, 12.4 Hz, 1H), 1.92-1.74 (m, 3H), 1.73-1.65 (m, 1H), 1.57 - 1.48 (m, 1H), 1.17 (dt, $J = 2.0$ Hz, 7.2 Hz, 6H). LCMS m/z $[M+H]^+$ 445.
172	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.23$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.52 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.99 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.76 (m, 4H), 3.75-3.65 (m, 1H), 3.18-3.08 (m, 4H), 2.72 (dd, $J = 7.6$ Hz, 18.4 Hz, 1H), 2.68-2.55 (m, 5H), 2.55-2.46 (m, 1H), 2.46-2.27 (m, 2H), 2.26-2.10 (m, 2H), 2.01-1.72 (m, 5H), 1.59-1.52 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 427.
173	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.24$ (dd, $J = 1.6$, 4.8 Hz, 1H), 7.51 (dd, $J = 1.6$, 7.6 Hz, 1H), 7.00 (dd, $J = 4.8$, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.94-3.75 (m, 4H), 3.20-3.12 (m, 4H), 3.08 (t, $J = 4.8$ Hz, 4H), 2.73-2.51 (m, 5H), 2.42-2.26 (m, 2H), 2.25-2.10 (m, 3H), 1.97-1.82 (m, 3H), 1.79-1.75 (m, 1H), 1.64-1.52 (m, 1H), 1.43-1.29 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 477.
174	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.29$ -8.24 (m, 1H), 7.48 (br d, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 7.2$ Hz, 1H), 6.91 (dd, $J = 4.8$, 7.2 Hz, 1H), 6.73 (s, 1H), 6.54 (br d, $J = 7.2$ Hz, 1H), 4.10 (d, $J = 7.2$ Hz, 2H), 3.92-3.81 (m, 2H), 3.81-3.75 (m, 2H), 3.59 (s, 3H), 3.24 (br s, 4H), 2.48 (br s, 5H), 2.11 (br dd, $J = 6.8$, 12.0 Hz, 1H), 1.99-1.79 (m, 3H), 1.71 (br s, 1H), 1.57-1.48 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 452.
175	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.25$ (dd, $J = 1.6$, 4.8 Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.69 (br d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.47 (dd, $J = 1.6$, 7.2 Hz, 1H), 6.93 (dd, $J = 4.8$, 7.2 Hz, 1H), 4.42 (s, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.73 (m, 4H), 3.23 (s, 3H), 3.10 (br s, 4H), 2.54-2.23 (m, 5H), 2.12-2.01 (m, 1H), 1.96-1.74 (m, 3H), 1.71-1.57 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 490.
176	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.93$ -8.83 (m, 2H), 8.13 (d, $J = 3.20$ Hz, 1H), 7.36 (dd, $J = 2.80$, 8.40 Hz, 1H), 4.09 (dd, $J = 7.20$, 14.40 Hz, 2H), 3.98-3.81 (m, 2H), 3.79-3.74 (m, 2H), 3.29-2.88 (m, 4H), 2.85 - 2.23 (m, 5H), 2.19-2.06 (m, 1H), 2.01-1.78 (m, 3H), 1.76-1.61 (m, 1H), 1.52-1.35 (m, 1H), 1.23 (t, $J = 7.20$ Hz, 3H). LCMS m/z $[M+H]^+$ 446.
177	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.01$ (d, $J = 3.20$ Hz, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.31 (dd, $J = 2.80$ Hz, 8.80 Hz, 1H), 4.10 (dd, $J = 7.20$ Hz, 14.40 Hz, 2H), 3.97-3.96 (m, 3H), 3.94-3.88 (m, 1H), 3.86-3.83 (m, 1H), 3.81-3.76 (m, 2H), 3.22-2.95 (m, 4H), 2.71-2.35 (m, 5H), 2.16-2.09 (m, 1H), 2.02-1.76 (m, 4H), 1.75-1.64 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.
178	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.92$ (s, 2H), 8.16 (d, $J = 2.8$ Hz, 1H), 7.29-7.26 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.89-3.75 (m, 4H), 3.13-2.98 (m, 4H), 2.80 (s, 3H), 2.63-2.37 (m, 5H), 2.14-2.02 (m, 1H), 1.95-1.85 (m, 2H), 1.82-1.75 (m, 1H), 1.71-1.54 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
179	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.21$ (s, 1H), 9.02 (s, 2H), 8.19 (d, $J = 2.8$ Hz, 1H), 7.30 (dd, $J = 2.8$, 8.0 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.72 (m, 4H), 3.21-2.92 (m, 4H), 2.70-2.30 (m, 5H), 2.15-2.03 (m, 1H), 1.97-1.84 (m, 2H), 1.83-1.76 (m, 1H), 1.72-1.50 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
180	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 7.77$ (s, 1H), 7.64 (s, 1H), 7.55 (t, $J = 8.4$ Hz, 1H), 6.46 (dd, $J = 3.6$, 8.0 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 3H), 3.91-3.71 (m, 4H), 3.17 (s, 4H), 2.61-2.40 (m, 5H), 2.15-2.06 (m, 1H), 1.98-1.79 (m, 3H), 1.76-1.64 (m, 1H), 1.56-1.44 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.

181	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.97-7.82 (m, 2H), 7.55-7.23 (m, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.49 (dd, J = 3.2, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.68 (m, 4H), 3.19 (s, 4H), 2.48 (s, 5H), 2.10 (dd, J = 6.8, 12.0 Hz, 1H), 1.99-1.76 (m, 3H), 1.69 (t, J = 10.4 Hz, 1H), 1.56-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
182	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.92 (d, J = 1.6 Hz, 2H), 8.21 (d, J = 2.8 Hz, 1H), 7.29 (dd, J = 2.8 Hz, 8.0 Hz, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.89-3.80 (m, 2H), 3.79-3.72 (m, 2H), 3.10-2.95 (m, 4H), 2.62-2.35 (m, 5H), 2.15-2.03 (m, 1H), 1.94-1.78 (m, 3H), 1.74-1.66 (m, 1H), 1.55-1.44 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 459.
183	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.80-8.70 (m, 2H), 7.58-7.41 (m, 1H), 6.60-6.50 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.75 (m, 4H), 3.40-3.00 (m, 4H), 2.96-2.35 (m, 5H), 2.34-2.24 (m, 1H), 2.15-2.05 (m, 1H), 1.96-1.79 (m, 3H), 1.71-1.64 (m, 1H), 1.55-1.50 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.20-1.11 (m, 4H). LCMS m/z [M+H] ⁺ 481.
184	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.03-8.98 (m, 1H), 8.20 (d, J = 3.2 Hz, 1H), 8.10 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.75 (m, 4H), 3.17-2.90 (m, 4H), 2.64-2.30 (m, 5H), 2.15-2.04 (m, 1H), 1.98-1.66 (m, 4H), 1.52-1.38 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 465.
185	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.88 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 3.2 Hz, 1H), 7.81 (d, J = 6.8 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.00-3.80 (m, 4H), 3.28 (br s, 4H), 2.56 (br s, 5H), 2.20-2.10 (m, 1H), 2.05-1.80 (m, 4H), 1.60-1.50 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
186	Example 4	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.88 (s, 1H), 8.76 (s, 1H), 8.12 (d, J = 2.8 Hz, 1H), 7.35 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.81 (m, 2H), 3.81-3.74 (m, 2H), 3.22-2.91 (m, 4H), 2.71-2.37 (m, 5H), 2.16-2.06 (m, 1H), 1.98-1.80 (m, 3H), 1.77-1.72 (m, 1H), 1.60-1.47 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 430.
187	Example 5	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.23-8.18 (m, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.44(s, 1H), 6.92-6.86 (m, 1H), 6.71 (s, 1H), 4.59-4.50 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.73 (m, 4H), 3.28-3.11 (m, 4H), 2.66-2.36 (m, 5H), 2.15-2.04 (m, 1H), 1.98-1.77 (m, 3H), 1.750-1.65 (m, 2H), 1.59-1.51 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
188	Example 5	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.31 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.60-7.58 (m, 1H), 7.39 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.88 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 6.23 (d, J = 1.6 Hz, 1H), 4.35-4.27 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.88-3.72 (m, 4H), 3.19-3.12 (m, 4H), 2.53-2.34 (m, 5H), 2.10-2.03 (m, 1H), 1.93-1.76 (m, 3H), 1.71-1.59 (m, 2H), 1.48-1.33 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
189	Example 5	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.85 (br d, J = 4.4 Hz, 2H), 8.29 (br s, 1H), 7.93 (br d, J = 6.8 Hz, 1H), 7.22 (br s, 1H), 6.88 (br s, 1H), 4.10 (br d, J = 7.2 Hz, 2H), 3.91-3.80 (m, 2H), 3.77 (br s, 2H), 3.26 (br, 4H), 2.47 (br, 5H), 2.09 (br s, 1H), 2.00-1.80 (m, 3H), 1.74-1.67 (m, 1H), 1.55-1.46 (m, 1H), 1.24 (br t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 423.
190	Example 5	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.55-9.51 (m, 1H), 9.23 (d, J = 5.6 Hz, 1H), 8.34 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.69 (dd, J = 2.4 Hz, 5.2 Hz, 1H), 7.52 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.01 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.89-3.73 (m, 4H), 3.25-3.00 (m, 4H), 2.66-2.32 (m, 5H), 2.08 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.98-1.76 (m, 3H), 1.73-1.66 (m, 1H), 1.57-1.41 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 423.
191	Example 5	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.60 (dd, J = 2.8, 4.0 Hz, 1H), 8.37 (dd, J = 2.0, 4.8 Hz, 1H), 8.23-8.21 (m, 1H), 7.71 (dd, J = 2.0, 7.2 Hz, 1H), 7.03 (dd, J = 4.8, 7.2 Hz, 1H), 4.12-4.06 (m, 2H), 3.91-3.72 (m, 4H), 3.27 (t, J = 4.8 Hz,

		4H), 2.86-2.61 (m, 5H), 2.11 (dd, $J = 7.2$, 12.8 Hz, 1H), 2.02-1.87 (m, 3H), 1.85-1.73 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
192	Example 6	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.24$ (d, $J = 1.6$ Hz, 1H), 8.65 (dd, $J = 1.2$ Hz, 2.4 Hz, 1H), 8.47 (d, $J = 2.8$ Hz, 1H), 8.33 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.87 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.73 (s, 1H), 7.02 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.03-3.91 (m, 4H), 3.17 (t, $J = 4.8$ Hz, 4H), 2.59-2.49 (m, 1H), 2.48 (br, $J = 0.8$ Hz, 4H), 2.21-2.18 (m, 1H), 2.02-2.00 (m, 1H), 1.92-1.88 (m, 2H), 1.76-1.75 (m, 1H), 1.55-1.54 (m, 1H). LCMS m/z $[M+H]^+$ 435.
193	Example 6	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.23$ (d, $J = 1.2$ Hz, 1H), 8.73-8.60 (m, 1H), 8.47 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.86 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.00 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.27 (t, $J = 8.8$ Hz, 2H), 3.82-3.70 (m, 4H), 3.15 (t, $J = 4.8$ Hz, 4H), 2.80 (t, $J = 9.2$ Hz, 2H), 2.61-2.38 (m, 5H), 2.21-2.05 (m, 1H), 2.02-1.79 (m, 3H), 1.74-1.67 (m, 1H), 1.54-1.44 (m, 1H). LCMS m/z $[M+H]^+$ 420.
194	Example 7	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.17$ (d, $J = 1.0$ Hz, 1H), 8.58 (s, 1H), 8.40 (d, $J = 2.4$ Hz, 1H), 8.26 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.80 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.94 (dd, $J = 4.8$, 7.60 Hz, 1H), 4.61-4.53 (m, 1H), 4.50-4.40 (m, 1H), 4.29-4.22 (m, 1H), 4.21-4.13 (m, 1H), 3.92-3.67 (m, 4H), 3.09 (br t, $J = 4.6$ Hz, 4H), 2.57-2.29 (m, 5H), 2.10-1.70 (m, 5H), 1.62 (dd, $J = 10.0$, 12.6 Hz, 1H), 1.53-1.36 (m, 1H). LCMS m/z $[M+H]^+$ 441.
195	Example 7	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.09$ (s, 1H), 8.60 (s, 1H), 8.44 (d, $J = 2.0$ Hz, 1H), 8.24 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.81 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.08-7.00 (m, 1H), 4.58 (d, $J = 2.4$ Hz, 2H), 4.05-3.83 (m, 2H), 3.73 (s, 2H), 3.39 (br s, 3H), 2.70 (br s, 4H), 2.38 (t, $J = 2.4$ Hz, 1H), 2.17-2.10 (m, 1H), 1.99-1.85 (m, 2H), 1.83-1.76 (m, 1H), 1.30-1.15 (m, 4H). LCMS m/z $[M+H]^+$ 433.
196	Example 8	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.24$ (s, 1H), 8.65 (s, 1H), 8.47 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.86 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.67-4.62 (m, 2H), 3.93-3.76 (m, 4H), 3.15 (s, 4H), 2.62-2.37 (m, 5H), 2.25-2.14 (m, 2H), 2.06 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.96-1.76 (m, 3H), 1.73-1.67 (m, 3H), 1.57-1.48 (m, 3H), 0.95 (t, $J = 7.6$ Hz, 9H). LCMS m/z $[M+H]^+$ 475.
197	Example 8	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.23$ (s, 1H), 8.65-8.64 (m, 1H), 8.46 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.87-7.85 (m, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.70 (t, $J = 1.6$ Hz, 2H), 4.12 (t, $J = 2.0$ Hz, 2H), 3.90-3.79 (m, 4H), 3.37 (s, 3H), 3.15 (t, $J = 4.8$ Hz, 4H), 2.58-2.44 (m, 5H), 2.06 (dd, $J = 5.6$ Hz, 12.8 Hz, 1H), 1.93-1.80 (m, 3H), 1.70-1.65 (m, 1H), 1.55-1.43 (m, 1H). LCMS m/z $[M+H]^+$ 476.
198	Example 9	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.35$ (s, 1H), 8.66 (s, 1H), 8.51 (d, $J = 2.4$ Hz, 1H), 8.19 (d, $J = 3.2$ Hz, 1H), 7.73 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.07-3.95 (m, 1H), 3.91-3.67 (m, 4H), 3.37-2.96 (m, 4H), 2.87-2.27 (m, 5H), 2.17-2.03 (m, 1H), 1.98-1.70 (m, 4H), 1.56-1.38 (m, 1H), 0.75-0.56 (m, 4H). LCMS m/z $[M+H]^+$ 453.
199	Example 9	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.23$ (d, $J = 1.6$ Hz, 1H), 8.69-8.61 (m, 1H), 8.47 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.87 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 3.83 (dd, $J = 8.4$ Hz, 22.0 Hz, 2H), 3.78-3.73 (m, 2H), 3.16 (s, 4H), 2.59-2.52 (m, 1H), 2.46 (s, 4H), 2.08 (dd, $J = 7.2$ Hz, 12.6 Hz, 1H), 1.94-1.79 (m, 3H), 1.64 (s, 1H), 1.51 (s, 1H). LCMS m/z $[M+H]^+$ 428.
200	Example 10	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.23$ (d, $J = 1.2$ Hz, 1H), 8.69-8.61 (m, 1H), 8.47 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.86 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 3.83 (dd, $J = 8.4$ Hz, 22.0 Hz, 2H), 3.78-3.73 (m, 2H), 3.15 (s, 4H), 2.58-2.51 (m, 1H), 2.46 (s, 4H), 2.07 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.93-1.78 (m, 3H), 1.70-1.64 (m, 1H), 1.58-1.42 (m, 1H). LCMS m/z $[M+H]^+$ 428.

201	Example 12	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.23 (s, 1H), 8.76-8.60 (m, 2H), 8.55 (br s, 1H), 8.47 (br s, 1H), 8.33 (dd, J = 2.0, 4.8 Hz, 1H), 7.87 (dd, J = 2.0, 7.6 Hz, 1H), 7.72 (br d, J = 8.0 Hz, 1H), 7.02 (dd, J = 4.8, 7.6 Hz, 1H), 4.28-3.99 (m, 4H), 3.17 (br s, 4H), 2.70-2.36 (m, 5H), 2.23-2.08 (m, 1H), 2.03-1.74 (m, 4H), 1.57-1.47 (m, 1H). LCMS m/z [M+H] ⁺ 474.
202	Example 12	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.26 (br d, J = 17.6 Hz, 2H), 8.99 (s, 2H), 8.65 (s, 1H), 8.47 (br s, 1H), 8.37-8.28 (m, 1H), 7.87 (dd, J = 2.0, 7.6 Hz, 1H), 7.02 (dd, J = 4.8, 7.6 Hz, 1H), 4.31-3.99 (m, 4H), 3.16 (br s, 4H), 2.67-2.38 (m, 5H), 2.23-2.08 (m, 1H), 2.05-1.72 (m, 4H), 1.57-1.47 (m, 1H). LCMS m/z [M+H] ⁺ 457.
203	Example 13	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.24 (s, 1H), 8.68 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.96-7.76 (m, 2H), 7.08-6.96 (m, 1H), 4.12-3.96 (m, 4H), 3.16 (br s, 4H), 2.64-2.36 (m, 5H), 2.24-2.16 (m, 1H), 2.00 (br d, J = 9.2 Hz, 1H), 1.96-1.64 (m, 3H), 1.96-1.64 (m, 1H). LCMS m/z [M+H] ⁺ 419.
204	Example 14	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.26 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.74-7.70 (m, 1H), 7.40 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.96 - 6.89 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.74 (m, 4H), 3.07-2.91 (m, 4H), 2.59-2.35 (m, 5H), 2.34-2.24 (m, 3H), 2.15-2.05 (m, 1H), 1.96-1.76 (m, 3H), 1.72-1.64 (m, 1H), 1.53-1.47 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 425.
205	Example 14	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.30 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.05 (s, 1H), 7.74 (dd, J = 1.6 Hz, 8.0 Hz, 1H), 6.98 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.74 (m, 4H), 3.09-2.91 (m, 4H), 2.62-2.37 (m, 5H), 2.09 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.97-1.78 (m, 3H), 1.75-1.67 (m, 1H), 1.55-1.48 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
206	Example 14	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.30-8.17 (m, 2H), 8.09 (s, 1H), 7.77 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 6.98 (dd, J = 4.8, 7.6 Hz, 1H), 4.07 (q, J = 6.8 Hz, 2H), 3.90 (d, J = 8.4 Hz, 1H), 3.80 (d, J = 8.8 Hz, 1H), 3.78-3.71 (m, 2H), 3.45-3.20 (m, 4H), 3.02-2.72 (m, 5H), 2.20-2.15 (m, 4H), 2.04-1.92 (m, 2H), 1.86-1.71 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
207	Example 15	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.84 (d, J = 6.0 Hz, 1H), 6.91-6.82 (m, 1H), 6.81-6.72 (m, 1H), 4.69-4.56 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.94-3.75 (m, 4H), 3.64-3.28 (m, 4H), 2.82-2.50 (m, 5H), 2.50-2.42 (m, 2H), 2.27-2.11 (m, 3H), 2.02-1.81 (m, 4H), 1.79-1.65 (m, 2H), 1.53-1.42 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 415.
208	Example 15	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.91 (d, J = 3.2 Hz, 1H), 6.87-6.81 (m, 2H), 4.66-4.63 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.88-3.86 (m, 2H), 3.78 (s, 2H), 3.46 (br, 3H), 3.13-3.06 (m, 3H), 2.78-2.71 (m, 7H), 2.19-1.84 (m, 6H), 1.24 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 451.
209	Example 19	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.22 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.18-7.13 (m, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 6.83 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.81-3.72 (m, 2H), 3.69-3.64 (m, 2H), 3.13-3.00 (m, 4H), 2.46-2.12 (m, 5H), 2.07 (s, 3H), 2.01-1.93 (m, 1H), 1.88-1.68 (m, 3H), 1.63-1.57 (m, 1H), 1.45-1.38 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
210	Example 19	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.95 (d, J = 2.0 Hz, 1H), 8.36 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.72 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.98-6.93 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.91-3.74 (m, 4H), 3.51-3.13 (m, 4H), 2.77-2.24 (m, 8H), 2.20-2.06 (m, 1H), 2.03-1.72 (m, 4H), 1.58-1.46 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
211	Example 19	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.48 (s, 1H), 8.32 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.54 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 6.94 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.87-3.72 (m, 4H), 3.17-3.06 (m, 4H), 2.76 (s, 3H), 2.51-2.42

		(m, 1H), 2.37-2.27 (m, 4H), 2.16-2.11 (s, 3H), 2.09-2.01 (m, 1H), 1.94-1.74 (m, 3H), 1.71-1.65 (m, 1H), 1.53-1.41 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 451.
212	Example 19	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.49$ (d, $J = 2.0$ Hz, 1H), 8.34 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.70 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.92 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.88-3.73 (m, 4H), 3.24-3.14 (m, 4H), 2.78 (s, 3H), 2.56-2.31 (m, 5H), 2.11-2.04 (m, 1H), 1.94-1.76 (m, 3H), 1.73-1.64 (m, 1H), 1.55-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
213	Example 20	1H NMR (CDCl₃ 400 MHz) $\delta_H = 7.78$ (d, $J = 4.8$ Hz, 1H), 6.89 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 6.66 (d, $J = 7.6$ Hz, 1H), 4.38 (d, $J = 6.0$ Hz, 1H), 4.10 (q, $J = 6.8$ Hz, 2H), 3.95-3.88 (m, 1H), 3.88-3.83 (m, 1H), 3.83-3.74 (m, 3H), 3.27-2.93 (m, 6H), 2.74-2.54 (m, 4H), 2.53-2.32 (m, 2H), 2.21-2.08 (m, 1H), 2.03-1.89 (m, 2H), 1.88-1.73 (m, 2H), 1.70-1.61 (m, 2H), 1.24 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+$ 450.
214	Example 20	1H NMR (CDCl₃ 400MHz) $\delta_H = 7.85$ (dd, $J = 1.2$ Hz, 4.8 Hz, 1H), 6.86 (dd, $J = 4.8$ Hz, 8.0 Hz, 1H), 6.73 (dd, $J = 1.2$ Hz, 8.0 Hz, 1H), 5.48-5.20 (m, 1H), 4.21-4.06 (m, 4H), 3.92-3.76 (m, 6H), 3.21 (s, 4H), 2.70-2.44 (m, 5H), 2.20-2.09 (m, 1H), 1.98-1.81 (m, 3H), 1.80-1.70 (m, 1H), 1.63-1.57 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 418.
215	Example 21	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.29$ (d, $J = 5.2$ Hz, 1H), 7.36-7.28 (m, 2H), 7.23-7.15 (m, 2H), 6.95-6.85 (m, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.77 (m, 2H), 3.76-3.68 (m, 2H), 3.20-3.06 (m, 4H), 2.55-2.34 (m, 1H), 2.33-2.16 (m, 4H), 2.10 (s, 3H), 2.07-1.99 (m, 1H), 1.94-1.65 (m, 4H), 1.52-1.41 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 469.
216	Example 22	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.19$ (d, $J = 1.6$ Hz, 1H), 8.77 (dd, $J = 1.6$, 2.4 Hz, 1H), 8.61 (d, $J = 2.4$ Hz, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.74 (m, 4H), 3.28-3.17 (m, 4H), 2.73 (s, 1H), 2.61 (s, 4H), 2.19 (dd, $J = 7.6$, 12.8 Hz, 1H), 2.02-1.82 (m, 3H), 1.73 (dd, $J = 9.6$, 12.8 Hz, 1H), 1.62-1.49 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 491.
217	Example 23	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.29$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.81 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.04 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 6.62 (s, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.94-3.74 (m, 4H), 3.15 (br s, 4H), 2.64 (br s, 5H), 2.13 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 2.01-1.82 (m, 3H), 1.80-1.72 (m, 1H), 1.58-1.51 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 411.
218	Example 23	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.18$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.68 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.77 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 5.60 (s, 1H), 4.12-4.07 (m, 2H), 3.91-3.81 (m, 2H), 3.80-3.074 (m, 2H), 3.47-3.33 (m, 4H), 3.11-3.01 (m, 6H), 2.64 (m, 3H), 2.56-2.45 (m, 5H), 2.16-2.05 (m, 1H), 1.98-1.80 (m, 3H), 1.77-1.67 (m, 1H), 1.58-1.52 (m, 1H), 1.25-1.21 (m, 3H). LCMS m/z $[M+H]^+$ 425.
219	Example 23	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.34$ -8.16 (m, 1H), 7.82-7.67 (m, 1H), 7.01 (dd, $J = 5.2$ Hz, 7.6 Hz, 1H), 6.37 (s, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.81 (m, 2H), 3.79 (s, 2H), 3.14 (br s, 4H), 2.62 (br s, 5H), 2.35 (s, 3H), 2.17-2.04 (m, 1H), 2.01-1.60 (m, 5H), 1.24 (t, $J = 7.6$ Hz, 3H). LCMS m/z $[M+H]^+$ 425.
220	Example 23	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.19$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.83 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 6.88 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 6.49 (s, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.97-3.81 (m, 5H), 3.80-3.75 (m, 2H), 3.42-3.04 (m, 4H), 2.76-2.36 (m, 5H), 2.31 (s, 3H), 2.18-2.07 (m, 1H), 1.99-1.69 (m, 4H), 1.59-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
221	Example 23	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.26$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.59 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.46 (s, 1H), 6.96 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.75 (m, 4H), 3.20-3.05 (m, 4H), 2.65-2.40 (m, 5H), 2.16

		(s, 3H), 2.15-2.05 (m, 1H), 2.02-1.74 (m, 3H), 1.74-1.68 (m, 1H), 1.57-1.50 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 425.
222	Example 23	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.32 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.17 (s, 1H), 7.58 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.89 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.94-3.67 (m, 4H), 3.23-3.10 (m, 4H), 2.61-2.31 (m, 5H), 2.14-2.05 (m, 1H), 2.04 (s, 3H), 1.97-1.77 (m, 3H), 1.73-1.62 (m, 1H), 1.54-1.46 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 426.
223	Example 24	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.17 (dd, J = 1.2, 4.8 Hz, 1H), 7.92 (s, 1H), 7.90 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 6.90 (dd, J = 5.6, 7.2 Hz, 1H), 4.86 (t, J = 4.4 Hz, 1H), 4.74 (t, J = 4.4 Hz, 1H), 4.49 (t, J = 4.8 Hz, 1H), 4.42 (t, J = 4.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.81 (m, 2H), 3.81-3.75 (m, 2H), 3.17 (s, 4H), 2.54 (s, 5H), 2.11 (dd, J = 7.2, 12.8 Hz, 1H), 1.96-1.80 (m, 3H), 1.77-1.69 (m, 1H), 1.67-1.61 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 457.
224	Example 24	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.17 (dd, J = 1.6, 4.8 Hz, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.54 (dd, J = 1.6, 7.6 Hz, 1H), 6.91 (dd, J = 4.8, 7.6 Hz, 1H), 4.30 (t, J = 4.4 Hz, 2H), 4.13-4.08 (m, 2H), 4.07-4.03 (m, 2H), 3.90 (d, J = 8.0 Hz, 1H), 3.84 (d, J = 8.4 Hz, 1H), 3.81-3.75 (m, 2H), 3.19 (s, 4H), 2.99 (s, 1H), 2.56 (s, 5H), 2.19-2.07 (m, 1H), 1.97-1.80 (m, 3H), 1.75 (s, 1H), 1.57-1.44 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
225	Example 25	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 11.10 (s, 1H), 9.33 (d, J = 1.2 Hz, 1H), 8.88-8.72 (m, 1H), 8.63 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 2.8 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.94-3.68 (m, 4H), 3.39 (t, J = 12.0 Hz, 2H), 3.25-3.11 (m, 5H), 3.05-2.86 (m, 2H), 2.26 (dd, J = 7.6 Hz, 12.8 Hz, 1H), 2.12-2.04 (m, 1H), 2.03-1.70 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 440.
226	Example 25	¹H NMR (CDCl₃ 400MHz) δ_{H} = 7.90 (s, 1H), 7.86-7.75 (m, 2H), 7.16 (d, J = 2.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 3.91-3.75 (m, 4H), 3.04 (br s, 4H), 2.75-2.45 (m, 5H), 2.11 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.96-1.79 (m, 4H), 1.77-1.72 (m, 1H), 1.63-1.46 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 441.
227	Example 33	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 7.92 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.79 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.00-3.87 (m, 1H), 3.87-3.82 (m, 1H), 3.82-3.75 (m, 2H), 3.67-3.36 (m, 9H), 3.36-3.28 (m, 1H), 2.76-2.49 (m, 7H), 2.21-2.11 (m, 1H), 2.09-2.01 (m, 2H), 1.97-1.60 (m, 7H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 458.
228	Example 33	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 7.66 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.02 (dd, J = 1.6 Hz, 8.0 Hz, 1H), 6.84 (dd, J = 4.8 Hz, 8.0 Hz, 1H), 4.48 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.82 (m, 2H), 3.82-3.76 (m, 2H), 3.12-2.99 (m, 4H), 2.87-2.34 (m, 5H), 2.18-2.09 (m, 1H), 1.97-1.72 (m, 4H), 1.57-1.50 (m, 1H), 1.38 (s, 9H), 1.24 (d, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 416.
229	Example 33	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 8.44 (s, 1H), 7.74 (d, J = 4.4 Hz, 1H), 6.82 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.95-3.82 (m, 2H), 3.79-3.68 (m, 6H), 3.57-3.29 (m, 4H), 3.04-2.77 (m, 5H), 3.32-2.10 (m, 6H), 2.09-1.87 (m, 5H), 1.84-1.78 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 440.
230	Example 34	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 7.84 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.78 (dd, J = 4.8 Hz, 8.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.95-3.83 (m, 2H), 3.82-3.71 (m, 4H), 3.46-2.99 (m, 4H), 2.82 (br d, J = 9.6 Hz, 1H), 2.77-2.34 (m, 5H), 2.21-2.12 (m, 1H), 2.01-1.70 (m, 4H), 1.56-1.48 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.63-0.43 (m, 2H). LCMS m/z [M+H] ⁺ 426.
231	Example 33	¹H NMR (CDCl₃ 400 MHz) δ_{H} = 7.81 (d, J = 4.4 Hz, 1H), 6.83 (dd, J = 4.8, 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 4.27-4.16 (m, 1H), 4.13-4.05 (m, 4H), 3.93-3.86 (m, 1H), 3.86-3.82 (m, 1H), 3.82-3.74 (m, 2H), 3.63-3.55 (m, 2H), 3.33

		(s, 3H), 3.21 (s, 4H), 2.68-2.54 (m, 5H), 2.13 (dd, $J = 6.8, 12.8$ Hz, 1H), 2.00-1.88 (m, 2H), 1.84 (dd, $J = 5.2, 13.6$ Hz, 1H), 1.80-1.70 (m, 1H), 1.65-1.54 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 430.
232	Example 33	1H NMR (CDCl₃ 400 MHz) $\delta_H = 7.94$ (dd, $J = 1.2, 4.4$ Hz, 1H), 7.12 (dd, $J = 1.6, 8.0$ Hz, 1H), 6.81 (dd, $J = 4.8, 7.6$ Hz, 1H), 4.88-4.66 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.78 (m, 4H), 3.50 (s, 3H), 3.24 (s, 2H), 2.97 (s, 2H), 2.67-2.50 (m, 5H), 2.20-2.11 (m, 1H), 2.10-1.69 (m, 9H), 1.63-1.53 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 446.
233	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.01$ (d, $J = 2.8$ Hz, 1H), 7.15 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 5.94 (s, 1H), 4.31 (d, $J = 2.4$ Hz, 2H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.05-3.80 (m, 5H), 3.77 (s, 3H), 3.64-2.99 (m, 4H), 2.79-2.39 (m, 5H), 2.29-1.77 (m, 5H), 1.54-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 445.
234	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.03$ (d, $J = 2.8$ Hz, 1H), 7.25-7.22 (m, 1H), 4.17-4.02 (m, 4H), 4.00-3.91 (m, 1H), 3.89-3.84 (m, 1H), 3.83-3.76 (m, 2H), 3.57-3.48 (m, 2H), 3.11 (dd, $J = 7.6$ Hz, 15.2 Hz, 5H), 2.92-2.60 (m, 4H), 2.28-2.13 (m, 1H), 1.97 (d, $J = 10.4$ Hz, 2H), 1.87 (dd, $J = 7.2$ Hz, 12.4 Hz, 2H), 1.76-1.61 (m, 6H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 447.
248	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.06$ (d, $J = 5.2$ Hz, 1H), 7.61 (s, 1H), 7.46 (s, 1H), 6.77 (br d, $J = 4.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.97 (s, 3H), 3.87-3.75 (m, 4H), 3.07 (br s, 4H), 2.56-2.29 (m, 5H), 2.21 (s, 3H), 2.09 (br dd, $J = 7.2, 11.6$ Hz, 1H), 1.92-1.78 (m, 3H), 1.72-1.66 (m, 1H), 1.58-1.54 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
249	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.84$ (s, 2H), 8.21-8.09 (m, 1H), 8.14 (d, $J = 2.8$ Hz, 1H), 7.24 (dd, $J = 2.8$ Hz, 8.2 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.73 (m, 4H), 3.04 (br s, 4H), 2.58-2.36 (m, 5H), 2.08 (br dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.94-1.80 (m, 3H), 1.64 (br s, 1H), 1.51 (br s, 1H), 1.28-1.13 (m, 7H). LCMS m/z $[M+H]^+$ 481.
250	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.58$ (d, $J = 5.2$ Hz, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.74 (br d, $J = 5.2$ Hz, 1H), 6.81 (br d, $J = 8.0$ Hz, 1H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.89-3.80 (m, 2H), 3.77 (d, $J = 1.6$ Hz, 2H), 3.19 (br s, 4H), 2.78 (s, 3H), 2.56-2.39 (m, 8H), 2.09 (br dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.93-1.79 (m, 3H), 1.72-1.65 (m, 1H), 1.57-1.50 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 451.
251	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 13.54$ -13.15 (m, 1H), 8.28 (d, $J = 4.8$ Hz, 1H), 7.99 (d, $J = 6.8$ Hz, 1H), 7.77-7.65 (m, 2H), 7.34-7.27 (m, 1H), 4.25-4.13 (m, 2H), 4.12-4.03 (m, 3H), 4.02-3.94 (m, 1H), 3.89 (d, $J = 8.8$ Hz, 1H), 3.76 (s, 2H), 3.65-3.45 (m, 3H), 3.34 (d, $J = 5.2$ Hz, 3H), 2.52-2.41 (m, 1H), 2.33 (s, 1H), 2.24-2.09 (m, 3H), 1.93-1.85 (m, 1H), 1.67 (s, 9H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 467.
252	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 12.59$ (br s, 1H), 8.15 (d, $J = 3.2$ Hz, 1H), 7.41 (d, $J = 6.8$ Hz, 1H), 7.29 (dd, $J = 2.8$ Hz, 8.2 Hz, 1H), 6.73 (s, 1H), 6.70-6.64 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.88-3.75 (m, 4H), 3.16 (br s, 4H), 2.47 (br s, 5H), 2.13-2.07 (m, 1H), 1.96-1.83 (m, 3H), 1.81 (br d, $J = 7.2$ Hz, 1H), 1.53 (br s, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 456.
253	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.72$ (d, $J = 1.8$ Hz, 1H), 8.10 (d, $J = 2.8$ Hz, 1H), 7.85 (dd, $J = 2.0$ Hz, 8.0 Hz, 1H), 7.26-7.20 (m, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.73 (m, 4H), 3.04 (br s, 4H), 2.61 (s, 3H), 2.55-2.34 (m, 5H), 2.07 (br dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.94-1.82 (m, 3H), 1.79 (br d, $J = 7.2$ Hz, 1H), 1.71-1.62 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 454.
254	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.00$ (d, $J = 2.8$ Hz, 1H), 7.12 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 5.90-5.80 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.82 (m, 2H), 3.81-3.76 (m, 2H), 3.24 (br s, 4H), 3.12 (br s, 2H), 2.62 (br s, 4H), 2.56 (br s, 5H), 2.41 (s, 3H), 2.14 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.98-1.90 (m, 2H), 1.89-

		1.75 (m, 2H), 1.60-1.53 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458.
255	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.20$ (d, $J = 3.2$ Hz, 1H), 7.94 (s, 2H), 7.59-7.51 (m, 1H), 6.92 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.75 (q, $J = 8.4$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.87 (m, 1H), 3.85-3.82 (m, 1H), 3.81-3.76 (m, 2H), 3.16 (br s, 4H), 2.52 (br s, 5H), 2.11 (dd, $J = 7.2$ Hz, 12.4 Hz, 1H), 2.00-1.63 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 493.
256	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.06$ (s, 1H), 8.01 (d, $J = 2.8$ Hz, 1H), 7.91 (s, 1H), 7.36 (dd, $J = 2.8$ Hz, 8.8 Hz, 1H), 7.3-7.33 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.88 (m, 1H), 3.86-3.82 (m, 1H), 3.82-3.76 (m, 2H), 3.11 (br s, 4H), 2.56 (br s, 5H), 2.13 (dd, $J = 6.8$ Hz, 10.0 Hz, 1H), 1.99-1.80 (m, 3H), 1.79-1.71 (m, 1H), 1.65-1.64 (m, 9H), 1.60-1.52 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 485.
257	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.11$ (d, $J = 2.8$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.64 (s, 1H), 7.30-7.27 (m, 1H), 4.43 (s, 2H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.88-3.79 (m, 2H), 3.79-3.73 (m, 2H), 3.24 (s, 3H), 3.031 (br s, 4H), 2.55-2.21 (m, 5H), 2.12-2.02 (m, 1H), 1.95-1.76 (m, 3H), 1.71-1.59 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 508.
258	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.16$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.54 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.90 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.11 (m, 4H), 3.92-3.86 (m, 1H), 3.86-3.80 (m, 1H), 3.78 (s, 2H), 3.16 (s, 4H), 2.67-2.41 (m, 5H), 2.19-2.08 (m, 1H), 1.97-1.91 (m, 5H), 1.88-1.74 (m, 2H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.95 (t, $J = 7.6$ Hz, 3H). LCMS m/z $[M+H]^+$ 453.
259	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.16$ (d, $J = 4.8$ Hz, 1H), 7.90-7.76 (m, 2H), 7.58-7.52 (m, 1H), 6.91 (dd, $J = 5.2$ Hz, 6.8 Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.95-3.80 (m, 2H), 3.78 (s, 2H), 3.32-3.07 (m, 4H), 2.71-2.39 (m, 5H), 2.17-2.08 (m, 1H), 2.01-1.80 (m, 4H), 1.75-1.60 (m, 1H), 1.55-1.51 (m, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
260	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.93$ (s, 1H), 8.59-8.50 (m, 1H), 8.27 (dd, $J = 1.2$ Hz, 4.8 Hz, 1H), 7.97-7.86 (m, 1H), 7.21-7.12 (m, 1H), 4.06-3.96 (m, 2H), 3.84-3.75 (m, 1H), 3.73-3.60 (m, 4H), 3.46 (s, 2H), 3.27-3.06 (m, 6H), 2.19-2.02 (m, 2H), 1.98-1.78 (m, 2H), 1.77-1.61 (m, 1H), 1.60-1.42 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 478.
261	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.13$ (dd, $J = 1.2$, 4.8 Hz, 1H), 8.09 (t, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.52-7.47 (m, 1H), 6.62-6.56 (m, 1H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.89-3.79 (m, 2H), 3.75 (s, 2H), 3.17 (s, 4H), 2.57-2.35 (m, 5H), 2.11-2.03 (m, 1H), 1.92-1.78 (m, 3H), 1.70-1.64 (m, 1H), 1.54-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
262	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.10$ (s, 1H), 7.96 (s, 1H), 7.60 (t, $J = 8.0$ Hz, 1H), 7.22 (t, $J = 6.0$ Hz, 1H), 6.55-6.48 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.92-3.75 (m, 4H), 3.40-3.05 (m, 4H), 2.76-2.33 (m, 5H), 2.21-2.04 (m, 1H), 2.02-1.74 (m, 4H), 1.55-1.41 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 479.
263	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.14$ (d, $J = 2.8$ Hz, 1H), 7.35-7.32 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.02 (d, $J = 8.8$ Hz, 1H), 3.89 (d, $J = 8.8$ Hz, 1H), 3.84-3.75 (m, 4H), 3.72-3.57 (m, 4H), 3.56-3.41 (m, 2H), 3.08 (d, $J = 13.2$ Hz, 2H), 2.94-2.78 (m, 5H), 2.74-2.61 (m, 2H), 2.49-2.25 (m, 2H), 2.19-2.08 (m, 4H), 1.96-1.86 (m, 4H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 460.
264	Example 1	LCMS m/z $[M+H]^+$ 464.
265	Example 1	LCMS m/z $[M+H]^+$ 485.
266	Example 1	LCMS m/z $[M+H]^+$ 498.
267	Example 1	LCMS m/z $[M+H]^+$ 473.
268	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.14$ (d, $J = 2.8$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.29 (br d, $J = 12.0$ Hz, 2H), 7.24-7.20 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H),

		3.98 (s, 3H), 3.90-3.80 (m, 2H), 3.80-3.75 (m, 2H), 3.04 (br s, 4H), 2.54-2.28 (m, 5H), 2.09 (br d, $J = 5.2$ Hz, 1H), 1.96-1.77 (m, 3H), 1.67 (br s, 1H), 1.52-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 494.
269	Example 1	LCMS m/z $[M+H]^+$ 473.
270	Example 1	LCMS m/z $[M+H]^+$ 458.
271	Example 1	LCMS m/z $[M+H]^+$ 464.
272	Example 1	LCMS m/z $[M+H]^+$ 484.
273	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.65$ (d, $J = 1.6$ Hz, 1H), 8.31 (d, $J = 1.6$ Hz, 1H), 8.13 (d, $J = 2.8$ Hz, 1H), 8.11 (s, 1H), 7.31 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.98 (s, 3H), 3.90-3.79 (m, 2H), 3.73 (s, 2H), 3.17 (br s, 4H), 2.77-2.38 (m, 5H), 2.11-2.04 (m, 1H), 1.88-1.75 (m, 5H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 494.
274	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.12$ (d, $J = 2.8$ Hz, 1H), 7.53 (dd, $J = 2.0$ Hz, 6.8 Hz, 1H), 7.37-7.29 (m, 2H), 7.18-7.12 (m, 1H), 4.70 (br d, $J = 2.4$ Hz, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.93-3.81 (m, 2H), 3.74 (s, 2H), 3.21 (br s, 4H), 2.79 - 2.47 (m, 5H), 2.29-2.18 (m, 1H), 2.11 (br dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 2.01-1.86 (m, 4H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 487.
275	Example 1	LCMS m/z $[M+H]^+$ 440.
276	Example 1	LCMS m/z $[M+H]^+$ 493.
277	Example 1	LCMS m/z $[M+H]^+$ 469.
278	Example 1	LCMS m/z $[M+H]^+$ 493.
279	Example 1	LCMS m/z $[M+H]^+$ 493.
280	Example 1	LCMS m/z $[M+H]^+$ 493.
281	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.08$ (d, $J = 2.8$ Hz, 1H), 7.94 (s, 1H), 7.77 - 7.69 (m, 2H), 7.59 (br d, $J = 9.2$ Hz, 1H), 7.31 (dd, $J = 2.9$, 8.8 Hz, 1H), 4.26 (s, 3H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.87 - 3.78 (m, 2H), 3.74 (s, 2H), 3.07 (br s, 4H), 2.53 - 2.29 (m, 5H), 2.04 (br dd, $J = 7.2$, 12.8 Hz, 1H), 1.91 - 1.77 (m, 3H), 1.68 - 1.61 (m, 1H), 1.52 - 1.42 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 479.
282	Example 1	LCMS m/z $[M+H]^+$ 465.
283	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.07$ (d, $J = 2.8$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.25 - 7.23 (m, 1H), 7.25 - 7.20 (m, 1H), 4.76 (d, $J = 5.6$ Hz, 2H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.87 - 3.78 (m, 1H), 3.76 (s, 2H), 3.91 - 3.66 (m, 1H), 3.26 - 2.88 (m, 4H), 2.67 - 2.19 (m, 5H), 2.14 - 2.02 (m, 1H), 1.90 - 1.77 (m, 3H), 1.74 - 1.65 (m, 1H), 1.52 - 1.43 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 469.
284	Example 1	LCMS m/z $[M+H]^+$ 493.
285	Example 1	LCMS m/z $[M+H]^+$ 493.
286	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.39$ (s, 1H), 8.27 (d, $J = 3.2$ Hz, 1H), 7.83 - 7.75 (m, 2H), 7.72 (dd, $J = 2.8$, 9.2 Hz, 1H), 7.39 (dd, $J = 1.2$, 8.8 Hz, 1H), 4.19 (s, 3H), 3.99 (s, 2H), 3.64 - 3.31 (m, 8H), 2.96 - 2.86 (m, 4H), 2.27 (br dd, $J = 8.0$, 12.8 Hz, 1H), 2.03 - 1.58 (m, 6H), 1.14 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 493.
287	Example 1	LCMS m/z $[M+H]^+$ 470.
288	Example 1	LCMS m/z $[M+H]^+$ 499.
289	Example 1	LCMS m/z $[M+H]^+$ 458.
290	Example 1	LCMS m/z $[M+H]^+$ 497.
291	Example 1	LCMS m/z $[M+H]^+$ 484.
292	Example 1	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.36$ (s, 1H), 8.28 (d, $J = 2.8$ Hz, 1H), 8.11 (d, $J = 2.8$ Hz, 1H), 7.52 (s, 1H), 7.31 - 7.27 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.84 (br d, $J = 16.0$ Hz, 2H), 3.77 (s, 2H), 3.24 - 2.97 (m, 4H), 2.73 - 2.31 (m, 5H), 2.09 - 2.01 (m, 1H), 1.96 - 1.69 (m, 6H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 456.

293	Example 1	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.01 (d, J = 2.8 Hz, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.33 (dd, J = 2.8, 8.8 Hz, 1H), 6.15-5.96 (m, 1H), 5.33 (dd, J = 1.2, 10.4 Hz, 1H), 5.27 (dd, J = 1.2, 17.2 Hz, 1H), 4.79 (d, J = 6.0 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.82 (m, 2H), 3.78 (s, 2H), 3.12 (br s, 4H), 2.73-2.38 (m, 5H), 2.12 (dd, J = 7.6, 12.4 Hz, 1H), 1.96-1.81 (m, 3H), 1.80-1.70 (m, 1H), 1.57-1.45 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 469.
294	Example 1	LCMS m/z [M+H] ⁺ 475.
295	Example 1	LCMS m/z [M+H] ⁺ 498.
296	Example 1	LCMS m/z [M+H] ⁺ 475.
297	Example 1	LCMS m/z [M+H] ⁺ 493.
298	Example 1	LCMS m/z [M+H] ⁺ 483.
299	Example 1	LCMS m/z [M+H] ⁺ 459.
300	Example 1	LCMS m/z [M+H] ⁺ 494.
301	Example 1	LCMS m/z [M+H] ⁺ 496.
302	Example 1	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.53 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.55-7.47 (m, 1H), 7.44 (dd, J = 3.2 Hz, 8.4 Hz, 1H), 7.40-7.32 (m, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.92-3.79 (m, 2H), 3.77-3.71 (m, 2H), 3.37-3.01 (m, 4H), 2.78-2.24 (m, 5H), 2.17-2.02 (m, 1H), 1.99-1.77 (m, 4H), 1.54-1.40 (m, 1H), 1.22 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 458.
303	Example 1	LCMS m/z [M+H] ⁺ 493.
304	Example 1	LCMS m/z [M+H] ⁺ 496.
305	Example 1	LCMS m/z [M+H] ⁺ 455.
306	Example 1	LCMS m/z [M+H] ⁺ 487.
307	Example 1	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.15 (d, J = 2.8 Hz, 1H), 8.03 (s, 1H), 7.83 (br d, J = 8.8 Hz, 1H), 7.31 (br dd, J = 2.0 Hz, 8.1 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.88 - 3.79 (m, 2H), 3.75 (s, 2H), 3.03 (br s, 4H), 2.52-2.45 (m, 1H), 2.43-2.27 (m, 8H), 2.06 (br dd, J = 7.2 Hz, 12.4 Hz, 1H), 1.92-1.78 (m, 3H), 1.54-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 472.
308	Example 1	LCMS m/z [M+H] ⁺ 454.
309	Example 1	LCMS m/z [M+H] ⁺ 487.
310	Example 1	LCMS m/z [M+H] ⁺ 472.
311	Example 1	LCMS m/z [M+H] ⁺ 473.
312	Example 1	LCMS m/z [M+H] ⁺ 473.
313	Example 1	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.19 (d, J = 2.8 Hz, 1H), 7.31 (dd, J = 2.8 Hz, 8.0 Hz, 1H), 7.11 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.82 (m, 2H), 3.77 (s, 2H), 3.31-3.00 (m, 4H), 2.75-2.31 (m, 5H), 2.18-2.09 (m, 1H), 2.05-1.70 (m, 5H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 476.
314	Example 1	LCMS m/z [M+H] ⁺ 484.
315	Example 1	LCMS m/z [M+H] ⁺ 496.
316	Example 1	LCMS m/z [M+H] ⁺ 472.
317	Example 1	LCMS m/z [M+H] ⁺ 473.
318	Example 1	LCMS m/z [M+H] ⁺ 483.
319	Example 1	LCMS m/z [M+H] ⁺ 454.
320	Example 1	LCMS m/z [M+H] ⁺ 493.
321	Example 1	LCMS m/z [M+H] ⁺ 483.
322	Example 1	LCMS m/z [M+H] ⁺ 454.
323	Example 1	LCMS m/z [M+H] ⁺ 473.
324	Example 1	LCMS m/z [M+H] ⁺ 484.
325	Example 1	LCMS m/z [M+H] ⁺ 473.
326	Example 1	LCMS m/z [M+H] ⁺ 499.
327	Example 1	LCMS m/z [M+H] ⁺ 471.
328	Example 1	LCMS m/z [M+H] ⁺ 443.
329	Example 1	LCMS m/z [M+H] ⁺ 487.

330	Example 1	LCMS m/z [M+H] ⁺ 479.
331	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.05 (d, J = 2.8 Hz, 1H), 7.62 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.26-7.20 (m, 2H), 4.76 (d, J = 5.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.85 (m, 1H), 3.84-3.79 (m, 1H), 3.76 (s, 2H), 3.21-2.96 (m, 4H), 2.56-2.35 (m, 7H), 2.13-2.04 (m, 1H), 1.98-1.59 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 483.
332	Example 1	LCMS m/z [M+H] ⁺ 496.
333	Example 1	LCMS m/z [M+H] ⁺ 494.
334	Example 1	LCMS m/z [M+H] ⁺ 476.
335	Example 1	LCMS m/z [M+H] ⁺ 487.
336	Example 1	LCMS m/z [M+H] ⁺ 473.
337	Example 1	LCMS m/z [M+H] ⁺ 458.
338	Example 1	LCMS m/z [M+H] ⁺ 499.
339	Example 1	LCMS m/z [M+H] ⁺ 479.
340	Example 1	LCMS m/z [M+H] ⁺ 472.
341	Example 1	LCMS m/z [M+H] ⁺ 487.
342	Example 1	LCMS m/z [M+H] ⁺ 488.
343	Example 1	LCMS m/z [M+H] ⁺ 493.
344	Example 1	LCMS m/z [M+H] ⁺ 479.
345	Example 1	LCMS m/z [M+H] ⁺ 483.
346	Example 1	LCMS m/z [M+H] ⁺ 469.
347	Example 1	LCMS m/z [M+H] ⁺ 455.
348	Example 1	LCMS m/z [M+H] ⁺ 458.
349	Example 1	LCMS m/z [M+H] ⁺ 455.
350	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.08 (d, J = 3.2 Hz, 1H), 7.73 (dd, J = 2.8 Hz, 9.6 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.18 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 6.64 (d, J = 9.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.81 (m, 2H), 3.80-3.75 (m, 2H), 3.61 (s, 3H), 3.19-3.04 (m, 4H), 2.63-2.41 (m, 5H), 2.10 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.98-1.80 (m, 4H), 1.61-1.47 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 470.
351	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.04 (d, J = 2.8 Hz, 1H), 7.73 (dd, J = 2.8 Hz, 9.2 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 3.2 Hz, 1H), 6.52 (dd, J = 1.6 Hz, 3.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.76 (m, 4H), 3.25-3.05 (m, 4H), 2.70-2.54 (m, 5H), 2.14 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 2.00-1.80 (m, 4H), 1.67-1.56 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 429.
352	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.50 (s, 1H), 8.30 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.41 (dd, J = 1.8 Hz, 7.2 Hz, 1H), 6.94 (dd, J = 5.2 Hz, 7.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.86 (m, 1H), 3.85-3.81 (m, 1H), 3.81-3.75 (m, 2H), 3.16 (br, 4H), 2.53 (br, 1H), 2.45 (br, 4H), 2.33 (s, 3H), 2.16-2.05 (m, 1H), 2.00-1.78 (m, 3H), 1.70 (br s, 1H), 1.55-1.43 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 426.
353	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.05 (d, J = 3.2 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 6.8 Hz, 3H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.70 (m, 4H), 3.25-2.85 (m, 4H), 2.65-2.21 (m, 8H), 2.15-2.05 (m, 1H), 1.97-1.77 (m, 3H), 1.73-1.65 (m, 1H), 1.56-1.46 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
354	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.05 (d, J = 3.2 Hz, 1H), 7.45-7.35 (m, 2H), 7.34-7.28 (m, 1H), 7.24 (d, J = 2.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.97-3.69 (m, 4H), 3.45-2.85 (m, 4H), 2.40 (s, 7H), 2.00-1.78 (m, 3H), 1.71-1.51 (m, 3H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
355	Example 1	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.16 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 8.8 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.91-3.65 (m, 4H), 3.15-2.80 (m, 4H), 2.49-2.20 (m, 4H), 2.15 (s, 3H), 2.08-1.99 (m,

		1H), 1.94-1.74 (m, 3H), 1.69-1.59 (m, 1H), 1.55-1.38 (m, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 472.
356	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.29$ (s, 1 H), 8.07 (d, $J = 3.2$ Hz, 1H), 7.59-7.49 (m, 2H), 7.23 (dd, $J = 3.2, 8.4$ Hz, 1H), 7.13 (t, $J = 8.8$ Hz, 2H), 4.08 (dd, $J = 7.2, 14.0$ Hz, 2H), 3.95-3.89 (m, 1H), 3.86-3.80 (m, 1H), 3.78-3.71 (m, 2H), 3.26-3.15 (m, 4H), 2.81-2.57 (m, 5H), 2.20-2.08 (m, 1H), 2.04-1.77 (m, 5H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 457.
357	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.09$ (d, $J = 2.8$ Hz, 1H), 7.46-7.38 (m, 1H), 7.35-7.30 (m, 2H), 7.29-7.27 (m, 1H), 7.12-7.02 (m, 1H), 4.09 (dd, $J = 7.2, 14.4$ Hz, 2H), 3.99-3.90 (m, 1H), 3.89-3.82 (m, 1H), 3.76 (s, 2H), 3.43-3.06 (m, 4H), 2.97-2.39 (m, 5H), 2.30-2.10 (m, 1H), 2.04-1.94 (m, 2H), 1.88-1.77 (m, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 457.
358	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.14$ (d, $J = 2.80$ Hz, 1 H), 7.79-7.67 (m, 4 H), 7.26-7.24 (m, 1 H), 4.09 (dd, $J = 6.80, 14.00$ Hz, 2 H), 3.95-3.79 (m, 2 H), 3.79-3.74 (m, 2 H), 3.29-2.77 (m, 4 H), 2.74-2.20 (m, 5 H), 2.17-2.06 (m, 1 H), 2.04-1.86 (m, 2 H), 1.85-1.66 (m, 2 H), 1.66-1.59 (m, 1 H), 1.23 (t, $J = 7.20$ Hz, 3 H). LCMS m/z $[M+H]^+$ 464.
359	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.53$ (s, 1H), 8.14 (d, $J = 2.8$ Hz, 1H), 7.70 (d, $J = 10.0$ Hz, 1H), 7.27 (d, $J = 2.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.89-3.73 (m, 4H), 3.04 (br t, $J = 4.8$ Hz, 4H), 2.58 (d, $J = 2.8$ Hz, 3H), 2.55-2.48 (m, 1H), 2.41 (br s, 4H), 2.08 (dd, $J = 6.8, 12.8$ Hz, 1H), 1.95-1.78 (m, 3H), 1.66 (dd, $J = 9.6, 12.8$ Hz, 1H), 1.53-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 472.
360	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.30$ -8.10 (m, 1H), 7.52 (dd, $J = 2.0$ Hz, 6.8 Hz, 1H), 7.36 (br d, $J = 4.8$ Hz, 1H), 7.15-6.97 (m, 1H), 6.23 (t, $J = 6.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.79 (m, 2H), 3.75 (s, 2H), 3.62 (s, 3H), 2.93 (br s, 4H), 2.64-2.23 (m, 5H), 2.08 (br d, $J = 12.4$ Hz, 1H), 1.97-1.76 (m, 3H), 1.72-1.64 (m, 1H), 1.53-1.43 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 470.
361	Example 1	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.06$ (d, $J = 3.2$ Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.18 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.93-3.74 (m, 4H), 3.64-3.58 (m, 3H), 3.11 (br s, 4H), 2.60-2.35 (m, 5H), 2.21 (s, 3H), 2.10 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 1.98-1.75 (m, 3H), 1.74-1.64 (m, 1H), 1.55-1.44 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 484.
362	Example 2	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 7.74$ (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 6.41-6.52 (m, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.89-3.99 (m, 3H), 3.15-3.43 (m, 8H), 2.78 (s, 1H), 2.43 (s, 4H), 1.85-2.18 (m, 6H), 1.16-1.33 (m, 3H). LCMS m/z $[M+H]^+$ 443.
363	Example 2	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 7.76$ (s, 1H), 7.63 (s, 1H), 7.58-7.50 (m, 1H), 6.51-6.31 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 3H), 3.48-3.13 (m, 8H), 2.73 (s, 1H), 2.37 (s, 4H), 2.10-2.00 (m, 2H), 1.98-1.76 (m, 4H), 1.30-1.17 (m, 3H). LCMS m/z $[M+H]^+$ 443.
364	Example 2	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 9.24$ -9.12 (m, 1H), 8.70-8.60 (m, 1H), 8.48 (s, 1H), 8.32 (dd, $J = 2.0, 4.8$ Hz, 1H), 7.87 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.10-6.97 (m, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.47-3.11 (m, 8H), 2.91-2.68 (m, 1H), 2.64-2.30 (m, 4H), 2.10 (s, 2H), 2.01-1.70 (m, 4H), 1.31-1.18 (m, 3H). LCMS m/z $[M+H]^+$ 423.
365	Example 2	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 9.37$ (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 8.19 (d, $J = 2.8$ Hz, 1H), 7.73 (dd, $J = 2.8, 8.4$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.48-3.19 (m, 4H), 3.09 (s, 4H), 2.79-2.65 (m, 1H), 2.34 (s, 4H), 2.03 (s, 2H), 1.94-1.78 (m, 4H), 1.25-1.21 (m, 3H). LCMS m/z $[M+H]^+$ 441.
366	Example 2	¹H NMR (CDCl₃ 400 MHz) $\delta_H = 8.01$ (br s, 1H), 7.90 (s, 1H), 7.81 (br s, 1H), 7.31 (br d, $J = 8.4$ Hz, 1H), 4.16-4.07 (m, 2H), 3.96 (s, 3H), 3.49-3.34 (m,

		3H), 3.31 (br s, 1H), 3.25 (br s, 1H), 3.09 (br s, 4H), 2.75 (br s, 1H), 2.39 (br s, 4H), 2.05 (br s, 1H), 1.97-1.83 (m, 3H), 1.31-1.20 (m, 4H).
367	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.32 (d, J = 5.2 Hz, 1H), 7.68 (s, 1H), 7.52 (s, 1H), 7.20 (d, J = 5.2 Hz, 1H), 6.60 - 6.12 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 3.92 - 3.80 (m, 2H), 3.76 (s, 2H), 3.12 (br s, 4H), 2.44 (br s, 5H), 2.12 (br dd, J = 6.4 Hz, 12.0 Hz, 1H), 2.01-1.66 (m, 5H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 475.
368	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.02 (d, J = 2.8 Hz, 1H), 7.71 (s, 1H), 7.61 (s, 1H), 7.20 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 3.93-3.80 (m, 2H), 3.76 (s, 2H), 3.46-3.17 (m, 2H), 3.17-2.96 (m, 4H), 2.95-2.79 (m, 1H), 2.21-1.96 (m, 2H), 1.95-1.68 (m, 7H), 1.55-1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 469.
369	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.02 (d, J = 2.8 Hz, 1H), 7.71 (s, 1H), 7.61 (s, 1H), 7.20 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.97 (s, 3H), 3.93-3.79 (m, 2H), 3.76 (s, 2H), 3.38-3.17 (s, 2H), 3.17-2.92 (m, 4H), 2.92-2.74 (m, 1H), 2.17-1.94 (m, 2H), 1.93-1.62 (m, 7H), 1.54-1.41 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 469.
370	Example 2	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.31 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.68 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.89 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.73 (m, 4H), 3.30-3.10 (m, 4H), 3.72 (s, 3H), 2.58-2.46 (m, 4H), 2.44-2.30 (m, 4H), 2.13-2.03 (m, 1H), 1.96-1.85 (m, 2H), 1.81-1.76 (m, 1H), 1.73-1.63 (m, 1H), 1.58-1.48 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 469.
371	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.17 (s, 2H), 8.38 (dd, J = 1.6, 4.8 Hz, 1H), 7.68-7.40 (m, 1H), 7.18-6.96 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.98-3.87 (m, 1H), 3.86-3.81 (m, 1H), 3.78-3.75 (m, 2H), 3.44-3.02 (m, 4H), 2.78-2.31 (m, 4H), 2.19-2.08 (m, 1H), 2.06-1.78 (m, 4H), 1.72-1.47 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 491.
372	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.93-8.86 (m, 1H), 8.53 (d, J = 4.0 Hz, 1H), 8.36 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.38-8.34 (m, 1H), 8.03 (dd, J = 1.6 Hz, 4.0 Hz, 1H), 7.98 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.04 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.86 (m, 1H), 3.85-3.81 (m, 1H), 3.81-3.75 (m, 2H), 3.22 (br s, 4H), 2.67-2.45 (m, 5H), 2.12 (br dd, J = 7.2, 12.0 Hz, 1H), 1.99-1.79 (m, 3H), 1.70 (br s, 1H), 1.54 (br s, 1H), 1.24 (t, J = 7.2 Hz, 3H).
373	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.22 (s, 1H), 8.53 (s, 1H), 8.17-8.14 (m, 1H), 7.73-7.68 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.92-3.75 (m, 4H), 3.29-3.11 (m, 4H), 2.74-2.55 (m, 8H), 2.17-2.07 (m, 1H), 2.03-1.92 (m, 2H), 1.90-1.85 (m, 1H), 1.84-1.73 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
374	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.88 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.96 - 3.85 (m, 2H), 3.84-3.78 (m, 2H), 3.51 (s, 4H), 2.68 (s, 5H), 2.17 (dd, J = 7.2, 12.4 Hz, 1H), 2.08-1.70 (m, 5H), 1.26 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 448.
375	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.91 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.95-3.85 (m, 2H), 3.84-3.79 (m, 2H), 3.50 (s, 4H), 2.65 (s, 5H), 2.16 (dd, J = 6.8, 12.7 Hz, 1H), 2.04-1.67 (m, 5H), 1.26 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 491.
376	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.20-8.12 (m, 1H), 7.91-7.82 (m, 1H), 6.96-6.86 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.99 - 3.79 (m, 4H), 3.72-3.44 (m, 5H), 3.39-3.31 (m, 4H), 2.51-2.40 (m, 1H), 2.20 (m, 1H), 2.10-1.91 (m, 3H), 1.87-1.74 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 389.
377	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.23 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.63 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.91 (dd, J = 5.2 Hz, 7.2 Hz, 1H), 4.20-4.04 (m, 6H), 3.95-3.74 (m, 4H), 3.45-3.36 (m, 4H), 2.74-2.61 (m, 5H), 2.41-2.28 (m, 2H),

		2.25-2.15 (m, 1H), 2.04-1.83 (m, 3H), 1.81-1.70 (m, 1H), 1.64-1.51 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 428.
378	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.27$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.61 (d, $J = 6.8$ Hz, 1H), 6.83 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.9-3.75 (m, 5H), 3.52-3.25 (m, 4H), 2.80-2.40 (m, 5H), 2.20-2.10 (m, 1H), 2.03-1.88 (m, 2H), 1.85-1.62 (m, 11H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
379	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.23$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.02 (s, 1H), 7.65 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.54 (dd, $J = 2.4$ Hz, 8.0 Hz, 1H), 6.96-6.63 (m, 2H), 6.60 (d, $J = 7.6$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.89-3.73 (m, 4H), 3.31-3.06 (m, 4H), 2.63-2.28 (m, 5H), 2.08 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.96-1.78 (m, 3H), 1.71-1.62 (m, 1H), 1.60-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 488.
380	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.26$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.63 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.80 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.16-4.06 (m, 3H), 3.91-3.75 (m, 4H), 3.41-3.26 (m, 4H), 2.67-2.46 (m, 5H), 2.33-2.20 (m, 2H), 2.19-2.08 (m, 3H), 2.04-1.81 (m, 5H), 1.72 (dd, $J = 9.6$ Hz, 12.4 Hz, 1H), 1.56-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 427.
381	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.71$ (s, 1H), 8.26 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.79 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.97 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.62 (s, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.73 (m, 4H), 3.18 (br s, 4H), 2.71-2.34 (m, 5H), 2.20-2.01 (m, 1H), 2.01-1.77 (m, 3H), 1.75-1.70 (m, 1H), 1.55-1.45 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 438.
382	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.67$ (d, $J = 1.2$ Hz, 1H), 8.19 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.95 (d, $J = 1.2$ Hz, 1H), 7.74 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.92 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 5.01-4.80 (m, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 3.89-3.76 (m, 2H), 3.75-3.56 (m, 2H), 3.14 (br s, 4H), 3.00 (d, $J = 5.2$ Hz, 3H), 2.60-2.38 (m, 5H), 2.08-2.03 (m, 1H), 1.95-1.71 (m, 3H), 1.68-1.63 (m, 1H), 1.56-1.41 (m, 1H), 1.20 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 452.
383	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.66$ (d, $J = 5.2$ Hz, 1H), 8.17 (d, $J = 3.2$ Hz, 1H), 7.94-7.86 (m, 1H), 7.83 (dd, $J = 3.2$ Hz, 8.8 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.92-3.73 (m, 4H), 3.40-3.00 (m, 4H), 2.80 (s, 3H), 2.72-2.32 (m, 5H), 2.17-2.02 (m, 1H), 1.97-1.85 (m, 2H), 1.83-1.76 (m, 1H), 1.73-1.62 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
384	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.92$ -8.82 (m, 1H), 8.30 (d, $J = 1.2$ Hz, 1H), 8.12 (d, $J = 2.8$ Hz, 1H), 7.72-7.64 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.03 (s, 3H), 3.95-3.72 (m, 4H), 3.38-2.97 (m, 4H), 2.86-2.34 (m, 5H), 2.21-2.09 (m, 1H), 2.04-1.91 (m, 2H), 1.88-1.82 (m, 1H), 1.75-1.53 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 471.
385	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 8.85$ -8.68 (m, 1H), 8.39-8.20 (m, 1H), 7.91-7.73 (m, 3H), 7.02-6.90 (m, 1H), 4.15-4.05 (m, 2H), 3.92-3.74 (m, 4H), 3.18 (br s, 4H), 2.62-2.35 (m, 5H), 2.16-2.07 (m, 1H), 2.00-1.78 (m, 4H), 1.72 (br d, $J = 8.8$ Hz, 1H), 1.28-1.20 (m, 3H). LCMS m/z $[M+H]^+$ 502.
386	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 9.16$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 8.28-8.18 (m, 2H), 7.86 (dd, $J = 3.2$ Hz, 8.4 Hz, 1H), 7.52 (dd, $J = 4.8$ Hz, 8.6 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.93-3.79 (m, 2H), 3.76 (s, 2H), 3.07 (br s, 4H), 2.62-2.33 (m, 5H), 2.14-2.01 (m, 1H), 1.97-1.63 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
387	Example 3	$^1\text{H NMR}$ (CDCl_3, 400 MHz) $\delta_{\text{H}} = 9.26$ (s, 1H), 8.73 (d, $J = 4.8$ Hz, 1H), 8.09 (t, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 4.8$ Hz, 1H), 6.56 (d, $J = 6.4$ Hz, 1H), 4.09 (q, $J = 6.8$ Hz, 2H), 3.93-3.82 (m, 2H), 3.76 (s, 2H), 3.52-3.13 (m, 4H), 2.76-2.30 (m, 5H), 2.28-2.03 (m, 2H), 1.97-1.77 (m, 4H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.

388	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.62 (d, J = 5.2 Hz, 1H), 8.04 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 5.2 Hz, 1H), 6.56-6.48 (m, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.90-3.80 (m, 2H), 3.77 (s, 2H), 3.22 (s, 4H), 2.78 (s, 3H), 2.61-2.39 (m, 5H), 2.15-2.04 (m, 1H), 1.95-1.78 (m, 3H), 1.75-1.64 (m, 1H), 1.56-1.44 (m, 1H), 1.23 (t, J = 7.2 Hz). LCMS m/z [M+H] ⁺ 455.
389	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.71 (t, J = 7.6 Hz, 1H), 7.65 (s, 1H), 6.50 (dd, J = 3.2, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 1H), 3.90-3.79 (m, 2H), 3.75 (s, 2H), 3.02 (s, 4H), 2.58-2.36 (m, 8H), 2.12-2.04 (m, 1H), 1.97-1.77 (m, 4H), 1.59-1.48 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
390	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.81 (t, J = 8.4 Hz), 6.28 (dd, J = 3.2, 8.4 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.81 (m, 6H), 3.78 (s, 2H), 2.66-2.53 (m, 5H), 2.16-2.09 (m, 1H), 1.99-1.81 (m, 3H), 1.77-1.69 (m, 1H), 1.58-1.49 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 388.
391	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.23 (d, J = 2.8 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 8.16-8.11 (m, 1H), 7.41 (dd, J = 3.2 Hz, 8.0 Hz, 1H), 4.11-4.07 (m, 2H), 3.96 (s, 3H), 3.87-3.80 (m, 2H), 3.75 (s, 2H), 3.03 (s, 4H), 2.54-2.40 (m, 1H), 2.39-2.19 (s, 4H), 2.09-2.02 (m, 1H), 1.94-1.76 (m, 4H), 1.74-1.51 (m, 1H), 1.25-1.21 (m, 3H). LCMS m/z [M+H] ⁺ 471.
392	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.23 (s, 1H), 8.18-8.14 (m, 1H), 8.13-8.10 (m, 1H), 4.19 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 3.95-3.83 (m, 2H), 3.82-3.71 (m, 2H), 3.09 (br s, 4H), 2.66-2.44 (m, 5H), 2.18-2.09 (m, 1H), 2.04-1.81 (m, 4H), 1.79-1.62 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
393	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.30 (d, J = 2.8 Hz, 1H), 7.62-7.51 (m, 1H), 4.22-4.16 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.97-3.83 (m, 3H), 3.82-3.76 (m, 2H), 3.35-3.22 (m, 3H), 2.75-2.52 (m, 5H), 2.23-2.08 (m, 1H), 2.02-1.84 (m, 4H), 1.81-1.67 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 430.
394	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.23 (d, J = 2.8 Hz, 0.5H), 8.12 (d, J = 2.8 Hz, 0.5H), 7.97 (s, 0.5H), 7.87 (d, J = 0.4 Hz, 0.5H), 7.67 (dd, J = 2.8, 7.6 Hz, 0.5H), 7.47 (d, J = 2.8 Hz, 0.5H), 4.17-4.04 (m, 2H), 3.99-3.70 (m, 4H), 3.29 (d, J = 4.0 Hz, 1H), 2.92 (s, 2H), 2.72-2.52 (m, 2H), 2.52-2.34 (m, 5H), 2.24-2.05 (m, 1H), 1.99-1.79 (m, 3H), 1.59 (s, 5H), 1.31-1.17 (m, 3H). LCMS m/z [M+H] ⁺ 444.
395	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.06 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 6.57 (dd, J = 3.2, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.79 (m, 2H), 3.76 (s, 2H), 3.16 (s, 4H), 2.76 (s, 3H), 2.57-2.35 (m, 5H), 2.11-2.03 (m, 1H), 1.96-1.77 (m, 3H), 1.70-1.64 (m, 1H), 1.55-1.44 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
396	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.04 (d, J = 2.8 Hz, 1H), 7.76 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 4.57-4.50 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.81 (m, 2H), 3.79-3.75 (m, 2H), 3.21 (br s, 4H), 2.75-2.62 (m, 5H), 2.13 (d, J = 5.6 Hz, 1H), 2.01-1.80 (m, 4H), 1.74-1.67 (m, 1H), 1.55 (d, J = 6.4 Hz, 6H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 471.
397	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.77 (d, J = 1.6 Hz, 1H), 8.23-8.06 (m, 2H), 7.87-7.67 (m, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.89-3.80 (m, 2H), 3.79-3.74 (m, 2H), 3.19-3.10 (m, 6H), 3.10-3.04 (m, 4H), 2.58-2.49 (m, 1H), 2.48-2.37 (m, 4H), 2.12-2.02 (m, 1H), 1.95-1.79 (m, 3H), 1.72-1.64 (m, 1H), 1.55-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 511.
398	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ = 8.80-8.58 (m, 2H), 8.50 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 6.87 (d, J = 5.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.87-3.77 (m, 2H), 3.73 (s, 2H), 3.01 (s, 4H), 2.50-2.18 (m, 5H), 2.13 (s, 3H), 2.06-1.98 (m, 1H), 1.96-1.66 (m, 4H), 1.51-1.39 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 437.

399	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.00 (s, 1H), 8.37-8.30 (m, 1H), 8.02-7.95 (m, 1H), 7.92 (s, 1H), 7.07-6.98 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.80 (m, 2H), 3.80-3.74 (m, 2H), 3.15 (s, 4H), 2.59-2.27 (m, 8H), 2.17-2.02 (m, 1H), 1.97-1.77 (m, 3H), 1.76-1.66 (m, 1H), 1.53-1.47 (m, 1H), 1.24 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 437.
400	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.00 (s, 1H), 8.51 (s, 1H), 7.91 (t, J = 8.0 Hz, 1H), 8.55 (dd, J = 3.2 Hz, 8.0 Hz, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.91-3.69 (m, 4H), 3.33-3.03 (m, 4H), 2.75-2.33 (m, 8H), 2.13-2.03 (m, 1H), 1.96-1.85 (m, 2H), 1.82-1.75 (m, 1H), 1.58-1.47 (m, 2H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
401	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.17 (t, J = 8.4 Hz, 1H), 7.48-7.35 (m, 2H), 6.52 (dd, J = 3.6 Hz, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.68 (m, 7H), 3.22 (s, 4H), 2.55 (s, 5H), 2.20-2.10 (m, 1H), 1.98-1.80 (m, 2H), 1.78-1.70 (m, 1H), 1.63-1.47 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 443.
402	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.60 (t, J = 7.6 Hz, 2H), 6.51 (dd, J = 3.6, 8.4 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.92-3.80 (m, 2H), 3.74 (s, 2H), 3.24-2.92 (m, 4H), 2.68-2.30 (m, 5H), 2.20 (s, 3H), 2.14-2.05 (m, 1H), 1.99-1.76 (m, 5H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
403	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.11 (d, J = 2.8 Hz, 1H), 8.66 (d, J = 1.6 Hz, 1H), 8.25 (d, J = 3.2 Hz, 1H), 7.52 (dd, J = 3.2 Hz, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.88-3.73 (m, 4H), 3.12 (br s, 4H), 2.38 (br s, 5H), 2.08 (br s, 1H), 2.05-1.87 (m, 2H), 1.84 (br s, 1H), 1.79 (br s, 2H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 459.
404	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.15 (s, 1H), 8.29 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.02 (s, 1H), 7.88 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.98 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.45 (s, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.90-3.68 (m, 4H), 3.32-3.05 (m, 7H), 2.66-2.25 (m, 5H), 2.08 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 1.98-1.76 (m, 3H), 1.73-1.65 (m, 1H), 1.57-1.47 (m, 1H), 1.22 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 491.
405	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.96 (d, J = 2.0 Hz, 1H), 8.28 (m, 1H), 8.18 (d, J = 3.2 Hz, 1H), 7.98 (dd, J = 2.0 Hz, 8.3 Hz, 1H), 7.78 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.75 (m, 4H), 3.10 (m, 4H), 2.61-2.32 (m, 5H), 2.15-2.05 (m, 1H), 1.97-1.78 (m, 3H), 1.73-1.63 (m, 1H), 1.54-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 466.
406	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.00 (br s, 1H), 8.68 (br s, 1H), 8.55 (br s, 1H), 8.19 (br s, 1H), 7.58 (br s, 1H), 4.11-4.05 (m, 2H), 3.91-3.74 (m, 4H), 3.18 (br s, 4H), 3.04-2.71 (m, 3H), 2.69-2.36 (m, 2H), 2.33-2.03 (m, 3H), 2.00-1.84 (m, 4H), 1.82 (br s, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 467.
407	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.01 (d, J = 1.6 Hz, 1H), 8.73-8.61 (m, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 3.2 Hz, 1H), 7.64-7.51 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.91-3.70 (m, 4H), 3.19 (s, 2H), 3.16-2.64 (m, 5H), 2.06-1.88 (m, 2H), 1.88-1.72 (m, 4H), 1.70-1.63 (m, 2H), 1.48 (s, 2H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 467.
408	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.32 (d, J = 5.2 Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.16 (d, J = 5.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.92-3.80 (m, 2H), 3.76 (s, 2H), 3.14 (br s, 4H), 2.40 (br s, 5H), 2.08 (br dd, J = 7.2, 12.4 Hz, 1H), 1.98-1.66 (m, 5H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 492.
409	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.19 (d, J = 2.8 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.71 (m, 4H), 3.08 (s, 4H), 2.77 (s, 3H), 2.64-2.21 (m, 5H), 2.14-2.04 (m, 1H), 1.98-1.77 (m, 3H), 1.73-1.65 (m, 1H), 1.37 (d, J = 7.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.

410	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.92 (d, J = 1.2 Hz, 1H), 8.84-8.75 (m, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.71 (m, 4H), 3.11 (br s, 4H), 2.56-2.31 (m, 5H), 2.10-2.00 (m, 1H), 1.97-1.70 (m, 4H), 1.48 (s, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 448.
411	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.22 (s, 1H), 8.65-8.56 (m, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.89-3.79 (m, 2H), 3.79-3.73 (m, 2H), 3.12 (br s, 4H), 2.63-2.32 (m, 5H), 2.08 (dd, J = 7.2 Hz, 12.4 Hz, 1H), 2.01-1.94 (m, 1H), 1.92-1.77 (m, 3H), 1.66 (s, 1H), 1.51 (s, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.12-1.05 (m, 2H), 0.99-0.91 (m, 2H). LCMS m/z [M+H] ⁺ 463.
412	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.70 (dd, J = 1.6, 2.4 Hz, 1H), 8.66 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 6.60 (d, J = 5.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.87-3.79 (m, 2H), 3.78 (s, 3H), 3.77-3.71 (m, 2H), 3.06 (br s, 4H), 2.51-2.20 (m, 5H), 2.07-2.02 (m, 1H), 1.92-1.72 (m, 4H), 1.55-1.39 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
413	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.72 (dd, J = 1.6 Hz, 2.4 Hz, 1H), 8.64 (d, J = 1.2 Hz, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 7.28 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.77 (m, 2H), 3.72 (s, 2H), 3.08 (br s, 4H), 2.44 (br s, 1H), 2.24 (br s, 4H), 2.04 (br dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.92-1.76 (m, 4H), 1.48 (br s, 1H), 1.20 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 491.
414	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.26 (t, J = 8.4 Hz, 1H), 7.95 (s, 1H), 6.59 (dd, J = 3.2, 8.0 Hz, 1H), 4.17 (s, 3H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.75 (m, 4H), 3.19 (br s, 4H), 2.79-2.29 (m, 5H), 2.12 (br dd, J = 7.2, 12.8 Hz, 1H), 1.99-1.80 (m, 3H), 1.74 (br s, 1H), 1.59-1.54 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
415	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.77-8.63 (m, 2H), 8.55 (d, J = 2.0 Hz, 1H), 6.25 (d, J = 7.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.91-3.71 (m, 4H), 3.40-2.95 (m, 4H), 2.66-2.13 (m, 5H), 2.11-1.99 (m, 1H), 1.95-1.77 (m, 3H), 1.72-1.63 (m, 1H), 1.53-1.39 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 459.
416	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.76 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 2.4 Hz, 9.6 Hz, 1H), 4.56-4.44 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.02-3.76 (m, 6H), 3.66-3.56 (m, 2H), 3.52-3.10 (m, 4H), 2.95-2.30 (m, 5H), 2.17 (dd, J = 6.8 Hz, 12.0 Hz, 1H), 2.07-1.76 (m, 8H), 1.56-1.39 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 463.
417	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.21 (s, 1H), 8.11 (d, J = 3.2 Hz, 1H), 7.84 (dd, J = 3.2 Hz, 8.8 Hz, 1H), 4.89-4.82 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.75 (m, 4H), 3.11 (br s, 4H), 2.59 (br s, 5H), 2.14-2.09 (m, 1H), 1.99-1.82 (m, 3H), 1.77-1.74 (m, 1H), 1.62 (d, J = 6.8 Hz, 6H), 1.58-1.52 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 472.
418	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.20 (s, 1H), 8.76-8.61 (m, 1H), 8.52 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.85-6.18 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.92-3.80 (m, 2H), 3.76 (s, 2H), 3.20 (br s, 4H), 2.63-2.38 (m, 5H), 2.08 (br dd, J = 6.4 Hz, 12.4 Hz, 1H), 1.97-1.66 (m, 5H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 473.
419	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.38 (d, J = 1.6 Hz, 1H), 8.33 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.55-7.46 (m, 2H), 7.00 (s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.80 (m, 2H), 3.76 (s, 2H), 3.41-2.95 (m, 4H), 2.78 (s, 3H), 2.45 (s, 5H), 2.09 (s, 1H), 2.02-1.81 (m, 3H), 1.80 (s, 1H), 1.68-1.61 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 437.
420	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.26 (d, J = 2.8 Hz, 1H), 8.25-8.18 (m, 1H), 8.15 (d, J = 2.8 Hz, 1H), 6.64 (dd, J = 6.0 Hz, 8.8 Hz, 1H), 4.08 (q, J = 7.2

		Hz, 2H), 3.96 (s, 3H), 3.86-3.73 (m, 4H), 3.23-3.04 (m, 4H), 2.52-2.23 (m, 5H), 2.04 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 1.93-1.73 (m, 3H), 1.63-1.55 (m, 1H), 1.46 (d, $J = 9.2$ Hz, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 471$.
421	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.25$ (s, 1H), 8.31 (d, $J = 2.4$ Hz, 1H), 8.02 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94 - 3.75 (m, 4H), 3.40 - 3.16 (m, 4H), 2.99 - 2.79 (m, 3H), 2.08 - 1.95 (m, 2H), 1.95 - 1.77 (m, 6H), 1.75 - 1.66 (m, 1H), 1.56 - 1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 476$.
422	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 7.76$ (d, $J = 2.4$ Hz, 1H), 6.66 (dd, $J = 2.4, 9.6$ Hz, 1H), 4.78 (s, 2H), 4.72 (s, 2H), 4.55-4.47 (m, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.94-3.85 (m, 2H), 3.84-3.78 (m, 2H), 3.37 (br s, 4H), 2.89-2.82 (m, 2H), 2.64 (br s, 5H), 2.45-2.39 (m, 2H), 2.17 (dd, $J = 6.8, 12.8$ Hz, 1H), 2.01-1.91 (m, 2H), 1.90-1.84 (m, 1H), 1.83-1.74 (m, 1H), 1.61-1.51 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 475$.
423	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.56$ (d, $J = 4.4$ Hz, 1H), 8.25 (dd, $J = 6.0$ Hz, 8.8 Hz, 1H), 7.52 (t, $J = 8.8$ Hz, 1H), 7.41-7.33 (m, 1H), 6.65 (dd, $J = 5.6$ Hz, 8.8 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.86-3.72 (m, 4H), 3.15 (d, $J = 4.4$ Hz, 4H), 2.52-2.28 (m, 5H), 2.04 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 1.91-1.78 (m, 3H), 1.63-1.57 (m, 1H), 1.53-1.40 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 458$.
424	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.20$ (dd, $J = 5.6$ Hz, 8.8 Hz, 1H), 7.75 (d, $J = 1.6$ Hz, 1H), 6.66 (dd, $J = 5.6$ Hz, 9.2 Hz, 1H), 4.20 (s, 3H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.91-3.74 (m, 4H), 3.21 (t, $J = 4.4$ Hz, 4H), 2.67-2.37 (m, 5H), 2.09 (dd, $J = 6.8, 12.4$ Hz, 1H), 1.98-1.79 (m, 3H), 1.77-1.68 (m, 1H), 1.59-1.49 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 444$.
425	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.48$ (d, $J = 2.4$ Hz, 1H), 8.26 (dd, $J = 5.6$ Hz, 8.8 Hz, 1H), 7.37-7.30 (m, 1H), 6.67 (dd, $J = 5.6$ Hz, 8.4 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.64 (m, 4H), 3.30-3.05 (m, 4H), 2.65-2.23 (m, 5H), 2.07-2.05 (m, 1H), 1.93-1.77 (m, 3H), 1.75-1.66 (m, 1H), 1.61-1.46 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 476$.
426	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.56$ (s, 1H), 9.03 (s, 1H), 8.26 (d, $J = 3.2$ Hz, 1H), 7.83 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.92-3.77 (m, 4H), 3.31-3.03 (m, 4H), 2.75-2.41 (m, 5H), 2.13 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.99-1.82 (m, 3H), 1.80-1.72 (m, 1H), 1.59-1.47 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 509$.
427	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.48$ (br s, 1H), 8.26 (d, $J = 2.8$ Hz, 1H), 7.94 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.81 (m, 2H), 3.76 (s, 2H), 3.31-2.92 (m, 4H), 2.78-2.26 (m, 5H), 2.19-2.05 (m, 1H), 2.01-1.71 (m, 4H), 1.55-1.45 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 509$.
428	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 13.00$ (s, 1H), 8.20 (d, $J = 2.4$ Hz, 1H), 7.50-7.39 (m, 2H), 6.71 (d, $J = 1.2$ Hz, 1H), 6.59 (dd, $J = 1.2, 6.8$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.94-3.70 (m, 4H), 3.25 (s, 4H), 2.51 (s, 5H), 2.11 (dd, $J = 7.2, 12.4$ Hz, 1H), 1.99-1.83 (m, 3H), 1.78 (s, 1H), 1.58 (s, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 472$.
429	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.13$ (s, 1H), 8.70 (s, 1H), 8.58 (s, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.79 (m, 2H), 3.78-3.72 (m, 2H), 3.35 (br s, 4H), 2.85-2.31 (m, 5H), 2.14-2.06 (m, 1H), 1.98-1.76 (m, 4H), 1.59-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 468$.
430	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 7.74$ -7.71 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.93-3.82 (m, 5H), 3.80-3.74 (m, 2H), 3.42-3.27 (m, 4H), 2.65-2.52 (m, 5H), 2.46-2.36 (m, 3H), 2.16-2.10 (m, 1H), 1.98-1.89 (m, 2H), 1.86-1.81 (m, 1H),

		1.78-1.70 (m, 1H), 1.64-1.53 (m, 1H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+ 435$.
431	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.25$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.79 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.94 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.42 (s, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.95-3.85 (m, 2H), 3.83-3.75 (m, 2H), 3.44 (s, 3H), 3.30-3.20 (m, 4H), 2.64 (br, 5H), 2.18-2.14 (m, 1H), 2.03-1.85 (m, 3H), 1.83-1.75 (m, 1H), 1.60-1.55 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 389$.
432	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.14$ (s, 1H), 8.63 (s, 1H), 8.46 (d, $J = 2.0$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.67-7.28 (m, 1H), 6.57 (d, $J = 8.0$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.90-3.80 (m, 2H), 3.77 (s, 2H), 3.17 (br s, 4H), 2.62-2.39 (m, 5H), 2.09 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.97-1.78 (m, 3H), 1.69 (br d, $J = 9.6$ Hz, 1H), 1.51 (br s, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 489$.
433	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.23$ -9.17 (m, 1H), 8.60 (s, 1H), 8.38 (d, $J = 2.4$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 3H), 3.91-3.80 (m, 2H), 3.78 (s, 2H), 3.20 (br s, 4H), 2.49 (br s, 5H), 2.10 (br dd, $J = 6.8$, 12.0 Hz, 1H), 1.97-1.77 (m, 3H), 1.68 (t, $J = 10.8$ Hz, 1H), 1.53 (br s, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 453$.
434	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.19$ (br s, 1H), 8.61 (br s, 1H), 8.41 (br s, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 6.53 (br d, $J = 8.0$ Hz, 1H), 4.94-4.14 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.81 (m, 2H), 3.77 (s, 2H), 3.21 (br s, 4H), 2.49 (br s, 5H), 2.10 (br s, 1H), 2.00-1.78 (m, 3H), 1.74-1.65 (m, 1H), 1.57-1.45 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.83-0.77 (m, 4H). LCMS m/z $[M+H]^+ 479$.
435	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.19$ (d, $J = 1.2$ Hz, 1H), 8.74-8.68 (m, 1H), 8.57 (d, $J = 2.4$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.92-3.81 (m, 2H), 3.79 (s, 2H), 3.22 (t, $J = 4.8$ Hz, 4H), 2.62-2.52 (m, 1H), 2.51-2.39 (m, 4H), 2.10 (dd, $J = 7.2$, 12.5 Hz, 1H), 1.99 - 1.78 (m, 3H), 1.69 (dd, $J = 9.6$, 12.5 Hz, 1H), 1.55 - 1.48 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 448$.
436	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 7.78$ (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.97 (s, 3H), 3.91-3.76 (m, 4H), 3.35-3.05 (m, 4H), 2.71-2.35 (m, 5H), 2.11 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.97-1.79 (m, 3H), 1.71 (s, 1H), 1.66-1.61 (m, 1H), 1.56-1.48 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 450$.
437	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.67$ (d, $J = 5.2$ Hz, 1H), 8.18 (d, $J = 3.2$ Hz, 1H), 7.90 (br d, $J = 4.4$ Hz, 1H), 7.83 (dd, $J = 3.2$ Hz, 8.4 Hz, 1H), 4.16-4.04 (m, 5H), 4.02-3.96 (m, 1H), 3.12 (br s, 4H), 3.01-2.84 (m, 3H), 2.80 (s, 3H), 2.67-2.42 (m, 5H), 2.13-1.99 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 473$.
438	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.36$ (s, 1H), 8.67 (s, 1H), 8.51 (s, 1H), 8.19 (d, $J = 3.2$ Hz, 1H), 7.76-7.72 (m, 1H), 4.16-4.01 (m, 5H), 4.00-3.96 (m, 1H), 3.19-2.75 (m, 7H), 2.70-2.39 (m, 5H), 2.13-1.95 (m, 1H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+ 459$.
439	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.87$ (d, $J = 4.8$ Hz, 2H), 8.17 (d, $J = 3.2$ Hz, 1H), 7.8-7.71 (m, 1H), 7.29-7.27 (m, 1H), 4.14-4.04 (m, 5H), 4.01-3.96 (m, 1H), 3.32-3.06 (m, 4H), 3.02-2.82 (m, 3H), 2.78-2.34 (m, 5H), 2.19-1.90 (m, 1H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+ 459$.
440	Example 3	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.18$ (d, $J = 0.8$ Hz, 1H), 8.62 (dd, $J = 1.6$ Hz, 2.4 Hz, 1H), 8.45 (d, $J = 2.8$ Hz, 1H), 7.81 (d, $J = 9.6$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.79 (m, 2H), 3.78-3.71 (m, 2H), 3.14 (br s, 4H), 2.65-2.36 (m, 5H), 2.23 (s, 3H), 2.07 (br dd, $J = 7.2$ Hz, 12.4 Hz, 1H), 1.97-1.74 (m, 3H), 1.74-1.66 (m, 1H), 1.55-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+ 455$.

441	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.30-8.18 (m, 2H), 8.10 (d, J = 2.8 Hz, 1H), 7.36 (dd, J = 2.8, 8.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.96-3.76 (m, 4H), 3.13 (s, 4H), 2.58 (s, 5H), 2.20-2.07 (m, 1H), 2.03-1.80 (m, 3H), 1.73-1.65 (m, 1H), 1.57-1.40 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 497.
442	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.46-7.31 (m, 5H), 7.28 (d, J = 7.2 Hz, 1H), 5.01 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.94-3.71 (m, 4H), 3.70-3.25 (m, 4H), 2.80-2.30 (m, 5H), 2.12 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.99-1.75 (m, 4H), 1.66-1.50 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 457, 459.
443	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.52 (s, 1H), 9.26 (dd, J = 1.2 Hz, 5.6 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 2.4 Hz, 5.2 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.89-3.70 (m, 4H), 3.09 (t, J = 4.8 Hz, 4H), 2.63-2.26 (m, 5H), 2.07 (dd, J = 7.2 Hz, 12.4 Hz, 1H), 1.96-1.75 (m, 3H), 1.65 (d, J = 3.2 Hz, 1H), 1.55-1.40 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 457.
444	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.85 (d, J = 2.4 Hz, 1H), 7.01-6.91 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.98-3.82 (m, 4H), 3.82-3.75 (m, 2H), 3.73-3.66 (m, 2H), 3.37 (br s, 4H), 2.77-2.39 (m, 5H), 2.18-2.08 (m, 1H), 2.03-1.70 (m, 8H), 1.53-1.45 (m, 1H), 1.36 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 477.
445	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.54 (s, 1H), 9.25 (d, J = 5.2 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.69 (dd, J = 2.4 Hz, 5.2 Hz, 1H), 7.32 (dd, J = 2.8 Hz, 8.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.72 (m, 4H), 3.04 (t, J = 4.8 Hz, 4H), 2.60-2.32 (m, 5H), 2.10-2.01 (m, 1H), 1.94-1.76 (m, 3H), 1.68-1.62 (m, 1H), 1.55-1.43 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 441.
446	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.16 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.51 (dd, J = 4.8 Hz, 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90-3.68 (m, 4H), 3.20-3.00 (m, 4H), 2.59-2.28 (m, 5H), 2.06 (dd, J = 6.4 Hz, 12.4 Hz, 1H), 1.96-1.74 (m, 3H), 1.70-1.61 (m, 1H), 1.55-1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 457.
447	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.21 (s, 1H), 8.19-8.08 (m, 2H), 7.23 (t, J = 60.4 Hz, 1H), 6.73 (dd, J = 5.6 Hz, 9.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.71 (m, 4H), 3.30-3.00 (m, 4H), 2.64-2.40 (m, 5H), 2.10 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 1.98-1.78 (m, 3H), 1.73-1.67 (m, 1H), 1.58-1.47 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
448	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.18 (d, J = 4.4 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 6.96 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.13-4.06 (m, 4H), 3.93-3.83 (m, 2H), 3.82-3.77 (m, 2H), 3.52 (t, J = 10.8 Hz, 2H), 3.14-3.06 (m, 5H), 2.64 (br s, 5H), 2.15 (d, J = 6.8 Hz, 12.4 Hz, 1H), 1.99-1.71 (m, 8H), 1.55-1.50 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 429.
449	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.56-8.50 (m, 1H), 7.86 (t, J = 8.4 Hz, 1H), 7.80 (dd, J = 4.4 Hz, 8.8 Hz, 1H), 7.50-7.42 (m, 1H), 6.51 (dd, J = 3.2 Hz, 8.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.80 (m, 2H), 3.79-3.73 (m, 2H), 3.16 (br s, 4H), 2.60-2.40 (m, 5H), 2.08 (m, 1H), 1.95-1.79 (m, 3H), 1.72-1.68 (m, 1H), 1.57-1.46 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 458.
450	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.44 (d, J = 2.4 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.33 - 7.27 (m, 1H), 6.44 (dd, J = 3.2, 8.4 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.87 - 3.79 (m, 2H), 3.78 - 3.72 (m, 2H), 3.18 (br s, 4H), 2.50 (br d, J = 6.4 Hz, 1H), 2.37 (br s, 4H), 2.06 (dd, J = 7.2, 12.4 Hz, 1H), 1.93 - 1.78 (m, 3H), 1.72 - 1.66 (m, 1H), 1.51 (br s, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 476.
451	Example 3	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.55 (t, J = 8.4 Hz, 1H), 6.55 (dd, J = 3.2 Hz, 8.4 Hz, 1H), 4.14-4.05 (m, 4H), 3.94-3.83 (m, 2H), 3.82-3.76 (m, 2H), 3.56-3.47 (m, 2H), 3.12 (br s, 4H), 3.08-2.98 (m, 1H), 2.62 (br s, 5H), 2.14 (dd, J =

		7.2 Hz, 12.4 Hz, 1H), 1.99-1.82 (m, 3H), 1.80-1.75 (m, 1H), 1.74-1.65 (m, 4H), 1.59-1.52 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 447.
452	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.85$ (d, $J = 2.0$ Hz, 1H), 8.24 (d, $J = 1.6$ Hz, 1H), 8.10 (s, 1H), 8.06-7.98 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 1H), 3.93-3.72 (m, 4H), 3.20-3.10 (m, 4H), 2.70-2.40 (m, 5H), 2.11 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 1.98-1.78 (m, 3H), 1.76-1.68 (m, 1H), 1.62-1.49 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 446.
453	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 7.93$ (t, $J = 8.0$ Hz, 1H), 7.81 (q, $J = 8.0$ Hz, 1H), 7.69 (dd, $J = 2.0$ Hz, 7.5 Hz, 1H), 6.84 (dd, $J = 2.8$ Hz, 8.0 Hz, 1H), 6.49 (dd, $J = 3.2$ Hz, 8.0 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89-3.73 (m, 4H), 3.20 (br s, 4H), 2.60-2.33 (m, 5H), 2.10-2.05 (m, 1H), 1.96-1.78 (m, 3H), 1.77-1.68 (m, 1H), 1.58-1.45 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458.
454	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.51$ (d, $J = 4.4$ Hz, 1H), 7.69 (t, $J = 8.4$ Hz, 1H), 7.47 (t, $J = 8.8$ Hz, 1H), 7.35-7.27 (m, 1H), 6.43 (dd, $J = 3.2$ Hz, 8.0 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.87-3.79 (m, 2H), 3.77-3.72 (m, 2H), 3.18 (br s, 4H), 2.54-2.44 (m, 1H), 2.35 (br s, 4H), 2.15-2.05 (m, 1H), 1.94-1.76 (m, 3H), 1.60-1.64 (m, 1H), 1.52-1.43 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458.
455	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.06$ (d, $J = 2.8$ Hz, 1H), 7.73 (d, $J = 6.4$ Hz, 1H), 7.39 (d, $J = 2.0$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 4.13-4.04 (m, 5H), 3.95 (s, 3H), 3.12 (br s, 4H), 3.00-2.89 (m, 3H), 2.65-2.58 (m, 4H), 2.11-2.02 (m, 1H), 1.72 (br s, 2H), 1.23 (t, $J = 6.8$ Hz, 3H). LCMS m/z $[M+H]^+$ 461.
456	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.83$ (s, 2H), 7.51 (t, $J = 8.0$ Hz, 1H), 6.55 (dd, $J = 3.6$ Hz, 8.0 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.73 (m, 4H), 3.15 (br s, 4H), 2.79 (s, 3H), 2.61-2.33 (m, 5H), 2.10-2.05 (m, 1H), 1.97-1.75 (m, 3H), 1.75-1.73 (m, 1H), 1.57-1.40 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
457	Example 3	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.09$ (s, 1H), 8.57 (s, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 6.54 (dd, $J = 2.8$ Hz, 8.0 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.70 (m, 4H), 3.10 (br s, 4H), 2.60-2.21 (m, 8H), 2.11-1.99 (m, 1H), 1.95-1.75 (m, 3H), 1.71-1.62 (m, 1H), 1.52-1.41 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 455.
458	Example 4	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.49$ (s, 1H), 8.31-8.27 (m, 1H), 7.42-7.37 (m, 1H), 6.95-6.90 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.74 (m, 4H), 3.23-3.08 (m, 4H), 2.61-2.38 (m, 5H), 2.32 (s, 3H), 2.13-2.05 (m, 1H), 1.97-1.77 (m, 3H), 1.75-1.65 (m, 1H), 1.56-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 426.
459	Example 4	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.17$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.86 (d, $J = 12.8$ Hz, 2H), 7.52 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.89 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.6 (t, $J = 6.4$ Hz, 2H), 4.18-4.07 (m, 4H), 3.90-3.76 (m, 4H), 3.16 (s, 4H), 2.94 (t, $J = 6.4$ Hz, 2H), 2.55 (s, 5H), 2.15-2.10 (m, 1H), 2.00-1.82 (m, 3H), 1.79-1.67 (m, 2H), 1.29-1.18 (m, 6H). LCMS m/z $[M+H]^+$ 511.
460	Example 4	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.09$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.43 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 6.85 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.42 (t, $J = 6.0$ Hz, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.91-3.83 (m, 1H), 3.81-3.70 (m, 3H), 3.22 (s, 4H), 2.93-2.79 (m, 7H), 2.17-2.06 (m, 1H), 2.03-1.86 (m, 3H), 1.85-1.75 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 483.
461	Example 4	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.29$ -8.22 (m, 2H), 7.75-7.65 (m, 4H), 7.49-7.44 (m, 1H), 7.00 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.92-3.72 (m, 4H), 3.35-3.23 (m, 4H), 2.96-2.69 (m, 5H), 2.19-2.11 (m, 1H), 2.09-1.90 (m, 3H), 1.90-1.76 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 446.

462	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.25 (d, J = 1.6 Hz, 1H), 8.19 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.73 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.40 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 6.91 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.56 (br s, 2H), 4.11-4.07 (m, 2H), 3.92-3.79 (m, 2H), 3.78-3.69 (m, 2H), 3.16 (s, 4H), 2.61-2.52 (m, 1H), 2.46 (s, 4H), 2.15-2.03 (m, 1H), 1.98-1.67 (m, 4H), 1.63-1.48 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 437.
463	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.31 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.46 (dd, J = 2.0 Hz, 7.2 Hz, 1H), 7.37-7.27 (m, 1H), 7.03-6.95 (m, 2H), 6.93-6.87 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.89-3.78 (m, 2H), 3.77-3.71 (m, 2H), 3.28-2.97 (m, 4H), 2.63-2.15 (m, 5H), 2.12-2.00 (m, 1H), 1.96-1.64 (m, 4H), 1.53-1.43 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 457.
464	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.32 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.41 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.33-7.27 (m, 2H), 7.12-7.06 (m, 1H), 6.96-6.88 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.89-3.77 (m, 2H), 3.76-3.71 (m, 2H), 3.28-3.03 (m, 4H), 2.52-2.14 (m, 5H), 2.11-1.98 (m, 1H), 1.94-1.58 (m, 4H), 1.52-1.48 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 473. Mixture of atropisomers.
465	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.26 (dd, J = 2.0 Hz, 5.2 Hz, 1H), 7.40 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.33-7.27 (m, 1H), 6.87 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 6.81-6.75 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.88-3.71 (m, 7H), 3.20-3.07 (m, 4H), 2.50-2.22 (m, 5H), 2.09-2.01 (m, 1H), 1.94-1.72 (m, 3H), 1.69-1.64 (m, 1H), 1.54-1.44 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 469. Mixture of atropisomers.
466	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.22 (d, J = 3.6 Hz, 1H), 7.32-7.27 (m, 1H), 6.92-6.85 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.72 (m, 7H), 3.32-3.01 (m, 4H), 2.65-2.28 (m, 5H), 2.16 (s, 3H), 2.14 (s, 3H), 2.12-2.07 (m, 1H), 2.01-1.77 (m, 4H), 1.62-1.52 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 453.
467	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.36-8.27 (m, 1H), 7.46-7.39 (m, 2H), 7.38-7.33 (m, 1H), 7.30-7.27 (m, 1H), 7.01-6.93 (m, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.98-3.81 (m, 2H), 3.77-3.71 (m, 2H), 3.55-3.25 (m, 4H), 3.02-2.25 (m, 5H), 2.21-1.78 (m, 6H), 1.22 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 489.
468	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.13 (br s, 1H), 7.64-7.57 (m, 1H), 6.94 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.96-3.85 (m, 2H), 3.83-3.75 (m, 2H), 3.72-3.63 (m, 1H), 3.20 (br, 4H), 2.69 (br, 5H), 2.45-2.32 (m, 2H), 2.20-1.80 (m, 9H), 1.62-1.49 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 399.
469	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.16 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.30 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.81 (dd, J = 5.2 Hz, 7.6 Hz, 1H), 5.99-5.94 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.83 (m, 2H), 3.81-3.76 (m, 2H), 3.48-3.15 (m, 6H), 2.85-2.79 (m, 2H), 2.74-2.38 (m, 7H), 2.20-2.11 (m, 1H), 2.01-1.70 (m, 4H), 1.53-1.43 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 443.
470	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.13 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 6.78 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 5.81 (s, 1H), 4.21-4.06 (m, 4H), 3.92-3.82 (m, 2H), 3.81-3.75 (m, 2H), 3.34 (br s, 4H), 2.71-2.38 (m, 9H), 2.29 (s, 1H), 2.19-2.08 (m, 2H), 1.95-1.73 (m, 5H), 1.62-1.49 (m, 1H), 1.31-1.21 (m, 6H). LCMS m/z [M+H] ⁺ 497.
471	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.22 (d, J = 4.8 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.31-7.27 (m, 1H), 6.90-6.78 (m, 1H), 6.62 (d, J = 8.2 Hz, 2H), 4.08 (q, J = 2.4 Hz, 2H), 3.90-3.78 (m, 2H), 3.77-3.71 (m, 8H), 3.26-2.98 (m, 4H), 2.52-2.15 (m, 5H), 2.12-2.07 (m, 1H), 1.95-1.63 (m, 4H), 1.51-1.40 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 481.
472	Example 4	¹ H NMR (CDCl ₃ , 400 MHz) δ _H = 8.83 (d, J = 1.6 Hz, 1H), 8.57 (d, J = 3.2 Hz, 1H), 8.27 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.96-7.89 (m, 1H), 7.45 (dd, J = 2.0

		Hz, 7.6 Hz, 1H), 7.55 (dd, $J = 4.0$ Hz, 8.0 Hz, 1H), 6.95 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.89-3.71 (m, 4H), 3.10 (t, $J = 4.8$ Hz, 4H), 2.57-2.45 (m, 1H), 2.39 (br, 4H), 2.11-2.01 (m, 1H), 1.96-1.78 (m, 3H), 1.71-1.60 (m, 1H), 1.56-1.42 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 422.
473	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.28$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.43 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.87 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 6.04 (s, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.89-3.80 (m, 2H), 3.79-3.73 (m, 2H), 3.67 (s, 3H), 3.28-3.07 (m, 4H), 2.64-2.34 (m, 5H), 2.29 (s, 3H), 2.14-2.05 (m, 1H), 1.98-1.70 (m, 4H), 1.56-1.47 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
474	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.27$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.48 (dd, $J = 1.2$ Hz, 7.2 Hz, 1H), 6.98 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.94-3.83 (m, 2H), 3.83-3.77 (m, 2H), 3.14 (br t, $J = 4.8$ Hz, 4H), 3.03-2.96 (m, 2H), 2.78-2.72 (m, 2H), 2.64 (br, 5H), 2.15 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 2.00-1.89 (m, 2H), 1.89-1.83 (m, 1H), 1.82-1.77 (m, 1H), 1.65-1.54 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 398.
475	Example 4	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.63$ (s, 1H), 7.74 (dd, $J = 2.0$ Hz, 8.0 Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 6.50 (d, $J = 5.2$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.95-3.66 (m, 4H), 3.38-2.91 (m, 4H), 2.75-2.20 (m, 8H), 2.15-2.00 (m, 1H), 1.97-1.77 (m, 3H), 1.71-1.64 (m, 1H), 1.53-1.41 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 454.
476	Example 5	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.70$ -8.65 (m, 1H), 8.22-8.19 (m, 1H), 8.11-8.04 (m, 1H), 7.95-7.89 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.97-3.82 (m, 2H), 3.77 (s, 2H), 3.52-3.14 (m, 4H), 2.92-2.42 (m, 5H), 2.20-2.11 (m, 1H), 2.06-1.80 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 459.
477	Example 5	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.12$ -8.97 (m, 1H), 8.31 (s, 1H), 8.21 (d, $J = 2.8$ Hz, 1H), 7.91 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90-3.76 (m, 4H), 3.20-3.09 (m, 4H), 2.63-2.45 (m, 5H), 2.11 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 1.98-1.80 (m, 3H), 1.77-1.69 (m, 1H), 1.58-1.49 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 475.
478	Example 5	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.78$ -8.64 (m, 1H), 8.33-8.23 (m, 1H), 8.04-7.79 (m, 3H), 7.11-6.84 (m, 1H), 5.89 (t, $J = 7.2$ Hz, 1H), 4.96-4.83 (m, 1H), 4.77-4.64 (m, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.90-3.69 (m, 4H), 3.31-2.95 (m, 5H), 2.82-2.68 (m, 1H), 2.63-2.20 (m, 5H), 2.14-2.02 (m, 1H), 1.97-1.73 (m, 3H), 1.71-1.61 (m, 1H), 1.53-1.46 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 478.
479	Example 5	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.31$ (s, 1H), 8.66-8.63 (m, 1H), 8.47 (t, $J = 2.0$ Hz, 1H), 8.39-8.36 (m, 1H), 7.91 (dd, $J = 1.6$ Hz, 7.2 Hz, 1H), 7.06 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.09 (qd, $J = 7.2$ Hz, 3.6 Hz, 2H), 3.89-3.72 (m, 4H), 3.57-3.51 (m, 1H), 3.10 (t, $J = 4.8$ Hz, 2H), 2.53-2.41 (m, 3H), 2.40-2.22 (m, 2H), 2.11-1.94 (m, 1H), 1.90-1.72 (m, 3H), 1.69-1.60 (m, 1H), 1.53-1.39 (m, 1H), 1.26-1.21 (m, 3H), 1.05 (t, $J = 6.4$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
480	Example 6	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.25$ (d, $J = 1.6$ Hz, 1H), 8.65 (dd, $J = 1.6$ Hz, 2.4 Hz, 1H), 8.47 (d, $J = 2.8$ Hz, 1H), 8.33 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.87 (dd, $J = 2.0$ Hz, 3.6 Hz, 1H), 7.57 (d, $J = 2.8$ Hz, 1H), 7.33 (d, $J = 2.8$ Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.07-3.95 (m, 4H), 3.89 (s, 3H), 3.17 (t, $J = 4.0$ Hz, 4H), 2.61-2.48 (m, 5H), 2.16 (dd, $J = 4.0$ Hz, 12.0 Hz, 1H), 2.03-1.83 (m, 3H), 1.72 (dd, $J = 9.6$ Hz, 12.4 Hz, 1H), 1.54-1.51 (m, 1H). LCMS m/z $[M+H]^+$ 459.
481	Example 6	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.24$ (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H), 8.33-8.32 (m, 1H), 7.87 (dd, $J = 2.0$ Hz, 3.6 Hz, 1H), 7.03-6.99 (m, 1H), 4.06-3.99 (m, 5H), 3.98-3.92 (m, 2H), 3.17 (br, 4H), 2.65-2.34 (m, 5H), 2.15 (br, 1H), 2.06-1.80 (m, 3H), 1.71 (br, 1H), 1.52-1.43 (m, 1H). LCMS m/z $[M+H]^+$ 465.

482	Example 7	LCMS m/z [M+H]⁺ 477.
483	Example 7	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.24 (s, 1H), 8.71-8.65 (m, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.87 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 7.00 (dd, J = 5.2 Hz, 10.4 Hz, 1H), 4.04-4.00 (m, 1H), 3.83-3.74 (m, 4H), 3.15 (s, 4H), 2.53-2.45 (m, 5H), 2.06 (dd, J = 6.4 Hz, 12.0 Hz, 1H), 1.92-1.78 (m, 3H), 1.69-1.63 (m, 1H), 1.51 (br, 1H), 0.70-0.62 (m, 4H). LCMS m/z [M+H]⁺ 435.
484	Example 8	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.23 (d, J = 1.6 Hz, 1H), 8.65-8.64 (m, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.88-7.86 (m, 1H), 7.01 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.61 (d, J = 2.4 Hz, 2H), 3.90-3.77 (m, 4H), 3.20-3.09 (m, 4H), 2.61-2.39 (m, 5H), 2.11-2.03 (m, 1H), 1.95-1.79 (m, 3H), 1.65 (s, 1H), 1.57-1.44 (m, 1H), 1.33-1.23 (m, 1H), 0.79-0.68 (m, 4H). LCMS m/z [M+H]⁺ 473.
485	Example 9	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.37 (s, 1H), 8.69-8.63 (m, 1H), 8.51 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 3.2 Hz, 1H), 7.73 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 4.06-3.97 (m, 1H), 3.89-3.70 (m, 4H), 3.25-2.97 (m, 4H), 2.68-2.29 (m, 5H), 2.14-1.98 (m, 1H), 1.96-1.64 (m, 4H), 1.55-1.43 (m, 1H), 0.69-0.62 (m, 4H). LCMS m/z [M+H]⁺ 453.
486	Example 12	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.24 (br s, 1H), 8.66 (s, 1H), 8.48 (br s, 1H), 8.33 (dd, J = 1.6, 4.8 Hz, 1H), 7.88 (br d, J = 7.2 Hz, 1H), 7.03 (br s, 1H), 4.39-4.15 (m, 2H), 3.99-3.84 (m, 2H), 3.16 (br s, 4H), 2.65-2.38 (m, 5H), 2.14 (br s, 1H), 2.02-1.81 (m, 3H), 1.73 (br s, 1H), 1.54-1.43 (m, 1H), 1.37-1.30 (m, 2H), 1.23-1.14 (m, 2H). LCMS m/z [M+H]⁺ 437.
487	Example 14	¹H NMR (CDCl₃ 400 MHz) δ_H = 8.19 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.93 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 5.87 (d, J = 2.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 3.90-3.74 (m, 4H), 3.08-3.01 (m, 4H), 2.57-2.44 (m, 5H), 2.10 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.97-1.78 (m, 3H), 1.74-1.66 (m, 1H), 1.54-1.50 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H]⁺ 441.
488	Example 16	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.19 (s, 1H), 8.70-8.25 (m, 2H), 7.13 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 5.10-4.80 (m, 1H), 4.22 (d, J = 8.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.81 (d, J = 9.2 Hz, 1H), 3.77-3.66 (m, 2H), 3.27-3.18 (m, 4H), 2.81-2.65 (m, 4H), 2.55-2.41 (m, 1H), 2.25-2.12 (m, 1H), 2.04-1.83 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H]⁺ 447.
489	Example 16	¹H NMR (CDCl₃ 400 MHz) δ_H = 8.54 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.35 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.20 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.95-3.85 (m, 2H), 3.85-3.77 (m, 2H), 3.45-3.30 (m, 7H), 2.75-2.60 (m, 5H), 2.13 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 2.03-1.83 (m, 3H), 1.82-1.72 (m, 1H), 1.66-1.62 (m, 1H), 1.24 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H]⁺ 423.
490	Example 16	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.27 (d, J = 1.2 Hz, 1H), 8.65-8.62 (m, 1H), 8.47 (d, J = 2.8 Hz, 1H), 8.32 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.86 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.02 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.86-3.72 (m, 4H), 3.57-3.43 (m, 1H), 3.14-2.85 (m, 6H), 2.16 (dd, J = 6.4, 12.4 Hz, 1H), 1.95-1.85 (m, 2H), 1.80-1.73 (m, 1H), 1.56 (t, J = 11.2 Hz, 1H), 1.44-1.32 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 0.69 (br s, 2H), 0.44-0.36 (m, 2H). LCMS m/z [M+H]⁺ 449.
491	Example 16	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.19 (s, 1H), 8.32-8.26 (m, 1H), 7.75 (d, J = 7.6 Hz, 1H), 6.84-6.76 (m, 1H), 4.49 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.91-3.68 (m, 4H), 3.44 (s, 1H), 3.08-2.68 (m, 5H), 2.01-1.86 (m, 2H), 1.86-1.72 (m, 4H), 1.69-1.64 (m, 1H), 1.51-1.35 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H]⁺ 441.
492	Example 16	¹H NMR (CDCl₃ 400 MHz) δ_H = 9.20 (d, J = 1.6 Hz, 1H), 8.46-8.36 (m, 2H), 7.12 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.10 (dq, J = 4.4 Hz, 7.2 Hz, 2H), 3.93-3.74 (m, 4H), 3.32-3.15 (m, 2H), 3.15-2.91 (m, 4H), 2.84-2.69 (m, 1H), 2.61-2.47

		(m, 1H), 2.10-1.70 (m, 5H), 1.62-1.54 (m, 1H), 1.23 (dt, $J = 4.0$ Hz, 7.2 Hz, 3H), 1.11 (d, $J = 5.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443.
493	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.14$ (s, 1H), 8.67-8.64 (m, 1H), 8.48 (d, $J = 2.8$ Hz, 1H), 8.33 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.72 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.00 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.13-4.05 (m, 2H), 3.88-3.72 (m, 4H), 3.23-2.98 (m, 5H), 2.85 (s, 1H), 2.58 (s, 1H), 2.40 (s, 1H), 1.94-1.75 (m, 3H), 1.74-1.65 (m, 3H), 1.26-1.21 (m, 3H), 0.98 (d, $J = 4.0$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
494	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.31$ (s, 1H), 8.65-8.62 (m, 1H), 8.48-8.45 (m, 1H), 8.39-8.36 (m, 1H), 7.91 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.05 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.13-4.06 (m, 2H), 3.89-3.72 (m, 4H), 3.55 (s, 1H), 3.14-3.06 (m, 2H), 2.54-2.22 (m, 5H), 2.13-1.95 (m, 1H), 1.94-1.69 (m, 4H), 1.67-1.61 (m, 1H), 1.26-1.21 (m, 3H), 1.06 (d, $J = 6.4$ Hz, 3H). LCMS m/z $[M+H]^+$ 437.
495	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.14$ (s, 1H), 8.67-8.64 (m, 1H), 8.48 (d, $J = 2.8$ Hz, 1H), 8.33 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 8.82 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.01 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.09 (qd, $J = 3.6$ Hz, 7.2 Hz, 2H), 3.89-3.72 (m, 4H), 3.24-2.97 (m, 5H), 2.89-2.77 (m, 1H), 2.64-2.53 (m, 1H), 2.44-2.35 (m, 1H), 2.11-1.85 (m, 2H), 1.84-1.74 (m, 2H), 1.73-1.62 (m, 2H), 1.23 (td, $J = 3.6$ Hz, 6.8 Hz, 3H), 1.09-0.89 (m, 3H). LCMS m/z $[M+H]^+$ 437.
496	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.22$ (s, 1H), 8.43-8.34 (m, 1H), 8.32-8.22 (m, 1H), 7.07 (ddd, $J = 2.4$ Hz, 4.8 Hz, 7.6 Hz, 1H), 4.10 (dq, $J = 2.8$ Hz, 7.2 Hz, 2H), 3.94-3.55 (m, 8H), 3.43-3.26 (m, 2H), 3.19-2.99 (m, 2H), 2.95-2.78 (m, 2H), 2.58 (br d, $J = 11.2$ Hz, 1H), 2.15-2.05 (m, 1H), 2.00-1.82 (m, 3H), 1.80-1.68 (m, 1H), 1.55-1.45 (m, 1H), 1.24 (dt, $J = 2.4$ Hz, 7.2 Hz, 3H). LCMS m/z $[M+H]^+$ 459.
497	Example 16	LCMS m/z $[M+H]^+$ 435.
498	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 8.81$ -8.70 (m, 1H), 8.65-8.57 (m, 1H), 8.52-8.45 (m, 1H), 3.35-8.24 (m, 1H), 7.65-7.53 (m, 1H), 6.83 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 4.07 (t, $J = 7.2$ Hz, 2H), 3.87-3.74 (m, 4H), 3.53-3.43 (m, 4H), 3.28-3.19 (m, 2H), 3.06-2.96 (m, 1H), 2.41-2.33 (m, 1H), 2.01-1.90 (m, 1H), 1.80-1.71 (m, 2H), 1.67-1.56 (m, 2H), 1.48 (d, $J = 8.4$ Hz, 1H), 1.44-1.34 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 435.
499	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.21$ (s, 1H), 8.52-8.44 (m, 2H), 7.21-7.15 (m, 1H), 4.20-4.12 (m, 3H), 4.10-4.00 (m, 3H), 3.95-3.90 (m, 1H), 3.83-3.72 (m, 1H), 3.25-3.15 (m, 4H), 3.10-3.02 (m, 1H), 2.72-2.65 (m, 2H), 2.63-2.55 (m, 2H), 2.40-2.30 (m, 1H), 2.17-2.10 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 431.
500	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.23$ (s, 1H), 8.65 (s, 1H), 8.52-8.45 (m, 1H), 8.37-8.27 (m, 1H), 7.91-7.81 (m, 1H), 7.07-6.97 (m, 1H), 4.14-4.04 (m, 3H), 4.02-3.92 (m, 3H), 3.89-3.84 (m, 1H), 3.71-3.65 (m, 1H), 3.19-3.10 (m, 4H), 2.99-2.89 (m, 1H), 2.54-2.43 (m, 2H), 2.42-2.33 (m, 2H), 2.32-2.24 (m, 1H), 2.07-1.97 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 425.
501	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 9.20$ -9.02 (m, 1H), 8.53 (s, 1H), 8.31 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.85 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 7.01 (dd, $J = 5.2$ Hz, 7.2 Hz, 1H), 4.15-4.04 (m, 3H), 4.02-3.92 (m, 3H), 3.87 (d, $J = 8.8$ Hz, 1H), 3.69 (t, $J = 8.0$ Hz, 1H), 3.25-3.06 (m, 4H), 3.02-2.87 (m, 1H), 2.61 (s, 3H), 2.55-2.43 (m, 2H), 2.43-2.33 (m, 2H), 2.29 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 2.04 (dd, $J = 8.4$ Hz, 12.4 Hz, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
502	Example 16	^1H NMR (CDCl_3 400 MHz) $\delta_{\text{H}} = 8.63$ -8.43 (m, 1H), 8.40-8.16 (m, 1H), 7.68-7.41 (m, 2H), 7.20 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 6.94 (dd, $J = 4.8$ Hz, 7.3 Hz, 1H), 4.15-4.02 (m, 3H), 4.01-3.79 (m, 4H), 3.71-3.52 (m, 1H), 3.08 (s, 4H), 2.92-2.71 (m, 1H), 2.41-2.09 (m, 8H), 1.99 (s, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 438.

503	Example 16	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.59-9.48 (m, 1H), 9.32-9.14 (m, 1H), 8.34 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.68 (dd, J = 2.4 Hz, 5.2 Hz, 1H), 7.53 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.03 (dd, J = 5.2 Hz, 7.6 Hz, 1H), 4.15-4.02 (m, 3H), 4.02-3.91 (m, 3H), 3.90-3.84 (m, 1H), 3.71-3.63 (m, 1H), 3.25-3.03 (m, 4H), 3.01-2.86 (m, 1H), 2.52-2.40 (m, 2H), 2.38-2.23 (m, 3H), 2.08-1.96 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 447.
504	Example 16	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.84-8.68 (m, 2H), 8.34-8.23 (m, 1H), 7.62-7.48 (m, 1H), 7.06-6.92 (m, 1H), 4.16-4.06 (m, 3H), 4.05-3.95 (m, 3H), 3.93-3.85 (m, 1H), 3.77-3.68 (m, 1H), 3.22-3.07 (m, 4H), 3.03-2.92 (m, 1H), 2.63-2.51 (m, 2H), 2.50-2.40 (m, 2H), 2.38-2.26 (m, 2H), 2.14-2.01 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 436.
505	Example 16	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.27 - 9.04 (m, 1H), 8.45-8.25 (m, 1H), 8.16-8.05 (m, 1H), 8.04-7.97 (m, 1H), 7.49 (dd, J = 4.8 Hz, 8.4 Hz, 1H), 7.05 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.17-4.03 (m, 3H), 4.02-3.91 (m, 3H), 3.89-3.84 (m, 1H), 3.68 (t, J = 8.0 Hz, 1H), 3.21-3.03 (m, 4H), 3.00-2.76 (m, 1H), 2.50-2.37 (m, 2H), 2.37-2.21 (m, 3H), 2.06-1.95 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 425.
506	Example 16	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 10.97 (s, 1H), 8.37-8.25 (m, 1H), 7.85 (d, J = 9.6 Hz, 1H), 7.78-7.68 (m, 1H), 7.09-6.88 (m, 2H), 4.18-4.05 (m, 3H), 4.04-3.93 (m, 3H), 3.92-3.86 (m, 1H), 3.76-3.64 (m, 1H), 3.30-3.08 (m, 4H), 3.01-2.85 (m, 1H), 2.58-2.45 (m, 2H), 2.45-2.36 (m, 2H), 2.31 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 2.14-1.90 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 441.
507	Example 16	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.29 (d, J = 1.2 Hz, 1H), 8.73 (d, J = 5.2 Hz, 1H), 8.32 (dd, J = 1.6, 4.8 Hz, 1H), 8.00-7.96 (m, 2H), 7.03-6.98 (m, 1H), 4.14-4.07 (m, 3H), 4.02-3.94 (m, 3H), 3.88 (d, J = 8.8 Hz, 1H), 3.70 (t, J = 7.6 Hz, 1H), 3.19 (t, J = 4.8 Hz, 4H), 3.00-2.87 (m, 1H), 2.53-2.45 (m, 2H), 2.42-2.34 (m, 2H), 2.34-2.25 (m, 1H), 2.10-2.00 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 425.
508	Example 17	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.16 (s, 1H), 8.25 (d, J = 9.2 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.99-3.68 (m, 4H), 3.09 (br s, 4H), 2.65 (br s, 5H), 2.50 (d, J = 2.8 Hz, 3H), 2.13 (s, 1H), 2.05-1.67 (m, 4H), 1.65-1.58 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 461.
509	Example 17	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.19 (s, 1H), 8.63 (m, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.77 (dd, J = 1.6 Hz, 7.2 Hz, 1H), 6.92 (dd, J = 5.2 Hz, 7.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.96-3.88 (m, 2H), 3.86-3.70 (m, 4H), 2.63-2.43 (m, 3H), 2.27-2.16 (m, 2H), 2.01-1.72 (m, 7H), 1.70-1.56 (m, 2H), 1.47-1.36 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 449.
510	Example 17	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.92 (d, J = 1.2 Hz, 1H), 8.75-8.70 (m, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.78 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.07 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.94-3.73 (m, 4H), 3.29-3.24 (m, 2H), 3.17-3.02 (m, 4H), 2.93-2.82 (m, 1H), 2.16-2.06 (m, 1H), 1.99-1.80 (m, 5H), 1.71-1.60 (m, 3H), 1.53-1.43 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 449.
511	Example 17	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.21 (s, 1H), 8.31 (d, J = 2.8 Hz, 1H), 8.07-7.96 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.94-3.82 (m, 2H), 3.78 (s, 2H), 3.41-3.18 (m, 4H), 2.98-2.77 (m, 3H), 2.09-1.97 (m, 2H), 1.95-1.80 (m, 6H), 1.76-1.66 (m, 1H), 1.55-1.44 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 473.
512	Example 17	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.03 (s, 1H), 8.51-8.46 (m, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.15 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.70 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 6.86 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.01 (d, J = 8.4 Hz, 2H), 3.91 (q, J = 7.2 Hz, 2H), 3.69-3.61 (m, 2H), 3.47 (d, J = 8.4 Hz, 1H), 3.04 (s, 4H), 2.81-

		2.66 (m, 1H), 2.34 (d, $J = 1.6$ Hz, 4H), 2.09-1.88 (m, 2H), 1.79-1.66 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
513	Example 17	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.23$ (s, 1H), 8.70-8.63 (m, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 8.34 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.88 (dd, $J = 1.6$ Hz, 7.4 Hz, 1H), 7.03 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 5.08-4.83 (m, 1H), 4.20 (d, $J = 8.8$ Hz, 1H), 4.15-4.06 (m, 2H), 3.83-3.73 (m, 3H), 3.17 (br s, 4H), 2.98-2.88 (m, 1H), 2.46 (br d, $J = 1.6$ Hz, 4H), 2.27-2.11 (m, 2H), 1.90 (br dd, $J = 1.6$ Hz, 3.6 Hz, 1H), 1.82-1.73 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
514	Example 17	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.19$ (s, 1H), 8.50-8.41 (m, 2H), 7.15 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.16-4.06 (m, 3H), 4.05-3.95 (m, 3H), 3.92-3.87 (m, 1H), 3.77-3.71 (m, 1H), 3.22-3.10 (m, 4H), 3.07-2.98 (m, 1H), 2.70-2.59 (m, 2H), 2.58-2.48 (m, 2H), 2.38-2.29 (m, 1H), 2.13-2.04 (m, 1H), 1.23 (t, $J = 7.6$ Hz, 3H). LCMS m/z $[M+H]^+$ 431.
515	Example 17	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.24$ (d, $J = 1.6$ Hz, 1H), 8.66 (dd, $J = 1.6$, 2.4 Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H), 8.33 (dd, $J = 2.0$, 4.8 Hz, 1H), 7.88 (dd, $J = 2.0$, 7.6 Hz, 1H), 7.13-6.96 (m, 1H), 4.20-3.86 (m, 6H), 3.20-3.08 (m, 4H), 2.99-2.81 (m, 3H), 2.61-2.45 (m, 5H), 2.09-1.97 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
516	Example 17	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.22$ (s, 1H), 8.40-8.25 (m, 2H), 4.29-3.88 (m, 7H), 3.23-2.94 (m, 7H), 2.85-2.70 (m, 3H), 2.62-2.48 (m, 1H), 2.25-2.02 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 465. Peak 1.
517	Example 17	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 8.63$ -8.58 (m, 1H), 7.49 (s, 1H), 7.36 (dd, $J = 2.4$ Hz, 8.0 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.91-3.80 (m, 2H), 3.78-3.72 (m, 2H), 3.18-2.95 (br s, 2H), 2.67-2.51 (m, 2H), 2.48 (s, 3H), 2.12-2.00 (m, 3H), 1.99-1.85 (m, 4H), 1.81-1.65 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443. Peak 1.
518	Example 18	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.24$ (d, $J = 1.6$ Hz, 1H), 8.66 (dd, $J = 1.6$, 2.4 Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H), 8.33 (dd, $J = 1.6$, 4.8 Hz, 1H), 7.88 (dd, $J = 2.0$, 7.6 Hz, 1H), 7.13-6.96 (m, 1H), 4.15-3.95 (m, 6H), 3.19-3.13 (m, 4H), 2.99-2.83 (m, 3H), 2.61-2.44 (m, 5H), 2.09-1.97 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
519	Example 18	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.19$ (s, 1H), 8.49-8.39 (m, 2H), 7.15 (dd, $J = 5.2$ Hz, 7.6 Hz, 1H), 4.14-4.06 (m, 3H), 4.05-3.96 (m, 3H), 3.94-3.87 (m, 1H), 3.79-3.70 (m, 1H), 3.22-3.11 (m, 4H), 3.09-2.96 (m, 1H), 2.72-2.59 (m, 2H), 2.58-2.48 (m, 2H), 2.39-2.29 (m, 1H), 2.14-2.03 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 431.
520	Example 18	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.23$ (s, 1H), 8.69-8.62 (m, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 8.34 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.88 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.03 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 5.06-4.84 (m, 1H), 4.20 (d, $J = 8.8$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.85-3.74 (m, 3H), 3.17 (br s, 4H), 2.99-2.87 (m, 1H), 2.45 (br s, 4H), 2.27-2.12 (m, 2H), 1.96-1.83 (m, 1H), 1.82-1.69 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
521	Example 18	^1H NMR (Methanol-<i>d</i>₄ 400 MHz) $\delta_{\text{H}} = 9.12$ (d, $J = 1.6$ Hz, 1H), 8.65 (dd, $J = 1.6$ Hz, 2.4 Hz, 1H), 8.46 (d, $J = 2.4$ Hz, 1H), 8.24 (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.86 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 7.05 (dd, $J = 5.2$ Hz, 7.6 Hz, 1H), 4.10 (d, $J = 8.4$ Hz, 1H), 4.00 (q, $J = 7.2$ Hz, 2H), 3.89 (t, $J = 6.0$ Hz, 1H), 3.73-3.59 (m, 3H), 3.05 (t, $J = 4.8$ Hz, 4H), 2.53 (q, $J = 8.4$ Hz, 1H), 2.42 (d, $J = 4.4$ Hz, 4H), 2.18-2.10 (m, 1H), 2.05-1.97 (m, 1H), 1.91-1.82 (m, 1H), 1.45-1.34 (m, 1H), 1.16 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 439.
522	Example 18	^1H NMR (CDCl₃ 400 MHz) $\delta_{\text{H}} = 9.25$ (s, 1H), 8.31 (d, $J = 2.4$ Hz, 1H), 8.02 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.75 (m, 4H), 3.40-3.16 (m, 4H), 2.99-2.79 (m, 3H), 2.08-1.95 (m, 2H), 1.95-1.77 (m, 6H), 1.75-1.66 (m, 1H), 1.56-1.48 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 473.

523	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.92 (d, J = 1.6 Hz, 1H), 8.75-8.67 (m, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.78 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.07 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.92-3.72 (m, 4H), 3.30-3.24 (m, 2H), 3.19-3.03 (m, 4H), 2.96-2.82 (m, 1H), 2.17-2.06 (m, 1H), 1.99-1.80 (m, 5H), 1.71-1.59 (m, 3H), 1.53-1.43 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 449.
524	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.19 (s, 1H), 8.63 (m, 1H), 8.44 (d, J = 2.8 Hz, 1H), 8.24 (dd, J = 1.2 Hz, 4.8 Hz, 1H), 7.77 (dd, J = 1.2 Hz, 7.2 Hz, 1H), 6.92 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.99-3.87 (m, 2H), 3.86-3.62 (m, 4H), 2.71-2.43 (m, 3H), 2.28-2.14 (m, 2H), 2.00-1.72 (m, 7H), 1.71-1.57 (m, 2H), 1.48-1.34 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 449.
525	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.41-8.90 (m, 1H), 8.25 (d, J = 9.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.97-3.77 (m, 4H), 3.10 (br s, 4H), 2.91-2.54 (m, 5H), 2.50 (d, J = 2.8 Hz, 3H), 2.14 (s, 1H), 2.05-1.69 (m, 4H), 1.66-1.60 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 461.
526	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.20 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.76 (m, 4H), 3.29-3.09 (m, 4H), 2.71-2.45 (m, 5H), 2.16-2.05 (m, 1H), 1.98-1.77 (m, 4H), 1.75-1.67 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 463.
527	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.22 (s, 1H), 8.41-8.29 (m, 2H), 4.38-3.66 (m, 7H), 3.26-2.87 (m, 6H), 2.85-2.65 (m, 4H), 2.64-2.49 (m, 1H), 2.13 (s, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 465. Peak 2.
528	Example 18	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.66-8.55 (m, 1H), 7.49 (s, 1H), 7.36 (dd, J = 2.4 Hz, 8.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.92-3.80 (m, 2H), 3.78-3.72 (m, 2H), 3.18-2.95 (m, 2H), 2.65-2.50 (m, 2H), 2.48 (s, 3H), 2.13-1.98 (m, 3H), 1.97-1.83 (m, 4H), 1.71-1.58 (m, 5H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 443. Peak 2.
529	Example 19	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.57-8.52 (m, 1H), 8.33 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.65 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 7.53-7.43 (m, 1H), 7.37-7.31 (m, 1H), 6.94 (dd, J = 4.8 Hz, 7.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.91-3.71 (m, 4H), 3.26-3.06 (m, 4H), 2.58-2.17 (m, 5H), 2.15-2.02 (m, 1H), 1.97-1.77 (m, 3H), 1.69-1.65 (m, 2H), 1.34-1.19 (m, 3H). LCMS m/z [M+H] ⁺ 440.
530	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.80 (s, 1H), 8.62 (br s, 2H), 8.55 (br s, 1H), 8.01 (br d, J = 7.2 Hz, 1H), 7.49-7.35 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.96 (br s, 2H), 3.91-3.82 (m, 2H), 3.79 (s, 2H), 3.10-2.96 (m, 2H), 2.83 (br s, 2H), 2.63 (br d, J = 7.8 Hz, 1H), 2.06 (br dd, J = 6.8 Hz, 12.0 Hz, 1H), 1.94 (br d, J = 12.0 Hz, 1H), 1.85 (br d, J = 4.8 Hz, 2H), 1.78-1.75 (m, 1H), 1.54 (br d, J = 5.6 Hz, 1H), 1.24 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 437.
531	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.06 (d, J = 1.6 Hz, 1H), 8.68 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.88 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.07 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.89 (br s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.91-3.86 (m, 1H), 3.84 (d, J = 8.0 Hz, 2H), 3.80-3.75 (m, 3H), 3.50 (br d, J = 3.2 Hz, 2H), 3.22 (t, J = 5.2 Hz, 2H), 2.10 (dd, J = 8.0 Hz, 13.2 Hz, 1H), 1.95-1.83 (m, 3H), 1.79-1.71 (m, 1H), 1.65-1.60 (m, 1H), 1.26-1.21 (m, 3H). LCMS [M+H] ⁺ 437.
532	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.05 (br s, 1H), 8.67 (br s, 1H), 8.51 (br s, 1H), 8.35-8.31 (m, 1H), 7.90-7.86 (m, 1H), 7.09-7.03 (m, 1H), 4.88 (br s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.85 (m, 1H), 3.84-3.80 (m, 2H), 3.79-3.74 (m, 3H), 3.52-3.46 (m, 2H), 3.21 (t, J = 4.8 Hz, 2H), 2.12-2.06 (m, 1H), 1.94-1.84 (m, 3H), 1.79-1.71 (m, 1H), 1.60-1.55 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS [M+H] ⁺ 437. Peak 1.

533	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.05 (br s, 1H), 8.67 (br s, 1H), 8.51 (br s, 1H), 8.35-8.29 (m, 1H), 7.90-7.85 (m, 1H), 7.09-7.03 (m, 1H), 4.88 (br s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.85 (m, 1H), 3.84-3.80 (m, 2H), 3.79-3.74 (m, 3H), 3.54-3.46 (m, 2H), 3.25-3.18 (m, 2H), 2.13-2.06 (m, 1H), 1.94-1.84 (m, 3H), 1.79-1.71 (m, 1H), 1.60-1.55 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS [M+H] ⁺ 437. Peak 2.
534	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.80 (s, 1H), 8.67-8.58 (m, 2H), 8.55 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.42 (dd, J = 4.8 Hz, 8.0 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 4.01 (s, 2H), 3.87 (dd, J = 8.4 Hz, 20.4 Hz, 2H), 3.79 (s, 2H), 3.19-2.98 (m, 2H), 2.89 (s, 2H), 2.72 (s, 1H), 2.15-2.03 (m, 1H), 2.01-1.93 (m, 1H), 1.91-1.78 (m, 3H), 1.60 (s, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 437. Peak 2.
535	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.79 (s, 1H), 8.65-8.57 (m, 2H), 8.54 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.41 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.96 (s, 2H), 3.86 (dd, J = 8.4 Hz, 18.0 Hz, 2H), 3.78 (s, 2H), 3.09-2.95 (m, 2H), 2.82 (s, 2H), 2.67-2.57 (m, 1H), 2.05 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.97-1.91 (m, 1H), 1.86-1.79 (m, 2H), 1.77-1.73 (m, 1H), 1.60-1.47 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). LCMS m/z [M+H] ⁺ 437. Peak 1.
536	Example 21	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.20 (s, 1H), 8.47-8.41 (m, 2H), 7.14 (dd, J = 5.2 Hz, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.95-3.88 (m, 2H), 3.87-3.83 (m, 2H), 3.28-3.05 (m, 4H), 2.83-2.59 (m, 4H), 2.11-1.93 (m, 3H), 1.82 (br d, J = 11.6 Hz, 2H), 1.55-1.60 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.05 (br s, 3H). LCMS [M+H] ⁺ 443.
537	Example 22	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.77-8.66 (m, 2H), 8.53 (d, J = 2.4 Hz, 1H), 8.15 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.86-3.77 (m, 2H), 3.73 (s, 2H), 2.92 (t, J = 4.8 Hz, 4H), 2.50-2.38 (m, 1H), 2.24 (s, 4H), 2.08 (d, J = 2.0 Hz, 3H), 2.06-1.97 (m, 1H), 1.92-1.84 (m, 1H), 1.82-1.73 (m, 2H), 1.62-1.58 (m, 1H), 1.50-1.37 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 455.
538	Example 22	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.09 (d, J = 1.2 Hz, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 7.93 (t, J = 8.0 Hz, 1H), 6.71-6.39 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.44-3.11 (m, 8H), 2.71 (s, 1H), 2.32 (s, 4H), 2.01 (s, 2H), 1.86 (q, J = 6.8 Hz, 4H), 1.29-1.17 (m, 3H). LCMS m/z [M+H] ⁺ 441.
539	Example 32	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.18 (br d, J = 3.2 Hz, 1H), 7.79 (br dd, J = 2.8 Hz, 8.4 Hz, 1H), 6.70 (br s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.77 (m, 4H), 3.28 (br s, 4H), 2.70 (br s, 5H), 2.38 (s, 3H), 2.18 (br s, 1H), 2.07-1.99 (m, 2H), 1.96-1.92 (m, 1H), 1.90-1.83 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
540	Example 32	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.26-8.14 (m, 2H), 7.45-7.37 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.93-3.74 (m, 4H), 3.49-3.15 (m, J = 10.0 Hz, 4H), 2.63 (br s, 5H), 2.17 (br s, 2H), 2.07 (s, 3H), 1.97 (br s, 1H), 1.85 (br d, J = 4.4 Hz, 2H), 1.82-1.71 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 444.
541	Example 32	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.25 (d, J = 1.2 Hz, 1H), 8.49 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 8.43 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.20 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.12 (dt, J = 2.0 Hz, 4.8 Hz, 2H), 4.12 (dq, J = 3.2 Hz, 7.2 Hz, 2H), 3.94-3.77 (m, 4H), 3.53-3.21 (m, 4H), 3.11-2.86 (m, 3H), 2.72 (d, J = 10.4 Hz, 1H), 2.28-2.09 (m, 1H), 2.06-1.82 (m, 3H), 1.72 (dt, J = 9.2 Hz, 12.4 Hz, 1H), 1.61-1.44 (m, 1H), 1.26 (dt, J = 2.8 Hz, 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 479.
542	Example 32	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.16 (s, 1H), 8.38 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.32 (d, J = 6.0 Hz, 1H), 7.09 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.97-4.71 (m, 1H), 4.66-4.46 (m, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.86-3.69 (m, 4H), 3.49-3.15 (m, 4H), 3.11-2.49 (m, 4H), 2.22-1.65 (m, 6H), 1.17 (dt, J = 2.4 Hz, 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 461.

543	Example 32	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 9.53 (s, 1H), 8.55-8.37 (m, 2H), 8.28 (d, J = 4.8 Hz, 1H), 5.13-4.95 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.00-3.84 (m, 4H), 3.18 (t, J = 5.2 Hz, 4H), 2.95-2.71 (m, 5H), 2.43-2.12 (m, 3H), 1.75 (dd, J = 10.8 Hz, 12.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 447.
544	Example 33	¹ H NMR (CD ₃ OD 400 MHz) δ _H = 7.87 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.15 (dd, J = 1.6 Hz, 8.0 Hz, 1H), 6.88 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.96-3.76 (m, 4H), 3.74-3.65 (m, 1H), 3.58-3.38 (m, 4H), 2.91-2.77 (m, 2H), 2.75-2.63 (m, 8H), 2.49-2.34 (m, 2H), 2.26-2.18 (m, 1H), 2.02-1.84 (m, 3H), 1.81-1.71 (m, 1H), 1.65-1.51 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 464.
545	Example 33	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.96 (dd, J = 1.6, 4.8 Hz, 1H), 7.09 (dd, J = 1.6, 7.6 Hz, 1H), 6.83 (dd, J = 4.8, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.94-3.76 (m, 4H), 3.56 (s, 8H), 3.03 (s, 4H), 2.69-2.42 (m, 5H), 2.22-2.08 (m, 1H), 2.01-1.69 (m, 4H), 1.64-1.58 (m, 1H), 1.49 (s, 9H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 529.
546	Example 33	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.94 (d, J = 4.4 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.82 (dd, J = 4.8, 7.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.76 (m, 4H), 3.52 (br s, 4H), 3.03 (br s, 8H), 2.59 (br s, 5H), 2.16 (dd, J = 7.2, 12.4 Hz, 1H), 2.01-1.84 (m, 3H), 1.75 (d, J = 10.0 Hz, 1H), 1.59-1.51 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 429.
547	Example 33	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 7.79 (d, J = 3.6 Hz, 1H), 6.84-6.79 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 4.36-4.24 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.96-3.72 (m, 8H), 3.20 (s, 3H), 2.70-2.50 (m, 6H), 2.20-2.07 (m, 3H), 2.02-1.70 (m, 5H), 1.28-1.16 (m, 5H). LCMS m/z [M+H] ⁺ 456.
548	Example 34	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.03 (d, J = 2.8 Hz, 1H), 7.21 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 5.61 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.82 (m, 2H), 3.82-3.76 (m, 2H), 3.32-3.22 (m, 2H), 3.16-3.05 (m, 4H), 3.00-2.92 (m, 2H), 2.55 (s, 5H), 2.51 (t, J = 7.6 Hz, 2H), 2.19-2.09 (m, 1H), 2.03-1.68 (m, 5H), 1.26-1.21 (m, 3H), 1.10 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 462.
549	Example 35	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.19 (d, J = 3.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 6.90-6.83 (m, 1H), 6.20 (s, 1H), 4.46 (d, J = 12.8 Hz, 2H), 4.29 (d, J = 13.6 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.93-3.76 (m, 4H), 3.26 (s, 4H), 2.57 (s, 5H), 2.19-1.58 (m, 6H), 1.51 (s, 9H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 512.
550	Example 35	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.21 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 6.96 (dd, J = 5.2 Hz, 8.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.92-3.77 (m, 5H), 3.65 (s, 2H), 3.41 (s, 1H), 3.27-3.09 (m, 5H), 2.63 (s, 5H), 2.31-2.09 (m, 2H), 2.01-1.71 (m, 5H), 1.59-1.56 (m, 1H), 1.48 (d, J = 6.8 Hz, 9H), 1.24 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 514.
551	Example 35	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.75-8.71 (m, 1H), 8.29-8.21 (m, 1H), 7.89-7.81 (m, 2H), 7.73 (br d, J = 3.2 Hz, 1H), 7.02-6.91 (m, 1H), 6.75 (s, 1H), 4.34-4.28 (m, 2H), 4.23-4.17 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.91-3.71 (m, 4H), 3.40-3.09 (m, 4H), 2.60-2.38 (m, 5H), 2.13-2.01 (m, 1H), 1.96-1.80 (m, 3H), 1.73-1.55 (m, 1H), 1.40-1.35 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 506.
552	Example 35	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.70-8.62 (m, 1H), 8.25 (dd, J = 2.0 Hz, 4.8 Hz, 1H), 7.87-7.80 (m, 2H), 7.73 (dd, J = 2.4 Hz, 8.0 Hz, 1H), 6.97 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 4.71 (dd, J = 2.8 Hz, 10.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.99-3.74 (m, 9H), 3.51 (dd, J = 12.0 Hz, 11.6 Hz, 1H), 3.29 (br s, 4H), 2.75-2.60 (m, 5H), 2.15-1.25 (m, 6H), 1.22 (t, J = 7.2 Hz, 3H). LCMS m/z [M+H] ⁺ 508.
553	Example 35	¹ H NMR (CDCl ₃ 400 MHz) δ _H = 8.29 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 7.61 (dd, J = 2.0 Hz, 7.6 Hz, 1H), 6.92 (dd, J = 4.8 Hz, 7.6 Hz, 1H), 6.69 (s, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.91-3.77 (m, 4H), 3.26 (br s, 4H), 3.08 (m, 2H), 2.62-2.50

		(m, 7H), 2.12 (m, 1H), 1.98-1.58 (m, 5H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 425.
554	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.13$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.54-7.46 (m, 1H), 6.91 (dd, $J = 5.2$ Hz, 7.6 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.97-3.70 (m, 4H), 3.30-3.13 (m, 5H), 2.75-2.51 (m, 5H), 2.18-2.03 (m, 3H), 2.00-1.90 (m, 2H), 1.89-1.81 (m, 3H), 1.80-1.74 (m, 1H), 1.73-1.66 (m, 2H), 1.65-1.57 (m, 1H), 1.55-1.43 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 413.
555	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.13$ -8.09 (m, 1H), 7.31-7.27 (m, 1H), 6.81-6.76 (m, 1H), 5.82-5.78 (m, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.97-3.74 (m, 4H), 3.64-3.15 (m, 4H), 2.98-2.43 (m, 5H), 2.34 (s, 2H), 2.23-2.12 (m, 3H), 2.06-1.90 (m, 2H), 1.85 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 1.75-1.61 (m, 5H), 1.58-1.52 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 425.
556	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.17$ -8.11 (m, 1H), 7.29 (d, $J = 5.6$ Hz, 1H), 6.84-6.75 (m, 1H), 5.72 (s, 1H), 4.10 (q, $J = 7.2$ Hz, 3H), 3.94-3.82 (m, 2H), 3.81-3.76 (m, 2H), 3.34 (s, 4H), 2.77-2.44 (m, 7H), 2.39 (s, 1H), 2.23-2.11 (m, 2H), 2.01-1.89 (m, 3H), 1.85 (dd, $J = 6.0$, 13.6 Hz, 1H), 1.81-1.69 (m, 2H), 1.65-1.57 (m, 2H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 441.
557	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.16$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.31 (dd, $J = 2.0$ Hz, 7.2 Hz, 1H), 6.82 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 5.80 (s, 1H), 4.16-4.01 (m, 4H), 3.93-3.74 (m, 4H), 3.63-3.53 (m, 2H), 3.47-3.20 (m, 4H), 2.70-2.41 (m, 7H), 2.17-2.09 (m, 1H), 1.99-1.79 (m, 3H), 1.78-1.64 (m, 1H), 1.58-1.54 (m, 1H), 1.52-1.47 (m, 9H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 526.
558	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.18$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.43 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.95 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.38-4.17 (m, 2H), 4.10 (q, $J = 6.8$ Hz, 2H), 3.94-3.76 (m, 4H), 3.23-3.03 (m, 4H), 2.97 (t, $J = 12.0$ Hz, 1H), 2.87-2.73 (m, 2H), 2.72-2.51 (m, 5H), 2.15 (dd, $J = 7.6$ Hz, 12.8 Hz, 1H), 1.98-1.82 (m, 3H), 1.81-1.70 (m, 3H), 1.62-1.60 (m, 1H), 1.57-1.52 (m, 2H), 1.50-1.47 (m, 9H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 528.
559	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.15$ (dd, $J = 2.0$ Hz, 4.8 Hz, 1H), 7.32 (dd, $J = 2.0$ Hz, 7.6 Hz, 1H), 6.80 (dd, $J = 4.8$ Hz, 7.2 Hz, 1H), 5.86-5.82 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.92-3.75 (m, 4H), 3.57-3.52 (m, 2H), 3.39-3.28 (m, 4H), 3.06 (t, $J = 5.6$ Hz, 2H), 2.62-2.51 (m, 5H), 2.50-2.44 (m, 2H), 2.14 (dd, $J = 6.8$ Hz, 12.4 Hz, 1H), 2.00-1.75 (m, 5H), 1.63-1.50 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 426.
560	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.16$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.57-7.51 (m, 1H), 6.94 (dd, $J = 4.8$ Hz, 7.6 Hz, 1H), 4.17 (s, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.93-3.83 (m, 2H), 3.82-3.76 (m, 2H), 3.12 (br s, 4H), 2.83 (t, $J = 11.6$ Hz, 1H), 2.63 (s, 5H), 2.15 (dd, $J = 7.2$ Hz, 12.8 Hz, 1H), 1.98-1.76 (m, 8H), 1.68 (d, $J = 13.2$ Hz, 2H), 1.63 (s, 3H), 1.32 (d, $J = 2.8$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443. Peak 1.
561	Example 35	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.16$ (dd, $J = 1.6$ Hz, 4.8 Hz, 1H), 7.43 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H), 6.96-6.87 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.95-3.81 (m, 2H), 3.80 (m, 2H), 3.73 (br s, 1H), 3.12 (br s, 4H), 2.85-2.56 (m, 6H), 2.18-2.08 (m, 3H), 2.01-1.91 (m, 2H), 1.89-1.82 (m, 3H), 1.81-1.74 (m, 1H), 1.58-1.35 (m, 6H), 1.24 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 443. Peak 2.
562	Example 46	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.21$ -9.05 (m, 1H), 8.70 (dd, $J = 1.6$ Hz, 2.4 Hz, 1H), 8.54 (d, $J = 2.4$ Hz, 1H), 7.98-7.75 (m, 1H), 7.38-7.25 (m, 1H), 4.28-4.12 (m, 1H), 3.70-3.32 (m, 7H), 3.30-3.16 (m, 6H), 2.86 (s, 1H), 2.40-2.12 (m, 2H), 2.01-1.68 (m, 3H), 1.65-1.49 (m, 1H). LCMS m/z $[M+H]^+$ 367.
563	Example 48	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.67$ -8.54 (m, 3H), 8.52-8.46 (m, 1H), 7.34 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.95-3.71 (m, 4H), 2.94-2.76 (m, 2H), 2.71-2.35 (m, 3H), 2.28-2.14 (m, 2H), 2.13-1.96 (m, 3H), 1.96-

		1.75 (m, 4H), 1.64-1.41 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458. Peak 1.
564	Example 49	1H NMR (CDCl₃ 400 MHz) $\delta_H = 8.66-8.54$ (m, 3H), 8.52-8.46 (m, 1H), 7.35 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.93-3.70 (m, 4H), 3.05-2.8 (m, 2H), 2.70-2.37 (m, 3H), 2.34-2.14 (m, 2H), 2.13-1.98 (m, 3H), 1.96-1.72 (m, 4H), 1.63-1.49 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458. Peak 2.
565	Example 48	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.31-9.22$ (m, 1H), 9.12 (s, 1H), 8.52 (d, $J = 2.4$ Hz, 1H), 7.38 (dd, $J = 2.4$ Hz, 5.2 Hz, 1H), 7.20 (dd, $J = 2.4$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.94-3.72 (m, 4H), 3.04-2.69 (m, 2H), 2.65-2.35 (m, 3H), 2.11 (d, $J = 13.2$ Hz, 4H), 1.91-1.88 (m, 1H), 1.87-1.75 (m, 3H), 1.75-1.67 (m, 1H), 1.58-1.42 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458. Peak 1.
566	Example 49	1H NMR (CDCl₃ 400 MHz) $\delta_H = 9.24$ (d, $J = 5.2$ Hz, 1H), 9.12 (s, 1H), 8.52 (d, $J = 2.4$ Hz, 1H), 7.38 (dd, $J = 1.6$ Hz, 5.2 Hz, 1H), 7.20 (dd, $J = 2.8$ Hz, 8.4 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.92-3.70 (m, 4H), 2.84 (s, 2H), 2.66-2.33 (m, 3H), 2.30-1.92 (m, 4H), 1.89 (s, 1H), 1.86-1.74 (m, 3H), 1.73-1.67 (m, 1H), 1.58-1.41 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H). LCMS m/z $[M+H]^+$ 458. Peak 2.

Biological Assays

FLIPR Assay

[0251] Fluorescence Imaging Plate Reader (FLIPR) assays were performed using the intracellular calcium sensitive dye, Fluo 8, that exhibits increased fluorescence intensity upon calcium binding. Stimulation of a Gq-coupled G-protein coupled receptors (GPCRs), result in an efflux of calcium from the endoplasmic reticulum to the cytoplasm (Berridge, 1993), thus rendering this assay appropriate for the assessment of M1, M3 and M5 receptors. CHO-K1 cells overexpressing the M1, M3, or M5 muscarinic acetylcholine receptor (mAChR) were dispensed at 15,000 cells per well in 30 μ l volume to 384-well plates and grown overnight at 37 °C in a 5% CO₂ atmosphere. Fluo-8 Solution, 10 μ l per well, was added to each well and incubated for 30 minutes at 37°C in a 5% CO₂ atmosphere. Compounds diluted in Hanks' balanced salt solution (HBSS) were transferred to the cell assay plate at 10 μ l per well, and then read on a FLIPR instrument. **EC₅₀ and E_{max} figures were calculated from the resulting data for each receptor subtype.**

cAMP Assay

[0252] The M2 and M4 mACh receptors are G_i-coupled receptors which, upon activation, produce a decrease in cAMP. Assays were developed that measured the potency and efficacy of compounds at the M2 or M4 mAChR using M2- or M4- overexpressing CHO-K1 cell lines. Time-resolved fluorescence resonance energy transfer (TR-FRET) technology was used, where signal occurs as a result of transfer of energy if the donor molecule is in close proximity to an acceptor molecule when the molecules have bound to the molecule of interest. The cAMP detection is a competition binding assay, where cAMP produced by cells competes for binding with the labeled donor molecule to the anti-cAMP acceptor antibody. Due to the low basal levels of cAMP in the CHO-K1 cell line, forskolin was used to increase cAMP levels to enable assessment of agonist activity at the mAChR of interest.

Table 2

Cmpd	M4 EC ₅₀ (nM)	M4 Emax (%)	M1 EC ₅₀ (nM)	M1 Emax (%)	M2 EC ₅₀ (nM)	M2 Emax (%)	M3 EC ₅₀ (nM)	M3 Emax (%)	M5 EC ₅₀ (nM)	M5 Emax (%)
1	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
2	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
3	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
4	+++	*	+	***	+++	**	I.A	****	++	***
5	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
6	+	**	+	***	NT	NT	I.A	****	I.A	****
7	++	***	I.A	****	NT	NT	I.A	****	I.A	****
8	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
9	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
10	++	**	I.A	****	NT	NT	I.A	****	I.A	****
11	I.A	****	I.A	****	I.A	****	I.A	****	I.A	****
12	+	*	I.A	****	I.A	***	I.A	****	I.A	****
13	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
14	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
15	++	*	+	***	NT	NT	I.A	****	I.A	****
16	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
17	++	**	I.A	****	I.A	****	I.A	****	I.A	****
18	+++	*	+++	****	I.A	****	I.A	****	I.A	****
19	+++	*	++	****	NT	NT	I.A	****	I.A	****
20	+++	*	+	***	NT	NT	I.A	****	I.A	****
21	+++	*	+	***	NT	NT	I.A	****	I.A	****
22	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
23	+++	*	+++	***	NT	NT	I.A	****	++	***
24	+++	*	+++	***	+++	**	I.A	****	++	***
25	++	*	I.A	****	I.A	****	I.A	****	I.A	****
26	I.A	****	I.A	****	I.A	****	I.A	****	I.A	****
27	+++	*	+++	***	NT	NT	I.A	****	I.A	****
28	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
29	++	*	I.A	****	NT	NT	I.A	****	I.A	****
30	+++	*	+++	***	NT	NT	I.A	****	I.A	****
31	+++	*	++	***	NT	NT	I.A	****	I.A	****
32	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
33	+++	*	++	***	NT	NT	I.A	****	I.A	****
34	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
35	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
36	+++	**	I.A	****	I.A	****	I.A	****	I.A	****
37	+++	*	I.A	****	+++	***	I.A	****	I.A	****
38	+++	*	I.A	****	I.A	****	I.A	v	I.A	****
39	+++	*	I.A	****	+++	***	I.A	****	I.A	****
40	+++	*	I.A	****	+++	***	I.A	****	I.A	****

41	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
42	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
43	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
44	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
45	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
46	+++	*	I.A	****	+++	***	I.A	****	+	***
47	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
48	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
49	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
50	+++	*	+++	***	I.A	***	I.A	****	I.A	****
51	+++	*	+++	***	I.A	***	I.A	****	I.A	****
52	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
53	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
54	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
55	+++	*	+++	***	I.A	****	I.A	****	I.A	****
56	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
57	+++	*	+++	***	I.A	**	I.A	****	I.A	****
58	++	*	I.A	****	+++	****	I.A	****	I.A	****
59	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
60	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
61	+++	*	I.A	****	+++	***	I.A	****	I.A	****
62	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
63	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
64	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
65	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
66	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
67	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
68	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
69	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
70	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
71	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
72	+++	*	I.A	****	+++	**	I.A	****	I.A	****
73	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
74	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
75	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
76	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
77	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
78	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
79	+++	*	+++	***	+++	**	I.A	****	I.A	****
80	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
81	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
82	+++	*	I.A	****	+++	***	I.A	****	I.A	****
83	+++	**	I.A	****	I.A	****	I.A	****	I.A	****
84	++	**	I.A	****	I.A	****	I.A	****	I.A	****

85	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
86	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
87	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
88	+++	*	I.A	****	I.A	****	I.A	****	+	***
89	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
90	+++	*	I.A	****	+++	***	I.A	****	I.A	****
91	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
92	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
93	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
94	+++	*	I.A	****	I.A	****	I.A	****	+	***
95	+++	*	I.A	****	I.A	***	I.A	****	I.A	****
96	++	*	I.A	****	I.A	****	I.A	****	I.A	****
97	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
98	+++	*	I.A	****	I.A	***	I.A	****	+	***
99	+++	*	I.A	****	I.A	****	I.A	****	+	***
100	+++	*	+	****	I.A	****	I.A	****	I.A	****
101	+++	*	++	***	NT	NT	I.A	****	I.A	****
102	I.A.	NT	NT	NT	NT	NT	NT	NT	NT	NT
103	+++	**	++	***	I.A	****	I.A	****	I.A	****
104	+++	**	+++	***	NT	NT	I.A	****	I.A	****
105	+++	*	+	***	NT	NT	I.A	****	I.A	****
106	I.A	****	I.A	****	NT	NT	I.A	****	I.A	****
107	+	***	I.A	****	I.A	****	I.A	****	NT	NT
108	+++	*	+	***	NT	NT	I.A	****	I.A	****
109	+++	***	I.A	****	NT	NT	I.A	****	I.A	****
110	+++	***	NT	NT	NT	NT	NT	NT	NT	NT
111	I.A	****	NT	NT	NT	NT	NT	NT	NT	NT
112	I.A	****	NT	NT	NT	NT	NT	NT	NT	NT
113	+++	*	I.A	****	NT	NT	I.A	****	+	***
114	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
115	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
116	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
117	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
118	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
119	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
120	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
121	+++	*	I.A	****	+++	***	I.A	****	I.A	****
122	+++	*	++	***	NT	NT	I.A	****	I.A	****
123	+++	*	+++	***	NT	NT	I.A	****	I.A	****
124	+++	*	++	***	+++	**	I.A	****	+	***
125	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
126	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
127	++	*	I.A	****	I.A	****	I.A	****	I.A	****
128	+++	*	I.A	****	++	***	I.A	****	NT	NT

129	+++	*	+++	***	+++	**	I.A	****	NT	NT
130	++	*	I.A	****	I.A	****	I.A	****	NT	NT
131	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
132	+++	*	++	****	I.A	****	I.A	****	I.A	****
133	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
134	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
135	+++	*	I.A	****	+++	***	I.A	****	I.A	****
136	++	*	I.A	****	I.A	****	I.A	****	I.A	****
137	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
138	+++	*	++	***	NT	NT	I.A	****	+	***
139	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
140	+++	*	I.A	****	I.A	****	I.A	****	+	***
141	+++	*	I.A	****	+++	***	I.A	****	+	****
142	+++	*	I.A	****	NT	NT	I.A	****	++	***
143	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
144	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
145	+++	*	I.A	****	+++	**	I.A	****	I.A	****
146	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
147	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
148	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
149	+++	*	I.A	****	I.A	****	I.A	****	I.A	****
150	+++	*	I.A	****	+++	**	I.A	****	NT	NT
151	+++	*	+++	***	NT	NT	I.A	****	++	***
152	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
153	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
154	+++	*	I.A	****	NT	NT	I.A	****	+++	**
155	+++	**	I.A	****	NT	NT	I.A	****	+++	***
156	+++	*	I.A	****	NT	NT	I.A	****	++	***
157	+++	*	+++	***	NT	NT	I.A	****	++	***
158	+++	*	I.A	****	NT	NT	I.A	****	+	***
159	+++	*	+++	***	NT	NT	I.A	****	+++	**
160	+++	*	I.A	****	NT	NT	I.A	****	+	***
161	+++	*	+++	***	NT	NT	I.A	****	+++	***
162	+++	*	I.A	****	NT	NT	I.A	****	+++	**
163	+++	*	I.A	****	NT	NT	I.A	****	++	***
164	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
165	+++	*	++	****	NT	NT	I.A	****	I.A	****
166	+++	*	I.A	****	NT	NT	I.A	****	+++	**
167	+++	*	++	***	NT	NT	I.A	****	I.A	****
168	+++	*	+++	***	NT	NT	I.A	****	I.A	****
169	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
170	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
171	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
172	+++	*	+++	***	NT	NT	I.A	****	I.A	****

173	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
174	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
175	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
176	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
177	+++	*	I.A	****	+++	***	I.A	****	I.A	****
178	+++	*	+++	***	+++	**	I.A	****	I.A	****
179	+++	*	+++	***	+++	**	I.A	****	++	***
180	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
181	+++	*	I.A	****	I.A	****	I.A	****	NT	NT
182	+++	*	I.A	****	+++	**	I.A	****	I.A	****
183	+++	*	+++	***	+++	**	I.A	****	I.A	****
184	+++	*	I.A	****	+++	**	I.A	****	NT	NT
185	+++	*	I.A	****	I.A	****	I.A	****	NT	NT
186	+++	*	+++	***	I.A	**	I.A	****	I.A	****
187	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
188	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
189	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
190	+++	*	++	***	NT	NT	I.A	****	I.A	****
191	+++	*	I.A	****	I.A	****	I.A	****	NT	NT
192	+++	*	+	***	NT	NT	I.A	****	I.A	****
193	+	*	NT	NT	NT	NT	NT	NT	NT	NT
194	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
195	+++	*	+	***	NT	NT	I.A	****	I.A	****
196	I.A	****	I.A	****	NT	NT	I.A	****	I.A	****
197	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
198	+	***	I.A	****	NT	NT	I.A	****	I.A	****
199	+++	*	++	***	NT	NT	I.A	****	I.A	****
200	+	*	I.A	****	NT	NT	I.A	****	I.A	****
201	I.A	***	I.A	****	I.A	****	I.A	****	I.A	****
202	I.A	****	I.A	****	I.A	****	I.A	****	I.A	****
203	++	*	I.A	****	NT	NT	I.A	****	I.A	****
204	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
205	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
206	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
207	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
208	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
209	+++	*	+	***	NT	NT	I.A	****	I.A	****
210	++	*	NT	NT	NT	NT	NT	NT	NT	NT
211	++	**	NT	NT	NT	NT	NT	NT	NT	NT
212	++	**	NT	NT	NT	NT	NT	NT	NT	NT
213	++	*	+	***	NT	NT	I.A	****	I.A	****
214	+++	*	+++	***	I.A	****	I.A	****	NT	NT
215	+++	*	++	***	NT	NT	I.A	****	+	***
216	+++	*	I.A	****	NT	NT	I.A	****	I.A	****

217	+++	*	+++	***	NT	NT	I.A	****	I.A	****
218	+++	**	I.A	****	NT	NT	I.A	****	I.A	****
219	+++	*	I.A	****	NT	NT	I.A	****	+++	**
220	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
221	+++	*	I.A	****	NT	NT	I.A	****	+	***
222	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
223	+++	*	I.A	****	+++	***	I.A	****	++	***
224	+++	*	+++	***	+++	**	I.A	****	++	***
225	+	*	I.A	****	I.A	****	I.A	****	I.A	****
226	++	*	I.A	****	I.A	****	I.A	****	I.A	****
227	+++	*	+	***	NT	NT	I.A	****	+	****
228	+++	*	I.A	****	NT	NT	I.A	****	I.A	****
229	+++	*	I.A	****	NT	NT	I.A	****	++	****
230	+++	*	+++	***	NT	NT	I.A	****	I.A	****
231	+++	*	+++	***	NT	NT	I.A	****	+	***
232	+++	*	I.A	****	+++	*	I.A	****	NT	NT
233	+++	*	I.A	****	+++	***	I.A	****	+++	****
234	+++	**	I.A	****	I.A	****	I.A	****	I.A	****
235	++	**	+++	***	+	NT	I.A.	NT	+	**
236	++	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
237	+++	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
238	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
239	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
240	++	**	+++	***	+	****	I.A.	NT	I.A.	NT
241	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
242	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
243	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
244	+	NT	NT	NT	I.A.	NT	NT	NT	NT	NT
245	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
246	++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
247	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
248	+++	*	++	***	NT	NT	I.A.	NT	I.A.	NT
249	+++	*	+++	***	I.A.	NT	I.A.	NT	++	***
250	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
251	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
252	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
253	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	++	***
254	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
255	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
256	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
257	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
258	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
259	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
260	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT

261	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
262	+++	*	I.A.	NT	I.A.	****	I.A.	NT	I.A.	NT
263	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
264	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
265	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
266	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
267	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
268	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
269	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
270	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
271	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
272	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
273	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
274	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
275	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
276	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
277	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
278	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
279	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
280	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
281	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
282	++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
283	NT	NT	I.A.	NT	NT	NT	I.A.	NT	+	***
284	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
285	++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
286	+++	*	+++	***	+	***	I.A.	NT	+	***
287	+++	*	+++	***	+	NT	I.A.	NT	I.A.	NT
288	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
289	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
290	+++	*	+++	***	+++	**	I.A.	NT	I.A.	NT
291	+++	*	+++	**	+	NT	I.A.	NT	++	***
292	+++	*	I.A.	NT	+	***	I.A.	NT	I.A.	NT
293	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
294	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
295	+++	*	+++	**	+	NT	NT	NT	++	***
296	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
297	+++	*	I.A.	NT	+	***	I.A.	NT	I.A.	NT
298	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
299	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
300	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
301	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
302	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
303	+++	*	I.A.	NT	+	****	I.A.	NT	++	***
304	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT

305	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
306	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
307	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
308	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
309	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
310	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
311	+++	*	+	***	+	NT	I.A.	NT	I.A.	NT
312	+++	*	++	***	++	****	I.A.	NT	I.A.	NT
313	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
314	+++	*	I.A.	NT	+	***	I.A.	NT	I.A.	NT
315	+++	*	+++	**	+++	*	I.A.	NT	++	***
316	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
317	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
318	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
319	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
320	+++	*	I.A.	NT	+	NT	NT	NT	I.A.	NT
321	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
322	+++	**	I.A.	NT	+	****	I.A.	NT	I.A.	NT
323	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
324	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
325	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
326	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
327	+++	*	+	NT	+	NT	I.A.	NT	I.A.	NT
328	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
329	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
330	+++	*	I.A.	NT	+	***	I.A.	NT	I.A.	NT
331	+++	*	I.A.	NT	+	***	I.A.	NT	+	***
332	+	NT	I.A.	NT	+	****	I.A.	NT	I.A.	NT
333	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
334	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
335	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
336	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
337	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
338	+++	*	+++	***	+	NT	I.A.	NT	+	**
339	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
340	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
341	++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
342	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
343	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
344	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
345	+++	*	I.A.	NT	+	****	I.A.	NT	+	***
346	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
347	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
348	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT

349	+++	*	I.A.	NT	+	NT	I.A.	NT	+	***
350	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
351	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
352	+++	*	+	***	NT	NT	I.A.	NT	I.A.	NT
353	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
354	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
355	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
356	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
357	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
358	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
359	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
360	+	NT	NT	NT	I.A.	NT	NT	NT	NT	NT
361	++	***	NT	NT	NT	NT	NT	NT	NT	NT
362	++	***	I.A.	NT	I.A.	****	I.A.	NT	I.A.	NT
363	+++	*	+++	***	+	***	I.A.	NT	I.A.	NT
364	+	NT	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
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366	+++	*	++	***	NT	NT	I.A.	NT	I.A.	NT
367	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
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370	+	NT	NT	NT	NT	NT	NT	NT	NT	NT
371	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
372	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
373	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
374	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
375	+++	*	+++	***	I.A.	NT	I.A.	NT	I.A.	NT
376	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
377	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
378	++	***	++	***	NT	NT	I.A.	NT	I.A.	NT
379	++	***	+	***	NT	NT	I.A.	NT	I.A.	NT
380	++	***	NT	NT	NT	NT	NT	NT	NT	NT
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382	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
383	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
384	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
385	+++	*	I.A.	NT	NT	NT	I.A.	NT	++	**
386	+++	*	I.A.	NT	I.A.	****	I.A.	NT	I.A.	NT
387	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
388	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
389	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
390	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
391	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
392	+++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT

393	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
394	+++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
395	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
396	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
397	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
398	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
399	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
400	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
401	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
402	++	**	I.A.	NT	+	****	I.A.	NT	+	***
403	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
404	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
405	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
406	+	****	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
407	++	***	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
408	++	**	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
409	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
410	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
411	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
412	++	**	I.A.	NT	NT	NT	I.A.	NT	NT	NT
413	+++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
414	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
415	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
416	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
417	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
418	+++	*	+	***	I.A.	NT	I.A.	NT	I.A.	NT
419	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
420	+++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
421	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
422	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
423	++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
424	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
425	+++	*	++	***	I.A.	NT	I.A.	NT	I.A.	NT
426	++	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
427	+++	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
428	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
429	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
430	+++	*	+++	***	NT	NT	I.A.	NT	I.A.	NT
431	+++	**	+++	***	NT	NT	I.A.	NT	I.A.	NT
432	+++	*	I.A.	NT	I.A.	****	I.A.	NT	I.A.	NT
433	+++	*	++	***	++	***	I.A.	NT	+	***
434	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
435	++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
436	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT

437	+	NT	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
438	+	NT	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
439	+	NT	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
440	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
441	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
442	+	NT	NT	NT	I.A.	NT	NT	NT	NT	NT
443	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
444	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
445	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
446	+++	**	NT	NT	I.A.	NT	NT	NT	NT	NT
447	+++	*	NT	NT	+++	***	NT	NT	NT	NT
448	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
449	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
450	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
451	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
452	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
453	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
454	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
455	+	NT	I.A.	****	I.A.	NT	I.A.	NT	I.A.	NT
456	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
457	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
458	+++	*	++	***	NT	NT	I.A.	NT	++	**
459	+++	*	+++	***	NT	NT	I.A.	NT	++	***
460	+++	*	++	****	NT	NT	I.A.	NT	I.A.	NT
461	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
462	+++	*	+++	***	NT	NT	I.A.	NT	I.A.	NT
463	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
464	+++	*	++	***	NT	NT	I.A.	NT	+	***
465	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
466	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
467	+++	*	+	***	NT	NT	I.A.	NT	+	***
468	+++	*	+++	***	NT	NT	I.A.	NT	++	***
469	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
470	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
471	+	***	NT	NT	NT	NT	NT	NT	NT	NT
472	+++	*	++	***	NT	NT	I.A.	NT	++	**
473	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
474	+++	**	I.A.	NT	NT	NT	I.A.	NT	++	***
475	+++	*	I.A.	NT	NT	NT	I.A.	NT	NT	NT
476	+++	*	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
477	++	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
478	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
479	I.A.	NT	NT	NT	NT	NT	NT	NT	NT	NT
480	+	****	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT

481	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
482	+	***	NT	NT	NT	NT	NT	NT	NT	NT
483	+	***	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
484	+++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
485	+	***	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
486	++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
487	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
488	+	NT	NT	NT	NT	NT	NT	NT	NT	NT
489	I.A.	****	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
490	I.A.	****	NT	NT	NT	NT	NT	NT	NT	NT
491	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
492	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
493	I.A.	****	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
494	+	****	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
495	++	**	+	NT	NT	NT	I.A.	NT	I.A.	NT
496	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
497	+	NT	NT	NT	NT	NT	NT	NT	NT	NT
498	+	NT	NT	NT	NT	NT	NT	NT	NT	NT
499	+	NT	+	NT	NT	NT	I.A.	NT	I.A.	NT
500	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
501	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
502	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
503	+	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
504	++	*	+	***	NT	NT	I.A.	NT	I.A.	NT
505	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
506	++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
507	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
508	++	**	I.A.	NT	I.A.	****	I.A.	NT	I.A.	NT
509	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
510	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
511	+++	**	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
512	+++	*	+	***	I.A.	NT	I.A.	NT	I.A.	NT
513	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
514	+	NT	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
515	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
516	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
517	+	***	NT	NT	I.A.	NT	NT	NT	NT	NT
518	++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
519	+	***	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
520	NT	NT	++	**	NT	NT	I.A.	NT	+	***
521	+	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
522	+	****	I.A.	NT	+	NT	I.A.	NT	I.A.	NT
523	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
524	++	**	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT

525	+++	*	+++	***	I.A.	NT	I.A.	NT	I.A.	NT
526	+++	*	+++	***	+	NT	I.A.	NT	+	***
527	+	***	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
528	+++	***	NT	NT	I.A.	NT	NT	NT	NT	NT
529	+++	*	I.A.	****	NT	NT	I.A.	NT	I.A.	NT
530	I.A.	****	NT	NT	NT	NT	NT	NT	NT	NT
531	I.A.	****	NT	NT	NT	NT	NT	NT	NT	NT
532	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
533	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
534	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
535	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
536	+	NT	NT	NT	NT	NT	NT	NT	NT	NT
537	++	*	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
538	+++	*	+	***	I.A.	NT	I.A.	NT	I.A.	NT
539	+++	*	I.A.	NT	+	****	I.A.	NT	I.A.	NT
540	+++	*	I.A.	NT	+	****	I.A.	NT	+	***
541	NT	NT	I.A.	NT	NT	NT	I.A.	NT	+++	***
542	+	****	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
543	+	**	I.A.	NT	I.A.	NT	I.A.	NT	I.A.	NT
544	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
545	+++	*	++	***	NT	NT	I.A.	NT	I.A.	NT
546	+++	*	+++	***	++	***	I.A.	NT	+	***
547	+++	*	+++	***	NT	NT	I.A.	NT	++	***
548	+++	*	+++	***	NT	NT	I.A.	NT	NT	NT
549	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
550	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
551	+++	*	+	***	I.A.	NT	I.A.	NT	++	***
552	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
553	+++	*	NT	NT	NT	NT	NT	NT	NT	NT
554	+++	*	+++	***	NT	NT	I.A.	NT	++	**
555	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
556	+++	*	+++	***	NT	NT	I.A.	NT	++	***
557	+++	*	I.A.	NT	NT	NT	I.A.	NT	+	***
558	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
559	+++	*	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
560	NT	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
561	NT	NT	+++	***	NT	NT	I.A.	NT	+	***
562	+	NT	I.A.	NT	NT	NT	I.A.	NT	I.A.	NT
563	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
564	+	NT	NT	NT	I.A.	NT	NT	NT	NT	NT
565	+++	*	NT	NT	I.A.	NT	NT	NT	NT	NT
566	++	***	NT	NT	I.A.	NT	NT	NT	NT	NT

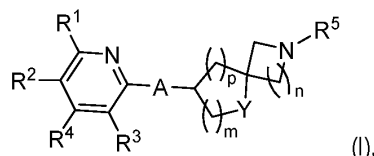
I.A. indicates IC₅₀ > 10 µM; NT indicates not tested.

"+" means ≥100 nM; "++" means 20 to 99.9 nM; and "+++" means <20 nM;

"*" means 80 to 100%; "***" means 50 to 79.9%; and "****" means 19 to 49.9%; and "*****" means <19%.

What is claimed is:

1. A compound having a structure of Formula (I):



or an *N*-oxide thereof, or a pharmaceutically acceptable salt of the compound or the *N*-oxide thereof,

wherein:

A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and is substituted with 0, 1, 2, or 3 R^A;

each R^A is independently C₁₋₃alkyl, halogen, =O, OH, C₁₋₃hydroxyalkyl, or C₁₋₃haloalkyl;

Y is a bond, S, O, CH₂, CHF, CF₂, or C(OH)H;

m is 1 or 2;

n is 1 or 2;

p is 1 or 2;

R¹ is H, halogen, CN, OH, NO₂, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle or -[O]₀₋₁-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -[O]₀₋₁-C₃₋₆cycloalkyl, -[O]₀₋₁-C₆₋₁₀aryl, -[O]₀₋₁-4-8 membered heterocycle, -[O]₀₋₁-5-10 membered heteroaryl, -NH-C₃₋₆cycloalkyl, -NH-C₆₋₁₀aryl, -NH-4-8 membered heterocycle, -NH-5-10 membered heteroaryl, -N(C₁₋₆alkyl)-C₃₋₆cycloalkyl, -N(C₁₋₆alkyl)-C₆₋₁₀aryl, -N(C₁₋₆alkyl)-4-8 membered heterocycle, or -N(C₁₋₆alkyl)-5-10 membered heteroaryl, R¹ is substituted with 0, 1, 2, or 3 substituents independently selected from halogen, CN, OH, =O, SO₂, and C₁₋₃alkyl;

R² is H, halogen, CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₂₋₆heteroalkyl, C₃₋₆cycloalkyl, or 4-8 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S;

R³ is halogen, C₀₋₆alkylene-CN, OH, -N(R⁶)(R⁷), C₁₋₆alkyl, C₂₋₆heteroalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-C(O)NHC₁₋₆alkyl, C₀₋₆alkylene-Cyc, O-C₀₋₆alkylene-Cyc, NH-Cyc, N(C₁₋₆alkyl)-Cyc, or C(O)Cyc;

Cyc is C₃₋₁₂cycloalkyl, C₃₋₆heterocycloalkyl, C₅₋₁₂spirocycloalkyl, C₅₋₁₂heterospirocycloalkyl, C₆₋₁₀aryl, 4-12 membered heterocycle, or 5-10 membered heteroaryl, the heterocycle or heteroaryl comprises 1, 2, or 3 ring heteroatoms independently selected from N, O, and S, and Cyc is substituted with 0, 1, 2, or 3 R^{3a} substituents;

each R^{3a} is independently selected from halogen, CN, OH, =O, =N(C₁₋₆alkyl), SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, C₀₋₆alkylene-C(O)C₁₋₆alkyl, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₀₋₆alkylene-C(O)NH₂, C₀₋₆alkylene-C(O)NH(C₁₋₆alkyl), C₀₋₆alkylene-C(O)N(C₁₋₆alkyl)₂, C₀₋₆alkylene-NHC(O)C₁₋₆alkyl,

C₀₋₆alkylene-COOH, C₀₋₆alkylene-CO₂C₁₋₆alkyl, C₀₋₆alkylene-C₃₋₆cycloalkyl, and C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S;

R⁴ is H, halogen, CN, OH, C₁₋₆alkyl, C₁₋₆-haloalkyl, or C₁₋₆alkoxy;

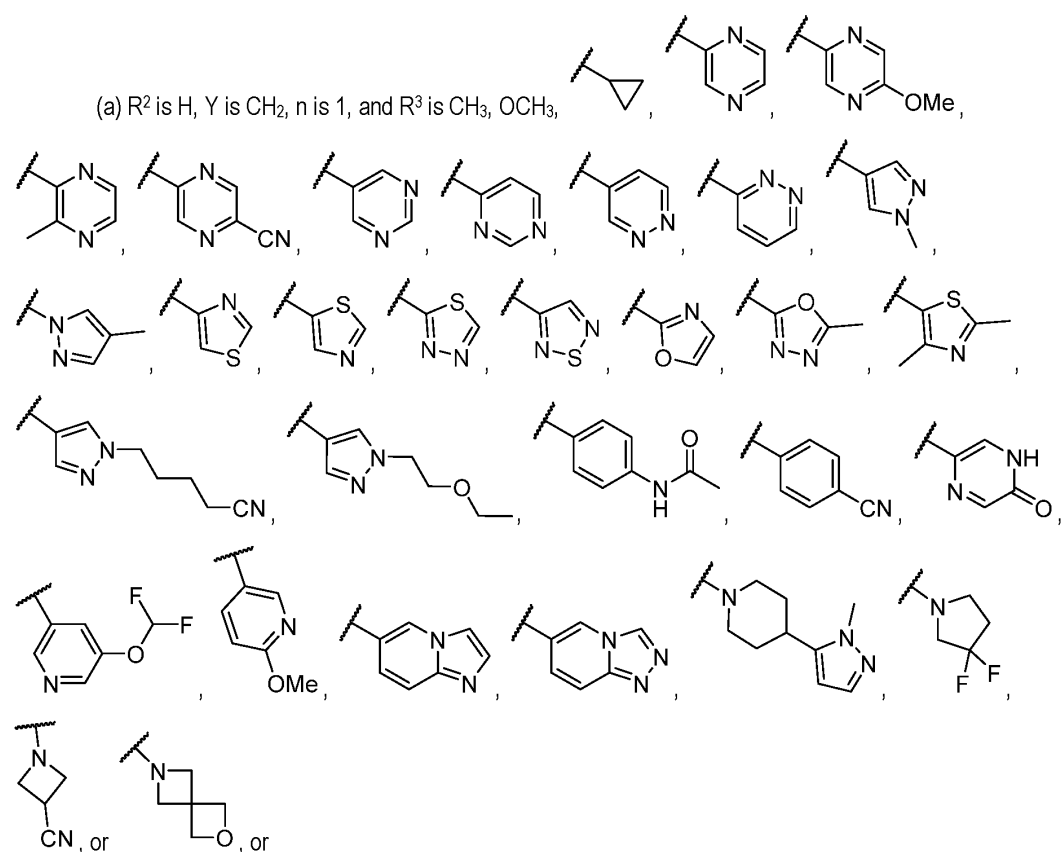
R⁵ is -CO₂-Z, or a bioisostere thereof;

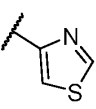
each R⁶ and R⁷ is independently H, C₁₋₆alkyl, C(O)-C₁₋₆alkyl, spiro or bicyclic C₈₋₁₄cycloalkyl, 8-14 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R⁶ or R⁷ is other than H, it is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, CN, =O, SO₂, OH, C₀₋₆alkylene-NH₂, C₀₋₆alkylene-NH(C₁₋₆alkyl), C₀₋₆alkylene-N(C₁₋₆alkyl)₂, C₀₋₆alkylene-SO₂C₁₋₆alkyl, C₁₋₆alkyl and C₁₋₆alkoxy, or

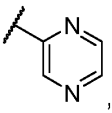
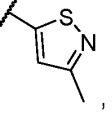
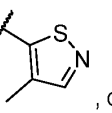
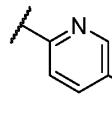
R⁶ and R⁷, together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N, O, and S; and

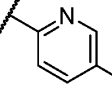
Z is C₁₋₇alkyl, C₁₋₇haloalkyl, C₃₋₆cycloalkyl, or C₂₋₆alkyne, and Z is substituted with 0, 1, 2, or 3 C₁₋₆alkoxy or C₃₋₆cycloalkyl;

with the proviso that when R¹ and R⁴ are each H, m and p are each 1, and A is , and

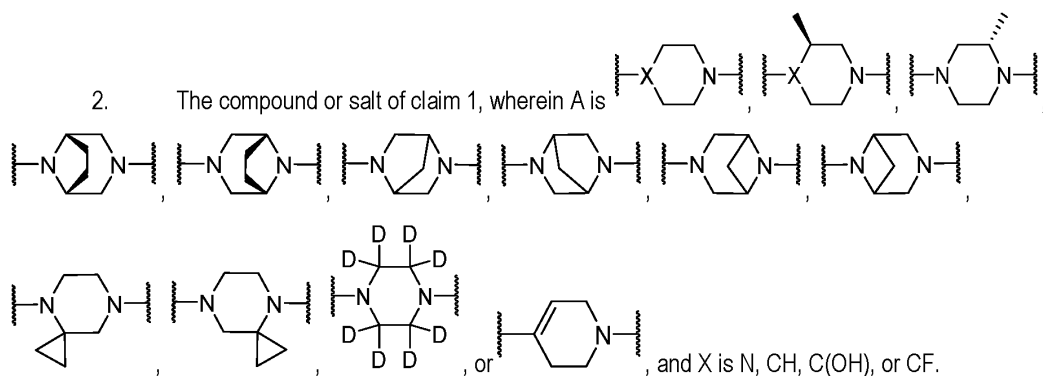


(b) R² is F, Y is CH₂, n is 1, and R³ is , or

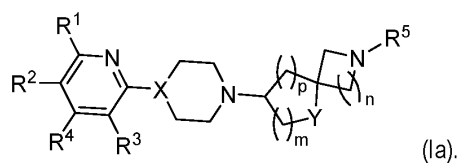
(c) R² is H, Y is a bond, n is 1, and R³ is , , , or , or

(d) R² is H, Y is a bond, n is 2, and R³ is ,

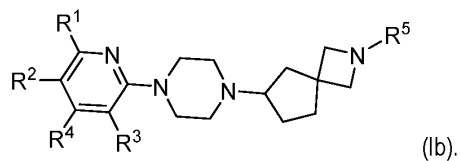
then R⁵ is not CO₂CH₂CH₃ or CO₂CH(CH₃)₃.



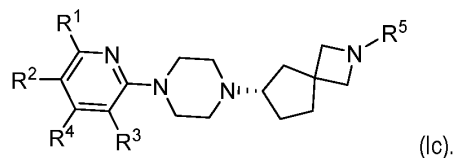
3. The compound or salt of claim 2, having a structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



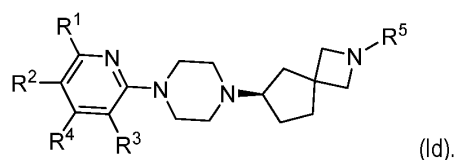
4. The compound or salt of any one of claims 1 to 3, wherein Y is CH₂, CHF, CF₂, or C(OH)H.
5. The compound or salt of claim 4, wherein Y is CH₂.
6. The compound or salt of any one of claims 1 to 5, wherein m is 1.
7. The compound or salt of any one of claims 1 to 6, wherein n is 1.
8. The compound or salt of any one of claims 1 to 7, wherein p is 1.
9. The compound or salt of claim 1, having a structure of Formula (Ib):



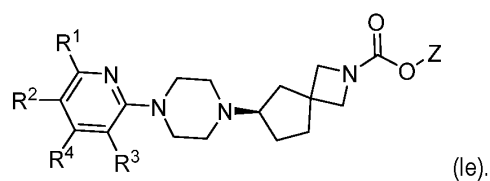
10. The compound or salt of claim 9, having a structure of Formula (lc):



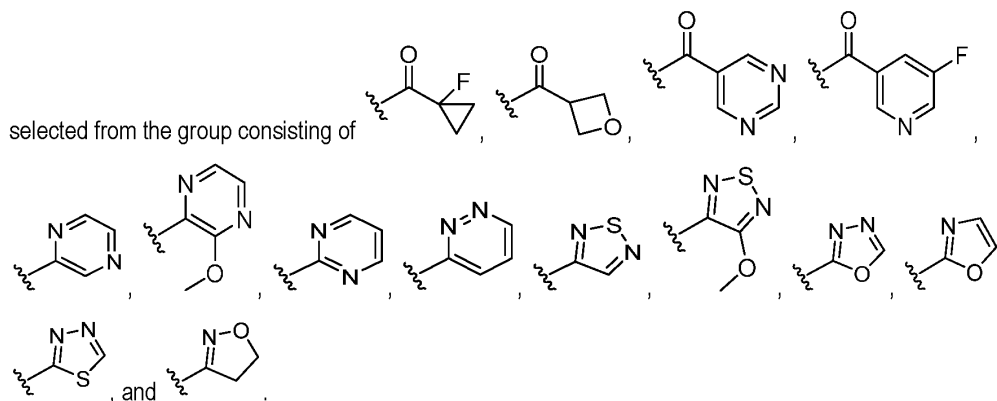
11. The compound or salt of claim 9, having a structure of Formula (ld):



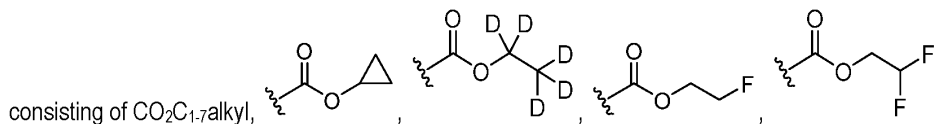
12. The compound or salt of claim 1, having a structure of Formula (le), or a pharmaceutically acceptable salt thereof:

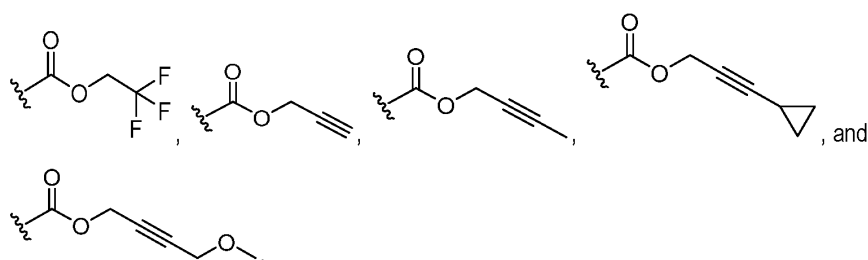


13. The compound or salt of any one of claims 1 to 11, wherein R⁵ is a CO₂Z bioisostere and is

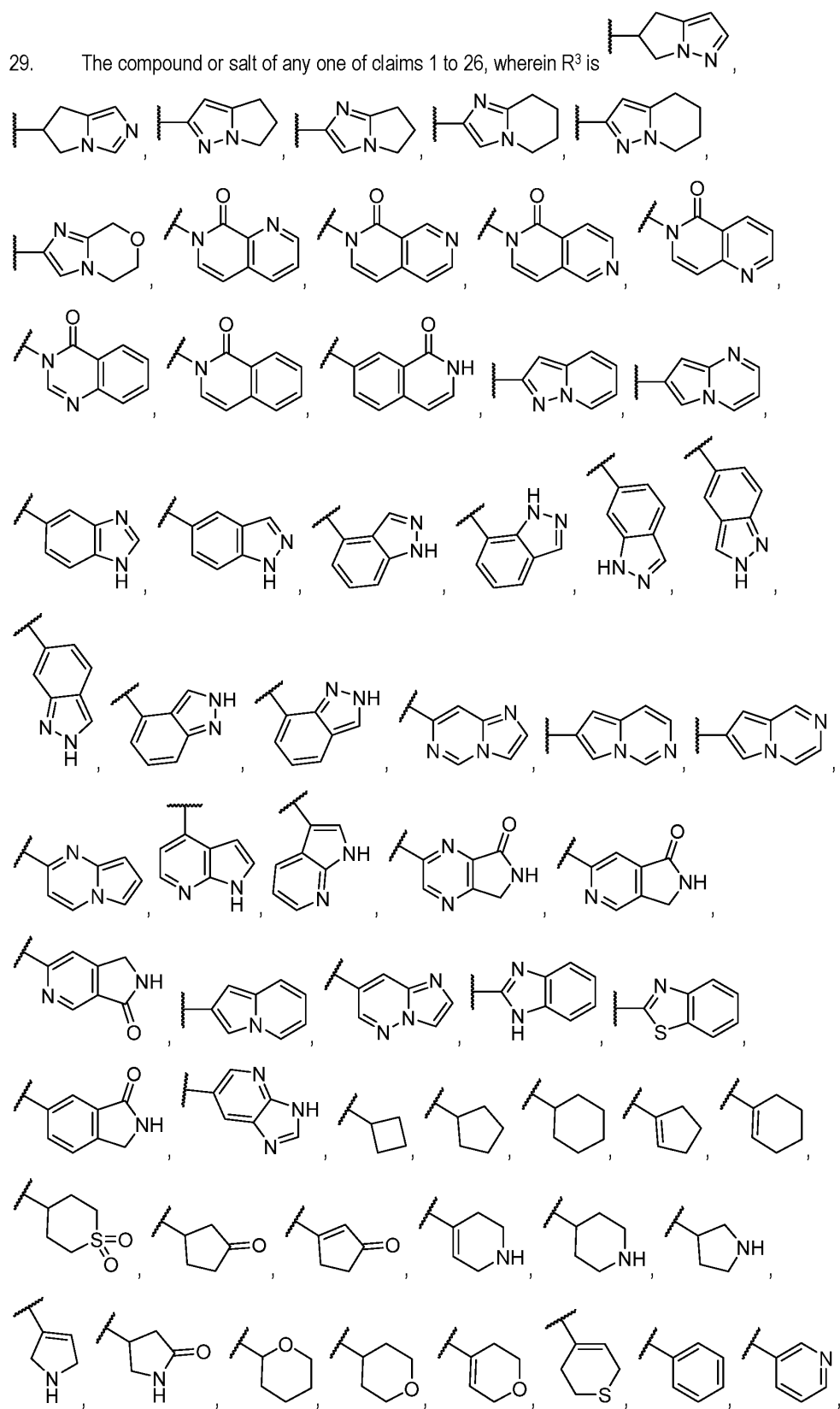


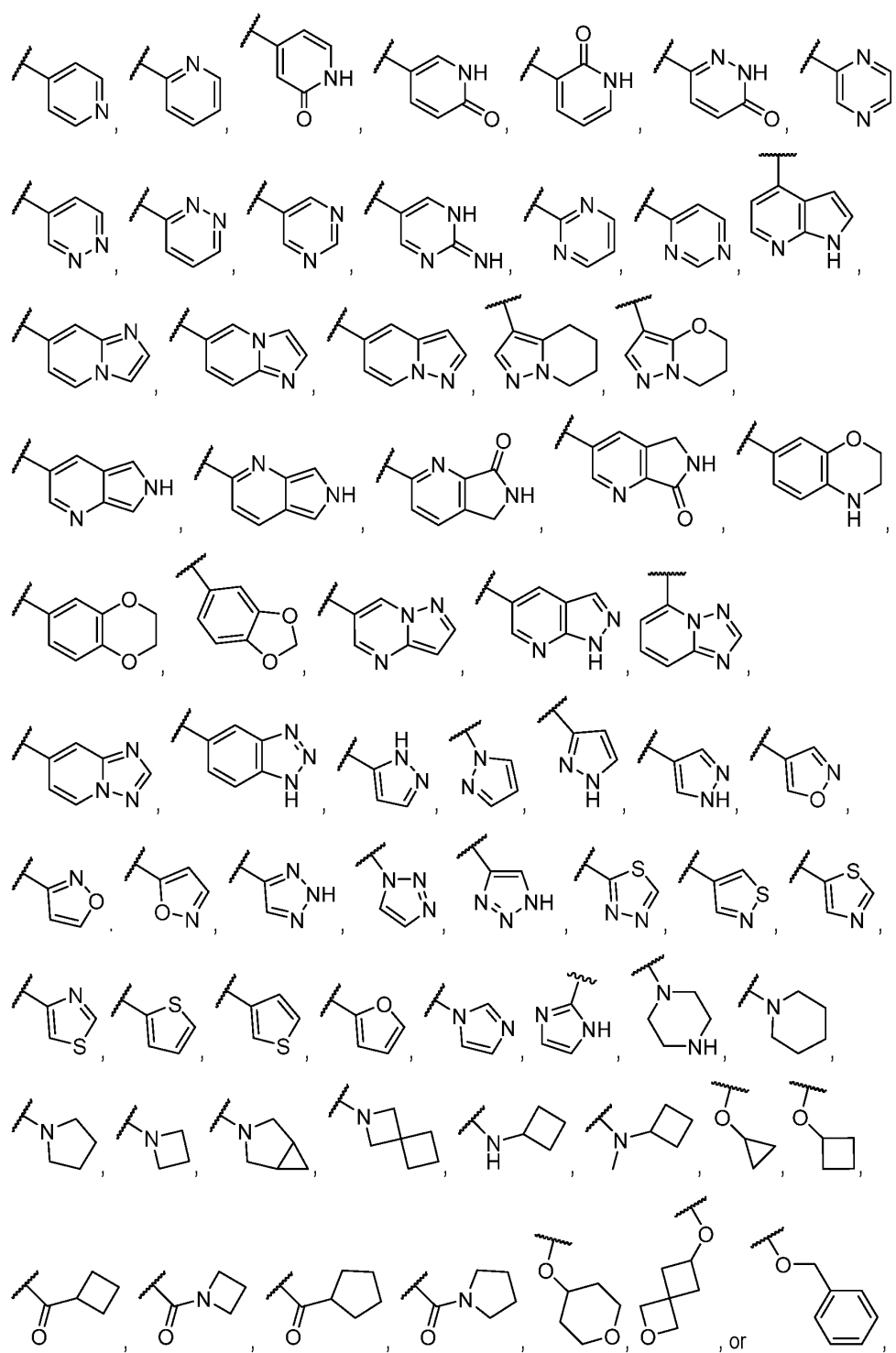
14. The compound or salt of any one of claims 1 to 12, wherein R⁵ is selected from the group





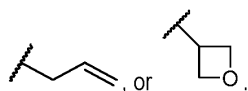
15. The compound or salt of claim 14, wherein R^5 is $\text{CO}_2\text{CH}_2\text{CH}_3$.
16. The compound or salt of any one of claims 1 to 15, wherein R^1 is H, halogen, CN, OH, $-\text{N}(\text{R}^6)(\text{R}^7)$, $\text{C}_{1-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkoxy}$.
17. The compound or salt of claim 16, wherein R^1 is H or halogen.
18. The compound or salt of any one of claims 1 to 17, wherein R^2 is H, halogen, CN, OH, $-\text{N}(\text{R}^6)(\text{R}^7)$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{haloalkyl}$, $\text{C}_{1-6}\text{alkoxy}$, or $\text{C}_{1-6}\text{haloalkoxy}$.
19. The compound or salt of claim 18, wherein R^2 is H, halogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkoxy}$, $\text{C}_{1-6}\text{haloalkyl}$, or $\text{C}_{1-6}\text{haloalkoxy}$.
20. The compound or salt of claim 19, wherein R^2 is H or halogen.
21. The compound or salt of any one of claims 1 to 20, wherein each R^6 and R^7 are independently H, $\text{C}_{1-6}\text{alkyl}$, or $\text{C}(\text{O})\text{-C}_{1-6}\text{alkyl}$.
22. The compound or salt of claim 21, wherein each R^6 and R^7 are independently H or $\text{C}_{1-6}\text{alkyl}$.
23. The compound or salt of any one of claims 1 to 20, wherein at least one R^6 and R^7 , together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N and O.
24. The compound or salt of any one of claims 1 to 23, wherein R^4 is H or halogen.
25. The compound or salt of any one of claims 1 to 24, wherein at least one of R^1 , R^2 , and R^4 is halogen.
26. The compound or salt of any one of claims 1 to 25, wherein at least one of R^1 , R^2 , and R^4 is F.
27. The compound or salt of any one of claims 1 to 26, wherein R^3 is $-\text{O}]_{0-1}\text{-C}_{3-6}\text{cycloalkyl}$, $-\text{O}]_{0-1}\text{-C}_{6-10}\text{aryl}$, $-\text{O}]_{0-1}\text{-4-8 membered heterocycle}$, or $-\text{O}]_{0-1}\text{-5-10 membered heteroaryl}$, and R^3 is substituted with 0, 1, 2, or 3 R^{3a} .
28. The compound or salt of claim 27, wherein R^3 is $\text{C}_{3-6}\text{ cycloalkyl}$, 5-10 membered heteroaryl, or 4-8 membered heterocycle, and R^3 is substituted with 0, 1, 2, or 3 R^{3a} .





34. The compound or salt of any one of claims 1 to 30, 32 and 33, wherein at least one R^{3a} is halogen, CN, OH, =O, SO₂, C₁₋₆alkyl, C₂₋₁₀alkene, C₁₋₆hydroxyalkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkylene-O-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, C₁₋₆alkylene-N(C₁₋₆alkyl)₂, -S-C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, C₁₋₆alkylene-NHC(O)C₁₋₆alkyl, or C₀₋₆alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S.

35. The compound or salt of claim 34, wherein at least one R^{3a} is CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, CF₃, CH₂CH₂F, CH₂CHF₂, CH₂OH, C(CH₃)₂OH, CH₂OCH₃, CH₂CH₂OCH₃, CH₂OCH₂CH₃, F, CN, =O, SO₂, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCHF₂, CH₂OCH₃, CH₂OCF₃, SCH₃, N(CH₃)₂, NHCOCH₃, CD₃,



36. The compound or salt of claim 35, wherein at least one R^{3a} is CH₃, CH₂CH₃, F, CN, OH, OCH₃, CF₃, CH₂OH, or OCHF₂.

37. A compound, or pharmaceutically acceptable salt thereof, as recited in Table A.

38. The salt of claim 37, wherein the salt is selected from HCl, HCl·H₂O, maleate, and maleate·H₂O.

39. A pharmaceutical formulation comprising a therapeutically effective amount of the compound or salt of any one of claims 1 to 38, and a pharmaceutically acceptable excipient.

40. A method for treating an M4-mediated (or M4-associated) disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of the compound or salt of any one of claims 1 to 38.

41. The method of claim 40, wherein the M4-mediated (or M4-associated) disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia or psychosis, pain, addiction, a sleep disorder, a cognitive disorder (e.g., mild cognitive impairment), Parkinson's disease, Parkinson's disease-levodopa-induced dyskinesia, Huntington's disease, dyskinesia, dry mouth, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, urinary incontinence, glaucoma, Trisomy 21 (Down syndrome), cerebral amyloid angiopathy, Alzheimer's disease psychosis, dementia-related psychosis, bipolar, hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes, autism, and atherosclerosis

42. The method of claim 41, wherein the M4-mediated (or M4-associated) disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain, addiction, Parkinson's disease, Parkinson's disease-levodopa-induced dyskinesia, and sleep disorder.