

2-ARYL CYCLOALKYL AND HETEROCYCLOALKYL INHIBITORS OF Na_v1.8 FOR THE TREATMENT OF PAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Provisional Patent Nos. 63/624,672 filed January 24, 2024, and 63/712,366 filed October 25, 2024. The entirety of both applications are incorporated by reference for all purposes.

FIELD

[0002] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions in treating conditions associated with voltage-gated sodium channel function, in particular Na_v1.8, for example pain and conditions associated with pain. Also provided herein are methods of treating pain in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject.

BACKGROUND

[0003] Voltage-gated sodium channels are large integral membrane protein complexes present in neurons and excitable tissues where they contribute to processes such as membrane excitability and muscle contraction (Ogata et al., *Jpn. J. Pharmacol.* (2002) 88(4) 365-77). They have been identified as a primary target for the treatment of pain. Genes encoding for nine distinct mammalian isoforms of Na_v channels (Na_v isoforms 1.1-1.9) have been sequenced. Variation in the gating properties of different Na_v isoforms, cellular distributions, and expression levels influence the physiology of nerve cell conduction. A mounting body of evidence suggests that individual Na_v isoforms Na_v 1.3, 1.7, 1.8 and 1.9 are disproportionately involved in pain signaling and nociception, and that an isoform-specific inhibitor of Na_v could provide pain relief without the accompanying undesirable effects of a non-specific Na_v antagonist or an opioid drug (Momin et al., *Curr Opin Neurobiol.* 18(4): 383-8, 2008; Rush et al., *J. Physiol.* 579(Pt 1): 1-14, 2007).

[0004] Na_v1.8 is selectively expressed in dorsal root ganglion (DRG) neurons, a type of pseudo-unipolar neuron that projects both centrally and peripherally and are implicated in nociception. As a result of its sensory neuron specificity, Na_v1.8 is particularly important in the pathophysiology of pain. The design of a drug which selectively inhibits Na_v 1.8 over the other Na_v channels is therefore desirable. Such a drug design is challenging given the high structural homology (75-96%) of the mammalian Na_v isoforms.

[0005] Isoform-selective selective inhibitors have been sought by a number of research groups and certain compounds have advanced to clinical development. Isoform-selective small molecule inhibitors of Nav 1.8 are disclosed in the following patent applications and publications: WO 2021/257490; WO 2021/257418; WO 2021/257420; WO 2021/113627; WO 2021/032074; WO 2020/261114; WO 2020/219867; WO 2020/146682; WO 2020/092187; WO 2020/092667; WO 2020/014246; WO 2020/014243; WO 2019/157505; WO 2019/014352; WO 2018/213426; WO 2015/089361; WO 2015/010065; WO 2014/120820; WO 2014/120815; WO 2014/120808; WO 2013/114250; WO 2013/061205; WO 2008/135830; Brown et al., *Bioorg Med Chem.* 27(1):230-239, 2019; Bagal et al., *Med Chem Comm.* 7(10), 2016; Bagal et al., *ACS Med Chem Lett.* 6(6):650-654, 2015; Jarvis et al., *PNAS* 104(20):8520-8525, 2007.

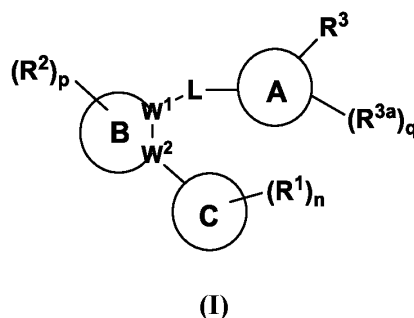
[0006] Previous efforts to develop isoform-selective inhibitors of Nav 1.8 as human therapeutics have encountered a number of challenges. These include insufficient selectivity over off-target human Nav 1.x isoforms, limited target engagement *in vivo* (due to insufficient potency for human Nav 1.8, high protein or tissue binding, state-dependent inhibition of Nav 1.8, safety concerns that preclude dose escalation, or a combination thereof), physico-chemical properties such as poor solubility that impeded oral dosing, and compound-specific issues such as toxicological findings or formation of metabolites that could pose safety risks to humans. Certain compounds also exhibit species variation in Nav 1.8 potency (see e.g. Bagal et al., *Med Chem Comm.* 7(10), 2016) such that it is challenging to evaluate their on-target pharmacodynamic effects in standard preclinical species *i.e.* mouse and rat.

[0007] There exists a need for compounds which treat pain and conditions associated with voltage-gated sodium channel function, particularly which selectively inhibit Nav 1.8 over other Nav isoforms.

SUMMARY

[0008] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions for the treatment of conditions modulated by voltage-gated sodium channels, in particular, Nav 1.8, and in some or any embodiments, in the treatment of pain. Also provided herein are methods of treating pain and/or conditions modulated by voltage-gated sodium channels in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject. In some or any embodiments, the subject is a human.

[0009] In the first aspect, provided herein is a compound of Formula (I):



wherein

W¹ is CR^x;

W² is CR^x or N;

each **R^x** is H or C₁₋₃ alkyl;

L is a bond or is -C(O)NH- where the nitrogen of -C(O)NH- is attached to **ring A**;

ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 5- to 10-membered heterocyclic ring or N-oxide thereof;

ring B is a 3- to 11 -membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

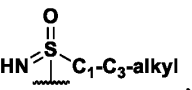
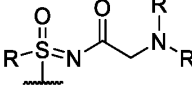
ring C is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where (R¹)_n is substituted on any substitutable ring atom;

R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl, ethyl, n-propyl, or isopropyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₆ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl or cyclobutyl; C₁-C₃ alkoxy, in some embodiments methoxy or ethoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; C₂-C₄ alkynyl, in some embodiments, ethynyl; and hydroxy;

R², independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl, ethyl, isopropyl, or tert-butyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl, cyclobutyl, or cyclopentyl; cyano; -C(O)C₁₋₆alkyl; -C(O)C₁₋₆haloalkyl; , -C(O)C₃₋₆ cycloalkyl, -C(O)aryl, and aryl, in some

embodiments, phenyl or naphthyl; and 5- to 6-membered heteroaryl, in some embodiments, pyridinyl or pyrimidinyl; wherein the C₃-C₆ cycloalkyl, aryl, and heteroaryl, each alone or as part of another group, are optionally substituted with 1, 2, or 3 **R**^{2a} groups independently selected from halo, -CN, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)N(**R**)₂, -S(O)₂NHR,

-S(O)₂C₁-C₆-alkyl, , , C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and 5- to 6-membered heteroaryl wherein each **R** is independently selected from hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof; wherein the compound is not 1-methyl-2-(3-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)quinolin-4(1H)-one; 2-(3-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one; or 2-(3-(4-chlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one.

[0010] In a second aspect provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating pain and/or conditions modulated by voltage-gated sodium channels which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Formula (**I**), Formula (**P-II**), or (**P-I**) and compounds 1-723.

[0011] In a third aspect, a method of treatment of condition associated with voltage-gated sodium channels function, including Na_v1.8, in a subject is provided comprising administering

to an individual in need thereof a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Formula (I), Formula (P-II), or (P-I) and compounds 1-723.

[0012] In a fourth aspect, provided is a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Formula (I), Formula (P-II), or (P-I) and compounds 1-723, or a therapeutically or prophylactically effective amount of a pharmaceutical composition for use in treating a condition associated with voltage-gated sodium channels function, including $\text{Na}_v1.8$, in a subject in need thereof.

[0013] In a fifth aspect, provided is a method of inhibiting voltage-gated sodium channels function, including $\text{Na}_v1.8$, comprising contacting $\text{Na}_v1.8$ with a compound provided herein, *e.g.*, of Formula (I), Formula (P-II), or (P-I), of some or any of the embodiments, and compounds 1-723. In some or any embodiments, the inhibition is done by contacting a subject or a sample with the compound.

BRIEF DESCRIPTION OF FIGURES

[0014] None.

DETAILED DESCRIPTION

[0015] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions in the treatment of pain and/or conditions modulated by voltage-gated sodium channels, in particular $\text{Na}_v1.8$. Also provided herein are methods of treating pain in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject. In an embodiment, the subject is a human.

Definitions

[0016] When referring to the compounds provided herein, the following terms have the following meanings unless indicated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. Unless specified otherwise, where a term is defined as being substituted, the groups in the list of substituents are themselves

unsubstituted. For example, a substituted alkyl group can be substituted, for example, with a cycloalkyl group, and the cycloalkyl group is not further substituted unless specified otherwise.

[0017] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”. As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with temperatures, doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms “about” and “approximately,” when used in this context, contemplate a dose, amount, or weight percent within 15%, within 10%, within 5%, within 4%, within 3%, within 2%, within 1%, or within 0.5% of the specified dose, amount, or weight percent.

[0018] The terms “a” or “an,” as used in herein means one or more, unless context clearly dictates otherwise.

[0019] The term “alkyl,” as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In some or any embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In some or any embodiments, the alkyl group includes one to ten carbon atoms, *i.e.*, C₁-C₁₀ alkyl. In some or any embodiments, the alkyl is a C₁-C₆ alkyl. In some or any embodiments, the alkyl is a C₁-C₃ alkyl. In some or any embodiments, the alkyl group is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, secbutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. In some or any embodiments, the alkyl group is selected from the group consisting of methyl, ethyl, tert-butyl, and neopentyl. In some or any embodiments, the alkyl group is methyl.

[0020] The term “alkenyl,” as used herein, unless otherwise specified, refers to an unsaturated straight or branched hydrocarbon, containing a carbon-carbon double bond. In some or any embodiments, the alkenyl group is cis or trans. In some or any embodiments, the alkenyl group is in an internal or terminal position. In some or any embodiments, the alkenyl group includes two to ten carbon atoms, *i.e.*, C₂-C₁₀ alkenyl. In some or any embodiments, the alkenyl group includes two to four carbon atoms, *i.e.*, C₂-C₄ alkenyl. In some or any embodiments, the alkenyl is C₂-C₃ alkenyl. In some or any embodiments, the alkenyl group is vinyl.

[0021] The term “alkynyl,” as used herein, and unless otherwise specified, refers to an unsaturated straight or branched hydrocarbon, containing a carbon-carbon triple bond. In some or any embodiments, the alkynyl group is in an internal or terminal position. In some or any embodiments, the alkynyl group includes two to ten carbon atoms, *i.e.*, C₂-C₁₀ alkynyl. In some or any embodiments, the alkynyl group includes two to four carbon atoms, *i.e.*, C₂-C₄ alkynyl. In some or any embodiments, the alkynyl is C₂-C₃ alkynyl. In some or any embodiments, the alkynyl group is ethynyl.

[0022] The term “alkoxy” as used herein, and unless otherwise specified, refers to the group -OR' where R' is alkyl, as defined herein. Alkoxy includes, in some or any embodiments, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexyloxy, 1,2-dimethylbutoxy, and the like. In some embodiments, alkoxy is C₁-C₆alkoxy. In some embodiments, alkoxy is C₁₋₃alkoxy.

[0023] The term “C₁-C₆ alkoxy carbonyl,” as used herein, and unless otherwise specified, refer to -C(O)OR' where R' is C₁-C₆ alkyl as defined herein. In some embodiments, C₁-C₆ alkoxy carbonyl is methoxycarbonyl or ethoxycarbonyl.

[0024] The term “amino” means -NH₂.

[0025] The term “amino-C₁-C₆alkyl” means a C₁-C₆alkyl, as provided herein, substituted with one or two amino groups, as defined herein. In some embodiments, amino-C₁-C₆alkyl is aminomethyl, 1-aminoethyl, 2-amino-ethyl, or 2-amino-prop-2-yl.

[0026] The term “aryl,” as used herein, and unless otherwise specified, refers to phenyl or naphthyl. In some or any embodiments, aryl is phenyl. In some or any embodiments, aryl is naphthyl.

[0027] The term “cycloalkyl,” as used herein, refers to a monovalent, saturated, monocyclic hydrocarbon or bicyclic (fused, bridged, or spirocyclic) ring. In some or any embodiments, the terms “fused cycloalkyl,” “spirocycloalkyl,” and “bridged cycloalkyl” are embodiments of the cycloalkyl group. In some or any embodiments, the cycloalkyl group includes three to six carbon atoms, *i.e.*, C₃ to C₆ cycloalkyl. In some or any embodiments, the cycloalkyl has 3, 4, or 5 (C₃₋₅); 3 or 4 (C₃₋₄); 3 (C₃); 4 (C₄); or 5 (C₅) carbon atoms. In some or any embodiments, the cycloalkyl group is C₃-C₆ cycloalkyl. In some or any embodiments, the cycloalkyl group is C₃-C₅cycloalkyl. In some or any embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some or any embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, or cyclopentyl. In some or any embodiments, the cycloalkyl group is cyclopropyl. In some or any embodiments, the cycloalkyl group is cyclobutyl. In some or any embodiments, the cycloalkyl group is cyclopentyl. In some or any

embodiments, the cycloalkyl group is bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, or adamantyl.

[0028] The term “cycloalkylene,” as used herein, refers to a divalent cycloalkyl, as otherwise defined above.

[0029] The term “3- to 11-membered cycloalkylene,” as used herein for ring **B**, refers to a saturated, monocyclic hydrocarbon or bicyclic (fused, bridged, or spirocyclic) ring where **L** and ring **C** (in Formula (I), (P-II), or (P-I) and embodiments thereof) are attached at adjacent carbon atoms of ring **B**. In some or any embodiments, the terms “fused cycloalkylene,” “spirocycloalkylene,” and “bridged cycloalkylene” are embodiments of the 3- to 11-membered cycloalkylene group. In some or any embodiments, the 3- to 11-membered cycloalkylene group includes three to six carbon atoms, *i.e.*, C₃ to C₆ cycloalkylene. In some or any embodiments, the 3- to 11-membered cycloalkylene has 3, 4, or 5 (C₃₋₅); 3 or 4 (C₃₋₄); 3 (C₃); 4 (C₄); or 5 (C₅) carbon atoms. In some or any embodiments, the 3- to 11-membered cycloalkylene has 5, 6, or 7 (C₅₋₇); 5 or 6 (C₅₋₆); 5 (C₅); 6 (C₆); or 7 (C₇) carbon atoms. In some or any embodiments, the 3- to 11-membered cycloalkylene is monocyclic. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cycloprop-di-yl, cyclobut-1,2-di-yl, cyclopent-1,2-di-yl, cyclohex-1,2-di-yl, or cyclohept-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cycloprop-di-yl, cyclobut-1,2-di-yl, cyclopent-1,2-di-yl, or cyclohex-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cycloprop-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cyclobut-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cyclopent-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cyclohex-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene group is cyclohept-1,2-di-yl. In some or any embodiments, the 3- to 11-membered cycloalkylene is bicyclic. In some or any embodiments, the bicyclic cycloalkylene has 7, 8, 9, or 10 (C₇₋₁₀); 7 or 8 (C₇₋₈); 7 (C₇); 8 (C₈); 9 (C₉); or 10 (C₁₀) carbon atoms. In some or any embodiments, the 3- to 11-membered cycloalkylene group is bicyclo[4.1.0]hept-di-yl (in some embodiments, bicyclo[4.1.0]hept-2,3-di-yl (where **L** and ring **C** are attached to the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**), bicyclo[4.1.0]hept-3,4-di-yl (where **L** and ring **C** are attached the 3- and 4-positions, respectively, of ring **B** or are attached to the 4- and 3-positions, respectively, of ring **B**), and bicyclo[4.1.0]hept-4,5-di-yl) (where **L** and ring **C** are attached the 4- and 5-positions, respectively, of ring **B** or are attached to the 5- and 4-positions, respectively, of ring **B**)); bicyclo[4.2.0]octan-di-yl (in some embodiments, bicyclo[4.2.0]octan-2,3-di-yl (where **L**

and ring **C** are attached the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**) or bicyclo[4.2.0]octan-3,4-di-yl (where **L** and ring **C** are attached the 3- and 4-positions, respectively, of ring **B** or are attached to the 4- and 3-positions, respectively, of ring **B**)); octahydro-1H-inden-di-yl (in some embodiments, octahydro-1H-inden-4,5-di-yl (where **L** and ring **C** are attached to the 4- and 5-positions, respectively, of ring **B** or are attached to the 5- and 4-positions, respectively, of ring **B**)); decahydronaphthalene-di-yl (in some embodiments, decahydronaphthalene-1,2-di-yl (where **L** and ring **C** are attached to the 1- and 2-positions, respectively, of ring **B** or are attached to the 2- and 1-positions, respectively, of ring **B**)); spiro[2.5]octan-di-yl (in some embodiments, spiro[2.5]octan-5,6-di-yl (where **L** and ring **C** are attached to the 5- and 6-positions, respectively, of ring **B** or are attached to the 6- and 5-positions, respectively, of ring **B**)); bicyclo[2.2.1]hept-di-yl (in some embodiments, bicyclo[2.2.1]hept-2,3-di-yl (where **L** and ring **C** are attached the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**)), bicyclo[2.2.2]oct-di-yl (in some embodiments, bicyclo[2.2.2]oct-2,3-di-yl (where **L** and ring **C** are attached to the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**)); and spiro[2.4]hept-di-yl (in some embodiments, spiro[2.4]heptan-4,5-di-yl (where **L** and ring **C** are attached to the 4- and 5-positions, respectively, of ring **B** or are attached to the 5- and 4-positions, respectively, of ring **B**)).

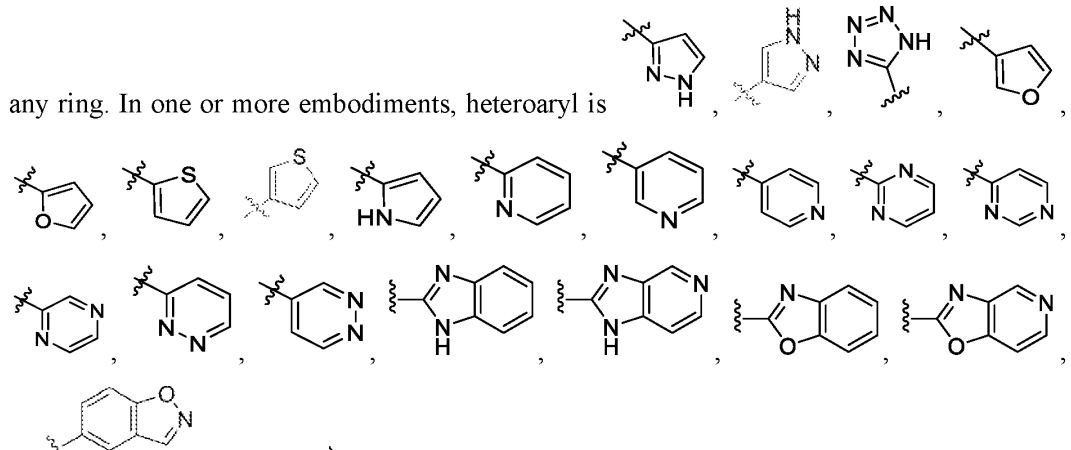
[0030] The term “deutero-alkoxy” as used herein, and unless otherwise specified, refers to –OR’ where R’ is alkyl, as defined herein, where one or more of the hydrogen atoms is replaced with deuterium and the deuterium composition of the atom or atoms is other than the naturally-occurring isotopic composition. In some or any embodiments, the deutero-alkoxy is deutero-C₁-C₃ alkoxy. Deutero-alkoxy includes, in some or any embodiments, methoxy-d₃, ethoxy-d₅, and the like.

[0031] The term “haloalkyl,” as used herein, and unless otherwise specified, refers to an alkyl group substituted with 1, 2, 3, 4, or 5 halo groups. In some or any embodiments, the haloalkyl is a halo-C₁₋₆alkyl. In some or any embodiments, the haloalkyl is a halo-C₁₋₃alkyl. In some or any embodiments, the haloalkyl is –CF₃, –CH₂F, –CHF₂, or –CH₂CF₃.

[0032] The term “haloalkoxy,” as used herein, and unless otherwise specified, refers to an –OR’ group where R’ is halo-C₁₋₁₀alkyl as defined herein. In some or any embodiments, the haloalkoxy is a halo-C₁₋₆alkoxy. In some or any embodiments, the haloalkoxy is a halo-C₁₋₃alkoxy.

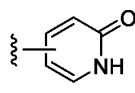
[0033] The terms “halogen” and “halo,” as used herein, and unless otherwise specified, are synonymous and refer to chloro, bromo, fluoro or iodo.

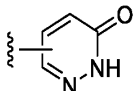
[0034] The term “heteroaryl,” as used herein, and unless otherwise specified, refers to a monocyclic aromatic ring system or bicyclic aromatic ring system wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the ring atoms is a heteroatom independently selected from O, S(O)₀₋₂, NH, and N, and the remaining ring atoms are carbon atoms, and where the ring may be optionally substituted as described herein. The heteroaryl group is bonded to the rest of the molecule through any atom in the ring system, valency rules permitting. In some or any embodiments, each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, or a combination thereof, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In some or any embodiments, the heteroaryl has from 5 to 20, from 5 to 15, from 5 to 6 ring atoms, or from 5 to 10 ring atoms. When heteroaryl is substituted, it can be substituted on

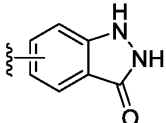
any ring. In one or more embodiments, heteroaryl is , wherein  indicates the point of attachment of the heteroaryl to the rest of the molecule.

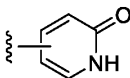
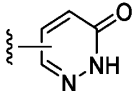
[0035] In some or any embodiments, monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl and triazolyl. In some or any embodiments, bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzoisothiazolyl, benzothieryl, benzotriazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indoliziny, indolyl, indazolyl, isobenzofuranyl, isobenzothieryl, isoindolyl, isoquinoliny, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl,

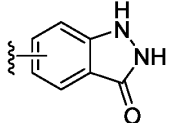
pyrrolopyridyl, quinoliny, quinoxaliny, or quiazoliny. In some or any embodiments, heteroaryl is indolyl, furanyl, pyridiny, pyrimidiny, imidazolyl, or pyrazolyl; each of which is optionally substituted with 1, 2, 3, or 4 groups as defined throughout the specification.

[0036] Heteroaryl, in some embodiments of Ring A, is pyridiny,  (i.e.

pyridiny when substituted with hydroxy), pyridaziny,  (i.e. pyridaziny when

substituted with hydroxy), pyraziny, indazolyl,  (i.e. indazolyl substituted with hydroxy), benzo[d]-isoxazolyl, benzo[d]-isothiazolyl, oxazolopyridiny, benzimidazolyl, imidazopyridiny; where each ring is substituted with R^3 and $(R^{3a})_q$, unless context dictates

otherwise. For example, the hydrogen in NH in  and , and the hydrogen

in NH at the 1-position in  is not replaced with a non-hydrogen R^3 or R^{3a} .

[0037] The term “heterocycloalkyl,” as used herein, and unless otherwise specified, refers to a monovalent, monocyclic or bicyclic saturated or partially unsaturated (but not aromatic), 3 to 10-membered ring system; wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the ring atoms is a heteroatom independently selected from O, S(O)₀₋₂, and N, and the remaining ring atoms are carbon atoms. In some or any embodiments, the heterocycloalkyl comprises one or two heteroatom(s) which are independently selected from nitrogen and oxygen. In some or any embodiments, the heterocycloalkyl comprises one or two heteroatom(s) which are nitrogen (where the nitrogen is substituted as described in any aspect or embodiment described herein). In some or any embodiments, heterocycloalkyl is bicyclic and comprises one or two heteroatoms in the same ring. In some or any embodiments, the heterocycloalkyl has from 5 to 9, 5 to 7, 5 to 6, or 6 to 7 ring atoms. In some or any embodiments, the heterocycloalkyl may be a bridged or non-bridged, spirocyclic or not spirocyclic, and/or fused or not fused group. One or more of the nitrogen and sulfur atoms may be optionally oxidized, one or more of the nitrogen atoms may be optionally quaternized, one or more of the carbon

atoms may be optionally replaced with . In some or any embodiments, the heterocycloalkyl 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is azetidiny, pyrrolidiny, piperidiny, azepany, morpholinyl, tetrahydropyrany, or 7-oxabicyclo[2.2.1]heptanyl.

[0038] The term “heterocycloalkylene,” as used herein, and unless otherwise specified, refers to a divalent heterocycloalkyl which is otherwise as defined above.

[0039] The term “5- to 10-membered heterocycloalkylene,” as used herein for Ring **B**, and unless otherwise specified, refers to a monocyclic or bicyclic saturated or partially unsaturated (but not aromatic) ring system; wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the ring atoms is a heteroatom independently selected from O, S(O)₀₋₂, and N, and the remaining ring atoms are carbon atoms; and wherein **L** and ring **C** (in Formula (I), (P-II), or (P-I) and embodiments thereof) are attached at adjacent atoms of ring **B**. In some or any embodiments, the 5- to 10-membered heterocycloalkylene comprises one or two heteroatom(s) which are independently selected from nitrogen and oxygen. In some or any embodiments, the 5- to 10-membered heterocycloalkylene comprises one or two heteroatom(s) which are nitrogen (where the nitrogen is substituted as described in any aspect or embodiment described herein). In some or any embodiments, 5- to 10-membered heterocycloalkylene is bicyclic and comprises one or two heteroatoms in the same ring. In some or any embodiments, the 5- to 10-membered heterocycloalkylene has from 5 to 7, 5 to 6, or 6 to 7 ring atoms. In some or any embodiments, the 5- to 10-membered heterocycloalkylene may be a bridged or non-bridged, spirocyclic or not spirocyclic, and/or fused or not fused group. One or more of the nitrogen and sulfur atoms may be optionally oxidized, one or more of the nitrogen atoms may be optionally

quaternized, one or more of the carbon atoms may be optionally replaced with . In some embodiments, the 5- to 10-membered heterocycloalkylene is piperidin-1,2-diyl (where **L** and ring **C** are attached to the 1- and 2-positions, respectively, of ring **B** or are attached to the 2- and 1-positions, respectively, of ring **B**), piperidin-2,3-diyl (where **L** and ring **C** are attached to the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**), piperidin-3,4-diyl (where **L** and ring **C** are attached to the 3- and 4-positions, respectively, of ring **B** or are attached to the 4- and 3-positions, respectively, of ring **B**), morpholin-2,3-diyl (where **L** and ring **C** are attached to the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**), tetrahydropyran-3,4-diyl (where **L**

and ring **C** are attached to the 3- and 4-positions, respectively, of ring **B** or are attached to the 4- and 3-positions, respectively, of ring **B**), or 7-oxabicyclo[2.2.1]hept-2,3-di-yl.

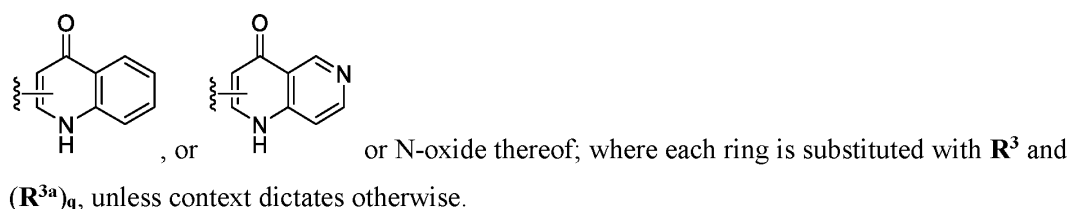
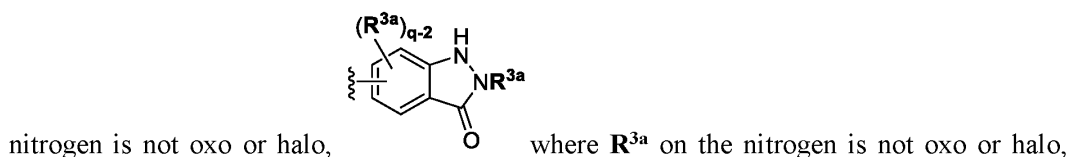
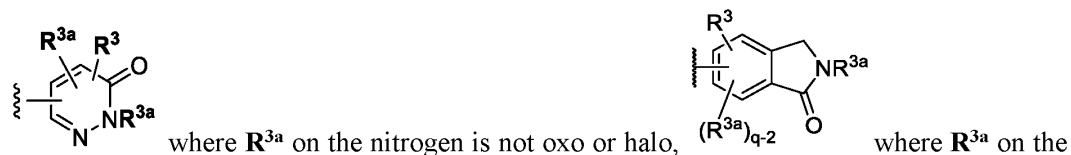
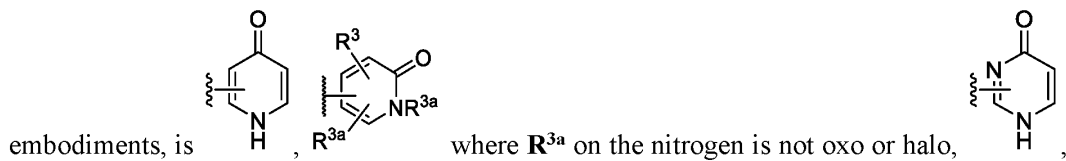
[0040] The term “5- to 10-membered heterocycloalkyl” when fused to benzo, as used herein for Ring **B** refers to 5- to 10-membered heterocycloalkyl, as defined above (including embodiments thereof), fused to a benzo group. 5- to 10-Membered heterocycloalkyl fused to benzo can be substituted on any atom of the ring system with $(R^2)_p$, valency rules permitting. In some embodiments, the 5- to 10-membered heterocycloalkyl fused to benzo is 3,4-dihydro-2H-benzo[b][1,4]oxazin-2,3-di-yl (where **L** and ring **C** are attached to the 2- and 3-positions, respectively, of ring **B** or are attached to the 3- and 2-positions, respectively, of ring **B**).

[0041] The term “heterocyclic,” as used herein, and unless otherwise specified, refers to a monovalent monocyclic, saturated or partially unsaturated (but not aromatic) ring system, (e.g. heterocycloalkyl) or a monovalent bicyclic ring system that contains at least one non-aromatic ring (e.g. not heteroaryl); wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the monocyclic ring atoms is a heteroatom independently selected from O, S(O)₀₋₂, and N, and the remaining ring atoms are carbon atoms; and wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of any of the ring atoms in the bicyclic ring system is a heteroatom(s) independently selected from O, S(O)₀₋₂, and N, and the remaining ring atoms are carbon. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are independently selected from nitrogen and oxygen. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are oxygen. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are nitrogen (where the nitrogen is substituted as described in any aspect or embodiment described herein). In some or any embodiments, heterocyclic is bicyclic and comprises one heteroatom in a non-aromatic ring, or comprises one heteroatom in an aromatic ring, or comprises two heteroatoms in an aromatic ring, or comprises two heteroatoms where one is in an aromatic ring and the other is in a non-aromatic ring. In some or any embodiments, the heterocyclic group, unless specified otherwise, has from 3 to 20, 3 to 15, 5 to 10, 3 to 10, 3 to 8, 4 to 7, 5 to 6, or 4 to 6 ring atoms. In some or any embodiments, the heterocyclic is monocyclic. In some or any embodiments, the heterocyclic is bicyclic. In some or any embodiments, the heterocyclic group may be a bridged or non-bridged, spirocyclic or not spirocyclic, and/or fused or not fused multicyclic group. One or more of the nitrogen and sulfur atoms may be optionally oxidized, one or more of the nitrogen atoms may be optionally quaternized, one or more of the carbon

atoms may be optionally replaced with . Some rings may be partially or fully saturated,

or aromatic provided that heterocyclic is not fully aromatic. In some embodiments, heterocyclic is heterocycloalkyl, as defined above. The monocyclic and bicyclic heterocyclic rings may be attached to the main structure at any heteroatom or carbon atom which results in a stable compound. The bicyclic heterocyclic may be attached to the main structure through any of its rings, including any aromatic or nonaromatic ring, regardless of whether the ring contains a heteroatom. When heterocyclic is substituted, it can be substituted on any ring, i.e. on any aromatic or nonaromatic ring comprised by heterocyclic. In some or any embodiments, such heterocyclic includes, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, 1,3-dihydroisobenzofuranyl, benzofuranonyl, benzopyranonyl, benzopyranyl, dihydrobenzofuranyl, benzotetrahydrothienyl, 2,2-dioxo-1,3-dihydrobenzo[c]thienyl, benzothiopyranyl, benzoxazinyl, chromanyl, chromonyl, coumarinyl, decahydroquinolinyl, decahydroisoquinolinyl, dihydrobenzothiazinyl, dihydrobenzoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, 2,4-dioxo-imidazolidinyl, imidazolyl, indolyl, 2-oxo-indolyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolyl, 1-oxo-isoindolyl, 1,3-dioxo-isoindolyl, isothiazolidinyl, isoxazolidinyl, 3-oxo-isoxazolidinyl, morpholinyl, 3,5-dioxo-morpholinyl, octahydroindolyl, octahydroisoindolyl, 1-oxo-octahydroisoindolyl, 1,3-dioxo-hexahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, 2,6-dioxo-piperazinyl, piperidinyl, 2,6-dioxo-piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolyl, pyrrolidinyl, pyrrolinyl, 2-oxopyrrolidinyl, 2,5-dioxopyrrolidinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiomorpholinyl, 3,5-dioxo-thiomorpholinyl, thiazolidinyl, 2,4-dioxo-thiazolidinyl, tetrahydroquinolinyl, phenothiazinyl, phenoxazinyl, and 1,3,5-trithianyl. In some or any embodiments, heterocyclic is benzo-1,4-dioxanyl, benzodioxolyl, indolyl, 2-oxo-indolyl, pyrrolidinyl, piperidinyl, 2,3-dihydrobenzofuranyl, or decahydroquinolinyl; each of which is optionally substituted with 1, 2, 3, or 4 groups as defined throughout the specification, including in some or any embodiments with group(s) independently selected from halo, alkyl, and phenyl. In some embodiments, heterocycloalkyl is pyrrolidinyl. In some embodiments, heterocycloalkyl is an N-linked heterocycloalkyl.

[0042] In Ring A, the 6- to 10-membered heterocyclic ring or N-oxide thereof, in some



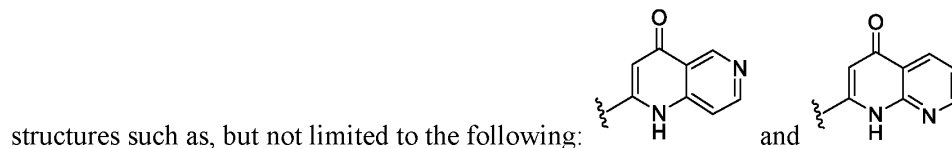
[0043] The term “hydroxyalkyl” as used herein, unless otherwise specified, refers to an alkyl, as defined herein, comprising an alcohol (hydroxy). In one or more embodiments, the alcohol group is a primary, secondary, or tertiary alcohol. In one or more embodiments, the hydroxyalkyl group includes one to ten carbons, *i.e.*, C_1 - C_{10} hydroxyalkyl. In one or more embodiments, the hydroxyalkyl group includes one or two alcohol (hydroxy) groups, provided that they are not on the same carbon. In one or more embodiments, the hydroxyalkyl group is hydroxy C_1 - C_6 alkyl. In one or more embodiments, the hydroxyalkyl group is hydroxy C_1 - C_3 alkyl. In one or more embodiments, the hydroxyalkyl group is selected from the group consisting of hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl. In one or more embodiments, the hydroxyalkyl group is a C_1 - C_6 hydroxyalkyl. In one or more embodiments, the hydroxyalkyl group is selected from the group consisting of hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxyprop-2-yl, 2-hydroxyprop-2-yl, and 2-hydroxyprop-2-yl.

[0044] The term “phenyl fused to HET,” as used herein in **ring C** is wherein the phenyl is attached to **ring B**; and wherein **HET** is a partially unsaturated (but not aromatic), monocyclic heterocycloalkyl, as defined above (including applicable embodiments included

in the definition above) fused to the phenyl. In some embodiments, phenyl fused to **HET** is benzo[d][1,3]dioxolyl or 2,3-dihydrobenzo[b][1,4]dioxinyl.

[0045] The term “phenyl fused to **CYC**,” as used herein in **ring C** is wherein the phenyl is attached to **ring B**; and wherein **CYC** is a partially unsaturated (but not aromatic) monocyclic cycloalkyl, as defined above (including applicable embodiments included in the definition above) fused to the phenyl. In some embodiments, phenyl fused to **CYC** is 2,3-dihydroindene.

[0046] “Naphthyridinonyl,” as used herein and unless otherwise specified, refers to



[0047] The term “oxo” as used herein and unless otherwise specified, refers to a keto group (C=O). An oxo group that is a substituent of a nonaromatic carbon results in a conversion of a -CH₂- to -C=O. An oxo group that is a substituent of an aromatic carbon results in a conversion of -CH- to -C=O. When a substituent is oxo, then two hydrogens on the atom are replaced. When an oxo group substitutes aromatic moieties, the corresponding partially unsaturated ring replaces the aromatic ring. For example, a pyridyl group substituted by an oxo group is a pyridonyl. The person of ordinary skill in the art will appreciate that in some embodiments that such a group, e.g. pyridonyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, 3(2*H*)-oxo-pyridazinyl, 4-oxo-1,4-dihydro-1,6-naphthyridinyl, and 3-oxo-1,2-dihydro-3*H*-indazolyl can exist in tautomeric form, e.g. hydroxypyridinyl, 2,4-dihydroxypyrimidinyl, hydroxy-pyridazinyl, 4-hydroxy-1,6-naphthyridinyl, and 3-hydroxy-1*H*-indazolyl, respectively. Both tautomeric forms are included unless stated otherwise or clearly dictated by context.

[0048] The term “protecting group,” as used herein, and unless otherwise specified, refers to a group that is added to an oxygen, nitrogen or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. (See for example those described in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Fourth Edition, 2006, hereby incorporated by reference.) “DMB,” as used herein, and unless otherwise specified refers to a 2,4-dimethoxybenzyl group.

[0049] The term “pharmaceutically acceptable salt,” as used herein, and unless otherwise specified, refers to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise desirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such

salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; and (2) base addition salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

[0050] Pharmaceutically acceptable salts further include, in some or any embodiments, and without limitation, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium salts and the like. When the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, tert-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate and the like.

[0051] The term “substantially free of” or “substantially in the absence of” stereoisomers with respect to a composition refers to a composition that includes at least 85 or 90% by weight, in some or any embodiments 95%, 98%, 99% or 100% by weight, of a designated stereoisomer of a compound in the composition. In some or any embodiments, in the methods and compounds provided herein, the compounds are substantially free of stereoisomers.

[0052] Similarly, the term “isolated” with respect to a composition refers to a composition that includes at least 85, 90%, 95%, 98%, 99% to 100% by weight, of a specified compound, the remainder comprising other chemical species or stereoisomers.

[0053] The term “isotopic composition,” as used herein, and unless otherwise specified, refers to the amount of each isotope present for a given atom, and “natural isotopic composition” refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as “non-enriched” atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as “H” or “hydrogen,” the position is understood to have hydrogen at its natural isotopic composition.

[0054] The term “isotopic enrichment,” as used herein, and unless otherwise specified, refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom’s natural isotopic abundance. In some or any embodiments, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0055] The term “isotopically enriched,” as used herein, and unless otherwise specified, refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. “Isotopically enriched” may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom

[0056] As used herein, the term “local anesthetic” means a drug which provides local numbness or pain relief. In some or any embodiments, local anesthetic includes aminoacylanilide compounds (in some or any embodiments, lidocaine, prilocaine, bupivacaine, ropivacaine, and mepivacaine) and related local anesthetic compounds having various

substituents on the ring system or amine nitrogen; aminoalkyl benzoate compounds (in some or any embodiments, procaine, chlorprocaine, propoxycaine, hexylcaine, tetracaine, cyclomethycaine, benoxinate, butacaine, and proparacaine) and related local anesthetic compounds; cocaine; amino carbonate compounds (in some or any embodiments, dipiperidone); N-phenylamidine compounds (in some or any embodiments, phenacaine); N-aminoalkyl amide compounds (in some or any embodiments, dibucaine); aminoketone compounds (in some or any embodiments, folicaine and dyclonine); and amino ether compounds (in some or any embodiments, pramoxine and dimethisoquin).

[0057] As used herein, “alkyl,” “hydroxyalkyl,” “carbocyclic,” “cycloalkyl,” “aryl,” “alkoxy,” “heterocycloalkyl,” and “heterocyclic” groups optionally comprise deuterium at one or more positions where hydrogen atoms are present, and wherein the deuterium composition of the atom or atoms is other than the natural isotopic composition.

[0058] Also as used herein, “alkyl,” “hydroxyalkyl,” “carbocyclic,” “cycloalkyl,” “aryl,” “alkoxy,” “heterocycloalkyl,” “heterocyclic” groups optionally comprise carbon-13 at an amount other than the natural isotopic composition.

[0059] As used herein, and unless otherwise specified, the term “IC₅₀” refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response.

[0060] As used herein, the term “sample” is obtained or derived from a subject, as defined herein. In certain embodiments, the sample is a biological sample, and in some embodiments, the biological sample is obtained from a subject selected from the group consisting of a mammal, microorganism, cells, and cell culture. In some embodiments, the biological sample is obtained from cells, cell culture, a microorganism, a mammalian organ, mammalian tissue, or a mammalian bodily fluid. In some embodiments, cells may include, without limitation, cell cultures and cell samples. In some embodiments, cell cultures may include, without limitation, HEK cells and CHO cells. By way of further example, mammalian bodily fluids include, without limitation, serum, plasma, cell lysates, and whole blood.

[0061] As used herein, the terms “subject” and “patient” are used interchangeably. The terms “subject” and “subjects” refer to an animal, such as a mammal including a non-primate (e.g., a cow, pig, horse, cat, dog, rat, and mouse) and a primate (e.g., a monkey such as a cynomolgous monkey, a chimpanzee and a human), and in some or any embodiments, a human. In some or any embodiments, the subject is a farm animal (e.g., a horse, a cow, a pig, etc.) or a pet (e.g., a dog or a cat). In some or any embodiments, the subject is a human.

[0062] As used herein, the terms “therapeutic agent” and “therapeutic agents” refer to any agent(s) which can be used in the treatment or prevention of a disorder or one or more symptoms thereof. In some or any embodiments, the term “therapeutic agent” includes a compound provided herein. In some or any embodiments, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment or prevention of a disorder or one or more symptoms thereof.

[0063] “Therapeutically effective amount” refers to an amount of a compound or composition that, when administered to a subject for treating a condition, is sufficient to affect such treatment for the condition. A “therapeutically effective amount” can vary depending on, inter alia, the compound, the condition and its severity, and the age, weight, etc., of the subject to be treated.

[0064] “Treating” or “treatment” of any condition or disorder refers, in some or any embodiments, to ameliorating a condition or disorder that exists in a subject, including prophylactically. In another embodiment, “treating” or “treatment” includes ameliorating at least one physical parameter, which may be indiscernible by the subject. In yet another embodiment, “treating” or “treatment” includes modulating the condition or disorder, either physically (e.g., stabilization of a discernible symptom) or physiologically (e.g., stabilization of a physical parameter) or both. In yet another embodiment, “treating” or “treatment” includes delaying the onset of the condition or disorder. In yet another embodiment, “treating” or “treatment” includes the reduction or elimination of either the condition (e.g. pain) or one or more symptoms (e.g. pain) of the condition (e.g. sciatica), or to retard the progression of the condition (e.g. pain) or of one or more symptoms (e.g. pain) of the condition (e.g. sciatica), or to reduce the severity of the condition (e.g. pain) or of one or more symptoms (e.g. pain) of the condition (e.g. sciatica). In yet another embodiment, “treating” or “treatment” includes administering a compound described herein prophylactically.

[0065] As used herein, the terms “prophylactic agent” and “prophylactic agents” refer to any agent(s) which can be used in the prevention of a condition or one or more symptoms thereof and/or which prevents or impedes the onset, development, progression and/or severity of a condition. In some or any embodiments, the term “prophylactic agent” includes a compound provided herein. In some or any other embodiments, the term “prophylactic agent” does not refer a compound provided herein. In some or any embodiments, the agent is administered prophylactically, for example before surgery to prevent or impede the onset, duration, progression and/or severity of pain (e.g., post surgical pain).

[0066] As used herein, the phrase “prophylactically effective amount” refers to the amount of a therapy (e.g., prophylactic agent) which is sufficient to result in the prevention or reduction of the development, recurrence or onset of one or more symptoms associated with a condition, or to enhance or improve the prophylactic effect(s) of another therapy (e.g., another prophylactic agent).

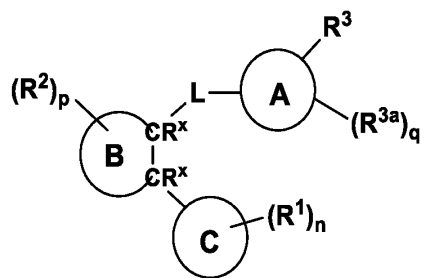
Compounds

[0067] Provided herein are compounds that can modulate the activity of voltage-gated ion channels (e.g., voltage-gated sodium channels). The compounds can be formed as described herein and used for the treatment of conditions associated with voltage-gated sodium channel function. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain or a condition associated with pain. In some or any embodiments, the condition associated with voltage-gated sodium channel function is a condition associated with pain. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain, itch, cough, epilepsy, Parkinson’s disease, a mood disorder, psychosis, amyotrophic lateral sclerosis, glaucoma, ischemia, spasticity disorders and obsessive compulsive disorder. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain (in some embodiments, subacute pain or chronic pain). In some embodiments, the pain associated with voltage-gated sodium channel function includes pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson’s disease, pain associated with ALS, and pain associated with surgery (in some embodiments, ocular surgery).

[0068] The aspects and embodiments described herein include the recited compounds as well as a pharmaceutically acceptable salt thereof and/or an isomer thereof.

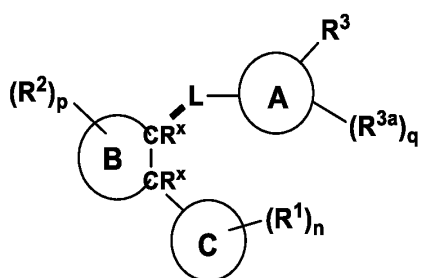
[0069] Included herein, if chemically possible, are all stereoisomers of the compounds, including diastereomers and enantiomers. Also included are mixtures of possible stereoisomers in any ratio, including, but not limited to, racemic mixtures. Unless stereochemistry is explicitly indicated in a structure at a particular atom, the structure is intended to embrace all possible stereoisomers of the compound depicted. If stereochemistry is explicitly indicated for one portion or portions of a molecule, but not for another portion or portions of a molecule, the structure is intended to embrace all possible stereoisomers for the portion or portions where stereochemistry is not explicitly indicated. For example, all compounds substituted with CR^x in the W¹ and W² position can independently exist as the cis-isomer, trans-isomer, or a mixture

thereof with respect to W^1 and W^2 as indicated by the solid and/or dashed rectangles. For

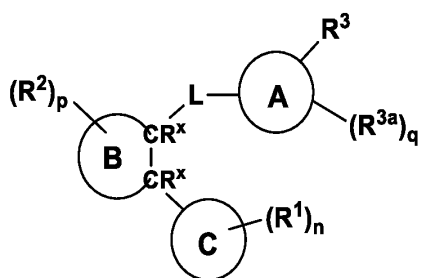


example, in some embodiments,

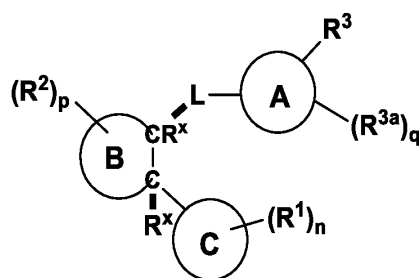
is



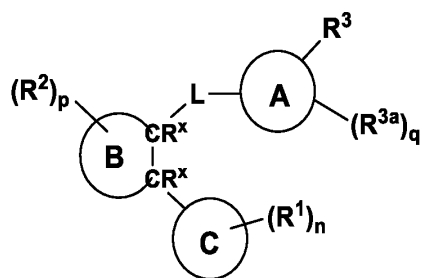
In some embodiments,



is

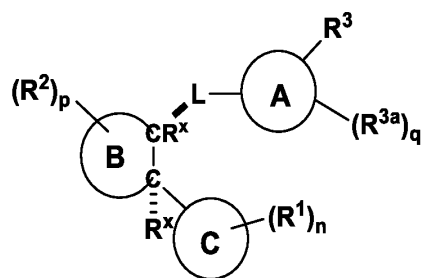


In some



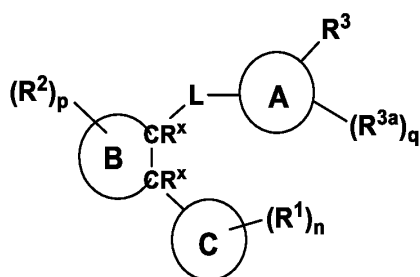
embodiments,

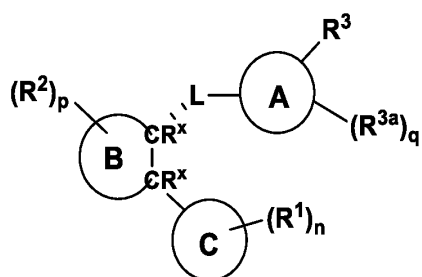
is



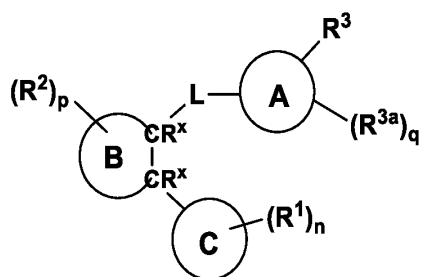
In some embodiments,

is

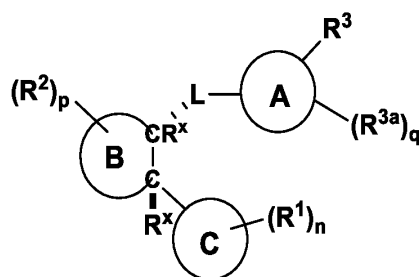




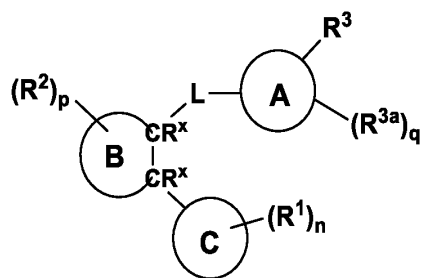
In some embodiments,



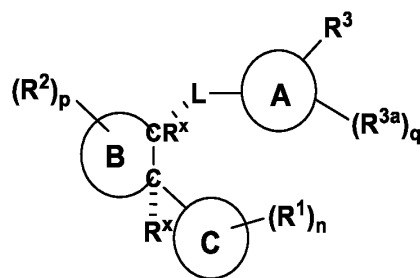
is



In some

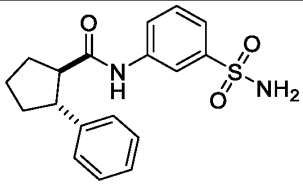
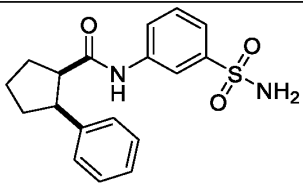


is



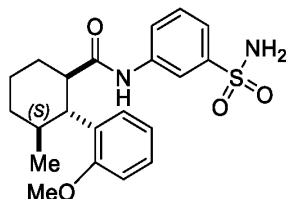
embodiments,

[0070] As used herein, solid and dashed rectangles are equivalent to solid and dashed wedges, respectively (Brecher, J. Pure Appl. Chem., Vol. 78, 10, pp-1897-1970, 2006). When used at the W¹ and W² positions, the solid and dashed rectangles denote relative stereochemistry, including in, for example, Compounds 1 and 3:

1	 where the stereochemistry is either (1R,2R) or (1S,2S)
3	

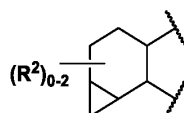
	where the stereochemistry is either (1R,2S) or (1S,2R)
--	---

unless context dictates otherwise. For example compound 34:



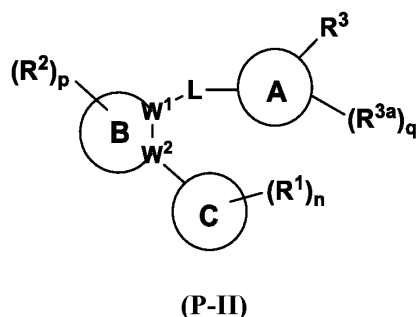
[0071] It will be apparent that certain structures recite specific stereochemistry at particular atoms.

[0072] Certain multicyclic structures provided herein are drawn with one or more floating substituents. Unless provided otherwise or otherwise clear from the context, the substituent(s) may be present on any atom of the multicyclic ring, where chemically feasible and valency rules permitting. For example, this ring:



depicts 0-2 R^2 groups on a bicyclic ring; these R^2 groups may be on a carbon in the cyclohexyl portion of the bicyclic ring and/or in the cyclopropyl portion of the bicyclic ring.

[0073] In one embodiment, provided herein is a compound of Formula (P-II):



wherein

W^1 is CH;

W^2 is CH or N;

L is a bond or is -C(O)NH- where the nitrogen of -C(O)NH- is attached to **ring A**;

ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 5- to 10-membered heterocyclic ring or N-oxide thereof;

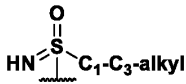
ring B is a 3- to 10-membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

ring C is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where $(R^1)_n$ is substituted on any substitutable ring atom;

R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₆ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl;

R², independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxy, carbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,

-S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and wherein **R** is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

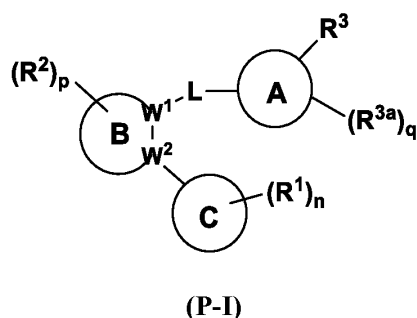
n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof; wherein the compound is not 1-methyl-2-(3-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)quinolin-4(1H)-one; 2-(3-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one; or 2-(3-(4-chlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one.

[0074] In one embodiment, the compound of Formula (I) is a compound of Formula (P-I):



wherein

W¹ is CH;

W² is CH or N;

L is a bond or is -C(O)NH- where the nitrogen of -C(O)NH- is attached to **ring A**;

ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 6- to 10-membered heterocyclic ring or N-oxide thereof;

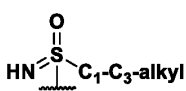
ring B is a 3- to 10-membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

ring C is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where **(R¹)_n** is substituted on any substitutable ring atom;

R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl;

R², independently in each instance, is selected from C₁-C₃ alkyl, in some embodiments, methyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,

-S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and wherein **R** is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

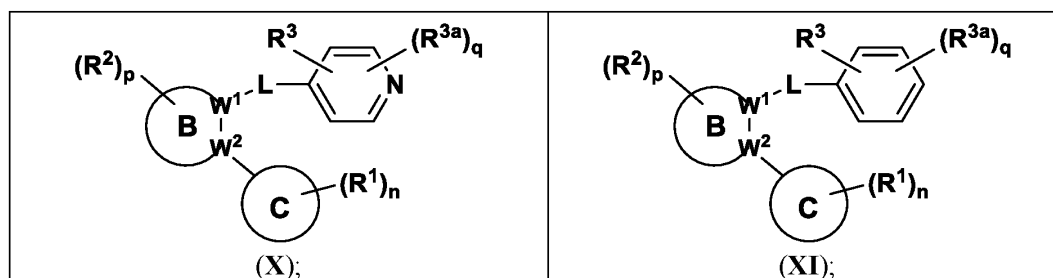
n is 0, 1, 2, 3, or 4;

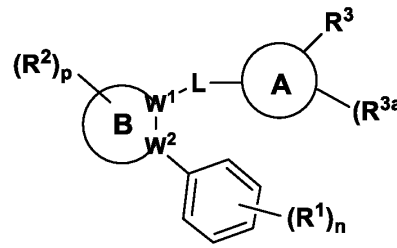
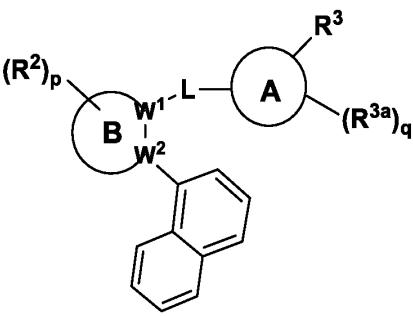
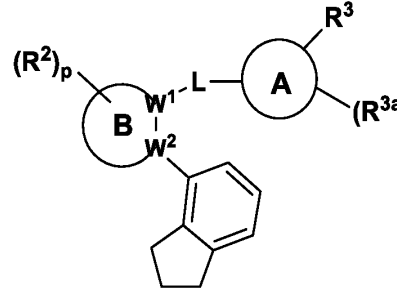
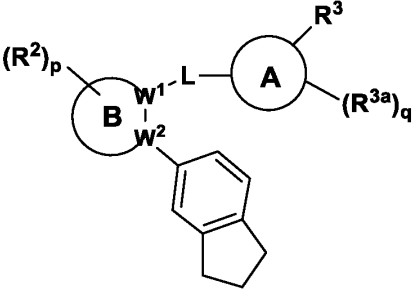
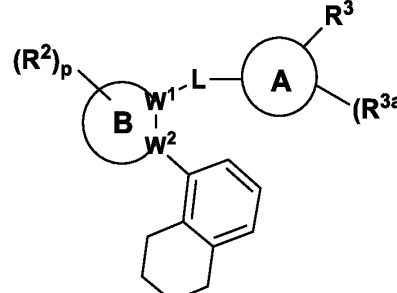
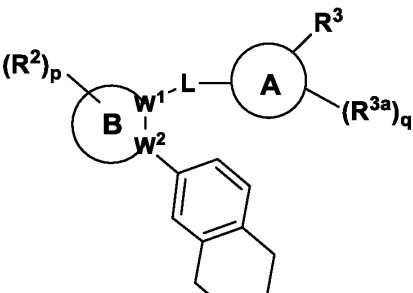
p is 0, 1, 2, or 3;

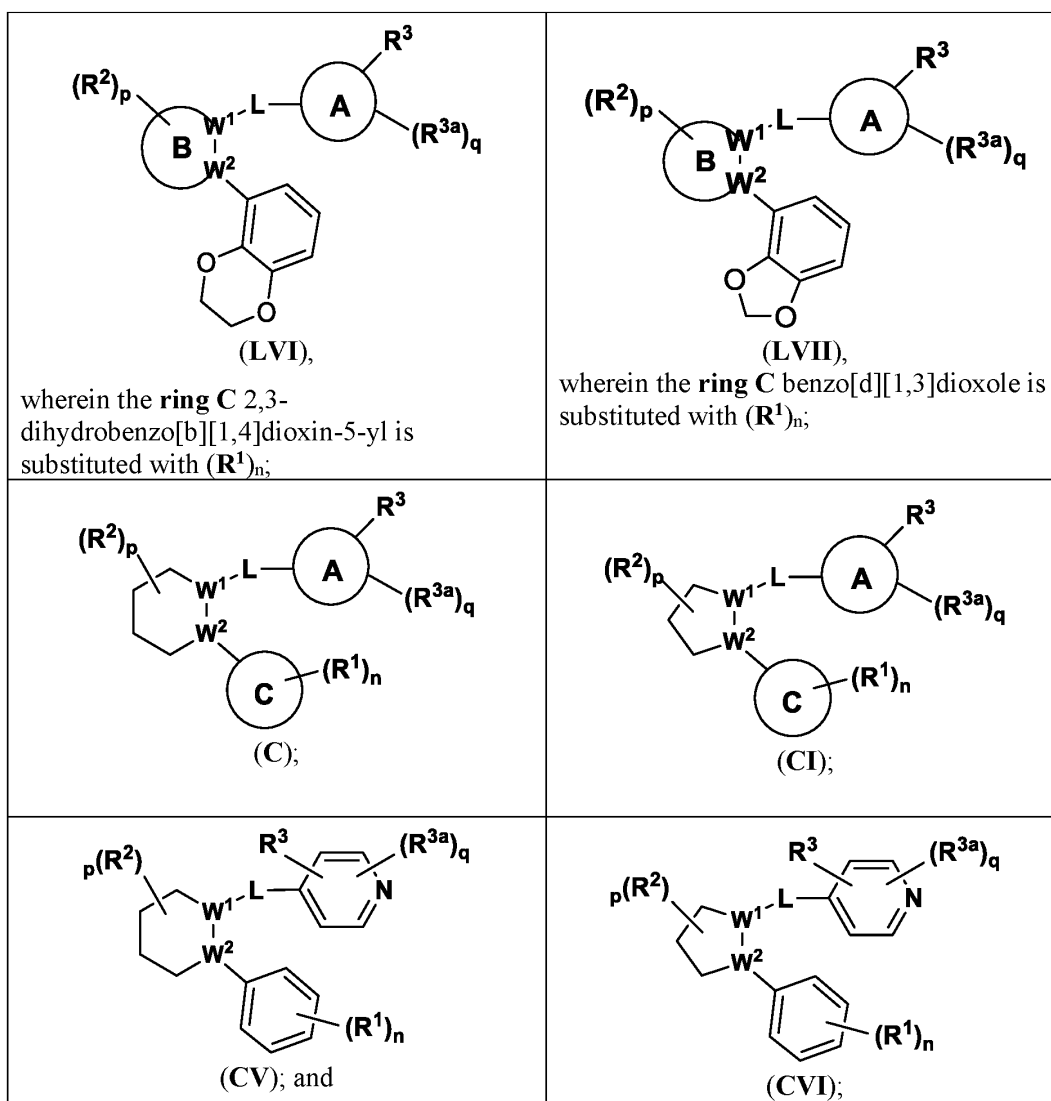
q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[0075] Embodiment A1: Provided herein is a compound according to any one of the following formulas:



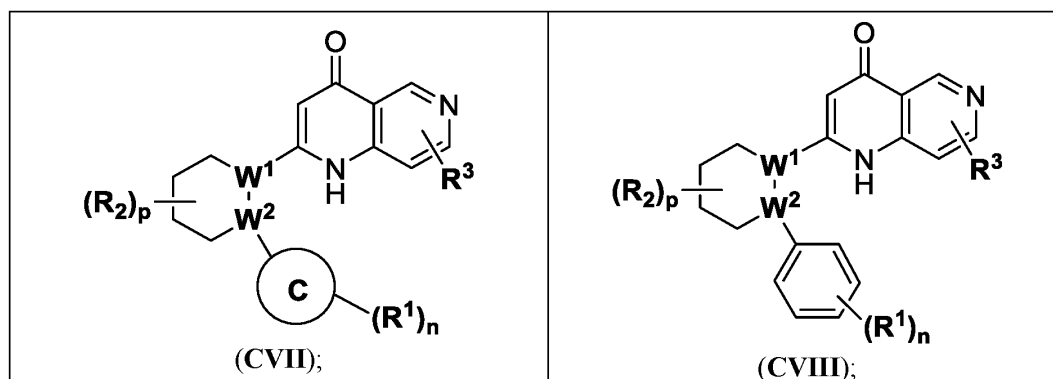
 (L);	 (LI), wherein the ring C naphthyl is substituted with $(R^1)_n$;
 (LII), wherein the ring C 2,3-dihydro-1H-inden-4-yl is substituted with $(R^1)_n$;	 (LIII), wherein the ring C 2,3-dihydro-1H-inden-5-yl is substituted with $(R^1)_n$;
 (LIV), wherein the ring C 1,2,3,4-tetrahydronaphthalen-5-yl is substituted with $(R^1)_n$;	 (LV), wherein the ring C 1,2,3,4-tetrahydronaphthalen-6-yl is substituted with $(R^1)_n$;



or a salt thereof,

wherein W^1 , W^2 , L , **ring A**, **ring B**, **ring C**, R^1 , R^2 , R^3 , R^{3a} , n , p , and q are as defined in the first aspect and any embodiments thereof.

[0076] Embodiment A2: Provided herein is a compound according to any one of the following formulas:



or a salt thereof,

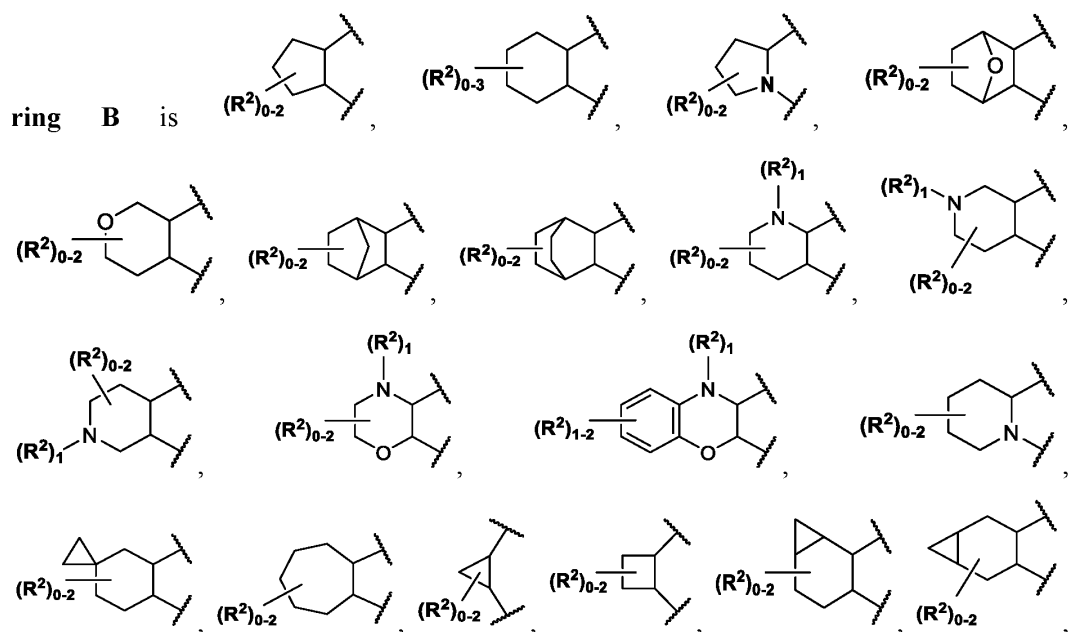
wherein **W¹**, **W²**, **L**, **ring C**, **R¹**, **R²**, **R³**, **n**, and **p** are as defined in the first aspect and any embodiments thereof.

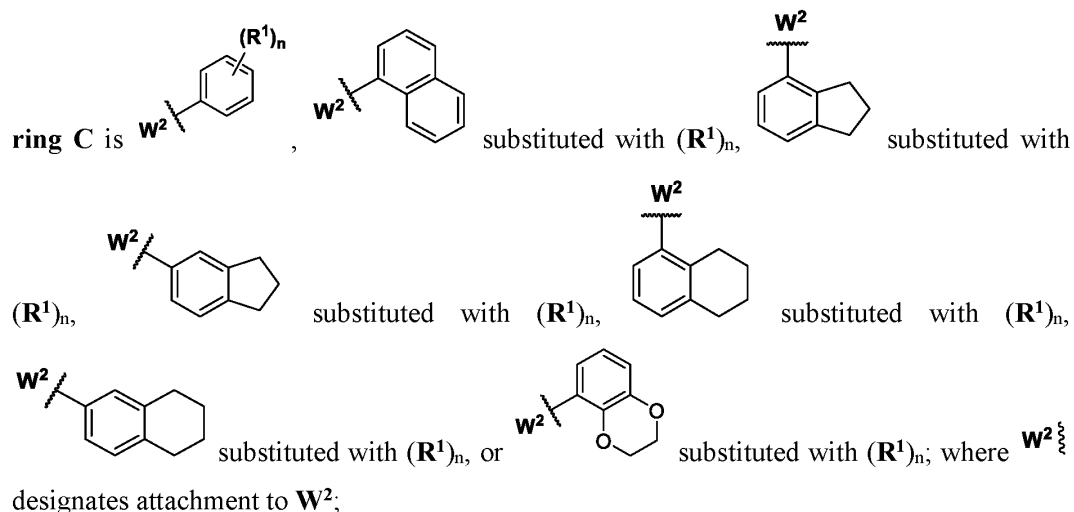
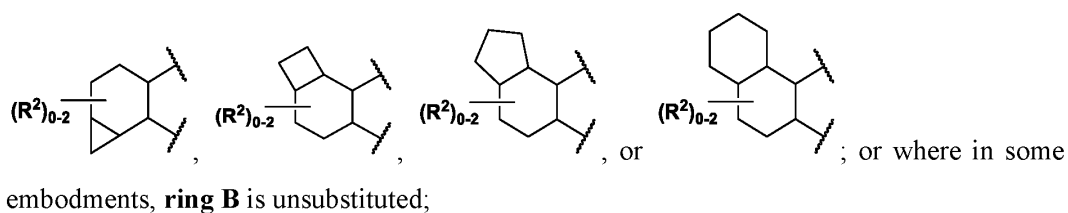
[0077] In one or more embodiments, the compound is according to Formula (X), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (XI), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (L), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LI), wherein the **ring C** naphthyl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LII), wherein the **ring C** 2,3-dihydro-1H-inden-4-yl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LIII), wherein the **ring C** 2,3-dihydro-1H-inden-5-yl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LIV), wherein the **ring C** 1,2,3,4-tetrahydronaphthalen-5-yl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LV), wherein the **ring C** 1,2,3,4-tetrahydronaphthalen-6-yl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LVI), wherein the **ring C** 2,3-dihydrobenzo[b][1,4]dioxin-5-yl is substituted with (R¹)_n, or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (LVII), wherein the **ring C** benzo[d][1,3]dioxole is substituted with (R¹)_n, or a

pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (C), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (CI), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (CV), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (CVI), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (CVII), or a pharmaceutically acceptable salt thereof and/or an isomer thereof. In one or more embodiments, the compound is according to Formula (CVIII), or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[0078] In some or any embodiments, provided herein is a compound of Formula (P-I) or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

ring A is phenyl substituted with R^3 , pyridyl substituted with R^3 , imidazopyridyl substituted with R^3 , benzimidazolyl substituted with R^3 , benzoxazolyl substituted with R^3 , oxazolopyridinyl substituted with R^3 , pyridinonyl (i.e. where R^3 is oxo), pyrimidinonyl (i.e. where R^3 is oxo), quinolinonyl (i.e. where R^3 is oxo), or naphthyridinonyl (i.e. where R^3 is oxo); where **ring A** is substituted with $(R^{3a})_q$; in some embodiments, R^3 is not -H;

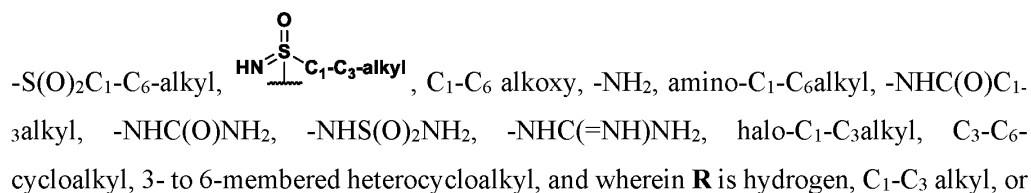




R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-C₁ alkoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; oxetanyl; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl or pyridazinyl; C₂-C₃ alkenyl, in some embodiments, vinyl; and C₂-C₃ alkynyl, in some embodiments, ethynyl;

R², independently in each instance, is selected from C₁-C₃ alkyl, in some embodiments, methyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,



C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

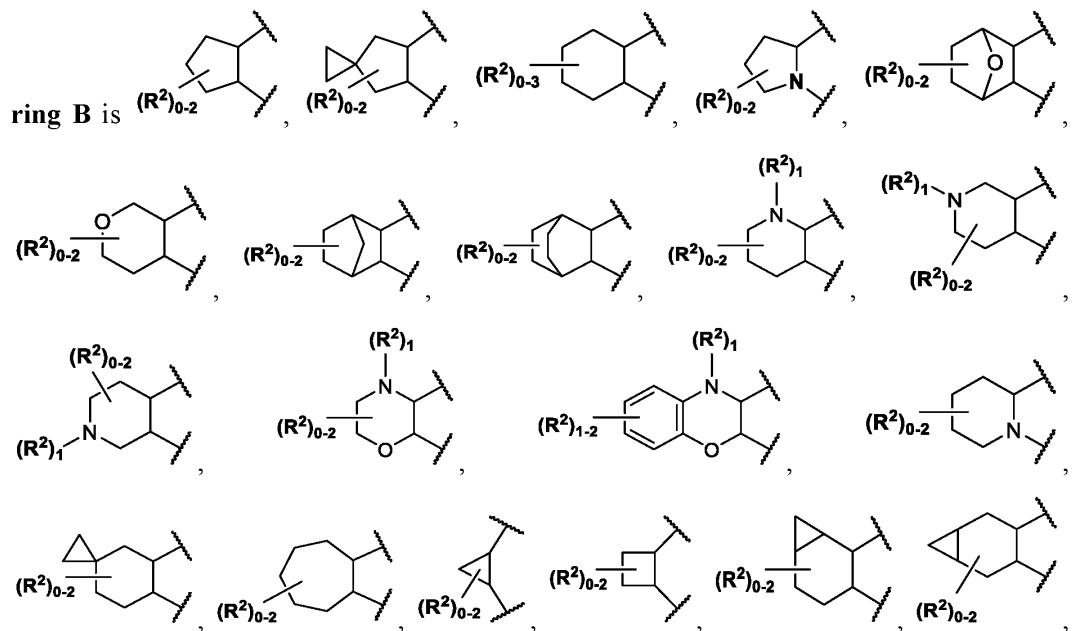
n is 0, 1, 2, 3, or 4;

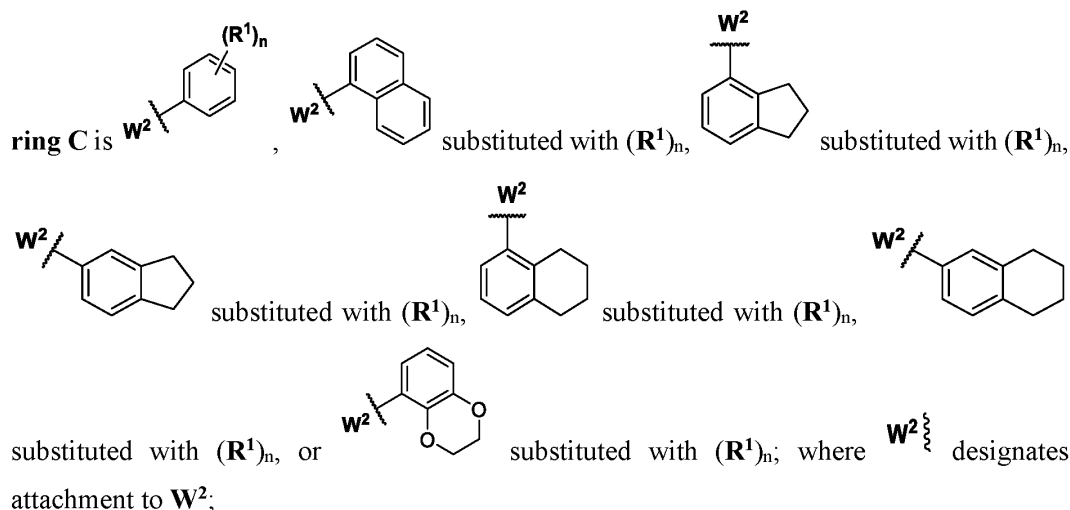
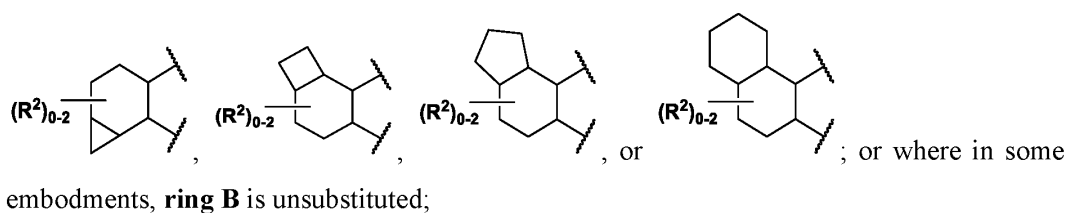
p is 0, 1, 2, or 3; and

q is 0, 1, 2, or 3.

[0079] In some or any embodiments, provided herein is a compound of Formula (P-II) or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

ring A is phenyl substituted with **R³**, pyridyl or an N-oxide thereof substituted with **R³**, imidazopyridyl substituted with **R³**, benzimidazolyl substituted with **R³**, benzoxazolyl substituted with **R³**, benzoisoxazolyl substituted with **R³**, oxazolopyridinyl substituted with **R³**, pyridinonyl (i.e. where **R³** is oxo), pyrimidinonyl (i.e. where **R³** is oxo), pyridazinyl substituted with **R³**, isoindolinonyl (i.e. where **R³** is oxo), indazolyl substituted with **R³**, indazolonyl (i.e. where **R³** is oxo), benzoisothiazolyl substituted with **R³**, quinolinonyl (i.e. where **R³** is oxo), naphthyridinonyl (i.e. where **R³** is oxo); where **ring A** is substituted with (**R^{3a}**)_q; in some embodiments, **R³** is not -H;

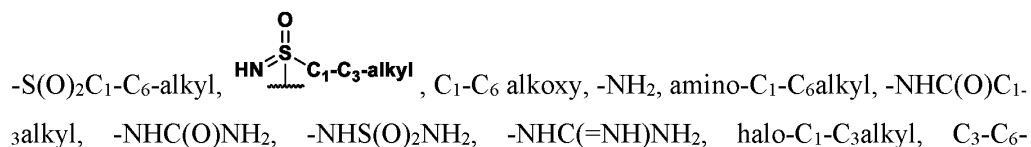




R^1 , independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₆ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-C₁ alkoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl;

R^2 , independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or ethyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R^3 is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,



cycloalkyl, 3- to 6-membered heterocycloalkyl, and wherein **R** is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

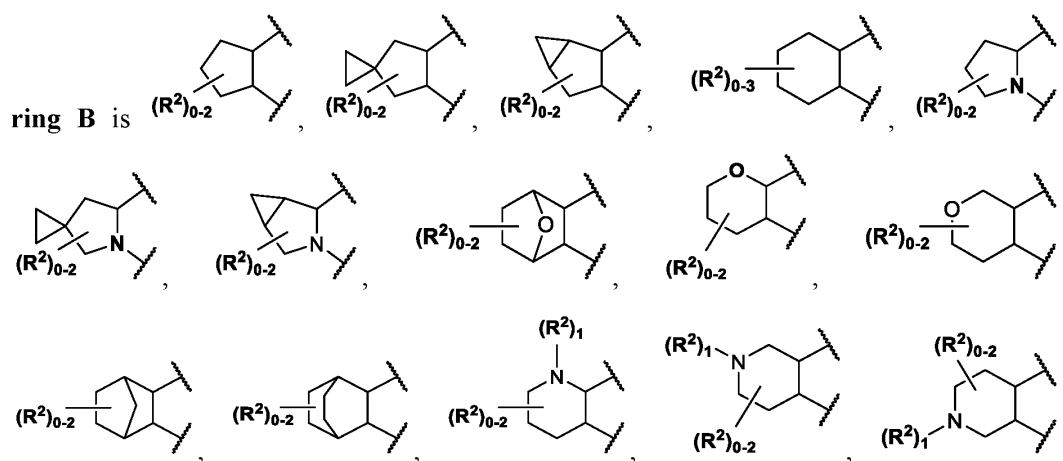
n is 0, 1, 2, 3, or 4;

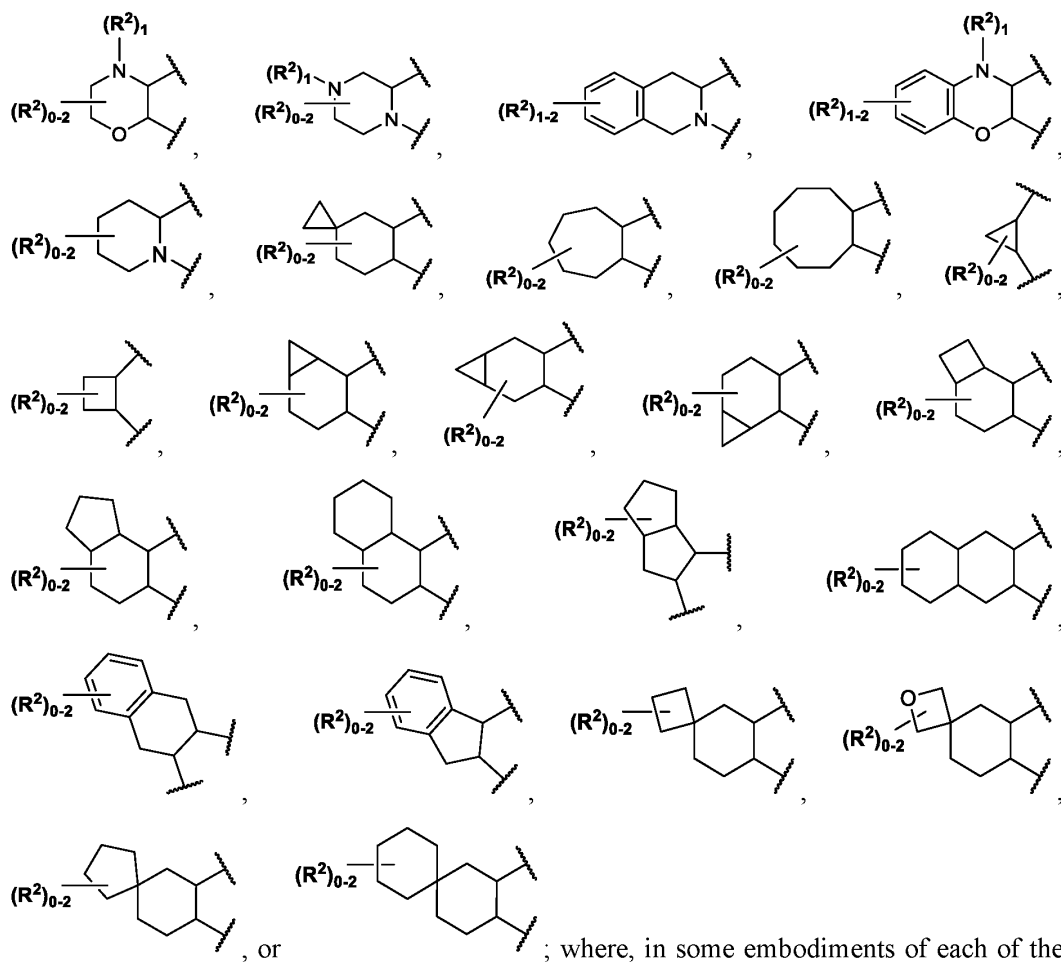
p is 0, 1, 2, or 3; and

q is 0, 1, 2, or 3.

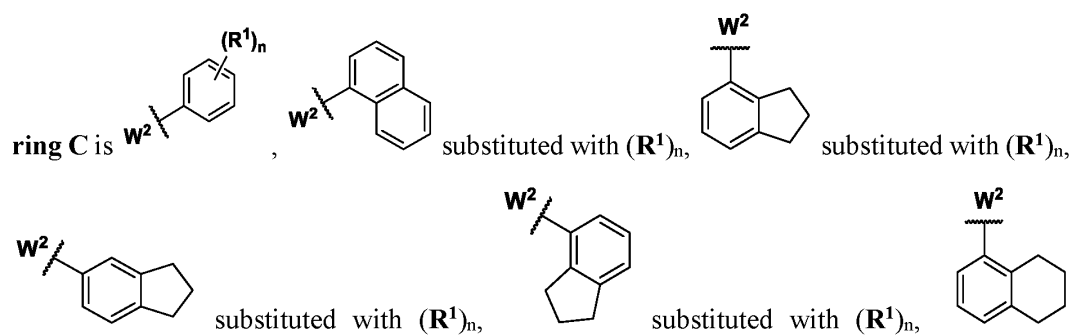
[0080] In some or any embodiments, provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

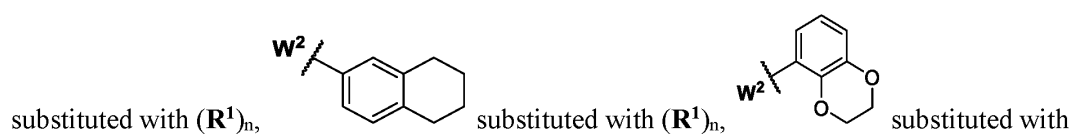
ring A is phenyl substituted with **R**³, pyridyl or an N-oxide thereof substituted with **R**³, imidazopyridyl substituted with **R**³, benzimidazolyl substituted with **R**³, benzoxazolyl substituted with **R**³, benzoisoxazolyl substituted with **R**³, oxazolopyridinyl substituted with **R**³, pyridinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyrimidinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyridazinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyridazinyl substituted with **R**³, isoindolinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, indazolyl substituted with **R**³, indazolonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, benzoisothiazolyl substituted with **R**³, quinolinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, naphthyridinonyl (i.e. where **R**^{3a} is oxo) or an N-oxide thereof substituted with **R**³; thiophenyl substituted with **R**³, where **ring A** is substituted with (**R**^{3a})_q; in some embodiments, **R**³ is not -H;





foregoing structures, the upper  is attached to **L**; or where in some embodiments, **ring B** is unsubstituted;



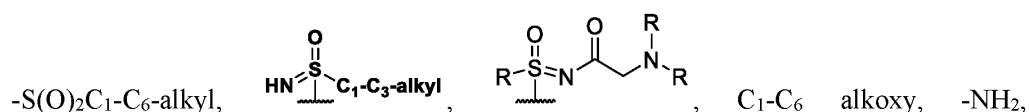


$(R^1)_n$; where W^2 designates attachment to W^2 ;

R^1 , independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl, ethyl, n-propyl, or isopropyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₆ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl or cyclobutyl; C₁-C₃ alkoxy, in some embodiments methoxy or ethoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-C₁ alkoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; C₂-C₄ alkynyl, in some embodiments, ethynyl; and hydroxy;

R^2 , independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl, ethyl, isopropyl, or tert-butyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl, cyclobutyl, or cyclopentyl; cyano; -C(O)C₁₋₆alkyl; -C(O)C₁₋₆haloalkyl; -C(O)cyclohexyl; -C(O)aryl, in some embodiments, -C(O)phenyl; aryl, in some embodiments, phenyl or naphthyl; and 5- to 6-membered heteroaryl, in some embodiments, pyridinyl or pyrimidinyl; wherein the C₃-C₆ cycloalkyl, aryl, and heteroaryl, each alone or as part of another group, are optionally substituted with 1, 2, or 3 R^{2a} groups independently selected from halo, -CN, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R^3 is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)N(R)₂, -S(O)₂NHR,



amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and 5- to 6-membered heteroaryl wherein each R is independently selected from hydrogen, C₁-C₃ alkyl, or C₃-C₆cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, or 3.

[0081] Additional embodiments of Formula (I), Formula (P-II), or (P-I) are where **R¹** is as provided in Embodiments 1-1g; **ring A** is as provided in Embodiments 2-2c; **W¹** is as provided in Embodiments 3-3b; **W²** is as provided in Embodiments 3-3b; **R²**, independently in each instance, is as provided in Embodiments 4-4c; **R³** is as provided in Embodiments 5-5d; **R^{3a}** is as provided in Embodiment 6-6b; **ring B** is as provided in Embodiments 7-7f; **ring C** is as provided in Embodiments 8-8c; **L** is as provided in Embodiment 9-9a; **n** is as provided in Embodiments 10-10a and 13-13a-2; **p** is as provided in Embodiments 11-11a and 13-13a-2; **q** is as provided in Embodiments 12-12a and 13-13a-2; and any combinations thereof.

[0082] Embodiment 1: In some or any embodiments, including Embodiment A, one **R¹** is C₁-C₆ alkyl. In some or any embodiments, including embodiment A, one **R¹** is halo. In some or any embodiments, including embodiment A, one **R¹** is C₁-C₆ haloalkyl. In some or any embodiments, including embodiment A, one **R¹** is C₁-C₃ haloalkyl. In some or any embodiments, including embodiment A, one **R¹** is cyano. In some or any embodiments, including embodiment A, one **R¹** is aryl. In some or any embodiments, including embodiment A, one **R¹** is C₃-C₆ cycloalkyl. In some or any embodiments, including embodiment A, one **R¹** is C₁-C₃ alkoxy. In some or any embodiments, including embodiment A, one **R¹** is deuterio-C₁-C₃ alkoxy. In some or any embodiments, including embodiment A, one **R¹** is halo-C₁-C₃ alkoxy. In some or any embodiments, including embodiment A, one **R¹** is 5- to 6-membered heteroaryl. In some or any embodiments, including embodiment A, one **R¹** is C₂-C₃ alkenyl. In some or any embodiments, including embodiment A, one **R¹** is C₂-C₃ alkynyl. In some or any embodiments, including embodiment A, one **R¹** is C₂-C₄ alkenyl. In some or any embodiments, including embodiment A, one **R¹** is C₂-C₄ alkynyl.

[0083] Embodiment 1a: In some or any embodiments, including Embodiment A, at least one **R¹** is C₁-C₆ alkyl. In some or any embodiments, including Embodiment A, at least one **R¹** is -CH₃. In some or any embodiments, including Embodiment A, at least one **R¹** is C₁-C₆alkoxy. In some or any embodiments, including Embodiment A, at least one **R¹** is -OCH₃. In some or any embodiments, including Embodiment A, at least one **R¹** is C₁-C₆ haloalkyl. In some or any embodiments, at least one **R¹** is -CF₃. In some or any embodiments, including Embodiment A, at least one **R¹** is halo-C₁-C₆ alkoxy. In some or any embodiments,

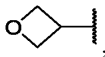
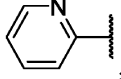
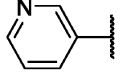
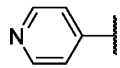
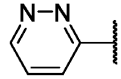
including Embodiment A, at least one **R**¹ is -OCF₃. In some or any embodiments, including Embodiment A, at least one **R**¹ is halogen. In some or any embodiments, including Embodiment A, at least one **R**¹ is -Cl. In some or any embodiments, including Embodiment A, at least one **R**¹ is -F. In some or any embodiments, including Embodiment A, at least one **R**¹ is C₃-C₆-cycloalkyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is C₃-C₆-cycloalkylC₁-C₃-alkyl.

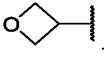
[0084] Embodiment 1b: In some or any embodiments, including Embodiment A, at least one **R**¹ is methyl or propyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is methyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is propyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is n-propyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is isopropyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is fluoro, chloro, or bromo. In some or any embodiments, including Embodiment A, at least one **R**¹ is fluoro. In some or any embodiments, including Embodiment A, at least one **R**¹ is chloro. In some or any embodiments, including Embodiment A, at least one **R**¹ is bromo. In some or any embodiments, including Embodiment A, at least one **R**¹ is C₁ haloalkyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is cyano. In some or any embodiments, including Embodiment A, at least one **R**¹ is phenyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is cyclopropyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is methoxy. In some or any embodiments, including Embodiment A, at least one **R**¹ is deuterio-C₁ alkoxy. In some or any embodiments, including Embodiment A, at least one **R**¹ is halo-C₁ alkoxy or halo-C₂ alkoxy. In some or any embodiments, including Embodiment A, at least one **R**¹ is halo-C₁ alkoxy. In some or any embodiments, including Embodiment A, at least one **R**¹ is halo-C₂ alkoxy. In some or any embodiments, including Embodiment A, at least one **R**¹ is oxetanyl, pyridinyl, or pyridazinyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is oxetanyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is pyridinyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is pyridazinyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is vinyl. In some or any embodiments, at least one **R**¹ is ethynyl.

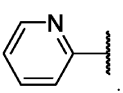
[0085] Embodiment 1b-1: In some or any embodiments, including Embodiment A, at least one **R**¹ is methyl, ethyl, n-propyl, or isopropyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is ethyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is cyclobutyl. In some or any embodiments, including Embodiment A, at least one **R**¹ is ethoxy. In some or any embodiments, at least one **R**¹ is hydroxy.

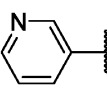
[0086] **Embodiment 1c:** In some or any embodiments, including Embodiment A, R^1 is independently in each instance selected from methyl, ethyl, propyl, cyclopropyl, -F, -Cl, -Br, -OMe, -OEt, -O-propyl, -OCD₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl, -CN, oxetanyl, pyridyl, pyridazinyl, -CHCH₂, and -CCH. In some or any embodiments, including Embodiment A, at least one R^1 is methyl (or -Me). In some or any embodiments, including Embodiment A, at least one R^1 is ethyl. In some or any embodiments, including Embodiment A, at least one R^1 is propyl. In some or any embodiments, including Embodiment A, at least one R^1 is cyclopropyl. In some or any embodiments, including Embodiment A, at least one R^1 is -F. In some or any embodiments, including Embodiment A, at least one R^1 is -Cl. In some or any embodiments, including Embodiment A, at least one R^1 is -Br. In some or any embodiments, including Embodiment A, at least one R^1 is -OMe. In some or any embodiments, at least one R^1 is -OEt. In some or any embodiments, including Embodiment A, at least one R^1 is -O-propyl. In some or any embodiments, including Embodiment A, at least one R^1 is -OCD₃. In some or any embodiments, including Embodiment A, at least one R^1 is -OCF₃. In some or any embodiments, including Embodiment A, at least one R^1 is -OCHF₂. In some or any embodiments, including Embodiment A, at least one R^1 is -OCH₂CF₃. In some or any embodiments, including Embodiment A, at least one R^1 is -CF₃. In some or any embodiments, including Embodiment A, at least one R^1 is phenyl. In some or any embodiments, including Embodiment A, at least one R^1 is -CN. In some or any embodiments, including Embodiment A, at least one R^1 is oxetanyl. In some or any embodiments, including Embodiment A, at least one R^1 is pyridyl. In some or any embodiments, including Embodiment A, at least one R^1 is pyridazinyl. In some or any embodiments, including Embodiment A, at least one R^1 is -CHCH₂. In some or any embodiments, at least one R^1 is -CCH.

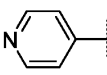
[0087] **Embodiment 1d:** In some or any embodiments, including Embodiment A, R^1 is independently in each instance selected from -Me, -Et, -CH(CH₃)₂, -F, -Cl, -Br, -OMe, -OEt, -OCH(CH₃)₂, -OCD₃,

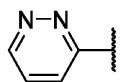
-OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl (or -Ph), -CN, , , , , , -CHCH₂, and -CCH. In some or any embodiments, including

Embodiment A, at least one R^1 is -CH(CH₃)₂. In some or any embodiments, at least one R^1 is -OCH(CH₃)₂. In some or any embodiments, including Embodiment A, at least one R^1 is . In some or any

embodiments, at least one R^1 is . In some or any embodiments, including

Embodiment A, at least one R^1 is . In some or any embodiments, including

Embodiment A, at least one R^1 is . In some or any embodiments, at least one R^1 is



[0088] **Embodiment 1e:** In some or any embodiments, including Embodiment A, R^1 is independently in each instance selected from -Me, propyl, -F, -Cl, -OMe, -OEt, -O-propyl, -OCD₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl, -CN, -CHCH₂, and -CCH.

[0089] **Embodiment 1f:** In some or any embodiments, including Embodiment A, R^1 is independently in each instance selected from -Me, -CH(CH₃)₂, -F, -Cl, -OMe, -OEt, -OCH(CH₃)₂, -OCD₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl, -CN, -CHCH₂, and -CCH.

[0090] **Embodiment 1g:** In some or any embodiments, including Embodiments A and 1-1f, one R^1 is present. In some or any embodiments, including Embodiments A and 1-1f, two R^1 are present. In some or any embodiments, including Embodiments A and 1-1f, three R^1 are present.

[0091] **Embodiment 2:** In some or any embodiments including embodiments A-1g, **ring A** is phenyl substituted with R^3 and optionally substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, **ring A** is a 5- to 10-membered heteroaryl or N-oxide thereof substituted with R^3 and optionally substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, **ring A** is a 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, **ring A** is a 5- to 10-membered heteroaryl N-oxide substituted with R^3 and optionally substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, **ring A** is a 6- to 10-membered heterocyclic ring or N-oxide thereof substituted with R^3 and optionally substituted with $(R^{3a})_q$.

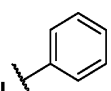
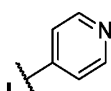
[0092] **Embodiment 2a:** In some or any embodiments including embodiments A-1g, **ring A** is phenyl substituted with R^3 , pyridyl or an N-oxide thereof substituted with R^3 , imidazopyridyl substituted with R^3 , benzimidazolyl substituted with R^3 , benzoxazolyl substituted with R^3 , benzoisoxazolyl substituted with R^3 , oxazolopyridinyl substituted with R^3 , pyridinonyl (i.e. where R^{3a} is oxo) substituted with R^3 , pyrimidinonyl (i.e. where R^{3a} is oxo)

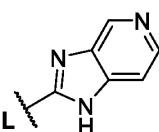
substituted with R^3 , pyridazinonyl (i.e. where R^{3a} is oxo) substituted with R^3 , pyridazinyl substituted with R^3 substituted with R^3 , isoindolinonyl (i.e. where R^{3a} is oxo) substituted with R^3 , indazolyl substituted with R^3 , indazolonyl (i.e. where R^{3a} is oxo) substituted with R^3 , benzoisothiazolyl substituted with R^3 , quinolinonyl (i.e. where R^{3a} is oxo) substituted with R^3 , naphthyridinonyl (i.e. where R^{3a} is oxo) or an N-oxide thereof substituted with R^3 ; thiophenyl substituted with R^3 , where ring A is substituted with $(R^{3a})_q$; in some embodiments, R^3 is not -H. In some or any embodiments including embodiments A-1g, **ring A** is pyridinonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is pyrimidinonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is pyridazinonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is isoindolinonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is indazolonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is quinolinonyl (i.e. where R^{3a} is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is naphthyridinonyl (i.e. where R^{3a} is oxo) or an N-oxide thereof substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is thiophenyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, R^3 is not -H.

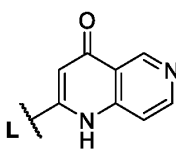
[0093] **Embodiment 2a-1:** In some or any embodiments including embodiments A-1g, **ring A** is phenyl substituted with R^3 , pyridyl substituted with R^3 , imidazopyridyl substituted with R^3 , benzimidazolyl substituted with R^3 , benzoxazolyl substituted with R^3 , oxazopyridinyl substituted with R^3 , pyridinonyl (i.e. where R^3 is oxo), pyrimidinonyl (i.e. where R^3 is oxo), quinolinonyl (i.e. where R^3 is oxo), or naphthyridinonyl (i.e. where R^3 is oxo); where **ring A** is substituted with $(R^{3a})_q$; in some embodiments, R^3 is not -H. In some or any embodiments including embodiments A-1g, **ring A** is phenyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is pyridyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is imidazopyridyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is benzimidazolyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is benzoxazolyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is oxazopyridinyl substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is pyridinonyl (i.e. where R^3 is oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is pyrimidinonyl (i.e. where R^3 is

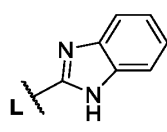
oxo) substituted with R^3 . In some or any embodiments including embodiments A-1g, **ring A** is quinolinonyl (i.e. where R^3 is oxo). In some or any embodiments including embodiments A-1g, **ring A** is naphthyridinonyl (i.e. where R^3 is oxo). In some or any embodiments including embodiments A-1g, **ring A** is substituted with $(R^{3a})_q$. In some or any embodiments including embodiments A-1g, R^3 is not -H.

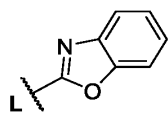
[0094] **Embodiment 2b:** In some or any embodiments including embodiments A-1g, **ring A** is

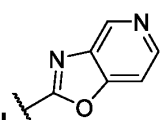
 substituted with R^3 and additionally with with one or more R^{3a} ,  or

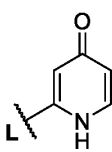
N-oxide thereof substituted with R^3 and additionally with with one or more R^{3a} , 

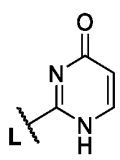
substituted with R^3 and additionally with with one or more R^{3a} ,  (i.e. where

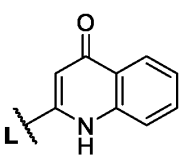
R^{3a} is oxo) substituted with R^3 and additionally with with one or more R^{3a} , 

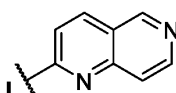
substituted with R^3 and additionally with with one or more R^{3a} ,  substituted with

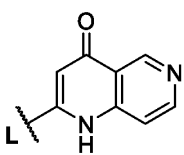
R^3 and additionally with with one or more R^{3a} ,  substituted with R^3 and

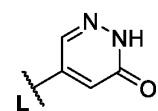
additionally with with one or more R^{3a} ,  (i.e. where R^{3a} is oxo) substituted with R^3

and additionally with with one or more R^{3a} ,  (i.e. where R^{3a} is oxo) substituted with

R^3 and additionally with with one or more R^{3a} ,  (i.e. where R^{3a} is oxo)

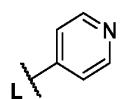
substituted with R^3 and additionally with with one or more R^{3a} ,  substituted

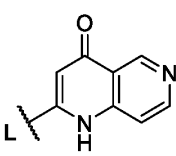
with R^3 and additionally with with one or more R^{3a} ,  (i.e. where R^{3a} is oxo)
or N-oxide thereof substituted with R^3 and additionally with with one or more R^{3a} ,

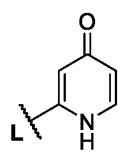
 (i.e. where R^{3a} is oxo) substituted with R^3 and additionally with with one or more

R^{3a} , or  substituted with R^3 and additionally with with one or more R^{3a} ; and where

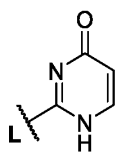
$L^{\sim}$ designates attachment to L . In some or any embodiments including embodiments A-1g,

ring A is  or N-oxide thereof substituted with R^3 and additionally with with one or more R^{3a} and where $L^{\sim}$ designates attachment to L . In some or any embodiments including

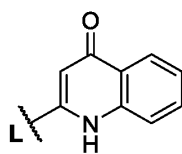
embodiments A-1g, ring A is  (i.e. where R^{3a} is oxo) substituted with R^3 and additionally with with one or more R^{3a} and where $L^{\sim}$ designates attachment to L . In some or

any embodiments including embodiments A-1g, ring A is  (i.e. where R^{3a} is oxo)

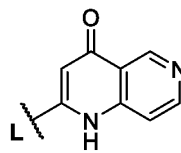
substituted with R^3 and and additionally with with one or more R^{3a} where $L^{\sim}$ designates attachment to L . In some or any embodiments including embodiments A-1g, ring A is



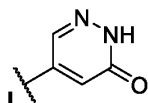
(i.e. where R^{3a} is oxo) substituted with R^3 and additionally with with one or more R^{3a} and where L designates attachment to L . In some or any embodiments including



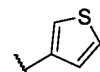
embodiments A-1g, **ring A** is (i.e. where R^{3a} is oxo) substituted with R^3 and additionally with with one or more R^{3a} and where L designates attachment to L . In some or



any embodiments including embodiments A-1g, **ring A** is (i.e. where R^{3a} is oxo) or N-oxide thereof substituted with R^3 and additionally with with one or more R^{3a} and where L designates attachment to L . In some or any embodiments including embodiments

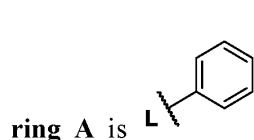


A-1g, **ring A** is (i.e. where R^{3a} is oxo) substituted with R^3 and additionally with with one or more R^{3a} and where L designates attachment to L . In some or any embodiments

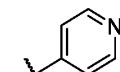


including embodiments A-1g, **ring A** is substituted with R^3 and where L designates attachment to L .

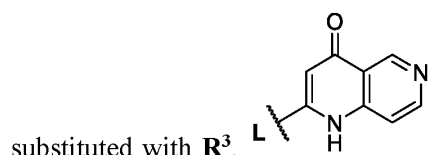
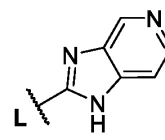
[0095] Embodiment 2b-1: In some or any embodiments including embodiments A-1g,



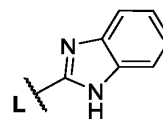
substituted with R^3 ,



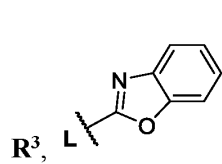
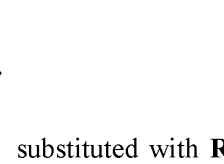
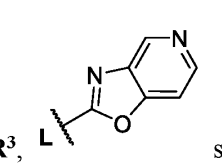
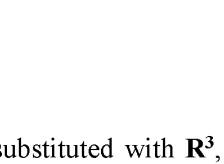
substituted with R^3 ,

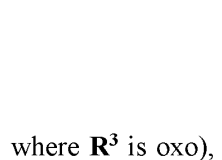
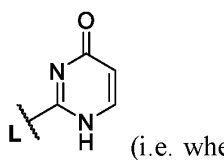


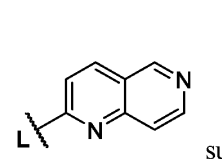
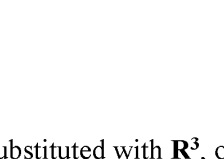
(i.e. where R^3 is oxo),

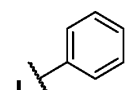


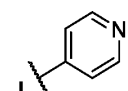
substituted with

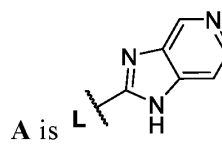
 substituted with R^3 ,  substituted with R^3 ,  substituted with R^3 ,  (i.e.

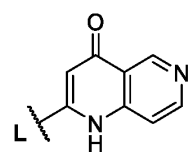
where R^3 is oxo),  (i.e. where R^3 is oxo),  (i.e. where R^3 is oxo),

 substituted with R^3 , or  (i.e. where R^3 is oxo); where **ring A** is substituted with $(R^{3a})_q$; and where $L^{\sim}$ designates attachment to **L**. In some or any

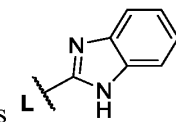
embodiments including embodiments A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments including

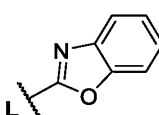
embodiments A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments including embodiments A-1g, **ring**

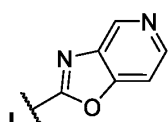
A is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to

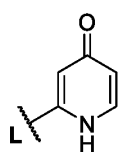
L. In some or any embodiments including embodiments A-1g, **ring A** is  (i.e.

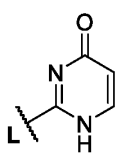
where R^3 is oxo) substituted with $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some

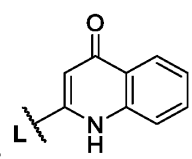
or any embodiments including embodiments A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments

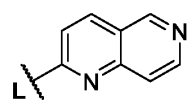
including embodiments A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments including embodiments

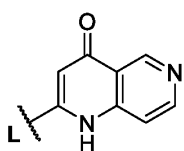
A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments including embodiments A-1g, **ring A** is

 (i.e. where R^3 is oxo) substituted with $(R^{3a})_q$, and where $L^{\sim}$ designates attachment

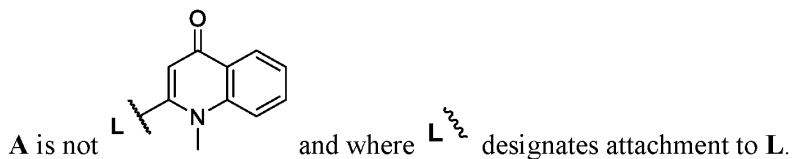
to **L**. In some or any embodiments including embodiments A-1g, **ring A** is  (i.e. where R^3 is oxo) substituted with $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some

or any embodiments including embodiments A-1g, **ring A** is  (i.e. where R^3 is oxo) substituted with $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any

embodiments including embodiments A-1g, **ring A** is  substituted with R^3 and $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**. In some or any embodiments including

embodiments A-1g, **ring A** is  (i.e. where R^3 is oxo) substituted with $(R^{3a})_q$, and where $L^{\sim}$ designates attachment to **L**.

[0096] **Embodiment 2c:** In some or any embodiments including embodiments A-1g, **ring**



[0097] **Embodiment 3:** In some or any embodiments, including embodiments A-2a1, **W¹** is CH and **W²** is CH. In some or any embodiments, including embodiments A-2a1, **W¹** is CH and **W²** is N.

[0098] **Embodiment 3a:** In some or any embodiments, including embodiments A-2a1, **W¹** is CR^x and **W²** is CH where **R^x** is C₁₋₃ alkyl. In some or any embodiments, including embodiments A-2a1, **W¹** is CH and **W²** is CR^x where **R^x** is C₁₋₃ alkyl. In some or any embodiments, including embodiments A-21a, **W¹** is CR^x and **W²** is N where **R^x** is C₁₋₃ alkyl. In some or any embodiments, including embodiments A-2a1, **W¹** is N and **W²** is CR^x where **R^x** is C₁₋₃ alkyl. In some or any embodiments, including embodiments A-2a1, **W¹** is CR^x and **W²** is CR^x where each **R^x** is C₁₋₃ alkyl.

[0099] **Embodiment 3b:** In some or any embodiments, including embodiments A-2a1, **W¹** is CR^x and **W²** is CH where **R^x** is methyl. In some or any embodiments, including embodiments A-2a1, **W¹** is CH and **W²** is CR^x where **R^x** is methyl. In some or any embodiments, including embodiments A-2a1, **W¹** is CR^x and **W²** is N where **R^x** is methyl. In some or any embodiments, including embodiments A-2a1, **W¹** is N and **W²** is CR^x where **R^x** is methyl. In some or any embodiments, including embodiments A-2a1, **W¹** is CR^x and **W²** is CR^x where each **R^x** is methyl.

[00100] **Embodiment 4:** In some or any embodiments including embodiments A-3b, at least one **R²** is C₁₋₆ alkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is C₁₋₃ alkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is halogen. In some or any embodiments including embodiments A-3b, at least one **R²** is C₁₋₃ haloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is C₃₋₆ cycloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is aryl.

[00101] **Embodiment 4a-1:** In some or any embodiments including embodiments A-3b, **R²**, independently in each instance, is -CH₃, -F, -CF₃, -CH₂CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some or any embodiments including embodiments A-3b, **R²**, independently in each instance, is selected from halo and C₁₋₃ haloalkyl. In some or any embodiments including embodiments A-3b, **R²** is -CH₃. In some or any embodiments

including embodiments A-3b, **R²** is -F. In some or any embodiments including embodiments A-3b, **R²** is -CF₃. In some or any embodiments including embodiments A-3b, **R²** is -CH₂CF₃. In some or any embodiments including embodiments A-3b, **R²** is cyclopropyl. In some or any embodiments including embodiments A-3b, **R²** is cyclobutyl. In some or any embodiments including embodiments A-3b, **R²** is cyclopentyl. In some or any embodiments including embodiments A-3b, **R²** is cyclohexyl. In some or any embodiments including embodiments A-3b, **R²** is phenyl.

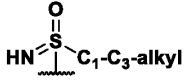
[00102] Embodiment 4a-2: In some or any embodiments including embodiments A-3b, **R²**, independently in each instance, is -CH₃, -CH₂CH₃, -F, -CF₃, -CH₂CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some or any embodiments including embodiments A-3b, **R²** is -CH₂CH₃.

[00103] Embodiment 4a-3: In some or any embodiments including embodiments A-3b, **R²**, independently in each instance, is -CH₃, -CH₂CH₃, -CH(CH₃)₂, -C(CH₃)₃, -F, -CF₃, -CH₂CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or naphthyl.

[00104] Embodiment 4b: In some or any embodiments including embodiments A-3b, at least one **R²** is cyano. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)C₁₋₆alkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)haloC₁₋₆alkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)C₃₋₆cycloalkyl optionally substituted with 1, 2, or 3 **R^{2a}** groups independently selected from halo, -CN, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)aryl optionally substituted with 1, 2, or 3 **R^{2a}** groups independently selected from halo, -CN, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is 5- to 6-membered heteroaryl. In some or any embodiments including embodiments A-3, at least one **R²** is -C(O)CH₃. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)CF₃. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)cyclohexyl optionally substituted with 1, 2, or 3 **R^{2a}** groups independently selected from halo, -CN, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is -C(O)phenyl optionally substituted with 1, 2, or 3 **R^{2a}** groups independently selected from halo, -CN, C₁₋₆alkyl, and C₁₋₆haloalkyl. In some or any embodiments including embodiments A-3b, at least one **R²** is pyridinyl. In some or any embodiments including embodiments A-3b, at least one **R²** is pyrimidinyl.

[00105] **Embodiment 4c:** In some or any embodiments, including Embodiments A-4a-3, one R^2 is present. In some or any embodiments, including Embodiments A-4a-3, two R^2 are present. In some or any embodiments, including Embodiments A-4a-3, three R^2 are present.

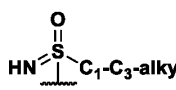
[00106] **Embodiment 5:** In some or any embodiments including embodiments A-4c, R^3 is H. In some or any embodiments including embodiments A-4c, R^3 is -CN. In some or any embodiments including embodiments A-4c, R^3 is halo. In some or any embodiments including embodiments A-4c, R^3 is -OH. In some or any embodiments including embodiments A-4c, R^3 is oxo. In some or any embodiments including embodiments A-4c, R^3 is -B(OH)₂. In some or any embodiments including embodiments A-4c, R^3 is -COOH. In some or any embodiments including embodiments A-4c, R^3 is C₁-C₆ alkoxycarbonyl. In some or any embodiments including embodiments A-4c, R^3 is C₁-C₆ alkyl. In some or any embodiments including embodiments A-4c, R^3 is hydroxy-C₁-C₆-alkyl. In some or any embodiments including embodiments A-4c, R^3 is -C(=NH)NH₂. In some or any embodiments including embodiments A-4c, R^3 is -C(O)NH₂. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂NHR, wherein R is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂NHR, wherein R is hydrogen. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂NHR, wherein R is C₁-C₃ alkyl. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂NHR, wherein R is C₃-C₅cycloalkyl. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂C₁-

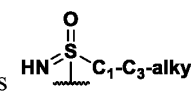
C₆-alkyl. In some or any embodiments including embodiments A-4c, R^3 is . In some or any embodiments including embodiments A-4c, R^3 is C₁-C₆ alkoxy. In some or any embodiments including embodiments A-4c, R^3 is -NH₂. In some or any embodiments including embodiments A-4c, R^3 is amino-C₁-C₆alkyl. In some or any embodiments including embodiments A-4c, R^3 is amino-C₁-C₆alkyl, wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo. In some or any embodiments including embodiments A-4c, R^3 is amino-C₁-C₆alkyl, wherein the alkyl in amino-C₁-C₆alkyl is further substituted with 1, 2, 3, or 4 halo. In some or any embodiments including embodiments A-4c, R^3 is -NHC(O)C₁₋₃alkyl. In some or any embodiments including embodiments A-4c, R^3 is -NHC(O)NH₂. In some or any embodiments including embodiments A-4b, R^3 is -NHS(O)₂NH₂. In some or any embodiments including embodiments A-4c, R^3 is -NHC(=NH)NH₂. In some or any embodiments including embodiments A-4c, R^3 is halo-C₁-C₃alkyl. In some or any embodiments including embodiments A-4c, R^3 is C₃-C₆-cycloalkyl. In

some or any embodiments including embodiments 1-4c, R^3 is C₃-C₆-cycloalkyl optionally substituted with one -NH₂. In some or any embodiments including embodiments A-4c, R^3 is C₃-C₆-cycloalkyl substituted with one -NH₂. In some or any embodiments including embodiments A-4c, R^3 is 3- to 6-membered heterocycloalkyl. In some or any embodiments including embodiments A-4c, R^3 is 3- to 6-membered heterocycloalkyl optionally substituted with one -NH₂. In some or any embodiments including embodiments A-4c, R^3 is 3- to 6-membered heterocycloalkyl substituted with one -NH₂.

[00107] **Embodiment 5a:** In some or any embodiments including embodiments A-4c, R^3 is -C(O)N(R)₂ wherein each R is C₁₋₃ alkyl. In some or any embodiments including embodiments A-4c, R^3 is 5- to 6-membered heteroaryl.

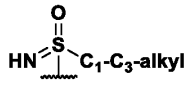
[00108] **Embodiment 5b:** In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -CN, -OH, oxo, C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -

C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR, -S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, or amino-C₁-C₆-alkyl, and wherein R is hydrogen or C₃-C₅-cycloalkyl. In some or any embodiments, R^3 is -CN, -OH, C₁-C₆ alkoxy, -C(O)NH₂, -S(O)₂NH₂, -COOEt, or oxo. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -CN. In some or any embodiments including embodiments A-4b, R^3 is not -H and R^3 is -OH. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is oxo. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is C₁-C₆ alkoxy. In some or any embodiments including embodiments A-4c, R^3 is -COOEt. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is C₁-C₆ alkyl. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is hydroxy-C₁-C₆-alkyl. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -C(=NH)NH₂. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -C(O)NH₂. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -S(O)₂NHR, wherein R is hydrogen or C₃-C₅-cycloalkyl. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -S(O)₂NH₂. In some or any embodiments including embodiments A-4c, R^3 is -S(O)₂NH₂. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -S(O)₂C₁-C₆-alkyl. In some or any

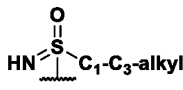
embodiments including embodiments A-4c, R^3 is not -H and R^3 is . In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is C₁-C₆ alkoxy. In

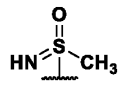
some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -NH₂. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is amino-C₁-C₆alkyl.

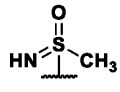
[00109] Embodiment 5b-1: In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -CN, -OH, oxo, C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy-C₁-C₆alkyl,

-C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR, -S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, or amino-C₁-C₆alkyl, and wherein R is alkyl. In some or any embodiments including embodiments A-4c, R^3 is not -H and R^3 is -S(O)₂NHR, wherein R is alkyl.

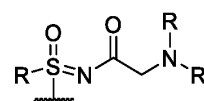
[00110] Embodiment 5c: In some or any embodiments including embodiments A-4c, R^3 is -CN, -OH, oxo, C₁-C₆ alkoxy, -C(O)NH₂,

-S(O)₂NH₂, -S(O)₂C₁-C₆-alkyl, , or C₁-C₆ alkoxy. In some or any embodiments, including embodiments A-4c, R^3 is -CN, -OH, oxo, -COOEt, -C(O)NH₂,

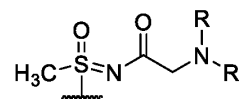
-S(O)₂NH₂, -S(O)₂CH₃, , or -OMe. In some or any embodiments including embodiments A-4b, R^3 is -S(O)₂CH₃. In some or any embodiments including embodiments A-

4c, R^3 is . In some or any embodiments including embodiments A-4b, R^3 is -OMe.

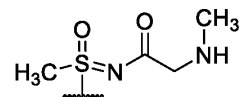
[00111] Embodiment 5d: In some or any embodiments including embodiments A-4c, R^3 is -COOH or -C(O)N(R)₂. In some or any embodiments including embodiments A-4c, R^3 is -COOH, C(O)NH₂, or -C(O)N(CH₃)₂. In some or any embodiments including embodiments A-4c, R^3 is -C(O)N(CH₃)₂. In some or any embodiments including embodiments A-4b, R^3 is



. In some or any embodiments including embodiments A-4c, R^3 is



. In some or any embodiments including embodiments A-4c, R^3 is



[00112] Embodiment 6: In some or any embodiments including embodiments A-5d, at least one R^{3a} is hydrogen. In some or any embodiments including embodiments A-5d, at least one R^{3a} is oxo. In some or any embodiments including embodiments A-5d, at least one R^{3a} is

halogen. In some or any embodiments including embodiments A-5d, at least one R^{3a} is C_1 - C_3 alkyl. In some or any embodiments including embodiments A-5d, at least one R^{3a} is C_3 - C_6 cycloalkyl.

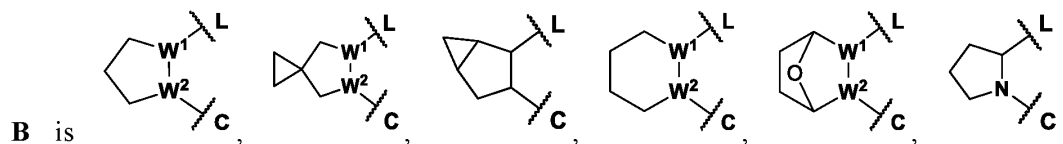
[00113] **Embodiment 6a:** In some or any embodiments including embodiments A-5d, at least one R^{3a} is -H, halo, oxo, or C_1 - C_3 alkyl. In some or any embodiments including embodiments A-5d, at least one R^{3a} is -H, -F, oxo, or $-CH_3$. In some or any embodiments including embodiments A-5d, at least one R^{3a} is -F. In some or any embodiments including embodiments A-5d, at least one R^{3a} is $-CH_3$.

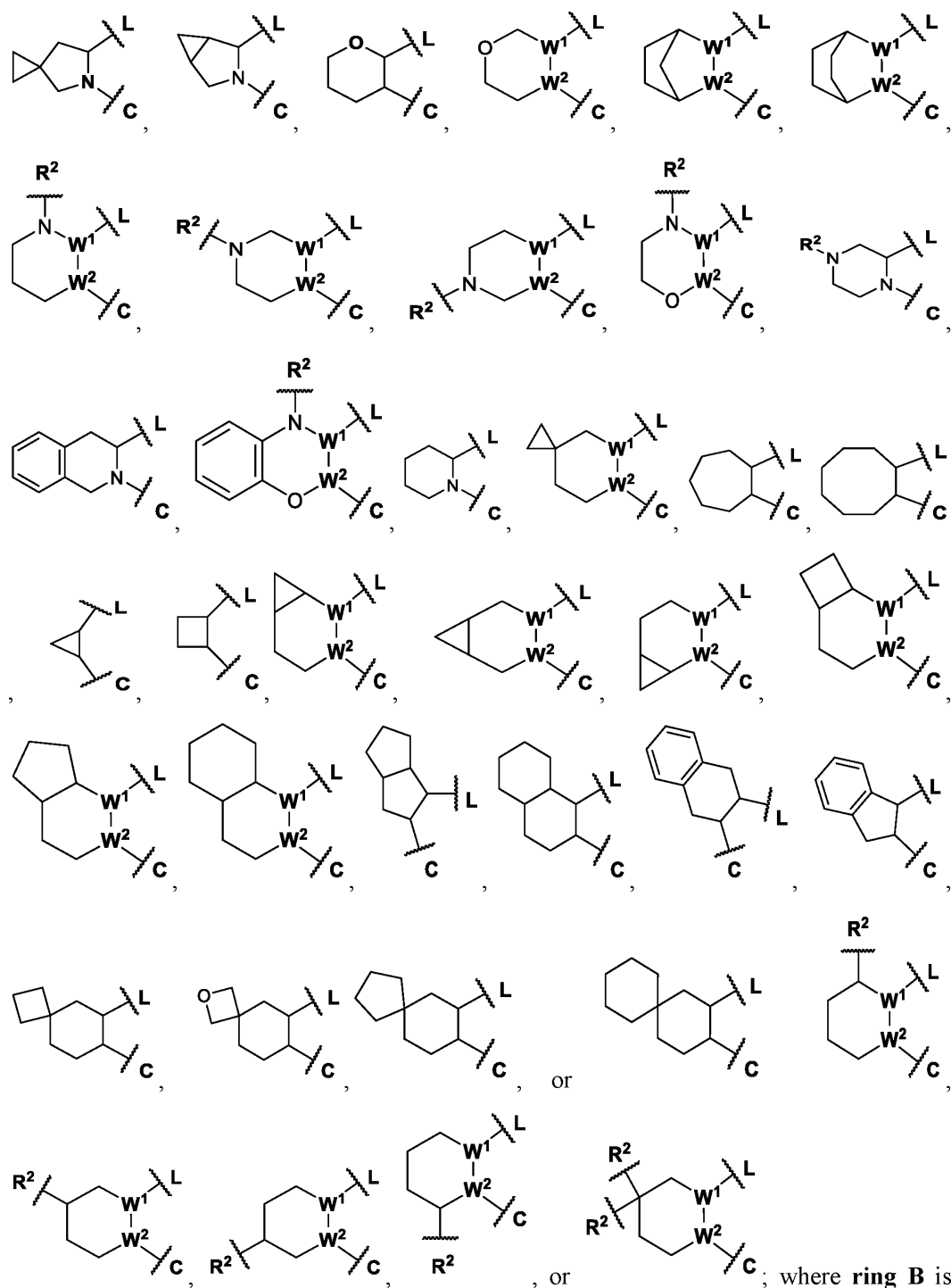
[00114] **Embodiment 6b:** In some or any embodiments, including Embodiments A-6a, one R^{3a} is present. In some or any embodiments, including Embodiments A-6a, two R^{3a} are present. In some or any embodiments, including Embodiments A-6a, three R^{3a} are present.

[00115] **Embodiment 7:** In some or any embodiments including embodiments A-6b, **ring B** is a 3- to 10-membered cycloalkylene. In some or any embodiments including embodiments A-6b, **ring B** is a 3- to 11-membered cycloalkylene (in some embodiments, 3- to 10-membered cycloalkylene) optionally fused to a benzo group. In some or any embodiments including embodiments A-6b, **ring B** is a 3- to 11-membered cycloalkylene (in some embodiments, 3- to 10-membered cycloalkylene) fused to a benzo group. In some or any embodiments including embodiments A-6b, **ring B** is a 5- to 10-membered heterocycloalkylene ring. In some or any embodiments including embodiments A-6b, **ring B** is a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group. In some or any embodiments including embodiments A-6b, **ring B** is a 5- to 10-membered heterocycloalkylene ring fused to a benzo group.

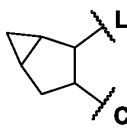
[00116] **Embodiment 7a:** In some or any embodiments including embodiments A-6b, **ring B** is a 3- to 11-membered cycloalkylene (in some embodiments, 3- to 10-membered cycloalkylene); or a 6-, 7-, or 10-membered heterocycloalkyl; where **ring B** is substituted with $(R^2)_p$. In some or any embodiments including embodiments A-6b, **ring B** is a 3- to 11-membered cycloalkylene (in some embodiments, 3- to 10-membered cycloalkylene) where **ring B** is substituted with $(R^2)_p$. In some or any embodiments including embodiments A-6b, **ring B** is a 6-, 7-, or 10-membered heterocycloalkyl where **ring B** is substituted with $(R^2)_p$.

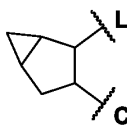
[00117] **Embodiment 7b:** In some or any embodiments including embodiments A-6b, **ring B**

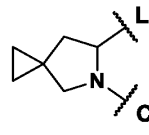


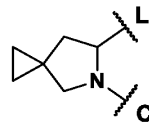


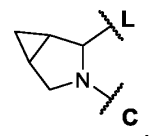
substituted with $(\mathbf{R}^2)_p$; and where $\overset{\text{wavy}}{\text{L}}$ designates attachment to $\mathbf{L}$, $\overset{\text{wavy}}{\mathbf{C}}$ designates attachment to **ring C**, and $\overset{\mathbf{R}^2}{\text{wavy}}$ designates attachment to $\mathbf{R}^2$. In some or any embodiments including

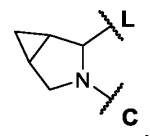


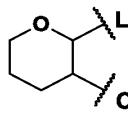
embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any

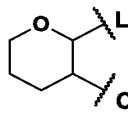


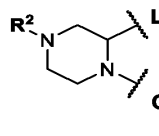
embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment

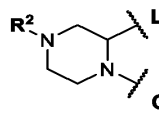


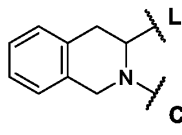
to **ring C**. In some or any embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments including embodiments A-

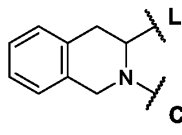


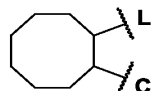
6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments including

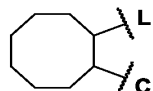


embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  R^2 designates attachment to R^2 . In some or any embodiments including embodiments A-6b, **ring B** is

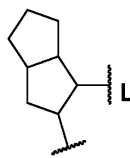


, where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments including

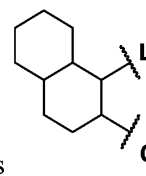


embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where

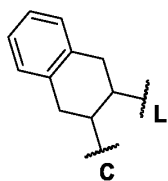
 **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any



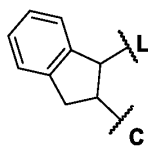
embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**.



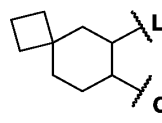
In some or any embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments including embodiments A-6b, **ring B** is



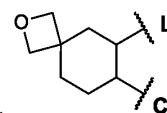
, where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments including



embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any

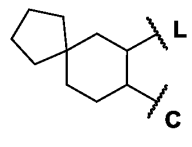


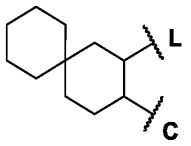
embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment



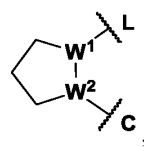
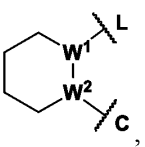
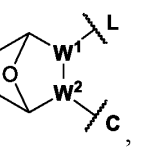
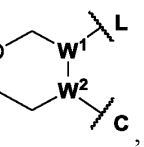
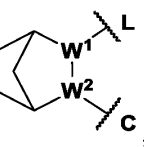
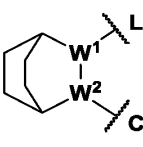
to **ring C**. In some or any embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,

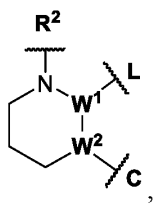
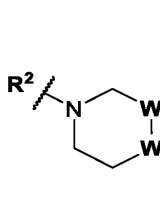
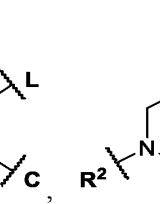
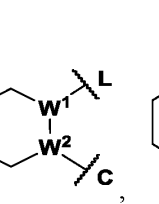
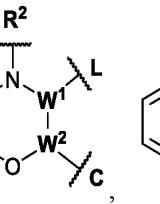
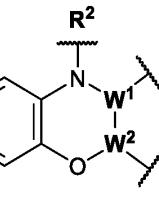
 **C** designates attachment to **ring C**. In some or any embodiments including embodiments A-

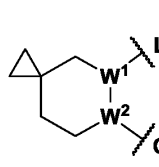
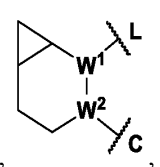
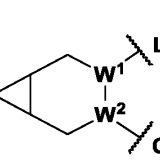
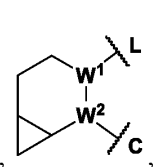
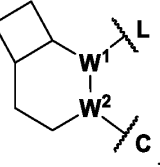
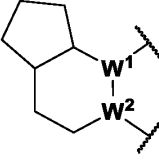
6b, **ring B** is , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**. In some or any embodiments

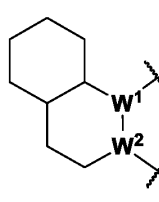
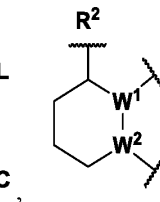
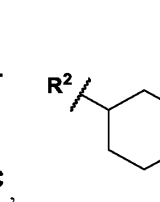
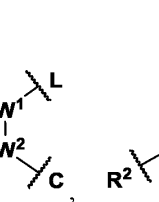
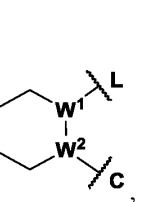
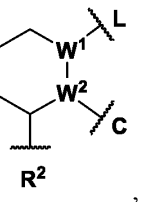
including embodiments A-6b, **ring B** is or , where **ring B** is substituted with $(R^2)_p$; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**.

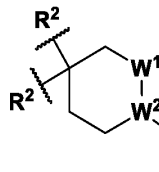
[00118] **Embodiment 7b-1:** In some or any embodiments including embodiments A-6b,

ring B is , , , , , ,

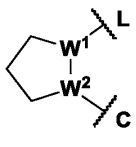
, , , , , ,

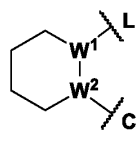
, , , , , ,

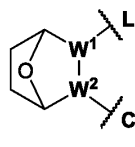
, , , , , , or

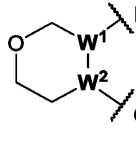
; where **ring B** is substituted with $(R^2)_p$; and where  **L** designates

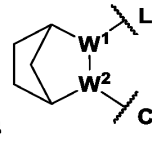
attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**.

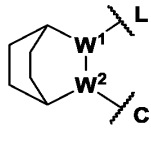
In some or any embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**. In some or any embodiments

including embodiments A-6b, **ring B** is , where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring**

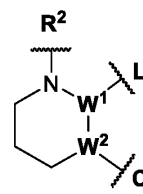
B is , where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**. In some or

any embodiments including embodiments A-6b, **ring B** is , where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**. In some or any embodiments including

embodiments A-6b, **ring B** is , where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to **L**,  **C** designates attachment to **ring C**, and  designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring B** is

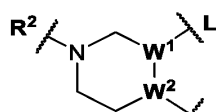
, where **ring B** is substituted with (**R²**)_p; and where  **L** designates attachment to

L,  C designates attachment to **ring C**, and  R² designates attachment to **R²**. In some or



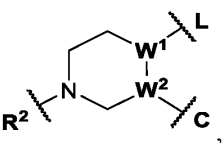
any embodiments including embodiments A-6b, **ring B** is

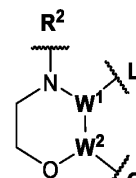
substituted with (R²)_p; and where  L designates attachment to **L**,  C designates attachment to **ring C**, and  R² designates attachment to **R²**. In some or any embodiments including



embodiments A-6b, **ring B** is

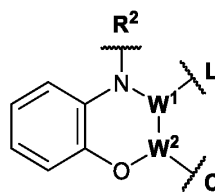
where  L designates attachment to **L**,  C designates attachment to **ring C**, and  R² designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring**

B is , where **ring B** is substituted with (R²)_p; and where  L designates attachment to **L**,  C designates attachment to **ring C**, and  R² designates attachment to **R²**.



In some or any embodiments including embodiments A-6b, **ring B** is

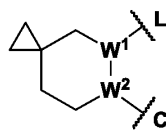
B is substituted with (R²)_p; and where  L designates attachment to **L**,  C designates attachment to **ring C**, and  R² designates attachment to **R²**. In some or any embodiments



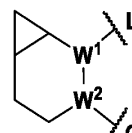
including embodiments A-6b, **ring B** is

(R²)_p; and where  L designates attachment to **L**,  C designates attachment to **ring C**, and

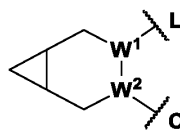
R^2 designates attachment to R^2 . In some or any embodiments including embodiments A-



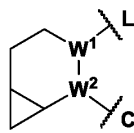
6b, **ring B** is substituted with $(\text{R}^2)_p$; and where L designates attachment to L , C designates attachment to **ring C**, and R^2 designates attachment to R^2 .



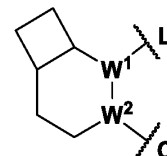
In some or any embodiments including embodiments A-6b, **ring B** is substituted with $(\text{R}^2)_p$; and where L designates attachment to L , C designates attachment to **ring C**, and R^2 designates attachment to R^2 . In some or any embodiments



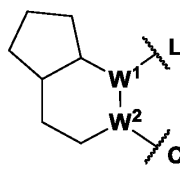
including embodiments A-6b, **ring B** is substituted with $(\text{R}^2)_p$; and where L designates attachment to L , C designates attachment to **ring C**, and R^2 designates attachment to R^2 . In some or any embodiments including embodiments A-



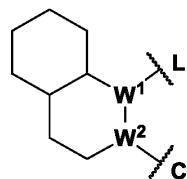
6b, **ring B** is substituted with $(\text{R}^2)_p$; and where L designates attachment to L , C designates attachment to **ring C**, and R^2 designates attachment to R^2 .



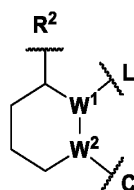
In some or any embodiments including embodiments A-6b, **ring B** is substituted with $(\text{R}^2)_p$; and where L designates attachment to L , C designates attachment to **ring C**, and R^2 designates attachment to R^2 . In some or any embodiments



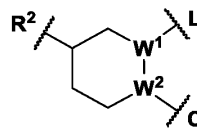
including embodiments A-6b, **ring B** is substituted with $(R^2)_p$; and where $\sim L$ designates attachment to **L**, $\sim C$ designates attachment to **ring C**, and $\sim R^2$ designates attachment to **R²**. In some or any embodiments including embodiments A-



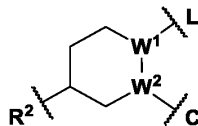
6b, **ring B** is substituted with $(R^2)_p$; and where $\sim L$ designates attachment to **L**, $\sim C$ designates attachment to **ring C**, and $\sim R^2$ designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring B** is



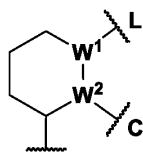
, where **ring B** is substituted with $(R^2)_p$; and where $\sim L$ designates attachment to **L**, $\sim C$ designates attachment to **ring C**, and $\sim R^2$ designates attachment to **R²**. In some or



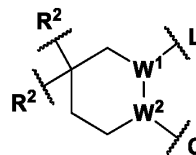
any embodiments including embodiments A-6b, **ring B** is substituted with $(R^2)_p$; and where $\sim L$ designates attachment to **L**, $\sim C$ designates attachment to **ring C**, and $\sim R^2$ designates attachment to **R²**. In some or any embodiments including



embodiments A-6b, **ring B** is substituted with $(R^2)_p$; and where $\sim L$ designates attachment to **L**, $\sim C$ designates attachment to **ring C**, and $\sim R^2$ designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring**

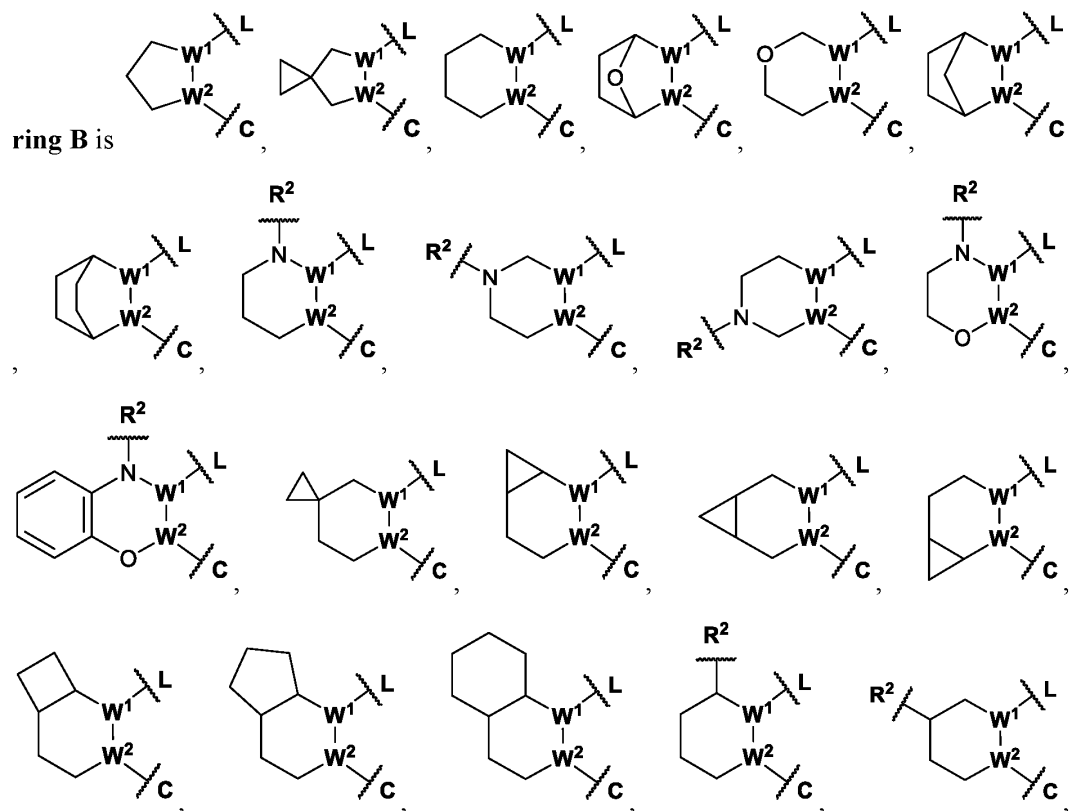


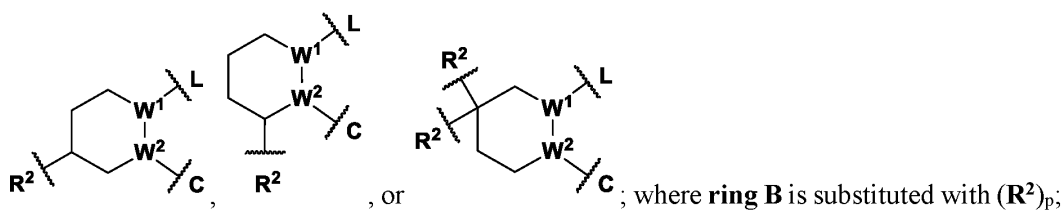
B is R^2 , where **ring B** is substituted with $(R^2)_p$; and where $\text{---}L$ designates attachment to **L**, $\text{---}C$ designates attachment to **ring C**, and $\text{---}R^2$ designates attachment to R^2 . In some or



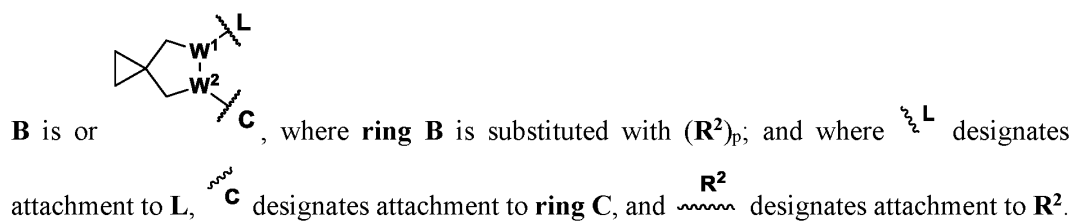
any embodiments including embodiments A-6b, **ring B** is substituted with $(R^2)_p$; and where $\text{---}L$ designates attachment to **L**, $\text{---}C$ designates attachment to **ring C**, and $\text{---}R^2$ designates attachment to R^2 .

[00119] **Embodiment 7b-2:** In some or any embodiments including embodiments A-6b,

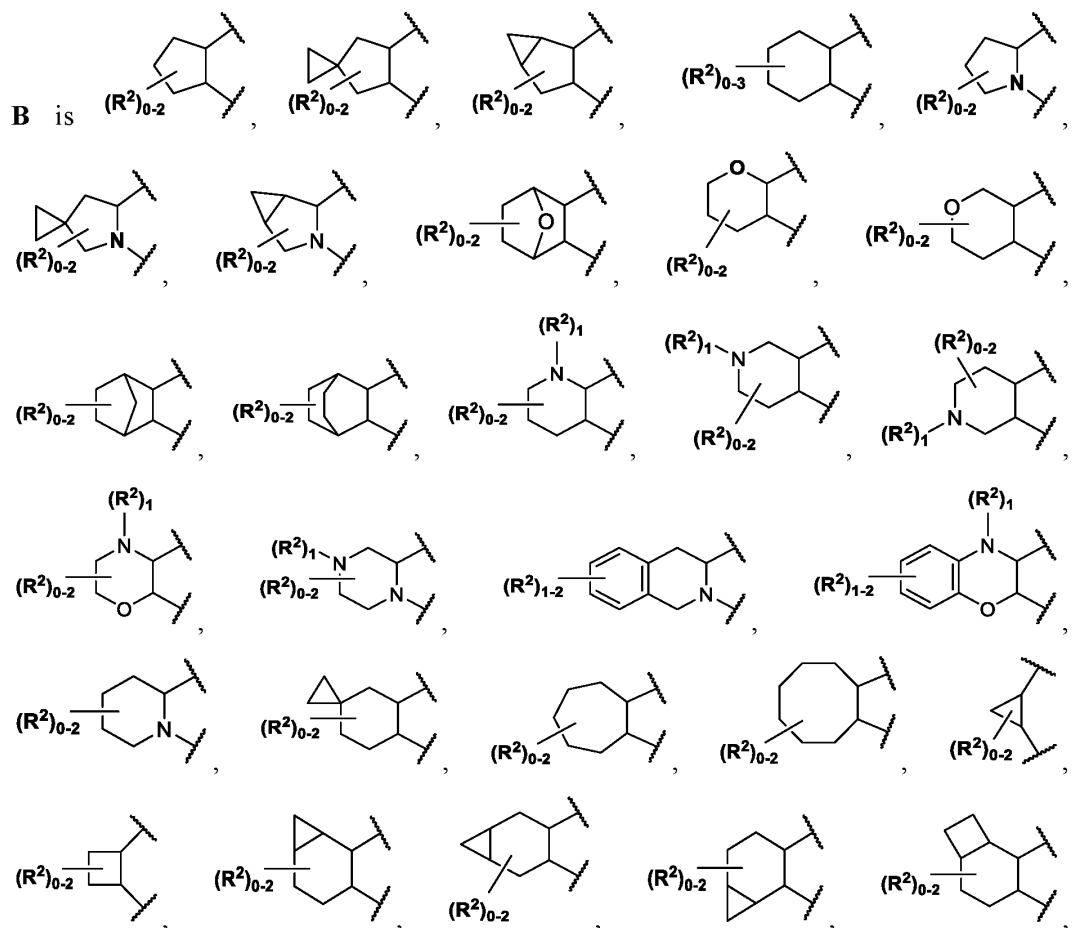


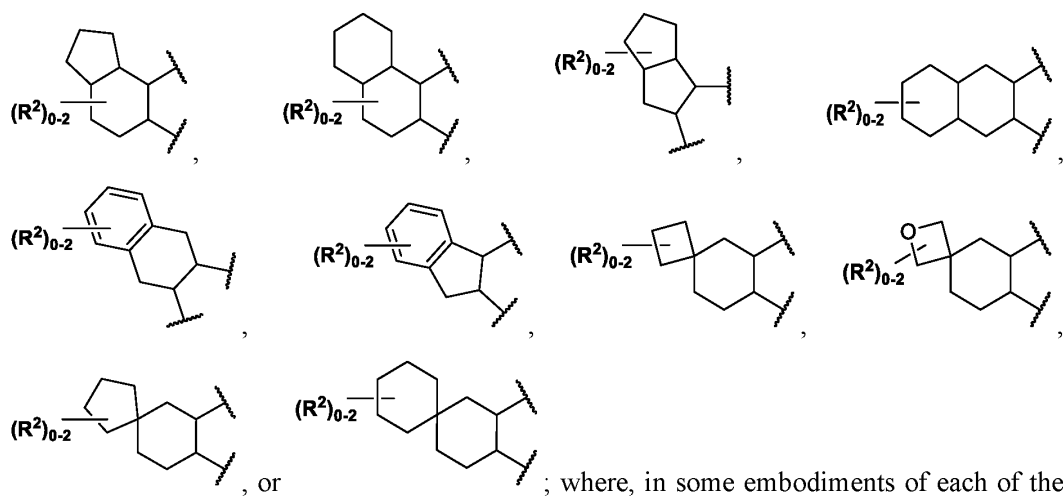


and where $\overset{\text{L}}{\sim}$ designates attachment to **L**, $\overset{\text{C}}{\sim}$ designates attachment to **ring C**, and $\overset{\text{R}^2}{\sim}$ designates attachment to **R²**. In some or any embodiments including embodiments A-6b, **ring**



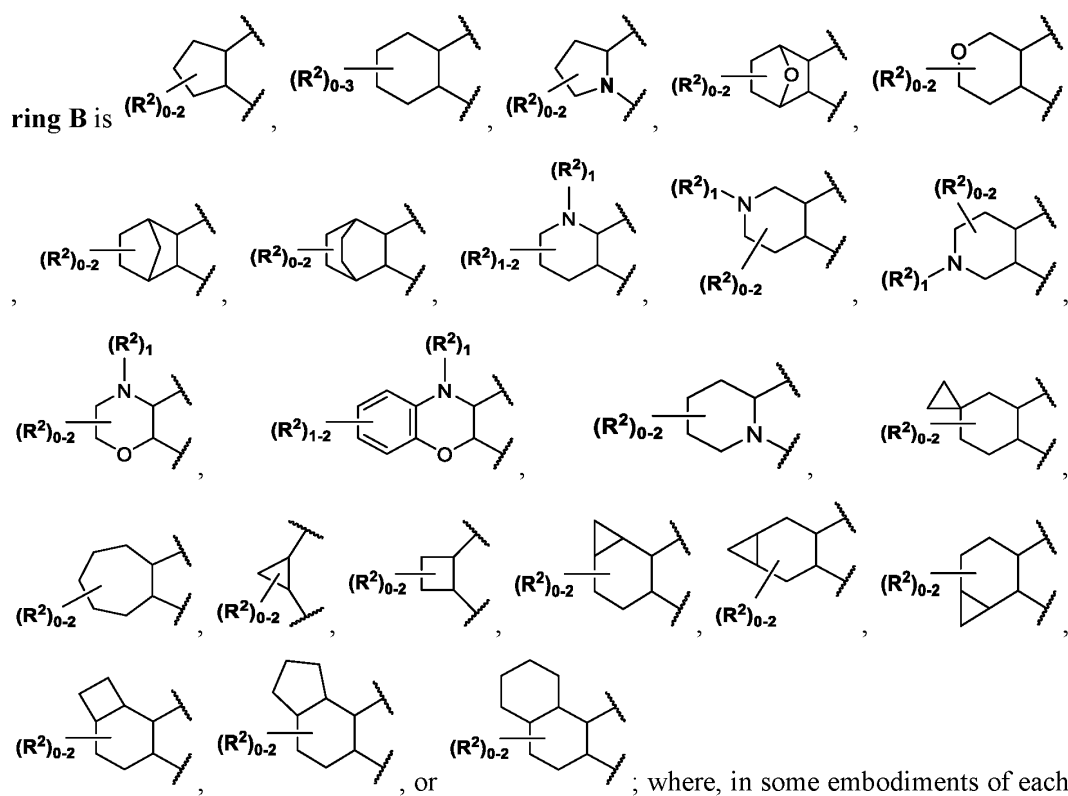
[00120] Embodiment 7c: In some or any embodiments including embodiments A-6b, **ring**





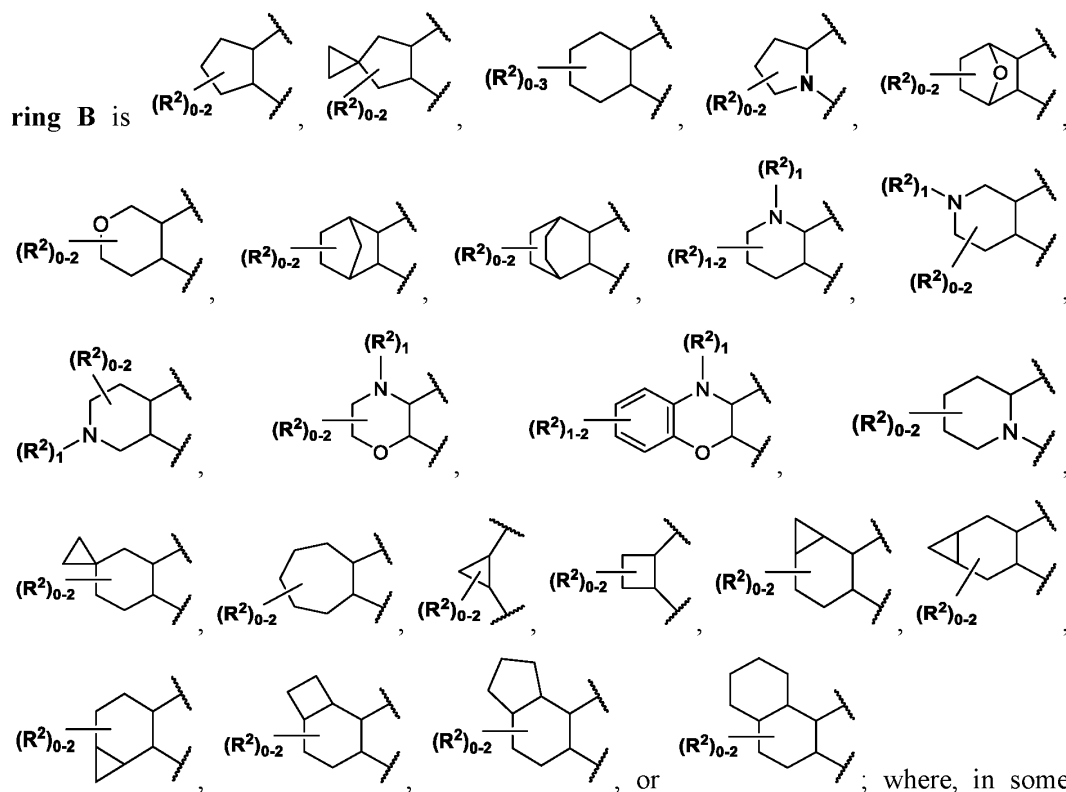
foregoing structures, the upper  is attached to L .

[00121] Embodiment 7c-1: In some or any embodiments including embodiments A-6b,



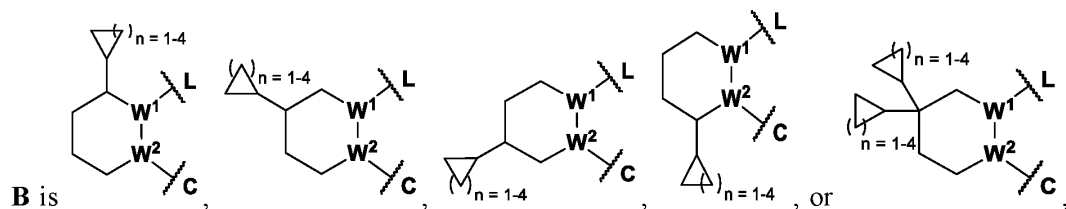
of the foregoing structures, the upper  is attached to **L**.

[00122] **Embodiment 7c-2:** In some or any embodiments including embodiments A-6b,



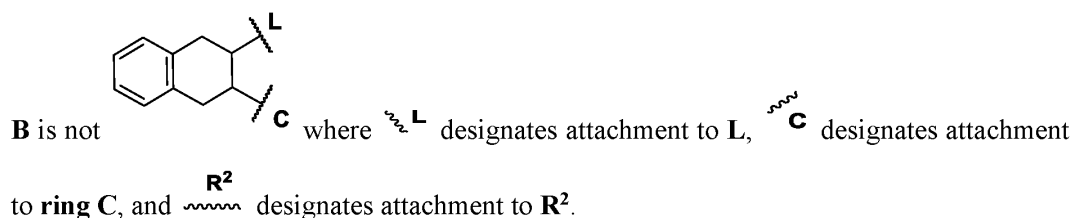
embodiments of each of the foregoing structures, the upper  is attached to L.

[00123] **Embodiment 7d:** In some or any embodiments including embodiments A-6b, ring

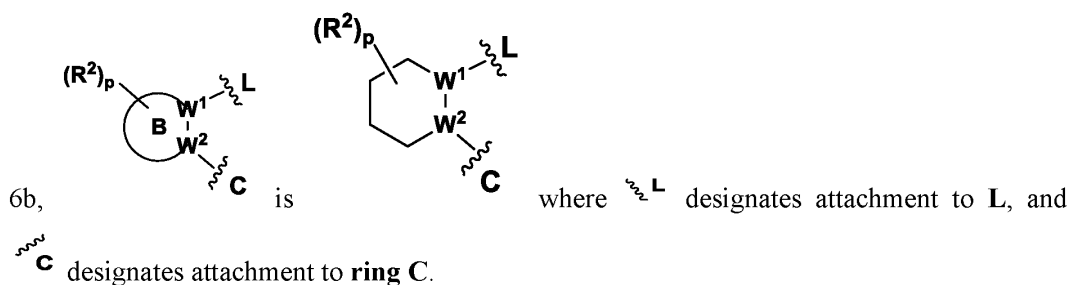
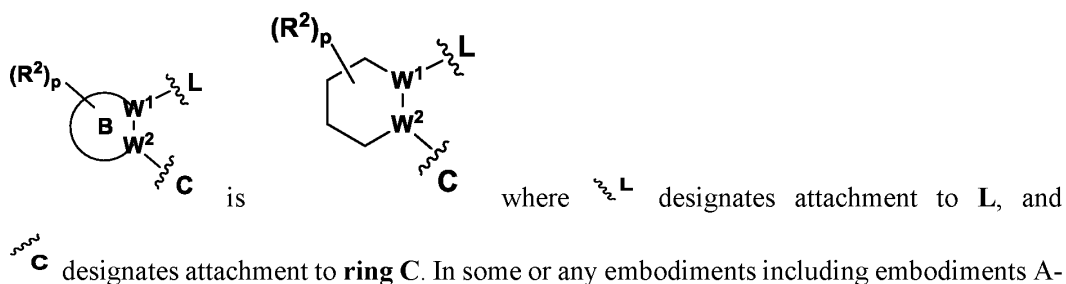


where  L designates attachment to L, and  C designates attachment to ring C.

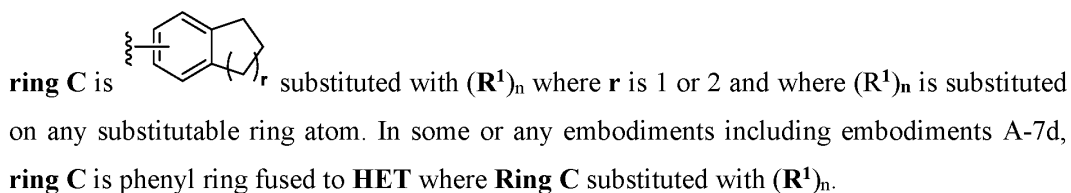
[00124] **Embodiment 7e:** In some or any embodiments including embodiments A-6b, ring



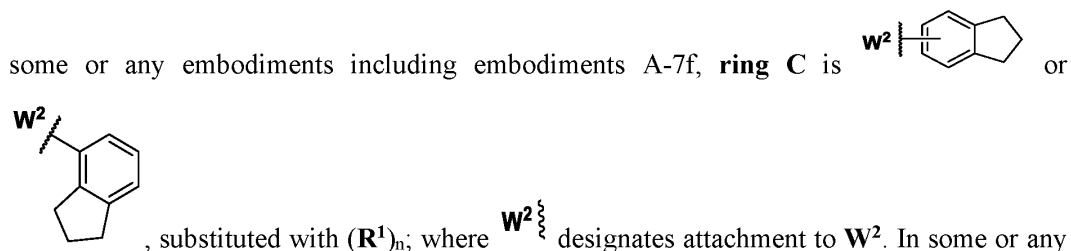
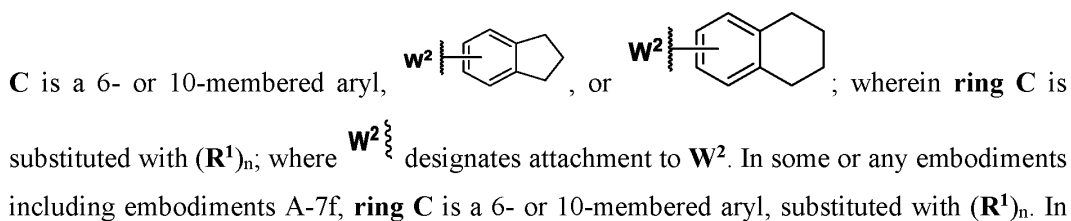
[00125] **Embodiment 7f:** In some or any embodiments including embodiments A-6b,

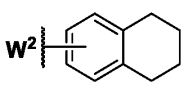


[00126] **Embodiment 8:** In some or any embodiments including embodiments A-7d, **ring C** is aryl substituted with $(\text{R}^1)_n$. In some or any embodiments including embodiments A-7d,



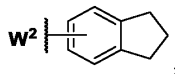
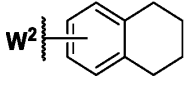
[00127] **Embodiment 8a:** In some or any embodiments including embodiments A-7f, **ring C**



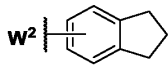
embodiments including embodiments A-7f, **ring C** is , substituted with $(R^1)_n$;

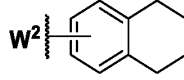
where W^2 designates attachment to W^2 .

[00128] **Embodiment 8a-1:** In some or any embodiments including embodiments A-7f,

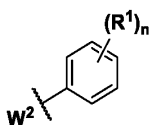
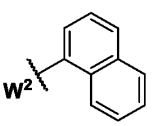
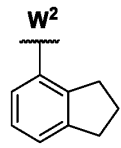
ring C is a 6- or 10-membered aryl, , or ; wherein **ring C** is

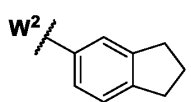
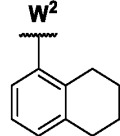
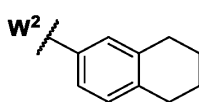
substituted with $(R^1)_n$; where W^2 designates attachment to W^2 . In some or any embodiments including embodiments A-7f, **ring C** is a 6- or 10-membered aryl, substituted with $(R^1)_n$. In

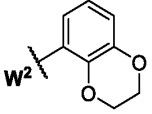
some or any embodiments including embodiments A-7f, **ring C** is , substituted with $(R^1)_n$; where W^2 designates attachment to W^2 . In some or any embodiments including

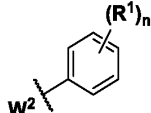
embodiments A-7f, **ring C** is , substituted with $(R^1)_n$; where W^2 designates attachment to W^2 .

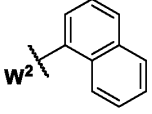
[00129] **Embodiment 8b:** In some or any embodiments including embodiments 1-7f, **ring**

C is , , substituted with $(R^1)_n$,  substituted with $(R^1)_n$,

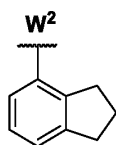
 substituted with $(R^1)_n$,  substituted with $(R^1)_n$, 

substituted with $(R^1)_n$, or  substituted with $(R^1)_n$; where W^2 designates attachment to W^2 . In some or any embodiments including embodiments A-7f, **ring C** is

, where W^2 designates attachment to W^2 . In some or any embodiments including

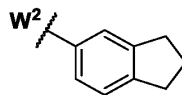
embodiments A-7f, **ring C** is  substituted with $(R^1)_n$, where W^2 designates

attachment to W^2 . In some or any embodiments including embodiments A-7f, **ring C** is



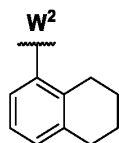
substituted with $(R^1)_n$, where W^2 designates attachment to W^2 . In some or any

embodiments including embodiments A-7f, **ring C** is



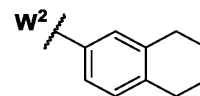
where W^2 designates attachment to W^2 . In some or any embodiments including embodiments

A-7f, **ring C** is



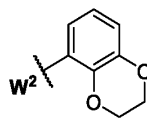
substituted with $(R^1)_n$, where W^2 designates attachment to W^2 . In

some or any embodiments including embodiments A-7f, **ring C** is



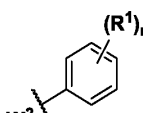
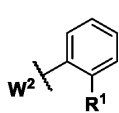
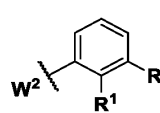
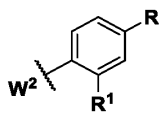
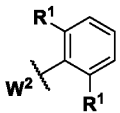
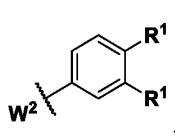
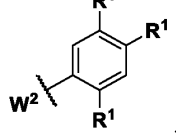
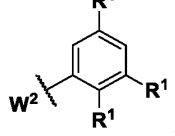
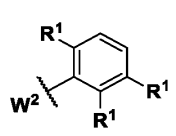
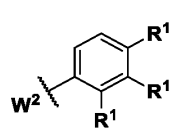
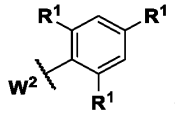
substituted with $(R^1)_n$, where W^2 designates attachment to W^2 . In some or any embodiments

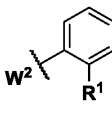
including embodiments A-7f, **ring C** is

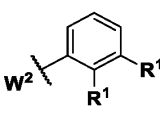


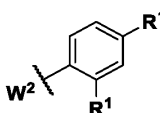
substituted with $(R^1)_n$ where W^2 designates attachment to W^2 .

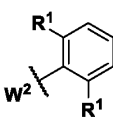
[00130] **Embodiment 8c:** In some or any embodiments including embodiments A-7f, where

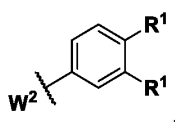
ring C is , **ring C** is , , , , , , , , , or ; where W^2 designates attachment to W^2 . In some or any embodiments

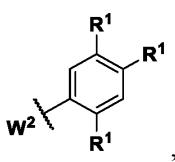
including embodiments A-7f, **ring C** is , where W^2 designates attachment to W^2 .

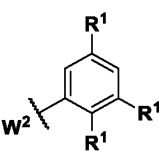
In some or any embodiments including embodiments A-7f, **ring C** is , where W^2 designates attachment to W^2 . In some or any embodiments including embodiments A-7d,

ring C is , where W^2 designates attachment to W^2 . In some or any

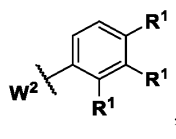
embodiments including embodiments A-7f, where **ring C** is , where W^2 designates attachment to W^2 . In some or any embodiments including embodiments A-7f, **ring C** is

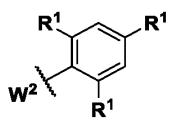
, where W^2 designates attachment to W^2 . In some or any embodiments

including embodiments A-7f, **ring C** is , where W^2 designates attachment to

W^2 . In some or any embodiments including embodiments A-7f, **ring C** is , where W^2 designates attachment to W^2 . In some or any embodiments including embodiments

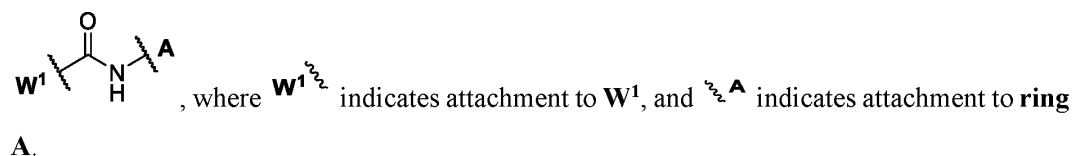
A-7f, **ring C** is , where W^2 designates attachment to W^2 . In some or any

embodiments including embodiments A-7f, **ring C** is , where W^2 designates attachment to W^2 . In some or any embodiments including embodiments A-7f, **ring C** is

 where W^2 designates attachment to W^2 .

[00131] **Embodiment 9:** In some or any embodiments including embodiments A-8c, **L** is a bond. In some or any embodiments including embodiments A-8c, **L** is -C(O)NH- where the nitrogen of -C(O)NH- is attached to **ring A**.

[00132] **Embodiment 9a:** In some or any embodiments including embodiments A-8c, **L** is



[00133] **Embodiment 10:** In some or any embodiments including embodiments A and 2-9a, **n** is 0. In some or any embodiments including embodiments A-1f and 2-9a, **n** is 1. In some or any embodiments including embodiments A-1f and 2-9a, **n** is 2. In some or any embodiments including embodiments A-1f and 2-9a, **n** is 3. In some or any embodiments including embodiments A-1f and 2-9a, **n** is 4.

[00134] **Embodiment 10a:** In some or any embodiments including embodiments A-1f and 2-9a, **n** is 1, 2, or 3.

[00135] **Embodiment 11:** In some or any embodiments including embodiments A-3 and 5-10a, **p** is 0. In some or any embodiments including embodiments A-4a and 5-10a, **p** is 1. In some or any embodiments including embodiments A-4a and 5-10a, **p** is 2. In some or any embodiments including embodiments A-4a and 5-10a, **p** is 3.

[00136] **Embodiment 11-1:** In some or any embodiments including embodiments A-3 and 5-10a, **p** is 4.

[00137] **Embodiment 11a:** In some or any embodiments including embodiments A-4a and 5-10a, **p** is 0, 1, or 2.

[00138] **Embodiment 12:** In some or any embodiments including embodiments A-5 and 7-11a, **q** is 0. In some or any embodiments including embodiments A-6a and 7-11a, **q** is 1. In some or any embodiments including embodiments A-6a and 7-11a, **q** is 2. In some or any embodiments including embodiments A-6a and 7-11a, **q** is 3.

[00139] **Embodiment 12a:** In some or any embodiments including embodiments A-6a and 7-11a, **q** is 0, 1, or 2.

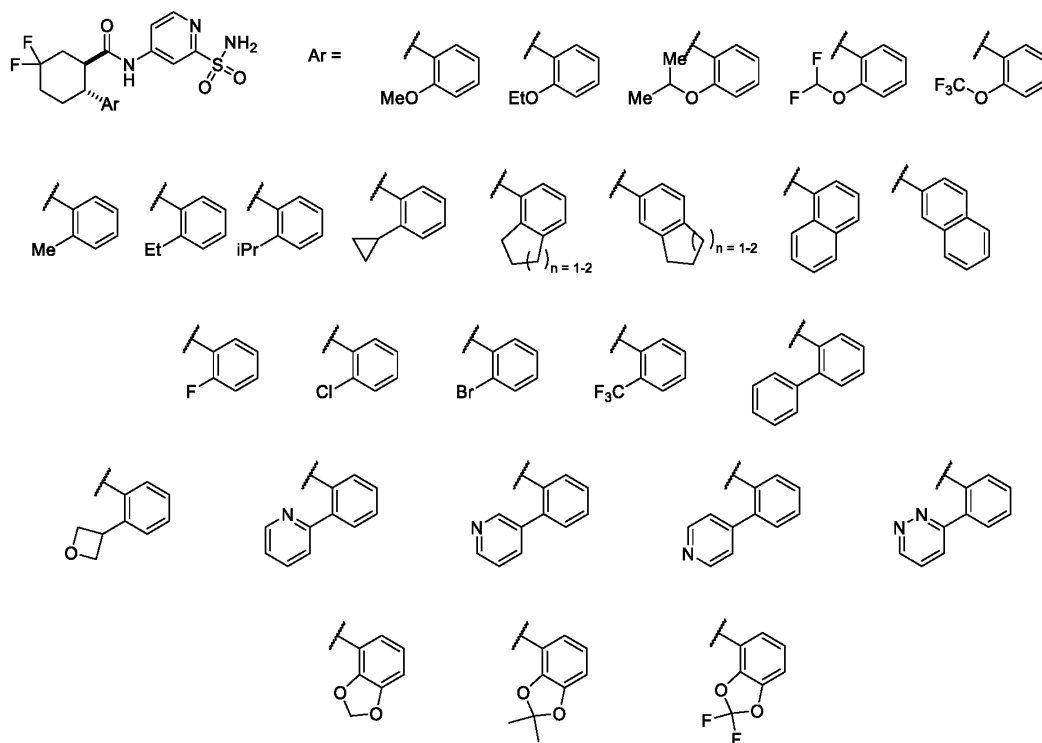
[00140] **Embodiment 13:** In some or any embodiments including embodiments A-12a, **n** is 0, 1, 2, or 3; **p** is 0, 1, 2, or 3; and **q** is 0 or 1.

[00141] **Embodiment 13a-1:** In some or any embodiments including embodiments A-12a, **n** is 0, **p** is 2, and **q** is 1; **n** is 1, **p** is 0, and **q** is 1; **n** is 1, **p** is 1, and **q** is 1; **n** is 1, **p** is 2, and **q**

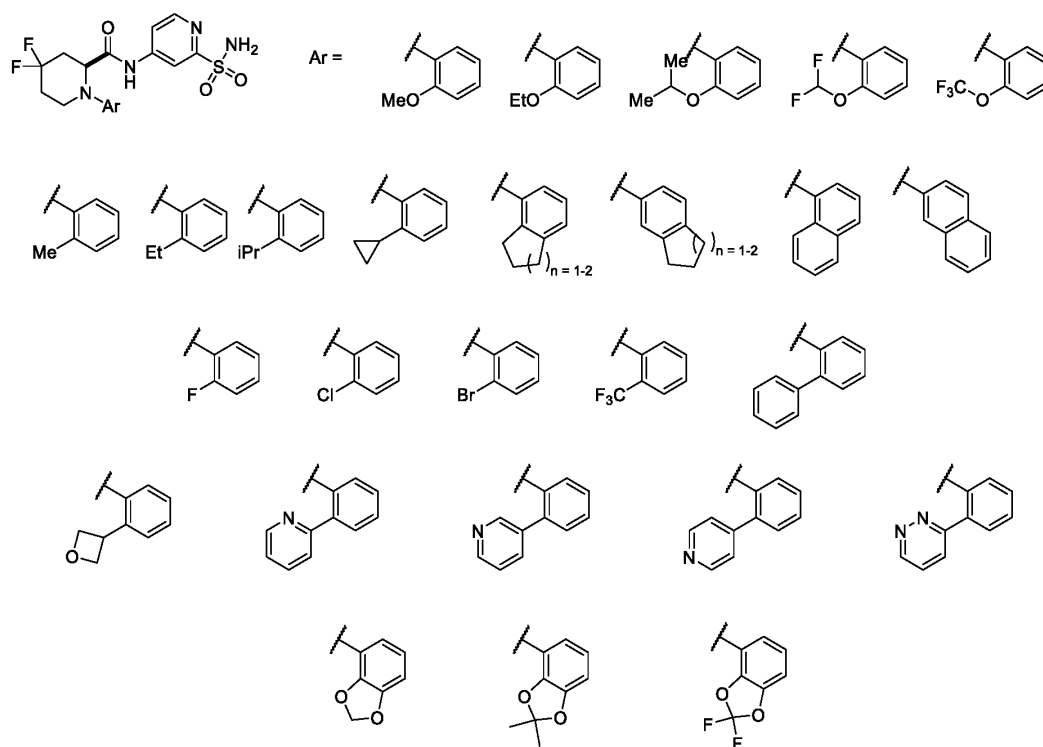
is 1; **n** is 2, **p** is 0, and **q** is 1; **n** is 2, **p** is 2, and **q** is 1; **n** is 3, **p** is 0, and **q** is 1; **n** is 3, **p** is 1, and **q** is 1; **n** is 3, **p** is 2, and **q** is 1; **n** is 3, **p** is 3, and **q** is 0; or **n** is 3, **p** is 3, and **q** is 1.

[00142] Embodiment 13a-2: In some or any embodiments including embodiments A-12a, **n** is 2, **p** is 1, and **q** is 1.

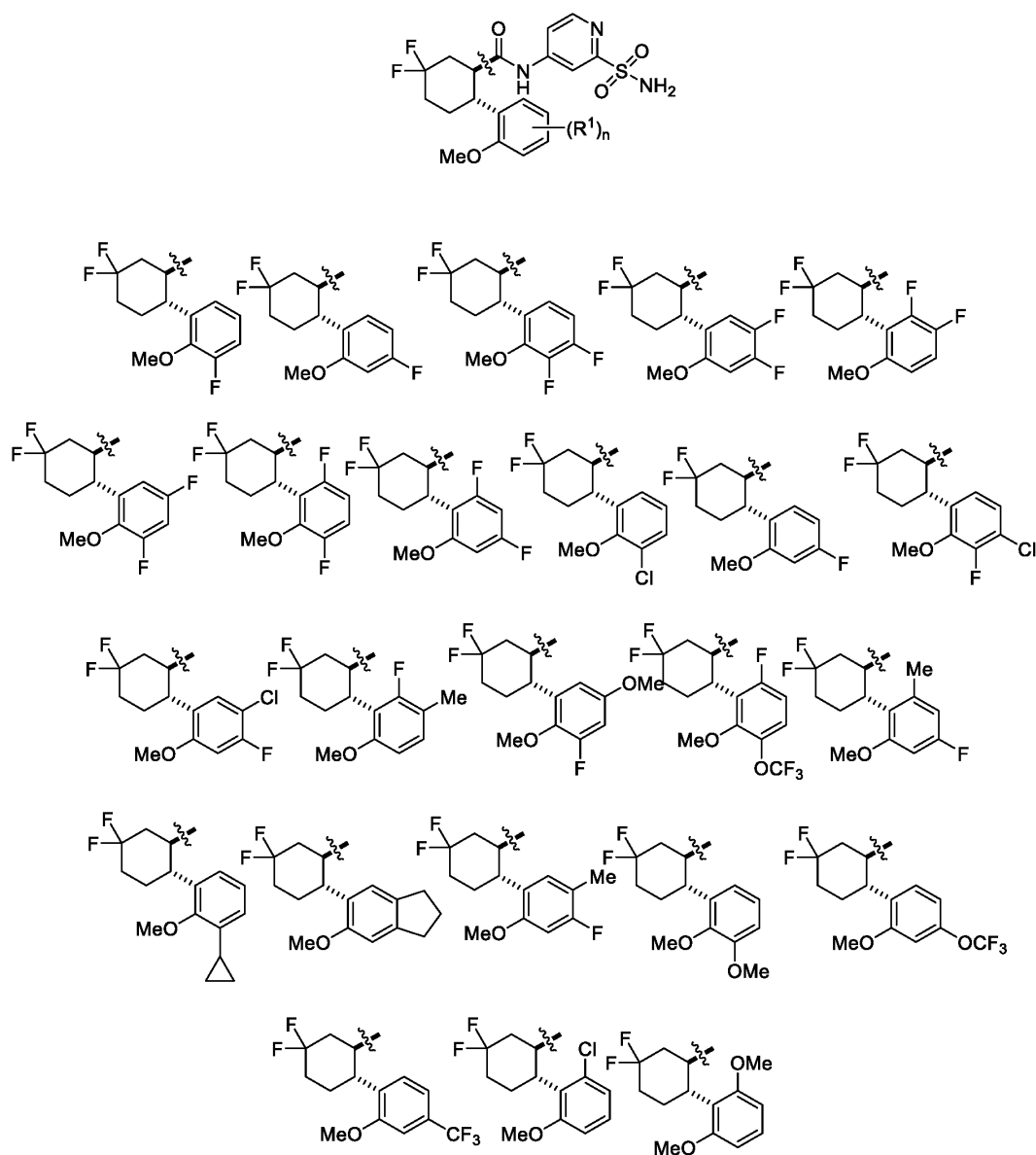
[00143] Embodiment 14: In some or any embodiments, the compound is selected from any of:



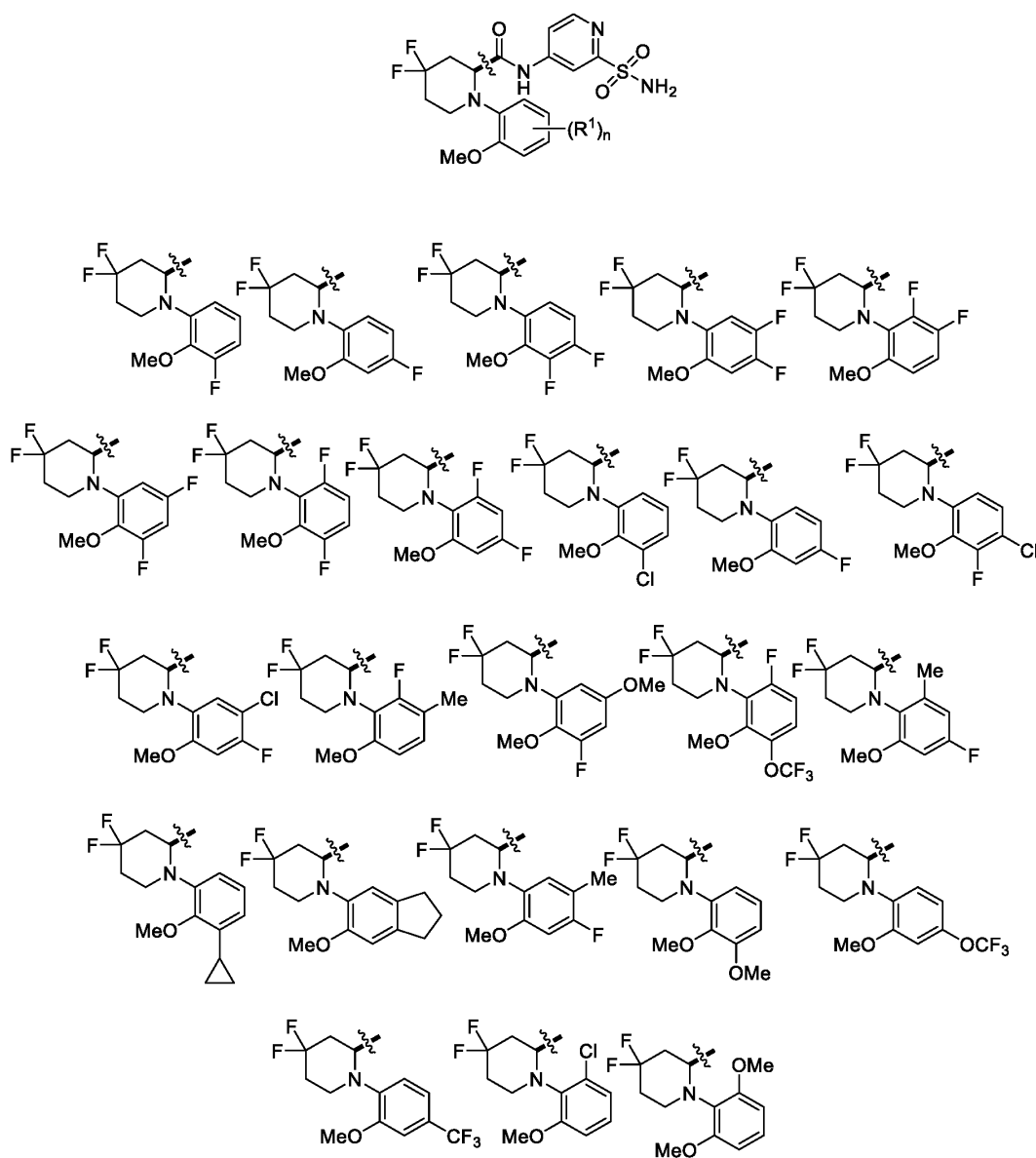
[00144] **Embodiment 14'**: In some or any embodiments, the compound is selected from any of:



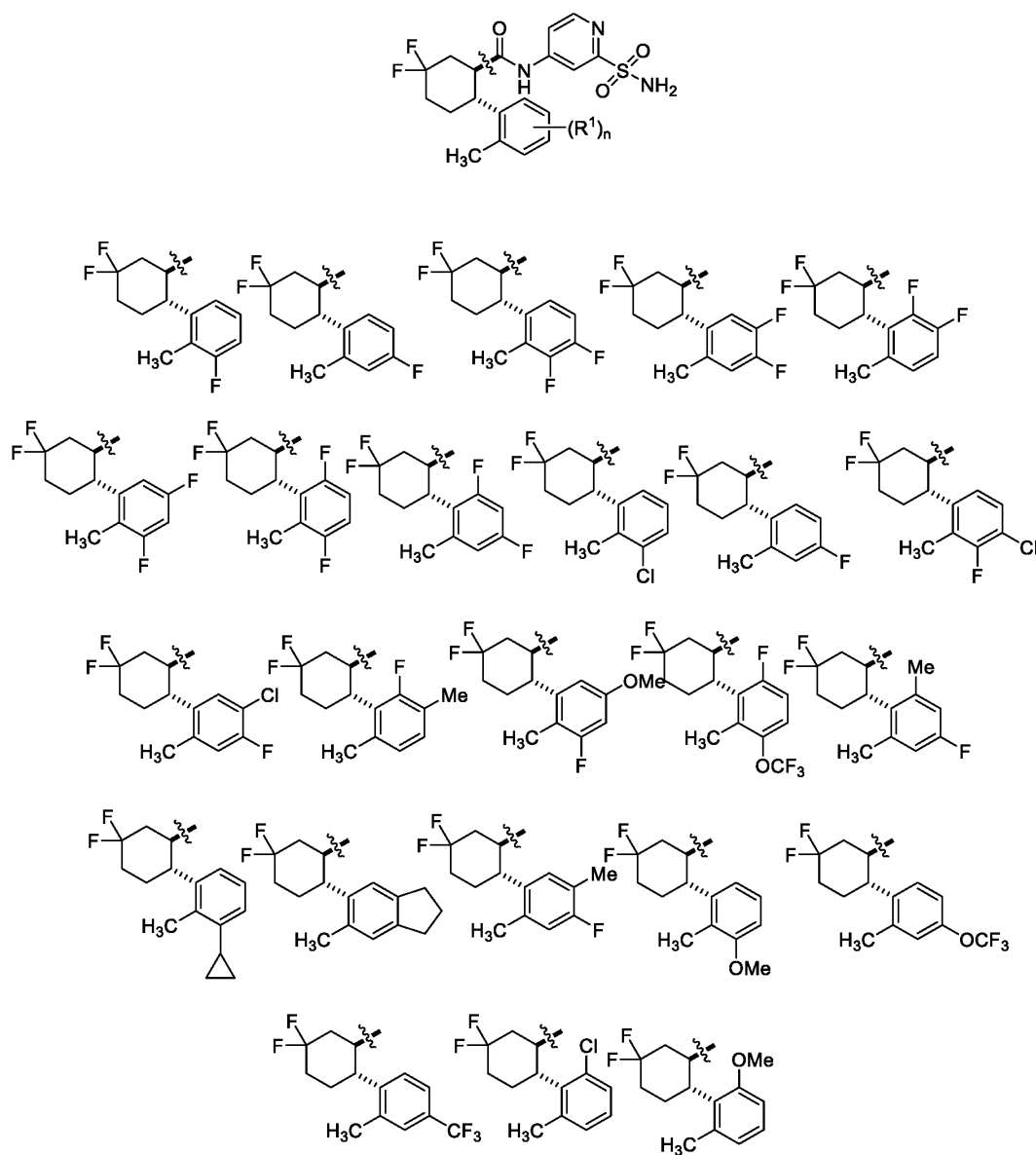
[00145] **Embodiment 14a:** In some or any embodiments, the compound is selected from any of:



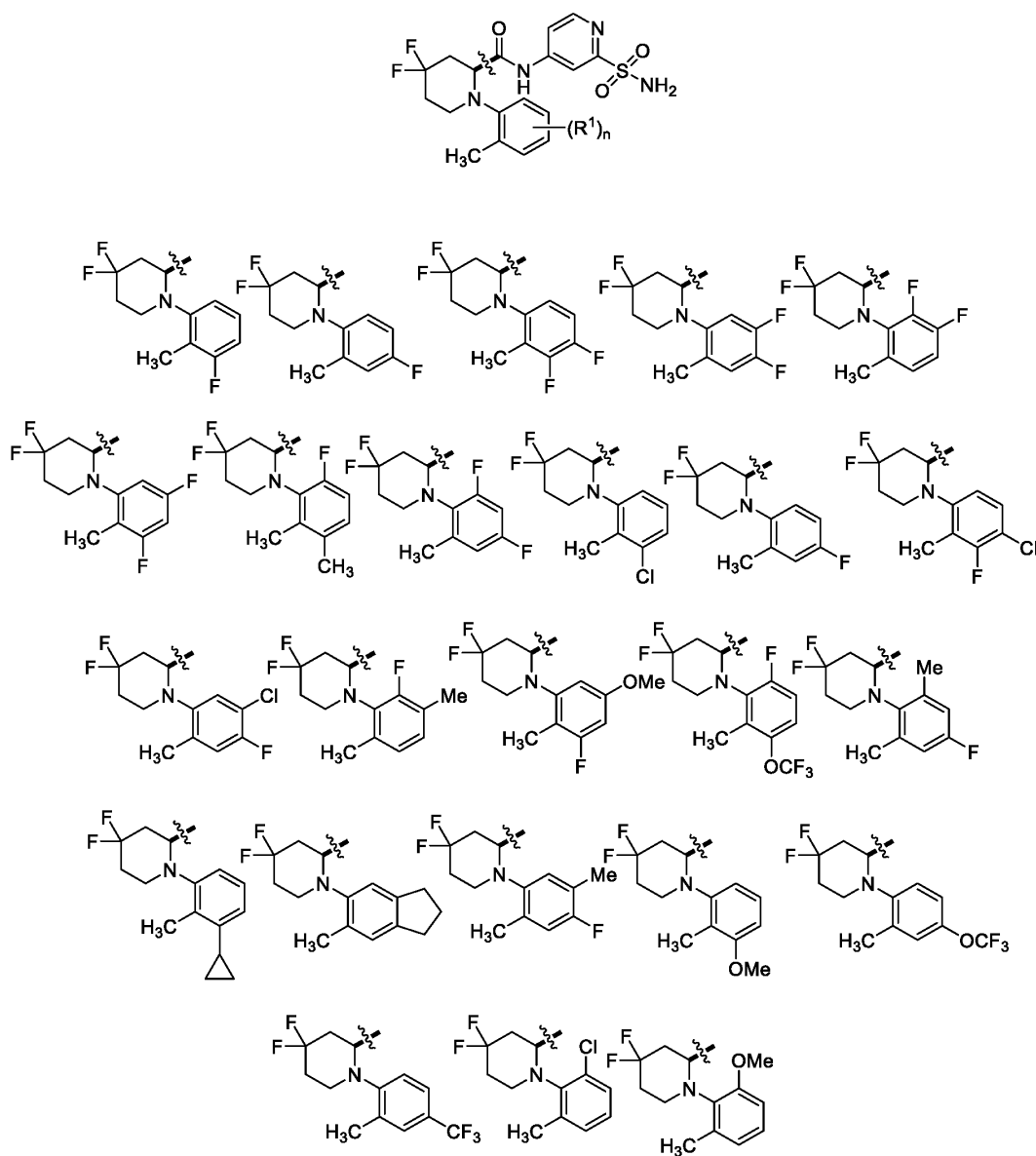
[00146] **Embodiment 14a'**: In some or any embodiments, the compound is selected from any of:



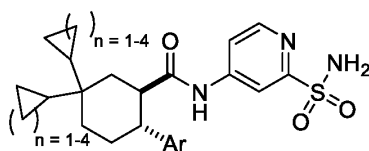
[00147] **Embodiment 14a-1:** In some or any embodiments, the compound is selected from any of:



[00148] **Embodiment 14a'-1:** In some or any embodiments, the compound is selected from any of:

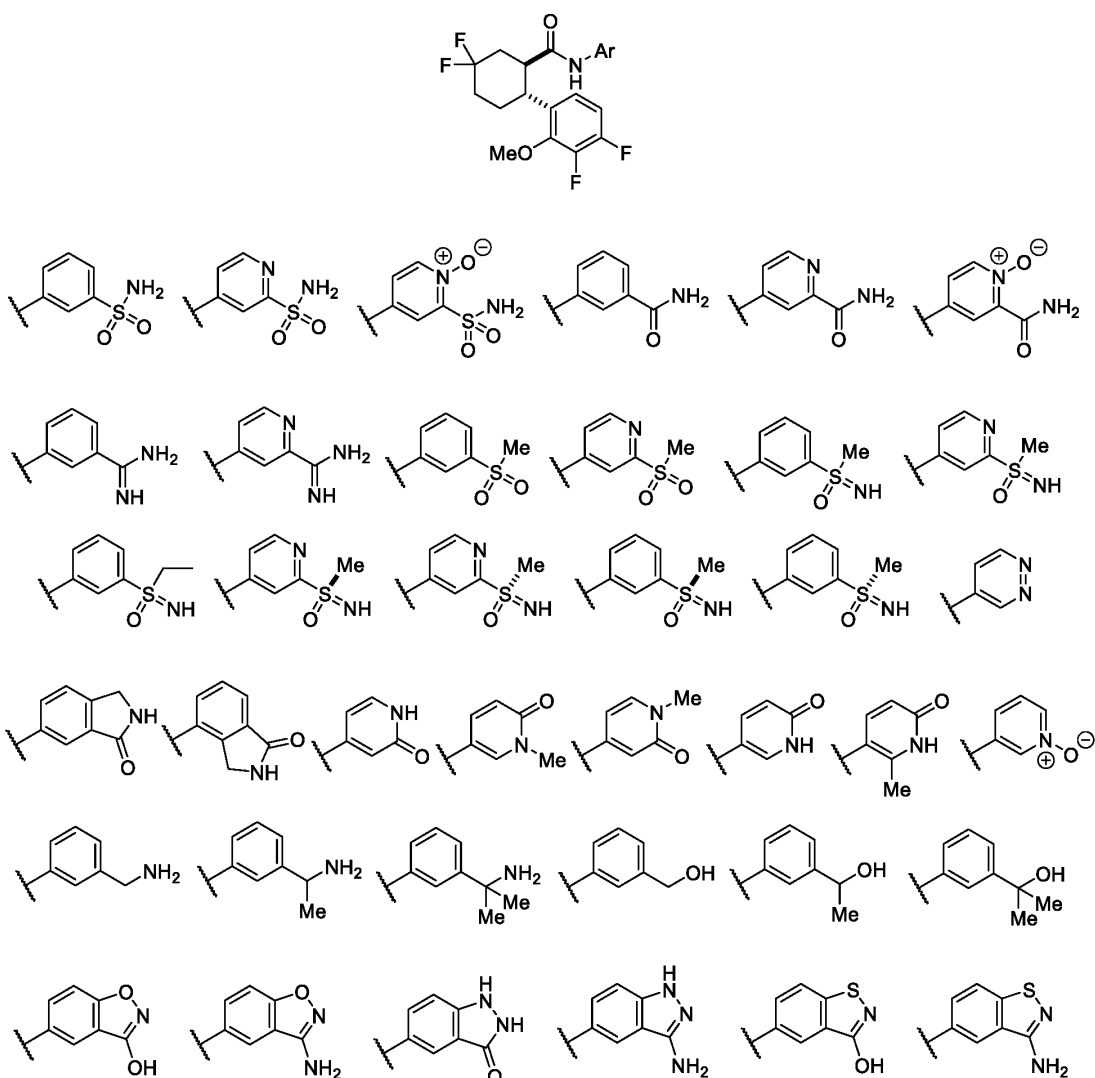


[00149] **Embodiment 14b:** In some or any embodiments, the compound is selected from any of:

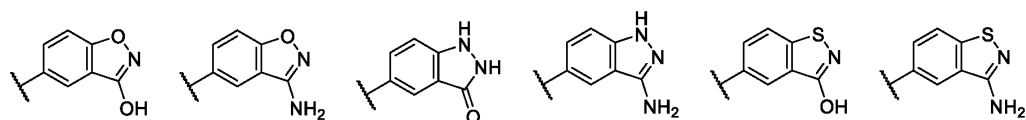
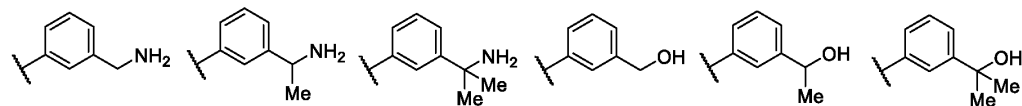
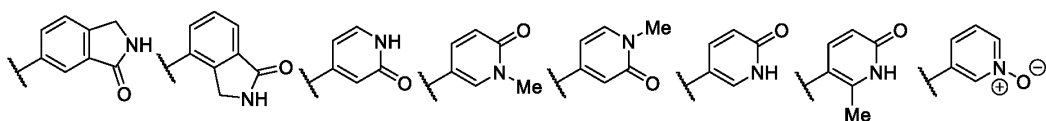
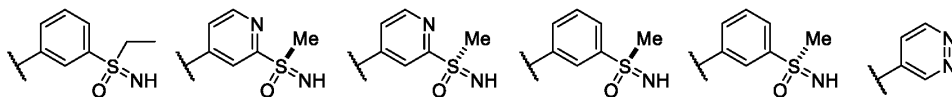
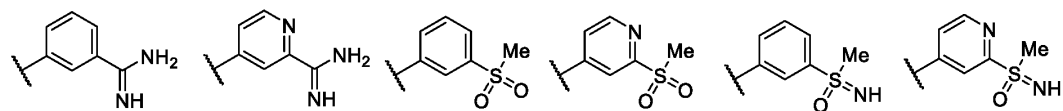
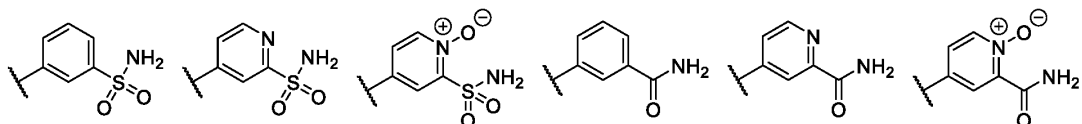
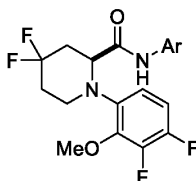


wherein Ar is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where (R¹)_n is substituted on any substitutable ring atom; **R**¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl.

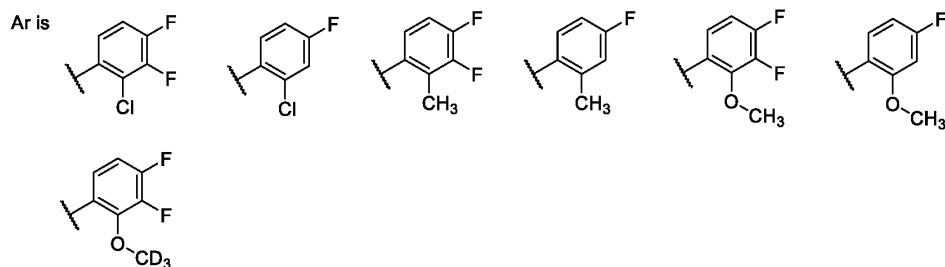
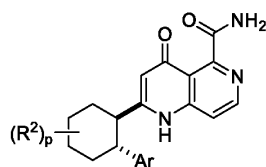
[00150] Embodiment 14c: In some or any, the compound is selected from any of:



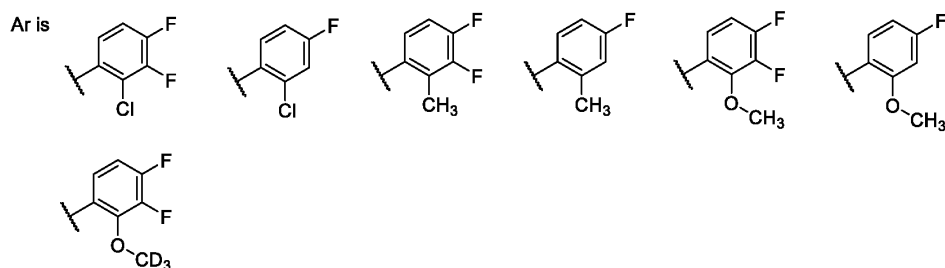
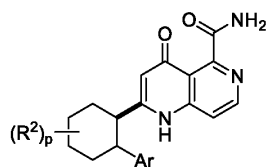
[00151] Embodiment 14c': In some or any embodiments, the compound is selected from any of:



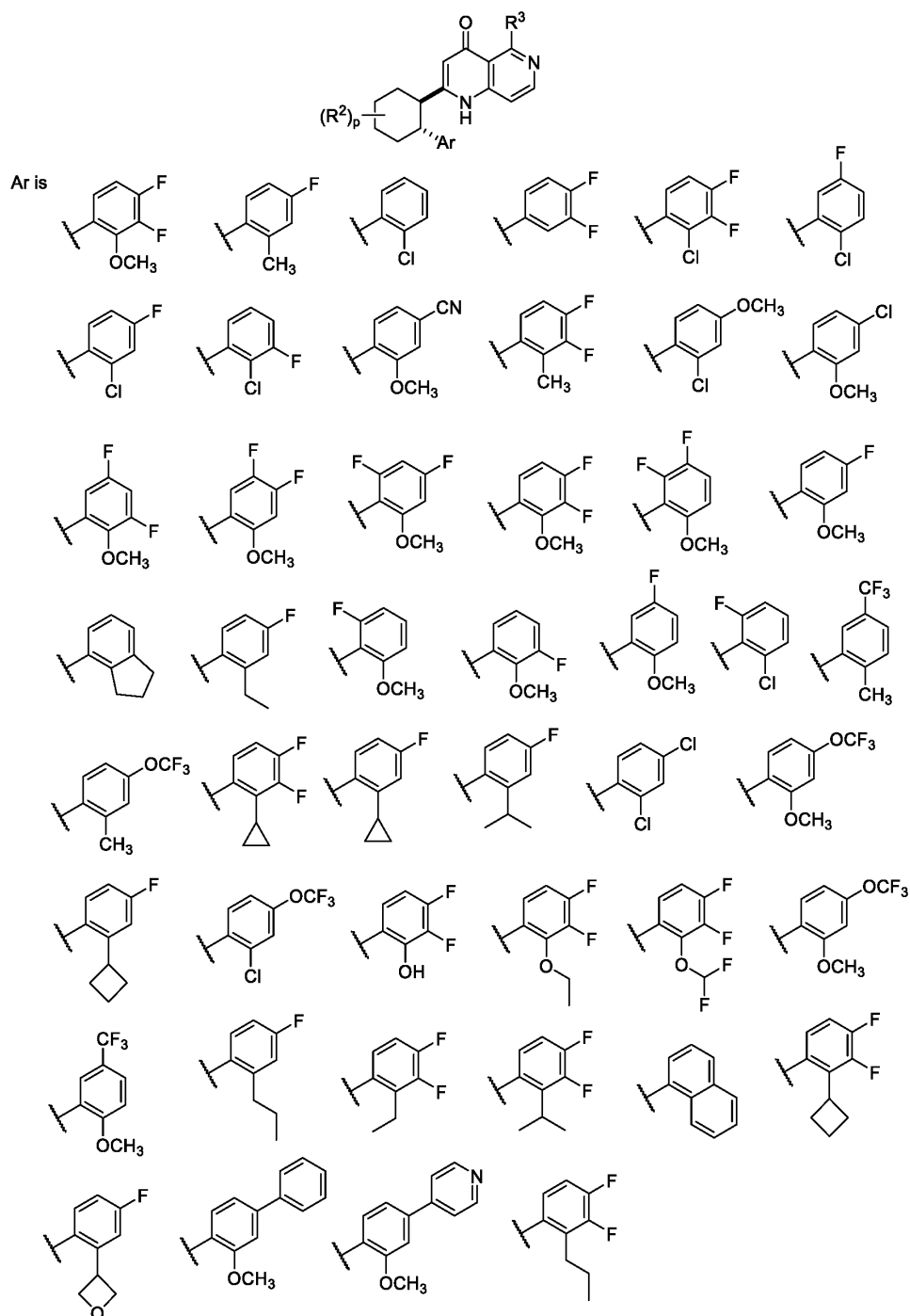
[00152] **Embodiment 14d:** In some or any embodiments, the compound is selected from any of:



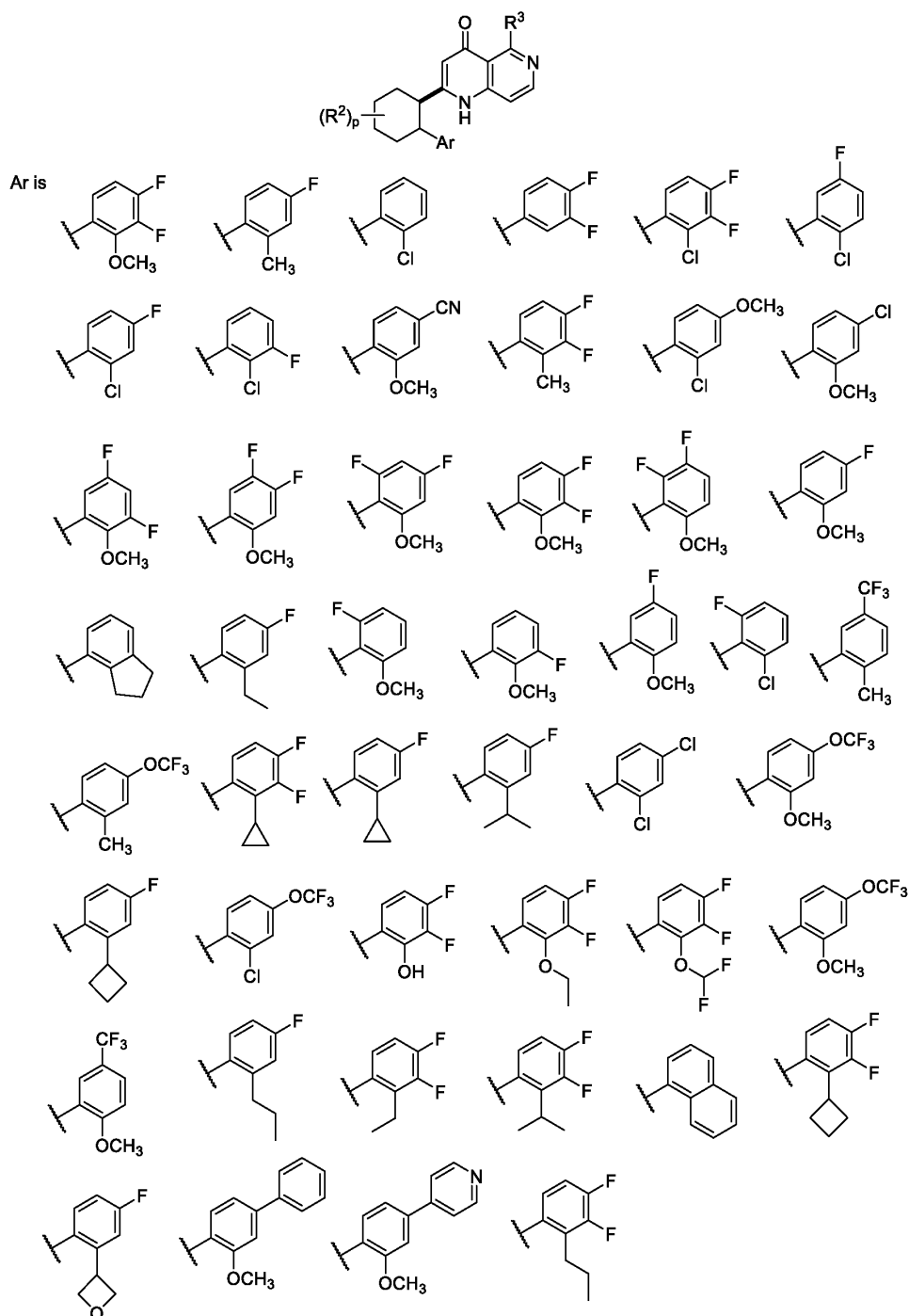
[00153] **Embodiment 14d':** In some or any embodiments, the compound is selected from any of:



[00154] **Embodiment 15:** In some or any embodiments, the compound is selected from any of:



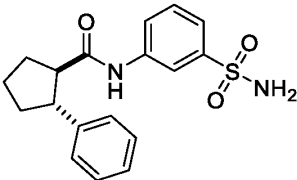
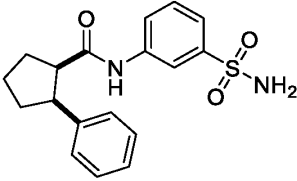
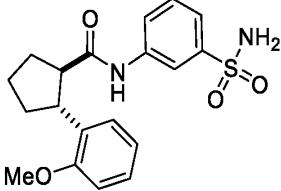
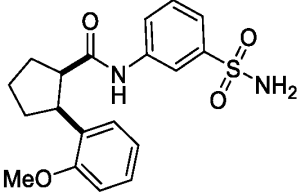
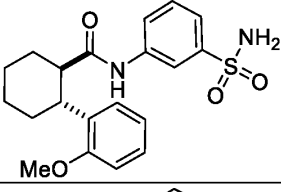
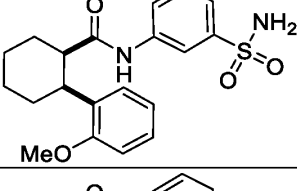
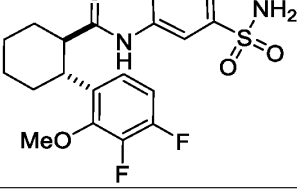
[00155] Embodiment 15': In some or any embodiments, the compound is selected from any of:

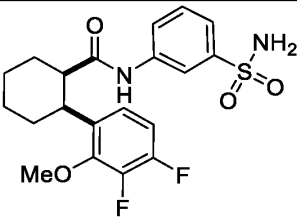
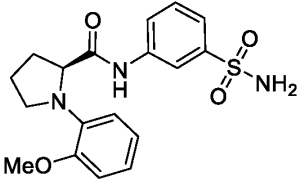
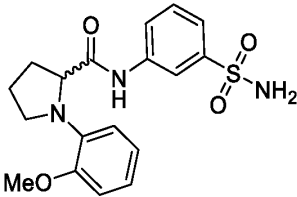
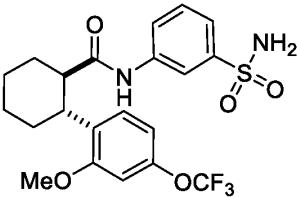
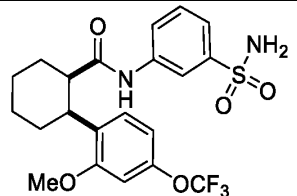
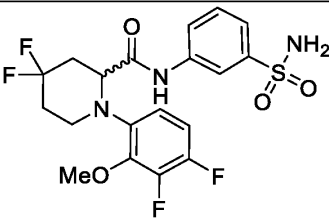
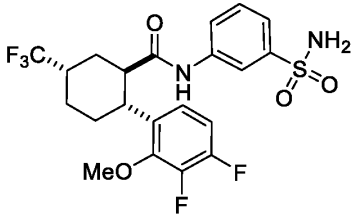


wherein R³ is hydrogen, -C(O)NH₂, -C(O)N(CH₃)₂, or COOH.

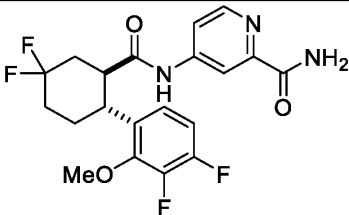
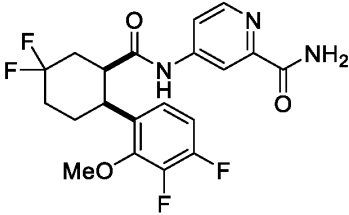
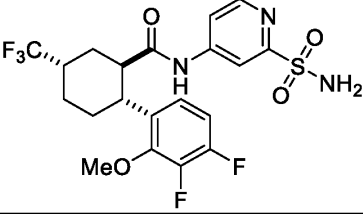
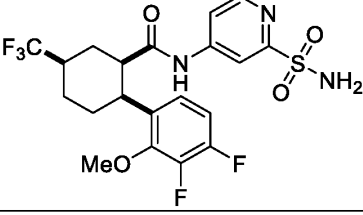
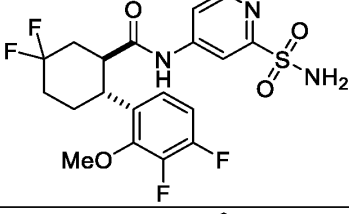
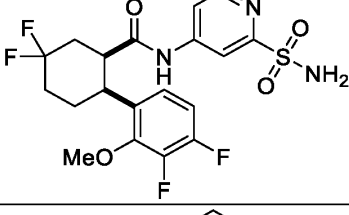
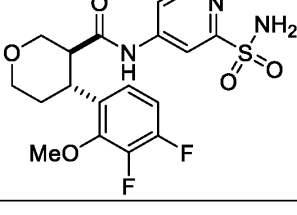
[00156] **Embodiment 16a:** In some or any embodiments, the compound is selected from any of compounds 1-183, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A-1.

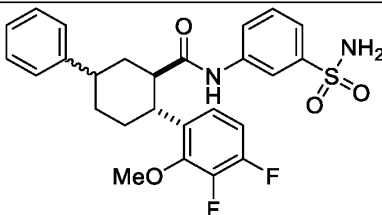
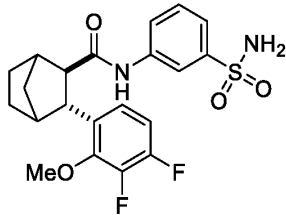
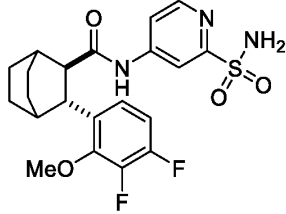
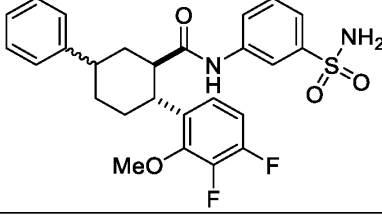
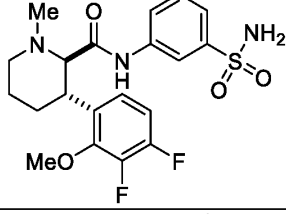
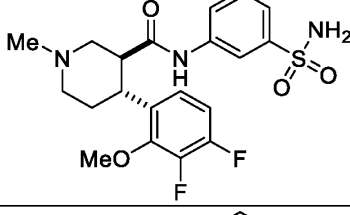
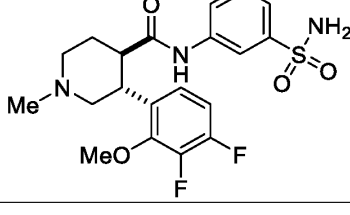
Table A-1

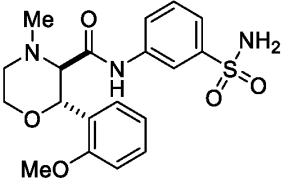
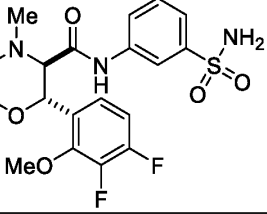
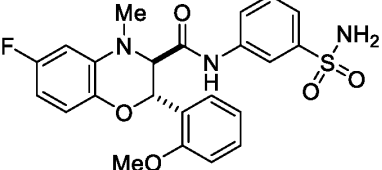
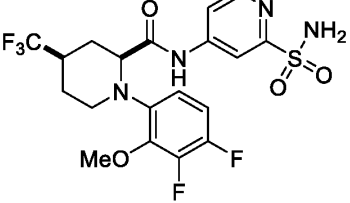
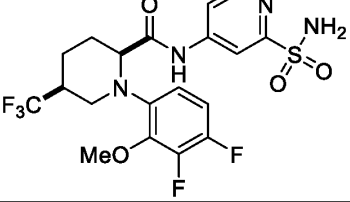
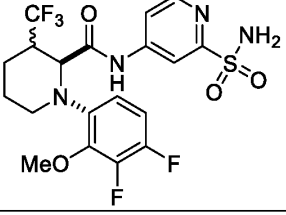
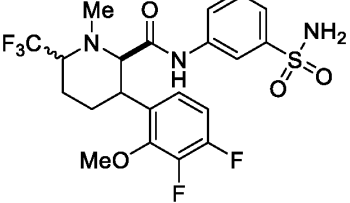
Compound No	Structure
1	
3	
5	
7	
9	
11	
13	

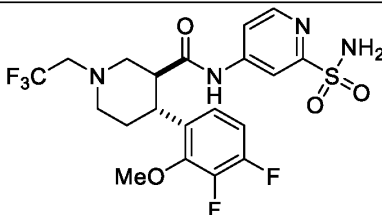
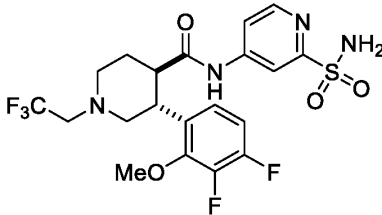
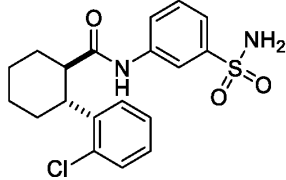
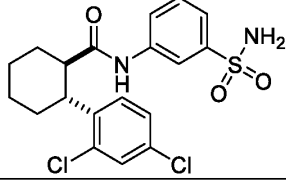
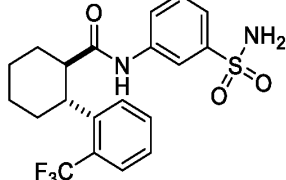
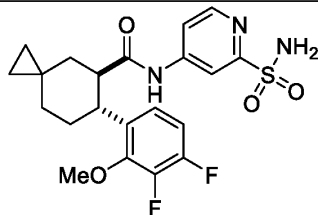
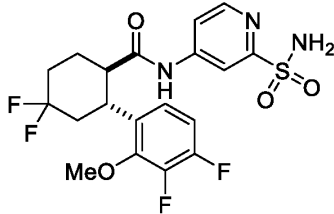
Compound No	Structure
15	
17	
18	
19	
21	
23	
24	

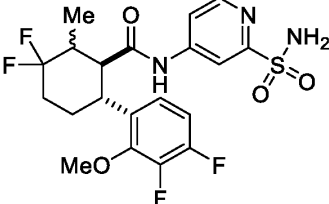
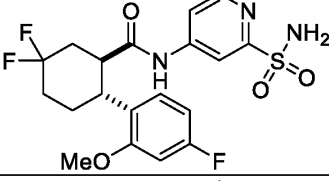
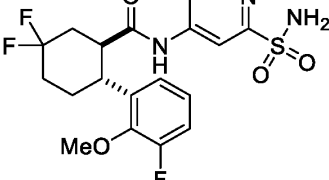
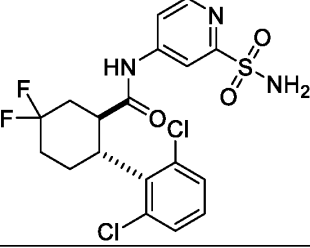
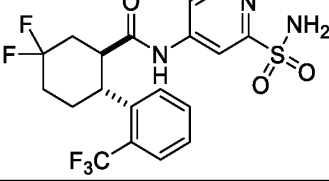
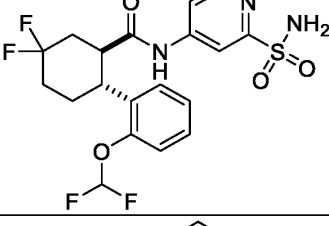
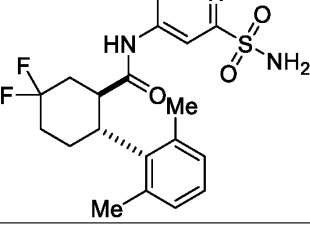
Compound No	Structure
26	
28	
30	
32	
34	
35	
36	

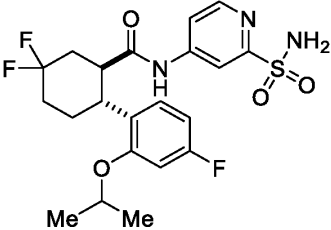
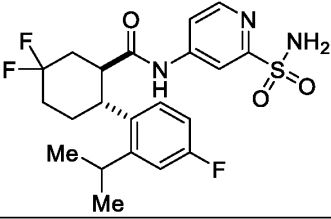
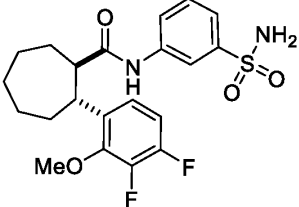
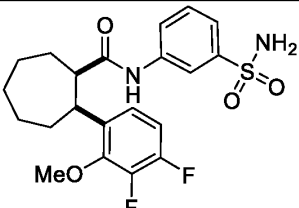
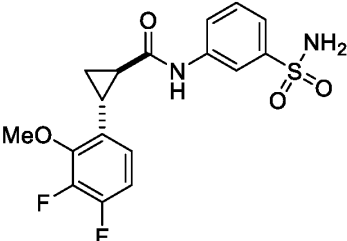
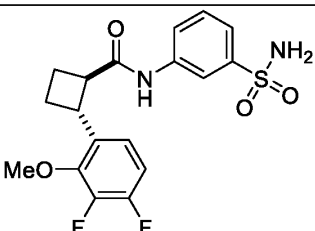
Compound No	Structure
37	
38	
39	
41	
43	
45	
47	

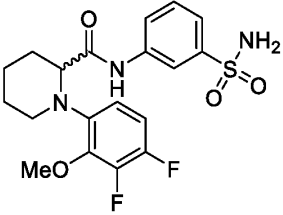
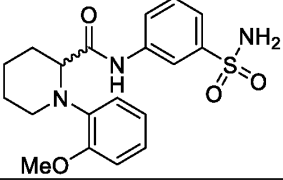
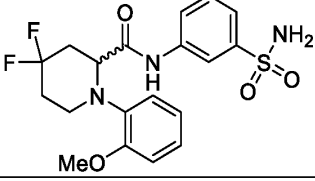
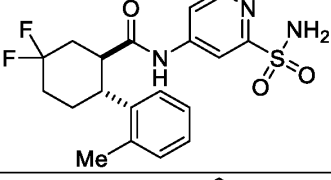
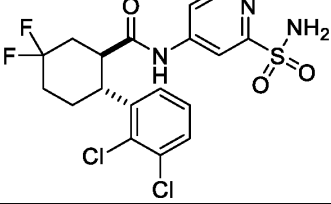
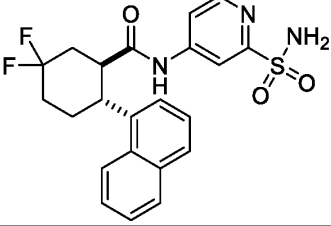
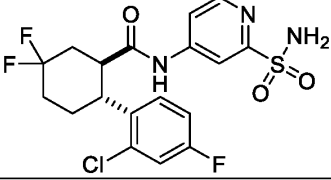
Compound No	Structure
48	
49	
50	
51	
53	
54	
55	

Compound No	Structure
56	
57	
58	
59	
60	
61	
62	

Compound No	Structure
63	
64	
65	
66	
67	
70	
71	

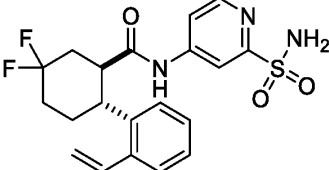
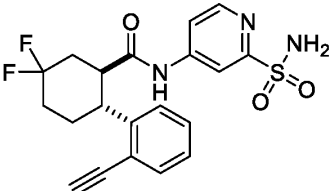
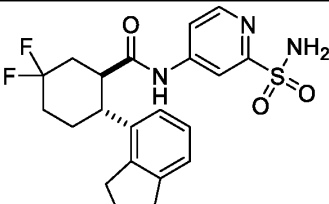
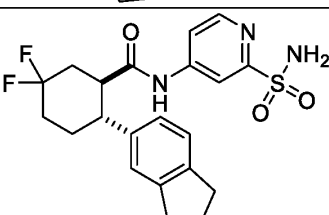
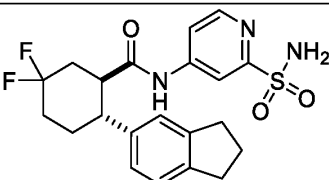
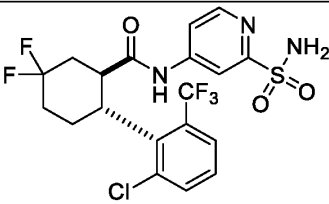
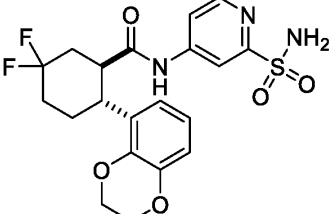
Compound No	Structure
72	
73	
74	
75	
76	
77	
78	

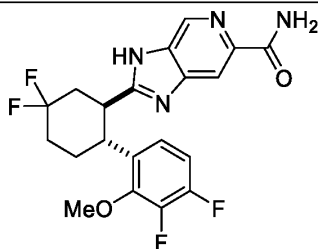
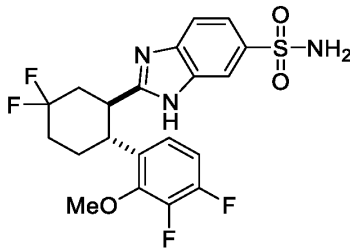
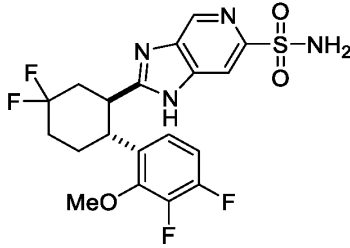
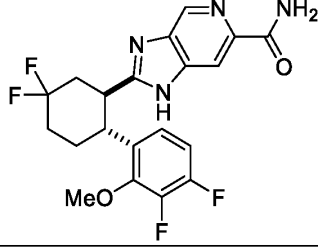
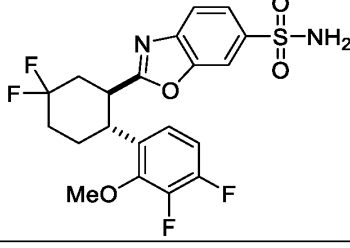
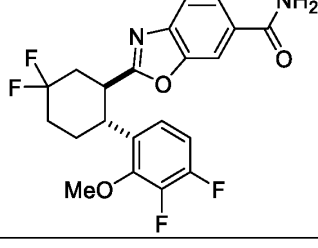
Compound No	Structure
79	
80	
81	
83	
85	
86	

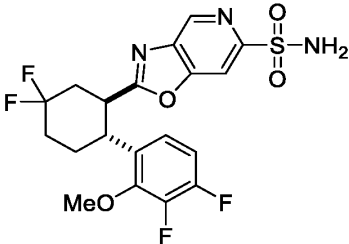
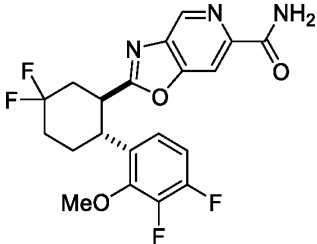
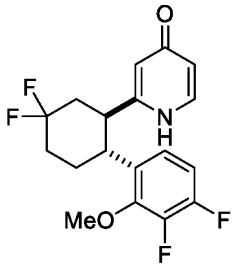
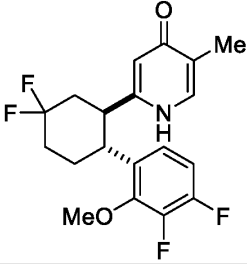
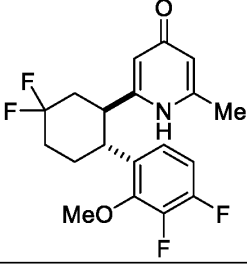
Compound No	Structure
87	
88	
89	
90	
91	
92	
93	

Compound No	Structure
94	
95	
96	
97	
98	
99	
100	

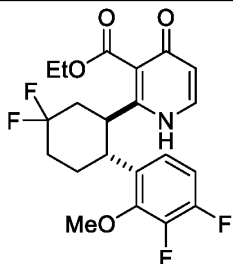
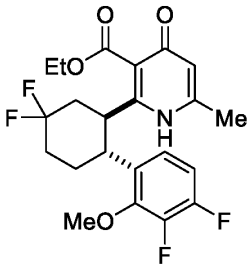
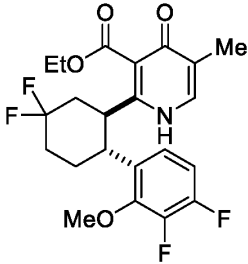
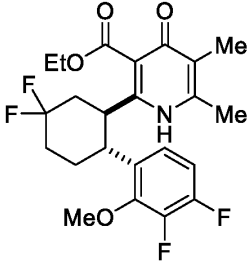
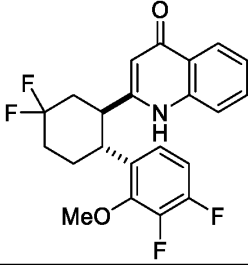
Compound No	Structure
101	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1C(F)(F)F</chem>
102	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1Cl</chem>
103	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1C(F)(F)F</chem>
104	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1C(F)(F)F</chem>
105	 <chem>Cc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1Cl</chem>
106	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1Cl</chem>
107	 <chem>Nc1cc(NC(=O)[C@H]2CC(F)(F)CC2)c3ccccc3c1C(F)(F)F</chem>

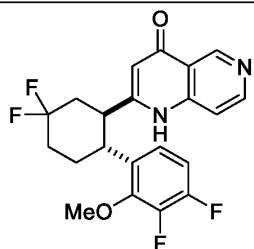
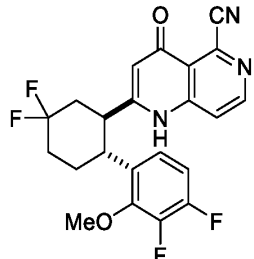
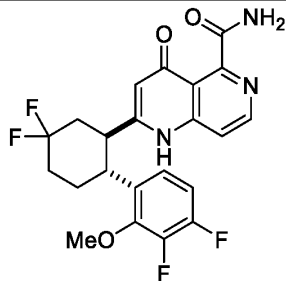
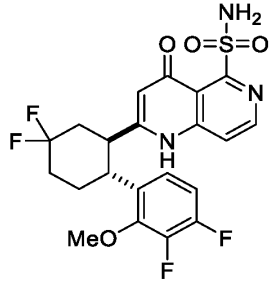
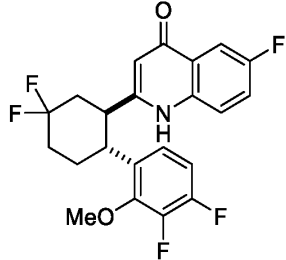
Compound No	Structure
108	
109	
110	
111	
112	
113	
114	

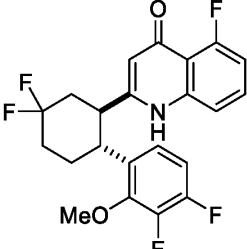
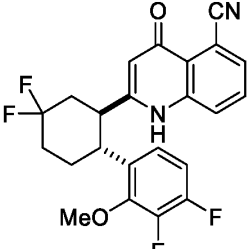
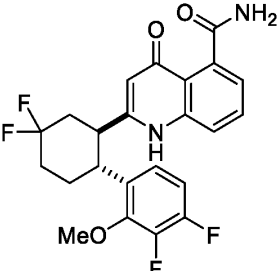
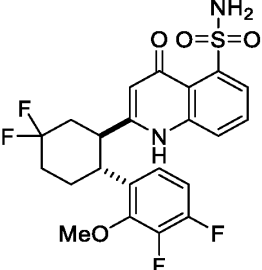
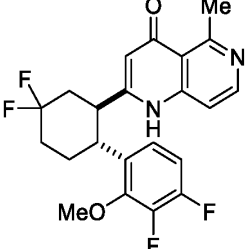
Compound No	Structure
115	
117	
119	
120	
121	
122	

Compound No	Structure
123	
124	
125	
126	
127	

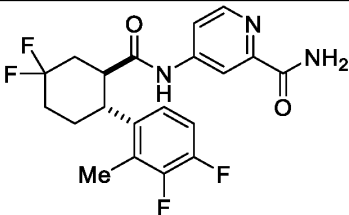
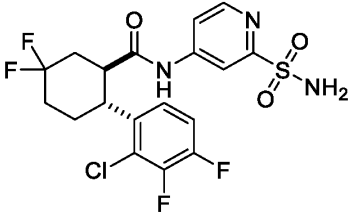
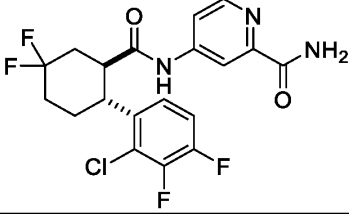
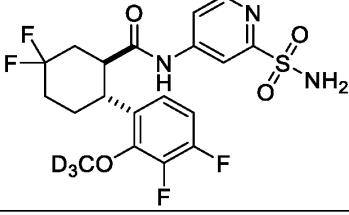
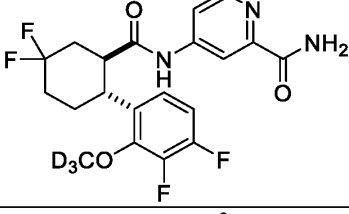
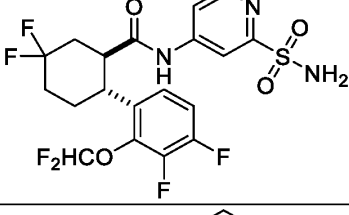
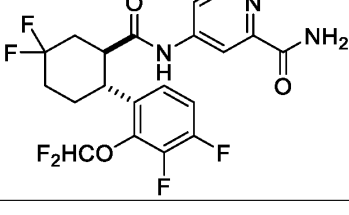
Compound No	Structure
128	 <chem>COC1=C(F)C=CC=C1N2C(=O)C(=C(C3CC(F)(F)CC3)NC2=O)S(=O)(=O)N</chem>
129	 <chem>COC1=C(F)C=CC=C1N2C(=O)C(=C(C3CC(F)(F)CC3)NC2=O)S(=O)(=O)C</chem>
130	 <chem>COC1=C(F)C=CC=C1N2C(=O)C(=C(C3CC(F)(F)CC3)NC2=O)S(=O)(=O)NC</chem>
131	 <chem>COC1=C(F)C=CC=C1N2C(=O)C=CC(=N2)N3CC(F)(F)CC3</chem>
132	 <chem>COC1=C(F)C=CC=C1N2C(=O)C(=C(C)C(=N2)C)N3CC(F)(F)CC3</chem>

Compound No	Structure
133	
134	
135	
136	
137	

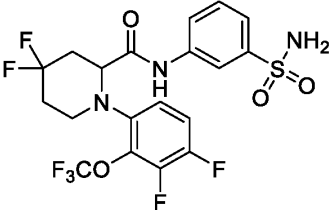
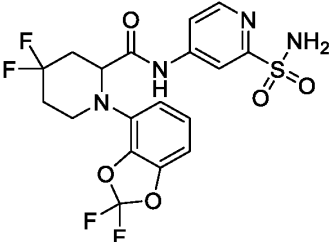
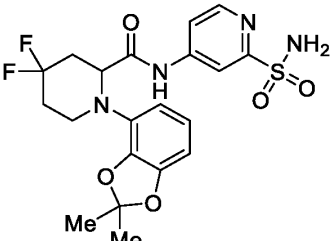
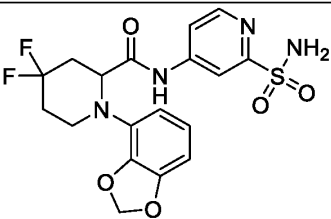
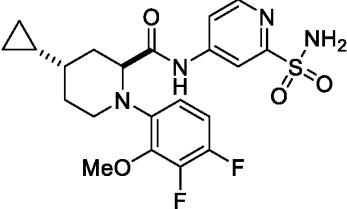
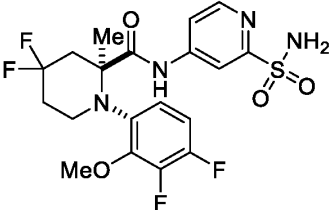
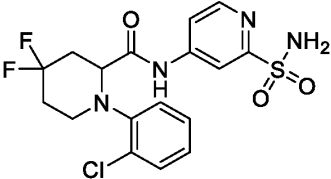
Compound No	Structure
138	
139	
140	
141	
142	

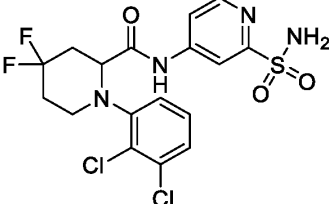
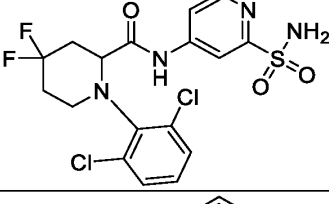
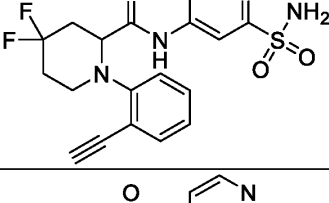
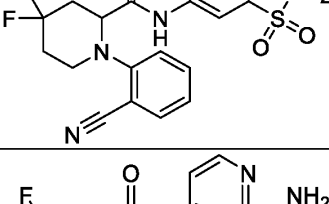
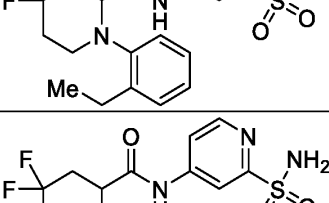
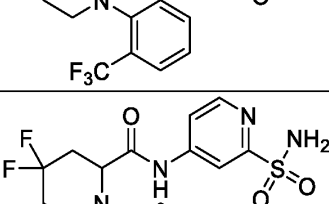
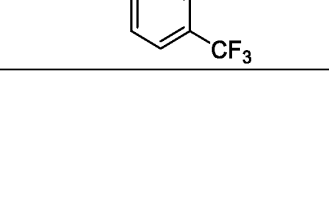
Compound No	Structure
143	
144	
145	
146	
147	

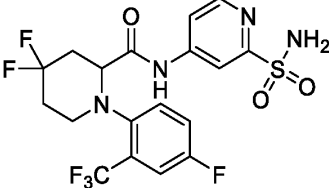
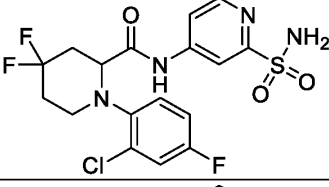
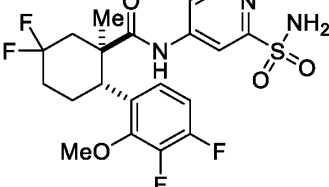
Compound No	Structure
148	 <chem>O=C1C=CC2=C(N1C3=CC(=CC=C3C(F)=C(OC)F)C(F)(F)CC4(F)CC(F)CC4)C=C(C=C2)O</chem>
149	 <chem>COC1=CC=CC2=C(N1C3=CC(=CC=C3C(F)=C(OC)F)C(F)(F)CC4(F)CC(F)CC4)C(=O)C=C(C=C2)OC</chem>
150	 <chem>COC1=CC=C2C(=C1)C(=O)C=C(N2C3=CC(=CC=C3C(F)=C(OC)F)C(F)(F)CC4(F)CC(F)CC4)C=C(C=C2)OC</chem>
151	 <chem>COC1=CC=CC2=C(N1C3=CC(=CC=C3C(F)=C(OC)F)C(F)(F)CC4(F)CC(F)CC4)C(=O)C=C(C=C2)OC</chem>
152	 <chem>[O-][N+]([O-])=C1C=CC2=C(N1C3=CC(=CC=C3C(F)=C(OC)F)C(F)(F)CC4(F)CC(F)CC4)C(=O)C=C(C=C2)C=C1</chem>
153	 <chem>NC(=O)S(=O)(=O)C1=CC=CC2=C(N1C3=CC(=CC=C3C(F)=C(C)F)C(F)(F)CC4(F)CC(F)CC4)C(=O)C=C(C=C2)C=C1</chem>

Compound No	Structure
154	
155	
156	
157	
158	
159	
160	

Compound No	Structure
161	 <chem>COc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem>
162	 <chem>COc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5C(=O)N4)cc3F</chem>
163	 <chem>COc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem> <chem>COc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem>
164	 <chem>Cc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem>
165	 <chem>Clc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem>
166	 <chem>C(F)(F)Fc1cc(F)c(NC(=O)N2CC(F)CC2)c(c1F)c3cc(NC(=O)N4C=CC=C5N=CC=C5S(=O)(=O)N4)cc3F</chem>

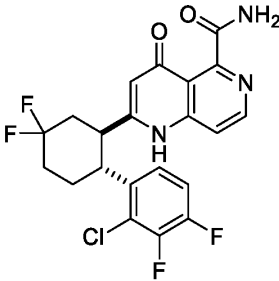
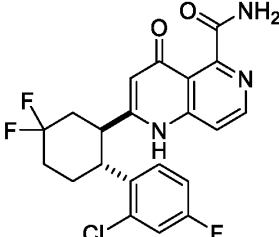
Compound No	Structure
167	
168	
169	
170	
171	
172	
173	

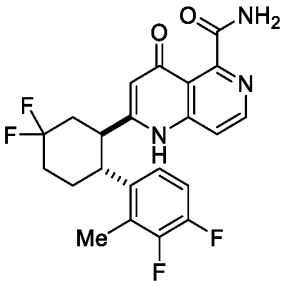
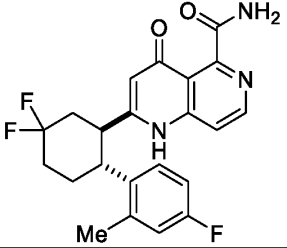
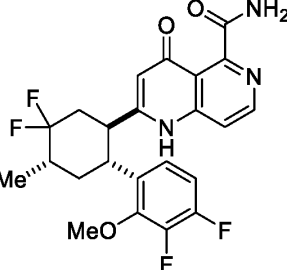
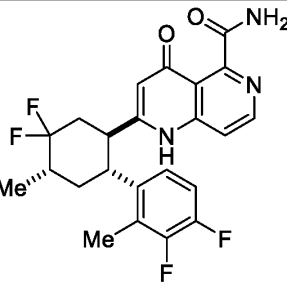
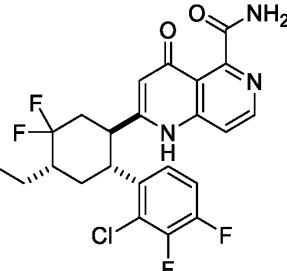
Compound No	Structure
174	
175	
176	
177	
178	
179	
180	

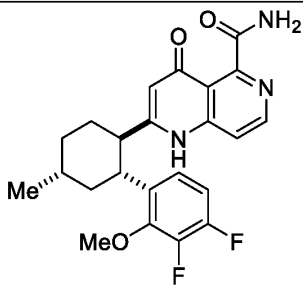
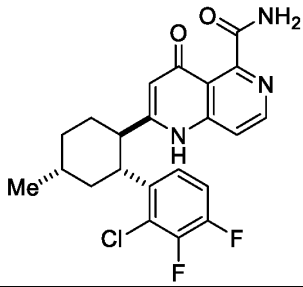
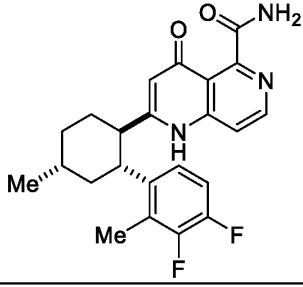
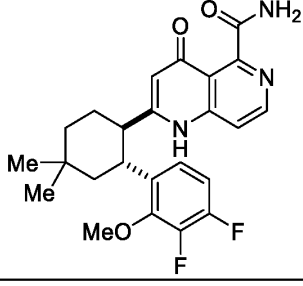
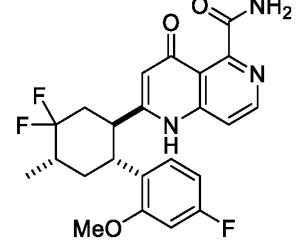
Compound No	Structure
181	
182	
183	

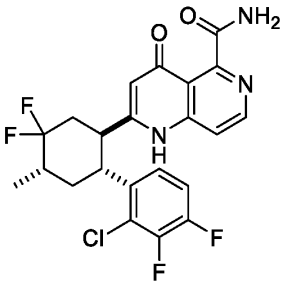
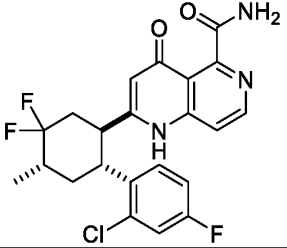
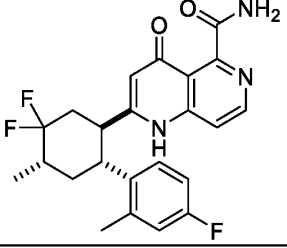
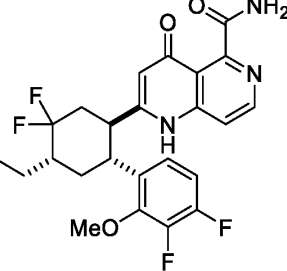
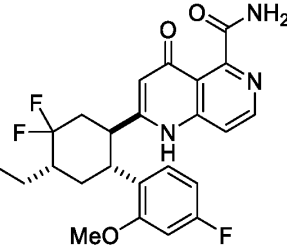
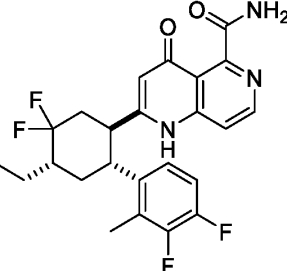
[00157] **Embodiment 16b:** In some or any embodiments, the compound is selected from any of compounds 184-211, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A-2.

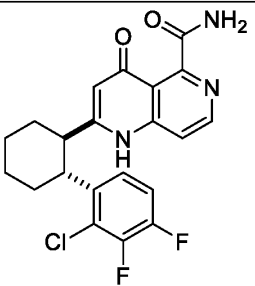
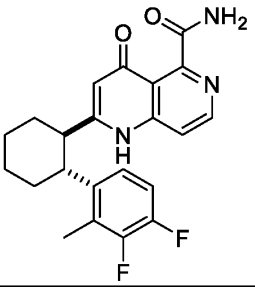
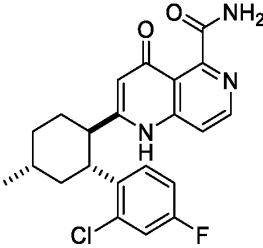
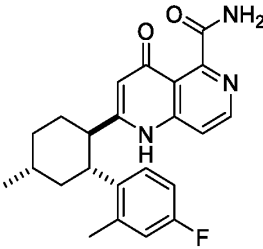
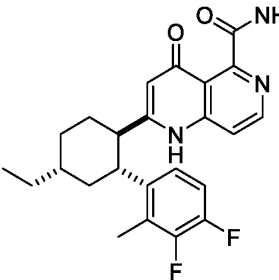
Table A-2

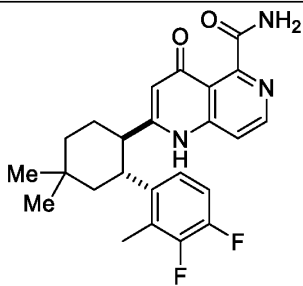
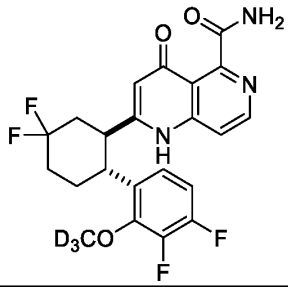
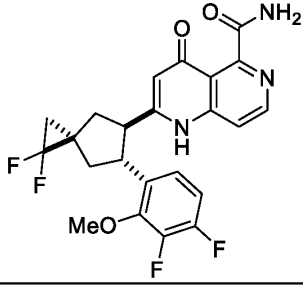
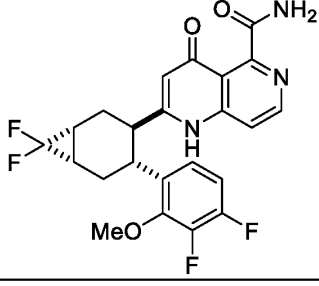
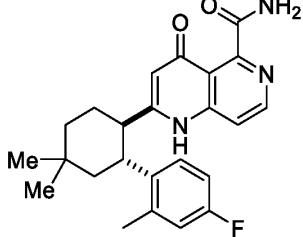
Compound No	Structure
184	
185	

186	
187	
188	
189	
190	

191	
192	
193	
194	
195	

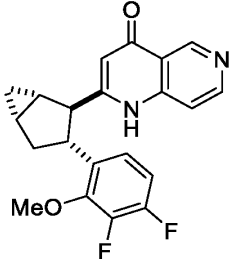
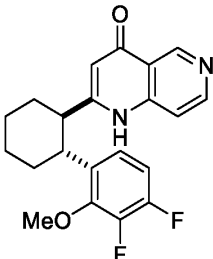
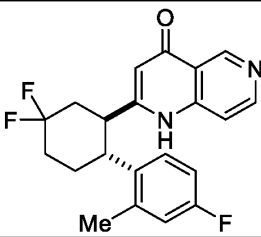
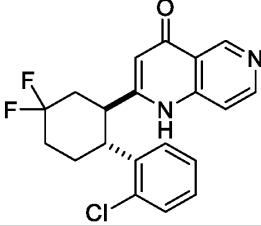
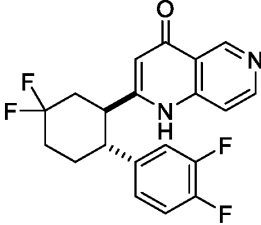
196	
197	
198	
199	
200	
201	

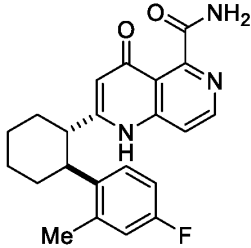
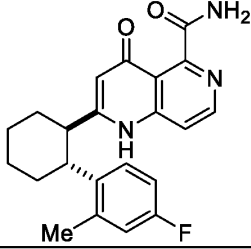
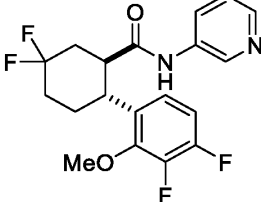
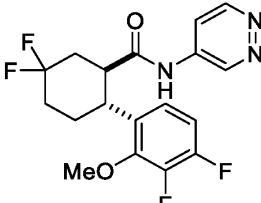
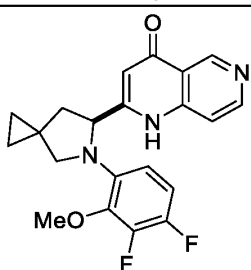
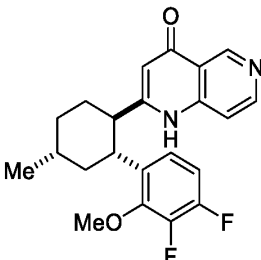
202	
203	
204	
205	
206	

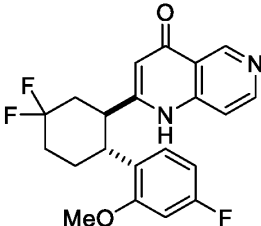
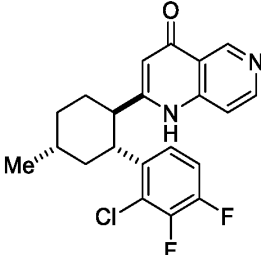
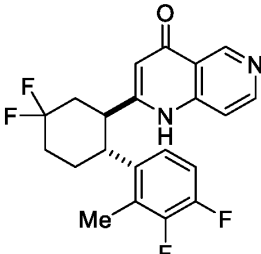
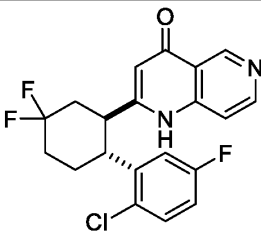
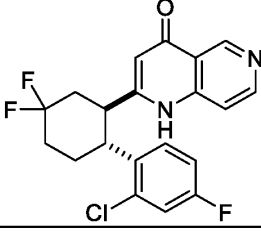
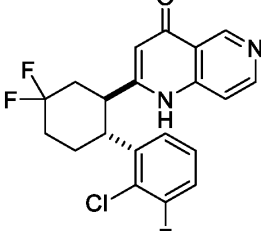
207	
208	
209	
210	
211	

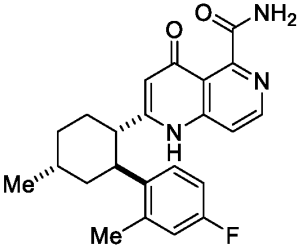
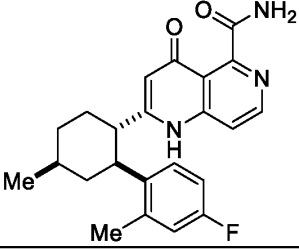
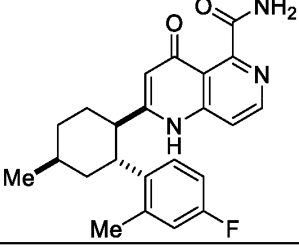
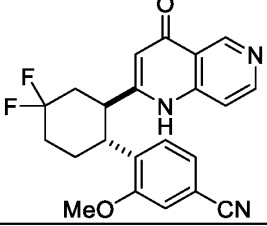
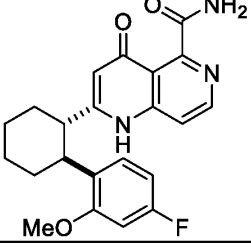
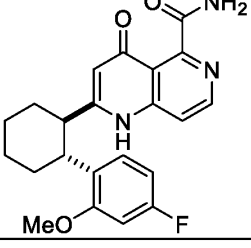
[00158] **Embodiment 16c:** In some or any embodiments, the compound is selected from any of compounds 212-723, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A-3.

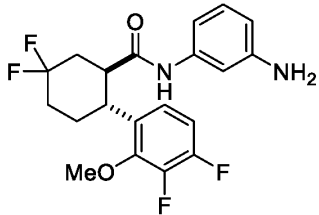
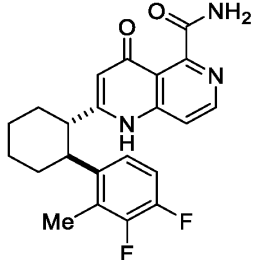
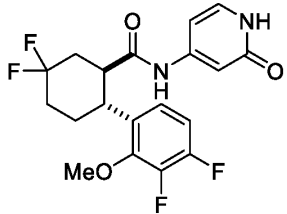
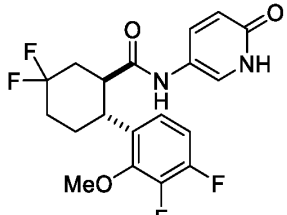
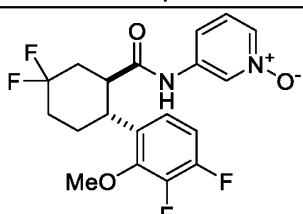
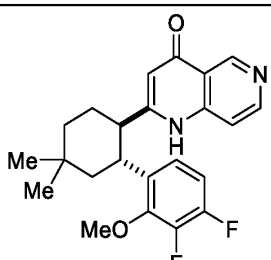
Table A-3

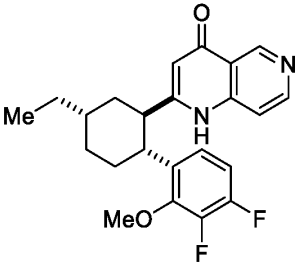
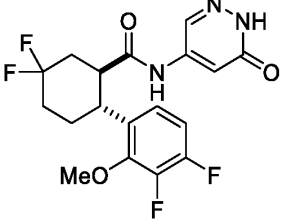
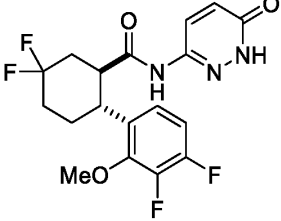
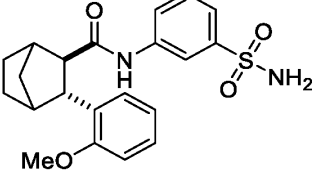
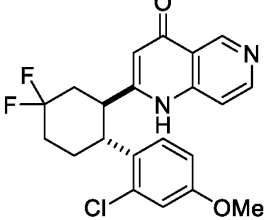
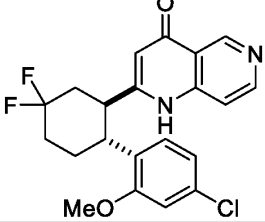
Compound No	Structure
212	
213	
214	
215	
216	

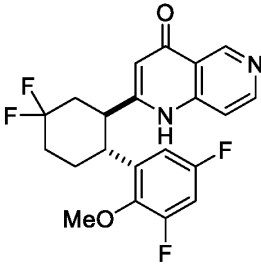
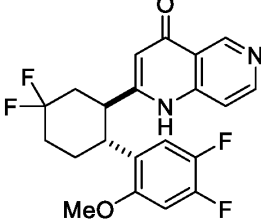
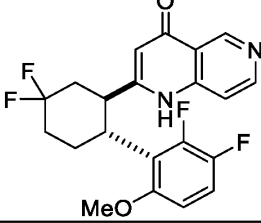
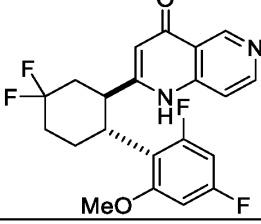
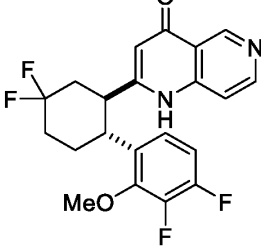
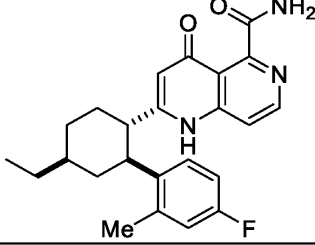
217	
218	
219	
220	
221	
222	

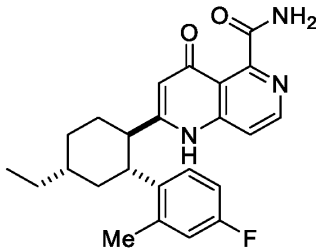
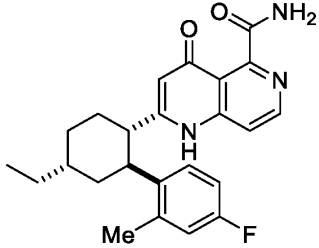
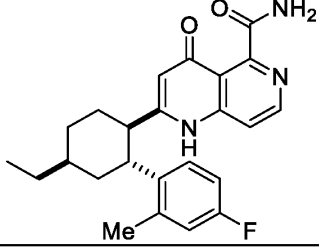
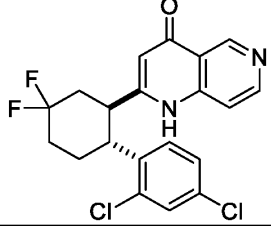
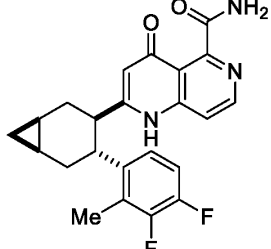
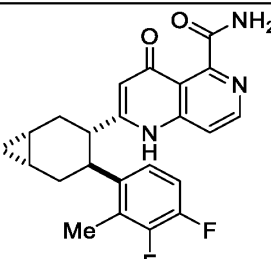
223	
224	
226	
227	
228	
229	

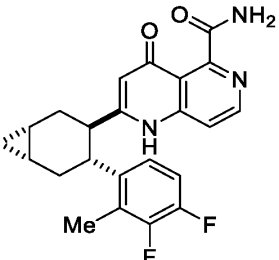
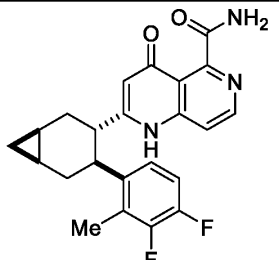
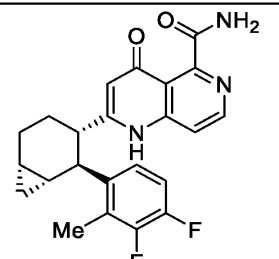
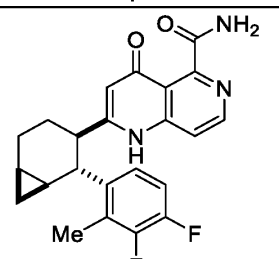
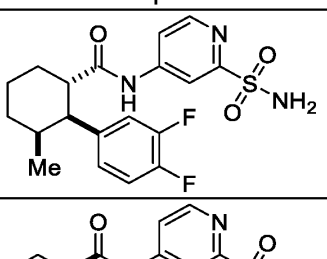
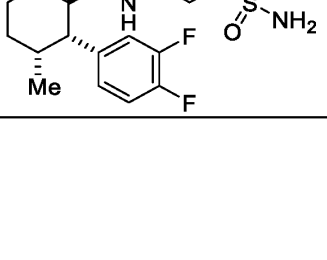
230	
231	
232	
233	
234	
235	

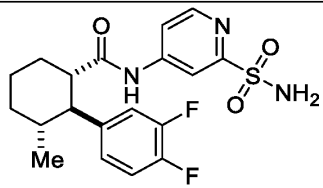
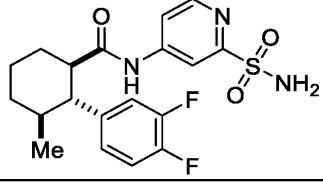
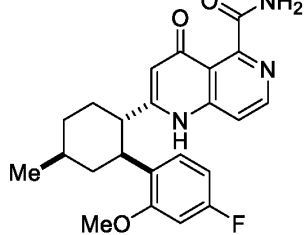
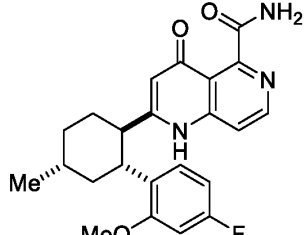
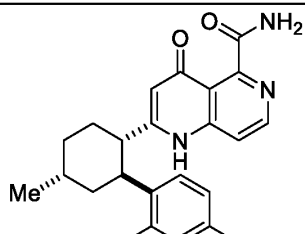
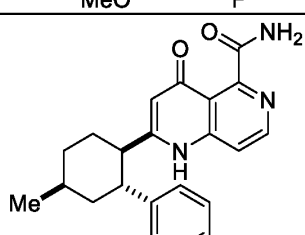
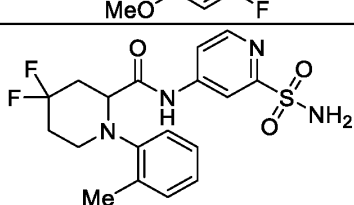
236	 <chem>Nc1ccc(NC(=O)[C@H]2CC(F)(F)CC[C@H]2c3cc(F)c(F)c(OC)c3)cc1</chem>
237	 <chem>NC(=O)c1nc2cc(NC(=O)[C@H]3CC[C@@H](C)[C@H]3c4cc(F)c(F)c(OC)c4)ccc2c1=O</chem>
238	 <chem>O=C1NC(=O)[C@H]2CC(F)(F)CC[C@H]2c3cc(F)c(F)c(OC)c3NC1=O</chem>
239	 <chem>O=C1NC(=O)[C@H]2CC(F)(F)CC[C@H]2c3cc(F)c(F)c(OC)c3NC1=O</chem>
240	 <chem>[O-][N+]([O-])=Cc1ccc(NC(=O)[C@H]2CC(F)(F)CC[C@H]2c3cc(F)c(F)c(OC)c3)cc1</chem>
241	 <chem>C[C@H]1CC[C@@H](C)[C@H]1c2cc(F)c(F)c(OC)c2NC(=O)c3nc4cc(NC(=O)[C@H]5CC[C@@H](C)[C@H]5c6cc(F)c(F)c(OC)c6)ccc4c3=O</chem>

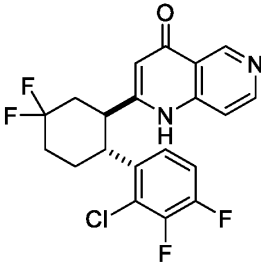
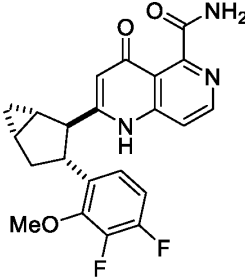
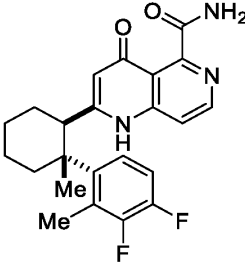
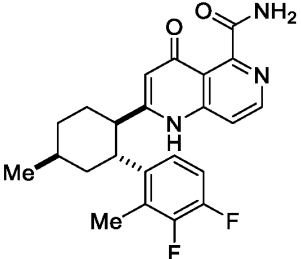
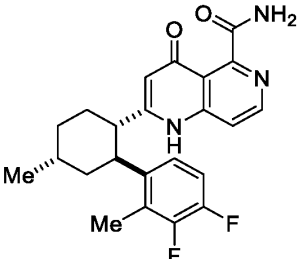
242	
243	
244	
245	
246	
247	

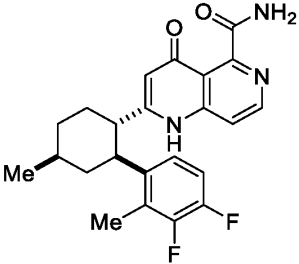
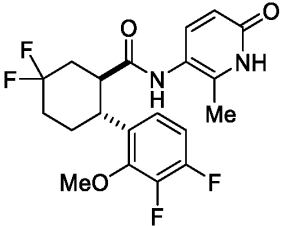
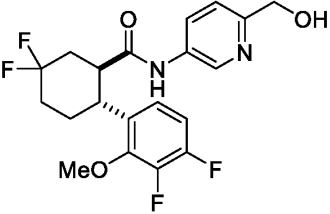
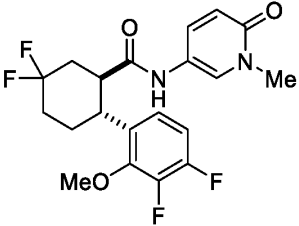
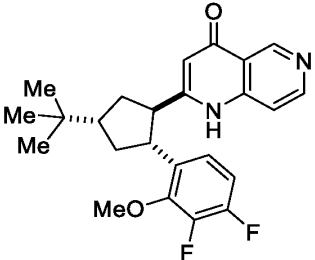
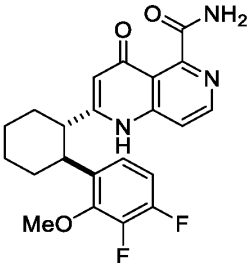
248	
249	
250	
251	
252	
253	

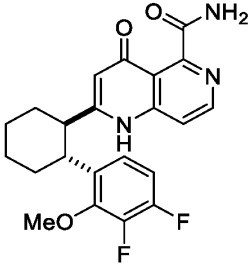
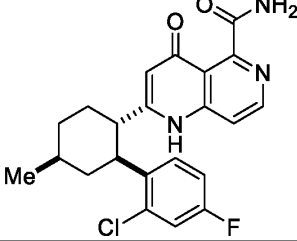
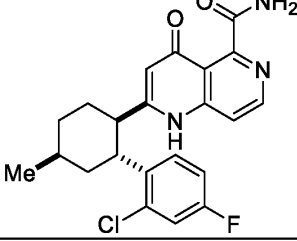
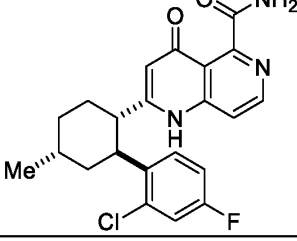
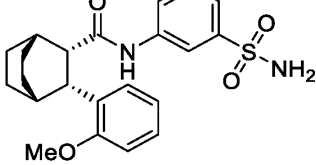
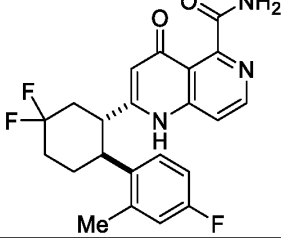
254	
255	
256	
257	
258	
259	

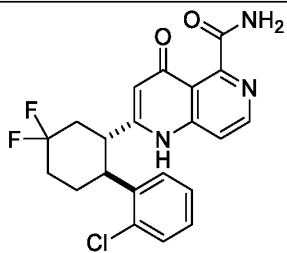
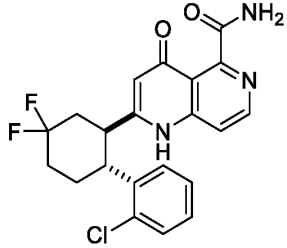
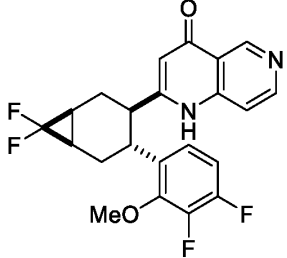
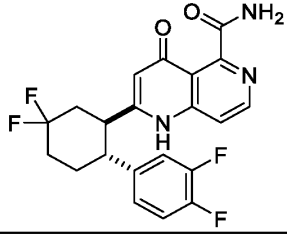
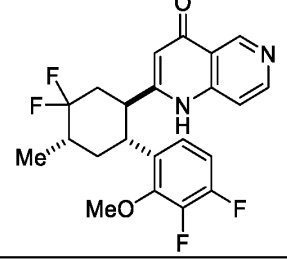
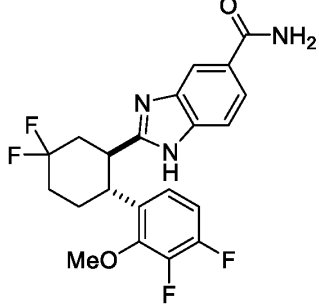
260	
261	
262	
263	
264	
265	

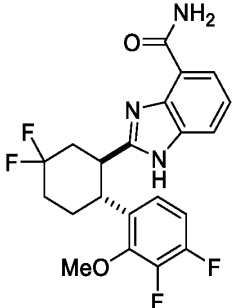
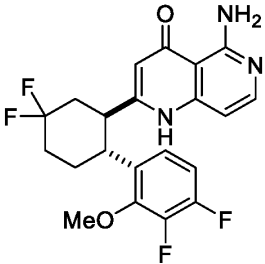
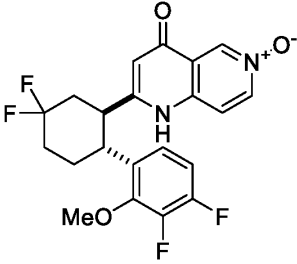
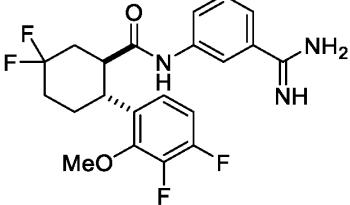
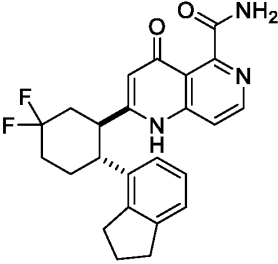
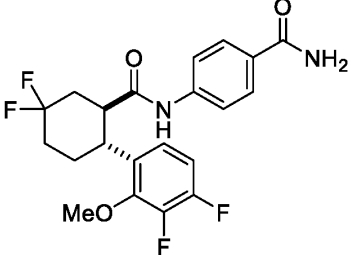
266	
267	
268	
269	
270	
271	
272	

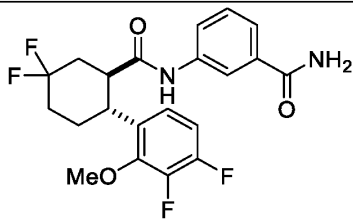
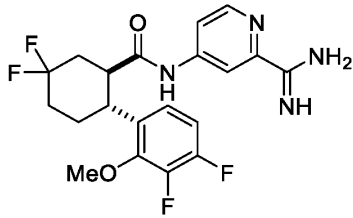
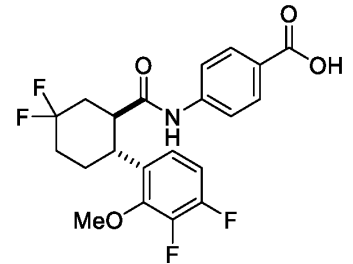
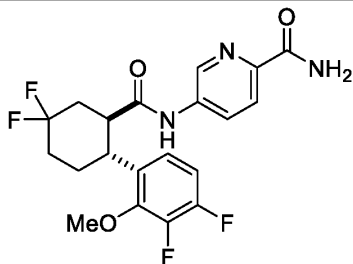
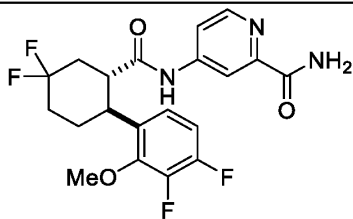
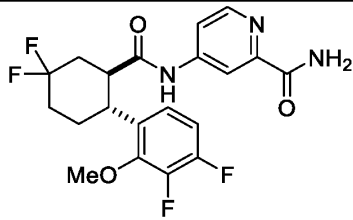
273	
274	
275	
276	
277	

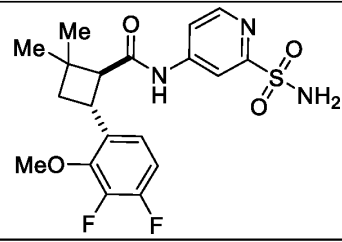
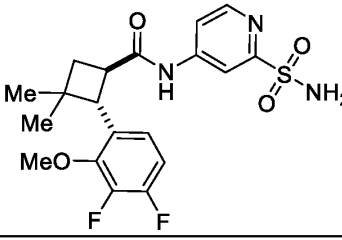
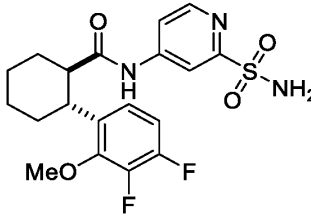
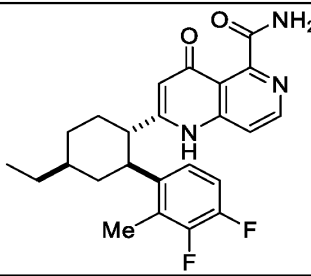
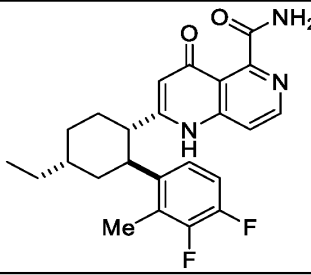
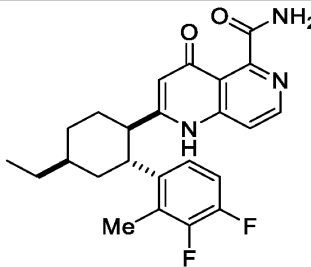
278	
279	
280	
281	
282	
283	

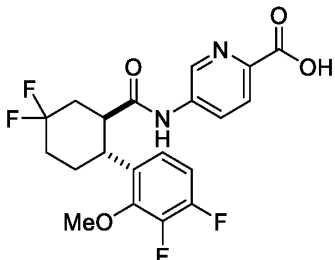
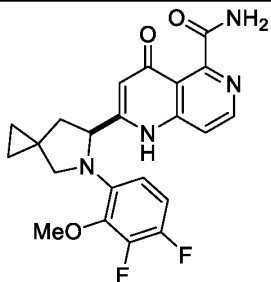
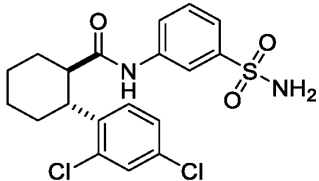
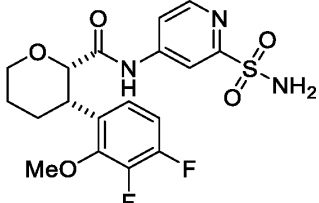
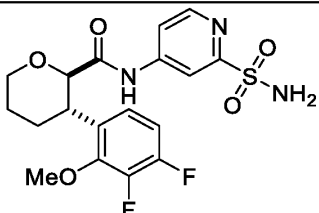
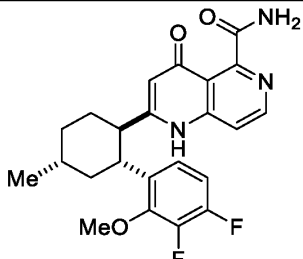
284	
285	
286	
287	
288	
289	

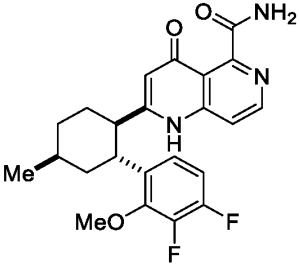
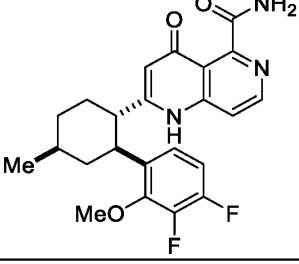
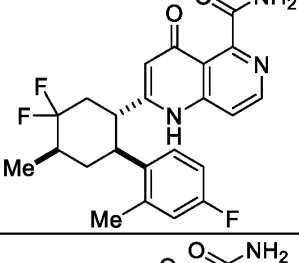
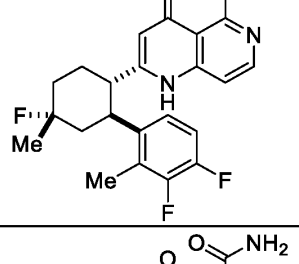
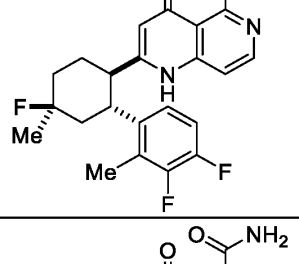
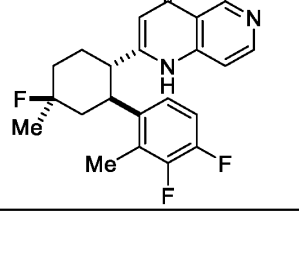
291	
292	
293	
294	
295	
296	

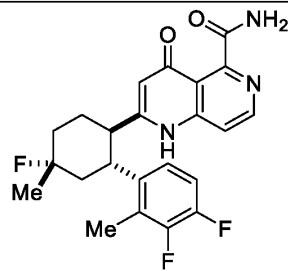
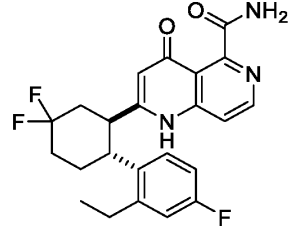
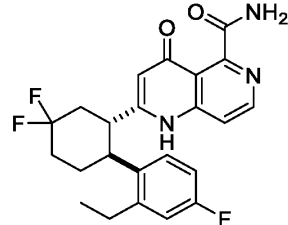
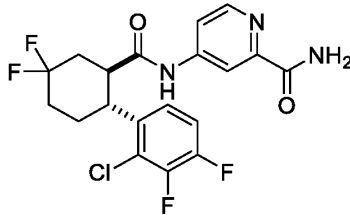
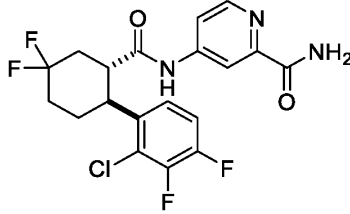
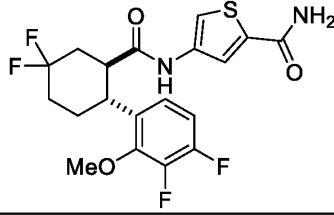
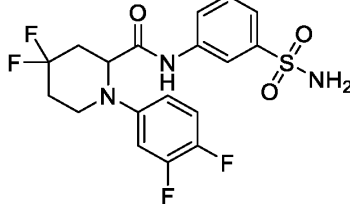
297	
298	
299	
300	
301	
302	

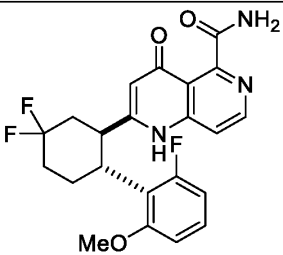
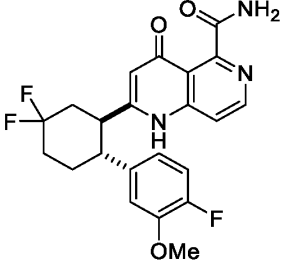
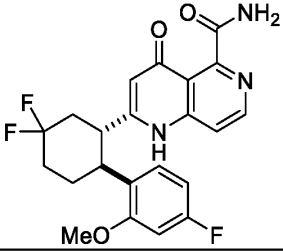
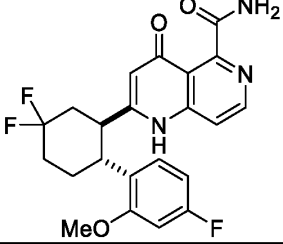
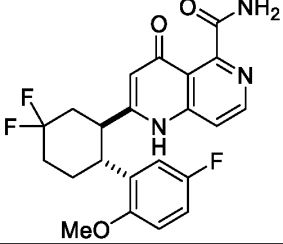
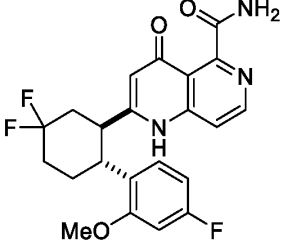
303	 <chem>NC(=O)c1ccc(NC(=O)[C@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3)cc1</chem>
304	 <chem>NC(=O)c1ccncc1NC(=O)[C@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3</chem>
305	 <chem>OC(=O)c1ccc(NC(=O)[C@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3)cc1</chem>
306	 <chem>NC(=O)c1ccncc1NC(=O)[C@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3</chem>
307	 <chem>NC(=O)c1ccncc1NC(=O)[C@@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3</chem>
308	 <chem>NC(=O)c1ccncc1NC(=O)[C@@H]2C(F)(F)CCC[C@H]2c3cc(F)c(F)c(OC)c3</chem>

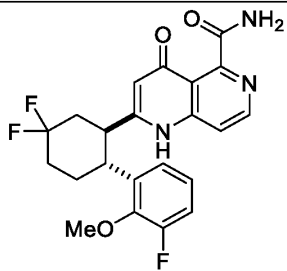
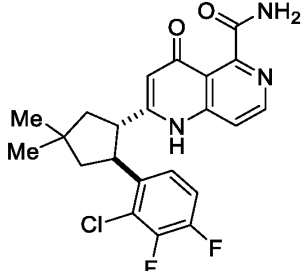
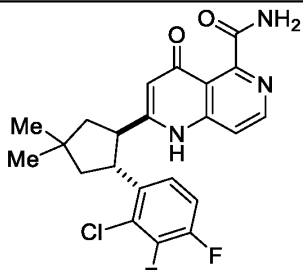
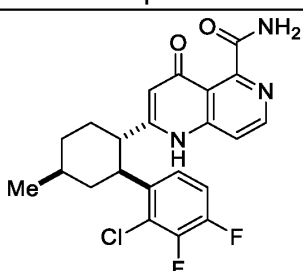
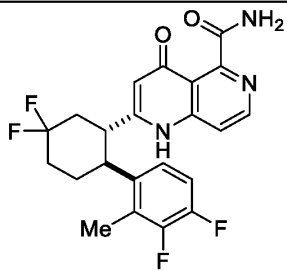
309	 <chem>C[C@H]1CC[C@H]1[C@@H](c2cc(F)c(F)cc2OC)C(=O)Nc3cc(N(S(=O)(=O)O)ccn3</chem>
310	 <chem>C[C@H]1CC[C@H]1[C@@H](c2cc(F)c(F)cc2OC)C(=O)Nc3cc(N(S(=O)(=O)O)ccn3</chem>
311	 <chem>C1CCC(CC1)[C@@H](c2cc(F)c(F)cc2OC)C(=O)Nc3cc(N(S(=O)(=O)O)ccn3</chem>
312	 <chem>CC[C@H]1CCCC[C@H]1[C@@H](c2cc(F)c(F)cc2C)Nc3cc4c(cnc3C(=O)N)ccc4=O</chem>
313	 <chem>CC[C@H]1CCCC[C@H]1[C@@H](c2cc(F)c(F)cc2C)Nc3cc4c(cnc3C(=O)N)ccc4=O</chem>
314	 <chem>CC[C@H]1CCCC[C@H]1[C@@H](c2cc(F)c(F)cc2C)Nc3cc4c(cnc3C(=O)N)ccc4=O</chem>

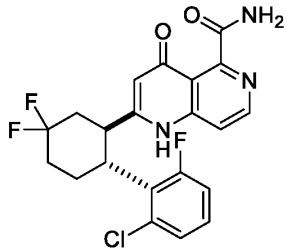
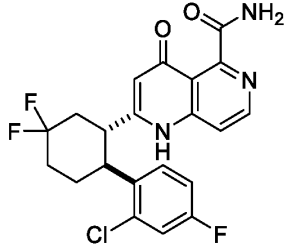
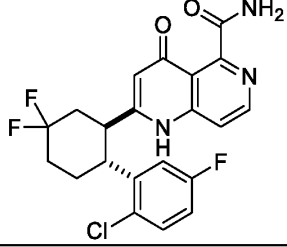
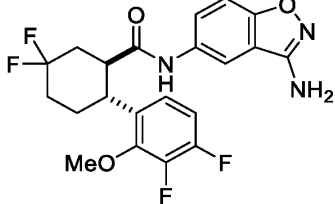
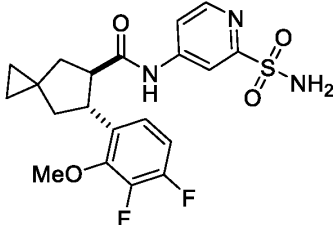
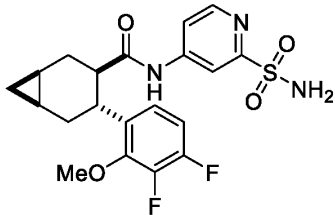
315	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>
316	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>
317	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>
318	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>
319	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>
320	 <chem>COc1cc(F)ccc1NC(=O)[C@H]2CC(F)CC2C(=O)Nc3ccc(C(=O)O)cn3</chem>

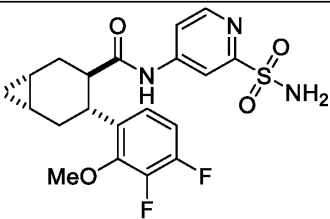
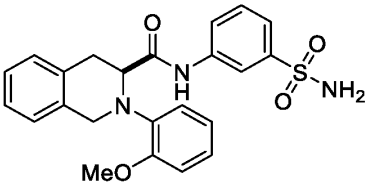
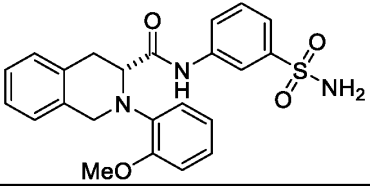
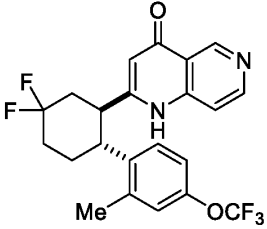
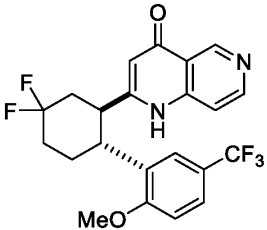
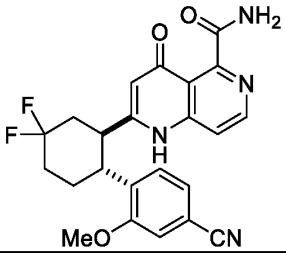
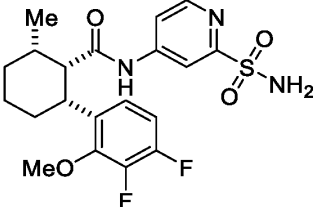
321	
322	
323	
324	
325	
326	

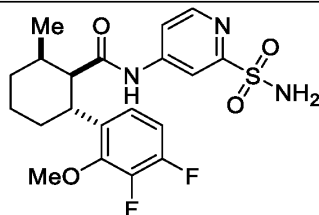
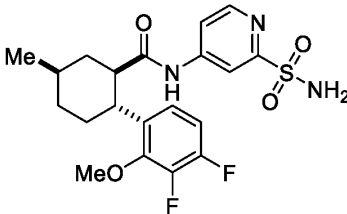
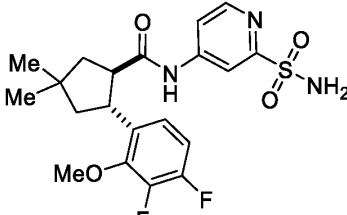
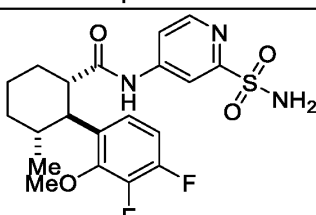
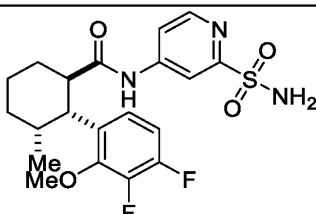
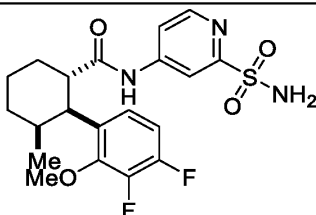
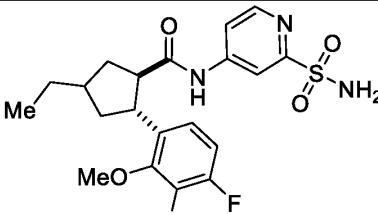
327	
328	
329	
330	
331	
332	
333	

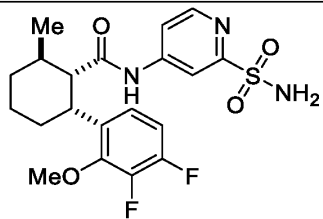
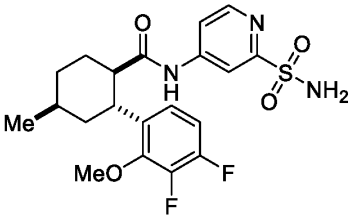
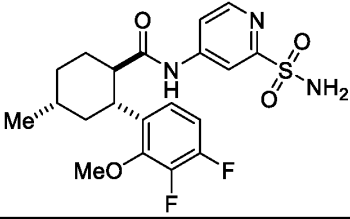
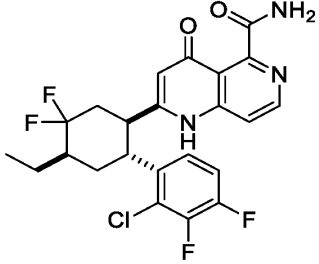
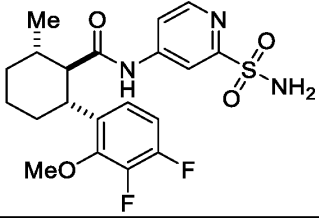
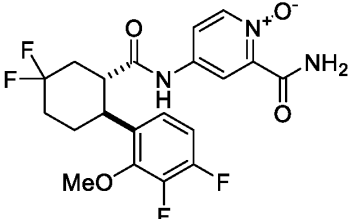
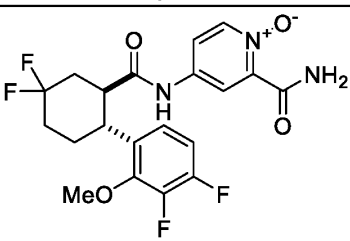
334	
335	
336	
337	
338	
339	

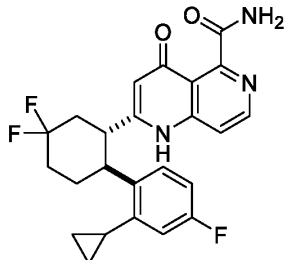
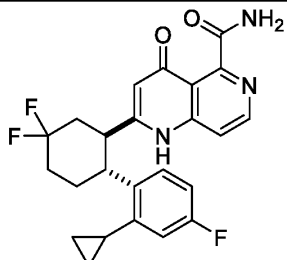
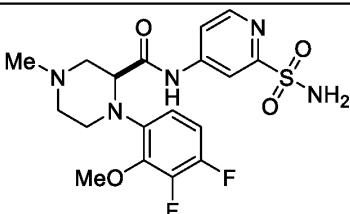
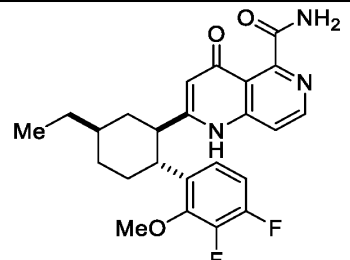
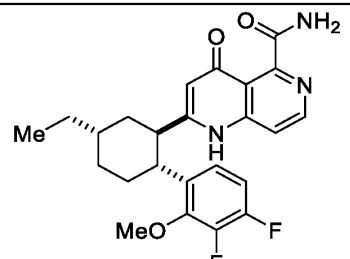
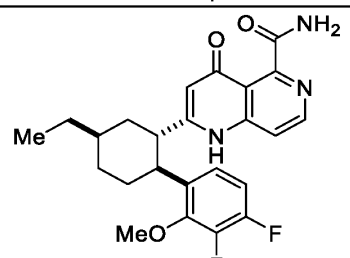
340	
341	
342	
344	
345	

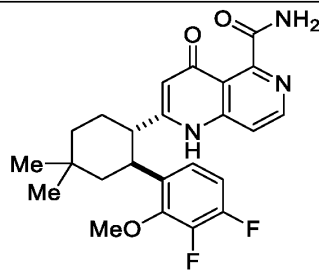
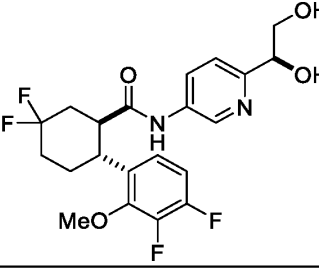
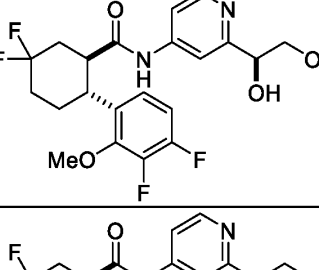
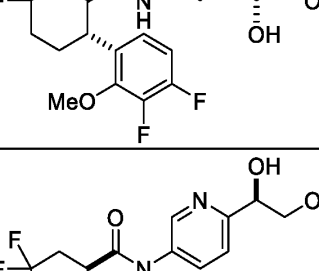
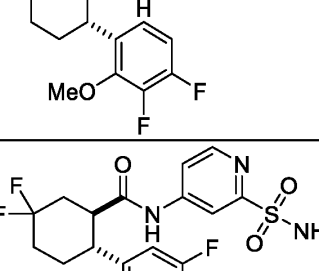
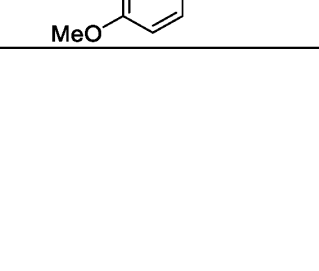
346	
348	
350	
351	
352	
353	

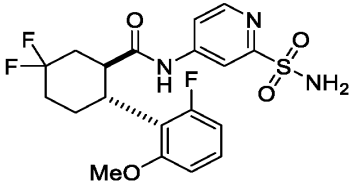
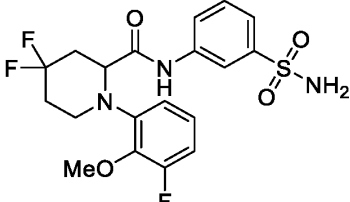
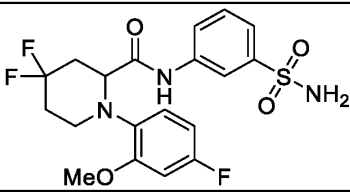
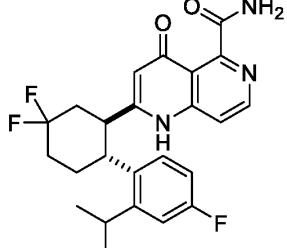
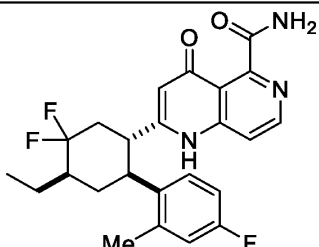
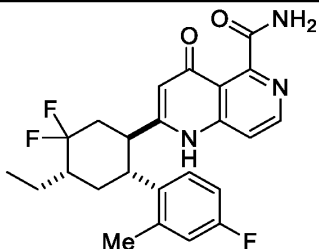
354	
355	
356	
357	
358	
359	
360	

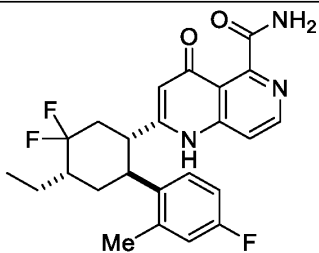
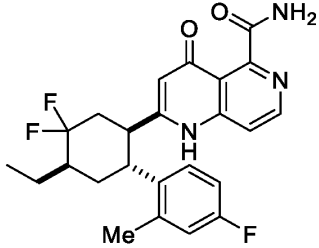
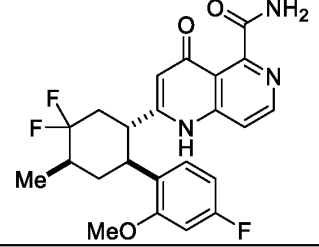
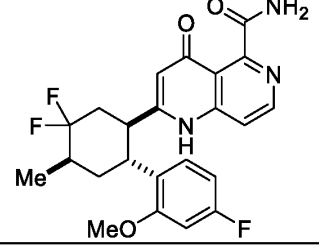
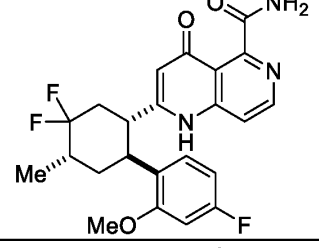
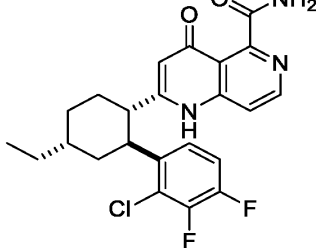
361	
362	
363	
364	
365	
366	
367	

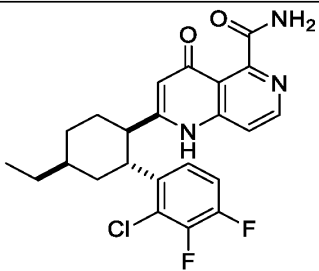
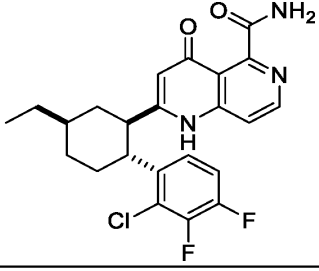
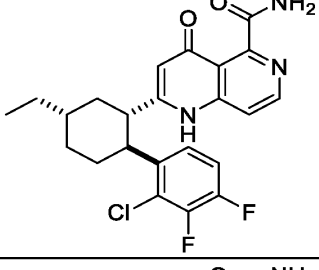
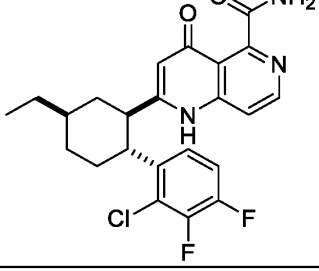
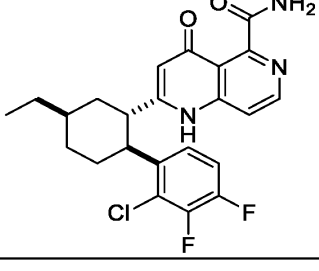
368	
369	
370	
371	
372	
373	
374	

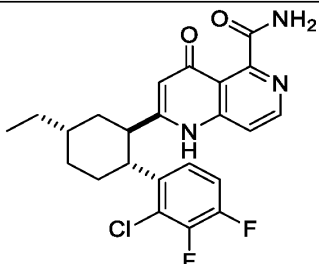
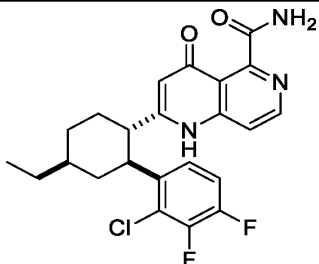
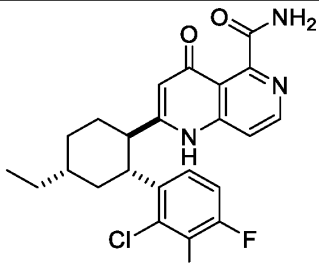
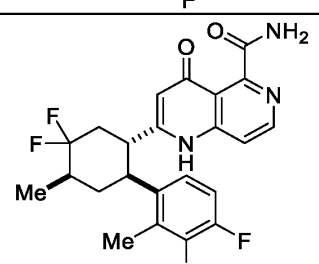
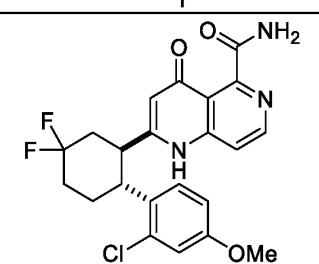
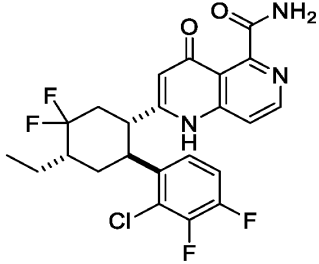
376	
377	
379	
381	
382	
383	

384	
385	
386	
387	
388	
389	

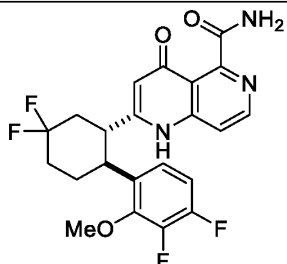
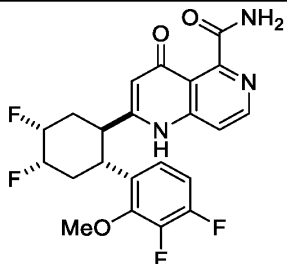
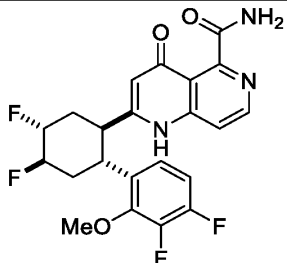
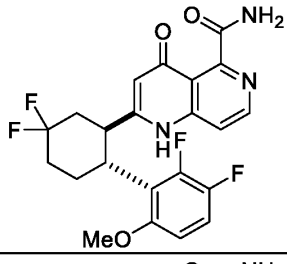
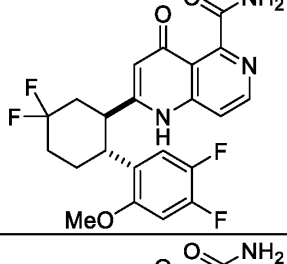
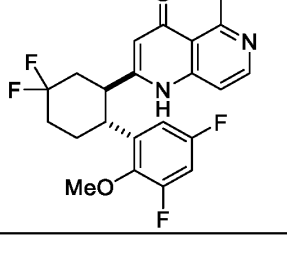
390	
392	
393	
394	
395	
396	

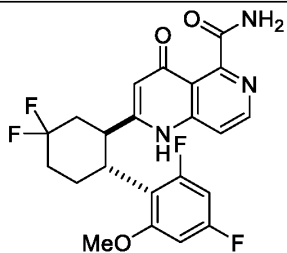
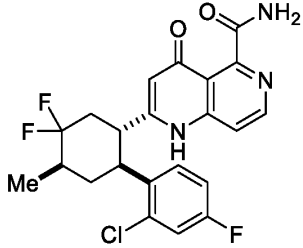
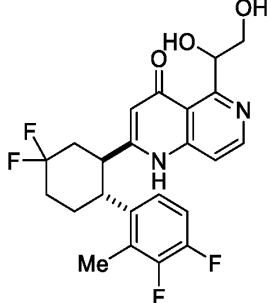
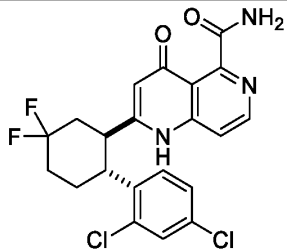
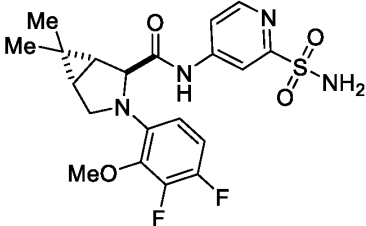
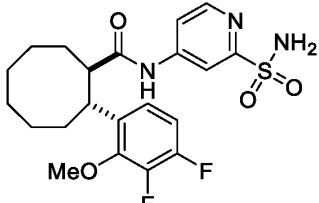
397	
398	
399	
400	
401	
402	

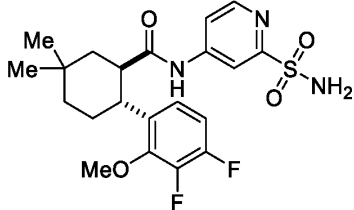
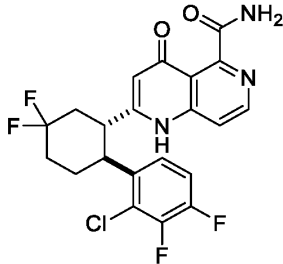
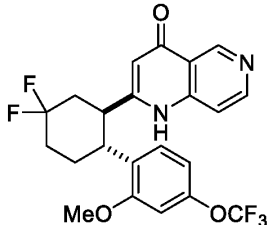
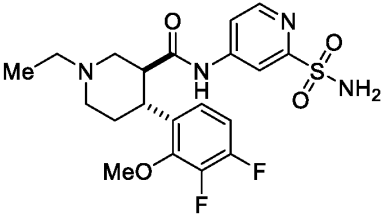
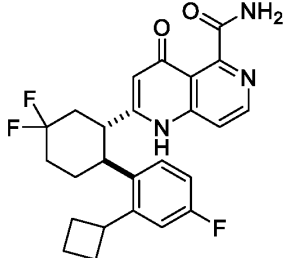
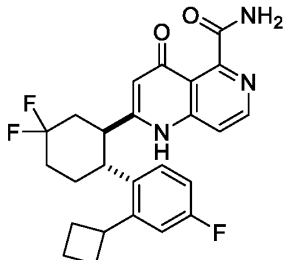
403	
404	
405	
406	
407	

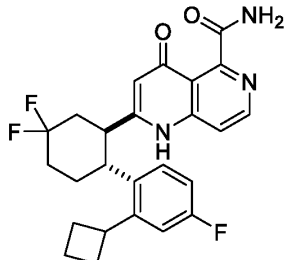
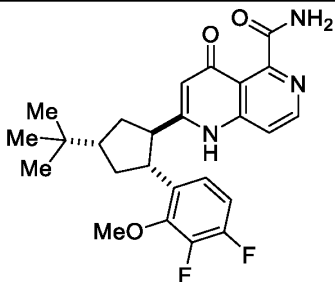
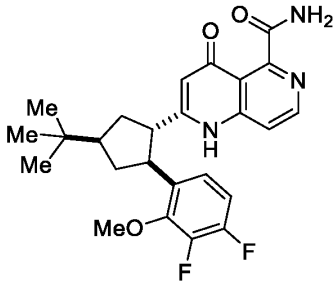
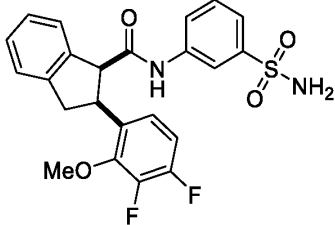
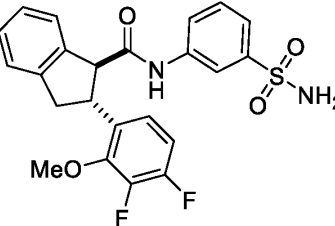
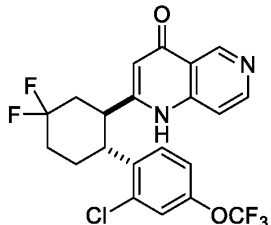
408	
409	
410	
411	
412	
413	

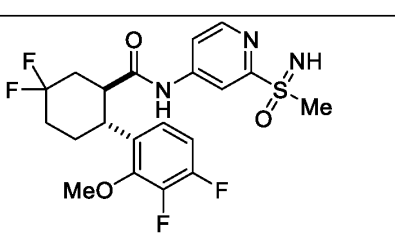
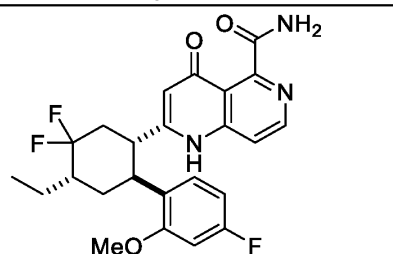
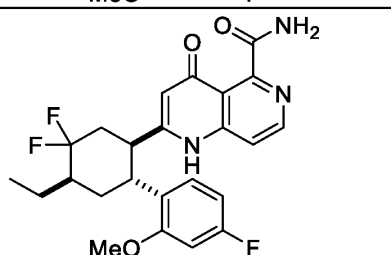
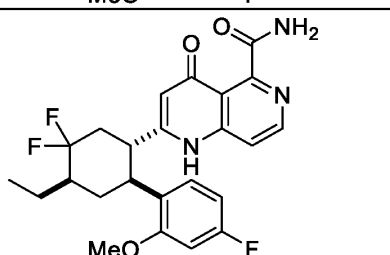
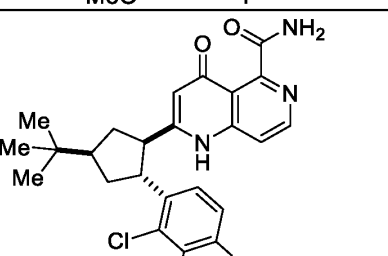
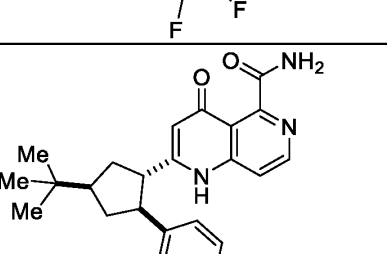
414	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(Cl)cc(OC)c4</chem>
415	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(F)c(OC)c(F)c4</chem>
416	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(F)c(OC)c(F)c4</chem>
417	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(F)c(OC)c(F)c4</chem>
418	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(F)c(OC)c(F)c4</chem>
419	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2C(=O)N)N[C@H]3CC(F)(F)CC3c4cc(F)c(OC)c(F)c4</chem>

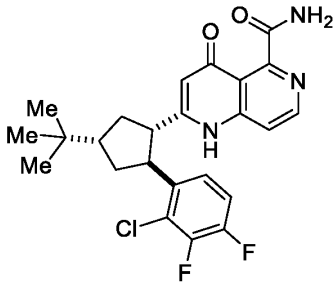
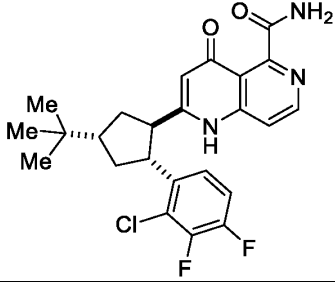
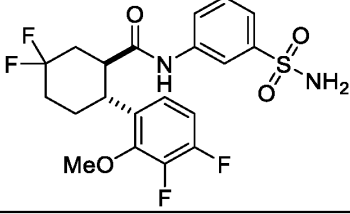
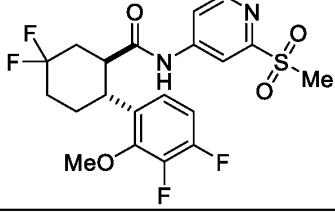
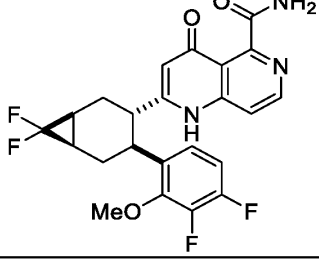
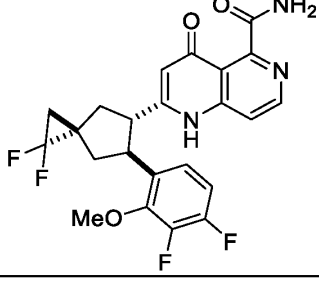
420	
421	
422	
423	
424	
425	

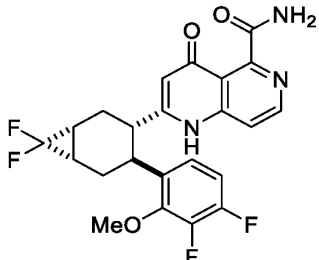
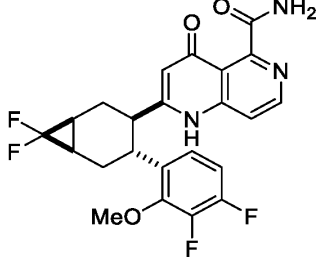
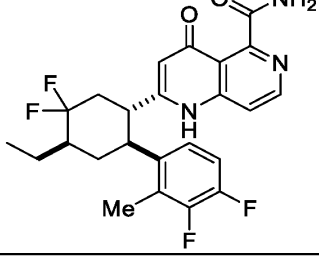
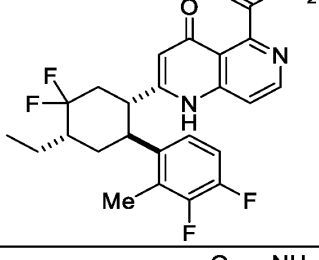
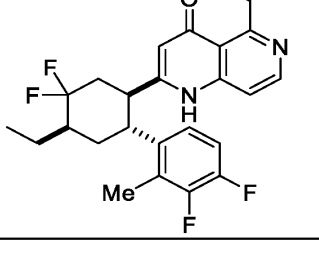
426	
427	
428	
429	
430	
431	

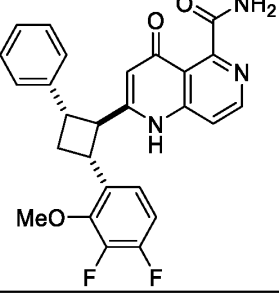
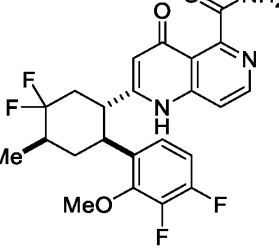
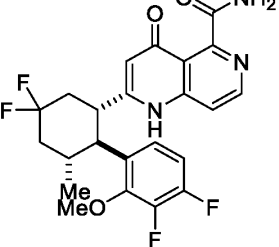
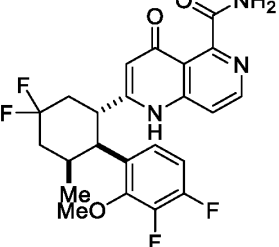
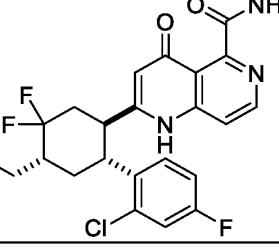
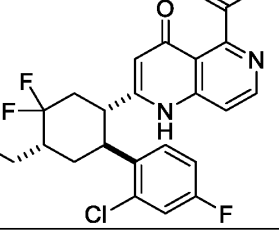
433	
434	
435	
436	
437	
438	

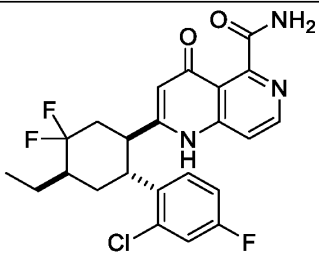
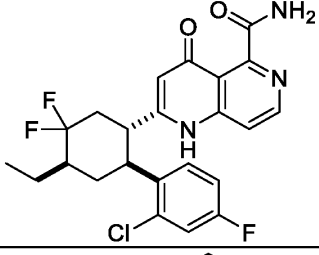
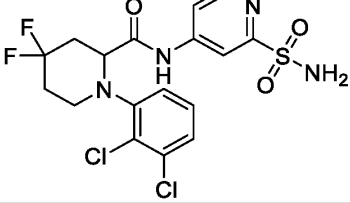
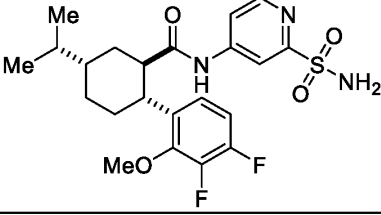
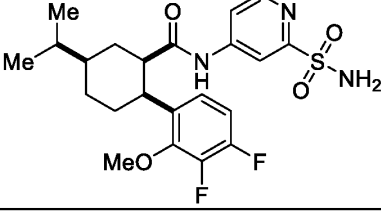
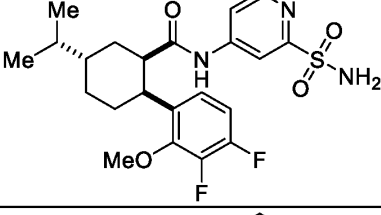
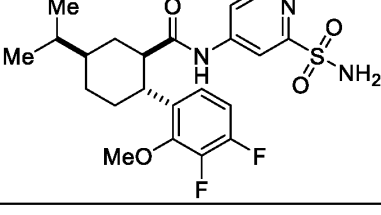
439	
440	
441	
442	
443	
444	

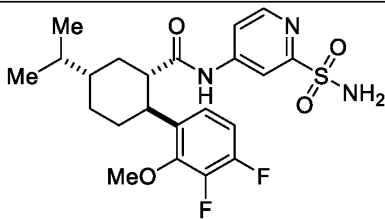
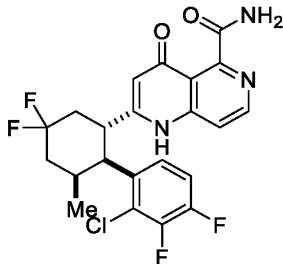
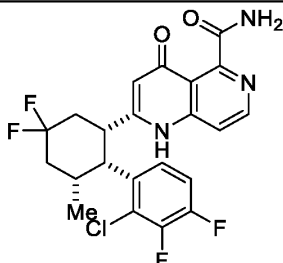
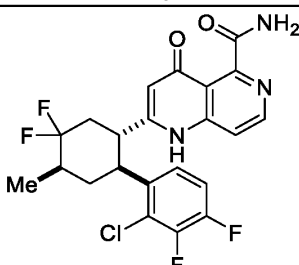
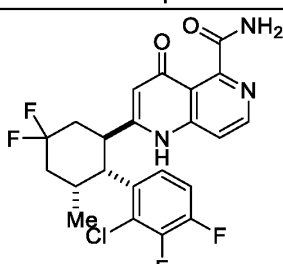
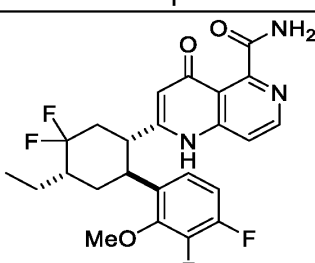
446	
447	
448	
449	
450	
451	

452	
453	
454	
455	
456	
457	

458	 <chem>COc1cc(F)c(NC2=CC(=O)c3cc(N)nc3C2=O)cc1C1CCC(CC1)C(F)(F)C</chem>
459	 <chem>COc1cc(F)c(NC2=CC(=O)c3cc(N)nc3C2=O)cc1C1CC1C(F)(F)C</chem>
462	 <chem>CC[C@H]1CC[C@@H](C(F)(F)C)CC1C2=CC(=O)c3cc(N)nc3N2C4=CC(=C(C)C(F)=C4)OC</chem>
463	 <chem>CC[C@@H]1CC[C@H](C(F)(F)C)CC1C2=CC(=O)c3cc(N)nc3N2C4=CC(=C(C)C(F)=C4)OC</chem>
464	 <chem>CC[C@H]1CC[C@@H](C(F)(F)C)CC1C2=CC(=O)c3cc(N)nc3N2C4=CC(=C(C)C(F)=C4)OC</chem>

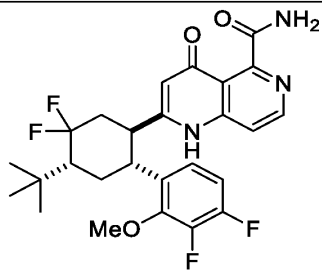
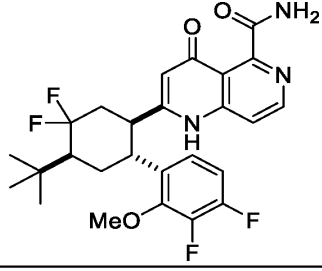
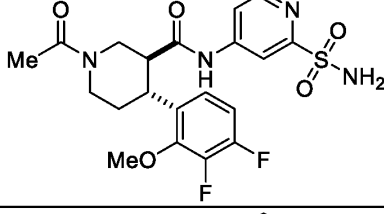
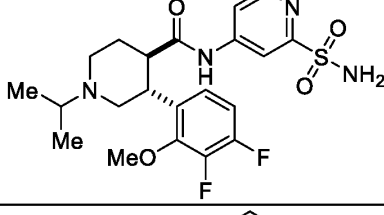
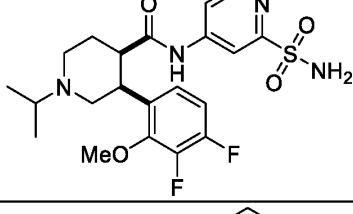
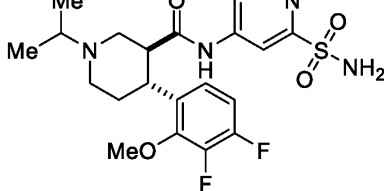
465	
466	
467	
468	
469	
470	

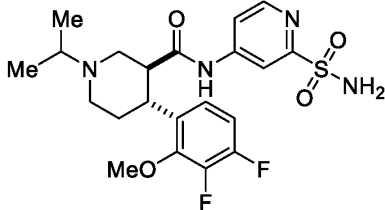
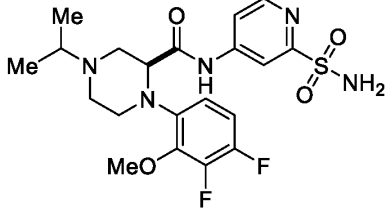
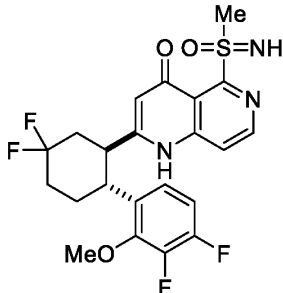
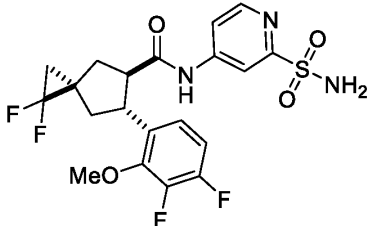
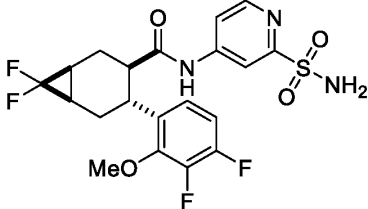
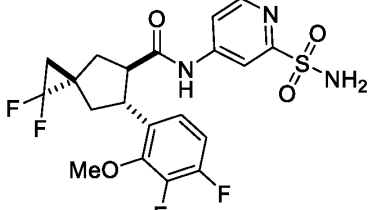
471	
472	
473	
474	
475	
476	
477	

478	
479	
480	
481	
482	
483	

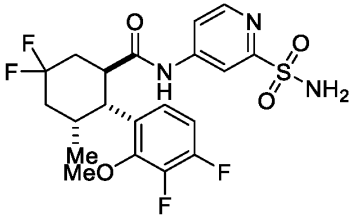
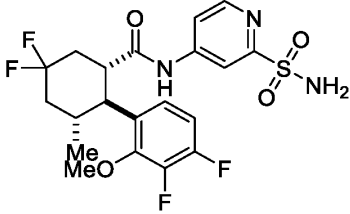
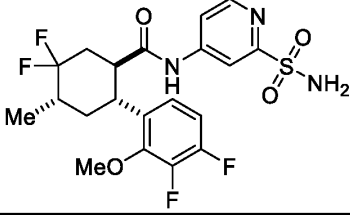
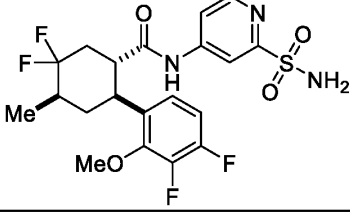
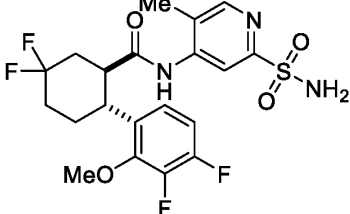
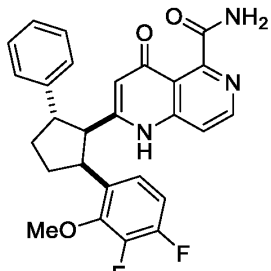
484	
485	
486	
487	
488	

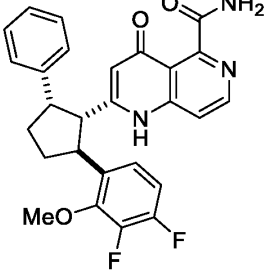
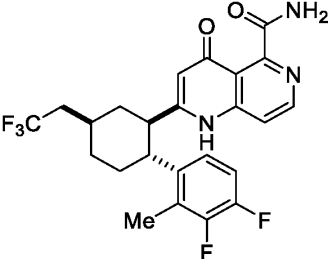
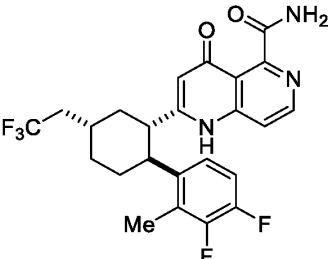
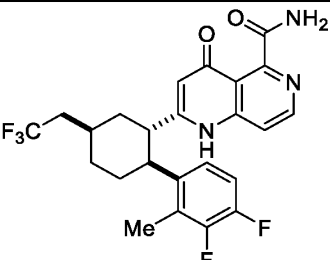
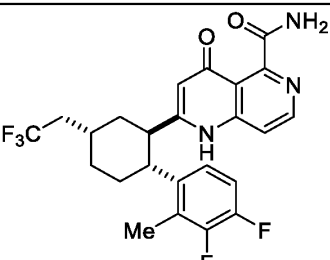
489	 <chem>N#Cc1ccc2c(c1)c3cc(F)c(F)c(CF(F)F)c3[nH]2C4CC(F)CC(F)C4</chem>
490	 <chem>N#Cc1ccc2c(c1)c3cc(F)c(F)c(CF(F)F)c3[nH]2C4CC(F)CC(F)C4</chem>
491	 <chem>N#Cc1ccc2c(c1)c3cc(F)c(F)c(CF(F)F)c3[nH]2C4CC(F)CC(F)C4</chem>
492	 <chem>N#Cc1ccc2c(c1)c3cc(F)c(F)c(CF(F)F)c3[nH]2C4CC(F)CC(F)C4</chem>
493	 <chem>N#Cc1ccc2c(c1)c3cc(F)c(F)c(CF(F)F)c3[nH]2C4CC(F)CC(F)C4</chem>

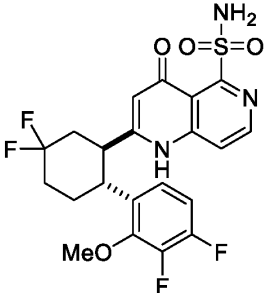
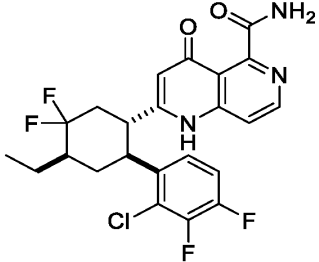
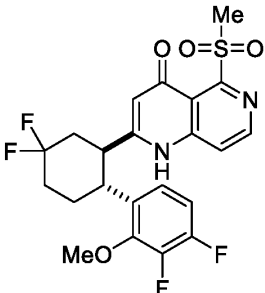
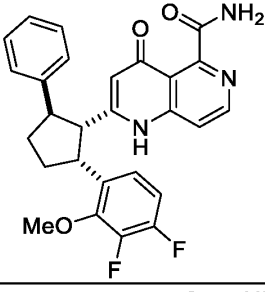
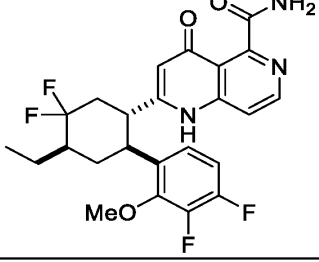
494	
495	
496	
497	
498	
499	

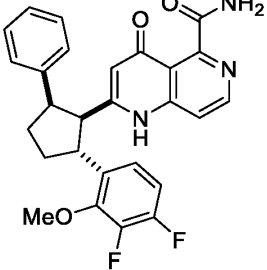
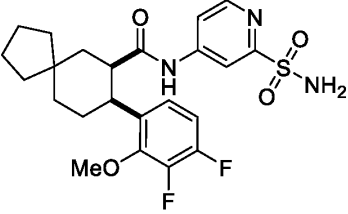
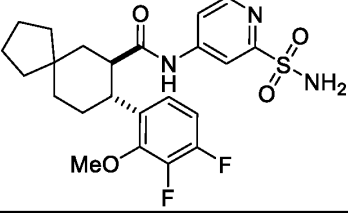
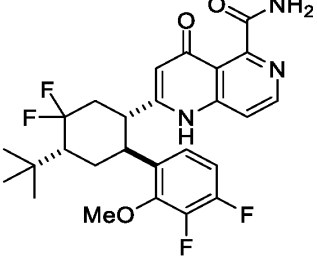
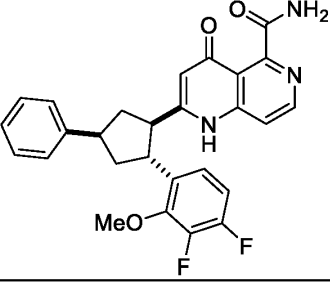
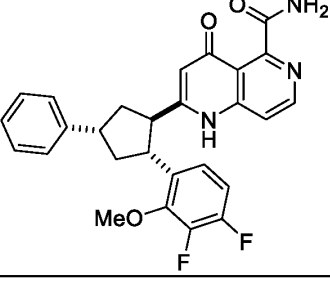
500	
501	
502	
503	
504	
505	

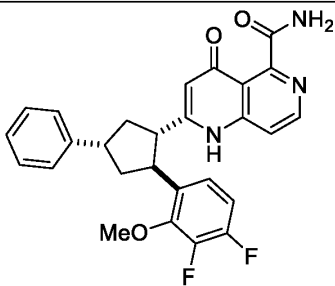
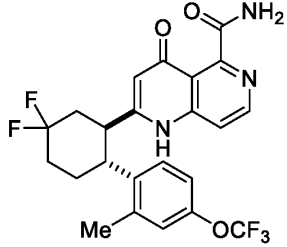
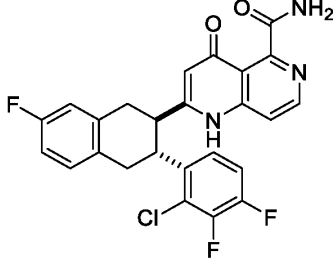
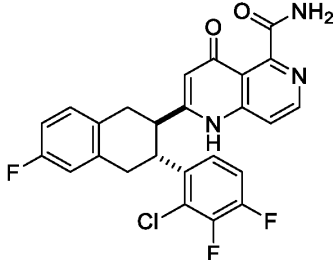
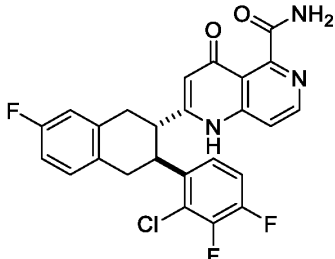
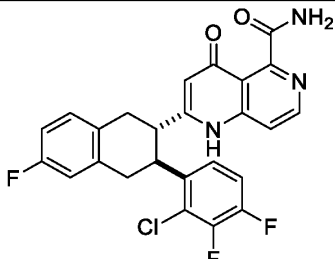
506	 <chem>NS(=O)(=O)c1ccc(cc1)NC(=O)[C@H]2C(F)(F)CC[C@@H]2c3cc(F)c(OC)cc3</chem>
507	 <chem>NS(=O)(=O)c1ccc(cc1)NC(=O)[C@H]2c3cc(F)c(OC)cc3[C@@H]4C=CC=CC=C4C2</chem>
508	 <chem>NC(=O)c1ccc2c(c1)cnc2C(=O)N[C@H]3C[C@@H](C(C)(C)C)[C@H]3c4cc(F)c(Cl)cc4</chem>
509	 <chem>NC(=O)c1ccc2c(c1)cnc2C(=O)N[C@H]3C[C@@H](C(C)(C)C)[C@H]3c4cc(F)c(Cl)cc4</chem>
510	 <chem>Nc1ccc2c(c1)cnc2C(=O)N[C@H]3C[C@@H](F)C(F)[C@H]3c4cc(F)c(OC)cc4</chem>
511	 <chem>NS(=O)(=O)c1ccc(cc1)NC(=O)[C@H]2C(F)C(F)C[C@@H](C)[C@H]2c3cc(F)c(OC)cc3</chem>

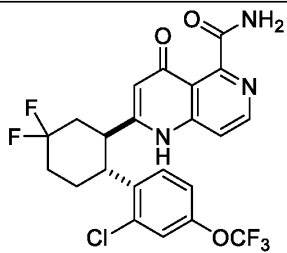
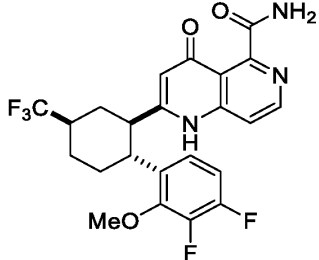
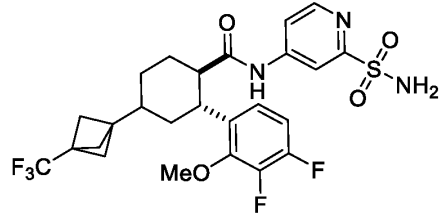
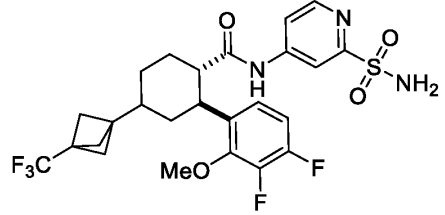
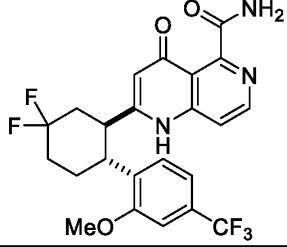
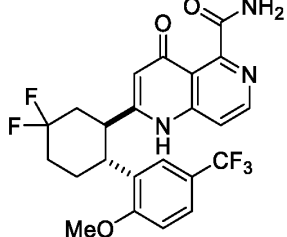
512	
513	
514	
515	
516	
517	

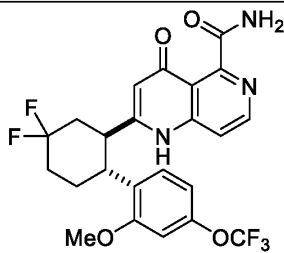
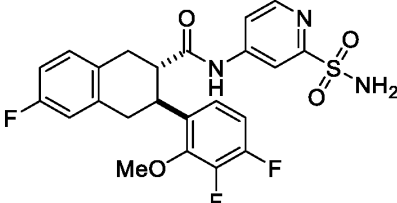
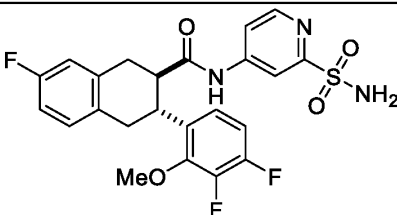
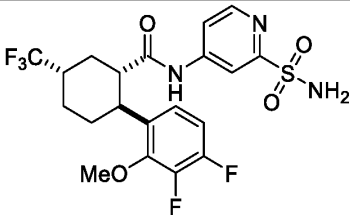
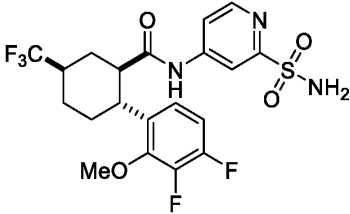
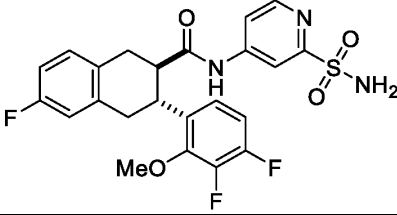
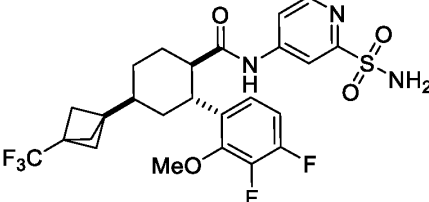
518	
519	
520	
521	
522	

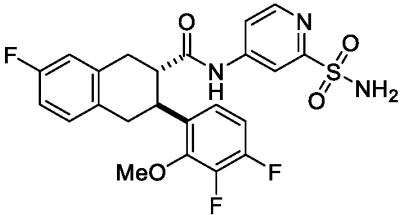
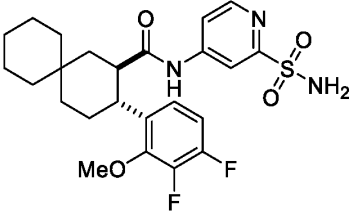
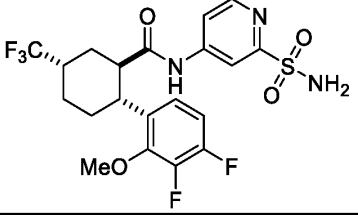
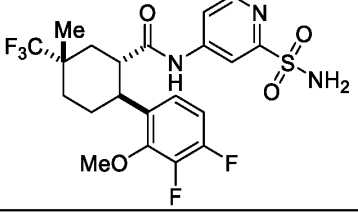
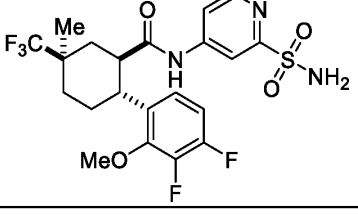
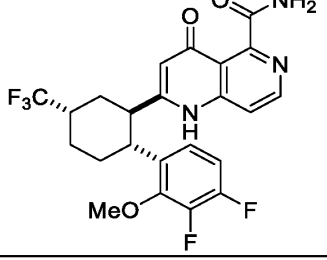
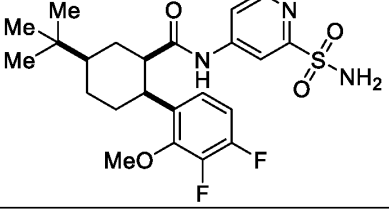
523	
524	
525	
526	
527	

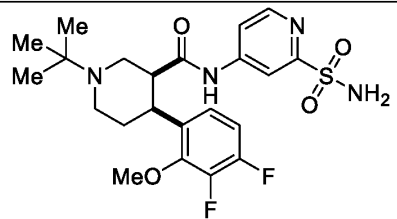
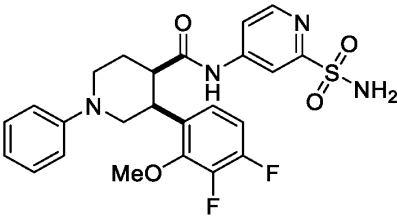
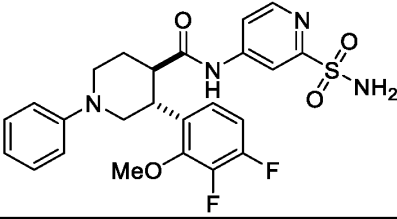
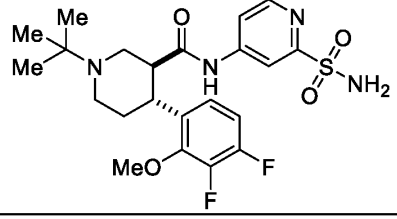
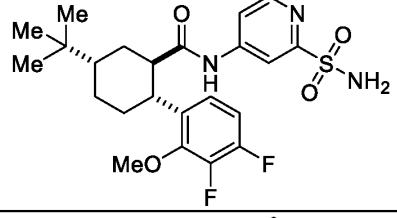
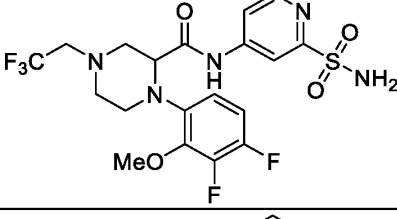
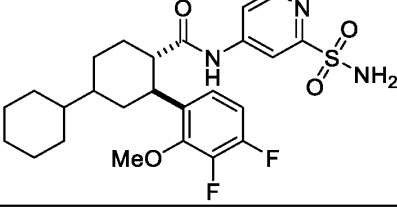
528	
529	
530	
531	
532	
533	

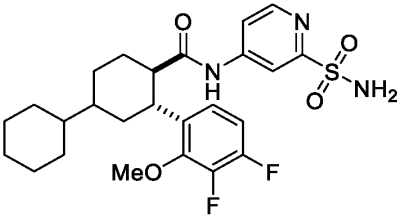
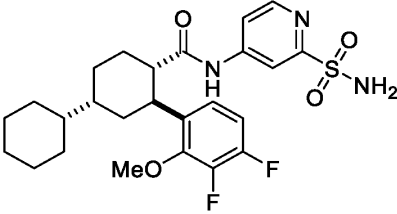
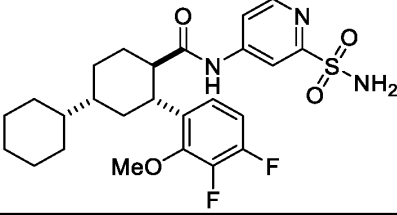
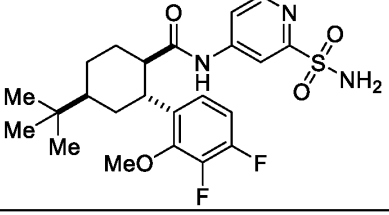
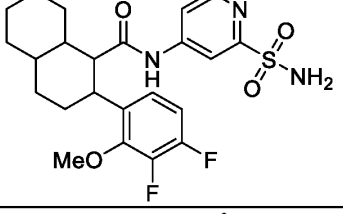
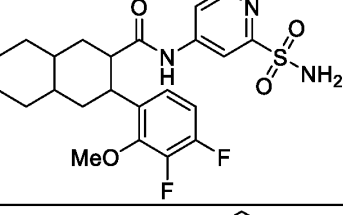
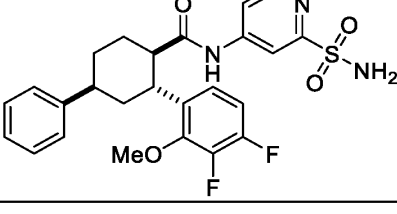
534	
535	
536	
537	
538	
539	

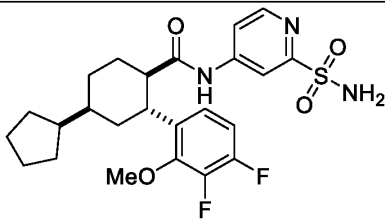
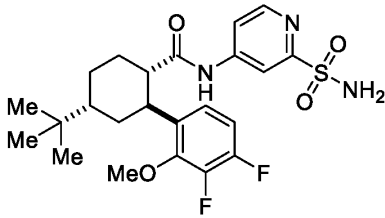
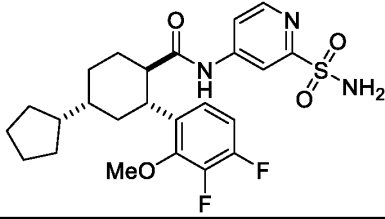
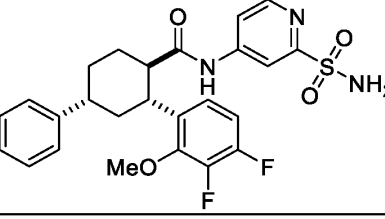
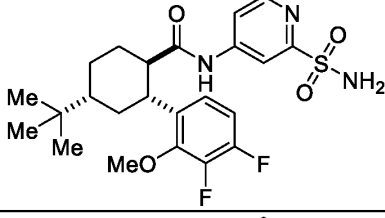
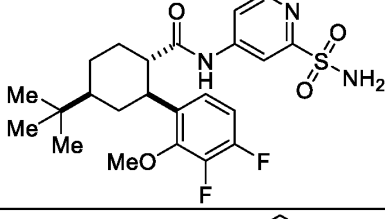
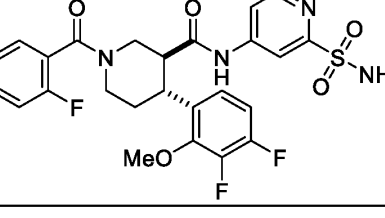
540	
541	
542	
543	
544	
545	

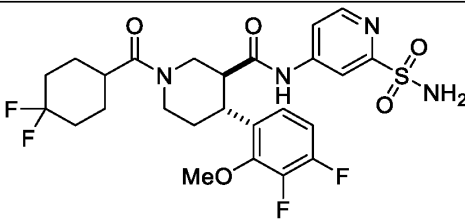
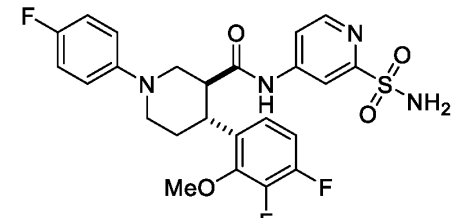
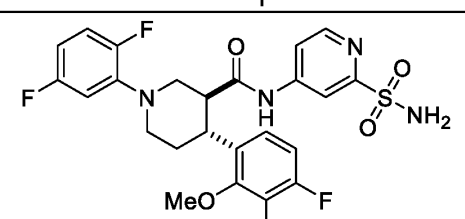
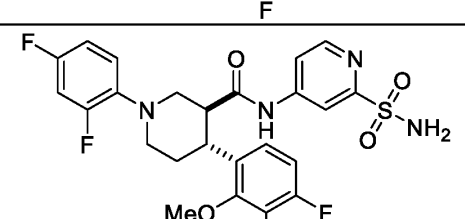
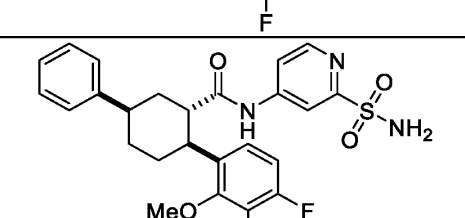
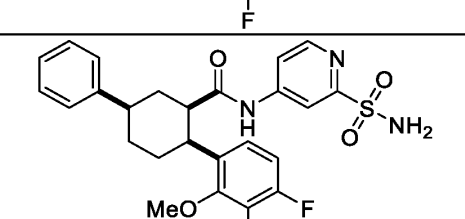
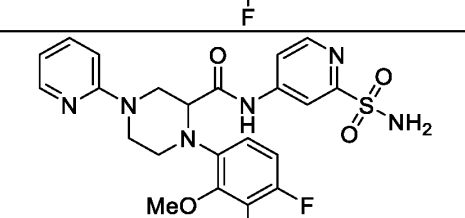
546	
547	
548	
549	
550	
551	
552	

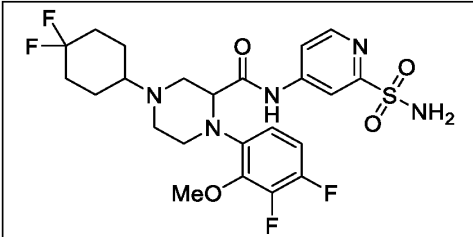
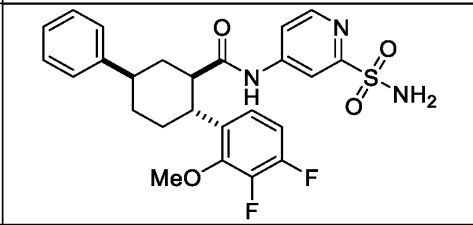
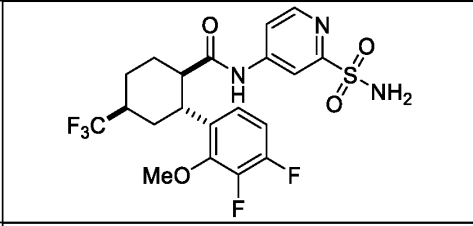
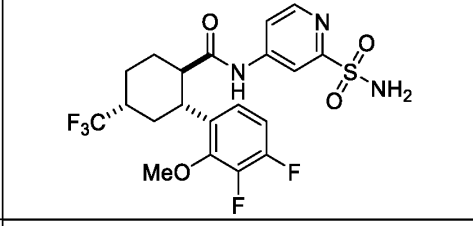
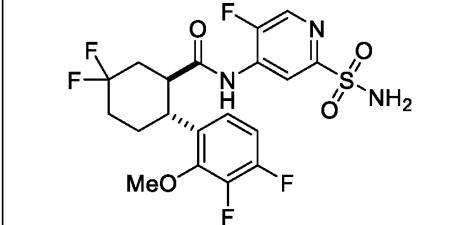
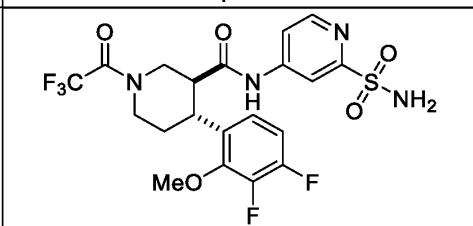
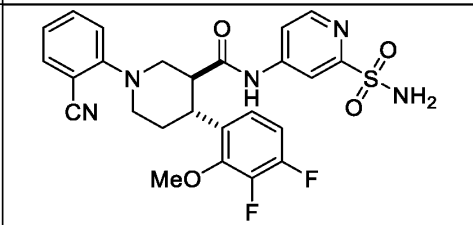
553	
554	
555	
556	
557	
558	
559	

560	
561	
562	
563	
564	
565	
566	

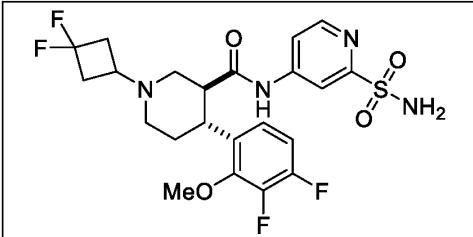
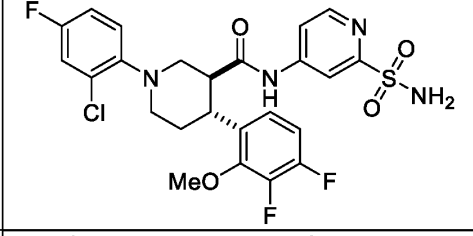
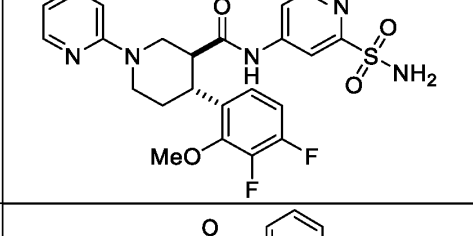
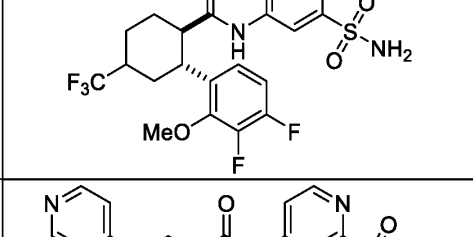
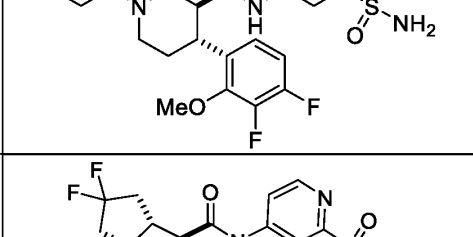
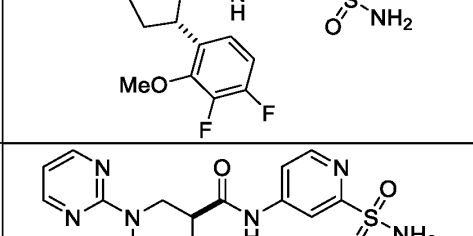
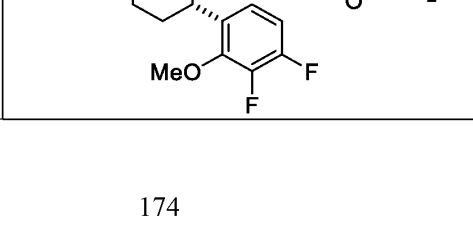
567	
568	
569	
570	
571	
572	
573	

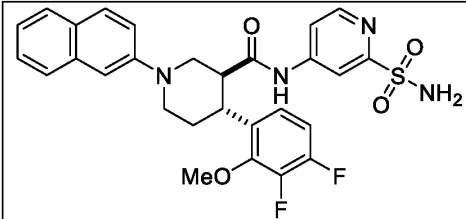
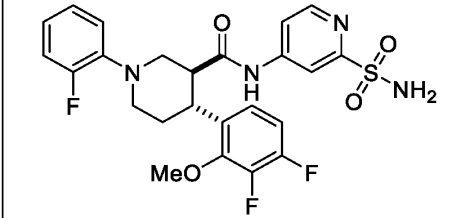
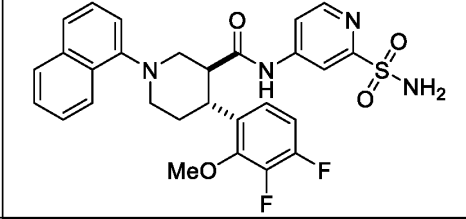
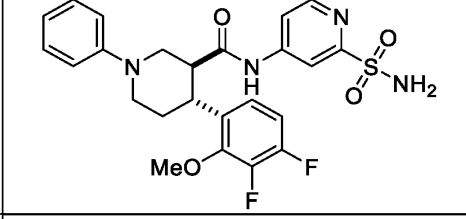
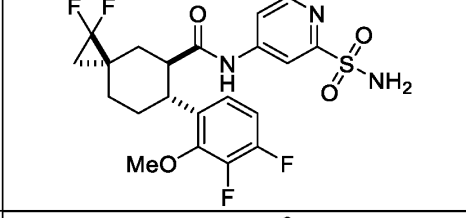
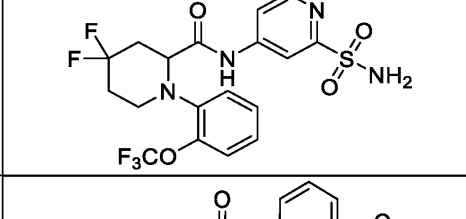
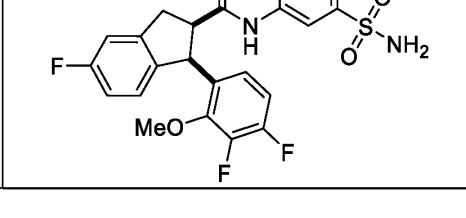
574	
575	
576	
577	
578	
579	
580	

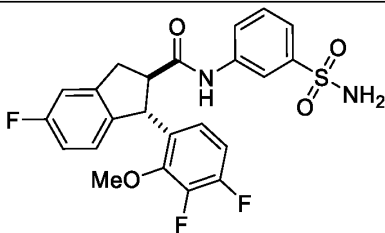
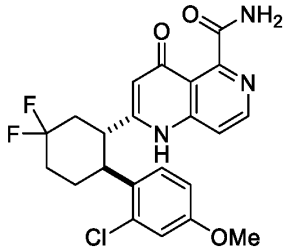
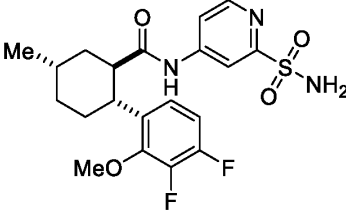
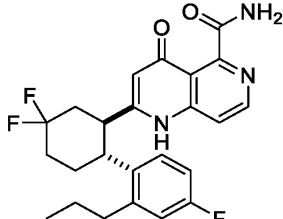
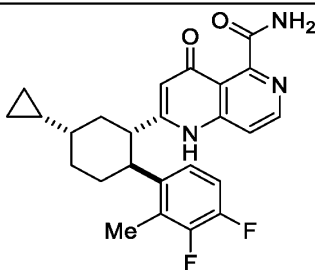
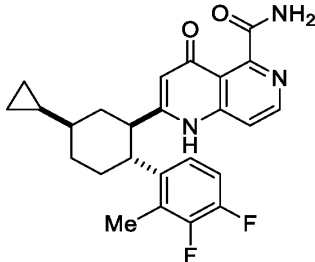
581	
582	
583	
584	
585	
586	
587	

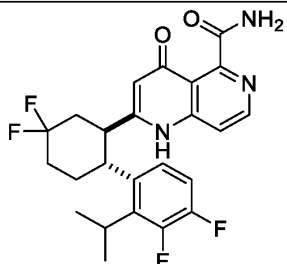
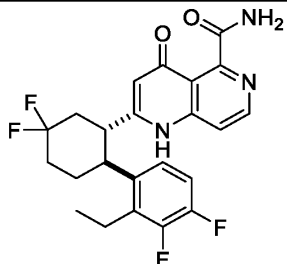
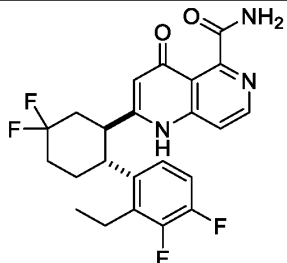
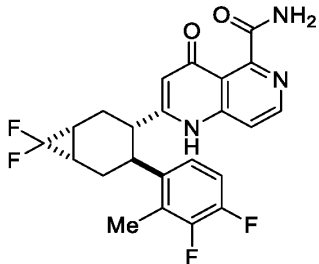
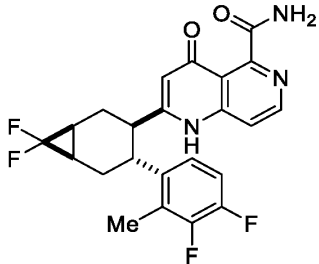
588	
589	
590	
591	
592	
593	
594	

595	
596	
597	
598	
599	
600	
601	

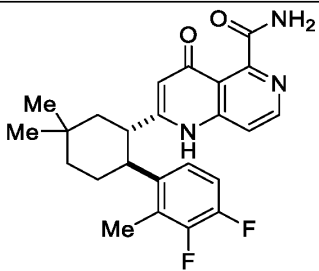
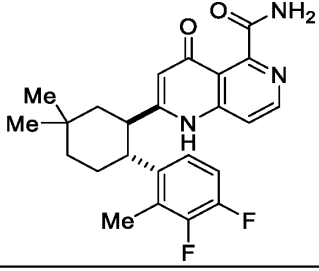
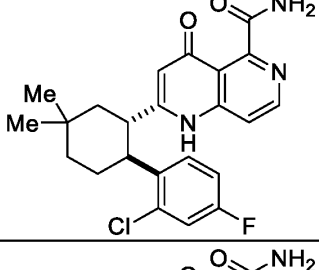
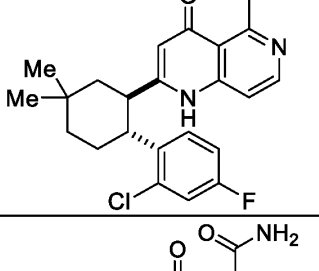
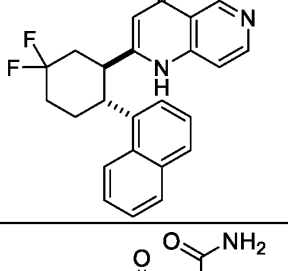
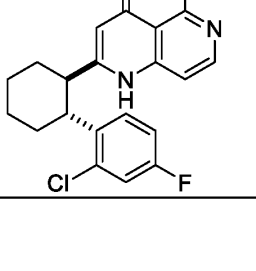
602	
603	
604	
605	
606	
607	
608	

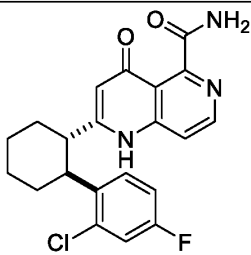
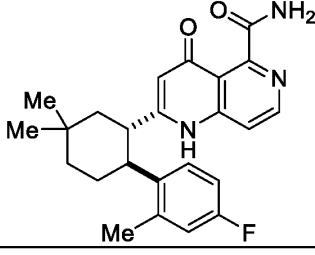
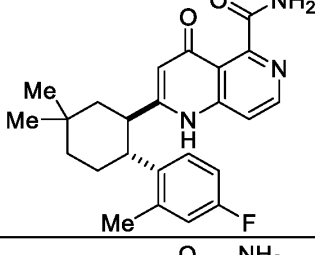
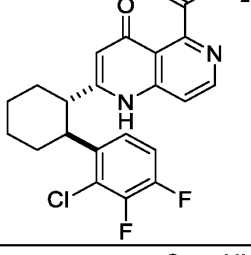
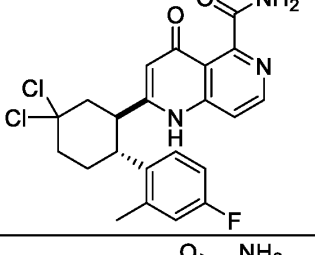
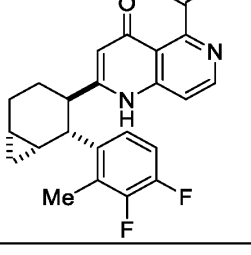
609	
610	
611	
612	
613	
614	
615	

616	
617	
618	
619	
620	
621	

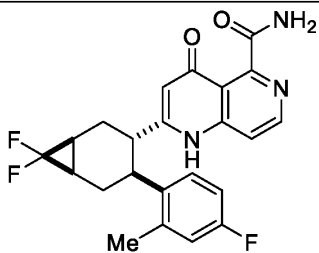
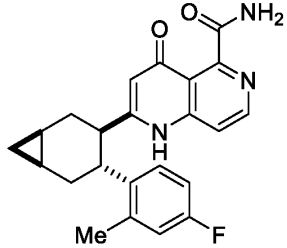
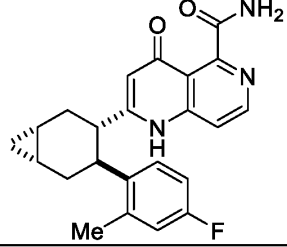
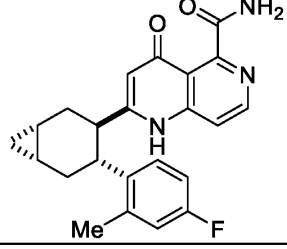
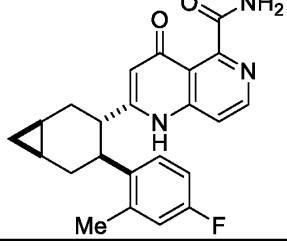
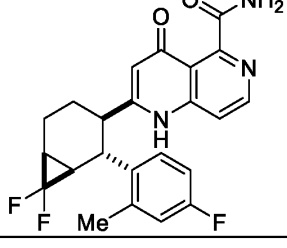
622	
623	
624	
625	
626	

627	
628	
629	
630	
631	

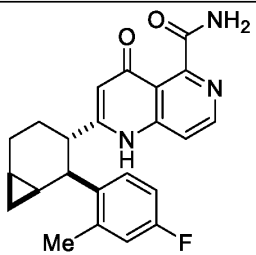
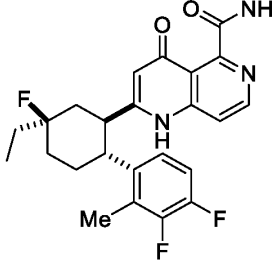
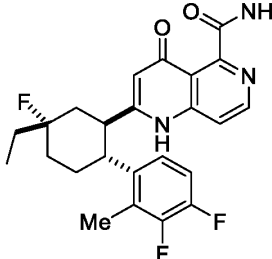
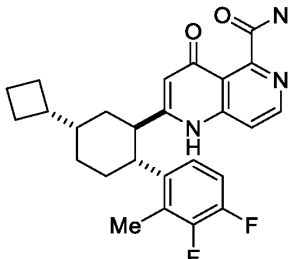
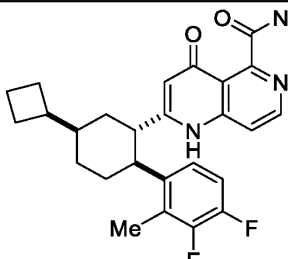
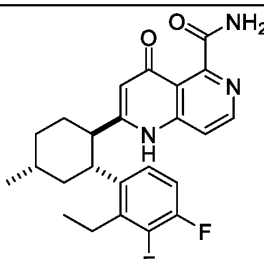
633	
634	
635	
636	
637	
638	

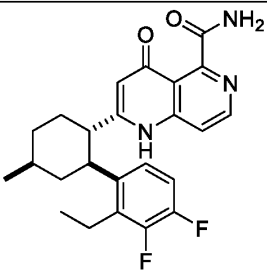
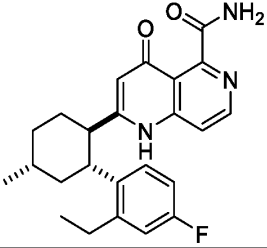
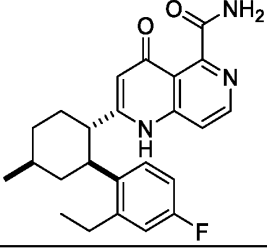
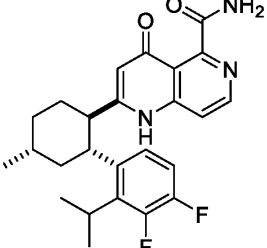
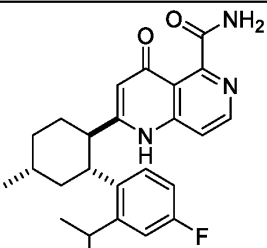
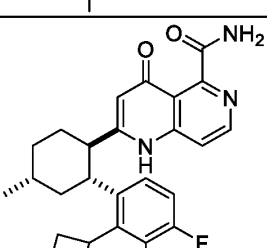
639	
640	
641	
643	
644	
645	

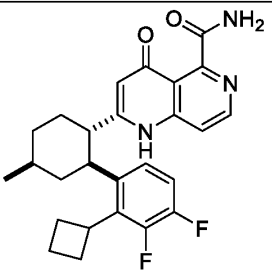
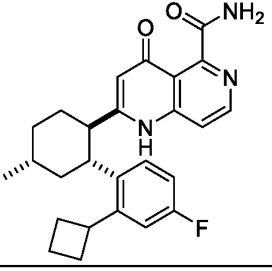
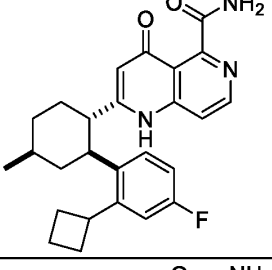
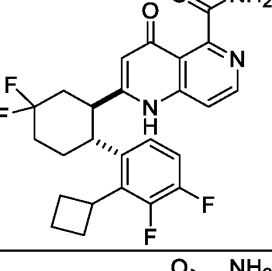
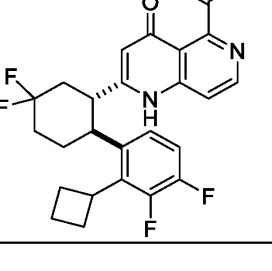
646	
647	
648	
649	
650	
651	

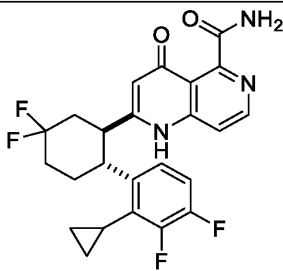
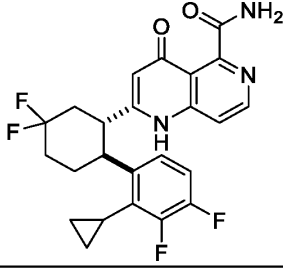
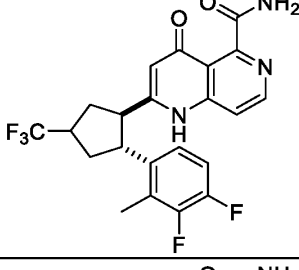
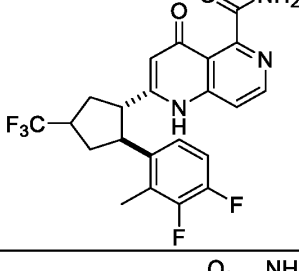
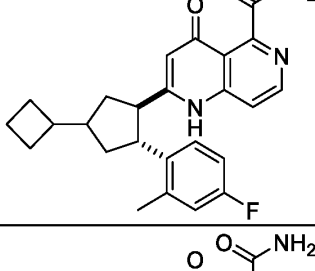
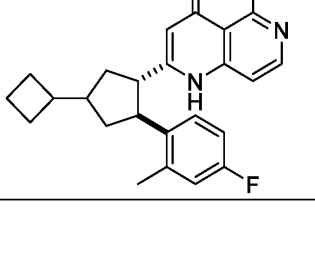
652	
653	
654	
655	
656	
657	

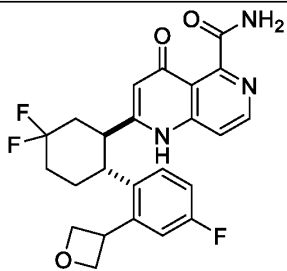
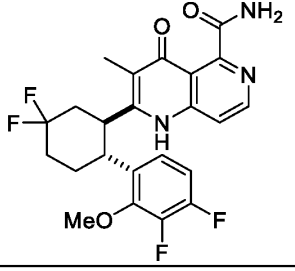
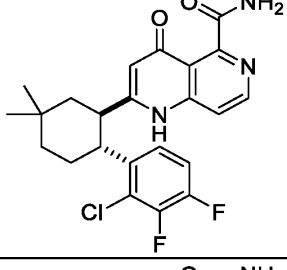
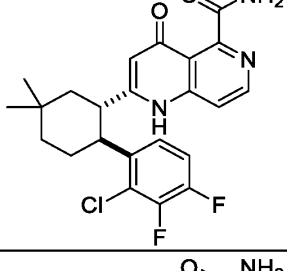
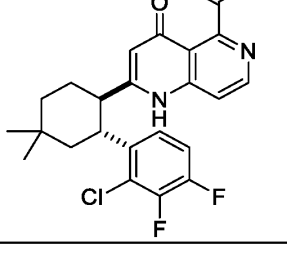
658	
659	
660	
661	
662	
663	

664	
665	
666	
667	
668	
669	

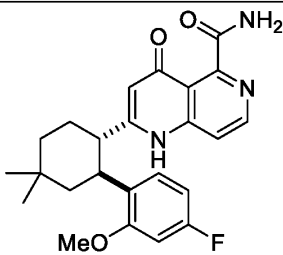
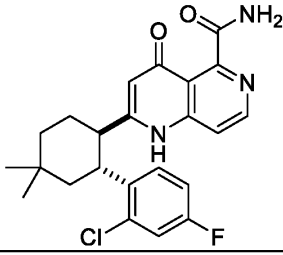
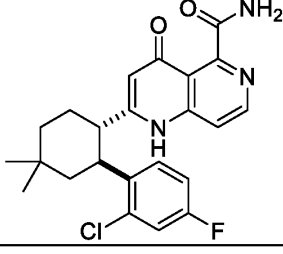
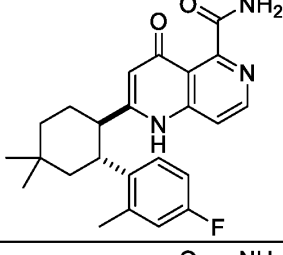
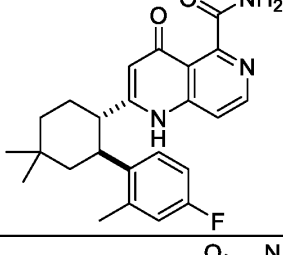
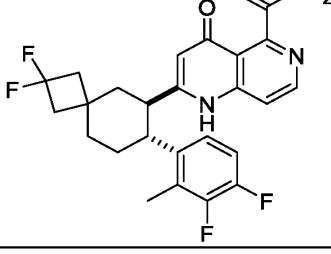
670	
671	
672	
673	
674	
675	

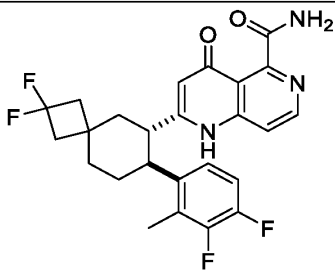
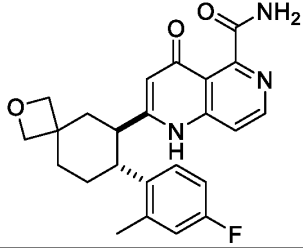
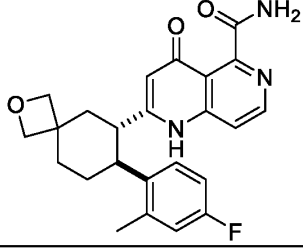
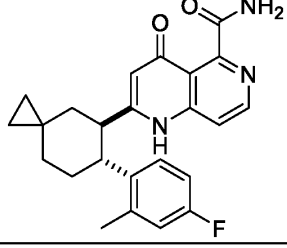
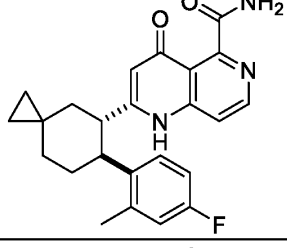
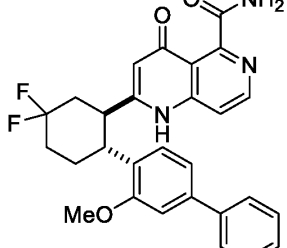
676	
677	
678	
679	
680	

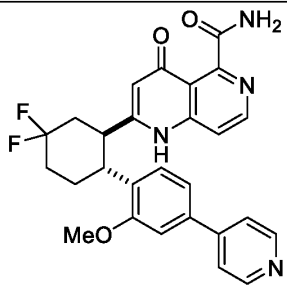
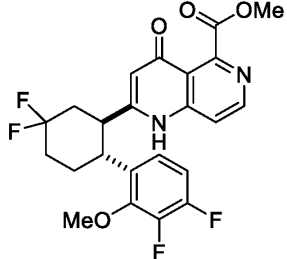
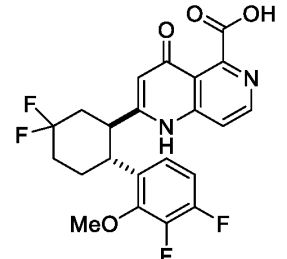
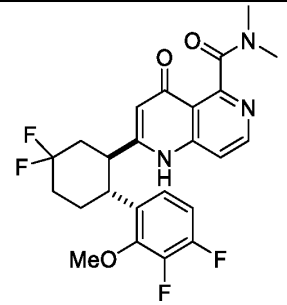
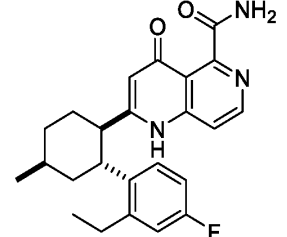
681	
682	
683	
684	
685	
686	

687	
688	
689	
690	
691	

692	
693	
694	
695	
696	
697	

698	
699	
700	
701	
702	
703	

704	
705	
706	
707	
708	
709	

710	
711	
712	
713	
714	

715	
716	
717	
718	
719	

720	
721	
722	

[00159] In some or any embodiments, provided herein are:

- (a) compounds as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 and pharmaceutically acceptable salts and compositions thereof;
- (b) compounds as described herein, *e.g.*, of Formula (I), (P-II), or (P-I), and Compounds 1-723 and pharmaceutically acceptable salts and compositions thereof for use in the treatment of pain and/or conditions modulated by voltage-gated sodium channels;
- (c) processes for the preparation of compounds as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 as described in more detail elsewhere herein;

- (d) pharmaceutical formulations comprising a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;
- (e) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or its pharmaceutically acceptable salt or composition;
- (f) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or its pharmaceutically acceptable salt or composition;
- (g) pharmaceutical formulations comprising a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or a pharmaceutically acceptable salt thereof together with one or more other effective agents for treating pain and/or conditions modulated by voltage-gated sodium channels, optionally in a pharmaceutically acceptable carrier or diluent;
- (h) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) Compounds 1-723 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain and/or conditions modulated by voltage-gated sodium channels;
- (i) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain; and
- (j) use of any compound described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or a composition comprising any compound described herein, *e.g.*, of Formula (I), (P-II), or (P-I) and Compounds 1-723 or a pharmaceutically acceptable salt or composition for the treatment of a condition associated with voltage-gated

sodium channel function described herein (e.g., pain), optionally in combination and/or alternation with one or more agent for the treatment of pain.

Optically Active Compounds

[00160] It is appreciated that compounds provided herein have several chiral centers and may exist in and be isolated in optically active and racemic forms. It is to be understood that any racemic, optically-active, diastereomeric, tautomeric, or stereoisomeric form, mixture, or combination thereof, of a compound provided herein, which possess the useful properties described herein is within the scope of the invention. It being well known in the art how to prepare optically active forms (in some or any embodiments, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[00161] In some or any embodiments, methods to obtain optically active materials are known in the art, and include at least the following.

- i) physical separation of crystals - a technique whereby macroscopic crystals of the individual stereoisomers are manually separated. This technique can be used if crystals of the separate stereoisomers exist, *i.e.*, the material is a conglomerate, and the crystals are visually distinct;
- ii) simultaneous crystallization - a technique whereby the individual stereoisomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;
- iii) enzymatic resolutions - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the stereoisomers with an enzyme;
- iv) enzymatic asymmetric synthesis - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an stereoisomerically pure or enriched synthetic precursor of the desired stereoisomer;
- v) chemical asymmetric synthesis - a synthetic technique whereby the desired stereoisomer is synthesized from an achiral precursor under conditions that produce asymmetry (*i.e.*, chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;
- vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by

- chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;
- vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;
- viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the stereoisomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;
- ix) stereospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired stereoisomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;
- x) chiral liquid chromatography - a technique whereby the stereoisomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;
- xi) chiral gas chromatography - a technique whereby the racemate is volatilized and stereoisomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;
- xii) extraction with chiral solvents - a technique whereby the stereoisomers are separated by virtue of preferential dissolution of one stereoisomer into a particular chiral solvent;
- xiii) transport across chiral membranes - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one stereoisomer of the racemate to pass through.

[00162] In some or any embodiments, provided is a composition of a compound that comprises a substantially pure designated stereoisomer of the compound. In some or any embodiments, in the methods and compounds, the compounds are substantially free of other

stereoisomer. In some or any embodiments, a composition includes a compound that is at least 85%, 90%, 95%, 98%, 99% or 100% by weight, of the designated stereoisomer, the remainder comprising other chemical species or stereoisomers.

Isotopically Enriched Compounds

[00163] Also provided herein are isotopically enriched compounds.

[00164] Isotopic enrichment (in some or any embodiments, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et al.*, Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky *et al.*, J. Nat. Cancer Inst., 69: 1127 (1982); Mangold *et al.*, Mutation Res. 308: 33 (1994); Gordon *et al.*, Drug Metab. Dispos., 15: 589 (1987); Zello *et al.*, Metabolism, 43: 487 (1994); Gately *et al.*, J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999).

[00165] Isotopic enrichment of a drug can be used, in some or any embodiments, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[00166] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). See, *e.g.*, Foster *et al.*, Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.*, Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999).

[00167] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C-H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle.

Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

[00168] Tritium (“T”) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium (“T”) for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ¹³C or ¹⁴C for carbon, ³³S, ³⁴S, or ³⁶S for sulfur, ¹⁵N for nitrogen, and ¹⁷O or ¹⁸O for oxygen, may lead to a similar kinetic isotope effect.

[00169] For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity.

[00170] In some embodiments, the compounds described herein may be used as radiopharmaceuticals such as, for example, imaging agents. In one instance, radiopharmaceuticals are positron emission tomography (PET) imaging agents. In such embodiments, substitution of radionuclides (e.g., positron emitting isotopes) for atoms in the compounds allows for the syntheses of radiopharmaceuticals that can function as imaging agents. In some embodiments, radionuclides which can be substituted in the compounds described herein include, and are not limited to, ¹⁸F, ¹¹C, ¹³N, ¹⁵O, ⁷⁶Br, and ¹²⁴I. In some embodiments, the compound is isotopically enriched at one or more atoms, one atom, two

atoms, or three atoms. In some embodiments, the compound is administered as an isotopic composition.

[00171] The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. In some or any embodiments, such enzymes include the cytochrome P450 enzymes (“CYPs”), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

[00172] Therefore, isotopic enrichment at certain positions of a compound provided herein will produce a detectable KIE that will affect the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition.

Preparation of Compounds

[00173] The compounds provided herein can be prepared, isolated or obtained by any method apparent to those of skill in the art. Compounds provided herein can be prepared according to the Exemplary Preparation Schemes provided below. Reaction conditions, steps and reactants not provided in the Exemplary Preparation Schemes would be apparent to, and known by, those skilled in the art.

[00174] Additional steps and reagents not provided in the Exemplary Preparation Scheme would be known to those of skill in the art. For example, intermediates and compounds could be prepared using the procedures known by one of ordinary skill in the art. Exemplary methods of preparation are described in detail in the Examples herein.

[00175] One of skill will understand that the order of steps for any process described herein may be changed. Other variations will be apparent to one of skill in the art and all such variations are contemplated within the scope of embodiments presented herein.

Pharmaceutical Compositions and Methods of Administration

[00176] The compounds provided herein can be formulated into pharmaceutical compositions using methods available in the art and those disclosed herein. Any of the

compounds disclosed herein can be provided in the appropriate pharmaceutical composition and be administered by a suitable route of administration. Provided herein are pharmaceutical compositions comprising a compound of Formula (I), (P-II), or (P-I), as described herein in some and any embodiments, and a pharmaceutically acceptable carrier. In some embodiments, the composition is an oral or injectable composition. In some of such embodiments, the injectable composition is a subcutaneously injectable composition.

[00177] The methods provided herein encompass administering pharmaceutical compositions containing at least one compound as described herein, including a compound of Formula (I), (P-II), or (P-I) if appropriate in a salt form, either used alone or in the form of a combination with one or more compatible and pharmaceutically acceptable carriers, such as diluents or adjuvants, or with another agent for the treatment of pain and/or conditions modulated by voltage-gated sodium channels.

[00178] In some or any embodiments, the second agent can be formulated or packaged with the compound provided herein. Of course, the second agent will only be formulated with the compound provided herein when, according to the judgment of those of skill in the art, such co-formulation should not interfere with the activity of either agent or the method of administration. In some or any embodiments, the compound provided herein and the second agent are formulated separately. They can be packaged together, or packaged separately, for the convenience of the practitioner of skill in the art.

[00179] In clinical practice the active agents provided herein may be administered by any conventional route, in particular orally, parenterally, rectally or by inhalation (*e.g.* in the form of aerosols). In some or any embodiments, the compound provided herein is administered orally.

[00180] Use may be made, as solid compositions for oral administration, of tablets, pills, hard gelatin capsules, powders or granules. In these compositions, the active product is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose or starch.

[00181] These compositions can comprise substances other than diluents, for example a lubricant, such as magnesium stearate, or a coating intended for controlled release.

[00182] Use may be made, as liquid compositions for oral administration, of solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents, such as water or liquid paraffin. These compositions can also comprise substances other than diluents, in some or any embodiments, wetting, sweetening or flavoring products.

[00183] The compositions for parenteral administration can be emulsions or sterile solutions. Use may be made, as solvent or vehicle, of propylene glycol, a polyethylene glycol,

vegetable oils, in particular olive oil, or injectable organic esters, in some or any embodiments, ethyl oleate. These compositions can also contain adjuvants, in particular wetting, isotonicizing, emulsifying, dispersing and stabilizing agents. Sterilization can be carried out in several ways, in some or any embodiments, using a bacteriological filter, by radiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

[00184] The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active principle, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

[00185] The compositions can also be aerosols. For use in the form of liquid aerosols, the compositions can be stable sterile solutions or solid compositions dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active principle is finely divided and combined with a water-soluble solid diluent or vehicle, in some or any embodiments, dextran, mannitol or lactose.

[00186] In some or any embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, a compound provided herein, or other prophylactic or therapeutic agent), and a typically one or more pharmaceutically acceptable carriers or excipients. In a specific embodiment and in this context, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” includes a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water can be used as a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Examples of suitable pharmaceutical carriers are described in Remington: The Science and Practice of Pharmacy, Pharmaceutical Press; 22 edition (September 15, 2012).

[00187] Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and in

some or any embodiments, suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a subject and the specific active ingredients in the dosage form. The composition or single unit dosage form, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[00188] Lactose free compositions provided herein can comprise excipients that are well known in the art and are listed, in some or any embodiments, in the U.S. Pharmacopeia (USP 36–NF 31 S2). In general, lactose free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose free dosage forms comprise an active ingredient, microcrystalline cellulose, pre gelatinized starch, and magnesium stearate.

[00189] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long term storage in order to determine characteristics such as shelf life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, New York, 1995, pp. 379 80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00190] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00191] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. In some or any embodiments, suitable packaging include, but are not limited

to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00192] Further provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00193] The pharmaceutical compositions and single unit dosage forms can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions and dosage forms will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent, in some or any embodiments, in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration. In a some or any embodiment, the pharmaceutical compositions or single unit dosage forms are sterile and in suitable form for administration to a subject, in some or any embodiments, an animal subject, such as a mammalian subject, in some or any embodiments, a human subject.

[00194] A pharmaceutical composition is formulated to be compatible with its intended route of administration. In some or any embodiments, routes of administration include, but are not limited to, parenteral, *e.g.*, intrathecal, epidural, local or regional for peripheral nerve block, intravenous, intradermal, subcutaneous, intramuscular, subcutaneous, oral, buccal, sublingual, inhalation, intranasal, transdermal, topical (including administration to the eye, and in some embodiments to the cornea), transmucosal, intra-tumoral, intra-synovial, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical (including administration to the eye, and in some embodiments to the cornea) administration to human beings. In a specific embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection.

[00195] In some or any embodiments, dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a subject, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil in water emulsions, or a water in oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a subject; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a subject.

[00196] The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. In some or any embodiments, a dosage form used in the initial treatment of pain may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the maintenance treatment of the same infection. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed herein will vary from one another will be readily apparent to those skilled in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00197] Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, in some or any embodiments, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachet indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[00198] Typical dosage forms comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day taken with food. Particular dosage forms can have about 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 100, 200, 250, 500 or 1000 mg of the active compound.

Oral Dosage Forms

[00199] Pharmaceutical compositions that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00200] In some or any embodiments, the oral dosage forms are solid and prepared under anhydrous conditions with anhydrous ingredients, as described in detail herein. However, the scope of the compositions provided herein extends beyond anhydrous, solid oral dosage forms. As such, further forms are described herein.

[00201] Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. In some or any embodiments, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. In some or any embodiments, excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00202] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00203] In some or any embodiments, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00204] In some or any embodiments, excipients that can be used in oral dosage forms include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[00205] In some or any embodiments, fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00206] In some or any embodiments, suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103 AVICEL RC 581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC 581. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103™ and Starch 1500 LM.

[00207] Disintegrants are used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[00208] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or

tapioca starch, pre gelatinized starch, other starches, clays, other algin, other celluloses, gums, and mixtures thereof.

[00209] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, in some or any embodiments, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

[00210] Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. In some or any embodiments, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500; each of which is incorporated herein by reference in its entirety. Such dosage forms can be used to provide slow or controlled release of one or more active ingredients using, in some or any embodiments, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein. Thus, encompassed herein are unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gel caps, and caplets that are adapted for controlled release.

[00211] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an

optimally designed controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[00212] Most controlled release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[00213] In some or any embodiments, the drug may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In some or any embodiments, a pump may be used (*see*, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, *i.e.*, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, *Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984)). Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)). The active ingredient can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated

polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

Parenteral Dosage Forms

[00214] In some or any embodiments, provided are parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. In some or any embodiments, parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[00215] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. In some or any embodiments, suitable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00216] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms.

Transdermal, Topical & Mucosal Dosage Forms

[00217] Also provided are transdermal, topical, and mucosal dosage forms. Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, e.g., Remington: The Science and Practice of Pharmacy;

Pharmaceutical Press; 22 edition (September 15, 2012); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include “reservoir type” or “matrix type” patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[00218] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed herein are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane 1,3 diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are nontoxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00219] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients provided. In some or any embodiments, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[00220] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery enhancing or penetration enhancing agent. Different salts,

hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Dosage and Unit Dosage Forms

[00221] In human therapeutics, the doctor will determine the posology which the doctor considers most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the infection and other factors specific to the subject to be treated. In some or any embodiments, doses are from about 1 to about 1000 mg per day for an adult, or from about 5 to about 250 mg per day or from about 10 to 50 mg per day for an adult. In some or any embodiments, doses are from about 5 to about 400 mg per day or 25 to 200 mg per day per adult. In some or any embodiments, dose rates of from about 50 to about 500 mg per day are also contemplated. In some or any embodiments, doses for subcutaneous administration are from about 1 to about 50 mg per day, or from about 1 to about 25 mg per day, or from about 1 to about 10 mg per day, or from about 1 to about 20 mg per day, or from about 5 to about 25 mg per day, or from about 5 mg to about 20 mg per day, or from about 10 to about 20 mg per day. In some or any embodiments, doses for oral administration are from about 5 to about 250 mg per day, from about 5 to 200 mg per day, or from about 50 mg to about 100 mg per day, or from about 75 mg to about 1125 mg per day, or from about 10 mg to about 200 mg per day. In some embodiments, the mg/day amounts are for an adult. In further aspects, provided are methods of treating a condition associated with voltage-gated sodium channel function and/or pain in a subject by administering, to a subject in need thereof, a therapeutically or prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. The amount of the compound or composition which will be therapeutically or prophylactically effective in the treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00222] In some or any embodiments, exemplary doses of a composition include milligram or microgram amounts of the active compound per kilogram of subject or sample weight (*e.g.*, about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms

per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to about 10 milligrams per kilogram). For compositions provided herein, in some or any embodiments, the dosage administered to a subject is 0.01 mg/kg to 3 mg/kg of the subject's body weight, or 0.10 mg/kg to 3 mg/kg of the subject's body weight, based on weight of the active compound. In some or any embodiments, the dosage administered to a subject is between 0.20 mg/kg and 2.00 mg/kg, or between 0.30 mg/kg and 1.50 mg/kg of the subject's body weight. In some embodiments, the dosage is administered subcutaneously to a subject and is between about 0.01 mg/kg to 1 mg/kg (inclusive), or between about 0.03 mg/kg to 0.5 mg/kg (inclusive) of the subject's body weight, based on weight of the active compound. In some embodiments, the dosage is administered orally to a subject and is between about 0.10 mg/kg to 5 mg/kg (inclusive) of the subject's body weight, or between about 0.10 mg/kg to 2 mg/kg (inclusive) of the subject's body weight, based on weight of the active compound.

[00223] In some or any embodiments, the recommended daily dose range of a composition provided herein for the conditions described herein lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose or as divided doses throughout a day. In some or any embodiments, the daily dose is administered twice daily in equally divided doses. In some or any embodiments, the daily dose is administered thrice daily in equally divided doses. In some or any embodiments, the daily dose is administered four times daily in equally divided doses. In some or any embodiments, a daily dose range should be from about 0.01 mg to about 400 mg per day, from about 0.1 mg to about 250 mg per day, from about 10 mg to about 200 mg per day, in other embodiments, or from about 10 mg and about 150 mg per day, in further embodiments, between about 25 and about 100 mg per day. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

[00224] Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the composition provided herein are also encompassed by the herein described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. In some or any embodiments, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition

or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[00225] In some or any embodiment, the dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 10 mg/kg, or 15 mg/kg or more of a subject's body weight. In another embodiment, the dosage of the composition or a composition provided herein administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is a unit dose of 0.1 mg to 200 mg, 0.1 mg to 100 mg, 0.1 mg to 50 mg, 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 10 mg, 0.1 mg to 7.5 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 mg to 7.5 mg, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 7.5 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

[00226] In some or any embodiments, treatment or prevention can be initiated with one or more loading doses of a compound or composition provided herein followed by one or more maintenance doses. In such embodiments, the loading dose can be, for instance, about 6 to about 40 mg per day, or about 10 to about 20 mg per day for one day to five weeks. The loading dose can be followed by one or more maintenance doses. In some or any embodiments, each maintenance does is, independently, about from about 1 mg to about 20 mg per day, between about 2.5 mg and about 15 mg per day, or between about 2.5 and about 8 mg per day. Maintenance doses can be administered daily and can be administered as single doses, or as divided doses.

[00227] In some or any embodiments, a dose of a compound or composition provided herein can be administered to achieve a steady-state concentration of the active ingredient in blood or serum of the subject. The steady-state concentration can be determined by measurement according to techniques available to those of skill or can be based on the physical characteristics of the subject such as height, weight and age. In some or any embodiments, a sufficient amount of a compound or composition provided herein is administered to achieve a steady-state concentration in blood or serum of the subject of from about 100 to about 1000 ng/mL, from about 150 to about 800 ng/mL, or from about 300 to about 600 ng/mL. In some or any embodiments, loading doses can be administered to achieve steady-state blood or serum concentrations of about 300 to about 2000 ng/mL, or about 400 to about 800 ng/mL for one to five days. In some or any embodiments, maintenance doses can be administered to achieve a steady-state concentration in blood or serum of the subject of from about 100 to about 1000

ng/mL, from about 150 to about 800 ng/mL, or from about 300 to about 600 ng/mL. In some or any embodiments, administration of the same composition may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00228] In some or any embodiments, provided herein are unit dosages comprising a compound, or a pharmaceutically acceptable salt thereof, in a form suitable for administration. Such forms are described in detail herein. In some or any embodiments, the unit dosage comprises 1 to 1000 mg, 1 to 100 mg or 10 to 50 mg active ingredient. In particular embodiments, the unit dosages comprise about 1, 5, 10, 25, 50, 100, 125, 250, 500 or 1000 mg active ingredient. Such unit dosages can be prepared according to techniques familiar to those of skill in the art.

[00229] In some or any embodiments, dosages of the second agents to be used in a combination therapy are provided herein. In some or any embodiments, dosages lower than those which have been or are currently being used to treat pain are used in the combination therapies provided herein. The recommended dosages of second agents can be obtained from the knowledge of those of skill in the art. For those second agents that are approved for clinical use, recommended dosages are described in, for example, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Therapeutics 9th Ed, McGraw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ; which are incorporated herein by reference in their entirety.

[00230] In various embodiments, the therapies (*e.g.*, a compound provided herein and the second agent) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. In various embodiments, the therapies are administered no more than 24 hours apart or no more

than 48 hours apart. In some or any embodiments, two or more therapies are administered within the same patient visit. In other embodiments, the compound provided herein and the second agent are administered concurrently.

[00231] In other embodiments, the compound provided herein and the second agent are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week apart, at about 1 to 2 weeks apart, or more than 2 weeks apart.

[00232] In some or any embodiments, administration of the same agent may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00233] In some or any embodiments, a compound provided herein and a second agent are administered to a patient, in some or any embodiments, a subject, such as a human, in a sequence and within a time interval such that the compound provided herein can act together with the other agent to provide an increased benefit than if they were administered otherwise. In some or any embodiments, the second active agent can be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In some or any embodiments, the compound provided herein and the second active agent exert their effect at times which overlap. Each second active agent can be administered separately, in any appropriate form and by any suitable route. In other embodiments, the compound provided herein is administered before, concurrently or after administration of the second active agent.

[00234] In some or any embodiments, the compound provided herein and the second agent are cyclically administered to a patient. Cycling therapy involves the administration of a first agent (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second agent and/or third agent (*e.g.*, a second and/or third prophylactic or therapeutic agent) for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00235] In some or any embodiments, the compound provided herein and the second active agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a

compound provided herein and the second agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

[00236] In other embodiments, courses of treatment are administered concurrently to a patient, *i.e.*, individual doses of the second agent are administered separately yet within a time interval such that the compound provided herein can work together with the second active agent. In some or any embodiments, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

[00237] The second agent can act additively or synergistically with the compound provided herein. In some or any embodiments, the compound provided herein is administered concurrently with one or more second agents in the same pharmaceutical composition. In another embodiment, a compound provided herein is administered concurrently with one or more second agents in separate pharmaceutical compositions. In still another embodiment, a compound provided herein is administered prior to or subsequent to administration of a second agent. Also contemplated are administration of a compound provided herein and a second agent by the same or different routes of administration, *e.g.*, oral and parenteral. In some or any embodiments, when the compound provided herein is administered concurrently with a second agent that potentially produces adverse side effects including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

Kits

[00238] Also provided are kits for use in methods of treatment of pain and/or a condition associated with voltage-gated sodium channel function or a pain-related disorder. The kits can include a compound or composition provided herein, a second agent or composition, and instructions providing information to a health care provider regarding usage for treating the pain or a pain-related disorder. Instructions may be provided in printed form or in the form of an electronic medium such as a floppy disc, CD, or DVD, or in the form of a website address where such instructions may be obtained. A unit dose of a compound or composition provided herein, or a second agent or composition, can include a dosage such that when administered to

a subject, a therapeutically or prophylactically effective plasma level of the compound or composition can be maintained in the subject for at least 1 day. In some or any embodiments, a compound or composition can be included as a sterile aqueous pharmaceutical composition or dry powder (*e.g.*, lyophilized) composition.

[00239] In some or any embodiments, suitable packaging is provided. As used herein, “packaging” includes a solid matrix or material customarily used in a system and capable of holding within fixed limits a compound provided herein and/or a second agent suitable for administration to a subject. Such materials include glass and plastic (*e.g.*, polyethylene, polypropylene, and polycarbonate) bottles, vials, paper, plastic, and plastic-foil laminated envelopes and the like. If e-beam sterilization techniques are employed, the packaging should have sufficiently low density to permit sterilization of the contents.

Methods of Use

[00240] Provided herein is a method for treating a condition associated with voltage-gated sodium channel function and/or pain in a subject, which comprises contacting the subject with a therapeutically or prophylactically effective amount of a compound of Formula (I), (P-II) or (P-I) including a single enantiomer, a mixture of an enantiomeric pair, an individual diastereomer, a mixture of diastereomers, an individual stereoisomer, a mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

[00241] Provided herein is a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject, comprising the administration of a therapeutically or prophylactically effective amount of a compound of Formula (I), (P-II), or (P-I) described herein or a pharmaceutical composition described herein.

[00242] In some embodiments, the subject is a human. In a group of embodiments, the condition is pain or the condition is associated with pain. In some embodiments, the condition is pain. In some embodiments, the condition is associated with pain. In some embodiments, the pain is nociceptive pain. In some embodiments, the pain is neuropathic pain. In some embodiments, the pain is inflammatory pain. In some embodiments, the pain is refractory to other forms of pain medications.

[00243] In a group of embodiments, the condition is selected from the group consisting of erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal neuralgia, multiple sclerosis, osteoarthritis, postherpetic neuralgia, cancer pain, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, and postsurgical pain. In a group of embodiments, the condition is selected from the group

consisting of epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotrophic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

[00244] In some or any embodiments, provided herein are methods for treating pain and/or a condition associated with voltage-gated sodium channel function in a subject. In some or any embodiments, the methods encompass the step of administering to the subject in need thereof an amount of a compound effective for the treatment pain and/or a condition associated with voltage-gated sodium channel function in combination with a second agent effective for the treatment or prevention of pain and/or a condition associated with voltage-gated sodium channel function. The compound can be any compound as described herein, and the second agent can be any second agent described in the art or herein. In some or any embodiments, the compound is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

[00245] In some or any embodiments, provided herein are methods for treating a condition associated with voltage-gated sodium channel function in a subject. In some or any embodiments, the methods encompass the step of administering to the subject in need thereof a therapeutically or prophylactically effective amount of a compound effective for the treatment of a condition associated with voltage-gated sodium channel function in combination with a second agent effective for the treatment of a condition associated with voltage-gated sodium channel function. The compound can be any compound as described herein, and the second agent can be any second agent described in the art or herein. In some or any embodiments, the compound is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

[00246] In some or any embodiments, provided herein is of inhibiting $NA_v1.8$ comprising contacting $NA_v1.8$ with a compound of Formula (I), (P-II), or (P-I) and Compounds 1-723.

[00247] In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is associated with a condition or is a condition selected from acute pain, anal fissures, back pain, chronic pain, dental pain, joint pain, neck pain, neuropathic pain, obstetric pain, post-herpetic neuralgia, shingles, tension headaches, trigeminal blepharospasm, pain associated with cardiac arrhythmia, focal dystonia, hyperhidrosis, muscle spasms, urinary bladder relaxation, visceral pain, sympathetically maintained pain, myositis pain, musculoskeletal pain, lower back pain, pain from sprains and strains, pain associated with functional bowel disorders, non-cardiac chest pain, pain associated with irritable bowel syndrome, pain associated with myocardial ischemia, toothache pain, pain from dysmenorrhea,

erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal neuralgia, multiple sclerosis, osteoarthritis, postherpetic neuralgia, cancer, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, dry eye syndrome, (acute) corneal injuries or abrasions, corneal infections, pain associated with Parkinson's disease, pain associated with ALS, and surgery (in some embodiments, post-surgery; in some embodiments, ocular surgery). In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is pain in an acute care setting, including post-surgery (post-surgical pain). In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is pain in an acute care setting, including post-surgery and the compound is administered intravenously. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is ocular pain. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is ocular pain and the compound is administered topically. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute pain or chronic pain. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute pain or chronic pain and the compound is administered subcutaneously. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute pain or chronic pain and the compound is administered orally.

[00248] In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from itch, cough, epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotrophic lateral sclerosis (ALS), cardiac arrhythmia, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder. In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from pain, itch, cough, glaucoma, and ischemia. In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from pain, itch, and cough. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain.

[00249] In some or any embodiments, the compounds described herein are used for delaying the onset of pain, or reducing the severity or duration of pain. In some or any embodiments, the compounds described herein are used for the reduction of the severity or duration of pain associated with voltage-gated sodium channel function. In some embodiments, the compounds described herein are used for delaying or preventing onset of pain.

[00250] In some or any embodiments, the compounds described herein are used for prevention of pain or of a condition associated with voltage-gated sodium channel function.

[00251] In some or any embodiments, the compounds described herein are used for treatment of pain or of a condition associated with voltage-gated sodium channel function.

Assay Methods

[00252] Compounds can be assayed for efficacy in treating pain and/or a condition associated with voltage-gated sodium channel function according to any assay known to those of skill in the art. Exemplary assay methods are provided elsewhere herein.

Second Therapeutic Agents

[00253] In some or any embodiments, the compounds and compositions provided herein are useful in methods of treatment of pain and/or a condition associated with voltage-gated sodium channel function, that comprise further administration of a second agent effective for the treatment of pain and/or a pain-related disorder and/or a condition associated with voltage-gated sodium channel function. The second agent can be any agent known to those of skill in the art to be effective for the treatment of pain and/or a pain-related disorder and/or a condition associated with voltage-gated sodium channel function, including those currently approved by the United States Food and Drug Administration, or other similar body of a country foreign to the United States. In some or any embodiments, the second agent is a local anesthetic (in some or any embodiments, a steroid), an opioid, a vasoconstrictor, a glucocorticoid, adrenergic drugs (in some or any embodiments, alpha agonists or mixed central-peripheral alpha-2- agonists), vanilloids, an anti-inflammatory agent (*e.g.* NSAID, or an anti-inflammatory agent associated with ocular conditions, including cyclosporine and lifitegrast) or a chemical permeation enhancer. In some embodiments, the second agent is an inhibitor of Nav 1.8. In some or any embodiments, chemical permeation enhancers include anionic surfactants, cationic surfactants, nonionic surfactants. In some or any embodiments, the second agent is bupivacaine, levobupivacaine, tetracaine, ropivacaine, epinephrine, phenylephrine, clonidine, sodium lauryl sulfate, sodium octyl sulfate, dodecyltrimethylammonium bromide, octyltrimethylammonium bromide, polyoxyethylene (20) sorbitan monolaurate, and/or polyoxyethylene (20) sorbitan monooleate.

[00254] In some or any embodiments, a compound provided herein is administered in combination with one second agent. In further embodiments, a compound provided herein is administered in combination with two second agents. In still further embodiments, a compound provided herein is administered in combination with two or more second agents.

[00255] As used herein, the term “in combination” includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). The use of the term “in combination”

does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to a subject with a disorder.

[00256] As used herein, the term “synergistic” includes a combination of a compound provided herein and another therapy (*e.g.*, a prophylactic or therapeutic agent) which has been or is currently being used to prevent, manage or treat a disorder, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a disorder. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention or treatment of a disorder). In addition, a synergistic effect can result in improved efficacy of agents in the prevention or treatment of a disorder. Finally, a synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

[00257] The active compounds provided herein can be administered in combination or alternation with another therapeutic agent, in particular an agent effective in the treatment of pain and/or a pain-related disorder and/or a condition associated with voltage-gated sodium channel function. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the pain or a pain-related disorder to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the

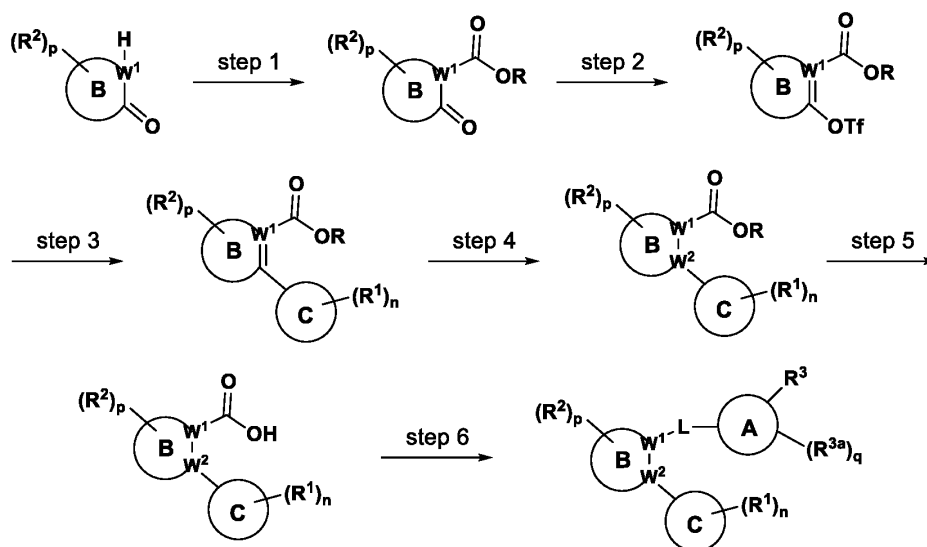
individual need and the professional judgment of the person administering or supervising the administration of the compositions.

EXAMPLES

[00258] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: ESI (electrospray ionization); g (grams); mg (milligrams); mL or ml (milliliters); μ L (microliters); μ M (micromolar); HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium); hr or hrs (hours); Hz (Hertz); MHz (megahertz); mmol (millimoles); MS (mass spectrometry); N (normality when referring to acid); psi (pounds per square inch); HPLC (high pressure liquid chromatography); Prep-HPLC (preparatory high pressure liquid chromatography); THF (tetrahydrofuran); DMSO (dimethylsulfoxide); and DMSO- d_6 (deuterated dimethylsulfoxide).

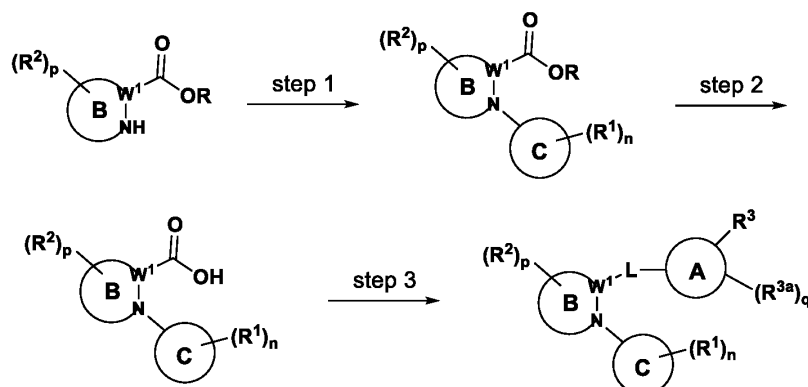
[00259] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in ° C (degrees Celsius). All reactions are conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

[00260] General Scheme 1



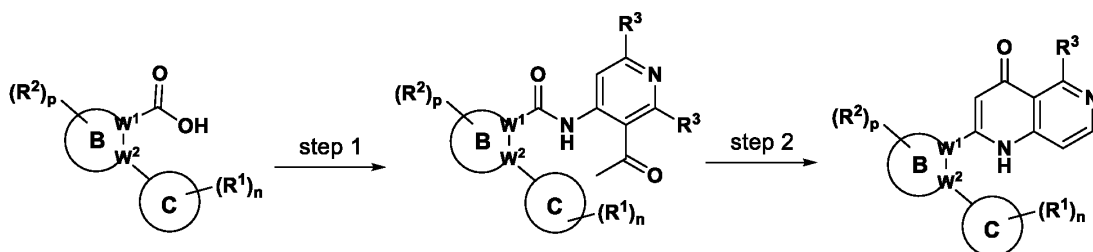
[00261] Step 1: base (in some embodiments, Et_3N , NaH), $X-CO_2R$ (in some embodiments, dimethyl carbonate, diethyl carbonate), solvent (in some embodiments, THF, DMF); Step 2: base (in some embodiments, iPr_2NEt , Et_3N , NaH , Tf_2O), solvent (in some embodiments, dichloromethane, THF); Step 3: boronic acid or boronic ester, base (in some embodiments, sodium carbonate, potassium carbonate), catalyst (in some embodiments, palladium acetate, palladium chloride), solvent (in some embodiments, EtOH, water, DMF); Step 4: hydrogen, catalyst (in some embodiments, Pd/C, Raney Ni), solvent (in some embodiments, MeOH, EtOH); Step 5: base (in some embodiments, LiOH, NaOH), solvent (in some embodiments, water, THF); Step 6: amine (in some embodiments, 3-aminobenzene-1-sulfonamide, 4-aminopyridine-1-sulfonamide, 4-amino-3-acetyl-pyridine), coupling agent (in some embodiments, HATU, HBTU, $POCl_3$) or oxalyl chloride, catalyst (in some embodiments, DMAP, DMF), base (in some embodiments, iPr_2NEt , Et_3N), solvent (in some embodiments, dichloromethane, DMF).

[00262] General Scheme 2



[00263] Step 1: X-Ar (in some embodiments, 1-bromo-3,4-difluoro-2-methoxybenzene), base (in some embodiments, potassium phosphate), catalyst (in some embodiments, copper iodide), solvent (in some embodiments, DMSO); Step 2: base (in some embodiments, LiOH, NaOH), solvent (in some embodiments, water, THF, MeOH); Step 3: amine (in some embodiments, 3-aminobenzene-1-sulfonamide, 4-aminopyridine-1-sulfonamide, 4-amino-3-acetyl-pyridine), coupling agent (in some embodiments, HATU, HBTU, POCl₃) or oxalyl chloride, catalyst (in some embodiments, DMAP, DMF), base (in some embodiments, iPr₂NEt, Et₃N), solvent (in some embodiments, dichloromethane, DMF).

[00264] General Scheme 3

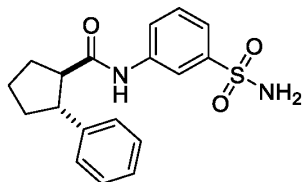


[00265] Step 1: amine (in some embodiments, 4-amino-3-acetyl-pyridine), coupling agent (in some embodiments, HATU, HBTU, POCl₃) or oxalyl chloride, catalyst (in some embodiments, DMAP, DMF), base (in some embodiments, iPr₂NEt, Et₃N), solvent (in some embodiments, dichloromethane, DMF); Step 2: base (in some embodiments, NaOH, NaO^tBu, KOH), solvent (in some embodiments, THF, water, DMSO, DMF).

Synthetic Examples

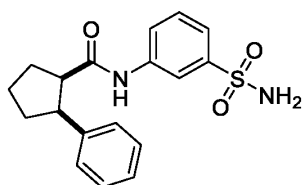
Compound 1

Synthesis of rac-(1R,2R)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

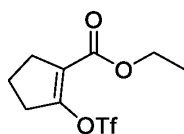


Compound 3

Synthesis of rac-(1R,2S)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

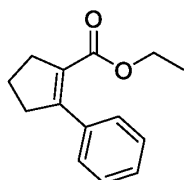


Synthesis of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate



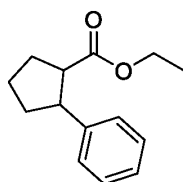
[00266] To a stirred solution of ethyl 2-oxocyclopentane-1-carboxylate (3.0 g, 19.2 mmol) in dichloromethane (30 mL) were added trifluoromethanesulfonic anhydride (6.4 mL, 38 mmol), and diisopropylethylamine (10 mL, 57 mmol) at -78 °C and the reaction mixture was stirred at room temperature for 12 hours. After reaction completion, saturated sodium bicarbonate was added followed by extraction with dichloromethane. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography using 30-40% ethyl acetate in hexane to afford ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate.

Synthesis of ethyl 2-phenylcyclopent-1-ene-1-carboxylate



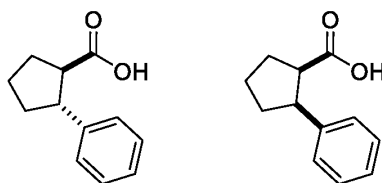
[00267] To a solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate (2.0 g, 6.9 mmol) and phenylboronic acid (1.0 g, 8.2 mmol) in ethanol (4 mL), acetonitrile (4 mL) was added water (2 mL) was added sodium carbonate (1.5 g, 13.8 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. Palladium acetate (0.016 g, 0.7 mmol) and bis(diphenylphosphino)butane (0.58 g, 1.38 mmol) were added and reaction mixture degassed with nitrogen for 5 minutes and heated under stirring at 100 °C for 12 hours. After reaction completion, the reaction mixture was concentrated, water was added, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography using 30-40% ethyl acetate in hexane to afford ethyl 2-phenylcyclopent-1-ene-1-carboxylate as a colorless oil.

Synthesis of ethyl 2-phenylcyclopentane-1-carboxylate



[00268] To a solution of ethyl 2-phenylcyclopent-1-ene-1-carboxylate (1.0 g, 4.6 mmol) in methanol (10 mL) was added 10% palladium on charcoal (0.48 g, 0.46 mmol). The reaction mixture was stirred under hydrogen atmosphere (50 psi) for 12 hours at room temperature. After reaction completion, the reaction mixture was filtered through a pad of Celite®, filtered, then concentrated to obtain ethyl 2-phenylcyclopentane-1-carboxylate as a colorless oil.

Synthesis of rac-(1R,2R)-2-phenylcyclopentane-1-carboxylic acid and rac-(1R,2S)-2-phenylcyclopentane-1-carboxylic acid



[00269] To a solution of ethyl 2-phenylcyclopentane-1-carboxylate (0.80 g, 3.7 mmol) in methanol (4 mL), tetrahydrofuran (4 mL) and water (4 mL) was added lithium hydroxide

monohydrate (0.60 g, 14.6 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, and the residue was acidified with 1N hydrochloric acid then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase Prep-HPLC to afford rac-(1R,2R)-2-phenylcyclopentane-1-carboxylic acid and rac-(1R,2S)-2-phenylcyclopentane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

To a solution of rac-(1R,2R)-2-phenylcyclopentane-1-carboxylic acid (0.3 g, 1.6 mmol) in dichloromethane (6 mL) under nitrogen atmosphere was added oxalyl chloride (0.16 g, 1.9 mmol) followed by 1-2 drops of *N,N*-dimethylformamide at 0 °C. After 1 hour stirring at room temperature, the reaction mixture was concentrated. The residue was dissolved in dichloromethane (6 mL) and was added to a solution of 3-aminobenzene-1-sulfonamide (0.32 g, 1.9 mmol) and diisopropylethylamine (1.5 mL, 8 mmol) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 1 hour at room temperature. After reaction completion, water was added then extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase Prep-HPLC to afford rac-(1R,2R)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide. MS (ESI) *m/z* 343.3 [M - H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (s, 1H), 8.15 (s, 1H), 7.68-7.65 (m, 1H), 7.45-7.42 (m, 2H), 7.32-7.25 (m, 6H), 7.19-7.15 (m, 1H), 3.40-3.36 (m, 1H), 2.93-2.86 (m, 1H), 2.17-2.10 (m, 2H), 1.84-1.69 (m, 4H).

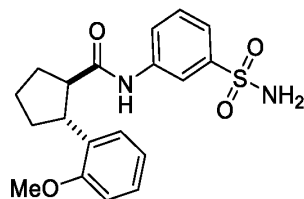
Synthesis of rac-(1S1R,2R2S)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

[00270] To a stirred solution of rac-(1S1R,2R2S)-2-phenylcyclopentane-1-carboxylic acid (0.20 g, 0.95 mmol) in dichloromethane (4 mL) was added HATU (0.54 g, 1.4 mmol) and DMAP (0.057 g, 0.47 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved in acetonitrile (4 mL) and added to a solution of 3-aminobenzenesulfonamide (0.19 g, 1.1 mmol) in acetonitrile (4 mL) and heated at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated, water was added, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase Prep-HPLC to afford rac-(1S1R,2R2S)-2-phenyl-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide. MS (ESI): *m/z*

345.20 [M + H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 9.85 (s, 1H), 7.88 (t, J = 2.0 Hz, 1H), 7.41-7.36 (m, 3H), 7.32 (br s, 2H), 7.24-7.22 (m, 2H), 7.18-7.14 (m, 2H), 7.08-7.04 (m, 1H), 3.43-3.37 (m, 1H), 3.22-3.17 (m, 1H), 2.17-2.01 (m, 5H), 1.92-1.75 (m, 1H).

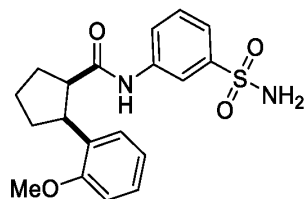
Compound 5

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

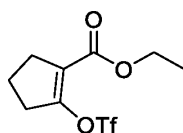


Compound 7

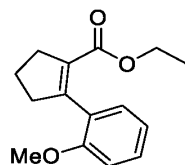
Synthesis of rac-(1R,2S)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide



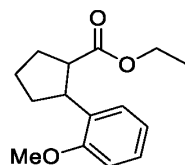
Synthesis of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate



[00271] To a stirred solution of ethyl 2-oxocyclopentane-1-carboxylate (1 g, 6.4 mmol) in dichloromethane (20 mL) was added *N,N*-diisopropylethylamine (2.48 g, 19.2 mmol) and trifluoromethanesulfonyl anhydride (3.61 g, 12.8 mmol) dropwise at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, water was added extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, concentrated. The residue was purified using flash column chromatography with a gradient of 10% ethyl acetate in hexane to afford ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate.

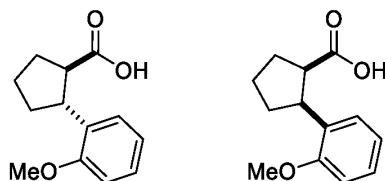
Synthesis of ethyl 2-(2-methoxyphenyl)cyclopent-1-ene-1-carboxylate

[00272] To a stirred solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate (2 g, 6.62 mmol) in acetonitrile (30 mL) and ethanol (20 mL), (2-methoxyphenyl)boronic acid (1.51 g, 9.92 mmol), 1,4-bis(diphenylphosphino)butane (56.4 mg, 0.132 mmol) and palladium bis(acetate) (0.015 mg, 0.066 mmol) were added at 0-5 °C. To the reaction mixture, an aqueous solution of sodium carbonate (2.1 g, 19.8 mmol) in water (10 mL) was added and the reaction mixture was slowly warmed to room temperature and then heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 20-30% ethyl acetate in heptane to afford ethyl 2-(2-methoxyphenyl)cyclopent-1-ene-1-carboxylate.

Synthesis of ethyl 2-(2-methoxyphenyl)cyclopentane-1-carboxylate

[00273] To a stirred solution of ethyl 2-(2-methoxyphenyl)cyclopent-1-ene-1-carboxylate (3 g, 12.2 mmol) in methanol (60 mL), 10% Pd/C (3 g, 2.82 mmol) was added and the reaction mixture was stirred for 16 hours at room temperature. After reaction completion, the reaction mixture was filtered through a pad of Celite[®], filtered, then concentrated. The residue was purified by column chromatography using 5-10% ethyl acetate in heptane to afford ethyl 2-(2-methoxyphenyl)cyclopentane-1-carboxylate.

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid



[00274] To a stirred solution of ethyl 2-(2-methoxyphenyl)cyclopentane-1-carboxylate (2.5 g, 10.1 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL), a solution of lithium hydroxide (2.41 g, 101 mmol) in water (10 mL) was added. The reaction mixture was stirred at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated. The residue was neutralized with 1N hydrochloric acid then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to afford rac-(1R,2R)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

[00275] To a stirred solution of (1R,2R)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid (0.4 g, 1.82 mmol) in dichloromethane (20 mL), HATU (1.04 g, 2.72 mmol) and *N,N*-dimethyl-4-pyridylamine (0.111 g, 0.908 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was concentrated and the residue was dissolved in acetonitrile (20 mL). To the solution was added 3-aminobenzenesulfonamide (0.375 g, 2.18 mmol) and the reaction mixture was heated at 80 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to get rac-(1R,2R)-2-(2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)cyclopentane-1-carboxamide was obtained. MS (ESI): *m/z* 373.3 [*M* - *H*]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.12 (s, 1H), 8.16 (s, 1H), 7.69-7.66 (m, 1H), 7.45-7.43 (m, 2H), 7.31 (br s, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H),

6.88 (t, $J = 7.2$ Hz, 1H), 3.71 (s, 3H), 3.68-3.61 (m, 1H), 3.04-2.98 (m, 2H), 2.09-2.07 (m, 2H), 1.83-1.80 (m, 3H), 1.67-1.60 (m, 1H).

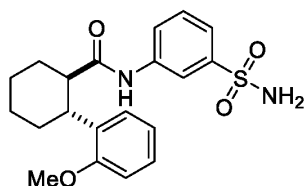
Synthesis of rac-(1R,2S)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide

To a stirred solution of rac-(1R,2S)-2-(2-methoxyphenyl)cyclopentane-1-carboxylic acid (0.13 g, 0.59 mmol) in dichloromethane (20 mL), HATU (0.337 g, 0.885 mmol) and *N,N*-dimethyl-4-pyridylamine (0.036 g, 0.295 mmol) were added at 0-5 °C. The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was concentrated and the residue was dissolved in acetonitrile (20 mL).

[00276] To the solution was added 3-aminobenzenesulfonamide (0.375 g, 2.18 mmol) and the reaction mixture was heated at 80 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to get rac-(1R,2S)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclopentane-1-carboxamide was obtained. MS (ESI): m/z 373.30 $[M - H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 9.63 (s, 1H), 7.88 (br s, 1H), 7.38-7.31 (m, 3H), 7.28 (br s, 2H), 7.16 (d, $J = 6.8$ Hz, 1H), 7.07-7.04 (m, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.75 (t, $J = 7.6$ Hz, 1H), 3.75 (s, 3H), 3.62-3.55 (m, 1H), 3.27-3.22 (m, 1H), 2.22-2.18 (m, 1H), 1.99-1.96 (m, 3H), 1.84-1.78 (m, 1H), 1.69-1.63 (m, 1H).

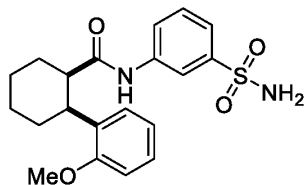
Compound 9

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

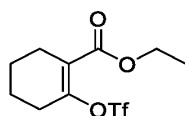


Compound 11

Synthesis of rac-(1R,2S)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

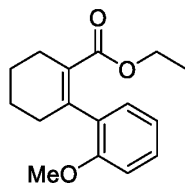


Synthesis of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate



[00277] To a stirred solution of ethyl 2-oxocyclohexane-1-carboxylate (3 g, 17.6 mmol) in dichloromethane (30 mL) was added *N,N*-ethylbis(isopropyl)amine (6.83 g, 52.9 mmol) and trifluoromethanesulfonic anhydride (7.46 g, 26.4 mmol) dropwise at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, ice cold water was added followed by extraction with dichloromethane. The organic layer dried over sodium sulfate, filtered, then concentrated. The residue was purified using flash column chromatography with a gradient of 10% ethyl acetate in hexane to afford ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate.

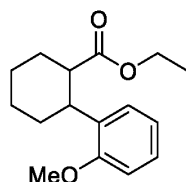
Synthesis of ethyl 2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



[00278] To a stirred solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (1 g, 3.31 mmol) in acetonitrile (15 mL) and ethanol (10 mL), (2-methoxyphenyl)boronic acid (0.754 g, 4.96 mmol), 1,4-bis(diphenylphosphino)butane (0.028 g, 0.066 mmol) and palladium bis(acetate) (0.007 g, 0.033 mmol) were added at 0-5 °C. To the reaction mixture, an aqueous solution of sodium carbonate (1.05 g, 9.92 mmol) in water (5 mL) was added and the reaction mixture was slowly warmed to room temperature and heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room

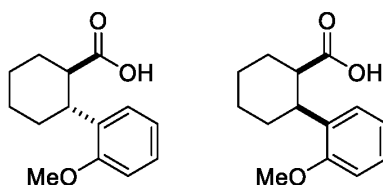
temperature, diluted with water followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography with a gradient of 20-30% ethyl acetate in heptane to afford ethyl 2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate.

Synthesis of ethyl 2-(2-methoxyphenyl)cyclohexane-1-carboxylate



[00279] To a stirred solution of ethyl 2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (1 g, 3.84 mmol) in methanol (20 mL), 10% Pd/C (1 g, 0.94 mmol) was added and the reaction mixture was stirred for 16 hours at room temperature. After reaction completion, the reaction mixture was filtered through a pad of Celite®, then concentrated. The residue was purified by column chromatography with a gradient of 5-10% ethyl acetate in heptane to afford ethyl 2-(2-methoxyphenyl)cyclohexane-1-carboxylate.

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid



[00280] To a stirred solution of ethyl 2-(2-methoxyphenyl)cyclohexane-1-carboxylate (1.2 g, 4.57 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) a solution of lithium hydroxide (1.1 g, 45.7 mmol) in water (5 mL) was added. The reaction mixture was stirred at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated. The residual aqueous solution was neutralized with 1N hydrochloric acid followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to afford rac-(1R,2R)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

[00281] To a stirred solution of rac-(1R,2R)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid (0.12 g, 0.512 mmol) in dichloromethane (10 mL), HATU (0.292 g, 0.768 mmol) and *N,N*-dimethyl-4-pyridylamine (0.031 g, 0.256 mmol) were added at 0-5 °C. The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. The reaction mixture was concentrated then dissolved in acetonitrile (10 mL) and 3-aminobenzenesulfonamide (0.106 g, 0.615 mmol) was added. The reaction mixture was heated at 80 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The organic layers were washed with brine, combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain rac-(1R,2R)-2-(2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide was obtained. MS (ESI): m/z 389.10 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.06 (s, 1H), 7.58-7.55 (br s, 1H), 7.42-7.37 (m, 2H), 7.28 (br s, 2H), 7.24-7.22 (m, 1H), 7.09-7.05 (m, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.82 (t, $J = 7.2$ Hz, 1H), 3.76 (s, 3H), 3.29-3.26 (m, 1H), 2.91-2.87 (m, 1H), 2.02-1.98 (m, 1H), 1.77-1.64 (m, 3H), 1.60-1.51 (m, 1H), 1.45-1.41 (m, 2H), 1.39-1.36 (m, 1H).

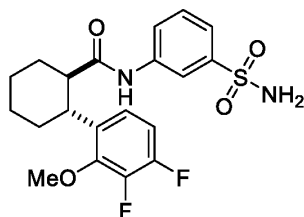
Synthesis of rac-(1R,2S)-2-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

[00282] To a stirred solution of rac-(1R,2S)-2-(2-methoxyphenyl)cyclohexane-1-carboxylic acid (0.2 g, 0.854 mmol) in dichloromethane (10 mL), HATU (0.487 g, 1.28 mmol) and *N,N*-dimethyl-4-pyridylamine (0.052 g, 0.427 mmol) were added at 0-5 °C. The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. The reaction mixture was concentrated then dissolved in acetonitrile (10 mL) and 3-aminobenzenesulfonamide (0.176 g, 1.02 mmol) was added and the reaction mixture was heated at 80 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The organic layers were washed with brine, combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain rac-(1R,2S)-2-(2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide was obtained. MS (ESI): m/z 387.30 $[M - H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 9.72 (s, 1H), 8.06-8.05 (m, 1H), 7.49-7.46 (m, 1H), 7.41-7.35 (m, 2H), 7.30 (br s, 2H), 7.23-7.21 (m, 1H), 7.12-7.07 (m, 1H), 6.93-

6.91 (m, 1H), 6.78-6.77 (m, 1H), 3.81 (s, 3H), 3.22-3.18 (m, 1H), 2.99-2.97 (m, 1H), 2.73-2.64 (m, 1H), 1.99-1.87 (m, 2H), 1.82-1.70 (m, 2H), 1.54-1.51 (m, 1H), 1.44-1.39 (m, 2H).

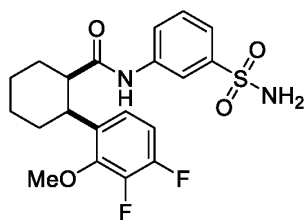
Compound 13

Rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

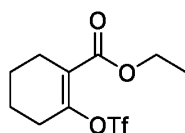


Compound 15

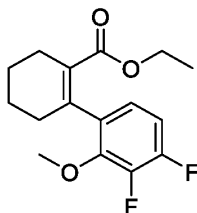
Rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide



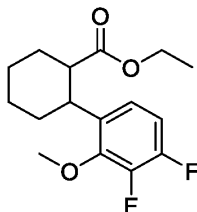
Synthesis of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate



[00283] To a stirred solution of ethyl 2-oxocyclohexanecarboxylate (2 g, 11.8 mmol) in dichloromethane (20 mL) were added *N,N*-diisopropylethylamine (4.56 g, 35.3 mmol) and trifluoromethanesulfonic anhydride (6.63 g, 23.5 mmol) at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was quenched with ice cold water followed by extraction with dichloromethane. The organic layers were dried over sodium sulfate, filtered, concentrated. The residue was purified using flash column chromatography with a gradient of 10% ethyl acetate in hexane to afford ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate.

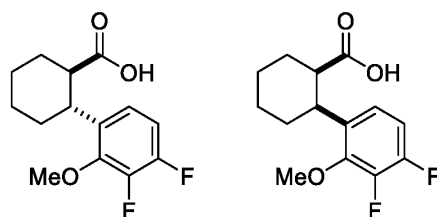
Synthesis of ethyl 3',4'-difluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate

[00284] To a stirred solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (1 g, 3.31 mmol) in acetonitrile (15 mL) and ethanol (10 mL), (3,4-difluoro-2-methoxyphenyl)boronic acid (0.754 g, 4.96 mmol), 1,4-bis(diphenylphosphino)butane (0.028 g, 0.066 mmol) and palladium acetate (0.007 g, 0.033 mmol) were added at 0-5 °C. To the reaction mixture, an aqueous solution of sodium carbonate (1.05 g, 9.92 mmol) in water (5 mL) was added and the reaction mixture was slowly warmed to room temperature. The reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was diluted with water, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography with a gradient of 20-30% ethyl acetate in heptane to afford ethyl 3',4'-difluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate.

Synthesis of ethyl 2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylate

[00285] To a stirred solution of ethyl 3',4'-difluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (1.2 g, 4.05 mmol) in methanol (50 mL), 10% Pd/C (1 g) was added at room temperature and the reaction mixture was stirred for 16 hours at room temperature under hydrogen atmosphere. After reaction completion, the reaction mixture was filtered through a pad of Celite[®], filtered, then concentrated. The residue was purified by column chromatography using 10-20% ethyl acetate in hexane to obtain ethyl 2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylate.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid



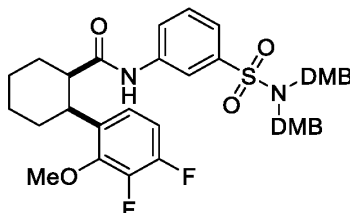
[00286] To a stirred solution of ethyl 2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylate (1.2 g, 4.57 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) a solution of lithium hydroxide monohydrate (1.1 g, 26.22 mmol) in water (5 mL) was added. The reaction mixture was stirred at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated. The resulting aqueous solution was neutralized with 1N hydrochloric acid followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep.-HPLC to afford (1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid and (1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

[00287] To a stirred solution of afford rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid (0.12 g, 0.44 mmol) in dichloromethane (10 mL), oxalyl chloride (0.11 g, 0.89 mmol) and 1 drop of *N,N*-dimethylformamide were added at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 2 hours. After reaction completion, the reaction mixture was concentrated. The residue was added to a mixture of 3-aminobenzenesulfonamide (0.09 g, 0.53 mmol) and *N,N*-diisopropylethylamine (0.23 g, 1.8 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. After reaction completion, water was added followed by extraction with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to afford rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide. MS (ESI): m/z 425.20 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 10.12 (br s, 1H), 8.01 (s, 1H), 7.60-7.57 (m, 1H), 7.42-7.39 (m, 2H), 7.27 (br s, 2H), 7.10-7.07 (m, 2H),

3.89 (s, 3H), 3.22-3.20 (m, 1H), 2.85-2.77 (m, 1H), 2.03-2.01 (m, 1H), 1.85-1.71 (m, 3H), 1.60-1.51 (m, 1H), 1.46-1.28 (m, 3H).

Synthesis of rac-(1R,2S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxamide



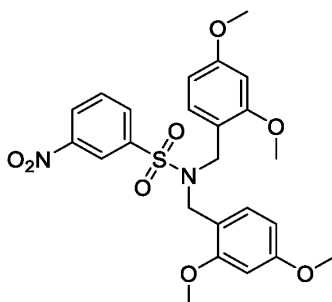
[00288] To a stirred solution of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxylic acid (0.12 g, 0.44 mmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (0.25 g, 0.53 mmol) in pyridine (5 mL) was added phosphorus oxychloride (0.34 g, 2.2 mmol) at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate followed by extraction with ethyl acetate. The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, then concentrated. The residue was used in the next step without any further purification.

Synthesis of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

[00289] To a stirred solution of rac-(1R,2S)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cyclohexane-1-carboxamide (0.2 g, 0.276 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (0.6 mL) at 0-5 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, then extracted with dichloromethane. The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide. MS (ESI): m/z 425.20 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 9.83 (br s, 1H), 8.05-8.04 (m, 1H), 7.50-7.48 (m, 1H), 7.43-7.37 (m, 2H), 7.27 (br s, 2H), 7.07-7.01 (m,

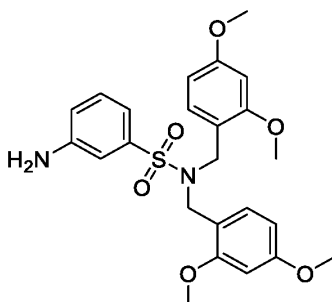
2H), 3.95 (s, 3H), 3.17-3.13 (m, 1H), 2.90-2.87 (m, 1H), 2.67-2.56 (m, 1H), 1.97-1.94 (m, 1H), 1.90-1.83 (m, 1H), 1.82-1.68 (m, 2H), 1.53-1.42 (m, 3H).

Synthesis of N,N-bis(2,4-dimethoxybenzyl)-3-nitrobenzenesulfonamide



[00290] To a stirred solution of bis(2,4-dimethoxybenzyl)amine (5 g, 10 mmol) in dichloromethane (100 ml) was added triethylamine (7.87 mL, 56.4 mmol) at room temperature and stirred for 5 minutes. The reaction mixture was cooled to 0-5 °C and m-(chlorosulfonyl)nitrobenzene (5 g, 22.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After reaction completion, water was added followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was used in the next step without any further purification.

Synthesis of 3-amino-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide

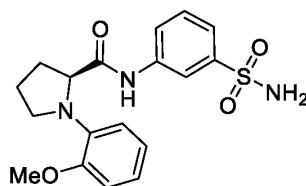


[00291] To a stirred solution of *N,N*-bis(2,4-dimethoxybenzyl)-3-nitrobenzenesulfonamide (5 g, 9.95 mmol) in ethanol (75 mL) was added ammonium chloride (5.32 g, 99.5 mmol) in water (25 mL) and zinc dust (6.51 g, 99.5 mmol) at room temperature. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was concentrated, and water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate,

filtered, then concentrated. The residue was triturated ethyl acetate and pentane to 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide. MS (ESI): m/z 473.40 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 7.19 (t, $J = 7.6$ Hz, 1H), 7.08-7.03 (m, 1H), 6.99-6.95 (m, 2H), 6.85-6.83 (m, 1H), 6.79-6.77 (m, 1H), 6.45-6.35 (m, 4H), 5.58 (br s, 2H), 4.15 (s, 4H), 3.70 (s, 6H), 3.57 (s, 6H).

Compound 17

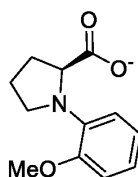
Synthesis of (S)-1-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)pyrrolidine-2-carboxamide



Synthesis of methyl (2-methoxyphenyl)-L-prolinate

[00292] A solution of methyl (*S*)-2-pyrrolidinecarboxylate hydrochloride (14.2 g, 85.5 mmol) and *o*-iodomethoxybenzene (2 g, 8.55 mmol) in dimethylformamide (20 mL) was degassed with nitrogen for 10 minutes followed by addition of cesium carbonate (27.8 g, 85.5 mmol), copper iodide (163 mg, 0.86 mmol) and 2-isobutyrylcyclohexanone (288 mg, 1.71 mmol). The reaction mixture was degassed for 5 minutes and heated under stirring at 100 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica column chromatography using 20% ethyl acetate in hexane to methyl (2-methoxyphenyl)-L-prolinate.

Synthesis of (2-methoxyphenyl)-L-proline



[00293] To a solution of methyl (2-methoxyphenyl)-L-prolinate (250 mg, 1.06 mmol) in tetrahydrofuran (3 mL) and methanol (0.5 mL), a solution of lithium hydroxide monohydrate (223 mg, 5.31 mmol) in water (1.5 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated,

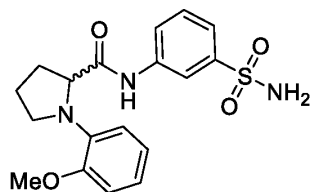
diluted with water, acidified with 1N HCl solution (pH~5), followed by extraction with ethyl acetate (2 × 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and *n*-pentane to afford crude (2-methoxyphenyl)-L-proline as brown oily liquid was used in the next step without any further purification.

Synthesis of (S)-1-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)pyrrolidine-2-carboxamide

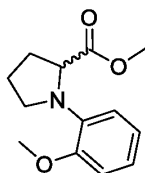
[00294] To a stirred solution of (2-methoxyphenyl)-L-proline (250 mg, 1.13 mmol) in dimethylformamide (5 mL) was added 3-aminobenzenesulfonamide (214 mg, 1.24 mmol) and HATU (644 mg, 1.69 mmol) at room temperature. The reaction mixture was cooled to 0 °C and 4-methylmorpholine (206 mg, 2.03 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. After reaction completion, water was added followed by extraction with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC (S)-1-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)pyrrolidine-2-carboxamide was obtained MS (ESI): m/z 376.25 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 9.96 (s, 1H), 8.19 (s, 1H), 7.81-7.79 (m, 1H), 7.46 (d, J = 5.2 Hz, 2H), 7.32 (br s, 2H), 6.86-6.80 (m, 2H), 6.74-6.69 (m, 2H), 4.44-4.41 (m, 1H), 3.57 (s, 3H), 3.55-3.50 (m, 1H), 3.25-3.21 (m, 1H), 1.96-1.86 (m, 1H), 1.48-1.24 (m, 3H).

Compound 18

Synthesis of 1-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)pyrrolidine-2-carboxamide

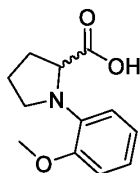


Synthesis of methyl (2-methoxyphenyl)prolinate



[00295] To a solution of methyl 2-pyrrolidinecarboxylate hydrochloride (14.9 g, 89.7 mmol) and *o*-iodomethoxybenzene (3 g, 12.8 mmol) in dimethylformamide (50 mL) was added triethylamine (1.3 g, 12.8 mmol). The reaction mixture was degassed with nitrogen for 10 minutes followed by addition of cesium carbonate (41.8 g, 128 mmol), copper iodide (1.22 g, 6.41 mmol) and 2-isobutyrylcyclohexanone (1.08 g, 6.41 mmol). The reaction mixture was degassed for 5 minutes and heated under stirring at 100 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 15-20% ethyl acetate in heptane to obtain methyl (2-methoxyphenyl)prolinate.

Synthesis of (2-methoxyphenyl)proline



[00296] To a solution of methyl (2-methoxyphenyl)prolinate (150 mg, 0.64 mmol) in tetrahydrofuran (1.8 mL) and methanol (0.3 mL), a solution of lithium hydroxide monohydrate (134 mg, 5.59 mmol) in water (0.9 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, acidified with 1N HCl solution (pH~5) followed by extraction with ethyl acetate (20 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by trituration with diethyl ether and n-pentane to afford (2-methoxyphenyl)proline.

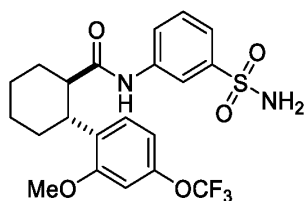
Synthesis of 1-(2-methoxyphenyl)-N-(3-sulfamoylphenyl)pyrrolidine-2-carboxamide

[00297] To a stirred solution of (2-methoxyphenyl)proline (250 mg, 1.13 mmol) and 3-aminobenzenesulfonamide (214 mg, 1.24 mmol) in dimethylformamide (5 mL) was added HATU (644 mg, 1.69 mmol) at room temperature. The reaction mixture was cooled to 0 °C and 4-methylmorpholine (206 mg, 2.03 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. After reaction completion, water was added followed by extraction with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain 1-(2-methoxyphenyl)-N-(3-

sulfamoylphenyl)pyrrolidine-2-carboxamide. MS (ESI): m/z 376.2 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 9.96 (s, 1H), 8.20 (s, 1H), 7.83-7.76 (m, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.36 (br s, 2H), 6.85-6.80 (m, 2H), 6.74-6.72 (m, 2H), 4.44-4.41 (m, 1H), 3.65 (s, 3H), 3.60-3.54 (m, 1H), 3.27-3.22 (m, 1H), 2.28-2.19 (m, 1H), 1.97-1.91 (m, 3H).

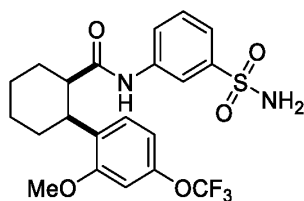
Compound 19

Synthesis of rac-(1R,2R)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

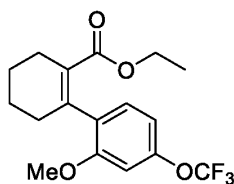


Compound 21

Synthesis of rac-(1R,2S)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide



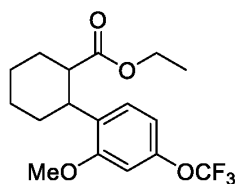
Synthesis of ethyl 2'-methoxy-4'-(trifluoromethoxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



[00298] To a stirred solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (1 g, 3.3 mmol) in acetonitrile (15 mL) and ethanol (10 mL), (2-methoxy-4-(trifluoromethoxy)phenyl)boronic acid (1.17 g, 5 mmol), 1,4-bis(diphenylphosphino)butane (0.028 g, 0.066 mmol) and palladium acetate (0.007 g, 0.033 mmol) were added at 0-5 °C. To the reaction mixture, an aqueous solution of sodium carbonate (1.05 g, 9.9 mmol) in water (5

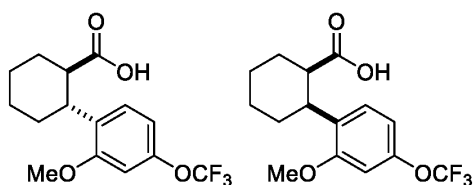
mL) was added and the reaction mixture was slowly warmed to room temperature and then heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was diluted with water followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography with a gradient of 20-30% ethyl acetate in heptane to afford ethyl 2'-methoxy-4'-(trifluoromethoxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate.

Synthesis of ethyl 2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylate



[00299] To a stirred solution of ethyl 2'-methoxy-4'-(trifluoromethoxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (3.0 g, 8.71 mmol) in methanol (100 mL), then 10% Pd/C was added and the reaction mixture was stirred for 16 hours at room temperature under hydrogen atmosphere. After reaction completion, the reaction mixture was filtered through a pad of Celite[®], filtered, then concentrated. The residue was purified by column chromatography using 10-20% ethyl acetate in hexane to obtain ethyl 2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylate.

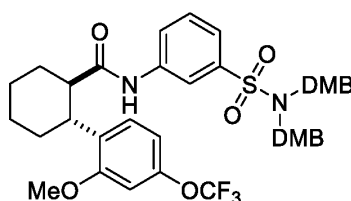
Synthesis of rac-(1R,2R)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid



[00300] To a stirred solution of ethyl 2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylate (4.0 g, 11.5 mmol) in methanol (40 mL) and tetrahydrofuran (40 mL) a solution of lithium hydroxide (1.61 g, 67 mmol) in water (40 mL) was added. The reaction mixture was stirred at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated and the aqueous solution was neutralized

with 1N hydrochloric acid, followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to afford rac-(1R,2R)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-N-(3-(N,N-bis(3,4-dimethylbenzyl)sulfamoyl)phenyl)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxamide



[00301] To a stirred solution of rac-((1R,2R)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid (0.2 g, 0.628 mmol) in dichloromethane (10 mL), and oxalyl dichloride (0.16 g, 1.26 mmol), 1 drop of *N,N*-dimethylformamide were added at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 2 hours. After 2 hours, the reaction mixture was concentrated, then the residue was dissolved in dichloromethane (10 mL). This solution was added dropwise into a mixture of 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (0.356 g, 0.754 mmol), *N,N*-diisopropylethylamine (0.406 g, 3.14 mmol) and dichloromethane (10 mL) at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 2 hours. After reaction completion, the reaction mixture was diluted with water, then extracted in dichloromethane. The organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was used in the next step without any further purification.

Synthesis of rac-(1R,2R)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

[00302] To a stirred solution of rac-(1R,2R)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxamide (0.4 g, 0.52 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (1.5 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate followed by extraction with

dichloromethane. The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain

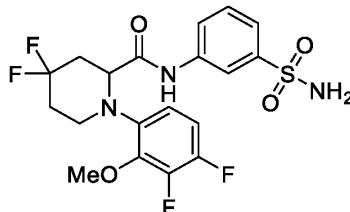
rac-(1*R*,2*R*)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide. MS (ESI): m/z 473.30 [M + H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.14 (br s, 1H), 8.06 (s, 1H), 7.56-7.54 (m, 1H), 7.43-7.38 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.28-3.25 (m, 1H), 2.88 (d, *J* = 8.8 Hz, 1H), 2.03-2.00 (m, 1H), 1.84-1.74 (m, 3H), 1.57-1.50 (m, 1H), 1.41-1.33 (m, 2H), 1.24-1.22 (m, 1H).

Synthesis of rac-(1*R*,2*S*)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

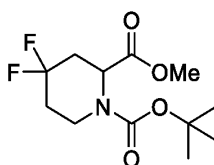
[00303] To a stirred solution of *rac*-(1*R*,2*S*)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)cyclohexane-1-carboxylic acid (0.2 g, 0.63 mmol) in dichloromethane (10 mL), and oxalyl dichloride (0.16 g, 1.26 mmol) was added 1 drop of *N,N*-dimethylformamide were added at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 2 hours. After 2 hours, the reaction mixture was concentrated and the residue was dissolved in dichloromethane (10 mL). This solution was added dropwise into a mixture of *m*-aminobenzenesulfonamide (0.13 g, 0.754 mmol), *N,N*-diisopropylethylamine (0.325 g, 2.51 mmol) and dichloromethane (10 mL) at 0-5 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain *rac*-(1*R*,2*S*)-2-(2-methoxy-4-(trifluoromethoxy)phenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide. MS (ESI): m/z 471.30 [M - H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.76 (br s, 1H), 8.07 (s, 1H), 7.43-7.38 (m, 3H), 7.31-7.29 (m, 3H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.19-3.15 (m, 1H), 2.98 (br s, 1H), 2.72-2.63 (m, 1H), 1.97-1.95 (m, 1H), 1.90-1.87 (m, 1H), 1.76-1.71 (m, 2H), 1.52-1.50 (m, 1H), 1.46-1.40 (m, 2H).

Compound 23

1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-N-(3-sulfamoylphenyl)piperidine-2-carboxamide

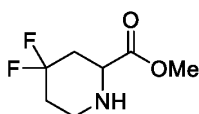


Synthesis of 1-(tert-butyl) 2-methyl 4,4-difluoropiperidine-1,2-dicarboxylate



[00304] To a stirred solution of 1-(*tert*-butyl) 2-methyl 4-oxopiperidine-1,2-dicarboxylate (5 g, 19.40 mmol) in dichloromethane (50 mL) was added diethylaminosulfur trifluoride (12.8 mL, 97.20 mmol) dropwise at -78 °C. The reaction mixture was slowly warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was added dropwise to a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was adsorbed on silica gel and purified by column chromatography using 20-30% ethyl acetate in hexane as an eluent to obtain 1-(*tert*-butyl) 2-methyl 4,4-difluoropiperidine-1,2-dicarboxylate.

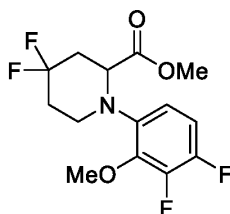
Synthesis of methyl 4,4-difluoropiperidine-2-carboxylate



[00305] To a stirred solution of 1-(*tert*-butyl) 2-methyl 4,4-difluoropiperidine-1,2-dicarboxylate (1.5 g, 5.37 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (4.5 mL) at 0-5 °C and the reaction mixture was stirred for 16 hours at room temperature. After reaction completion, water was added, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was

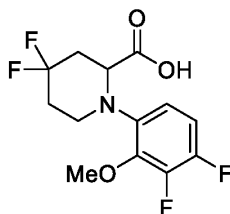
purified by column chromatography using 40-50% ethyl acetate in hexane as an eluent to obtain methyl 4,4-difluoropiperidine-2-carboxylate.

Synthesis of methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylate



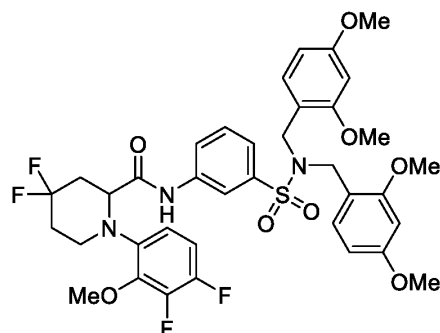
[00306] To a stirred solution of methyl 4,4-difluoropiperidine-2-carboxylate (0.6 g, 3.35 mmol) and 1-bromo-3,4-difluoro-2-methoxybenzene (0.896 g, 4.02 mmol) in dimethyl sulfoxide (12 mL) were added potassium phosphate (1.42 g, 6.7 mmol) and copper iodide (0.159 g, 0.837 mmol) at room temperature then stirred for 10 minutes. The reaction mixture was heated at 100 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 30-40% ethyl acetate in hexane as an eluent to obtain methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylate.

Synthesis of 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid



[00307] To a stirred solution of methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylate (0.060 g, 0.018 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) was added an aqueous solution of lithium hydroxide monohydrate (0.044 g, 1.05 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was concentrated, the aqueous solution was neutralized with 1N hydrochloric acid, followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to obtain 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid.

Synthesis of N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide



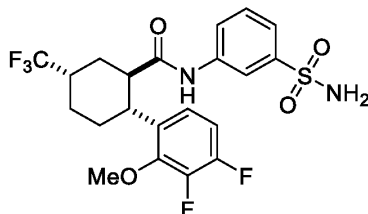
[00308] To a stirred solution of 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid (0.05 g, 0.163 mmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (0.092 g, 0.019 mmol) in pyridine (2 mL) was added phosphoryl trichloride (0.125 g, 0.814 mmol) at 0-5 °C and the reaction mixture was stirred at 0-5 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide.

Synthesis of 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-N-(3-sulfamoylphenyl)piperidine-2-carboxamide

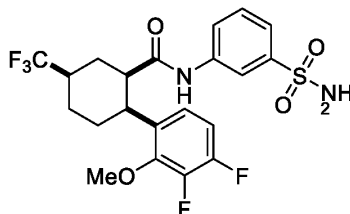
[00309] To a stirred solution of *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide (0.08 g, 0.105 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.4 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-*N*-(3-sulfamoylphenyl)piperidine-2-carboxamide. MS (ESI): m/z 462.30 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 10.32 (br s, 1H), 8.11 (s, 1H), 7.62-7.60 (m, 1H), 7.50-7.44 (m, 2H), 7.34 (br s, 2H), 7.10-7.04 (m, 1H), 6.98-6.96 (m, 1H), 4.37 (t, $J = 6.0$ Hz, 1H), 3.99 (s, 3H), 3.67-3.62 (m, 1H), 3.05-2.99 (m, 1H), 2.43-2.37 (m, 2H), 2.31-2.17 (m, 2H).

Compound 24

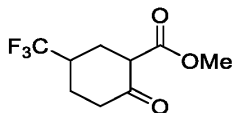
Synthesis of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

**Compound 26**

Synthesis of rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

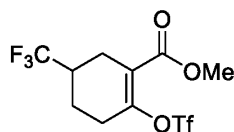


Synthesis of methyl 2-oxo-5-(trifluoromethyl)cyclohexane-1-carboxylate



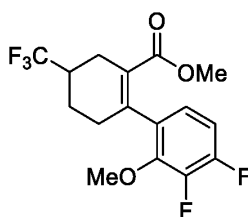
[00310] To a stirred solution of 60% sodium hydride in mineral oil (960 mg, 24 mmol) in tetrahydrofuran (40 mL) was added dimethyl carbonate (3.87 mL, 36 mmol) at 0 °C. The reaction mixture was heated at 60 °C for 30 minutes. The reaction mixture was cooled to 0 °C and a solution of 4-(trifluoromethyl)cyclohexanone (2 g, 12 mmol) in THF was added. The reaction mixture was heated under stirring at 60 °C for 12 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to obtain methyl 2-oxo-5-(trifluoromethyl)cyclohexane-1-carboxylate.

Synthesis of methyl 5-(trifluoromethyl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate



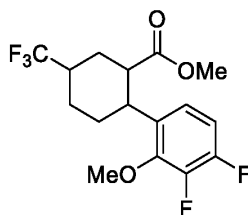
[00311] To a stirred solution of 60% sodium hydride in mineral oil (428 mg, 10.7 mmol) in dichloromethane (30 mL) was added methyl 2-oxo-5-(trifluoromethyl)cyclohexane-1-carboxylate (2 g, 8.92 mmol) at 0 °C and stirred for 30 minutes. The reaction mixture was cooled to 0 °C and trifluoro(trifluoromesyloxysulfonyl)methane (1.8 mL, 10.7 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 12 hours. After reaction completion, water was added followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain methyl 5-(trifluoromethyl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate.

Synthesis of methyl 3',4'-difluoro-2'-methoxy-4-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



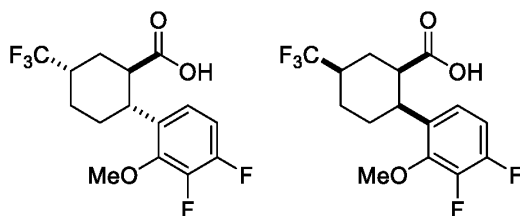
[00312] A solution of methyl 5-(trifluoromethyl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (4 g, 11.2 mmol), (3,4-difluoro-2-methoxyphenyl)boronic acid (3.17 g, 16.8 mmol) in acetonitrile (30 mL) and ethanol (10 mL) was degassed with nitrogen for 10 minutes followed by addition of sodium carbonate (3.57 g, 33.7 mmol) in water (10 mL), 1,4-bis(diphenylphosphino)butane (dppb, 955 mg, 2.24 mmol) and palladium acetate (252 mg, 1.12 mmol). The reaction mixture was degassed for 5 minutes and heated under stirring at 100 °C for 12 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to obtain methyl 3',4'-difluoro-2'-methoxy-4-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate.

Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylate



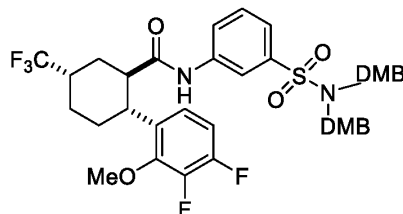
[00313] To a stirred solution of methyl 3',4'-difluoro-2'-methoxy-4-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (2.8 g, 7.99 mmol) in methanol (100 mL), was added 10% palladium on carbon at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 16 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite® then concentrated. The residue was purified by column chromatography using 10-20% ethyl acetate in hexane as an eluent to obtain methyl 2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylate.

Synthesis of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid and rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid



[00314] To a solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylate (1.2 g, 3.41 mmol) in tetrahydrofuran (10 mL) and methanol (2 mL) a solution of lithium hydroxide monohydrate (1.43 g, 34.1 mmol) in water (4 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1N hydrochloric acid (pH~6), followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid and rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid.

Synthesis of rac-(1R,2R,5S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide



[00315] To a stirred solution of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid (150 mg, 443 μ mol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (251 mg, 532 μ mol) in Pyridine (5 mL) was added phosphoryl trichloride (207 μ L, 2.22 mmol) at 0-5 °C and the reaction mixture was stirred for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2R,5S)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide. DMB is a 2,4-dimethoxybenzyl (DMB) group.

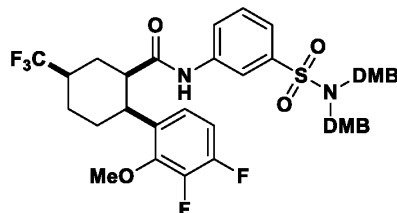
Synthesis of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

[00316] To a stirred solution of rac-(1R,2R,5S)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide (160 mg, 0.2 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (0.8 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide.

[00317] MS (ESI): m/z 491.3 [M-H]⁺; ¹H NMR (400 MHz, DMSO-d₆): 10.25 (br s, 1H), 7.99 (s, 1H), 7.63-7.60 (m, 1H), 7.45-7.39 (m, 2H), 7.31 (br s, 2H), 7.14-7.10 (m, 2H), 3.88 (s,

3H), 3.28-3.22 (m, 1H), 3.12-3.09 (m, 1H), 2.78-2.75 (m, 1H), 2.18-2.14 (m, 1H), 1.99-1.91 (m, 2H), 1.87-1.80 (m, 1H), 1.67-1.64 (m, 1H), 1.54-1.49 (m, 1H).

Synthesis of rac-(1R,2S,5R)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide



[00318] To a stirred solution of rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid (150 mg, 0.44 mmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (251 mg, 0.53 mmol) in pyridine (4 mL) was added phosphoryl trichloride (0.207 mL, 2.22 mmol) at 0-5 °C and the reaction mixture was stirred at 0-5 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2S,5R)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide.

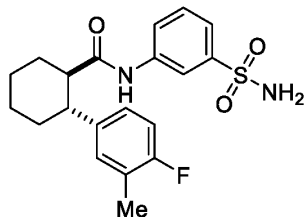
Synthesis of rac-((1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

[00319] To a stirred solution of rac-(1R,2S,5R)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide (150 mg, 189 μmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.6 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-*N*-(3-sulfamoylphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide. MS (ESI): *m/z* 491.30 [*M* - H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): 10.24 (br s, 1H), 8.02 (s, 1H), 7.58-7.54 (m, 1H), 7.44-7.39 (m, 2H), 7.31

(br s, 2H), 7.27-7.24 (m, 1H), 7.13-7.07 (m, 1H), 4.03 (brs, 1H), 3.81 (s, 3H), 3.09-3.04 (m, 1H), 2.61-2.51 (m, 1H), 2.13-2.03 (m, 1H), 1.98-1.83 (m, 3H), 1.71-1.68 (m, 1H), 1.35-1.29 (m, 1H).

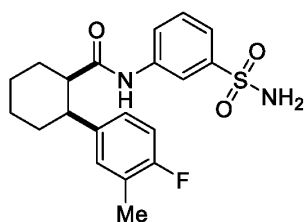
Compound 28

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide

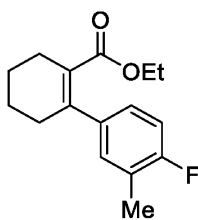


Compound 30

Synthesis of rac-(1R,2S)-2-(4-fluoro-3-methylphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide



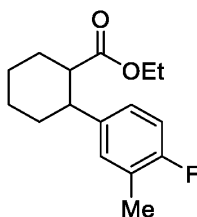
Synthesis of ethyl 4'-fluoro-3'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



[00320] To a stirred solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (4 g, 13.9 mmol) in acetonitrile (25 mL, 479 mmol) and ethanol (15 mL, 257 mmol), (4-fluoro-3-methylphenyl)boronic acid (3.21 g, 20.85 mmol) were added, 1,4-bis(diphenylphosphino)butane (1.78 g, 4.16 mmol) and palladium acetate (467 mg, 2.08 mmol) at room temperature. To the reaction mixture, an aqueous solution of sodium carbonate (4.41 g, 41.6 mmol) in water (10 mL) was added and the reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature,

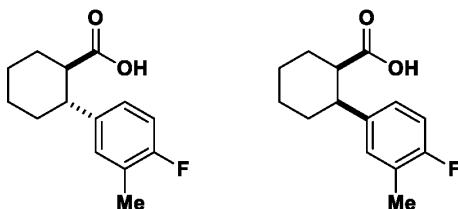
diluted with water, followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 10-20% ethyl acetate in hexane as an eluent to obtain 2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylate (1.5 g, 6.04 mmol).

Synthesis of ethyl 2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylate



[00321] To a stirred solution of ethyl 2-(4-fluoro-3-tolyl)-1-cyclohexene-1-carboxylate (2 g, 7.62 mmol) in methanol (30 mL), 10% Pd/C (0.2 g) was added at room temperature and the reaction mixture was stirred for 16 hours at room temperature under hydrogen atmosphere. After reaction completion, the reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated to obtain ethyl 2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylate, which was taken for next step without any purification.

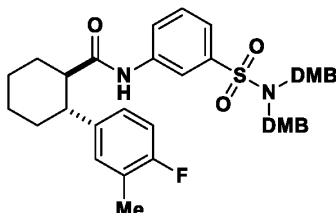
Synthesis of (1R,2R)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylic acid and (1R,2S)-2-(4-fluoro-3-tolyl)cyclohexanecarboxylic acid



[00322] To a stirred solution of ethyl 2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylate (1.7 g, 6.43 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide monohydrate (770 mg, 18.35 mmol) in water (5 mL) and methanol (5 mL) was added then the reaction mixture was stirred for 16 hours at 75 °C. After reaction completion, the reaction mixture was concentrated, neutralized with 1N hydrochloric acid, followed by extraction with ethyl acetate. The organic layers were combined and dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to afford rac-(1R,2R)-2-(4-fluoro-3-

methylphenyl)cyclohexane-1-carboxylic acid and rac-(1*R*,2*S*)-2-(4-fluoro-3-tolyl)cyclohexanecarboxylic acid.

*Synthesis of rac-(1*R*,2*R*)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide*

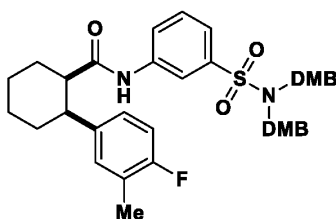


[00323] To a stirred solution rac-(1*R*,2*R*)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylic acid (0.1 g, 0.423 mmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (240 mg, 0.508 mmol) in pyridine (3 mL) was added phosphoryl trichloride (0.2 mL, 2.14 mmol) at 0-5 °C and the reaction mixture was stirred for 1 hour. After reaction completion, ice cold water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1*R*,2*R*)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide.

*Synthesis of rac-(1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-*N*-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide*

[00324] To a solution of rac-(1*R*,2*R*)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide (250 mg, 0.362 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL) at 0 °C and the reaction mixture was stirred at 45 °C for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by Prep-HPLC to obtain rac-(1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-*N*-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide. MS (ESI): m/z 389.20 [M - H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.04 (br s, 1H), 8.04 (s, 1H), 7.58-7.54 (m, 1H), 7.43-7.38 (m, 2H), 7.30 (br s, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.99-6.93 (m, 2H), 2.84-2.81 (m, 1H), 2.66 (dt, *J* = 11.6, 3.2 Hz, 1H), 2.11 (s, 3H), 1.97-1.95 (m, 1H), 1.87-1.76 (m, 3H), 1.57-1.47 (m, 1H), 1.46-1.33 (m, 3H).

Synthesis of rac-(1R,2S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide



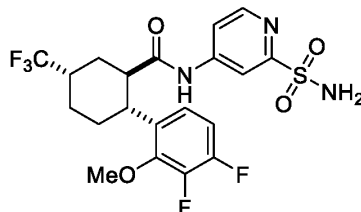
[00325] To a stirred solution of rac-(1R,2S)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxylic acid (0.1 g, 0.423 mmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (240 mg, 0.508 mmol) in pyridine (3 mL) was added phosphoryl trichloride (0.2 mL, 2.14 mmol) at 0-5 °C and the reaction mixture was stirred for 1 hour. After reaction completion, ice cold water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2S)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide.

Synthesis of rac-(1R,2S)-2-(4-fluoro-3-methylphenyl)-N-(3-sulfamoylphenyl)cyclohexane-1-carboxamide

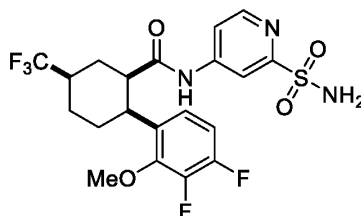
[00326] To a stirred solution of rac-(1R,2S)-*N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4-fluoro-3-methylphenyl)cyclohexane-1-carboxamide (150 mg, 217 μmol) in dichloromethane (20 mL) was added trifluoroacetic acid (0.6 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to obtain rac-(1R,2S)-2-(4-fluoro-3-methylphenyl)-*N*-(3-sulfamoylphenyl)cyclohexane-1-carboxamide. MS (ESI): *m/z* 391.20 [*M* + *H*]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.85 (br s, 1H), 8.05 (s, 1H), 7.54-7.51 (m, 1H), 7.44-7.38 (m, 2H), 7.28 (br s, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.02-6.99 (m, 2H), 2.95 (br s, 1H), 2.91-2.87 (m, 1H), 2.58-2.57 (m, 1H), 2.12 (s, 3H), 1.96-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.80-1.71 (m, 2H), 1.62-1.61 (m, 1H), 1.60-1.50 (m, 1H), 1.401.38 (m, 1H).

Compound 39

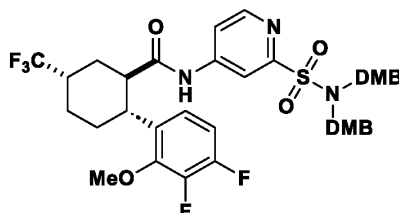
Synthesis of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

**Compound 41**

Synthesis of rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide



Synthesis of rac-(1R,2R,5S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

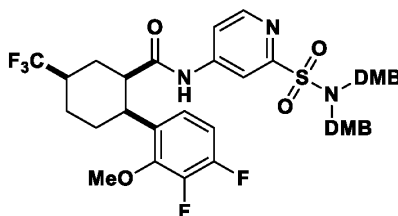


[00327] To a stirred solution of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid (80 mg, 236 μ mol) and 4-amino-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (134 mg, 0.28 μ mol) in pyridine (3 mL) was added phosphoryl trichloride (0.1 mL, 1.18 mmol) at 0-5 °C. The reaction mixture was stirred for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2R,5S)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide.

Synthesis of rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

[00328] To a stirred solution of rac-(1R,2R,5S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide (110 mg, 0.12 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain rac-(1R,2R,5S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide. MS (ESI): m/z 494.10 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): 10.67 (s, 1H), 8.48 (d, $J = 5.2$ Hz, 1H), 8.04 (d, $J = 2.0$ Hz, 1H), 7.62 (dd, $J = 5.2, 2.0$ Hz, 1H), 7.39 (br s, 2H), 7.15-7.08 (m, 1H), 7.06-7.02 (m, 1H), 3.90 (s, 3H), 3.29-3.23 (m, 1H), 3.14-3.09 (m, 1H), 2.80-2.77 (m, 1H), 2.22-2.18 (m, 1H), 2.01-1.92 (m, 2H), 1.90-1.81 (m, 1H), 1.68-1.65 (m, 1H), 1.58-1.52 (m, 1H).

Synthesis of (1R,2S,5R)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

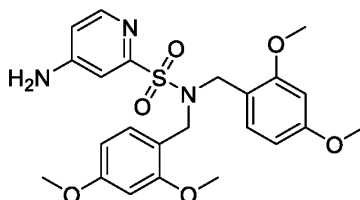


[00329] To a stirred solution of rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxylic acid (110 mg, 325 μ mol) and 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (154 mg, 325 μ mol) in pyridine (2.93 mL) was added phosphoryl trichloride (0.152 mL, 1.63 mmol) at 0-5 °C. The reaction mixture was stirred for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2S,5R)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridine-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide as pale-yellow solid.

Synthesis of rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide

[00330] To a stirred solution of rac-(1R,2S,5R)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)cyclohexane-1-carboxamide (0.1 g, 0.12 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL) at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain rac-(1R,2S,5R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)-5-(trifluoromethyl)cyclohexane-1-carboxamide. MS (ESI): m/z 494.30 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6): 10.69 (s, 1H), 8.47 (d, $J = 5.4$ Hz, 1H), 8.06 (d, $J = 1.4$ Hz, 1H), 7.58 (dd, $J = 5.4, 1.7$ Hz, 1H), 7.38 (br s, 2H), 7.25-7.21 (m, 1H), 7.14-7.08 (m, 1H), 4.05-4.02 (m, 1H), 3.80 (s, 3H), 3.14-3.08 (m, 1H), 2.61-2.60 (m, 1H), 2.10-1.69 (m, 4H), 1.72-1.69 (m, 1H), 1.37-1.28 (m, 1H).

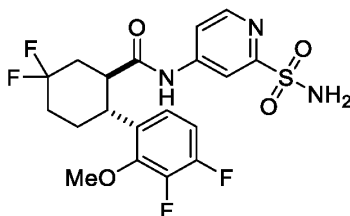
Synthesis of 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide



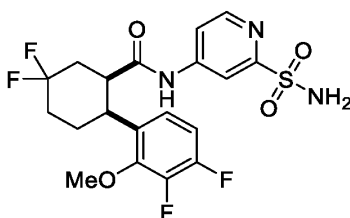
[00331] To a stirred solution of 4-bromo-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (1 g, 1.86 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was added copper(II) acetylacetonate (146 mg, 0.558 mmol), 2-acetylcyclohexanone (157 mg, 1.12 mmol), ammonium acetate (1.43 g, 18.6 mmol) and cesium carbonate (1.82 g, 5.58 mmol). The reaction mixture was stirred at room temperature for 10 minutes, followed by heating at 90 °C for 16 hours. After reaction completion, the reaction mixture was diluted with water followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 40-50% ethyl acetate in hexane as an eluent to obtain 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide.

Compound 43

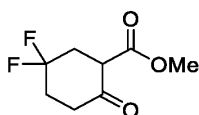
Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide

**Compound 45**

Synthesis of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide

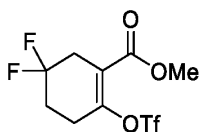


Synthesis of methyl 5,5-difluoro-2-oxocyclohexane-1-carboxylate



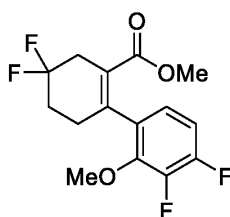
[00332] To a stirred solution of 60% sodium hydride in mineral oil (2.48 g, 59.6 mmol) in tetrahydrofuran (50 mL) was added dimethyl carbonate (4.79 mL, 44.7 mmol) at 0 °C and heated under stirring at 60 °C for 30 minutes. A solution of 4,4-difluorocyclohexanone (2 g, 14.9 mmol) in THF was added at 0 °C and the reaction mixture was heated under stirring at 60 °C for 12 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, then concentrated to obtain methyl 5,5-difluoro-2-oxocyclohexanecarboxylate.

Synthesis of methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate

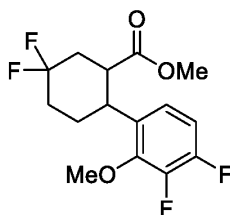


[00333] To a solution of 60% sodium hydride in mineral (0.5 g, 12.5 mmol) in dichloromethane (18 mL) was added methyl 5,5-difluoro-2-oxocyclohexanecarboxylate (2 g, 10.4 mmol) and the reaction mixture was stirred for 30 minutes. The reaction mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (2.1 mL, 12.5 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 12 hours. After reaction completion, water was added, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate.

Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-1-cyclohexene-1-carboxylate

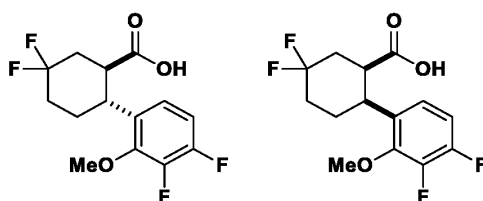


[00334] To a stirred solution of methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (2 g, 6.17 mmol) and (3,4-difluoro-2-methoxyphenyl)boronic acid (1.74 g, 9.25 mmol) in acetonitrile (11 mL) and ethanol (7.5 mL) were added 1,4-bis(diphenylphosphino)butane (789 mg, 1.85 mmol) and palladium acetate (208 mg, 0.93 mmol). The reaction mixture was purged with argon for 10 minutes. An aqueous solution of disodium carbonate (1.96 g, 18.5 mmol) in water (3.73 mL) was added and the reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 10-20% ethyl acetate in hexane as an eluent to obtain methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-1-cyclohexene-1-carboxylate.

Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexanecarboxylate

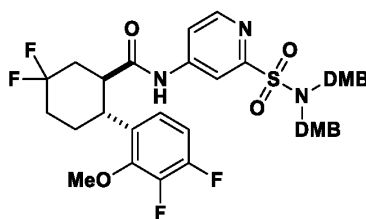
[00335] To a stirred solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-1-cyclohexene-1-carboxylate (1.4 g, 4.4 mmol) in methanol (50 mL) were added 10% palladium on carbon at room temperature and the reaction mixture was stirred for 16 hours at room temperature under hydrogen atmosphere. After reaction completion, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated to obtain the product methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexanecarboxylate.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid



[00336] To a stirred solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexanecarboxylate (1.4 g, 4.37 mmol) in tetrahydrofuran (7.82 mL) and methanol (1.3 mL) was added lithium hydroxide monohydrate (1.83 g, 43.7 mmol) in water (3.91 mL). The reaction mixture was heated to 40 °C and stirred for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1N hydrochloric acid (pH~6), followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep-HPLC to obtain rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid and rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid.

Synthesis of rac-(1R,2R)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide

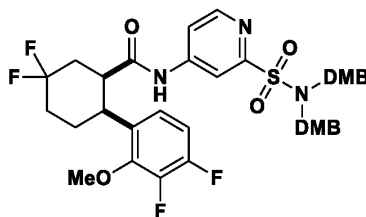


[00337] To a stirred solution of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (120 mg, 0.392 mmol) and 4-amino-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (223 mg, 0.47 mmol) in pyridine (1 mL) was added phosphoryl trichloride (0.3 g, 1.96 mmol) at 0-5 °C. The reaction mixture was stirred for 1 hour at room temperature. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2R)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide

[00338] To a solution of rac-(1R,2R)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide (120 mg, 0.16 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by Prep-HPLC method to afford rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-*N*-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide. MS (ESI): m/z 462.30 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 10.70 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 8.02 (d, $J = 1.6$ Hz, 1H), 7.57 (dd, $J = 5.6, 2.0$ Hz, 1H), 7.39 (br s, 2H), 7.12-7.08 (m, 2H), 3.90 (s, 3H), 3.41-3.60 (m, 1H), 3.19-3.14 (m, 1H), 2.44-2.42 (m, 1H), 2.23-2.09 (m, 3H), 1.84-1.81 (m, 1H), 1.62-1.60 (m, 1H).

Synthesis of rac-(1R,2S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide



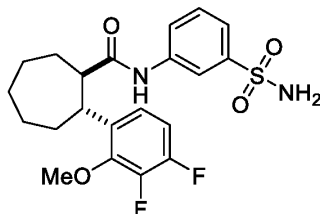
[00339] To a stirred solution of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (80 mg, 0.26 mmol) and 4-amino-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (148 mg, 0.31 mmol) in pyridine (0.89 mL) was added phosphoryl trichloride (0.2 g, 1.31 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 4 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2S)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide.

Synthesis of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide

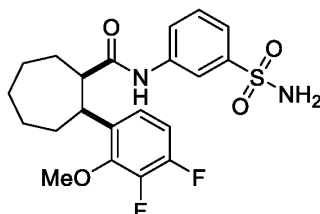
[00340] To a solution of (1R,2S)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide (50 mg, 65.6 μmol) in dichloromethane (6.0 mL) was added trifluoroacetic acid (0.2 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by prep-HPLC method to afford rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluoro-*N*-(2-sulfamoylpyridin-4-yl)cyclohexane-1-carboxamide. MS (ESI): *m/z* 462.20 [*M* + *H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.53 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 7.37 (br s, 2H), 7.24-7.21 (m, 1H), 7.11-7.04 (m, 1H), 3.91 (s, 3H), 3.44-3.42 (m, 1H), 3.28-3.27 (m, 1H), 2.71-2.63 (m, 1H), 2.44-2.42 (m, 2H), 2.14-2.03 (m, 2H), 1.84-1.81 (m, 1H).

Compound 81

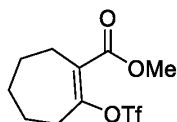
Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide

**Compound 83**

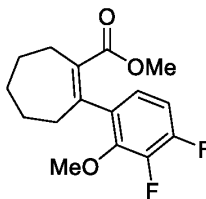
Synthesis of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide



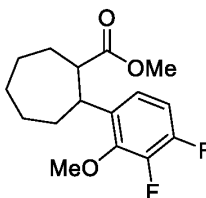
Synthesis of methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohept-1-ene-1-carboxylate



[00341] To a stirred solution of 60% sodium hydride in mineral oil (564 mg, 14.1 mmol) in dichloromethane (40 mL) was added methyl 2-oxocycloheptanecarboxylate (2 g, 11.8 mmol) at 0 °C and stirred for 30 minutes. The reaction mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (2.37 mL, 14.1 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. After reaction completion, water was added, followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohept-1-ene-1-carboxylate.

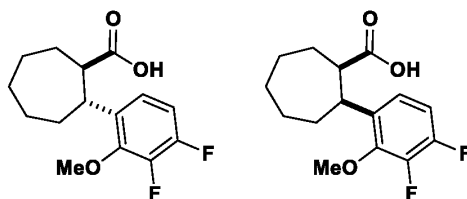
Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)cyclohept-1-ene-1-carboxylate

[00342] To a stirred solution of methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohept-1-ene-1-carboxylate (650 mg, 2.15 mmol) in acetonitrile (6.5 mL) and ethanol (4.33 mL) were added (3,4-difluoro-(3,4-difluoro-2-methoxyphenyl)boronic acid (606 mg, 3.23 mmol), 1,4-bis(diphenylphosphino)butane (18.3 mg, 43 μ mol) and palladium acetate (4.83 mg, 0.0215 mmol) at room temperature. To the reaction mixture, an aqueous solution of disodium carbonate (684 mg, 6.45 mmol) in water (1.95 mL) was added and the reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 20-30% ethyl acetate in hexane as an eluent to obtain methyl 2-(3,4-difluoro-2-methoxyphenyl)cyclohept-1-ene-1-carboxylate.

Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxylate

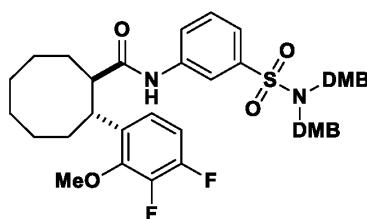
[00343] To a stirred solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)-1-cycloheptene-1-carboxylate (3.5 g, 11.8 mmol) in methanol (50 mL) were added 10% palladium on carbon and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 16 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite® and the filtrate concentrated to obtain 2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxylate.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxylic acid and rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxylic acid



[00344] To a stirred solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)cycloheptanecarboxylate (2 g, 6.7 mmol) and lithium hydroxide monohydrate (2.81 g, 67 mmol) in tetrahydrofuran (12 mL), water (6 mL) and methanol (2 mL) at room temperature. The reaction mixture was heated to 80 °C and stirred for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1N hydrochloric acid (pH~6), followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, concentrated. The residue was purified by prep-HPLC to obtain rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptanecarboxylic acid and rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptanecarboxylic acid.

Synthesis of rac-(1R,2R)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide



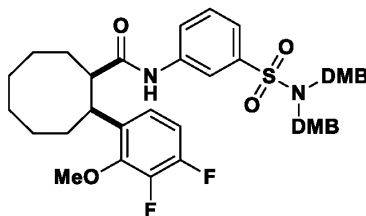
[00345] To a stirred solution of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptanecarboxylic acid (0.2 g, 703 μmol) and 3-amino-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (399 mg, 0.84 mmol) in pyridine (3 mL) was added phosphoryl trichloride (539 mg, 3.52 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue purified by silica gel column chromatography using 50% ethyl acetate in hexane as an eluent to obtain rac-(1R,2R)-*N*-(3-(*N,N*-bis(2,4-

dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide.

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide

[00346] To a solution of rac-(1R,2R)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide (140 mg, 0.18 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by prep-HPLC method to afford rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide. MS (ESI): m/z 439.3 $[M + H]^+$; 1H NMR (400 MHz, DMSO- d_6): δ 10.01 (s, 1H), 7.99 (s, 1H), 7.58-7.54 (m, 1H), 7.43-7.48 (m, 2H), 7.30 (br s, 2H), 7.07-7.01 (m, 2H), 3.89 (s, 3H), 3.47-3.41 (m, 1H), 2.95-2.89 (m, 1H), 1.96-1.90 (m, 1H), 1.82-1.72 (m, 3H), 1.70-1.65 (m, 4H), 1.59-1.54 (m, 2H).

Synthesis of rac-(1R,2S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide



[00347] To a stirred solution of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptanecarboxylic acid (80 mg, 0.28 mmol) and 3-amino-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide (160 mg, 0.34 mmol) in pyridine (1.2 mL) was added phosphoryl trichloride (216 mg, 1.41 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain rac-(1R,2S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide.

Synthesis of rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide

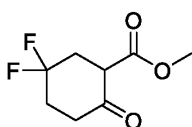
[00348] To a solution of (1R,2S)-N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(3,4-difluoro-2-methoxyphenyl)cycloheptane-1-carboxamide (0.1 g, 0.135 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by Prep-HPLC method to afford rac-(1R,2S)-2-(3,4-difluoro-2-methoxyphenyl)-N-(3-sulfamoylphenyl)cycloheptane-1-carboxamide. MS (ESI): m/z 437.2 [M-H]⁺; ¹H NMR (400 MHz, DMSO-d₆): δ 9.76 (s, 1H), 7.94 (s, 1H), 7.47-7.36 (m, 3H), 7.19 (br s, 2H), 7.05-6.97 (m, 2H), 3.92 (s, 3H), 3.47-3.43 (m, 1H), 2.92-2.87 (m, 1H), 2.45-2.39 (m, 1H), 2.03-1.98 (m, 1H), 1.91-1.84 (m, 4H), 1.70-1.67 (m, 1H), 1.51-1.43 (m, 3H).

The following compounds were prepared using similar procedures as described above: 1, 3, 5, 7, 9, 11, 13, 15, 19, 21, 24, 26, 28, 30, 32, 34, 37, 38, 39, 41, 43, 45, 47, 53, 54, 63, 65, 66, 70, 81, 83, 117, 138, 139, 140, 141, 148, 153, 154, 155, 156, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 207, 208, 209, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 264, 265, 266, 267, 268, 269, 270, 271, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 291, 292, 294, 295, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 311, 312, 313, 314, 315, 317, 318, 319, 320, 321, 322, 323, 328, 329, 330, 331, 332, 334, 335, 336, 337, 338, 339, 340, 341, 342, 344, 345, 346, 348, 350, 351, 352, 357, 358, 359, 362, 363, 364, 364, 366, 367, 368, 369, 370, 371, 373, 374, 375, 376, 377, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 420, 423, 424, 425, 426, 427, 428, 429, 431, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 457, 462, 463, 464, 467, 468, 469, 470, 471, 472, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 505, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 540, 541, 544, 545, 546, 549, 550, 554, 555, 556, 557, 558, 559, 560, 561, 562,

563, 564, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 627, 628, 629, 630, 631, 633, 634, 635, 636, 637, 638, 639, 640, 641, 643, 644, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724

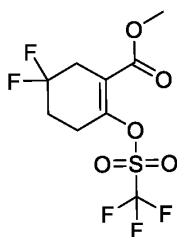
Compound 140

Synthesis of methyl 5,5-difluoro-2-oxocyclohexane-1-carboxylate



To a stirred solution of 4,4-difluorocyclohexan-1-one (850 g, 6.34 mol) in THF (10V) was added NaH (304 g, 12.7 mol) between 0-10 °C. The reaction was stirred between 0-10 °C for 30 minutes, followed by the addition of dimethyl carbonate (1.7 kg, 19 mol). The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was added to an aqueous solution of citric acid and n-heptane was added. The organic layer was separated, and the aqueous phase was extracted with MTBE. Another batch was set up using the same procedure. The organic layers were combined, washed with brine, filtered, then concentrated. The residue was purified by distillation to give methyl 5,5-difluoro-2-oxocyclohexane-1-carboxylate (1.9 kg, 72%).

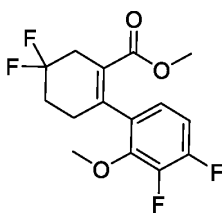
Synthesis of methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate



To a stirred solution of methyl 5,5-difluoro-2-oxocyclohexane-1-carboxylate (950 g, 2.9 mol) was added TEA (445 g, 4.4 mol) and DCM (10V). The reaction mixture was cooled between -50 and -30 °C then Tf₂O (1 kg, 3.5 mol) was added dropwise. The reaction mixture was

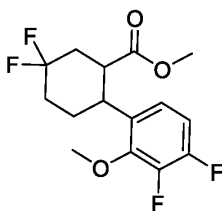
stirred between -50 and -30°C for 30 minutes, then the reaction mixture was warmed to room temperature. Water was added to the reaction mixture and the organic layer was separated. The aqueous phase was extracted with DCM. Another batch was set up using the same procedure. The organic layers were combined then filtered using silica gel to give methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (3 kg, 86%).

Synthesis of methyl 3',4,4',4'-tetrafluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



To a stirred solution of methyl 5,5-difluoro-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (1.23 kg, 3.85 mol) was added dioxane (10V), water (2V), (3,4-difluoro-2-methoxyphenyl)boronic acid (760 g, 4 mol), and K₃PO₄ (2.5 kg, 11.6 mol). The atmosphere was replaced with nitrogen then Pd(dppf)₂Cl₂ was added. The reaction mixture was heated to 100 °C and stirred for 2 hours. After reaction completion, water and MTBE was added to the reaction mixture. The organic layers separated, and the aqueous phase was extracted with MTBE. Another batch was set up using the same procedure. The organic layers were combined, washed with water, extracted with n-pentane, filtered using silica gel, then concentrated to give methyl 3',4,4',4'-tetrafluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (2.9 kg, 91%).

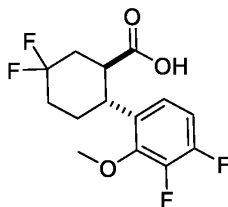
Synthesis of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylate



To a stirred solution of methyl 3',4,4',4'-tetrafluoro-2'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (1.9 kg, 6 mol) was added Raney Ni and MeOH (7.5V). The atmosphere was replaced with hydrogen (1 MPa) and the reaction mixture was stirred at 105 °C for 16 hours. After reaction completion, the reaction mixture was filtered, and the filter

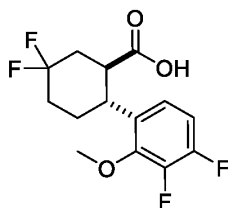
cake was washed with methanol. The filtrate was concentrated to give methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylate (1 kg, 96%).

Synthesis of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid



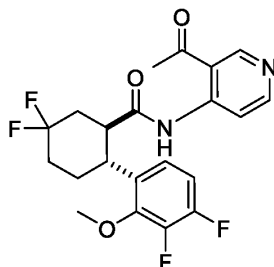
To a stirred solution of methyl 2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylate (920 g, 2.9 mol) was added MeOH (6V) and 30% NaOMe in MeOH (11.5 mol). The reaction mixture was heated to 70 °C and stirred for 16 hours. After reaction completion, 20% aqueous NaOH (11.5 mol) was added to the reaction mixture and the reaction mixture was stirred for 2 hours. After reaction completion, the reaction mixture was concentrated. 3M HCl was added dropwise to the residue to adjust the pH to 1~2 at 10~25 °C. The mixture was extracted with ethyl acetate. The organic layers were combined and concentrated to give rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (845 g, 96%).

Synthesis of (1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid



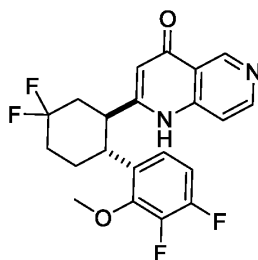
To a solution of rac-(1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (660 g, 2.2 mol) in EtOH (10V) was added L-1-phenylethylamine (1.1 eq). The reaction mixture was stirred at room temperature for 30 minutes. After reaction completion, the reaction mixture was filtered. The solid was dissolved in water, acidified using 2M HCl, then extracted with DCM. The organic layers were combined, washed with water, then concentrated. The residue was dried at 55 °C for 16 hours to give (1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (250 g, 38%).

Synthesis of (1R,2R)-N-(3-acetylpyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide



To a solution of (1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxylic acid (225 g, 735 mmol) in DMF (20V) was added HATU (420 g, 1.1 mol). The reaction mixture was stirred for 30 minutes, then DIPEA (475 g, 3.7 mol) and 1-(4-aminopyridin-3-yl)ethan-1-one (120 g, 880 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. After reaction completion, water was added to the reaction mixture followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, then concentrated. The residue was purified by column chromatography to give (1R,2R)-N-(3-acetylpyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide (270 g, 98%).

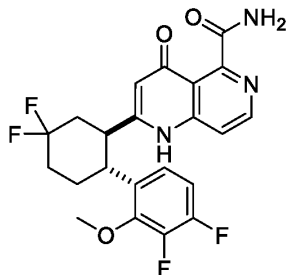
Synthesis of 2-((1R,2R)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexyl)-1,6-naphthyridin-4(1H)-one



To a solution of (1R,2R)-N-(3-acetylpyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexane-1-carboxamide (283 g, 667 mol) in DMAc (25V) was added K₃PO₄ (700 g, 3.3 mol). The reaction mixture was heated at 135 °C and stirred for 16 hours. After reaction completion, the reaction mixture was filtered using Celite. Water was added to the filtrate and the solution was extracted using ethyl acetate. The organic layers were combined, washed with brine, then concentrated. MTBE was added to the residue and the solution was

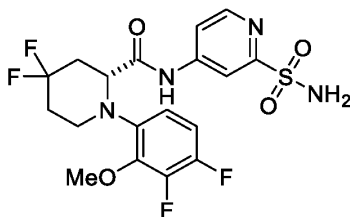
stirred for 2 hours. The mixture was filtered to give 2-((1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexyl)-1,6-naphthyridin-4(1*H*)-one (202 g, 99%).

*Synthesis of 2-((1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide*

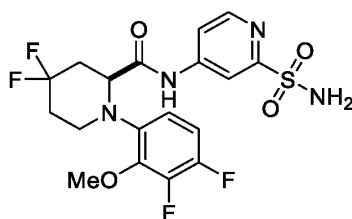


To a solution of 2-((1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexyl)-1,6-naphthyridin-4(1*H*)-one (180 g, 440 mmol) in formamide (10V), NHPI (72 g, 440 mmol), and TFA (100 g, 890 mmol). The reaction mixture was heated at 75 °C then CAN (485 g, 880 mmol) was added in three batches. After reaction completion, water was added to the reaction mixture. 2M HCl was used to acidify the reaction mixture followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, filtered, then concentrated. IPA was added to the residue and the mixture was stirred for 2 hours. The mixture was filtered, and the precipitate was purified by chiral SFC to give 2-((1*R*,2*R*)-2-(3,4-difluoro-2-methoxyphenyl)-5,5-difluorocyclohexyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide (48.5 g, 99%).

Compound 163

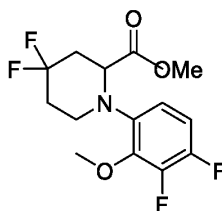


(R)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-*N*-(2-sulfamoylpyridin-4-yl)piperidine-2-carboxamide



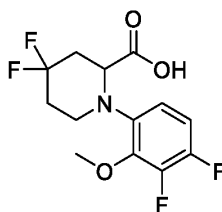
(S)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-*N*-(2-sulfamoylpyridin-4-yl)piperidine-2-carboxamide

Synthesis of methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylate



To a stirred solution of methyl 4,4-difluoro-2-piperidinecarboxylate and 1-bromo-3,4-difluoro-2-methoxybenzene in dimethyl sulfoxide were added potassium phosphate and copper iodide at room temperature. The reaction mixture was stirred for 10 minutes then heated at 100 °C for 16 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography to give methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-2-piperidinecarboxylate.

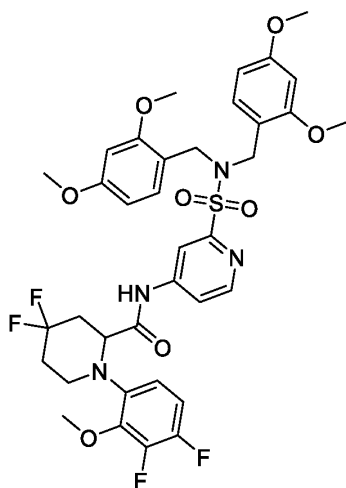
Synthesis of 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid



To a stirred solution of methyl 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylate in tetrahydrofuran and methanol was added an aqueous solution of lithium hydroxide in water. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was concentrated and the remaining aqueous solution

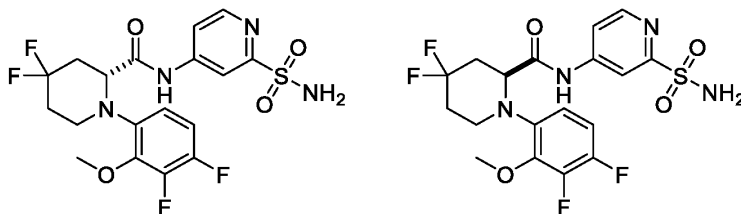
was neutralized with 1M hydrochloric acid, followed by extraction with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to give 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide



To a stirred solution of 1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxylic acid and 2 4-amino-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide in pyridine was added phosphoryl chloride at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 1 hour. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to give *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide.

Synthesis (S)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-N-(2-sulfamoylpyridin-4-yl)piperidine-2-carboxamide and (R)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-N-(2-sulfamoylpyridin-4-yl)piperidine-2-carboxamide



To a stirred solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoropiperidine-2-carboxamide in dichloromethane was added trifluoroacetic acid at 0-5 °C. The reaction mixture was stirred for 16 hours at room temperature. After reaction completion, water was added to the reaction mixture. The solution was neutralized with saturated aqueous solution of sodium bicarbonate then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by prep HPLC to obtain 4-[1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-2-piperidylcarbonylamino]-2-pyridinesulfonamide, which was further purified by chiral SFC to give 4-[(*S*)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-2-piperidylcarbonylamino]-2-pyridinesulfonamide and 4-[(*R*)-1-(3,4-difluoro-2-methoxyphenyl)-4,4-difluoro-2-piperidylcarbonylamino]-2-pyridinesulfonamide.

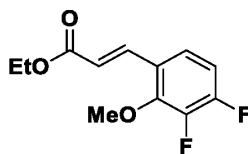
Peak-1: ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.70 (br s, 1H), 8.52 (d, *J* = 5.44, 1H), 8.16 (s, 1H), 7.65-7.63 (m, 1H), 7.41 (br s, 2H), 7.11-7.04 (m, 1H), 6.97-6.93 (m, 1H), 7.31 (br s, 2H), 4.45 (t, *J* = 5.8 Hz, 1H), 3.97 (s, 3H), 3.72-3.66 (m, 1H), 3.12-3.06 (m, 1H), 2.19-2.15 (m, 2H). MS (ESI): *m/z* 463.30 [*M* + *H*]⁺.

Peak-2 ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.70 (br s, 1H), 8.52 (d, *J* = 5.44, 1H), 8.16 (s, 1H), 7.65-7.63 (m, 1H), 7.41 (br s, 2H), 7.11-7.04 (m, 1H), 6.97-6.93 (m, 1H), 7.31 (br s, 2H), 4.45 (t, *J* = 5.8 Hz, 1H), 3.97 (s, 3H), 3.79-3.66 (m, 1H), 3.12-3.06 (m, 1H), 2.19-2.12 (m, 2H). MS (ESI): *m/z* 463.30 [*M* + *H*]⁺.

The following compounds were prepared using similar procedures as described above: 17, 18, 23, 59, 87, 88, 89, 163, 164, 165, 166, 168, 169, 170, 173, 174, 177, 178, 179, 180, 181, 182, 221, 272, 316, 333, 355, 356, 379, 392, 393, 418, 419, 430, 473, 485, 565, 587, 588, 599, 614

Compound 353 and Compound 354

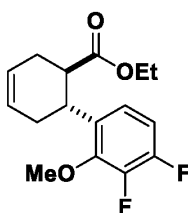
Synthesis of ethyl (E)-3-(3,4-difluoro-2-methoxyphenyl)acrylate



A mixture of 1-bromo-3,4-difluoro-2-methoxybenzene, ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate, potassium phosphate and [1,1-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) in dioxane and water was degassed and purged with nitrogen for 3 times,

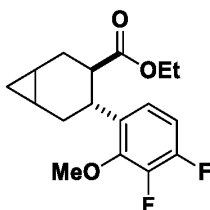
the reaction mixture was stirred at 80 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 0-10% ethyl acetate in hexane as an eluent to obtain ethyl (E)-3-(3,4-difluoro-2-methoxyphenyl)acrylate as a white solid.

Synthesis of rac-ethyl (1R,2R)-3',4'-difluoro-2'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate



A solution of toluene and ethyl (E)-3-(3,4-difluoro-2-methoxyphenyl)acrylate and buta-1,3-diene in 1.9 M hexane was pumped (4 mL/min) to flow reactor (HC, Coils reactor, 3.175 mm, 130 mL, 280 °C) with backpressure of 4.6 MPa. The residence time of flow reactor 1 was 30 min. The reaction mixture was collected with a bottle. After reaction completion, the reaction mixture was concentrated. The residue was purified by prep HPLC to obtain *rac*-ethyl (1R,2R)-3',4'-difluoro-2'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate as a colorless oil.

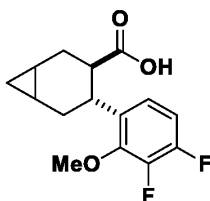
Synthesis of rac-ethyl (3R,4R)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylate



To a solution of *rac*-ethyl (1R,2R)-3',4'-difluoro-2'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate in 1,2-dichloroethane was dropwise added 1M diethylzinc at 0 °C under nitrogen atmosphere. Chloriodomethane was dropwise added. The reaction mixture was stirred at 0 °C for 30 minutes and warmed to room temperature for 16 hours. After reaction completion, water was added followed by extraction with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The

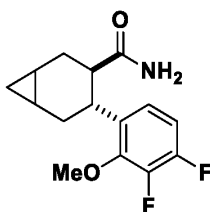
residue was purified by prep HPLC to obtain *rac*-ethyl (3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylate as a colorless oil.

Synthesis of rac-(3R,4R)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylic acid



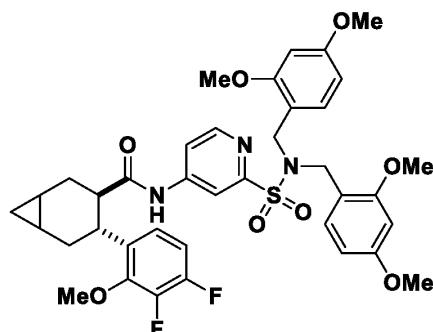
To a solution of *rac*-ethyl (3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylate in ethanol and tetrahydrofuran was added lithium hydroxide in water. The reaction mixture was heated at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated and the resulting aqueous solution was acidified with 1N hydrochloric acid followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtained *rac*-(3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylic acid as a light yellow oil.

Synthesis of rac-(3R,4R)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide



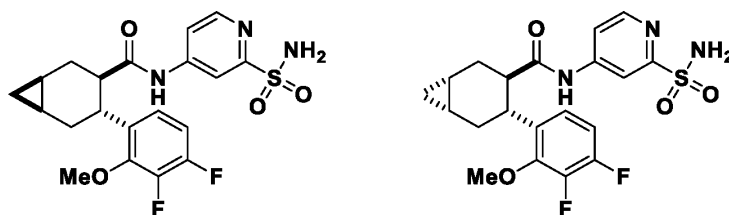
To a solution of *rac*-(3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxylic acid and ammonium chloride in dimethylformamide (3 mL) was added HATU and triethylamine. The mixture was stirred at 50 °C for 5 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 0-50% ethyl acetate in hexane as an eluent to obtain *rac*-(3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide as a white solid.

Synthesis of rac- (3R,4R)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide



To a solution of *rac*-(3*R*,4*R*)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide and 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide in dioxane was added BrettPhos Pd G3 and cesium carbonate. The mixture was stirred at 100 °C for 4 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, followed by extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography obtain *rac*-(3*R*,4*R*)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide.

Synthesis of rac-(1S,3R,4R,6R)-4-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)bicyclo[4.1.0]heptane-3-carboxamide and rac- (1R,3R,4R,6S)-4-(3,4-difluoro-2-methoxyphenyl)-N-(2-sulfamoylpyridin-4-yl)bicyclo[4.1.0]heptane-3-carboxamide



To a solution of *rac*-(3*R*,4*R*)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-4-(3,4-difluoro-2-methoxyphenyl)bicyclo[4.1.0]heptane-3-carboxamide in dichloromethane was added 2,2,2-trifluoroacetic acid. The reaction mixture was stirred at 40 °C for 1 hour. After reaction completion, the reaction mixture was purified by prep HPLC to afford *rac*-(1*S*,3*R*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-*N*-(2-sulfamoylpyridin-4-yl)bicyclo[4.1.0]heptane-3-carboxamide as a white solid and *rac*-(1*R*,3*R*,4*R*,6*S*)-4-(3,4-

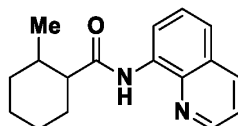
difluoro-2-methoxyphenyl)-*N*-(2-sulfamoylpyridin-4-yl)bicyclo[4.1.0]heptane-3-carboxamide as a white solid.

Compound 353: ^1H NMR (400 MHz, DMSO- d_6): δ 10.55 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 2.0, 5.6 Hz, 1H), 7.37 (br. s., 2H), 7.11 - 7.02 (m, 2H), 3.89 (d, J = 0.8 Hz, 3H), 3.03 - 2.92 (m, 1H), 2.83 - 2.71 (m, 1H), 2.49 - 2.41 (m, 1H), 2.01 - 1.93 (m, 1H), 1.80 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.14 - 1.00 (m, 2H), 0.77 - 0.65 (m, 1H), 0.27 - 0.18 (m, 1H). MS (ESI): m/z 438.1 $[\text{M} + \text{H}]^+$. Compound 354: ^1H NMR (400 MHz, DMSO- d_6): δ 10.57 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 2.0, 5.6 Hz, 1H), 7.36 (br. s., 2H), 7.07 - 7.00 (m, 1H), 6.98 - 6.91 (m, 1H), 3.92 (s, 3H), 3.12 - 3.02 (m, 1H), 2.74 - 2.65 (m, 1H), 2.28 - 2.15 (m, 2H), 2.06 - 1.97 (m, 1H), 1.40 - 1.29 (m, 1H), 1.13 - 0.99 (m, 2H), 0.77 - 0.65 (m, 1H), 0.24 - 0.14 (m, 1H). MS (ESI): m/z 438.1 $[\text{M} + \text{H}]^+$.

The following compounds were prepared using similar procedures as described above: 36, 71, 210, 258, 259, 260, 261, 262, 263, 293, 324, 325, 326, 327, 353, 354, 421, 422, 456, 458, 459, 504, 506, 507, 536, 537, 538, 539, 542, 543, 547, 548, 551, 552, 553, 625, 626, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665

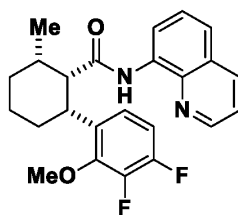
Compound 372

Synthesis of rac-2-methyl-N-(quinolin-8-yl)cyclohexanecarboxamide



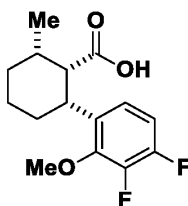
To a solution of *rac*-2-methylcyclohexanecarboxylic acid and quinolin-8-amine in dimethylformamide was added HATU and diisopropylethylamine. The mixture was stirred at room temperature for 5 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography to obtain *rac*-2-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide.

Synthesis of rac-(1S,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methyl-N-(quinolin-8-yl)cyclohexanecarboxamide



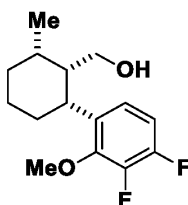
To a solution of *rac*-2-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide in tertbutyl alcohol was added diacetoxypalladium and silver carbonate. The reaction mixture was stirred at 80 °C for 12 hours. After reaction completion, the reaction mixture was cooled to room temperature, filtered, then concentrated. The residue was purified by column chromatography using 0-30% ethyl acetate in hexane as an eluent to obtain *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide.

Synthesis of rac-(1S,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid



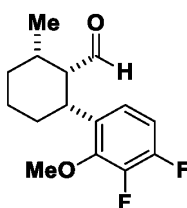
To a solution of *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide in methylbenzene and water was added trifluoromethanesulfonic acid. The reaction mixture was stirred at 100 °C for 5 hours. After reaction completion, the reaction mixture was concentrated to obtain a residue. The residue was purified by prep-HPLC to obtain *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid.

Synthesis of rac-((1S,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexyl)methanol



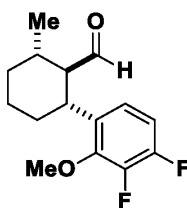
To a solution of *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid in tetrahydrofuran was added borane dimethyl sulfide complex at 0 °C. The reaction mixture was stirred at 70 °C for 3 hours. After reaction completion, the reaction mixture was added methanol (25 mL) dropwise at 0 °C then stirred at 80 °C for 3 hours. The reaction mixture was concentrated. The residue was purified by column chromatography to obtain *rac*-((1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexyl)methanol.

Synthesis of rac-(1S,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarbaldehyde



To a solution of methyl *rac*-((1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexyl)methanol in dichloromethane was added Dess-Martin at 0°C. The reaction mixture was warmed to room temperature and stirred for 1 hour. After reaction completion, a mixed solution of sodium sulfite and sodium bicarbonate was added. Then the mixture was extracted by dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtained *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarbaldehyde.

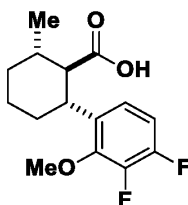
Synthesis of rac-(1R,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarbaldehyde



To a solution of *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarbaldehyde in methyl alcohol was added potassium hydroxide. The reaction mixture was stirred at room temperature for 0.5 hour. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain *rac*-

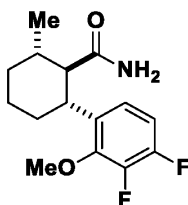
(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid as a yellow oil.

*Synthesis of rac-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid*



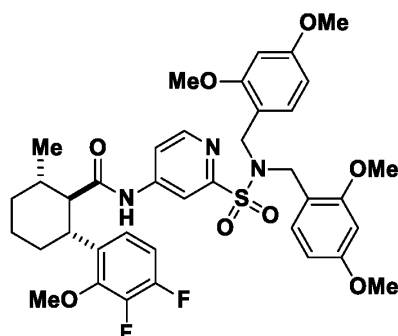
To a solution of *rac*-(1*S*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid in tert-butyl alcohol and water was added 2-methyl-2-butene and sodium dihydrogen phosphate and 80% sodium hypochlorite. The mixture was stirred at room temperature for 0.5 hour. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to obtain *rac*-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid.

*Synthesis of rac-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxamide*



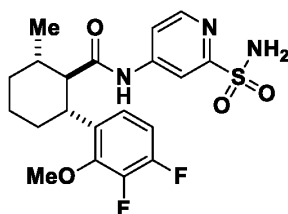
To a solution of *rac*-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxylic acid and ammonium chloride in dimethylformamide was added HATU and triethylamine. The mixture was stirred at 50 °C for 3 hours. After reaction completion, water was added followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 10-100% ethyl acetate in hexane as an eluent to obtain *rac*-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxamide.

Synthesis of rac-(1R,2R,6S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxamide



To a solution of *rac*-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methylcyclohexanecarboxamide and 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide in dioxane was added BrettPhos-Pd-G₃ and cesium carbonate. The reaction mixture was stirred at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was concentrated. The residue was purified by column chromatography to obtain *rac*-(1*R*,2*R*)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-3-methylcyclohexanecarboxamide.

Synthesis of rac-(1R,2R,6S)-2-(3,4-difluoro-2-methoxyphenyl)-6-methyl-N-(2-sulfamoylpyridin-4-yl)cyclohexanecarboxamide



To a solution of *rac*-(1*R*,2*R*)-*N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(3,4-difluoro-2-methoxyphenyl)-3-methylcyclohexanecarboxamide (70.0 mg, 94.6 μmol) in formic acid (10 mL). The reaction mixture was stirred at 50 °C for 2 hours. After reaction completion, the reaction mixture was purified by prep-HPLC to afford *rac*-(1*R*,2*R*,6*S*)-2-(3,4-difluoro-2-methoxyphenyl)-6-methyl-*N*-(2-sulfamoylpyridin-4-yl)cyclohexanecarboxamide as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.47 (br s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.02 (s, 1H), 7.67 - 7.59 (m, 1H), 7.37 (s, 2H), 7.23 - 7.00 (m, 2H), 3.84 (s, 3H), 3.29 - 3.23

(m, 1H), 2.48 - 2.42 (m, 1H), 1.85 - 1.64 (m, 4H), 1.56 - 1.40 (m, 1H), 1.38 - 1.25 (m, 1H), 1.21 - 1.08 (m, 1H), 0.95 - 0.87 (m, 3H). MS (ESI): m/z 440.1 $[M + H]^+$.

The following compounds were prepared using similar procedures as described above: 309, 310, 360, 361, 372, 466

Compound Characterization Data

Compound 1

^1H NMR (400 MHz, DMSO- d_6) δ 10.15 (s, 1H), 8.15 (s, 1H), 7.68-7.65 (m, 1H), 7.45-7.42 (m, 2H), 7.32-7.25 (m, 6H), 7.19-7.15 (m, 1H), 3.40-3.36 (m, 1H), 2.93-2.86 (m, 1H), 2.17-2.10 (m, 2H), 1.84-1.69 (m, 4H). MS (ESI) m/z 343.3 $[M - H]^-$

Compound 3

^1H NMR (400 MHz, DMSO- d_6) δ 9.85 (s, 1H), 7.88 (t, $J = 2.0$ Hz, 1H), 7.41-7.36 (m, 3H), 7.32 (br s, 2H), 7.24-7.22 (m, 2H), 7.18-7.14 (m, 2H), 7.08-7.04 (m, 1H), 3.43-3.37 (m, 1H), 3.22-3.17 (m, 1H), 2.17-2.01 (m, 5H), 1.92-1.75 (m, 1H). MS (ESI): m/z 345.20 $[M + H]^+$.

Compound 5

^1H NMR (400 MHz, DMSO- d_6) δ 10.12 (s, 1H), 8.16 (s, 1H), 7.69-7.66 (m, 1H), 7.45-7.43 (m, 2H), 7.31 (br s, 1H), 7.25 (d, $J = 7.6$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.88 (t, $J = 7.2$ Hz, 1H), 3.71 (s, 3H), 3.68-3.61 (m, 1H), 3.04-2.98 (m, 2H), 2.09-2.07 (m, 2H), 1.83-1.80 (m, 3H), 1.67-1.60 (m, 1H). MS (ESI): m/z 373.3 $[M - H]^-$

Compound 7

^1H NMR (400 MHz, DMSO- d_6) δ 9.63 (s, 1H), 7.88 (br s, 1H), 7.38-7.31 (m, 3H), 7.28 (br s, 2H), 7.16 (d, $J = 6.8$ Hz, 1H), 7.07-7.04 (m, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.75 (t, $J = 7.6$ Hz, 1H), 3.75 (s, 3H), 3.62-3.55 (m, 1H), 3.27-3.22 (m, 1H), 2.22-2.18 (m, 1H), 1.99-1.96 (m, 3H), 1.84-1.78 (m, 1H), 1.69-1.63 (m, 1H). MS (ESI): m/z 373.30 $[M - H]^-$

Compound 9

^1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.06 (s, 1H), 7.58-7.55 (br s, 1H), 7.42-7.37 (m, 2H), 7.28 (br s, 2H), 7.24-7.22 (m, 1H), 7.09-7.05 (m, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.82 (t, $J = 7.2$ Hz, 1H), 3.76 (s, 3H), 3.29-3.26 (m, 1H), 2.91-2.87 (m, 1H), 2.02-1.98 (m, 1H), 1.77-1.64 (m, 3H), 1.60-1.51 (m, 1H), 1.45-1.41 (m, 2H), 1.39-1.36 (m, 1H). MS (ESI): m/z 389.10 $[M+H]^+$

Compound 11

^1H NMR (400 MHz, DMSO- d_6) δ 9.72 (s, 1H), 8.06-8.05 (m, 1H), 7.49-7.46 (m, 1H), 7.41-7.35 (m, 2H), 7.30 (br s, 2H), 7.23-7.21 (m, 1H), 7.12-7.07 (m, 1H), 6.93-6.91 (m, 1H), 6.78-6.77 (m, 1H), 3.81 (s, 3H), 3.22-3.18 (m, 1H), 2.99-2.97 (m, 1H), 2.73-2.64 (m, 1H), 1.99-1.87 (m, 2H), 1.82-1.70 (m, 2H), 1.54-1.51 (m, 1H), 1.44-1.39 (m, 2H). MS (ESI): m/z 387.30 $[M - H]^-$

Compound 13

¹H NMR (400 MHz, DMSO-d₆): δ 10.12 (br s, 1H), 8.01 (s, 1H), 7.60-7.57 (m, 1H), 7.42-7.39 (m, 2H), 7.27 (br s, 2H), 7.10-7.07 (m, 2H), 3.89 (s, 3H), 3.22-3.20 (m, 1H), 2.85-2.77 (m, 1H), 2.03-2.01 (m, 1H), 1.85-1.71 (m, 3H), 1.60-1.51 (m, 1H), 1.46-1.28 (m, 3H). MS (ESI): *m/z* 425.20 [M + H]⁺

Compound 15

¹H NMR (400 MHz, DMSO-d₆): δ 9.83 (br s, 1H), 8.05-8.04 (m, 1H), 7.50-7.48 (m, 1H), 7.43-7.37 (m, 2H), 7.27 (br s, 2H), 7.07-7.01 (m, 2H), 3.95 (s, 3H), 3.17-3.13 (m, 1H), 2.90-2.87 (m, 1H), 2.67-2.56 (m, 1H), 1.97-1.94 (m, 1H), 1.90-1.83 (m, 1H), 1.82-1.68 (m, 2H), 1.53-1.42 (m, 3H). MS (ESI): *m/z* 425.20 [M + H]⁺

Compound 17

¹H NMR (400 MHz, DMSO-d₆): δ 9.96 (s, 1H), 8.19 (s, 1H), 7.81-7.79 (m, 1H), 7.46 (d, *J* = 5.2 Hz, 2H), 7.32 (br s, 2H), 6.86-6.80 (m, 2H), 6.74-6.69 (m, 2H), 4.44-4.41 (m, 1H), 3.57 (s, 3H), 3.55-3.50 (m, 1H), 3.25-3.21 (m, 1H), 1.96-1.86 (m, 1H), 1.48-1.24 (m, 3H). MS (ESI): *m/z* 376.25 [M + H]⁺

Compound 18

¹H NMR (400 MHz, DMSO-d₆): δ 9.96 (s, 1H), 8.20 (s, 1H), 7.83-7.76 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.36 (br s, 2H), 6.85-6.80 (m, 2H), 6.74-6.72 (m, 2H), 4.44-4.41 (m, 1H), 3.65 (s, 3H), 3.60-3.54 (m, 1H), 3.27-3.22 (m, 1H), 2.28-2.19 (m, 1H), 1.97-1.91 (m, 3H). MS (ESI): *m/z* 376.2 [M + H]⁺

Compound 19

¹H NMR (400 MHz, DMSO-d₆): δ 10.14 (br s, 1H), 8.06 (s, 1H), 7.56-7.54 (m, 1H), 7.43-7.38 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.28-3.25 (m, 1H), 2.88 (d, *J* = 8.8 Hz, 1H), 2.03-2.00 (m, 1H), 1.84-1.74 (m, 3H), 1.57-1.50 (m, 1H), 1.41-1.33 (m, 2H), 1.24-1.22 (m, 1H). MS (ESI): *m/z* 473.30 [M + H]⁺

Compound 21

¹H NMR (400 MHz, DMSO-d₆): δ 9.76 (br s, 1H), 8.07 (s, 1H), 7.43-7.38 (m, 3H), 7.31-7.29 (m, 3H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.19-3.15 (m, 1H), 2.98 (br s, 1H), 2.72-2.63 (m, 1H), 1.97-1.95 (m, 1H), 1.90-1.87 (m, 1H), 1.76-1.71 (m, 2H), 1.52-1.50 (m, 1H), 1.46-1.40 (m, 2H). MS (ESI): *m/z* 471.30 [M - H]⁻

Compound 23

¹H NMR (400 MHz, DMSO-d₆): δ 10.16 (br s, 1H), 8.15 (s, 1H), 7.60-7.59 (m, 1H), 7.45-7.42 (m, 2H), 7.31 (br s, 2H), 7.07-7.00 (m, 1H), 6.70-6.84 (m, 1H), 4.16-4.13 (m, 1H), 3.98 (s, 3H), 3.64-3.61 (m, 1H), 2.76-2.72 (m, 1H), 1.99-1.93 (m, 2H), 1.73-1.65 (m, 3H), 1.53 (br s, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺

Compound 24

¹H NMR (400 MHz, DMSO-d₆): 10.25 (br s, 1H), 7.99 (s, 1H), 7.63-7.60 (m, 1H), 7.45-7.39 (m, 2H), 7.31 (br s, 2H), 7.14-7.10 (m, 2H), 3.88 (s, 3H), 3.28-3.22 (m, 1H), 3.12-3.09 (m, 1H), 2.78-2.75 (m, 1H), 2.18-2.14 (m, 1H), 1.99-1.91 (m, 2H), 1.87-1.80 (m, 1H), 1.67-1.64 (m, 1H), 1.54-1.49 (m, 1H). MS (ESI): *m/z* 491.3 [M-H]⁺.

Compound 26

¹H NMR (400 MHz, DMSO-d₆): 10.24 (br s, 1H), 8.02 (s, 1H), 7.58-7.54 (m, 1H), 7.44-7.39 (m, 2H), 7.31 (br s, 2H), 7.27-7.24 (m, 1H), 7.13-7.07 (m, 1H), 4.03 (brs, 1H), 3.81 (s, 3H), 3.09-3.04 (m, 1H), 2.61-2.51 (m, 1H), 2.13-2.03 (m, 1H), 1.98-1.83 (m, 3H), 1.71-1.68 (m, 1H), 1.35-1.29 (m, 1H). MS (ESI): *m/z* 491.30 [M - H]⁺.

Compound 28

¹H NMR (400 MHz, DMSO-d₆): δ 10.04 (br s, 1H), 8.04 (s, 1H), 7.58-7.54 (m, 1H), 7.43-7.38 (m, 2H), 7.30 (br s, 2H), 7.11 (t, J = 8.0 Hz, 1H), 6.99-6.93 (m, 2H), 2.84-2.81 (m, 1H), 2.66 (dt, J = 11.6, 3.2 Hz, 1H), 2.11 (s, 3H), 1.97-1.95 (m, 1H), 1.87-1.76 (m, 3H), 1.57-1.47 (m, 1H), 1.46-1.33 (m, 3H). MS (ESI): *m/z* 389.20 [M - H]⁻.

Compound 30

¹H NMR (400 MHz, DMSO-d₆): δ 9.85 (br s, 1H), 8.05 (s, 1H), 7.54-7.51 (m, 1H), 7.44-7.38 (m, 2H), 7.28 (br s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.02-6.99 (m, 2H), 2.95 (br s, 1H), 2.91-2.87 (m, 1H), 2.58-2.57 (m, 1H), 2.12 (s, 3H), 1.96-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.80-1.71 (m, 2H), 1.62-1.61 (m, 1H), 1.60-1.50 (m, 1H), 1.40-1.38 (m, 1H). MS (ESI): *m/z* 391.20 [M + H]⁺.

Compound 32

¹H NMR (400 MHz, DMSO-d₆): δ 9.76 (br s, 1H), 8.07 (s, 1H), 7.43-7.38 (m, 3H), 7.31-7.29 (m, 3H), 6.92 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.19-3.15 (m, 1H), 2.98 (br s, 1H), 2.72-2.63 (m, 1H), 1.97-1.95 (m, 1H), 1.90-1.87 (m, 1H), 1.76-1.71 (m, 2H), 1.52-1.50 (m, 1H), 1.46-1.40 (m, 2H). MS (ESI): *m/z* 471.30 [M - H]⁻.

Compound 34

¹H NMR (400 MHz, DMSO-d₆): δ 9.82 (br s, 1H), 7.97 (s, 1H), 7.52-7.47 (m, 1H), 7.41 (m, 2H), 7.31-7.28 (m, 2H), 7.08-7.01 (m, 1H), 6.92-6.82 (m, 2H), 3.77 (s, 3H), 3.22-3.11 (m, 1H), 2.68-2.61 (m, 1H), 1.99-1.90 (m, 1H), 1.89-1.72 (m, 2H), 1.68-1.38 (m, 4H), 0.58 (d, J = 6.5 Hz, 3H). MS (ESI): *m/z* 403.40 [M + H]⁺.

Compound 36

¹H NMR (400 MHz, DMSO-d₆): δ 10.30 (br s, 1H), 8.14-8.13 (m, 1H), 7.78-7.74 (m, 1H), 7.51-7.46 (m, 1H), 7.34 (br s, 2H), 7.27-7.23 (m, 2H), 6.99-6.93 (m, 2H), 4.79 (t, J = 4.8 Hz, 1H), 4.70 (d, J = 4.3 Hz, 1H), 4.06 (t, J = 5.3 Hz, 1H), 3.10 (d, J = 6.2 Hz, 1H), 1.72-1.61 (m, 2H), 1.40-1.32 (m, 2H). MS (ESI): *m/z* 403.30 [M + H]⁺.

Compound 37

¹H NMR (400 MHz, DMSO-d₆): δ 10.54 (s, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 8.03 (br s, 1H), 7.61-7.60 (m, 2H), 7.14-7.07 (m, 2H), 3.90 (s, 3H), 3.41-3.35 (m, 1H), 3.19-3.14 (m, 1H), 2.44-2.41 (m, 1H), 2.23-2.03 (m, 3H), 1.84-1.81 (m, 1H), 1.62-1.60 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺.

Compound 38

¹H NMR (400 MHz, DMSO-d₆): δ 10.40 (s, 1H), 8.39 (d, *J* = 5.5 Hz, 1H), 8.12 (d, *J* = 1.8 Hz, 1H), 8.05 (br s, 1H), 7.61 (br s, 1H), 7.56-7.54 (m, 1H), 7.24-7.21 (m, 1H), 7.10-7.0, 3.92 (s, 3H), 3.45-3.43 (m, 1H), 3.28-3.27 (m, 1H), 2.70-2.63 (m, 1H), 2.42-2.39 (m, 1H), 2.14-2.01 (m, 2H), 1.84-1.82 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺.

Compound 39

¹H NMR (400 MHz, DMSO-d₆): 10.67 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.39 (br s, 2H), 7.15-7.08 (m, 1H), 7.06-7.02 (m, 1H), 3.90 (s, 3H), 3.29-3.23 (m, 1H), 3.14-3.09 (m, 1H), 2.80-2.77 (m, 1H), 2.22-2.18 (m, 1H), 2.01-1.92 (m, 2H), 1.90-1.81 (m, 1H), 1.68-1.65 (m, 1H), 1.58-1.52 (m, 1H). MS (ESI): *m/z* 494.10 [M + H]⁺.

Compound 41

¹H NMR (400 MHz, DMSO-d₆): 10.69 (s, 1H), 8.47 (d, *J* = 5.4 Hz, 1H), 8.06 (d, *J* = 1.4 Hz, 1H), 7.58 (dd, *J* = 5.4, 1.7 Hz, 1H), 7.38 (br s, 2H), 7.25-7.21 (m, 1H), 7.14-7.08 (m, 1H), 4.05-4.02 (m, 1H), 3.80 (s, 3H), 3.14-3.08 (m, 1H), 2.61-2.60 (m, 1H), 2.10-1.69 (m, 4H), 1.72-1.69 (m, 1H), 1.37-1.28 (m, 1H). MS (ESI): *m/z* 494.30 [M + H]⁺.

Compound 43

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (br s, 1H), 8.48 (d, *J* = 5.4 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.57-7.08 (m, 5H), 3.91 (s, 3H), 3.41-3.35 (m, 1H), 3.19-3.14 (m, 1H), 2.44 (br s, 1H), 2.23-2.01 (m, 3H), 1.84-1.81 (m, 1H), 1.62-1.60 (m, 1H). MS (ESI): *m/z* 462.30 [M + H]⁺.

Compound 45

¹H NMR (400 MHz, DMSO-d₆): δ 10.53 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 7.37 (br s, 2H), 7.24-7.21 (m, 1H), 7.11-7.04 (m, 1H), 3.91 (s, 3H), 3.44-3.42 (m, 1H), 3.28-3.27 (m, 1H), 2.71-2.63 (m, 1H), 2.44-2.42 (m, 2H), 2.14-2.03 (m, 2H), 1.84-1.81 (m, 1H). MS (ESI): *m/z* 462.20 [M + H]⁺.

Compound 47

¹H NMR (400 MHz, DMSO-d₆): δ 10.72 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.57 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.38 (br s, 2H), 7.20-7.08 (m, 2H), 4.21-4.18 (m, 1H), 3.97-3.92 (m, 4H), 3.54-3.51 (m, 2H), 3.50-3.42 (m, 1H), 3.18-3.11 (m, 1H), 1.69-1.56 (m, 2H). MS (ESI): *m/z* 428.30 [M + H]⁺.

Compound 53

MS (ESI): m/z 440.5 $[M + H]^+$

Compound 54

1H NMR (400 MHz, DMSO- d_6) δ 10.24 (s, 1H), 8.02 (s, 1H), 7.59 – 7.56 (m, 1H), 7.45 – 7.39 (m, 2H), 7.32 (s, 2H), 7.12 – 7.07 (s, 2H), 3.90 (s, 3H), 3.21 – 3.07 (m, 3H), 2.84 (d, J = 11.20 Hz, 1H), 2.23 (s, 3H), 2.11 – 2.01 (m, 2H), 1.70 – 1.66 (dd, J = 12.80 & 3.20 Hz, 1H), 1.58 – 1.48 (m, 1H). MS (ESI): m/z 440.30 $[M + H]^+$

Compound 55

MS (ESI): m/z 440.3 $[M + H]^+$

Compound 59

MS (ESI): m/z 495.2 $[M + H]^+$

Compound 63

1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), (s, 1H), 8.00 (s, 1H), 7.59 – 7.56 (m, 1H), 7.45 – 7.40 (m, 2H), 7.31 (s, 2H), 7.14 – 7.09 (m, 2H), 3.90 (s, 3H), 3.13 – 3.11 (m, 1H), 3.00 (d, J = 9.6 Hz, 1H), 2.63 – 2.53 (m, 3H), 1.69 – 1.63 (m, 1H), 1.55 – 1.53 (m, 1H). MS (ESI): m/z 506.40 $[M + H]^+$

Compound 64

MS (ESI): m/z 507.13 $[M + H]^+$

Compound 65

MS (ESI): m/z 393.3 $[M + H]^+$

Compound 66

MS (ESI): m/z 427.3 $[M + H]^+$

Compound 70

1H NMR (400 MHz, DMSO- d_6): δ 10.51 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 2.0, 5.6 Hz, 1H), 7.33 (br s, 2H), 7.12 - 7.04 (m, 2H), 3.93 - 3.88 (m, 3H), 3.30 - 3.21 (m, 1H), 3.07 - 2.97 (m, 1H), 2.08 - 1.97 (m, 1H), 1.95 - 1.85 (m, 1H), 1.78 - 1.62 (m, 1H), 1.56 - 1.39 (m, 1H), 1.25 - 1.20 (m, 1H), 1.03 - 0.87 (m, 1H), 0.43 - 0.30 (m, 4H). MS (ESI): m/z 452.1 $[M + H]^+$

Compound 71

1H NMR (400 MHz, DMSO- d_6): δ 10.69 (br. s., 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.68 - 7.56 (m, 1H), 7.36 (br. s., 2H), 7.23 - 7.02 (m, 2H), 3.96 - 3.87 (m, 3H), 3.61 - 3.50 (m, 1H), 3.03 - 2.91 (m, 1H), 2.25 - 2.15 (m, 2H), 2.14 - 1.99 (m, 3H), 1.84 - 1.69 (m, 1H). MS (ESI): m/z 462.1 $[M + H]^+$

Compound 81

¹H NMR (400 MHz, DMSO-d₆): δ 10.01 (s, 1H), 7.99 (s, 1H), 7.58-7.54 (m, 1H), 7.43-7.48 (m, 2H), 7.30 (br s, 2H), 7.07-7.01 (m, 2H), 3.89 (s, 3H), 3.47-3.41 (m, 1H), 2.95-2.89 (m, 1H), 1.96-1.90 (m, 1H), 1.82-1.72 (m, 3H), 1.70-1.65 (m, 4H), 1.59-1.54 (m, 2H). MS (ESI): *m/z* 439.3 [M + H]⁺.

Compound 83

¹H NMR (400 MHz, DMSO-d₆): δ 9.76 (s, 1H), 7.94 (s, 1H), 7.47-7.36 (m, 3H), 7.19 (br s, 2H), 7.05-6.97 (m, 2H), 3.92 (s, 3H), 3.47-3.43 (m, 1H), 2.92-2.87 (m, 1H), 2.45-2.39 (m, 1H), 2.03-1.98 (m, 1H), 1.91-1.84 (m, 4H), 1.70-1.67 (m, 1H), 1.51-1.43 (m, 3H). MS (ESI): *m/z* 437.2 [M-H]⁻.

Compound 87

¹H NMR (400 MHz, DMSO-d₆): δ 10.16 (br s, 1H), 8.15 (s, 1H), 7.60-7.59 (m, 1H), 7.45-7.42 (m, 2H), 7.31 (br s, 2H), 7.07-7.00 (m, 1H), 6.70-6.84 (m, 1H), 4.16-4.13 (m, 1H), 3.98 (s, 3H), 3.64-3.61 (m, 1H), 2.76-2.72 (m, 1H), 1.99-1.93 (m, 2H), 1.73-1.65 (m, 3H), 1.53 (br s, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺.

Compound 88

¹H NMR (400 MHz, DMSO-d₆): δ 9.93 (br s, 1H), 8.13 (s, 1H), 7.60-7.56 (m, 1H), 7.45-7.40 (m, 2H), 7.31 (br s, 2H), 7.12-7.11 (m, 1H), 6.97-6.92 (m, 2H), 6.87-6.82 (m, 1H), 4.14 (t, J = 5.4 Hz, 1H), 3.82 (s, 3H), 3.57-3.54 (m, 1H), 2.80-2.76 (m, 1H), 1.92-1.90 (m, 2H), 1.69-1.61 (m, 3H), 1.57-1.54 (m, 1H). MS (ESI): *m/z* 390.30 [M + H]⁺.

Compound 89

¹H NMR (400 MHz, DMSO-d₆): δ 10.17 (br s, 1H), 8.11 (s, 1H), 7.63-7.60 (m, 1H), 7.48-7.43 (m, 2H), 7.33 (br s, 2H), 7.15-7.13 (m, 1H), 7.00-6.95 (m, 2H), 6.87-6.83 (m, 1H), 4.39 (t, J = 5.7 Hz, 1H), 3.82 (s, 3H), 3.68-3.64 (m, 1H), 3.80-3.04 (m, 1H), 2.49-2.33 (m, 2H), 2.14-2.07 (m, 3H). MS (ESI): *m/z* 426.30 [M + H]⁺.

Compound 117

¹H NMR (400 MHz, DMSO-d₆): δ 12.36 (br s, 1H), 7.95 (br m, 2H), 7.63 (d, J = 8.2 Hz, 1H), 7.39 (br s, 1H), 7.16 (br s, 1H), 7.10 (m, 1H), 7.02-6.96 (m, 1H), 3.79 (s, 3H), 3.60 (br m, 2H), 2.49-2.41 (m, 2H), 2.21-2.06 (m, 2H), 1.90-1.87 (m, 1H), 1.78 (br m, 1H). MS (ESI): *m/z* 422.40 [M + H]⁺.

Compound 138

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H), 9.02 (s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.13-7.03 (m, 2H), 6.11 (s, 1H), 3.80-3.60 (m, 4H), 3.28-3.20 (m, 1H), 2.49-2.40 (m, 2H), 2.21-2.06 (m, 2H), 1.91-1.88 (m, 1H), 1.77-1.73 (m, 1H). MS (ESI): *m/z* 407.40 [M + H]⁺.

Compound 139

¹H NMR (400 MHz, DMSO-d₆): δ 12.02 (s, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 5.6 Hz, 1H), 7.20 - 6.98 (m, 2H), 6.24 (s, 1H), 3.82 (s, 3H), 3.71 - 3.53 (m, 1H), 3.31 - 3.24 (m, 1H), 2.48 - 2.35 (m, 2H), 2.23 - 2.02 (m, 2H), 1.95 - 1.84 (m, 1H), 1.82 - 1.61 (m, 1H). MS (ESI): *m/z* 432.2 [M + H]⁺.

Compound 140

¹H NMR (400 MHz, DMSO-d₆): δ 11.59 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 7.39 (br s, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 7.19-7.14 (m, 2H), 7.09-7.04 (m, 1H), 6.08 (s, 1H), 3.83 (s, 3H), 3.60 (br s, 1H), 3.27-3.22 (m, 1H), 2.42-2.38 (m, 2H), 2.19-2.07 (m, 2H), 1.92-1.88 (m, 1H), 1.75-1.60 (m, 1H). MS (ESI): *m/z* 450.4 [M + H]⁺.

Compound 141

¹H NMR (400 MHz, DMSO-d₆): δ 12.20 (s, 1H), 8.62 - 8.46 (m, 1H), 7.78 - 7.50 (m, 3H), 7.17 - 7.14 (m, 1H), 7.09 - 7.02 (m, 1H), 6.34 (s, 1H), 3.84 (s, 3H), 3.72 - 3.53 (m, 1H), 3.39 - 3.25 (m, 1H), 2.47 - 2.36 (m, 2H), 2.25 - 2.04 (m, 2H), 1.96 - 1.85 (m, 1H), 1.81 - 1.59 (m, 1H). MS (ESI): *m/z* 486.0 [M + H]⁺.

Compound 148

¹H NMR (400 MHz, DMSO-d₆): δ 13.39 (br s, 1H), 11.97 (br s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.26 - 7.10 (m, 1H), 7.07 - 6.95 (m, 1H), 6.70 - 6.61 (m, 1H), 6.57 (d, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 3.60 - 3.53 (m, 2H), 2.45 - 2.35 (m, 1H), 2.30 - 2.23 (m, 1H), 2.20 - 2.08 (m, 2H), 1.89 - 1.62 (m, 2H). MS (ESI): *m/z* 423.3 [M + H]⁺.

Compound 153

¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.47 (dd, *J* = 5.2, 0.4 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.38 (br s, 2H), 7.22-7.15 (m, 1H), 7.09-7.06 (m, 1H), 3.28-3.24 (m, 1H), 3.16-3.14 (m, 1H), 2.45-2.41 (m, 1H), 2.29-2.28 (m, 3H), 2.23-2.14 (m, 1H), 2.08-2.07 (m, 2H), 1.86-1.82 (m, 1H), 1.60-1.54 (m, 1H). MS (ESI): *m/z* 446.30 [M + H]⁺.

Compound 154

¹H NMR (400 MHz, DMSO-d₆): δ 10.52 (s, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.02 (br s, 1H), 7.61-7.55 (m, 2H), 7.14-7.07 (m, 2H), 3.91-3.90 (m, 3H), 3.41-3.34 (m, 1H), 3.19-3.13 (m, 1H), 2.39-2.38 (m, 1H), 2.23-2.01 (m, 3H), 1.84-1.76 (m, 1H), 1.68-1.52 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺.

Compound 155

¹H NMR (400 MHz, DMSO-d₆): δ 10.77 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.58 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.47-7.39 (m, 3H), 7.28-7.25 (m, 1H), 3.54-3.49 (m, 1H), 3.28-3.19 (m, 1H), 2.27-2.12 (m, 3H), 1.92-1.88 (m, 1H), 1.54 (br m, 1H). MS (ESI): *m/z* 466.3 [M + H]⁺.

Compound 156

¹H NMR (400 MHz, DMSO-d₆): δ 11.67-11.65 (m, 1H), 9.02 (s, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 6.73-6.58 (m, 2H), 5.60-5.98 (m, 1H), 3.80-3.51 (m, 5H), 2.40-2.30 (m, 2H), 2.29-2.01 (m, 3H), 1.90-1.78 (m, 1H). MS (ESI): *m/z* 407.4 [M + H]⁺.

Compound 164

¹H NMR (400 MHz, DMSO-d₆): δ 8.43 (d, J = 5.3 Hz, 1H), δ 8.01 (d, J = 1.5 Hz, 1H), 7.53-7.52 (m, 1H), 7.19-7.12 (m, 1H), 7.07-7.04 (m, 1H), 4.09-4.07 (m, 1H), 3.25-3.23 (m, 1H), 2.78-2.73 (m, 1H), 2.30-2.29 (m, 3H), 2.23-2.17 (m, 2H). Compound 165

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (br s, 1H), 8.52 (d, J = 5.4 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 5.5, 2.0 Hz, 1H), 7.43-7.37 (3H), 7.24-7.20 (m, 1H), 4.37 (t, J = 6.1 Hz, 1H), 3.69-3.66 (m, 1H), 3.02-2.96 (m, 1H), 2.57-2.56 (m, 2H), 2.20-2.15 (m, 2H). MS (ESI): *m/z* 467.30 [M + H]⁺

Compound 166

¹H NMR (400 MHz, DMSO-d₆): δ 10.73 (br s, 1H), 8.52 (d, J = 5.4 Hz, 1H), 8.08 (br s, 1H), 7.79-7.71 (m, 1H), 7.59 (dd, J = 5.4, 2.0 Hz, 1H), 7.42 (br s, 3H), 4.21-4.18 (m, 1H), 3.21-3.07 (m, 1H), 2.90 (br s, 1H), 2.59-2.57 (m, 2H), 2.19-2.02 (m, 2H). MS (ESI): *m/z* 501.30 [M + H]⁺

Compound 168

¹H NMR (400 MHz, DMSO-d₆): δ 10.75 (br s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 7.71 (dd, J = 5.5, 2.0 Hz, 1H), 7.41 (brs, 2H), 7.10 (t, J = 8.30 Hz, 1H), 6.92-6.90 (m, 1H), 6.89-6.87 (m, 2H), 4.74-4.72 (m, 1H), 3.79-3.72 (m, 1H), 3.66-3.63 (m, 1H), 2.72-2.61 (m, 1H), 2.59 (br s, 1H), 2.20-2.13 (m, 2H). MS (ESI): *m/z* 477.3 [M + H]⁺

Compound 169

¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (br s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 7.69 (dd, J = 5.5, 2.0 Hz, 1H), 7.39 (br s, 2H), 6.69 (t, J = 8.2 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.44 (dd, J = 7.7, 0.8 Hz, 1H), 4.68 (t, J = 5.1 Hz, 1H), 3.78-3.68 (m, 1H), 3.47-3.44 (m, 1H), 2.15-2.07 (m, 2H), 1.65 (s, 3H), 1.53 (s, 3H), 1.26-1.23 (m, 2H). MS (ESI): *m/z* 469.10 [M + H]⁺

Compound 170

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (br s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.19 (d, J = 1.72 Hz, 1H), 7.72-7.70 (dd, J = 5.4, 2.0 Hz, 1H), 6.75 (t, J = 8.3 Hz, 1H), 6.59-6.53 (m, 2H), 5.95 (dd, J = 7.5, 1.0 Hz, 2H), 4.70 (t, J = 4.9 Hz, 1H), 3.73-3.67 (m, 1H), 3.52-3.49 (m, 1H), 2.63-2.58 (m, 1H), 2.44-2.39 (m, 1H), 2.15-2.03 (m, 2H). MS (ESI): *m/z* 441.30 [M + H]⁺.

Compound 173

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.11 (d, J = 5.6 Hz, 1H), 7.60 (dd, J = 5.6, 2.0 Hz, 1H), 7.43-7.35 (m, 4H), 7.28-7.24 (m, 1H), 7.08-7.04 (m, 1H),

4.38 (t, J = 6.0 Hz, 1H), 3.71-3.66 (m, 1H), 2.99-2.94 (m, 1H), 2.46-2.45 (m, 2H, merged with the solvent signal), 2.24-2.15 (m, 2H). MS (ESI): m/z 431.20 [M + H]⁺.

Compound 174

¹H NMR (400 MHz, DMSO-d₆): δ 10.67 (br s, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 5.4, 2.0 Hz, 1H), 7.40 (br s, 2H), 7.36-7.20 (m, 3H), 4.40 (t, J = 6.1 Hz, 1H), 3.75-3.70 (m, 1H), 3.30-2.98 (m, 1H), 2.56-2.54 (m, 1H), 2.20-2.16 (m, 2H). MS (ESI): m/z 465.00 [M + H]⁺.

Compound 177

¹H NMR (400 MHz, DMSO-d₆): δ 10.75 (br s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 7.72 (dd, J = 7.7, 1.6 Hz, 1H), 7.67 (dd, J = 5.5, 2.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.41 (br s, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.19-7.13 (m, 1H), 4.65 (t, J = 5.3 Hz, 1H), 3.39-3.37 (m, 1H), 2.71-2.62 (m, 1H), 2.59-2.55 (m, 1H), 2.26-2.20 (m, 2H), 2.18-2.15 (m, 2H). MS (ESI): m/z 422.30 [M + H]⁺.

Compound 178

¹H NMR (400 MHz, DMSO-d₆): δ 10.56 (br s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.02 (s, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.35 (br s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 6.0 Hz, 1H), 7.04-7.01 (m, 1H), 4.09-4.06 (m, 1H), 3.14-3.12 (m, 1H), 2.87-2.80 (m, 2H), 2.77-2.71 (m, 2H), 2.27 (br s, 1H), 2.19-2.11 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 425.15 [M + H]⁺.

Compound 179

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (br s, 1H), 8.48 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.73-7.71 (m, 1H), 7.68-7.61 (m, 2H), 7.60-7.55 (m, 1H), 7.41 (br s, 2H), 7.38-7.31 (m, 1H), 4.28-4.17 (m, 1H), 3.39-3.36 (m, 1H), 2.86-2.79 (m, 1H), 2.53-2.51 (m, 1H), 2.44-2.35 (m, 1H), 2.18-2.08 (m, 2H). MS (ESI): m/z 465.30 [M + H]⁺.

Compound 180

¹H-NMR (400 MHz, DMSO-d₆): δ 10.65 (br s, 1H), 8.54 (d, J = 5.4 Hz, 1H), 8.21 (d, J = 1.8 Hz, 1H), 7.76 (dd, J = 5.5, 2.0 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.40 (br s, 2H), 7.12 (d, J = 8.8 Hz, 2H), 5.01-4.99 (m, 1H), 3.98-3.95 (m, 1H), 3.59-3.52 (m, 1H), 2.83 (br m, 1H), 2.56-2.52 (m, 1H), 2.11-2.03 (br m, 2H). MS (ESI): m/z 465.30 [M + H]⁺.

Compound 181

¹H NMR (400 MHz, DMSO-d₆): δ 10.63 (br s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.74-7.70 (m, 1H), 7.59-7.49 (m, 3H), 7.41 (br s, 2H), 4.18-4.15 (m, 1H), 3.37 (br s, 1H), 2.87-2.80 (m, 1H), 2.48-2.32 (m, 2H), 2.34-2.12 (m, 2H). MS (ESI): m/z 483.30 [M + H]⁺.

Compound 182

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.62 (br s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.11 (d, *J* = 1.7 Hz, 1H), 7.60 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.46-7.39 (m, 4H), 7.15 (dt, *J* = 8.4, 2.96 Hz, 1H), 4.32 (t, *J* = 6.1 Hz, 1H), 3.64-3.61 (m, 1H), 2.96-2.90 (m, 1H), 2.16-2.07 (m, 2H). MS (ESI): *m/z* 449.30 [M + H]⁺.

Compound 183

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.94 (br s, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.40 (br s, 2H), 7.12 - 6.81 (m, 2H), 3.87 - 3.66 (m, 4H), 2.92 - 2.73 (m, 1H), 2.34 - 2.02 (m, 4H), 1.79 - 1.54 (m, 1H), 1.25 - 1.11 (m, 3H). MS (ESI): *m/z* 476.0 [M + H]⁺.

Compound 184

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.62 (br s, 1H), 8.42 (d, *J* = 5.8 Hz, 1H), 7.44-7.33 (m, 4H), 7.20 (br s, 1H), 6.07 (s, 1H), 3.76-3.71 (m, 1H), 3.36 (br m, 1H), 2.49-2.42 (m, 2H), 2.22-2.01 (m, 2H), 1.98-1.91 (m, 1H), 1.69-1.60 (m, 1H). Compound 185

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.61 (br s, 1H), 8.41 (d, *J* = 5.7 Hz, 1H), 7.54-7.751- (m, 1H), 7.41 (br s, 1H), 7.34 (dd, *J* = 5.8 Hz, 1H), 7.28 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.20 (br s, 1H), 7.17-7.13 (m, 1H), 6.05 (s, 1H), 3.74-3.68 (m, 1H), 3.33-3.17 (m, 1H), 2.67-2.55 (m, 1H), 2.43-2.37 (m, 1H), 2.30-2.02 (m, 2H), 2.00-1.90 (m, 1H), 1.71-1.59 (m, 1H). MS (ESI): *m/z* 436.30 [M + H]⁺.

Compound 186

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.70 (s, 1H), 8.39 (d, *J* = 4.0 Hz, 1H), 7.38-7.34 (m, 2H), 7.17-7.11 (m, 3H), 6.11 (s, 1H), 3.54-3.48 (m, 1H), 3.26-3.25 (m, 1H), 2.42-2.39 (m, 1H), 2.22-2.09 (m, 6H), 1.93-1.90 (m, 1H), 1.59-1.56 (m, 1H). MS (ESI): *m/z* 434.05 [M + H]⁺.

Compound 187

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (br s, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.39-7.29 (m, 3H), 7.17 (s, 1H), 6.91-6.85 (m, 2H), 6.11 (s, 1H), 3.47-3.42 (m, 1H), 3.32-3.28 (m, 1H), 2.41-2.38 (m, 2H), 2.28 (s, 3H), 2.19-2.05 (m, 2H), 1.92-1.88 (m, 1H), 1.59-1.56 (m, 1H). MS (ESI): *m/z* 416.20 [M + H]⁺.

Compound 188

¹H NMR (400 MHz, CD₃OD): δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.18 - 6.96 (m, 1H), 6.94 - 6.77 (m, 1H), 6.23 (s, 1H), 3.90 (s, 3H), 3.78 - 3.58 (m, 1H), 3.27 - 3.22 (m, 1H), 2.56 - 2.43 (m, 1H), 2.41 - 2.19 (m, 2H), 1.98 - 1.86 (m, 1H), 1.82 - 1.54 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H). MS (ESI): *m/z* 464.1 [M + H]⁺.

Compound 189

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.62 (br. s., 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.40 (s, 1H), 7.32 (d, *J* = 5.6 Hz, 1H), 7.20 (s, 1H), 7.16 - 7.10 (m, 2H), 6.15 (s, 1H), 3.61 - 3.50 (m, 1H),

3.29 - 3.22 (m, 1H), 2.48 - 2.31 (m, 3H), 2.23 (d, $J = 2.0$ Hz, 3H), 1.93 - 1.81 (m, 1H), 1.43 - 1.28 (m, 1H), 1.02 (d, $J = 2.0$ Hz, 3H) MS (ESI): m/z 448.2 $[M + H]^+$

Compound 190

^1H NMR (400 MHz, DMSO- d_6): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 1H), 7.32 - 7.24 (m, 1H), 7.24 - 7.10 (m, 1H), 6.22 (s, 1H), 3.90 - 3.72 (m, 1H), 3.49 - 3.33 (m, 1H), 2.57 - 2.47 (m, 1H), 2.47 - 2.28 (m, 1H), 2.17 - 2.03 (m, 2H), 1.96 - 1.89 (m, 1H), 1.57 - 1.47 (m, 1H), 1.38 - 1.32 (m, 1H), 1.00 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 482.3 $[M + H]^+$

Compound 191

^1H NMR (400 MHz, DMSO- d_6): δ 11.50 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.58 - 7.29 (m, 2H), 7.26 - 6.83 (m, 3H), 5.91 (s, 1H), 3.80 (s, 3H), 3.53 - 3.45 (m, 1H), 3.02 - 2.83 (m, 1H), 1.99 (m, 1H), 1.86 (m, 1H), 1.77 (m, 3H), 1.22 - 1.08 (m, 2H), 0.95 (d, $J = 6.0$ Hz, 3H). MS (ESI): m/z 428.1 $[M + H]^+$

Compound 192

^1H NMR (400 MHz, DMSO- d_6): δ 8.52 - 8.40 (m, 1H), 7.54 - 7.43 (m, 1H), 7.30 - 7.23 (m, 1H), 7.21 - 7.11 (m, 1H), 6.14 - 6.03 (m, 1H), 3.72 - 3.60 (m, 1H), 3.02 - 2.91 (m, 1H), 2.18 - 2.10 (m, 1H), 2.01 - 1.85 (m, 3H), 1.81 - 1.75 (m, 1H), 1.29 - 1.21 (m, 2H), 1.07 - 0.98 (m, 3H) MS (ESI): m/z 432.1 $[M + H]^+$

Compound 193

^1H NMR (400 MHz, DMSO- d_6): δ 11.52 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.40 (d, $J = 5.6$ Hz, 2H), 7.26 - 7.04 (m, 3H), 5.94 (s, 1H), 3.35 - 3.27 (m, 1H), 3.01 - 2.89 (m, 1H), 2.20 (s, 3H), 2.04 - 1.92 (m, 1H), 1.90 - 1.59 (m, 4H), 1.25 - 1.00 (m, 2H), 0.92 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 412.2 $[M + H]^+$

Compound 194

^1H NMR (400 MHz, DMSO- d_6) δ 11.42 (s, 1H), 8.40 (d, $J = 5.6$ Hz, 1H), 7.41 (d, $J = 5.6$ Hz, 1H), 7.37 (br s, 1H), 7.22 - 7.10 (m, 2H), 7.08 - 6.98 (m, 1H), 5.93 (s, 1H), 3.82 (s, 3H), 3.67 - 3.52 (m, 1H), 2.96 - 2.76 (m, 1H), 1.97 - 1.80 (m, 2H), 1.61 - 1.52 (m, 1H), 1.50 - 1.37 (m, 3H), 1.17 (s, 3H), 0.97 (s, 3H). MS (ESI): m/z 442.2 $[M + H]^+$

Compound 195

^1H NMR (400 MHz, CD₃OD): δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.54 - 7.44 (m, 1H), 7.30 - 7.12 (m, 1H), 6.65 - 6.45 (m, 2H), 6.17 (s, 1H), 3.92 - 3.62 (m, 4H), 3.27 - 3.13 (m, 1H), 2.47 - 2.18 (m, 3H), 1.92 - 1.55 (m, 2H), 1.11 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 446.2 $[M + H]^+$

Compound 196

^1H NMR (400 MHz, CD₃OD): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.31 - 7.24 (m, 1H), 7.23 - 7.15 (m, 1H), 6.20 (s, 1H), 3.91 - 3.76 (m, 1H), 3.38 - 3.32 (m, 1H), 2.60 - 2.23 (m, 3H), 2.05 - 1.92 (m, 1H), 1.69 - 1.55 (m, 1H), 1.16 - 1.07 (m, 3H). MS (ESI): m/z 468.4 $[M + H]^+$

Compound 197

¹H NMR (400 MHz, DMSO-d₆): δ 8.47 (d, *J* = 5.6 Hz, 1H), 7.51 - 7.40 (m, 2H), 7.10 - 6.95 (m, 2H), 6.21 (s, 1H), 3.91 - 3.78 (m, 1H), 3.38 - 3.32 (m, 1H), 2.59 - 2.24 (m, 3H), 2.02 - 1.92 (m, 1H), 1.70 - 1.56 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H) MS (ESI): *m/z* 450.1 [M + H]⁺

Compound 198

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.60 (br. s., 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.34 - 7.32 (m, 1H), 7.32 - 7.16 (m, 2H), 6.96 - 6.83 (m, 2H), 6.13 (s, 1H), 3.60 - 3.44 (m, 1H), 3.30 - 3.19 (m, 1H), 2.48 - 2.31 (m, 3H), 2.28 (s, 3H), 1.94 - 1.81 (m, 1H), 1.43 - 1.29 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H) MS (ESI): *m/z* 430.1 [M + H]⁺

Compound 199

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.25 - 6.68 (m, 2H), 6.23 (s, 1H), 3.90 (s, 3H), 3.77 - 3.54 (m, 1H), 2.55 - 2.22 (m, 2H), 2.09 - 1.99 (m, 2H), 1.94 - 1.84 (m, 1H), 1.73 - 1.43 (m, 1H), 1.36 - 1.26 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H) MS (ESI): *m/z* 478.3 [M + H]⁺

Compound 200

¹H NMR (400 MHz, DMSO-d₆): δ 8.39 (d, *J* = 6.0 Hz, 1H), 7.46 - 7.38 (m, 1H), 7.36 (d, *J* = 6.0 Hz, 1H), 7.31 - 7.12 (m, 2H), 6.74 (dd, *J* = 2.0, 11.2 Hz, 1H), 6.67 - 6.52 (m, 1H), 6.00 (s, 1H), 3.81 - 3.58 (m, 4H), 3.23 - 3.05 (m, 1H), 2.47 - 2.27 (m, 2H), 2.10 - 1.88 (m, 2H), 1.83 - 1.72 (m, 1H), 1.53 - 1.12 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H). MS (ESI): *m/z* 460.3 [M + H]⁺

Compound 201

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 6.0 Hz, 1H), 7.16 - 7.04 (m, 1H), 6.99 (q, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 3.56 - 3.39 (m, 1H), 3.30 - 3.17 (m, 1H), 2.54 - 2.43 (m, 1H), 2.42 - 2.30 (m, 1H), 2.24 (s, 3H), 2.15 - 1.99 (m, 2H), 1.96 - 1.85 (m, 1H), 1.56 - 1.40 (m, 1H), 1.37 - 1.27 (m, 1H), 1.00 (t, *J* = 7.6 Hz, 3H) MS (ESI): *m/z* 462.6 [M + H]⁺

Compound 202

¹H NMR (400 MHz, DMSO-d₆): δ 11.58 (s, 1H), 8.34 (br m 1H), 7.35-7.14 (m, 5H), 5.83 (s, 1H), 3.55-3.50 (m, 1H), 3.01 (br s, 1H), 2.01-1.98 (m, 1H), 1.90-1.65 (m, 4H), 1.52-1.46 (m, 2H), 1.41-1.34 (m, 1H). MS (ESI): *m/z* 418.12 [M + H]⁺

Compound 203

¹H NMR (400 MHz, DMSO-d₆): δ 11.45 (s, 1H), 8.39 (d, *J* = 6.0 Hz, 1H), 7.38 (d, *J* = 5.6 Hz, 2H), 7.17-7.11 (m, 3H), 5.92 (s, 1H), 3.37-3.24 (m, 1H), 3.03-2.97 (m, 1H), 2.21 (s, 3H), 2.00-1.97 (m, 1H), 1.90-1.74 (m, 4H), 1.55-1.45 (m, 2H), 1.39-1.33 (m, 1H). MS (ESI): *m/z* 398.36 [M + H]⁺.

Compound 204

^1H NMR (400 MHz, CD_3OD) δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.49 (d, $J = 6.0$ Hz, 1H), 7.47 - 7.41 (m, 1H), 7.03 - 6.96 (m, 2H), 6.10 (s, 1H), 3.70 - 3.60 (m, 1H), 3.01 - 2.90 (m, 1H), 2.16 - 2.10 (m, 1H), 2.00 - 1.86 (m, 3H), 1.83 - 1.69 (m, 1H), 1.32 - 1.19 (m, 2H), 1.02 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 414.2 $[\text{M} + \text{H}]^+$

Compound 205

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.27 (dd, $J = 6.0, 8.4$ Hz, 1H), 6.79 (dt, $J = 2.4, 8.4$ Hz, 1H), 6.70 (dd, $J = 2.4, 10.0$ Hz, 1H), 6.15 (s, 1H), 3.30 - 3.21 (m, 1H), 3.02 - 2.91 (m, 1H), 2.27 (s, 3H), 2.12 (d, $J = 12.8$ Hz, 1H), 2.00 - 1.83 (m, 3H), 1.81 - 1.70 (m, 1H), 1.29 - 1.15 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 394.2 $[\text{M} + \text{H}]^+$

Compound 206

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 6.0$ Hz, 1H), 7.11 - 7.06 (m, 1H), 7.00 - 6.91 (m, 1H), 6.15 (s, 1H), 3.28 - 3.23 (m, 1H), 3.01 - 2.92 (m, 1H), 2.22 (d, $J = 2.0$ Hz, 3H), 2.18 - 2.13 (m, 1H), 2.08 - 2.03 (m, 1H), 1.96 - 1.90 (m, 1H), 1.88 - 1.79 (m, 1H), 1.62 - 1.53 (m, 1H), 1.39 - 1.31 (m, 2H), 1.26 - 1.13 (m, 2H), 0.96 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 426.3 $[\text{M} + \text{H}]^+$

Compound 207

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.56 (br s, 1H), 8.43 (d, $J = 5.5$ Hz, 1H), 7.48-7.44 (m, 2H), 7.31 (br s, 1H), 6.07 (s, 1H), 2.23-2.22 (m, 3H), 1.99-1.83 (m, 2H), 1.58-1.56 (m, 1H), 1.47-1.39 (m, 2H), 1.29-1.23 (m, 1H), 1.20 (s, 3H), 0.96 (s, 3H). MS (ESI): m/z 426.23 $[\text{M} + \text{H}]^+$.

Compound 208

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.58 (br s, 1H), 8.40 (d, $J = 5.8$ Hz, 1H), 7.39 (br s, 1H), 7.34 (d, $J = 5.8$ Hz, 1H), 7.20-7.10 (m, 2H), 7.10-7.00 (m, 1H), 6.07 (s, 1H), 3.59 (br m, 1H), 3.24-3.20 (m, 1H), 2.40-2.32 (m, 2H), 2.19-2.03 (br m, 2H), 1.95-1.85 (m, 1H), 1.80-1.60 (m, 1H). MS (ESI): m/z 453.37 $[\text{M} + \text{H}]^+$.

Compound 209

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.63 (br. s., 1H), 8.43 (d, $J = 5.6$ Hz, 1H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.42 - 7.35 (m, 1H), 7.33 - 7.27 (m, 1H), 7.23 - 7.17 (m, 1H), 7.16 - 7.08 (m, 1H), 6.02 (s, 1H), 3.97 - 3.86 (m, 1H), 3.77 (s, 3H), 3.67 - 3.58 (m, 1H), 2.42 - 2.29 (m, 2H), 2.21 - 2.12 (m, 1H), 1.98 - 1.85 (m, 1H), 1.65 - 1.56 (m, 1H), 1.55 - 1.46 (m, 1H) MS (ESI): m/z 462.0 $[\text{M} + \text{H}]^+$

Compound 210

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.55 (br s, 1H), 8.39 (d, $J = 5.6$ Hz, 1H), 7.39 (br s, 1H), 7.35 (d, $J = 5.6$ Hz, 1H), 7.17 (br s, 1H), 7.04 - 6.95 (m, 2H), 5.96 (s, 1H), 3.89 (s, 3H), 3.28 -

3.22 (m, 1H), 2.97 - 2.86 (m, 1H), 2.34 - 2.26 (m, 1H), 2.25 - 2.09 (m, 2H), 2.08 - 1.93 (m, 2H), 1.62 - 1.50 (m, 1H) MS (ESI): m/z 462.0 $[M + H]^+$

Compound 211

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 11.46 (br s, 1H), 8.40 (d, $J = 5.8$ Hz, 1H), 7.61-7.57 (m, 1H), 7.39-7.38 (m, 2H), 7.24 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.16-7.11 (m, 2H), 5.89 (s, 1H), 3.43-3.41 (m, 1H), 3.24-3.18 (m, 1H), 1.57-1.71 (br m, 6H), 1.13 (s, 3H), 1.02 (s, 3H). MS (ESI): m/z 428.10 $[M + H]^+$

Compound 212

$^1\text{H NMR}$ (400 MHz, CD_3OD): δ 9.30 (s, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.57 (d, $J = 6.0$ Hz, 1H), 7.10 - 7.01 (m, 1H), 6.98 - 6.85 (m, 1H), 6.33 (s, 1H), 4.15 - 3.98 (m, 1H), 3.81 - 3.69 (m, 3H), 3.12 - 3.03 (m, 1H), 2.69 - 2.55 (m, 1H), 1.95 - 1.76 (m, 2H), 1.70 - 1.59 (m, 1H), 1.09 - 0.96 (m, 1H), 0.72 - 0.62 (m, 1H) MS (ESI): m/z 369.1 $[M + H]^+$

Compound 213

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 11.53 (br s, 1H), 9.01 (s, 1H), 8.51 (d, $J = 5.8$ Hz, 1H), 7.41 (d, $J = 5.8$ Hz, 1H), 7.15 (br s, 1H), 7.07-7.03 (m, 1H), 5.93 (s, 1H), 3.78 (s, 3H), 3.42-3.38 (m, 1H), 2.99-2.94 (br m, 1H), 2.01-1.98 (m, 1H), 1.89-1.76 (m, 4H), 1.50-1.48 (m, 3H). MS (ESI): m/z 371.40 $[M + H]^+$

Compound 214

$^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 11.62 (br s, 1H), 9.00 (s, 1H), 8.50 (d, $J = 5.8$ Hz, 1H), 7.33-7.29 (m, 2H), 6.90-6.83 (m, 2H), 6.14 (s, 1H), 3.46-3.41 (m, 1H), 3.28-3.24 (m, 1H), 2.43-2.40 (m, 2H), 2.26 (s, 3H), 2.20-2.04 (m, 2H), 1.92-1.88 (m, 1H), 1.65-1.54 (m, 1H). MS (ESI): m/z 373.40 $[M + H]^+$

Compound 215

$^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 11.69 (s, 1H), 9.00 (s, 1H), 8.52 (d, $J = 5.8$ Hz, 1H), 7.47 (d, $J = 7.4$ Hz, 1H), 7.35 (d, $J = 5.8$ Hz, 1H), 7.29-7.23 (m, 1H), 7.13-7.09 (m, 1H), 6.09 (s, 1H), 3.75-3.69 (m, 1H), 3.35 (br m, 1H), 2.57-2.52 (m, 1H), 2.49-2.45 (m, 1H), 2.22-2.06 (m, 2H), 1.96-1.93 (m, 1H), 1.71-1.63 (m, 1H). MS (ESI): m/z 375.10 $[M + H]^+$

Compound 216

$^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 11.58 (br s, 1H), 9.02 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 7.33-7.29 (m, 2H), 7.23-7.16 (m, 1H), 6.97 (m, 1H), 6.16 (s, 1H), 3.23-3.11 (m, 2H), 2.43-2.30 (m, 2H), 2.21-2.06 (m, 2H), 2.02-1.95 (m, 1H), 1.85-1.76 (m, 1H). MS (ESI): m/z 377.30 $[M + H]^+$

Compound 217

$^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 11.45 (br s, 1H), 8.38 (d, $J = 6.4$ Hz, 1H), 7.39-7.29 (m, 3H), 7.15 (br s, 1H), 6.89-6.81 (m, 2H), 5.90 (s, 1H), 3.25-3.21 (m, 1H), 3.02-2.96 (m, 1H),

2.26 (s, 3H), 1.99-1.96 (m, 1H), 1.90-1.77 (m, 4H), 1.55-1.42 (m, 2H), 1.39-1.34 (m, 1H).
MS (ESI): m/z 380.34 $[M + H]^+$

Compound 218

^1H NMR (400 MHz, DMSO- d_6): δ 11.46 (br s, 1H), 8.37 (d, $J = 4.4$ Hz, 1H), 7.38-7.29 (m, 3H), 7.15 (br s, 1H), 6.89-6.81 (m, 2H), 5.90 (s, 1H), 3.26-3.21 (m, 1H), 3.01-2.96 (m, 1H), 2.26 (s, 3H), 1.99-1.96 (m, 1H), 1.90-1.74 (m, 4H), 1.57-1.45 (m, 2H), 1.39-1.30 (m, 1H).
MS (ESI): m/z 380.34 $[M + H]^+$

Compound 219

^1H NMR (400 MHz, DMSO- d_6): δ 10.15 (s, 1H), 8.52 (d, $J = 2.0$ Hz, 1H), 8.19 (dd, $J = 4.8$, 1.6 Hz, 1H), 7.84-7.81 (m, 1H), 7.25-7.24 (m, 1H), 7.12-7.09 (m, 2H), 3.89 (d, $J = 1.2$ Hz, 3H), 3.39-3.32 (m, 1H), 3.16-3.11 (m, 1H), 2.48-2.36 (m, 1H), 2.23-2.01 (m, 3H), 1.83-1.80 (m, 1H), 1.62-1.60 (m, 1H). MS (ESI): m/z 383.3 $[M + H]^+$.

Compound 220

^1H NMR (400 MHz, DMSO- d_6): δ 10.61 (br s, 1H), 9.11-9.10 (m, 1H), 8.95 (dd, $J = 5.9$, 0.9 Hz, 1H), 7.75 (dd, $J = 5.9$, 2.7 Hz, 1H), 7.12-7.08 (m, 2H), 3.91 (s, 3H), 3.42-3.33 (m, 1H), 3.21-3.15 (m, 1H), 2.47-2.45 (m, 1H), 2.24-2.06 (m, 3H), 1.85-1.82 (m, 1H), 1.66-1.63 (m, 1H). MS (ESI): 384.3 $[M + H]^+$

Compound 221

^1H NMR (400 MHz, DMSO- d_6): δ 9.01 (s, 1H), 8.50 (d, $J = 6.0$ Hz, 1H), 7.41 (d, $J = 6.0$ Hz, 1H), 7.21 - 6.92 (m, 2H), 5.94 (s, 1H), 3.78 (s, 3H), 3.51 - 3.43 (m, 1H), 2.97 - 2.84 (m, 1H), 1.99 (m, 1H), 1.88 - 1.68 (m, 4H), 1.26 - 1.09 (m, 2H), 0.94 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 385.1 $[M + H]^+$

Compound 222

^1H NMR (400 MHz, DMSO- d_6): δ 9.11 (s, 1H), 8.57 - 8.49 (m, 1H), 7.59 - 7.45 (m, 1H), 7.06 - 6.88 (m, 1H), 6.56 - 6.43 (m, 1H), 6.11 (s, 1H), 5.00 - 4.88 (m, 1H), 3.83 - 3.78 (m, 1H), 3.68 (s, 3H), 3.51 - 3.49 (m, 1H), 3.19 - 3.17 (m, 1H), 2.36 - 2.32 (m, 1H), 1.96 (dd, $J = 6.0$, 12.4 Hz, 1H), 0.72 - 0.49 (m, 4H). MS (ESI): m/z 384.1 $[M + H]^+$

Compound 223

^1H NMR (400 MHz, DMSO- d_6): δ 11.63 (br s, 1H), 9.01 (s, 1H), 8.50 (d, $J = 5.8$, 1H), 7.37 (d, $J = 5.8$, 1H), 7.24 (br s, 1H), 6.71 (d, $J = 10.8$ Hz, 1H), 6.62 (br s, 1H), 6.01 (s, 1H), 3.66 (br m, 4H), 3.21 (br m, 1H), 2.41-2.37 (m, 2H), 2.19-2.00 (m, 2H), 1.88-1.85 (m, 1H), 1.70 (m, 1H). MS (ESI): m/z 389.40 $[M + H]^+$.

Compound 224

^1H NMR (400 MHz, CD_3OD): δ 9.19 (s, 1H), 8.54 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.30 - 7.23 (m, 1H), 7.22 - 7.12 (m, 1H), 6.14 (s, 1H), 3.71 - 3.60 (m, 1H), 3.05 - 2.93

(m, 1H), 2.20 - 2.11 (m, 1H), 2.03 - 1.88 (m, 3H), 1.85 - 1.74 (m, 1H), 1.36 - 1.22 (m, 2H), 1.03 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 389.0 $[M + H]^+$

Compound 225

^1H NMR (400 MHz, DMSO- d_6): δ 11.59 (s, 1H), 8.41 (d, $J = 5.6$ Hz, 1H), 7.45 (s, 1H), 7.32 (d, $J = 5.6$ Hz, 1H), 7.27 - 7.16 (m, 2H), 6.91 - 6.75 (m, 2H), 6.19 (s, 1H), 3.58 - 3.46 (m, 1H), 3.08 - 2.88 (m, 1H), 2.46 - 2.34 (m, 2H), 2.27 - 2.06 (m, 3H), 1.93 - 1.73 (m, 1H). MS (ESI): m/z 390.1 $[M + H]^+$

Compound 226

^1H NMR (400 MHz, DMSO- d_6): δ 11.66 (br s, 1H), 9.01 (s, 1H), 8.52 (d, $J = 5.6$ Hz, 1H), 7.33 (d, $J = 6.0$ Hz, 1H), 7.15-7.12 (m, 2H), 6.16 (s, 1H), 3.51-3.46 (m, 1H), 3.30-3.25 (m, 1H), 2.43-2.36 (m, 2H), 2.28-2.21 (m, 5H), 1.94-1.91 (m, 1H), 1.65-1.53 (m, 1H). MS (ESI): m/z 391.4 $[M + H]^+$

Compound 227

^1H NMR (400 MHz, DMSO- d_6): δ 11.67 (br s, 1H), 9.01 (s, 1H), 8.53-8.52 (d, $J = 5.8$ Hz, 1H), 7.40-7.13 (m, 3H), 7.02-6.97 (m, 1H), 6.12 (s, 1H), 3.74-3.69 (m, 1H), 3.29 (br m, 1H), 2.59-2.56 (m, 1H), 2.44 (br m, 1H), 2.26-2.05 (m, 2H), 1.97-1.94 (m, 1H), 1.74-1.65 (m, 1H). MS (ESI): m/z 393.30 $[M + H]^+$

Compound 228

^1H NMR (400 MHz, DMSO- d_6): δ 11.67 (br s, 1H), 9.02 (s, 1H), 8.53 (d, $J = 5.6$ Hz, 1H), 7.54-7.51 (m, 1H), 7.34 (d, $J = 5.6$ Hz, 1H), 7.27 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.14 (td, $J = 8.4, 2.4$ Hz, 1H), 6.08 (s, 1H), 3.73-3.68 (m, 1H), 3.30-3.24 (m, 1H), 2.58-2.50 (m, 1H), 2.49-2.46 (m, 1H), 2.27-2.09 (m, 2H), 1.96-1.96 (m, 1H), 1.71-1.66 (m, 1H). MS (ESI): m/z 393.30 $[M + H]^+$

Compound 229

^1H NMR (400 MHz, DMSO- d_6): δ 11.68 (br s, 1H), 9.01 (s, 1H), 8.52 (d, $J = 5.8$ Hz, 1H), 7.34-7.26 (m, 3H), 7.17-7.12 (m, 1H), 6.09 (s, 1H), 3.79-3.74 (m, 1H), 2.61-2.51 (m, 1H), 2.45-2.41 (m, 1H), 2.23-2.11 (m, 2H), 2.08-1.96 (m, 1H), 1.75-1.65 (m, 1H). MS (ESI): m/z 393.30 $[M + H]^+$

Compound 230

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.26 (dd, $J = 5.6, 8.4$ Hz, 1H), 6.82 - 6.65 (m, 2H), 6.17 (s, 1H), 3.48 - 3.31 (m, 1H), 2.30 - 2.99 (m, 1H), 2.30 (s, 3H), 2.25 - 2.16 (m, 1H), 2.09 - 1.97 (m, 1H), 1.95 - 1.83 (m, 2H), 1.82 - 1.66 (m, 3H), 1.29 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 394.2 $[M + H]^+$

Compound 231

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.27 (dd, $J = 6.0, 8.4$ Hz, 1H), 6.79 (dt, $J = 2.4, 8.4$ Hz, 1H), 6.70 (dd, $J = 2.4, 10.0$ Hz, 1H), 6.15 (s,

1H), 3.30 - 3.21 (m, 1H), 3.02 - 2.91 (m, 1H), 2.27 (s, 3H), 2.12 (d, $J = 12.8$ Hz, 1H), 2.00 - 1.83 (m, 3H), 1.81 - 1.70 (m, 1H), 1.29 - 1.15 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 394.2 $[M + H]^+$

Compound 232

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.26 (dd, $J = 5.6, 8.4$ Hz, 1H), 6.82 - 6.65 (m, 2H), 6.17 (s, 1H), 3.48 - 3.31 (m, 1H), 2.30 - 2.99 (m, 1H), 2.30 (s, 3H), 2.25 - 2.16 (m, 1H), 2.09 - 1.97 (m, 1H), 1.95 - 1.83 (m, 2H), 1.82 - 1.66 (m, 3H), 1.29 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 394.2 $[M + H]^+$

Compound 233

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.64 (s, 1H), 9.01 (s, 1H), 8.52 (d, $J = 5.72$ Hz, 1H), 7.43 (br. s, 1H), 7.36 (d, $J = 5.8$ Hz, 1H), 7.31 (br s, 2H), 6.02 (s, 1H), 3.74 (s, 3H), 2.48-2.38 (m, 4H), 2.24-2.04 (m, 2H), 1.92-1.88 (m, 1H), 1.70-1.66 (m, 1H). MS (ESI): m/z 396.40 $[M + H]^+$

Compound 234

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.47 (br s, 1H), 8.37 (d, $J = 4.8$ Hz, 1H), 7.40-7.35 (m, 2H), 7.30-7.14 (m, 2H), 6.70 (dd, $J = 11.4, 2.0$ Hz, 1H), 6.60 (br m, 1H), 5.81 (s, 1H), 3.71 (s, 3H), 3.38 (br m, 1H), 2.91 (br m, 1H), 2.07-1.95 (m, 1H), 1.88-1.75 (m, 3H), 1.71-1.65 (m, 1H), 1.45-1.34 (m, 3H). MS (ESI): m/z 396.30 $[M + H]^+$

Compound 235

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.46 (br s, 1H), 8.37 (d, $J = 5.5$ Hz, 1H), 7.40-7.35 (m, 2H), 7.30-7.10 (m, 2H), 6.70 (dd, $J = 11.4, 1.9$ Hz, 1H), 6.61 (br m, 1H), 5.82 (s, 1H), 3.70 (s, 3H), 3.39 (br m, 1H), 2.91 (br m, 1H), 2.07-1.985 (m, 1H), 1.87-1.75 (m, 3H), 1.72-1.69 (m, 1H), 1.46-1.34 (m, 3H). MS (ESI): m/z 396.33 $[M + H]^+$

Compound 236

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.60 (s, 1H), 7.18 - 7.02 (m, 2H), 6.81 (t, $J = 8.0$ Hz, 1H), 6.73 (t, $J = 2.0$ Hz, 1H), 6.49 (dd, $J = 1.2, 8.0$ Hz, 1H), 6.18 (dd, $J = 1.2, 8.0$ Hz, 1H), 5.00 (br s, 2H), 3.89 (d, $J = 1.2$ Hz, 3H), 3.16 - 3.09 (m, 1H), 3.02 - 2.90 (m, 1H), 2.34 - 2.27 (m, 1H), 2.20 - 2.01 (m, 3H), 1.85 - 1.75 (m, 1H), 1.63 - 1.47 (m, 1H). MS (ESI): m/z 397.1 $[M + H]^+$

Compound 237

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.49 (s, 1H), 8.39 (d, $J = 6.0$ Hz, 1H), 7.38 (d, $J = 6.0$ Hz, 2H), 7.17-7.11 (m, 3H), 5.92 (s, 1H), 3.32-3.24 (m, 1H), 3.03-2.98 (m, 1H), 2.21 (d, $J = 1.6$ Hz, 3H), 2.21-2.20 (m, 1H), 1.90-1.74 (m, 4H), 1.55-1.45 (m, 2H), 1.39-1.33 (m, 1H). MS (ESI): m/z 398.36 $[M + H]^+$

Compound 238

^1H NMR (400 MHz, DMSO- d_6): δ 11.30 (br s, 1H), 10.06 (s, 1H), 7.25-7.20 (m, 1H), 7.15-6.94 (m, 2H), 6.56 (s, 1H), 6.19-6.17 (m, 1H), 3.89 (br m, 3H), 3.37-3.32 (m, 1H), 3.13-3.08 (m, 1H), 2.40-2.37 (m, 1H), 2.33-2.00 (m, 3H), 1.81-1.78 (m, 1H), 1.61-1.55 (m, 1H). MS (ESI): m/z 399.40 $[\text{M} + \text{H}]^+$

Compound 239

^1H NMR (400 MHz, DMSO- d_6): δ 11.26 (br s, 1H), 9.68 (br s, 1H), 7.58 (s, 1H), 7.20-7.05 (m, 3H), 6.26 (d, $J = 9.6$ Hz, 1H), 3.88 (s, 3H), 3.04-2.98 (m, 1H), 2.33-2.32 (m, 1H), 2.20-1.99 (m, 3H), 1.81-1.78 (m, 1H), 1.60-1.58 (m, 1H). MS (ESI): m/z 399.40 $[\text{M} + \text{H}]^+$

Compound 240

^1H NMR (400 MHz, DMSO- d_6): δ 10.32 (s, 1H), 8.46 (t, $J = 1.6$ Hz, 1H), 7.90-7.88 (m, 1H), 7.29-7.25 (m, 1H), 7.21-7.18 (m, 1H), 7.14-7.05 (m, 2H), 3.90 (d, $J = 1.6$ Hz, 3H), 3.39-3.35 (m, 1H), 3.13-3.06 (m, 1H), 2.48-2.36 (m, 1H), 2.22-2.04 (m, 3H), 1.83-1.80 (m, 1H), 1.63-1.61 (m, 1H). MS (ESI): m/z 399.3 $[\text{M} + \text{H}]^+$

Compound 241

^1H NMR (400 MHz, DMSO- d_6): δ 11.48 (s, 1H), 9.02 (s, 1H), 8.52 (d, $J = 5.6$ Hz, 1H), 7.41 (d, $J = 5.6$ Hz, 1H), 7.19 - 7.09 (m, 1H), 7.08 - 6.98 (m, 1H), 5.97 (s, 1H), 3.80 (s, 3H), 3.67 - 3.53 (m, 1H), 2.97 - 2.79 (m, 1H), 2.00 - 1.80 (m, 2H), 1.60 - 1.52 (m, 1H), 1.51 - 1.34 (m, 3H), 1.17 (s, 3H), 0.97 (s, 3H). MS (ESI): m/z 399.1 $[\text{M} + \text{H}]^+$

Compound 242

^1H NMR (400 MHz, DMSO- d_6): δ 11.64 (br. s., 1H), 9.01 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 7.42 (d, $J = 5.6$ Hz, 1H), 7.22 - 7.14 (m, 1H), 7.09 - 6.98 (m, 1H), 6.09 - 5.90 (m, 1H), 3.79 (s, 3H), 3.21 - 3.09 (m, 1H), 2.03 - 1.93 (m, 1H), 1.90 - 1.69 (m, 4H), 1.66 - 1.46 (m, 4H), 1.44 - 1.22 (m, 1H), 0.99 - 0.90 (m, 3H). MS (ESI): m/z 399.1 $[\text{M} + \text{H}]^+$

Compound 243

^1H NMR (400 MHz, DMSO- d_6): δ 12.72 (br s, 1H), 10.39 (br s, 1H), 7.67 (d, $J = 2.3$ Hz, 1H), 7.15-7.03 (m, 2H), 6.97 (t, $J = 3.9$ Hz, 1H), 3.90 (s, 3H), 3.38-3.33 (m, 1H), 3.15-3.10 (m, 1H), 2.46- 2.44 (m, 1H), 2.21- 2.01 (m, 3H), 1.83-1.79 (m, 1H), 1.64-1.61 (m, 1H). MS (ESI): 400.4 $[\text{M} + \text{H}]^+$

Compound 244

^1H NMR (400 MHz, DMSO- d_6): δ 12.63 (br s, 1H), 10.52 (s, 1H), 7.65 (d, $J = 10.1$ Hz, 1H), 7.20-7.07 (m, 2H), 6.82 (dd, $J = 10.2, 1.7$ Hz, 1H), 3.88-3.87 (m, 3H), 3.31 (br m, 1H), 3.23-3.18 (m, 1H), 2.39-2.32 (m, 1H), 2.20-2.01 (m, 3H), 1.81-1.78 (m, 1H), 1.60-1.54 (m, 1H). MS (ESI): m/z 400.4 $[\text{M} + \text{H}]^+$

Compound 245

¹H NMR (400 MHz, DMSO-d₆): δ 10.26 (br s, 1H), 8.19 (s, 1H), 7.74-7.71 (m, 1H), 7.50-7.46 (m, 2H), 7.32 (br s, 2H), 7.22-7.13 (m, 1H), 7.03-6.99 (m, 1H), 3.92-3.86 (m, 1H), 3.84 (s, 3H), 2.62-2.60 (m, 1H), 2.45-2.42 (m, 2H), 1.86-1.83 (m, 1H), 1.65-1.59 (m, 1H), 1.39-1.36 (m, 1H), 1.36-1.30 (m, 2H), 1.23-1.21 (m, 1H). MS (ESI): *m/z* 437.3 [M + H]⁺.

Compound 246

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H), 9.01 (s, 1H), 8.52 (d, J = 5.8 Hz, 1H), 7.37-7.35 (m, 2H), 6.85-6.84 (m, 1H), 6.83-6.80 (m, 2H), 6.08 (s, 1H), 3.65-3.61 (m, 4H), 3.29-3.25 (m, 1H), 2.43-2.38 (m, 2H), 2.30-2.20 (m, 2H), 1.94-1.90 (m, 1H), 1.67-1.59 (m, 1H). MS (ESI): *m/z* 405.30 [M - H]⁻.

Compound 247

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br s, 1H), 9.01 (s, 1H), 8.52 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.7 Hz, 1H), 7.24 (br m, 1H), 6.89-6.83 (m, 2H), 6.02 (s, 1H), 3.81-3.50 (br m, 4H), 3.20 (br m, 1H), 2.42-2.38 (m, 2H), 2.22-2.11 (m, 2H), 2.11-1.99 (m, 1H), 1.90-1.86 (m, 1H). MS (ESI): *m/z* 405.00 [M + H]⁺.

Compound 248

¹H NMR (400 MHz, DMSO-d₆): δ 11.73 (s, 1H), 9.02 (s, 1H), 8.52 (d, J = 5.8 Hz, 1H), 7.36 (d, J = 5.8 Hz, 1H), 6.93-6.84 (m, 2H), 6.10 (s, 1H), 3.72-3.66 (m, 4H), 3.43-3.40 (m, 1H), 2.43-2.39 (m, 2H), 2.23-2.10 (m, 3H), 2.00-1.98 (m, 1H). MS (ESI): *m/z* 407.40 [M + H]⁺.

Compound 249

¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (br s, 1H), 9.03 (s, 1H), 8.53 (d, J = 5.8 Hz, 1H), 7.38-7.28 (m, 2H), 6.98-6.93 (m, 1H), 6.05 (m, 1H), 3.19 (br m, 1H), 3.61 (br m, 4H), 2.40-2.37 (m, 2H), 2.28-2.00 (m, 3H), 1.90-1.65 (m, 1H). MS (ESI): *m/z* 407.00 [M + H]⁺.

Compound 250

¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (br s, 1H), 9.01 (s, 1H), 8.52 (d, J = 5.8 Hz, 1H), 7.38 (d, J = 5.8 Hz, 1H), 7.17-7.09 (m, 1H), 6.74-6.64 (m, 1H), 6.04-6.00 (m, 1H), 3.82-3.61 (m, 4H), 3.41-3.36 (m, 1H), 2.49-2.34 (m, 2H), 2.28-2.01 (m, 2H), 2.00-1.80 (m, 1H). MS (ESI): *m/z* 407.05 [M + H]⁺.

Compound 251

¹H NMR (400 MHz, DMSO-d₆): δ 11.67-11.65 (m, 1H), 9.02 (s, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 6.73-6.58 (m, 2H), 5.60-5.98 (m, 1H), 3.80-3.51 (m, 5H), 2.40-2.30 (m, 2H), 2.29-2.01 (m, 3H), 1.90-1.78 (m, 1H). MS (ESI): *m/z* 407.4 [M + H]⁺.

Compound 252

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H), 9.02 (s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.13-7.03 (m, 2H), 6.11 (s, 1H), 3.80-3.60 (m, 4H), 3.28-3.20 (m,

1H), 2.49-2.40 (m, 2H), 2.21-2.06 (m, 2H), 1.91-1.88 (m, 1H), 1.77-1.73 (m, 1H). MS (ESI): m/z 407.40 $[M + H]^+$.

Compound 253

^1H NMR (400 MHz, CD_3OD): δ 8.43 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 6.0$ Hz, 1H), 7.27 (dd, $J = 6.0, 8.8$ Hz, 1H), 6.84 - 6.75 (m, 1H), 6.70 (dd, $J = 2.8, 10.0$ Hz, 1H), 6.15 (s, 1H), 3.25 (dt, $J = 3.2, 12.0$ Hz, 1H), 2.96 (dt, $J = 3.2, 12.0$ Hz, 1H), 2.27 (s, 3H), 2.19 - 2.11 (m, 1H), 2.07 - 2.00 (m, 1H), 1.97 - 1.90 (m, 1H), 1.90 - 1.78 (m, 1H), 1.63 - 1.50 (m, 1H), 1.40 - 1.30 (m, 2H), 1.29 - 1.09 (m, 2H), 0.95 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 408.3 $[M + H]^+$

Compound 254

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 1H), 7.26 (dd, $J = 6.0, 8.8$ Hz, 1H), 6.84 - 6.74 (m, 1H), 6.69 (dd, $J = 2.8, 10.0$ Hz, 1H), 6.15 (s, 1H), 3.23 (dt, $J = 3.2, 11.6$ Hz, 1H), 2.95 (dt, $J = 3.2, 12.0$ Hz, 1H), 2.26 (s, 3H), 2.14 - 2.06 (m, 1H), 2.02 - 1.87 (m, 2H), 1.86 - 1.72 (m, 1H), 1.51 (br s, 1H), 1.38 - 1.27 (m, 2H), 1.24 - 1.06 (m, 2H), 0.94 (t, $J = 7.6$ Hz, 3H). Compound 255

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.27 (dd, $J = 6.0, 8.8$ Hz, 1H), 6.85 - 6.73 (m, 1H), 6.71 (dd, $J = 2.8, 10.0$ Hz, 1H), 6.15 (s, 1H), 3.44 - 3.34 (m, 1H), 3.01 (dt, $J = 4.4, 10.8$ Hz, 1H), 2.29 (s, 3H), 1.97 - 1.87 (m, 3H), 1.87 - 1.79 (m, 3H), 1.79 - 1.67 (m, 3H), 1.03 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 408.2 $[M + H]^+$

Compound 256 MS (ESI): m/z 408.1 $[M + H]^+$

Compound 257 MS (ESI): m/z 409.30 $[M + H]^+$.

Compound 258

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ (br. s., 1H), 8.39 (d, $J = 5.6$ Hz, 1H), 7.41 - 7.29 (m, 2H), 7.20 - 7.12 (m, 1H), 7.10 - 7.02 (m, 2H), 5.95 (s, 1H), 3.13 - 3.02 (m, 1H), 3.01 - 2.90 (m, 1H), 2.41 - 2.37 (m, 1H), 2.26 - 2.22 (m, 3H), 2.12 - 2.05 (m, 1H), 1.90 - 1.82 (m, 1H), 1.81 - 1.71 (m, 1H), 1.16 - 1.07 (m, 2H), 0.75 - 0.65 (m, 1H), 0.57 - 0.49 (m, 1H) MS (ESI): m/z 410.1 $[M + H]^+$

Compound 259

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ (br. s., 1H), 8.39 (d, $J = 5.6$ Hz, 1H), 7.41 - 7.29 (m, 2H), 7.20 - 7.12 (m, 1H), 7.10 - 7.02 (m, 2H), 5.95 (s, 1H), 3.13 - 3.02 (m, 1H), 3.01 - 2.90 (m, 1H), 2.41 - 2.37 (m, 1H), 2.26 - 2.22 (m, 3H), 2.12 - 2.05 (m, 1H), 1.90 - 1.82 (m, 1H), 1.81 - 1.71 (m, 1H), 1.16 - 1.07 (m, 2H), 0.75 - 0.65 (m, 1H), 0.57 - 0.49 (m, 1H) MS (ESI): m/z 410.1 $[M + H]^+$

Compound 260

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.39 (br. s., 1H), 8.38 (d, $J = 5.6$ Hz, 1H), 7.44 - 7.29 (m, 2H), 7.21 - 7.12 (m, 1H), 7.11 - 6.94 (m, 2H), 5.94 (s, 1H), 3.20 - 3.09 (m, 1H), 2.97 - 2.84 (m, 1H), 2.44 - 2.38 (m, 1H), 2.38 - 2.32 (m, 1H), 2.29 - 2.25 (m, 3H), 2.25 - 2.22 (m, 1H),

1.48 - 1.32 (m, 1H), 1.23 - 1.05 (m, 2H), 0.79 - 0.69 (m, 1H), 0.42 - 0.30 (m, 1H) Compound 261

^1H NMR (400 MHz, DMSO- d_6): δ 11.39 (br. s., 1H), 8.38 (d, $J = 5.6$ Hz, 1H), 7.44 - 7.29 (m, 2H), 7.21 - 7.12 (m, 1H), 7.11 - 6.94 (m, 2H), 5.94 (s, 1H), 3.20 - 3.09 (m, 1H), 2.97 - 2.84 (m, 1H), 2.44 - 2.38 (m, 1H), 2.38 - 2.32 (m, 1H), 2.29 - 2.25 (m, 3H), 2.25 - 2.22 (m, 1H), 1.48 - 1.32 (m, 1H), 1.23 - 1.05 (m, 2H), 0.79 - 0.69 (m, 1H), 0.42 - 0.30 (m, 1H) MS (ESI): m/z 410.1 $[\text{M} + \text{H}]^+$

Compound 262

^1H NMR (400 MHz, CD_3OD): δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.45 (d, $J = 5.6$ Hz, 1H), 7.28 - 7.16 (m, 1H), 7.12 - 6.97 (m, 1H), 6.10 - 5.97 (m, 1H), 3.38 - 3.32 (m, 1H), 2.81 - 2.68 (m, 1H), 2.61 - 2.08 (m, 5H), 1.87 - 1.73 (m, 1H), 1.70 - 1.57 (m, 1H), 1.38 - 1.17 (m, 1H), 0.94 - 0.76 (m, 2H), 0.59 - 0.47 (m, 1H) MS (ESI): m/z 410.2 $[\text{M} + \text{H}]^+$

Compound 263

^1H NMR (400 MHz, CD_3OD): δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 6.0$ Hz, 1H), 7.28 - 7.16 (m, 1H), 7.12 - 6.97 (m, 1H), 6.12 - 5.98 (m, 1H), 3.41 - 3.33 (m, 1H), 2.80 - 2.68 (m, 1H), 2.62 - 2.09 (m, 5H), 1.88 - 1.72 (m, 1H), 1.71 - 1.57 (m, 1H), 1.35 - 1.18 (m, 1H), 0.92 - 0.78 (m, 2H), 0.56 - 0.48 (m, 1H) MS (ESI): m/z 410.2 $[\text{M} + \text{H}]^+$

Compound 264

^1H NMR (400 MHz, DMSO- d_6): δ 10.71 (s, 1H), 8.53 - 8.46 (m, 1H), 8.13 - 8.05 (m, 1H), 7.67 - 7.55 (m, 1H), 7.41 - 7.33 (m, 2H), 7.32 - 7.23 (m, 2H), 7.06 - 6.99 (m, 1H), 3.23 - 3.16 (m, 1H), 3.14 - 3.04 (m, 1H), 2.11 - 1.98 (m, 2H), 1.85 - 1.71 (m, 1H), 1.69 - 1.46 (m, 4H), 0.70 (d, $J = 7.2$ Hz, 3H) MS (ESI): m/z 410.1 $[\text{M} + \text{H}]^+$

Compound 265

^1H NMR (400 MHz, DMSO- d_6): δ 10.34 (s, 1H), 8.49 - 8.40 (m, 1H), 8.06 - 7.99 (m, 1H), 7.58 - 7.51 (m, 1H), 7.35 (s, 2H), 7.30 - 7.21 (m, 2H), 7.02 - 6.95 (m, 1H), 2.76 - 2.59 (m, 1H), 2.47 - 2.40 (m, 1H), 2.04 - 1.91 (m, 1H), 1.87 - 1.75 (m, 2H), 1.73 - 1.61 (m, 1H), 1.59 - 1.39 (m, 2H), 1.20 - 1.08 (m, 1H), 0.68 - 0.55 (m, 3H) MS (ESI): m/z 410.1 $[\text{M} + \text{H}]^+$

Compound 266

^1H NMR (400 MHz, DMSO- d_6): δ 10.37 (s, 1H), 8.50 - 8.40 (m, 1H), 8.10 - 7.97 (m, 1H), 7.59 - 7.49 (m, 1H), 7.34 (s, 2H), 7.30 - 7.20 (m, 2H), 7.03 - 6.95 (m, 1H), 2.73 - 2.62 (m, 1H), 2.49 - 2.42 (m, 1H), 2.01 - 1.92 (m, 1H), 1.86 - 1.76 (m, 2H), 1.72 - 1.60 (m, 1H), 1.57 - 1.40 (m, 2H), 1.21 - 1.07 (m, 1H), 0.61 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 410.1 $[\text{M} + \text{H}]^+$

Compound 267

^1H NMR (400 MHz, DMSO- d_6): δ 10.73 (s, 1H), 8.53 - 8.42 (m, 1H), 8.13 - 8.04 (m, 1H), 7.64 - 7.56 (m, 1H), 7.36 (s, 2H), 7.33 - 7.23 (m, 2H), 7.05 - 6.98 (m, 1H), 3.24 - 3.15 (m, 1H), 3.13 - 3.04 (m, 1H), 2.13 - 1.96 (m, 2H), 1.82 - 1.70 (m, 1H), 1.68 - 1.41 (m, 4H), 0.69 (d, $J = 7.2$ Hz, 3H) MS (ESI): m/z 410.1 $[\text{M} + \text{H}]^+$

Compound 268

¹H NMR (400 MHz, DMSO-d₆): δ 11.47 (br s, 1H), 8.38 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.37 (br s, 1H), 7.30 - 7.07 (m, 2H), 6.71 (dd, *J* = 2.4, 11.6 Hz, 1H), 6.66 - 6.54 (m, 1H), 5.83 (s, 1H), 3.71 (s, 3H), 3.58 - 3.43 (m, 1H), 2.97 - 2.74 (m, 1H), 2.02 - 1.92 (m, 1H), 1.88 - 1.80 (m, 1H), 1.80 - 1.61 (m, 3H), 1.23 - 1.02 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H). MS (ESI): *m/z* 410.2 [M + H]⁺

Compound 269

¹H NMR (400 MHz, DMSO-d₆): δ 11.44 (br s, 1H), 8.38 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 6.0 Hz, 1H), 7.37 (br s, 1H), 7.30 - 7.10 (m, 2H), 6.71 (dd, *J* = 2.4, 11.6 Hz, 1H), 6.67 - 6.53 (m, 1H), 5.84 (s, 1H), 3.70 (s, 3H), 3.58 - 3.42 (m, 1H), 3.00 - 2.74 (m, 1H), 2.03 - 1.92 (m, 1H), 1.88 - 1.81 (m, 1H), 1.80 - 1.62 (m, 3H), 1.24 - 1.04 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H). MS (ESI): *m/z* 410.4 [M + H]⁺

Compound 270

¹H NMR (400 MHz, DMSO-d₆): δ 11.42 (s, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.37 (br s, 1H), 7.25 - 7.11 (m, 2H), 6.70 (dd, *J* = 2.4, 11.6 Hz, 1H), 6.60 (dt, *J* = 2.4, 8.4 Hz, 1H), 5.85 (d, *J* = 1.2 Hz, 1H), 3.71 (s, 3H), 3.65 - 3.56 (m, 1H), 2.99 - 2.84 (m, 1H), 2.17 - 2.07 (m, 1H), 1.95 - 1.83 (m, 1H), 1.81 - 1.69 (m, 3H), 1.66 - 1.53 (m, 2H), 1.20 (d, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 410.4 [M + H]⁺

Compound 271

¹H NMR (400 MHz, DMSO-d₆): δ 11.42 (br s, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.38 (br s, 1H), 7.26 - 7.10 (m, 2H), 6.70 (dd, *J* = 2.4, 11.6 Hz, 1H), 6.61 (dt, *J* = 2.4, 8.4 Hz, 1H), 5.86 (s, 1H), 3.72 (s, 3H), 3.67 - 3.53 (m, 1H), 3.02 - 2.81 (m, 1H), 2.18 - 2.06 (m, 1H), 1.96 - 1.83 (m, 1H), 1.82 - 1.68 (m, 3H), 1.67 - 1.51 (m, 2H), 1.20 (d, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 410.3 [M + H]⁺

Compound 272

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (br s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 4 Hz, 1H), 7.37 (br s, 2H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.10-7.06 (m, 1H), 6.98-6.94 (m, 1H), 4.14-4.11 (m, 1H), 3.26-3.23 (m, 1H), 2.77-2.71 (m, 1H), 2.48-2.41 (m, 2H), 2.23 (s, 3H), 2.26-2.13 (m, 2H). MS (ESI): *m/z* 411.40 [M + H]⁺

Compound 273

¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (br s, 1H), 9.02 (s, 1H), 8.53 (d, *J* = 5.8 Hz, 1H), 7.44-7.34 (m, 3H), 6.10 (s, 1H), 3.75 - 3.70 (m, 1H), 3.25 (m, 1H), 2.62-2.52 (m, 1H), 2.46-2.41 (m, 1H), 2.23-2.21 (m, 2H), 2.00-1.90 (m, 1H), 1.71-1.62 (m, 1H). MS (ESI): *m/z* 411.00 [M + H]⁺

Compound 274

¹H NMR (400 MHz, CD₃OD): δ 8.50 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 1H), 7.10 - 7.01 (m, 1H), 6.96 - 6.87 (m, 1H), 6.26 (s, 1H), 4.07 (m, 1H), 3.75 (m, 3H), 3.05 (m, 1H),

2.65 - 2.54 (m, 1H), 1.93 - 1.74 (m, 2H), 1.64 (m, 1H), 1.07 - 0.98 (m, 1H), 0.66 (m, 1H) MS (ESI): m/z 412.1 $[M + H]^+$

Compound 275

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.50 (d, $J = 6.0$ Hz, 1H), 6.95 - 6.89 (m, 1H), 6.87 - 6.80 (m, 1H), 5.75 (s, 1H), 3.62 (dd, $J = 3.6, 12.8$ Hz, 1H), 2.68 (d, $J = 4.0$ Hz, 3H), 2.62 - 2.53 (m, 1H), 2.32 - 2.21 (m, 1H), 2.07 - 1.99 (m, 1H), 1.93 - 1.89 (m, 1H), 1.86 - 1.78 (m, 2H), 1.73 - 1.64 (m, 1H), 1.61 - 1.57 (m, 1H), 1.55 (s, 3H). MS (ESI): m/z 412.0 $[M + H]^+$

Compound 276

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.46 (br s, 1H), 8.41 (d, $J = 6.0$ Hz, 1H), 7.40 (d, $J = 6.0$ Hz, 2H), 7.25 - 7.03 (m, 3H), 6.00 (s, 1H), 3.51 - 3.43 (m, 1H), 3.05 - 2.93 (m, 1H), 2.27 (s, 3H), 2.15 - 2.09 (m, 1H), 2.03 - 1.90 (m, 1H), 1.82 - 1.72 (m, 2H), 1.69 - 1.52 (m, 3H), 1.24 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 412.2 $[M + H]^+$

Compound 277

^1H NMR (400 MHz, CD_3OD): δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 1H), 7.11 - 7.02 (m, 1H), 6.99 - 6.89 (m, 1H), 6.16 (s, 1H), 3.51 - 3.40 (m, 1H), 3.06 - 2.94 (m, 1H), 2.29 - 2.16 (m, 4H), 2.08 - 1.96 (m, 1H), 1.96 - 1.84 (m, 2H), 1.82 - 1.67 (m, 3H), 1.30 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 412.2 $[M + H]^+$

Compound 278

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.49 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.39 (d, $J = 5.6$ Hz, 2H), 7.26 - 7.01 (m, 3H), 5.94 (s, 1H), 3.33 - 3.27 (m, 1H), 3.00 - 2.87 (m, 1H), 2.20 (s, 3H), 2.02 - 1.92 (m, 1H), 1.88 - 1.66 (m, 4H), 1.25 - 1.13 (m, 1H), 1.10 - 0.99 (m, 1H), 0.92 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 412.2 $[M + H]^+$

Compound 279

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.55 (br s, 1H), 9.23 (s, 1H), 7.20-7.07 (m, 2H), 6.95-6.91 (m, 1H), 6.05 (d, $J = 9.5$ Hz, 1H), 3.86 (s, 3H), 3.32-3.21 (m, 1H), 3.07-3.02 (m, 1H), 2.33-2.32 (m, 1H), 2.22-2.01 (m, 3H), 1.82-1.78 (m, 1H), 1.61-1.56 (m, 4H). MS (ESI): m/z 413.40 $[M + H]^+$

Compound 280

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.26 (br s, 1H), 8.52 (s, 1H), 7.90 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.43 (d, $J = 8.6$ Hz, 1H), 7.11-7.07 (m, 2H), 4.50 (s, 2H), 3.88 (s, 3H), 3.39-3.34 (m, 1H), 3.16-3.12 (m, 1H), 2.39-2.32 (m, 1H), 2.24-2.12 (m, 3H), 1.83-1.80 (m, 1H), 1.63-1.50 (m, 1H). MS (ESI): m/z 413.40 $[M + H]^+$

Compound 281

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.72 (br s, 1H), 7.89 (d, $J = 2.7$ Hz, 1H), 7.16-7.08 (m, 3H), 6.32 (d, $J = 9.6$ Hz, 1H), 3.90 (d, $J = 1.2$ Hz, 3H), 3.34 (s, 3H), 3.33-3.27 (m, 1H), 3.07-

3.02 (m, 1H), 2.36-2.32 (m, 1H), 2.19-2.00 (m, 3H), 1.83-1.79 (m, 1H), 1.60-1.58 (m, 1H)
MS (ESI): 413.40 [M + H]⁺

Compound 282

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.60 (s, 1H), 9.06 (s, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 7.24 - 7.17 (m, 1H), 7.14 - 7.05 (m, 1H), 6.01 (s, 1H), 3.74 (s, 3H), 3.71 - 3.64 (m, 1H), 3.23 - 3.12 (m, 1H), 2.23 - 2.13 (m, 2H), 2.09 - 2.01 (m, 1H), 1.95 - 1.85 (m, 1H), 1.58 - 1.48 (m, 1H), 0.91 (s, 9H). MS (ESI): *m/z* 413.2 [M + H]⁺

Compound 283

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.50 (br s, 1H), 8.38 (d, *J* = 4.8 Hz, 1H), 7.341-7.39 (m, 2H), 7.18-7.03 (m, 3H), 5.89 (s, 1H), 3.79 (s, 3H), 3.43-3.39 (m, 1H), 2.96 (br m, 1H), 1.99-1.96 (m, 1H), 1.90-1.75 (m, 4H), 1.52-1.45 (m, 3H). MS (ESI): *m/z* 414.30 [M + H]⁺

Compound 284

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.50 (br s, 1H), 8.38 (s, 1H), 7.38 (br s, 2H), 7.15-7.03 (m, 3H), 5.89 (s, 1H), 3.79 (s, 3H), 3.40 (br m, 1H), 2.96 (br m, 1H), 1.98-1.95 (m, 1H), 1.88-1.78 (m, 4H), 1.49-1.46 (m, 3H). MS (ESI): *m/z* 414.30 [M + H]⁺

Compound 285

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.47 - 7.42 (m, 1H), 7.03 - 6.95 (m, 2H), 6.10 (s, 1H), 3.70 - 3.60 (m, 1H), 3.00 - 2.90 (m, 1H), 2.16 - 2.08 (m, 1H), 1.99 - 1.86 (m, 3H), 1.82 - 1.72 (m, 1H), 1.34 - 1.19 (m, 2H), 1.01 (d, *J* = 6.4 Hz, 3H) MS (ESI): *m/z* 414.2 [M + H]⁺

Compound 286

¹H NMR (400 MHz, CD₃OD) δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.46 - 7.39 (m, 1H), 7.04 - 6.94 (m, 2H), 6.13 (s, 1H), 3.90 - 3.79 (m, 1H), 3.07 - 2.95 (m, 1H), 2.28 - 2.18 (m, 1H), 2.12 - 2.01 (m, 1H), 1.95 - 1.88 (m, 2H), 1.83 - 1.72 (m, 3H), 1.30 (d, *J* = 7.2 Hz, 3H) MS (ESI): *m/z* 414.2 [M + H]⁺

Compound 287

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.04 - 6.93 (m, 2H), 6.13 (s, 1H), 3.89 - 3.76 (m, 1H), 3.07 - 2.94 (m, 1H), 2.27 - 2.17 (m, 1H), 2.11 - 1.99 (m, 1H), 1.95 - 1.85 (m, 2H), 1.81 - 1.71 (m, 3H), 1.29 (d, *J* = 7.2 Hz, 3H) MS (ESI): *m/z* 414.2 [M + H]⁺

Compound 288

¹H NMR (400 MHz, DMSO-*d*₆): ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.22 (s, 1H), 8.19-8.18 (m, 1H), 7.72-7.67 (m, 1H), 7.48-7.42 (m, 2H), 7.30 (s, 2H), 7.30-7.27 (m, 1H), 7.21-7.17 (m, 1H), 6.97-6.93 (m, 2H), 3.89 (d, *J* = 8.32 Hz, 1H), 3.77 (s, 3H), 3.07 (d, *J* = 8.32 Hz, 1H), 1.99-1.95 (m, 1H), 1.79-1.74 (m, 3H), 1.62-1.56 (m, 3H), 1.50 - 1.38 (m, 2H), 1.32-1.22 (m, 1H). MS (ESI): *m/z* 415.3 [M + H]⁺.

Compound 289

¹H NMR (400 MHz, DMSO-d₆): δ 11.64 (br s, 1H), 8.38 (br m, 1H), 7.38-7.19 (m, 4H), 6.87 (br m, 1H), 6.11 (br m, 1H), 3.48-3.42 (m, 1H), 2.40-2.30 (m, 2H), 2.27 (s, 3H), 2.18-2.08 (br m, 2H), 1.86 (br m, 1H), 1.65-1.52 (m, 1H). MS (ESI): m/z 416.15 [M + H]⁺.

Compound 291

¹H NMR (400 MHz, DMSO-d₆): δ 11.65 (s, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.40 (br s, 1H), 7.33 (d, *J* = 5.5 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.19 (br s, 1H), 7.13-7.09 (m, 1H), 6.06 (s, 1H), 3.77-3.72 (m, 1H), 2.49-2.43 (m, 1H), 2.22-2.05 (m, 2H), 1.97-1.89 (m, 1H), 1.69-1.58 (m, 1H). MS (ESI): m/z 418.30 [M + H]⁺.

Compound 292

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H), 8.40 (d, *J* = 5.8 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.40 (br s, 1H), 7.34 (d, *J* = 5.6 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.19 (br s, 1H), 7.13-7.09 (m, 1H), 6.06 (s, 1H), 3.77-3.72 (m, 1H), 2.48-2.40 (m, 1H), 2.21-2.13 (m, 2H), 1.97-1.93 (m, 1H), 1.66-1.63 (m, 1H). MS (ESI): m/z 418.30 [M + H]⁺.

Compound 293

¹H NMR (400 MHz, DMSO-d₆): δ 11.53 (br s, 1H), 9.00 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 7.40 (d, *J* = 5.6 Hz, 1H), 7.15 - 7.07 (m, 1H), 7.05 - 6.96 (m, 1H), 5.89 (s, 1H), 3.86 (d, *J* = 1.6 Hz, 3H), 3.26 - 3.20 (m, 1H), 2.96 - 2.84 (m, 1H), 2.46 - 2.37 (m, 1H), 2.15 - 1.81 (m, 5H). MS (ESI): m/z 419.1 [M + H]⁺.

Compound 294

¹H NMR (400 MHz, DMSO-d₆): δ 11.48 (br s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.41 (br s, 1H), 7.36-7.31 (m, 2H), 7.26-7.19 (m, 2H), 7.00 (br m, 1H), 6.14 (s, 1H), 3.25-3.14 (m, 2H), 2.41-2.39 (m, 2H), 2.21-2.15 (m, 1H), 2.07-1.94 (m, 2H), 1.82-1.74 (m, 1H). MS (ESI): m/z 420.40 [M + H]⁺.

Compound 295

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (s, 1H), 9.03 (s, 1H), 8.60 - 8.45 (m, 1H), 7.37 (d, *J* = 6.0 Hz, 1H), 7.23 - 6.96 (m, 2H), 6.14 (s, 1H), 3.83 (s, 3H), 3.75 - 3.62 (m, 1H), 3.29 - 3.25 (m, 1H), 2.48 - 2.40 (m, 2H), 2.35 - 2.17 (m, 1H), 1.91 - 1.79 (m, 1H), 1.65 - 1.35 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H). MS (ESI): m/z 421.1 [M + H]⁺.

Compound 296

¹H NMR (400 MHz, DMSO-d₆): δ 12.36 (br s, 1H), 7.95 (br m, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.39 (br s, 1H), 7.16 (br s, 1H), 7.10 (m, 1H), 7.02-6.96 (m, 1H), 3.79 (s, 3H), 3.60 (br m, 2H), 2.49-2.41 (m, 2H), 2.21-2.06 (m, 2H), 1.90-1.87 (m, 1H), 1.78 (br m, 1H). MS (ESI): m/z 422.40 [M + H]⁺.

Compound 297

¹H NMR (400 MHz, DMSO-d₆): δ 12.66 (br s, 1H), 9.11 (br m, 2H), 7.73-7.72 (m, 1H), 7.65 (br s, 1H), 7.57-7.56 (m, 1H), 7.20 (br s, 1H), 7.13 (br m, 1H), 7.03-6.89 (m, 1H), 3.75 (s, 3H), 3.65 (br m, 2H), 2.21-2.12 (m, 2H), 1.90-1.87 (m, 1H), 1.79 (br m, 1H). MS (ESI): m/z 422.40 [M + H]⁺

Compound 298

¹H NMR (400 MHz, DMSO-d₆): δ 11.29 (br s, 1H), 8.99 (br s, 1H), 7.77 (d, *J* = 5.6 Hz, 1H), 7.20 - 7.00 (m, 2H), 6.96 - 6.80 (br s, 1H), 6.38 (d, *J* = 5.6 Hz, 1H), 5.97 (s, 1H), 3.83 (s, 3H), 3.63 - 3.48 (m, 1H), 3.26 - 3.15 (m, 1H), 3.07 - 2.79 (m, 1H), 2.41 - 2.35 (m, 1H), 2.22 - 2.03 (m, 2H), 1.94 - 1.83 (m, 1H), 1.78 - 1.56 (m, 1H). MS (ESI): m/z 422.3 [M + H]⁺

Compound 299

¹H NMR (400 MHz, DMSO-d₆): δ 12.09 (br s, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 6.0 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.19 - 6.99 (m, 2H), 6.09 (s, 1H), 3.80 (s, 3H), 3.65 - 3.51 (m, 1H), 3.29 - 3.20 (m, 1H), 2.49 - 2.35 (m, 2H), 2.22 - 1.99 (m, 2H), 1.94 - 1.58 (m, 2H). MS (ESI): m/z 423.2 [M + H]⁺

Compound 300

¹H NMR (400 MHz, DMSO-d₆): δ 10.34 (br s, 1H), 9.26 (br s, 1H), 8.88 (br s, 1H), 9.93-9.92 (m, 1H), 7.65-7.62 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.38-7.36 (m, 1H), 7.12-7.09 (m, 1H), 3.92 (s, 3H), 3.43-3.41 (m, 1H), 3.22-3.16 (m, 1H), 2.40-2.36 (m, 1H), 2.23-2.06 (m, 3H), 1.85-1.82 (m, 1H), 1.70-1.50 (m, 1H). MS (ESI): m/z 424.40 [M + H]⁺

Compound 301

¹H NMR (400 MHz, CD₃OD) δ 8.47 - 8.40 (m, 1H), 7.46 - 7.33 (m, 1H), 7.08 - 6.97 (m, 2H), 6.92 (d, *J* = 6.4 Hz, 1H), 6.26 (s, 1H), 3.28 - 3.20 (m, 1H), 2.98 - 2.66 (m, 5H), 2.54 - 2.41 (m, 1H), 2.31 - 2.17 (m, 2H), 2.07 - 1.83 (m, 5H). MS (ESI): m/z 424.2 [M + H]⁺

Compound 302

¹H NMR (400 MHz, DMSO-d₆): δ 10.13 (br s, 1H), 7.79 (br s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.20 (br s, 1H), 7.14-7.06 (m, 2H), 3.89 (br m, 3H), 3.40-3.37 (m, 1H), 3.18-3.12 (m, 1H), 2.45-2.30 (m, 1H), 2.23-2.03 (m, 3H), 1.86-1.74 (m, 1H), 1.68-1.53 (m, 1H). MS (ESI): m/z 425.40 [M + H]⁺

Compound 303

¹H NMR (400 MHz, DMSO-d₆): δ 10.08 (s, 1H), 7.88-7.85 (m, 2H), 7.58 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.56 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.30-7.28 (m, 2H), 7.15-7.09 (m, 2H), 3.89 (s, 3H), 3.40-3.33 (m, 1H), 3.18-3.11 (m, 1H), 2.36-2.32 (m, 1H), 2.23-2.04 (m, 3H), 1.83-1.79 (m, 1H), 1.60-1.57 (m, 1H). MS (ESI): m/z 425.40 [M + H]⁺

Compound 304

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.79 (br s, 1H), 9.45 (br s, 1H), 9.10 (br s, 1H), 8.60 (d, *J* = 5.5 Hz, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 7.7.66-7.64 (m, 2H), 7.11-7.08 (m, 3H), 3.91 (br m, 3H), 3.28-3.20 (m, 1H), 2.48-2.40 (m, 1H), 2.33-2.08 (m, 3H), 1.86-1.82 (m, 1H), 1.67-1.58 (m, 1H). MS (ESI): *m/z* 425.25 [M + H]⁺

Compound 305

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.32 (br s, 1H), 10.23 (br s, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.12-7.09 (m, 2H), 3.93.89 (m, 3H), 3.51-3.37 (m, 1H), 3.21-3.14 (m, 1H), 2.41-2.35 (m, 1H), 2.23-2.01 (m, 3H), 1.85-1.79 (m, 1H), 1.68-1.52 (m, 1H). MS (ESI): *m/z* 424.30 [M + H]⁺

Compound 306

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.43 (br s, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 8.00 (dkd, *J* = 8.6, 2.2 Hz, 1H), 7.92-7.90 (m, 2H), 7.48 (br s, 1H), 7.12-7.07 (2H), 3.90 (br m, 3H), 3.41-3.38 (m, 1H), 3.20-3.14 (m, 1H), 2.42 (br m, 1H), 2.25-2.03 (m, 3H), 1.86-1.78 (m, 1H), 1.72-1.58 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺

Compound 307

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.52 (s, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 1.9 Hz, 1H), 8.01 (br s, 1H), 7.61-7.55 (m, 2H), 7.13-7.06 (m, 2H), 3.91-3.90 (m, 3H), 3.41-3.34 (m, 1H), 3.19-3.13 (m, 3H), 2.39-2.38 (m, 1H), 2.23-2.01 (m, 3H), 1.84-1.70 (m, 1H), 1.63-1.60 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺

Compound 308

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.52 (s, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.02 (br s, 1H), 7.61-7.55 (m, 2H), 7.14-7.07 (m, 2H), 3.91-3.90 (m, 3H), 3.41-3.34 (m, 1H), 3.19-3.13 (m, 1H), 2.39-2.38 (m, 1H), 2.23-2.01 (m, 3H), 1.84-1.76 (m, 1H), 1.68-1.52 (m, 1H). MS (ESI): *m/z* 426.30 [M + H]⁺

Compound 309

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.44 (s, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.38 (s, 2H), 7.16 - 7.08 (m, 1H), 7.03 - 6.97 (m, 1H), 3.96 (q, *J* = 10.0 Hz, 1H), 3.81 (d, *J* = 2.0 Hz, 3H), 3.07 (d, *J* = 10.0 Hz, 1H), 2.13 (t, *J* = 10.0 Hz, 1H), 1.90 (t, *J* = 10.4 Hz, 1H), 1.28 (s, 3H), 1.11 (s, 3H). MS (ESI): *m/z* 426.1 [M + H]⁺

Compound 310

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.65 (s, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.39 (s, 2H), 7.18 - 7.08 (m, 2H), 3.91 (d, *J* = 2.0 Hz, 3H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.59 (q, *J* = 9.2 Hz, 1H), 1.96 (d, *J* = 8.8 Hz, 2H), 1.25 (s, 3H), 0.77 (s, 3H). MS (ESI): *m/z* 426.1 [M + H]⁺

Compound 311

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.57 (br. s., 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.68 - 7.53 (m, 1H), 7.35 (br. s., 2H), 7.11 - 7.03 (m, 2H), 3.90 (s, 3H), 3.28 - 3.17 (m, 1H), 2.89 - 2.78 (m, 1H), 2.10 - 2.01 (m, 1H), 1.86 - 1.80 (m, 1H), 1.79 - 1.69 (m, 2H), 1.60 - 1.48 (m, 1H), 1.46 - 1.27 (m, 3H) MS (ESI): m/z 426.0 [M + H]⁺

Compound 312

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.11 - 7.05 (m, 1H), 7.01 - 6.92 (m, 1H), 6.14 (s, 1H), 3.28 - 3.23 (m, 1H), 3.01 - 2.92 (m, 1H), 2.22 (d, J = 2.4 Hz, 3H), 2.19 - 2.13 (m, 1H), 2.10 - 2.02 (m, 1H), 1.96 - 1.90 (m, 1H), 1.88 - 1.79 (m, 1H), 1.64 - 1.52 (m, 1H), 1.39 - 1.31 (m, 2H), 1.27 - 1.13 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H) MS (ESI): m/z 426.3 [M + H]⁺

Compound 313

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.99 - 6.90 (m, 1H), 6.15 (s, 1H), 3.43 - 3.35 (m, 1H), 3.07 - 2.96 (m, 1H), 2.23 (d, J = 1.6 Hz, 3H), 1.96 - 1.90 (m, 3H), 1.88 - 1.80 (m, 3H), 1.79 - 1.70 (m, 3H), 1.03 (t, J = 7.6 Hz, 3H) MS (ESI): m/z 426.3 [M + H]⁺

Compound 314

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.11 - 7.06 (m, 1H), 6.99 - 6.90 (m, 1H), 6.15 (s, 1H), 3.42 - 3.35 (m, 1H), 3.06 - 2.97 (m, 1H), 2.23 (d, J = 2.0 Hz, 3H), 1.96 - 1.90 (m, 3H), 1.88 - 1.80 (m, 3H), 1.79 - 1.69 (m, 3H), 1.03 (t, J = 7.6 Hz, 3H) MS (ESI): m/z 426.3 [M + H]⁺

Compound 315

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.9 (br s, 1H), 10.50 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.05 (dd, J = 8.6, 2.5 Hz, 1H), 7.96-7.94 (m, 1H), 7.12-7.07 (2H), 3.90 (br m, 3H), 3.42-3.36 (m, 1H), 3.21-3.15 (m, 1H), 2.43 (br m, 1H), 2.25-2.09 (m, 3H), 1.87-1.81 (m, 1H), 1.68-1.58 (m, 1H). MS (ESI): m/z 426.30 [M + H]⁺

Compound 316

¹H NMR (400 MHz, CD₃OD): δ 8.49 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 6.0 Hz, 1H), 6.87 - 6.76 (m, 1H), 6.58 - 6.49 (m, 1H), 6.36 (s, 1H), 5.02 - 4.99 (m, 1H), 3.72 - 3.66 (m, 4H), 3.38 (d, J = 9.2 Hz, 1H), 2.55 - 2.48 (m, 1H), 1.97 - 1.91 (m, 1H), 0.76 - 0.62 (m, 3H), 0.55 - 0.49 (m, 1H) MS (ESI): m/z 427.1 [M + H]⁺

Compound 317

MS (ESI): m/z 427.3 [M + H]⁺

Compound 318

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.72 - 10.14 (m, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H), 7.78 (dd, J = 1.6, 5.2 Hz, 1H), 7.60 - 7.50 (m, 1H), 7.49 - 7.19 (m, 2H), 7.08 -

6.97 (m, 1H), 4.57 - 4.47 (m, 1H), 4.32 - 4.18 (m, 1H), 3.90 (s, 3H), 3.76 - 3.64 (m, 2H), 2.14 - 2.00 (m, 1H), 1.83 - 1.70 (m, 1H), 1.68 - 1.52 (m, 1H), 1.48 - 1.37 (m, 1H). MS (ESI): m/z 427.8 $[M + H]^+$

Compound 319

^1H NMR (400 MHz, DMSO- d_6): δ 10.81 - 10.33 (m, 1H), 8.49 (d, $J = 1.6$ Hz, 1H), 8.20 (d, $J = 1.6$ Hz, 1H), 7.76 (dd, $J = 1.6, 5.6$ Hz, 1H), 7.54 - 7.23 (m, 2H), 7.21 - 7.03 (m, 2H), 4.29 - 4.20 (m, 1H), 4.13 - 4.03 (m, 1H), 3.77 (s, 3H), 3.69 - 3.57 (m, 1H), 3.29 - 3.27 (m, 1H), 1.93 - 1.64 (m, 4H). MS (ESI): m/z 427.8 $[M + H]^+$

Compound 320

^1H NMR (400 MHz, DMSO- d_6): δ 11.50 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.58 - 7.29 (m, 2H), 7.26 - 6.83 (m, 3H), 5.91 (s, 1H), 3.80 (s, 3H), 3.53 - 3.45 (m, 1H), 3.02 - 2.83 (m, 1H), 1.99 (m, 1H), 1.86 (m, 1H), 1.77 (m, 3H), 1.22 - 1.08 (m, 2H), 0.95 (d, $J = 6.0$ Hz, 3H). MS (ESI): m/z 428.1 $[M + H]^+$

Compound 321

^1H NMR (400 MHz, DMSO- d_6): δ 11.47 (br s, 1H), 8.45 - 8.35 (d, $J = 5.6$ Hz, 1H), 7.50 - 7.30 (m, 2H), 7.14 (m, 2H), 7.07 - 6.97 (m, 1H), 5.92 (s, 1H), 3.82 (s, 3H), 3.64 - 3.59 (m, 1H), 2.97 - 2.89 (m, 1H), 2.20 - 2.07 (m, 1H), 2.01 - 1.88 (m, 1H), 1.80 - 1.55 (m, 5H), 1.22 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 428.2 $[M + H]^+$

Compound 322

^1H NMR (400 MHz, DMSO- d_6): δ 11.50 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.53 - 7.30 (m, 2H), 7.17 (m, 3H), 5.91 (s, 1H), 3.80 (s, 3H), 3.48 (m, 1H), 3.01 - 2.83 (m, 1H), 1.99 (m, 1H), 1.86 (m, 1H), 1.84 - 1.63 (m, 3H), 1.17 (m, 2H), 0.95 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 428.1 $[M + H]^+$

Compound 323

^1H NMR (400 MHz, DMSO- d_6): δ 11.62 (br. s., 1H), 8.40 (d, $J = 5.6$ Hz, 1H), 7.43 - 7.37 (m, 1H), 7.36 - 7.32 (m, 1H), 7.32 - 7.15 (m, 2H), 6.94 - 6.82 (m, 2H), 6.13 (s, 1H), 3.58 - 3.45 (m, 1H), 3.30 - 3.21 (m, 1H), 2.48 - 2.29 (m, 3H), 2.28 (s, 3H), 1.91 - 1.80 (m, 1H), 1.43 - 1.30 (m, 1H), 1.02 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 430.1 $[M + H]^+$

Compound 324

^1H NMR (400 MHz, DMSO- d_6): δ 11.53 (s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.45 (d, $J = 6.0$ Hz, 1H), 7.38 (s, 1H), 7.25 - 7.10 (m, 3H), 5.87 (s, 1H), 3.66 - 3.54 (m, 1H), 3.14 - 3.03 (m, 1H), 2.20 (d, $J = 2.0$ Hz, 3H), 2.14 - 1.94 (m, 3H), 1.91 - 1.74 (m, 2H), 1.73 - 1.59 (m, 1H), 1.42 - 1.32 (m, 3H). MS (ESI): m/z 430.0 $[M + H]^+$

Compound 325

^1H NMR (400 MHz, DMSO- d_6): δ 11.53 (s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.45 (d, $J = 5.6$ Hz, 1H), 7.38 (s, 1H), 7.24 - 7.11 (m, 3H), 5.87 (s, 1H), 3.63 - 3.56 (m, 1H), 3.13 - 3.03 (m,

1H), 2.20 (d, $J = 1.6$ Hz, 3H), 2.17 - 2.09 (m, 1H), 2.06 - 1.94 (m, 2H), 1.92 - 1.83 (m, 1H), 1.82 - 1.59 (m, 2H), 1.45 - 1.33 (m, 3H). MS (ESI): m/z 430.0 $[M + H]^+$

Compound 326

^1H NMR (400 MHz, DMSO- d_6): δ 11.45 (s, 1H), 8.41 (d, $J = 5.6$ Hz, 1H), 7.36 (d, $J = 6.0$ Hz, 2H), 7.24 - 7.09 (m, 3H), 6.06 (s, 1H), 3.44 - 3.35 (m, 1H), 3.15 - 3.04 (m, 1H), 2.23 (d, $J = 2.0$ Hz, 3H), 2.05 - 1.98 (m, 2H), 1.96 - 1.84 (m, 3H), 1.81 - 1.73 (m, 1H), 1.72 - 1.63 (m, 3H). MS (ESI): m/z 430.0 $[M + H]^+$

Compound 327

^1H NMR (400 MHz, DMSO- d_6): δ 11.46 (s, 1H), 8.42 (d, $J = 6.0$ Hz, 1H), 7.37 (d, $J = 5.6$ Hz, 2H), 7.26 - 7.10 (m, 3H), 6.07 (s, 1H), 3.43 - 3.36 (m, 1H), 3.17 - 3.03 (m, 1H), 2.23 (d, $J = 1.2$ Hz, 3H), 2.06 - 1.98 (m, 2H), 1.97 - 1.85 (m, 3H), 1.82 - 1.74 (m, 1H), 1.73 - 1.63 (m, 3H). MS (ESI): m/z 430.0 $[M + H]^+$

Compound 328

^1H NMR (400 MHz, CD_3OD) δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.47 - 7.28 (m, 2H), 6.85 (dt, $J = 2.4, 8.4$ Hz, 1H), 6.76 (dd, $J = 2.4, 10.0$ Hz, 1H), 6.31 (s, 1H), 3.49 - 3.34 (m, 2H), 2.77 - 2.74 (m, 1H), 2.63 - 2.35 (m, 3H), 2.32 - 2.10 (m, 2H), 2.05 - 1.82 (m, 2H), 1.16 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 430.2 $[M + H]^+$

Compound 329

^1H NMR (400 MHz, CD_3OD) δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.47 - 7.28 (m, 2H), 6.85 (dt, $J = 2.4, 8.4$ Hz, 1H), 6.76 (dd, $J = 2.4, 10.0$ Hz, 1H), 6.31 (s, 1H), 3.49 - 3.34 (m, 2H), 2.77 - 2.74 (m, 1H), 2.63 - 2.35 (m, 3H), 2.32 - 2.10 (m, 2H), 2.05 - 1.82 (m, 2H), 1.16 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 430.2 $[M + H]^+$

Compound 330

^1H NMR (400 MHz, DMSO- d_6): δ 10.62 (br s, 1H), 8.40 (d, $J = 5.4$ Hz, 1H), 8.06 - 8.03 (m, 2H), 7.60 (d, $J = 3.0$ Hz, 2H), 7.47 - 7.41 (m, 1H), 7.30 - 7.27 (m, 1H), 3.55 - 3.49 (m, 1H), 3.24 (br m, 1H), 2.49 (br m, 1H), 2.32 - 2.08 (m, 3H), 1.92 - 1.89 (m, 1H), 1.55 (m, 1H). MS (ESI): m/z 430.34 $[M + H]^+$

Compound 331

^1H NMR (400 MHz, DMSO- d_6): δ 10.63 (br s, 1H), 8.40 (d, $J = 5.4$ Hz, 1H), 8.07 - 8.03 (m, 2H), 7.60 (d, $J = 3.0$ Hz, 2H), 7.47 - 7.41 (m, 1H), 7.30 - 7.27 (m, 1H), 3.55 - 3.49 (m, 1H), 3.26 - 3.23 (m, 1H), 2.49 (br m, 1H), 2.32 - 2.08 (m, 3H), 1.92 - 1.89 (m, 1H), 1.55 (m, 1H). MS (ESI): m/z 430.34 $[M + H]^+$

Compound 332

^1H NMR (400 MHz, DMSO- d_6): δ 10.41 (br s, 1H), 7.99 (br s, 1H), 7.54 (br m, 1H), 7.47 (br m, 1H), 7.36 (br s, 1H), 7.10 - 7.06 (m, 2H), 3.90 (s, 3H), 3.39 - 3.36 (m, 1H), 3.11 - 3.09 (m,

1H), 2.40-2.30 (m, 1H), 2.20-2.00 (m, 3H), 1.85-1.75 (m, 1 H), 1.70-1.50 (m, 1H). MS (ESI): m/z 431.26 $[M + H]^+$.

Compound 333

^1H NMR (400 MHz, DMSO- d_6): δ 10.19 (br s, 1H), 8.14 (s, 1H), 7.71-7.67 (m, 1H), 7.51-7.45 (m, 2H), 7.33 (br s, 2H), 7.26 (q, $J = 9.5$ Hz, 1H), 7.11-7.05 (m, 1H), 6.78-6.75 (m, 1H), 4.70 (br s, 1H), 3.69-3.65 (m, 1H), 3.56-3.53 (m, 1H), 2.75-2.49 (m, 1H), 2.43-2.36 (m, 1H), 2.16-2.30 (m, 2H). MS (ESI): m/z 449.30 $[M + H]^+$.

Compound 334

^1H NMR (400 MHz, DMSO- d_6): δ 11.63-11.59 (m, 1H), 8.40 (d, $J = 5.7$ Hz, 1H), 7.41-7.36 (m, 2H), 7.19 (br s, 1H), 7.11-7.09 (m, 2H), 6.77-6.62 (m, 2H), 5.96-5.93 (m, 1H), 3.83-3.73 (m, 4H), 3.63-3.42 (m, 1H), 2.39-2.34 (m, 2H), 2.17-2.11 (m, 2H), 2.04 (br m, 1H), 1.90-1.76 (m, 1H). MS (ESI): m/z 432.40 $[M + H]^+$.

Compound 335

^1H -NMR (400 MHz, DMSO- d_6): δ 11.52 (br s, 1H), 8.39 (d, $J = 5.8$ Hz, 1H), 7.40 (br s, 1H), 7.31 (d, $J = 5.8$ Hz, 1H), 7.19 (br s, 1H), 6.99-6.95 (m, 2H), 6.70-6.67 (m, 1H), 6.14 (s, 1H), 3.77 (s, 3H), 3.18-3.16 (m, 2H), 2.41 (br m, 2H), 2.33-1.95 (m, 3H), 1.82-1.79 (m, 1H), MS (ESI): m/z 432.36 $[M + H]^+$.

Compound 336

^1H NMR (400 MHz, DMSO- d_6): δ 11.58 (br s, 1H), δ 8.40 (d, $J = 5.6$ Hz, 1H), 7.40 (br s, 1H), 7.35 (d, $J = 5.6$ Hz, 1H), 7.18 (br m, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 3.60 (br m, 1H), 3.24-3.19 (m, 1H), 2.36 (m, 1H), 2.17 (br m, 2H), 2.06-2.03 (m, 1H), 1.85 (br m, 1H), 1.65 (br s, 1H). MS (ESI): m/z 432.10 $[M + H]^+$.

Compound 337

^1H NMR (400 MHz, DMSO- d_6): δ 11.58 (br s, 1H), δ 8.40 (d, $J = 5.6$ Hz, 1H), 7.39 (br s, 1H), 7.36-7.35 (m, 1H), 7.18 (br s, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 3.56 (br m, 1H), 3.20-3.18 (m, 1H), 2.36 (br m, 1H), 2.17 (br m, 2H), 2.06-2.03 (m, 1H), 1.86 (br m, 1H), 1.64 (br s, 1H). MS (ESI): m/z 435.05 $[M + H]^+$.

Compound 338

^1H NMR (400 MHz, DMSO- d_6): δ 11.60 (br s, 1H), 8.41 (d, $J = 5.8$ Hz, 1H), 7.42 (br s, 1H), 7.36 (d, $J = 5.8$ Hz, 1H), 7.19 (br s, 1H), 7.14 (br s, 2H), 6.9-6.83 (m, 1H), 6.04 (s, 1H), 3.76-3.61 (m, 4H), 3.22 (br m, 1H), 2.42-2.34 (m, 2H), 2.19-2.07 (m, 2H), 1.92-1.88 (m, 1 H), 1.75-1.60 (m, 1H). MS (ESI): m/z 432.40 $[M + H]^+$.

Compound 339

^1H NMR (400 MHz, DMSO- d_6): δ 11.57 (br s, 1H), δ 8.40 (d, $J = 5.2$ Hz, 1H), 7.39 (br s, 1H), 7.35 (d, $J = 5.2$ Hz, 1H), 7.18 (br m, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s,

1H), 3.72 (s, 3H), 3.59-3.54 (m, 1H), 3.21 (br m, 1H), 2.40-2.33 (m, 2H), 2.30-2.00 (m, 2H), 1.99-1.80 (m, 1H), 1.79-1.55 (m, 1H). MS (ESI): m/z 432.40 [M + H]⁺.

Compound 340

¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.41 (br s, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.19 (br s, 1H), 7.13 (br s, 1H), 7.00-6.97 (m, 2H), 6.08 (s, 1H), 3.76 (s, 3H), 3.66 (br m, 1H), 3.27-3.22 (m, 1H), 2.39 (br m, 2H), 2.20-2.04 (m, 2H), 1.92-1.90 (m, 1H), 1.66 (br m, 1H). MS (ESI): m/z 432.40 [M + H]⁺.

Compound 341

¹H NMR (400 MHz, DMSO-d₆): δ 11.55 (br s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.51 - 7.35 (m, 4H), 7.19 (br s, 1H), 5.99 (s, 1H), 4.07 - 3.81 (m, 1H), 3.62 - 3.49 (m, 1H), 2.21 - 2.04 (m, 2H), 1.91 - 1.83 (m, 1H), 1.49 - 1.46 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H). MS (ESI): m/z 432.2 [M + H]⁺.

Compound 342

¹H NMR (400 MHz, DMSO-d₆): δ 11.55 (br s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.48 - 7.35 (m, 4H), 7.19 (br s, 1H), 5.99 (s, 1H), 3.99 - 3.87 (m, 1H), 3.57 - 3.55 (m, 1H), 2.21 - 2.06 (m, 2H), 1.92 - 1.82 (m, 1H), 1.49 - 1.47 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H). MS (ESI): m/z 432.2 [M + H]⁺.

Compound 344

¹H NMR (400 MHz, DMSO-d₆): δ 8.57 - 8.39 (m, 1H), 7.58 - 7.43 (m, 1H), 7.33 - 7.22 (m, 1H), 7.21 - 7.12 (m, 1H), 6.10 (s, 1H), 3.72 - 3.57 (m, 1H), 3.05 - 2.90 (m, 1H), 2.19 - 2.07 (m, 1H), 2.01 - 1.85 (m, 3H), 1.82 - 1.72 (m, 1H), 1.30 - 1.18 (m, 2H), 1.08 - 0.94 (m, 3H). MS (ESI): m/z 432.1 [M + H]⁺.

Compound 345

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.39 (br s, 1H), 7.33 (d, J = 5.6 Hz, 1H), 7.18-6.99 (m, 3H), 6.12 (s, 1H), 3.52-3.46 (m, 1H), 2.39 (m, 1H), 2.22-2.09 (m, 6H), 2.00-1.90 (m, 1H), 1.63-1.53 (m, 1H). MS (ESI): m/z 434.05 [M + H]⁺.

Compound 346

¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.43 (br s, 1H), 7.36 (d, J = 5.8 Hz, 1H), 7.21-7.07 (m, 4H), 6.02-6.01 (m, 1H), 3.89-3.80 (m, 1H), 3.53-3.47 (m, 1H), 2.58-2.51 (m, 1H), 2.43-2.39 (m, 1H), 2.22-1.92 (m, 5H). MS (ESI): m/z 436.32 [M + H]⁺.

Compound 348

¹H NMR (400 MHz, DMSO-d₆): δ 11.58 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.42 (br s, 1H), 7.34 (d, J = 5.8 Hz, 1H), 7.29 (dd, J = 8.8, 2.5 Hz, 1H), 7.21 (br s, 1H), 7.17-7.12 (m, 1H), 6.05 (s, 1H), 3.74-3.69 (m, 1H), 3.34-3.31 (m, 1H), 2.49-2.35 (m, 2H), 2.30-2.02 (m, 2H), 2.00-1.88 (m, 1H), 1.71-1.60 (m, 1H). MS (ESI): m/z 436.30 [M + H]⁺.

Compound 350

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.56-7.27 (m, 4H), 7.20 (br s, 1H), 7.03-6.98 (m, 1H), 6.09 (s, 1H), 3.75-3.70 (m, 1H), 2.61-2.53 (m, 1H), 2.45-2.39 (m, 1H), 2.21 (br m, 2H), 2.12-2.09 (m, 1H), 1.97-1.90 (m, 1H), 1.72-1.63 (m, 1H). MS (ESI): *m/z* 436.30 [M + H]⁺

Compound 351

¹H NMR (400 MHz, DMSO-d₆): δ 10.07 (br s, 1H), 7.33-7.27 (m, 2H), 7.16-7.07 (m, 2H), 6.32 (br s, 2H), 3.90 (br m, 3H), 3.41-3.37 (m, 1H), 3.20-3.13 (m, 1H), 2.39 (br m, 1H), 2.23-2.01 (m, 3H), 1.85-1.81 (m, 1H), 1.60-1.58 (m, 1H). MS (ESI): *m/z* 438.30 [M + H]⁺

Compound 352

¹H NMR (400 MHz, DMSO-d₆): δ 10.59 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.38 (s, 2H), 7.22 - 7.08 (m, 2H), 3.95 - 3.87 (m, 1H), 3.85 (d, *J* = 1.2 Hz, 3H), 3.26 - 3.22 (m, 1H), 2.08 - 2.00 (m, 1H), 1.98 - 1.89 (m, 2H), 1.78 (s, 1H), 0.63 - 0.46 (m, 4H). MS (ESI): *m/z* 439.1 [M + H]⁺

Compound 353

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.37 (br. s., 2H), 7.11 - 7.02 (m, 2H), 3.89 (d, *J* = 0.8 Hz, 3H), 3.03 - 2.92 (m, 1H), 2.83 - 2.71 (m, 1H), 2.49 - 2.41 (m, 1H), 2.01 - 1.93 (m, 1H), 1.80 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.14 - 1.00 (m, 2H), 0.77 - 0.65 (m, 1H), 0.27 - 0.18 (m, 1H). MS (ESI): *m/z* 438.1 [M + H]⁺

Compound 354

¹H NMR (400 MHz, DMSO-d₆): δ 10.57 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.36 (br. s., 2H), 7.07 - 7.00 (m, 1H), 6.98 - 6.91 (m, 1H), 3.92 (s, 3H), 3.12 - 3.02 (m, 1H), 2.74 - 2.65 (m, 1H), 2.28 - 2.15 (m, 2H), 2.06 - 1.97 (m, 1H), 1.40 - 1.29 (m, 1H), 1.13 - 0.99 (m, 2H), 0.77 - 0.65 (m, 1H), 0.24 - 0.14 (m, 1H). MS (ESI): *m/z* 438.1 [M + H]⁺

Compound 355

¹H NMR (400 MHz, DMSO-d₆): δ 10.09 (br s, 1H), 8.13 (s, 1H), 7.65-7.62 (m, 1H), 7.47-7.41 (m, 2H), 7.30 (br s, 2H), 7.21-7.16 (m, 4H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.02-7.00 (m, 2H), 6.90-6.85 (m, 1H), 4.69 (d, *J* = 15.2 Hz, 1H), 4.49-4.46 (m, 1H), 4.19 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.28-3.14 (m, 2H). MS (ESI): *m/z* 438.3 [M + H]⁺

Compound 336

¹H NMR (400 MHz, DMSO-d₆): δ 11.58 (br s, 1H), δ 8.40 (d, *J* = 5.6 Hz, 1H), 7.40 (br s, 1H), 7.35 (d, *J* = 5.6 Hz, 1H), 7.18 (br m, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 3.60 (br m, 1H), 3.24-3.19 (m, 1H), 2.36 (m, 1H), 2.17 (br m, 2H), 2.06-2.03 (m, 1H), 1.85 (br m, 1H), 1.65 (br s, 1H). MS (ESI): *m/z* 432.10 [M + H]⁺

Compound 337

¹H NMR (400 MHz, DMSO-d₆): δ 11.58 (br s, 1H), δ 8.40 (d, J = 5.6 Hz, 1H), 7.39 (br s, 1H), 7.36-7.35 (m, 1H), 7.18 (br s, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 3.56 (br m, 1H), 3.20-3.18 (m, 1H), 2.36 (br m, 1H), 2.17 (br m, 2H), 2.06-2.03 (m, 1H), 1.86 (br m, 1H), 1.64 (br s, 1H). MS (ESI): *m/z* 435.05 [M + H]⁺.

Compound 338

¹H NMR (400 MHz, DMSO-d₆): δ 11.60 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.42 (br s, 1H), 7.36 (d, J = 5.8 Hz, 1H), 7.19 (br s, 1H), 7.14 (br s, 2H), 6.9-6.83 (m, 1H), 6.04 (s, 1H), 3.76-3.61 (m, 4H), 3.22 (br m, 1H), 2.42-2.34 (m, 2H), 2.19-2.07 (m, 2H), 1.92-1.88 (m, 1H), 1.75-1.60 (m, 1H). MS (ESI): *m/z* 432.40 [M + H]⁺.

Compound 339

¹H NMR (400 MHz, DMSO-d₆): δ 11.57 (br s, 1H), δ 8.40 (d, J = 5.2 Hz, 1H), 7.39 (br s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.18 (br m, 2H), 6.75-6.72 (m, 1H), 6.62 (br m, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 3.59-3.54 (m, 1H), 3.21 (br m, 1H), 2.40-2.33 (m, 2H), 2.30-2.00 (m, 2H), 1.99-1.80 (m, 1H), 1.79-1.55 (m, 1H). MS (ESI): *m/z* 432.40 [M + H]⁺.

Compound 340

¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.41 (br s, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.19 (br s, 1H), 7.13 (br s, 1H), 7.00-6.97 (m, 2H), 6.08 (s, 1H), 3.76 (s, 3H), 3.66 (br m, 1H), 3.27-3.22 (m, 1H), 2.39 (br m, 2H), 2.20-2.04 (m, 2H), 1.92-1.90 (m, 1H), 1.66 (br m, 1H). MS (ESI): *m/z* 432.40 [M + H]⁺.

Compound 341

¹H NMR (400 MHz, DMSO-d₆): δ 11.55 (br s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.51 - 7.35 (m, 4H), 7.19 (br s, 1H), 5.99 (s, 1H), 4.07 - 3.81 (m, 1H), 3.62 - 3.49 (m, 1H), 2.21 - 2.04 (m, 2H), 1.91 - 1.83 (m, 1H), 1.49 - 1.46 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H). MS (ESI): *m/z* 432.2 [M + H]⁺.

Compound 342

¹H NMR (400 MHz, DMSO-d₆): δ 11.55 (br s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.48 - 7.35 (m, 4H), 7.19 (br s, 1H), 5.99 (s, 1H), 3.99 - 3.87 (m, 1H), 3.57 - 3.55 (m, 1H), 2.21 - 2.06 (m, 2H), 1.92 - 1.82 (m, 1H), 1.49 - 1.47 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H). MS (ESI): *m/z* 432.2 [M + H]⁺.

Compound 344

¹H NMR (400 MHz, DMSO-d₆): δ 8.57 - 8.39 (m, 1H), 7.58 - 7.43 (m, 1H), 7.33 - 7.22 (m, 1H), 7.21 - 7.12 (m, 1H), 6.10 (s, 1H), 3.72 - 3.57 (m, 1H), 3.05 - 2.90 (m, 1H), 2.19 - 2.07 (m, 1H), 2.01 - 1.85 (m, 3H), 1.82 - 1.72 (m, 1H), 1.30 - 1.18 (m, 2H), 1.08 - 0.94 (m, 3H). MS (ESI): *m/z* 432.1 [M + H]⁺.

Compound 345

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.39 (br s, 1H), 7.33 (d, J = 5.6 Hz, 1H), 7.18-6.99 (m, 3H), 6.12 (s, 1H), 3.52-3.46 (m, 1H), 2.39 (m, 1H), 2.22-2.09 (m, 6H), 2.00-1.90 (m, 1H), 1.63-1.53 (m, 1H). MS (ESI): m/z 434.05 [M + H]⁺

Compound 346

¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.43 (br s, 1H), 7.36 (d, J = 5.8 Hz, 1H), 7.21-7.07 (m, 4H), 6.02-6.01 (m, 1H), 3.89-3.80 (m, 1H), 3.53-3.47 (m, 1H), 2.58-2.51 (m, 1H), 2.43-2.39 (m, 1H), 2.22-1.92 (m, 5H). MS (ESI): m/z 436.32 [M + H]⁺

Compound 348

¹H NMR (400 MHz, DMSO-d₆): δ 11.58 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.42 (br s, 1H), 7.34 (d, J = 5.8 Hz, 1H), 7.29 (dd, J = 8.8, 2.5 Hz, 1H), 7.21 (br s, 1H), 7.17-7.12 (m, 1H), 6.05 (s, 1H), 3.74-3.69 (m, 1H), 3.34-3.31 (m, 1H), 2.49-2.35 (m, 2H), 2.30-2.02 (m, 2H), 2.00-1.88 (m, 1H), 1.71-1.60 (m, 1H). MS (ESI): m/z 436.30 [M + H]⁺

Compound 350

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 7.56-7.27 (m, 4H), 7.20 (br s, 1H), 7.03-6.98 (m, 1H), 6.09 (s, 1H), 3.75-3.70 (m, 1H), 2.61-2.53 (m, 1H), 2.45-2.39 (m, 1H), 2.21 (br m, 2H), 2.12-2.09 (m, 1H), 1.97-1.90 (m, 1H), 1.72-1.63 (m, 1H). MS (ESI): m/z 436.30 [M + H]⁺

Compound 351

¹H NMR (400 MHz, DMSO-d₆): δ 10.07 (br s, 1H), 7.33-7.27 (m, 2H), 7.16-7.07 (m, 2H), 6.32 (br s, 2H), 3.90 (br m, 3H), 3.41-3.37 (m, 1H), 3.20-3.13 (m, 1H), 2.39 (br m, 1H), 2.23-2.01 (m, 3H), 1.85-1.81 (m, 1H), 1.60-1.58 (m, 1H). MS (ESI): m/z 438.30 [M + H]⁺

Compound 352

¹H NMR (400 MHz, DMSO-d₆): δ 10.59 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 2.0, 5.6 Hz, 1H), 7.38 (s, 2H), 7.22 - 7.08 (m, 2H), 3.95 - 3.87 (m, 1H), 3.85 (d, J = 1.2 Hz, 3H), 3.26 - 3.22 (m, 1H), 2.08 - 2.00 (m, 1H), 1.98 - 1.89 (m, 2H), 1.78 (s, 1H), 0.63 - 0.46 (m, 4H). *Compound 353*

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 2.0, 5.6 Hz, 1H), 7.37 (br. s., 2H), 7.11 - 7.02 (m, 2H), 3.89 (d, J = 0.8 Hz, 3H), 3.03 - 2.92 (m, 1H), 2.83 - 2.71 (m, 1H), 2.49 - 2.41 (m, 1H), 2.01 - 1.93 (m, 1H), 1.80 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.14 - 1.00 (m, 2H), 0.77 - 0.65 (m, 1H), 0.27 - 0.18 (m, 1H). MS (ESI): m/z 438.1 [M + H]⁺

Compound 354

¹H NMR (400 MHz, DMSO-d₆): δ 10.57 (s, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 2.0, 5.6 Hz, 1H), 7.36 (br. s., 2H), 7.07 - 7.00 (m, 1H), 6.98 - 6.91 (m, 1H),

3.92 (s, 3H), 3.12 - 3.02 (m, 1H), 2.74 - 2.65 (m, 1H), 2.28 - 2.15 (m, 2H), 2.06 - 1.97 (m, 1H), 1.40 - 1.29 (m, 1H), 1.13 - 0.99 (m, 2H), 0.77 - 0.65 (m, 1H), 0.24 - 0.14 (m, 1H). MS (ESI): m/z 438.1 $[M + H]^+$

Compound 355

^1H NMR (400 MHz, DMSO- d_6): δ 10.09 (br s, 1H), 8.13 (s, 1H), 7.65-7.62 (m, 1H), 7.47-7.41 (m, 2H), 7.30 (br s, 2H), 7.21-7.16 (m, 4H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.02-7.00 (m, 2H), 6.90-6.85 (m, 1H), 4.69 (d, $J = 15.2$ Hz, 1H), 4.49-4.46 (m, 1H), 4.19 (d, $J = 15.2$ Hz, 1H), 3.82 (s, 3H), 3.28-3.14 (m, 2H). MS (ESI): m/z 438.3 $[M + H]^+$

Compound 356

^1H NMR (400 MHz, DMSO- d_6): δ 10.09 (br s, 1H), 8.13 (s, 1H), 7.65-7.62 (m, 1H), 7.46-7.41 (m, 2H), 7.30 (brs, 2H), 7.21-7.16 (m, 4H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.01-7.00 (m, 2H), 6.90-6.85 (m, 1H), 4.69 (d, $J = 15.2$ Hz, 1H), 4.49-4.46 (m, 1H), 4.19 (d, $J = 15.2$ Hz, 1H), 3.82 (s, 3H), 3.28-3.14 (m, 2H). MS (ESI): m/z 438.3 $[M + H]^+$

Compound 357

^1H NMR (400 MHz, DMSO- d_6): δ 11.63 (br s, 1H), 9.00 (s, 1H), 8.51 (d, $J = 6.0$ Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.32 (d, $J = 5.6$ Hz, 1H), 7.06 (d, $J = 8.8$ Hz, 1H), 7.06 (s, 1H), 6.17 (s, 1H), 3.51-3.46 (m, 1H), 3.31-3.29 (m, 1H), 2.49-2.43 (m, 2H), 2.29 (s, 3H), 2.23-2.06 (m, 2H), 1.95-1.92 (m, 1H), 1.66-1.59 (m, 1H). MS (ESI): m/z 439.30 $[M + H]^+$

Compound 358

^1H NMR (400 MHz, DMSO- d_6): δ 11.66 (br s, 1H), 9.00 (s, 1H), 8.52 (d, $J = 5.8$ Hz, 1H), 7.55 (br s, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.34 (d, $J = 5.8$ Hz, 1H), 6.06 (s, 1H), 3.75 (br m, 4H), 3.39-3.25 (m, 1H), 2.41 (br m, 2H), 2.24-2.07 (m, 2H), 1.99-1.91 (m, 1H), 1.71-1.59 (m, 1H). MS (ESI): m/z 439.30 $[M + H]^+$

Compound 359

^1H NMR (400 MHz, DMSO- d_6): δ 11.62 (s, 1H), 8.41 (d, $J = 5.8$ Hz, 1H), 7.44-7.30 (m, 5H), 7.19 (s, 1H), 6.01 (s, 1H), 3.78-3.72 (s, 4H), 3.22-3.17 (m, 1H), 2.44-2.39 (m, 2H), 2.22-2.04 (m, 2H), 1.90-1.88 (m, 1H), 1.75-1.56 (m, 1H). MS (ESI): m/z 439.40 $[M + H]^+$

Compound 360

^1H NMR (400 MHz, DMSO- d_6): δ 10.17 (s, 1H), 8.45 (d, $J = 5.6$ Hz, 1H), 8.04 (d, $J = 2.0$ Hz, 1H), 7.55 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (s, 2H), 7.01 - 6.86 (m, 2H), 3.97 (s, 3H), 3.22 - 3.18 (m, 1H), 2.82 - 2.75 (m, 1H), 1.95 - 1.87 (m, 2H), 1.78 - 1.70 (m, 1H), 1.50 - 1.40 (m, 3H), 1.25 - 1.22 (m, 1H), 0.91 (d, $J = 6.8$ Hz, 3H). MS (ESI): m/z 440.2 $[M + H]^+$

Compound 361

^1H NMR (400 MHz, DMSO- d_6): δ 10.65 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.59 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.36 (br s, 2H), 7.11 - 7.03 (m, 1H), 7.00 - 6.93 (m,

1H), 3.97 (s, 3H), 3.15 - 3.08 (m, 1H), 2.48 - 2.42 (m, 1H), 1.78 - 1.46 (m, 6H), 1.27 - 1.20 (m, 1H), 0.97 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 362

^1H NMR (400 MHz, DMSO- d_6): δ 10.64 (br. s., 1H), 8.53 (d, $J = 5.6$ Hz, 1H), 8.11 (d, $J = 1.6$ Hz, 1H), 7.77 - 7.55 (m, 1H), 7.31 - 7.03 (m, 2H), 3.96 (s, 3H), 3.29 - 3.24 (m, 1H), 3.06 - 2.90 (m, 1H), 2.11 - 2.01 (m, 1H), 1.87 - 1.72 (m, 2H), 1.68 - 1.60 (m, 1H), 1.51 - 1.26 (m, 2H), 1.24 - 1.11 (m, 1H), 1.02 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 363

^1H NMR (400 MHz, DMSO- d_6): δ 10.64 (s, 1H), 8.56 (d, $J = 5.6$ Hz, 1H), 8.20 (d, $J = 2.0$ Hz, 1H), 7.74 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.30 - 7.11 (m, 2H), 3.96 - 3.86 (m, 4H), 3.31 - 3.24 (m, 1H), 2.12 - 1.93 (m, 2H), 1.81 - 1.69 (m, 1H), 1.64 - 1.55 (m, 1H), 1.25 - 1.16 (m, 6H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 364

^1H NMR (400 MHz, DMSO- d_6): δ 10.42 (s, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 8.00 (s, 1H), 7.65 - 7.53 (m, 1H), 7.37 (s, 2H), 7.20 - 7.00 (m, 2H), 3.88 (s, 3H), 3.11 - 2.98 (m, 1H), 2.86 - 2.71 (m, 1H), 2.08 - 1.96 (m, 1H), 1.90 - 1.76 (m, 2H), 1.64 - 1.41 (m, 3H), 1.28 - 1.07 (m, 1H), 0.60 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 365

^1H NMR (400 MHz, DMSO- d_6): δ (d, $J = 5.6$ Hz, 1H), 8.06 (s, 1H), 7.58 (d, $J = 5.6$ Hz, 1H), 7.13 - 7.02 (m, 1H), 6.98 - 6.92 (m, 1H), 3.91 (s, 3H), 3.59 - 3.56 (m, 1H), 3.19 - 3.15 (m, 1H), 2.05 - 1.95 (m, 2H), 1.76 - 1.64 (m, 2H), 1.61 - 1.47 (m, 3H), 0.70 (d, $J = 7.2$ Hz, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 366

^1H NMR (400 MHz, DMSO- d_6): δ 10.60 (d, $J = 5.6$ Hz, 1H), 8.06 (s, 1H), 7.58 (d, $J = 5.6$ Hz, 1H), 7.13 - 7.02 (m, 1H), 6.98 - 6.92 (m, 1H), 3.91 (s, 3H), 3.59 - 3.56 (m, 1H), 3.19 - 3.15 (m, 1H), 2.05 - 1.95 (m, 2H), 1.76 - 1.64 (m, 2H), 1.61 - 1.47 (m, 3H), 0.70 (d, $J = 7.2$ Hz, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 367

^1H NMR (400 MHz, DMSO- d_6): δ 10.60 - 10.50 (m, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.19 - 8.09 (m, 1H), 7.76 - 7.65 (m, 1H), 7.39 (br s., 2H), 7.16 - 7.05 (m, 2H), 3.86 - 3.81 (m, 3H), 3.76 - 3.67 (m, 1H), 3.09 - 2.98 (m, 1H), 2.34 - 2.25 (m, 1H), 2.18 - 2.07 (m, 1H), 1.84 - 1.75 (m, 2H), 1.50 - 1.35 (m, 3H), 0.97 - 0.84 (m, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 368

^1H NMR (400 MHz, DMSO- d_6): δ 10.32 (s, 1H), 8.45 (d, $J = 5.6$ Hz, 1H), 8.09 (d, $J = 2.0$ Hz, 1H), 7.52 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (br s, 2H), 7.12 - 6.96 (m, 2H), 3.92 (d, $J = 1.6$ Hz, 3H), 3.54 - 3.46 (m, 1H), 2.69 - 2.63 (m, 1H), 2.45 - 2.32 (m, 1H), 2.27 - 2.16 (m, 1H),

2.03 - 1.91 (m, 1H), 1.70 - 1.60 (m, 2H), 1.56 - 1.47 (m, 1H), 1.36 - 1.27 (m, 1H), 1.18 (d, $J = 6.8$ Hz, 3H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 369

^1H NMR (400 MHz, DMSO- d_6): δ 10.58 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $J = 2.0$ Hz, 1H), 7.61 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.29 (br s, 2H), 7.14 - 7.03 (m, 2H), 3.91 (s, 3H), 3.57 - 3.45 (m, 1H), 2.87 - 2.75 (m, 1H), 2.13 - 2.05 (m, 1H), 1.88 - 1.72 (m, 2H), 1.71 - 1.48 (m, 4H), 1.13 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 370

^1H NMR (400 MHz, DMSO- d_6): δ 10.58 (br s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 1.6$ Hz, 1H), 7.61 (dd, $J = 1.6, 5.6$ Hz, 1H), 7.36 (br s, 2H), 7.15 - 7.01 (m, 2H), 3.90 (s, 3H), 3.32 - 3.26 (m, 1H), 2.85 - 2.75 (m, 1H), 2.10 - 2.02 (m, 1H), 1.86 - 1.78 (m, 1H), 1.74 - 1.66 (m, 1H), 1.66 - 1.52 (m, 2H), 1.13 - 0.97 (m, 2H), 0.90 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 371

MS (ESI): m/z 482.6 $[M + H]^+$

Compound 372

^1H NMR (400 MHz, DMSO- d_6): δ 10.47 (br s, 1H), 8.46 (d, $J = 5.6$ Hz, 1H), 8.02 (s, 1H), 7.67 - 7.59 (m, 1H), 7.37 (s, 2H), 7.23 - 7.00 (m, 2H), 3.84 (s, 3H), 3.29 - 3.23 (m, 1H), 2.48 - 2.42 (m, 1H), 1.85 - 1.64 (m, 4H), 1.56 - 1.40 (m, 1H), 1.38 - 1.25 (m, 1H), 1.21 - 1.08 (m, 1H), 0.95 - 0.87 (m, 3H). MS (ESI): m/z 440.1 $[M + H]^+$

Compound 373

^1H NMR (400 MHz, DMSO- d_6): δ 10.67 (s, 1H), 10.61 (d, $J = 4.4$ Hz, 1H), 8.27 (d, $J = 3.2$ Hz, 1H), 8.24-8.21 (m, 2H), 7.65 (dd, $J = 7.2, 3.2$ Hz, 1H), 7.14-7.05 (m, 2H), 3.91-3.90 (m, 3H), 3.40-3.36 (m, 1H), 3.15-3.09 (m, 1H), 2.45-2.40 (m, 1H), 2.22-2.08 (m, 3H), 1.84-1.80 (m, 1H), 1.62-1.60 (m, 1H). MS (ESI): m/z 442.40 $[M + H]^+$

Compound 374

^1H NMR (400 MHz, DMSO- d_6): δ 10.67 (br s, 1H), 10.61 (d, $J = 4.5$ Hz, 1H), 8.27 (d, $J = 3.2$ Hz, 1H), 8.24-8.21 (m, 2H), 7.65 (dd, $J = 7.2, 3.2$ Hz, 1H), 7.14-7.05 (m, 2H), 3.91-3.90 (m, 3H), 3.40-3.37 (m, 1H), 3.15-3.09 (m, 1H), 2.45-2.40 (m, 1H), 2.23-2.08 (m, 3H), 1.84-1.80 (m, 1H), 1.62-1.61 (m, 1H). MS (ESI): m/z 442.40 $[M + H]^+$

Compound 376

^1H NMR (400 MHz, DMSO- d_6): δ 10.68 (s, 1H), 8.50 (d, 1H, $J = 5.52$ Hz), 8.16 (d, 1H, $J = 1.76$ Hz), 7.63-7.58 (m, 1H), 7.09-7.02 (m, 1H), 6.88-6.84 (m, 1H), 4.45-4.40 (m, 1H), 3.91 (s, 3H), 3.76-3.71 (m, 1H), 2.98-2.90 (m, 2H), 2.69-2.63 (m, 2H), 2.33-2.29 (m, 1H), 2.21 (s, 3H). MS (ESI): m/z 442.40 $[M + H]^+$

Compound 377

¹H NMR (400 MHz, DMSO-d₆): δ 11.67 (br s, 1H), 8.40 (d, *J* = 4.8 Hz, 1H), 7.45 - 7.31 (m, 3H), 7.23 - 7.15 (m, 1H), 6.94 - 6.84 (m, 1H), 6.67 - 6.59 (m, 1H), 6.11 (br s, 1H), 3.96 - 3.80 (m, 1H), 3.26 - 3.22 (m, 1H), 2.44 - 2.40 (m, 1H), 2.24 - 2.21 (m, 2H), 2.13 - 2.06 (m, 2H), 2.00 - 1.95 (m, 1H), 1.64 - 1.58 (m, 1H), 0.98 - 0.92 (m, 2H), 0.66 - 0.59 (m, 1H), 0.43 - 0.37 (m, 1H). MS (ESI): *m/z* 442.1 [M + H]⁺

Compound 379

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (s, 1H), 8.50 (d, 1H, *J* = 5.52 Hz), 8.16 (d, 1H, *J* = 1.76 Hz), 7.63 - 7.58 (m, 1H), 7.09 - 7.02 (m, 1H), 6.88 - 6.84 (m, 1H), 4.45 - 4.40 (m, 1H), 3.91 (s, 3H), 3.76 - 3.71 (m, 1H), 2.98 - 2.90 (m, 2H), 2.69 - 2.63 (m, 2H), 2.33 - 2.29 (m, 1H), 2.21 (s, 3H). MS (ESI): *m/z* 442.40 [M + H]⁺.

Compound 381

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 - 11.38 (m, 1H), 8.50 - 8.25 (m, 1H), 7.57 - 7.33 (m, 2H), 7.27 - 6.96 (m, 3H), 5.96 - 5.85 (m, 1H), 3.89 - 3.74 (m, 3H), 3.26 - 3.18 (m, 1H), 3.10 - 2.92 (m, 1H), 2.05 - 1.94 (m, 1H), 1.89 - 1.83 (m, 1H), 1.76 - 1.42 (m, 4H), 1.35 - 1.22 (m, 3H), 0.95 - 0.88 (m, 3H). MS (ESI): *m/z* 442.1 [M + H]⁺

Compound 382

¹H NMR (400 MHz, DMSO-d₆): δ 11.47 (br.s., 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.48 - 7.33 (m, 2H), 7.18 - 7.10 (m, 2H), 7.08 - 6.95 (m, 1H), 5.95 (s, 1H), 3.81 (s, 3H), 3.34 - 3.30 (m, 1H), 3.20 - 3.00 (m, 1H), 2.04 - 1.90 (m, 1H), 1.89 - 1.70 (m, 4H), 1.68 - 1.50 (m, 4H), 1.01 - 0.81 (m, 3H). MS (ESI): *m/z* 442.1 [M + H]⁺

Compound 383

¹H NMR (400 MHz, DMSO-d₆): δ 11.47 (br.s., 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.48 - 7.33 (m, 2H), 7.18 - 7.10 (m, 2H), 7.08 - 6.95 (m, 1H), 5.95 (s, 1H), 3.81 (s, 3H), 3.34 - 3.30 (m, 1H), 3.20 - 3.00 (m, 1H), 2.04 - 1.90 (m, 1H), 1.89 - 1.70 (m, 4H), 1.68 - 1.50 (m, 4H), 1.01 - 0.81 (m, 3H). MS (ESI): *m/z* 442.1 [M + H]⁺

Compound 384

¹H NMR (400 MHz, DMSO-d₆): δ 8.41 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 5.6 Hz, 1H), 7.38 (br s, 1H), 7.23 - 7.09 (m, 2H), 7.09 - 6.99 (m, 1H), 5.94 (s, 1H), 3.83 (s, 3H), 3.68 - 3.55 (m, 1H), 2.97 - 2.80 (m, 1H), 2.01 - 1.80 (m, 2H), 1.61 - 1.53 (m, 1H), 1.53 - 1.35 (m, 3H), 1.18 (s, 3H), 0.98 (s, 3H). MS (ESI): *m/z* 442.2 [M + H]⁺

Compound 385

MS (ESI): *m/z* 443.40 [M + H]⁺

Compound 386

¹H NMR (400 MHz, DMSO-d₆): δ 10.32 (br s, 1H), 8.23 (d, *J* = 5.5 Hz, 1H), 7.51 - 7.47 (dd, *J* = 11.3, 1.6 Hz, 1H), 7.37 - 7.32 (m, 1H), 7.14 - 7.08 (m, 2H), 5.36 - 5.34 (m, 1H), 4.66 - 4.63 (m,

1H), 4.49-4.45 (m, 1H), 3.90 (s, 3H), 3.64-3.59 (m, 1H), 3.41-3.31 (m, 2H), 3.20-3.15 (m, 1H), 2.39-2.32 (m, 1H), 2.22-2.04 (m, 3H), 1.89-1.78 (m, 1H), 1.59-1.57 (m, 1H).

MS (ESI): m/z 443.40 $[M + H]^+$

Compound 386

^1H NMR (400 MHz, DMSO- d_6): δ 10.32 (br s, 1H), 8.23 (d, $J = 5.5$ Hz, 1H), 7.51-7.47 (dd, $J = 11.3, 1.6$ Hz, 1H), 7.37-7.32 (m, 1H), 7.14-7.08 (m, 2H), 5.36-5.34 (m, 1H), 4.66-4.63 (m, 1H), 4.49-4.45 (m, 1H), 3.90 (s, 3H), 3.64-3.59 (m, 1H), 3.41-3.31 (m, 2H), 3.20-3.15 (m, 1H), 2.39-2.32 (m, 1H), 2.22-2.04 (m, 3H), 1.89-1.78 (m, 1H), 1.59-1.57 (m, 1H). MS (ESI): m/z 443.40 $[M + H]^+$

Compound 387

^1H NMR (400 MHz, DMSO- d_6): δ 10.32 (br s, 1H), 8.24 (d, $J = 5.6$ Hz, 1H), 7.51-7.47 (dd, $J = 11.4, 1.9$ Hz, 1H), 7.37-7.32 (m, 1H), 7.14-7.06 (m, 2H), 5.36-5.34 (m, 1H), 4.66-4.63 (m, 1H), 4.49-4.45 (m, 1H), 3.90 (s, 3H), 3.64-3.59 (m, 1H), 3.41-3.31 (m, 2H), 3.20-3.13 (m, 1H), 2.42-2.32 (m, 1H), 2.21-2.01 (m, 3H), 1.84-1.77 (m, 1H), 1.76-1.52 (m, 1H). MS (ESI): m/z 443.40 $[M + H]^+$

Compound 388

^1H NMR (400 MHz, DMSO- d_6): δ 10.10 (br s, 1H), 8.43 (dd, $J = 6.0, 2.4$ Hz, m, 1H), 7.80-7.76 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.12-7.09 (m, 2H), 5.25 (d, $J = 4.4$ Hz, 1H), 4.59 (t, $J = 5.6$ Hz, 1H), 4.50-4.46 (m, 1H), 3.89 (s, 3H), 3.62-3.52 (m, 1H), 3.42-3.31 (m, 2H), 3.16-3.09 (m, 1H), 2.37-2.32 (m, 1H), 2.20-2.04 (m, 3H), 1.84-1.80 (m, 1H), 1.70-1.62 (m, 1H). MS (ESI): m/z 443.40 $[M + H]^+$

Compound 389

^1H NMR (400 MHz, DMSO- d_6): δ 10.65 (br s, 1H), 8.48 (d, $J = 5.4$ Hz, 1H), 8.04 (d, $J = 1.8$ Hz, 1H), 7.56 (dd, $J = 5.4, 2.0$ Hz, 1H), 7.38 (br s, 2H), 7.20-7.05 (m, 1H), 6.96-6.89 (m, 2H), 3.74 (s, 3H), 3.43-3.38 (m, 1H), 3.20-3.14 (m, 1H), 2.49 (br m, 1H), 2.23-2.00 (m, 3H), 1.98-1.83 (m, 1H), 1.64 (br m, 1H). MS (ESI): m/z 444.30 $[M + H]^+$

Compound 390

^1H NMR (400 MHz, DMSO- d_6): δ 10.59 (br s, 1H), 8.45 (d, $J = 5.4$ Hz, 1H), 8.04 (d, $J = 1.8$ Hz, 1H), 7.57 (dd, $J = 5.4, 1.9$ Hz, 1H), 7.33 (br s, 2H), 7.16-7.11 (m, 1H), 6.77-6.67 (m, 1H), 3.79 (s, 3H), 3.57-3.53 (m, 1H), 2.36-2.33 (m, 1H), 2.30-1.92 (m, 4H), 1.73 (br m, 1H). MS (ESI): m/z 444.40 $[M + H]^+$

Compound 392

^1H NMR (400 MHz, DMSO- d_6): δ 10.31 (br s, 1H), 8.13 (s, 1H), 7.64-7.62 (m, 1H), 7.50-7.44 (m, 2H), 7.33 (br s, 2H), 7.02-6.90 (m, 2H), 6.88-6.86 (m, 1H), 4.75 (t, $J = 5.7$ Hz, 1H), 3.91 (s, 3H), 3.75-3.69 (m, 1H), 3.15-3.09 (m, 1H), 2.53 (br s, 1H), 2.46-2.44 (m, 1H), 2.24-2.21 (m, 2H). MS (ESI): m/z 442.20 $[M + H]^+$.

Compound 392

¹H NMR (400 MHz, DMSO-d₆): δ 10.31 (br s, 1H), 8.13 (s, 1H), 7.64-7.62 (m, 1H), 7.50-7.44 (m, 2H), 7.33 (br s, 2H), 7.02-6.90 (m, 2H), 6.88-6.86 (m, 1H), 4.75 (t, J = 5.7 Hz, 1H), 3.91 (s, 3H), 3.75-3.69 (m, 1H), 3.15-3.09 (m, 1H), 2.53 (br s, 1H), 2.46-2.44 (m, 1H), 2.24-2.21 (m, 2H). MS (ESI): m/z 442.20 [M + H]⁺.

Compound 393

¹H NMR (400 MHz, DMSO-d₆): δ 10.15 (br s, 1H), 8.09 (d, J = 1.6 Hz, 1Hs, 1H), 7.62-7.57 (m, 1H), 7.48-7.43 (m, 2H), 7.34 (br s, 2H), 7.16-7.13 (m, 1H), 6.87 (dd, J = 11.0, 2.8 Hz, 1H), 6.87 (dt, J = 8.4, 2.8 Hz, 1H), 4.30 (t, J = 5.4 Hz, 1H), 3.82 (s, 3H), 3.60-3.54 (m, 1H), 3.04-2.98 (m, 1H), 2.43-2.23 (m, 2H), 2.13 (br s, 2H). MS (ESI): m/z 444.30 [M + H]⁺.

Compound 394

¹H NMR (400 MHz, CD₃OD) δ 8.44 (d, J = 6.0 Hz, 1H), 7.40 (d, J = 5.6 Hz, 1H), 7.32 (dd, J = 6.0, 9.2 Hz, 1H), 6.85 - 6.77 (m, 2H), 6.26 (s, 1H), 3.57 - 3.46 (m, 1H), 3.39 - 3.32 (m, 2H), 2.54 - 2.33 (m, 2H), 2.30 - 2.07 (m, 2H), 2.01 - 1.75 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H). MS (ESI): m/z 444.2 [M + H]⁺.

Compound 395

¹H NMR (400 MHz, CD₃OD) δ 8.44 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 6.0 Hz, 1H), 7.30 - 7.24 (m, 1H), 6.86 - 6.78 (m, 1H), 6.76 - 6.69 (m, 1H), 6.27 (s, 1H), 3.48 - 3.38 (m, 1H), 3.30 - 3.25 (m, 1H), 2.54 - 2.32 (m, 2H), 2.29 (s, 3H), 2.16 - 2.00 (m, 2H), 1.97 - 1.85 (m, 1H), 1.53 - 1.41 (m, 1H), 1.38 - 1.27 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 444.3 [M + H]⁺.

Compound 396

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 6.0 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.86 - 6.79 (m, 1H), 6.77 - 6.70 (m, 1H), 6.27 (s, 1H), 3.48 - 3.39 (m, 1H), 3.30 - 3.24 (m, 1H), 2.52 - 2.43 (m, 1H), 2.42 - 2.31 (m, 1H), 2.29 (s, 3H), 2.15 - 2.02 (m, 2H), 1.96 - 1.86 (m, 1H), 1.53 - 1.42 (m, 1H), 1.39 - 1.26 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 444.2 [M + H]⁺.

Compound 396

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 6.0 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.86 - 6.79 (m, 1H), 6.77 - 6.70 (m, 1H), 6.27 (s, 1H), 3.48 - 3.39 (m, 1H), 3.30 - 3.24 (m, 1H), 2.52 - 2.43 (m, 1H), 2.42 - 2.31 (m, 1H), 2.29 (s, 3H), 2.15 - 2.02 (m, 2H), 1.96 - 1.86 (m, 1H), 1.53 - 1.42 (m, 1H), 1.39 - 1.26 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 444.2 [M + H]⁺.

Compound 397

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 6.0 Hz, 1H), 7.45 (d, J = 6.0 Hz, 1H), 7.33 - 7.25 (m, 1H), 6.86 - 6.78 (m, 1H), 6.77 - 6.71 (m, 1H), 6.26 (s, 1H), 3.52 - 3.43 (m, 1H), 3.40 - 3.32 (m, 1H), 2.51 - 2.33 (m, 2H), 2.30 (s, 3H), 2.15 - 2.06 (m, 1H), 1.96 - 1.79 (m, 4H), 1.09 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 444.3 [M + H]⁺.

Compound 398

^1H NMR (400 MHz, CD_3OD): δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.44 (d, $J = 6.0$ Hz, 1H), 7.32 - 7.26 (m, 1H), 6.86 - 6.78 (m, 1H), 6.77 - 6.72 (m, 1H), 6.27 (s, 1H), 3.51 - 3.43 (m, 1H), 3.41 - 3.33 (m, 1H), 2.49 - 2.34 (m, 2H), 2.30 (s, 3H), 2.16 - 2.07 (m, 1H), 1.98 - 1.81 (m, 4H), 1.09 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 444.2 $[\text{M} + \text{H}]^+$

Compound 399

^1H NMR (400 MHz, CD_3OD): δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.54 - 7.46 (m, 1H), 7.31 - 7.08 (m, 1H), 6.65 - 6.45 (m, 2H), 6.17 (s, 1H), 3.90 - 3.61 (m, 4H), 3.27 - 3.07 (m, 1H), 2.55 - 2.13 (m, 3H), 1.93 - 1.80 (m, 1H), 1.79 - 1.44 (m, 1H), 1.10 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 446.2 $[\text{M} + \text{H}]^+$

Compound 400

^1H NMR (400 MHz, CD_3OD): δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.55 - 7.46 (m, 1H), 7.23 - 7.13 (m, 1H), 6.63 - 6.46 (m, 2H), 6.21 - 6.13 (m, 1H), 4.23 - 3.84 (m, 1H), 3.73 (s, 3H), 3.50 - 3.34 (m, 1H), 2.53 - 2.38 (m, 2H), 2.33 - 2.13 (m, 2H), 1.78 - 1.71 (m, 1H), 1.36 - 1.33 (m, 3H). MS (ESI): m/z 446.2 $[\text{M} + \text{H}]^+$

Compound 401

^1H NMR (400 MHz, CD_3OD): δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.57 - 7.48 (m, 1H), 7.28 - 7.19 (m, 1H), 6.63 - 6.49 (m, 2H), 6.21 - 6.09 (m, 1H), 4.04 - 3.79 (m, 1H), 3.73 (s, 3H), 3.28 - 3.12 (m, 1H), 2.50 - 2.34 (m, 2H), 2.31 - 2.17 (m, 2H), 1.79 - 1.70 (m, 1H), 1.36 - 1.31 (m, 3H). MS (ESI): m/z 446.2 $[\text{M} + \text{H}]^+$

Compound 402

^1H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.68 - 7.56 (m, 1H), 7.46 - 7.26 (m, 3H), 7.24 - 7.11 (m, 1H), 5.75 (s, 1H), 4.23 - 4.10 (m, 1H), 3.19 - 3.10 (m, 1H), 2.28 - 2.20 (m, 1H), 2.09 - 2.05 (m, 1H), 1.93 - 1.81 (m, 2H), 1.63 - 1.49 (m, 2H), 1.28 - 1.22 (m, 2H), 1.21 - 1.14 (m, 1H), 0.84 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 446.1 $[\text{M} + \text{H}]^+$

Compound 403

^1H NMR (400 MHz, DMSO-d_6): δ 12.76 (s, 1H), 8.39 (d, $J = 6.0$ Hz, 1H), 7.69 - 7.53 (m, 1H), 7.49 - 7.26 (m, 3H), 7.24 - 7.14 (m, 1H), 5.76 (s, 1H), 4.19 - 4.16 (m, 1H), 3.19 - 3.13 (m, 1H), 2.30 - 2.19 (m, 1H), 2.13 - 2.02 (m, 1H), 1.91 - 1.83 (m, 2H), 1.61 - 1.54 (m, 2H), 1.27 - 1.11 (m, 3H), 0.84 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 446.1 $[\text{M} + \text{H}]^+$

Compound 404

^1H NMR (400 MHz, DMSO-d_6): δ 11.72 (br.s., 1H), 8.40 (d, $J = 5.6$ Hz, 1H), 7.70 - 7.55 (m, 1H), 7.48 - 7.36 (m, 2H), 7.35 - 7.18 (m, 2H), 5.72 (s, 1H), 4.20 - 4.03 (m, 1H), 3.25 - 3.17 (m, 1H), 2.02 - 1.95 (m, 1H), 1.91 - 1.87 (m, 1H), 1.85 - 1.81 (m, 1H), 1.71 - 1.59 (m, 1H), 1.53 - 1.41 (m, 3H), 1.22 - 1.13 (m, 2H), 1.00 - 0.91 (m, 3H) MS (ESI): m/z 446.1 $[\text{M} + \text{H}]^+$

Compound 405

¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (br.s., 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.70 - 7.55 (m, 1H), 7.48 - 7.36 (m, 2H), 7.35 - 7.18 (m, 2H), 5.72 (s, 1H), 4.20 - 4.03 (m, 1H), 3.25 - 3.17 (m, 1H), 2.02 - 1.95 (m, 1H), 1.91 - 1.87 (m, 1H), 1.85 - 1.81 (m, 1H), 1.71 - 1.59 (m, 1H), 1.53 - 1.41 (m, 3H), 1.22 - 1.13 (m, 2H), 1.00 - 0.91 (m, 3H) MS (ESI): *m/z* 446.1 [M + H]⁺

Compound 407

¹H NMR (400 MHz, DMSO-d₆): δ 11.51 (br. s., 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.42 - 7.39 (m, 2H), 7.39 - 7.17 (m, 3H), 5.94 (s, 1H), 3.60 - 3.44 (m, 1H), 3.29 - 3.15 (m, 1H), 2.10 - 1.95 (m, 1H), 1.94 - 1.87 (m, 1H), 1.85 - 1.72 (m, 3H), 1.71 - 1.43 (m, 4H), 1.01 - 0.92 (m, 3H) MS (ESI): *m/z* 446.1 [M + H]⁺

Compound 408

¹H NMR (400 MHz, DMSO-d₆): δ 11.51 (br. s., 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.42 - 7.39 (m, 2H), 7.39 - 7.17 (m, 3H), 5.94 (s, 1H), 3.60 - 3.44 (m, 1H), 3.29 - 3.15 (m, 1H), 2.10 - 1.95 (m, 1H), 1.94 - 1.87 (m, 1H), 1.85 - 1.72 (m, 3H), 1.71 - 1.43 (m, 4H), 1.01 - 0.92 (m, 3H) MS (ESI): *m/z* 446.1 [M + H]⁺

Compound 409

¹H NMR (400 MHz, DMSO-d₆): δ 11.53 (br s, 1H), 8.48 - 8.34 (m, 1H), 7.44 - 7.31 (m, 4H), 7.24 - 7.11 (m, 1H), 5.88 (s, 1H), 3.69 - 3.60 (m, 1H), 3.10 - 3.01 (m, 1H), 1.85 - 1.66 (m, 8H), 1.29 (m, 1H), 1.00 - 0.93 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 428.1 [M + H]⁺

Compound 410

¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (br s, 1H), 8.39 (d, *J* = 6.0 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.35 (m, 2H), 7.25 - 7.12 (m, 1H), 5.89 (s, 1H), 3.64 (m, 1H), 3.11 - 3.04 (m, 1H), 1.84 - 1.73 (m, 6H), 1.71 - 1.65 (m, 2H), 1.28 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 428.1 [M + H]⁺

Compound 411

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br. s., 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 7.41 (s, 1H), 7.33 (d, *J* = 6.0 Hz, 1H), 7.20 (s, 1H), 7.17 - 7.09 (m, 2H), 6.15 (s, 1H), 3.61 - 3.51 (m, 1H), 3.30 - 3.24 (m, 1H), 2.48 - 2.29 (m, 3H), 2.23 (d, *J* = 1.6 Hz, 3H), 1.97 - 1.81 (m, 1H), 1.44 - 1.29 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H) MS (ESI): *m/z* 448.2 [M + H]⁺

Compound 412

¹H NMR (400 MHz, DMSO-d₆): δ 11.51 (br s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.41 (br s, 1H), 7.37-7.33 (m, 2H), 7.20 (br s, 1H), 6.87-6.86 (m, 1H), 6.83-6.81 (m, 1H), 6.05 (s, 1H), 3.69-3.60 (m, 4H), 3.29-3.25 (m, 1H), 2.43-2.40 (m, 2H), 2.20-2.04 (m, 2H), 1.93-1.89 (m, 1H), 1.65-1.56 (m, 1H). MS (ESI): *m/z* 448.30 [M + H]⁺.

Compound 413

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.48 (d, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.34 - 7.24 (m, 1H), 7.23 - 7.12 (m, 1H), 6.21 (s, 1H), 3.94 - 3.73 (m, 1H), 3.40 - 3.31 (m, 1H), 2.56 - 2.32 (m, 2H), 2.22 - 2.09 (m, 1H), 2.08 - 1.99 (m, 1H), 1.95 - 1.80 (m, 3H), 1.10 (t, *J* = 7.6 Hz, 3H) MS (ESI): *m/z* 482.2 [M + H]⁺

Compound 414

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.44 (br s, 1H), 8.40 (d, *J* = 5.7 Hz, 1H), 7.45-7.35 (m, 2H), 7.30-7.18 (m, 2H), 6.92 (br m, 1H), 6.88 -6.86 (m, 1H), 6.00 (s, 1H), 3.73 (s, 3H), 3.60 (br m, 1H), 3.20 (br m, 1H), 2.45-2.30 (m, 2H), 2.20-2.10 (m, 2H), 1.90-1.50 (m, 2H). MS (ESI): *m/z* 448.30 [M + H]⁺.

Compound 415

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.60 (br s, 1H), 8.13 (br s, 1H), 7.96 (br m, 1H), 7.95-7.93 (m, 1H), 7.65 (dd, *J* = 1.24 Hz, 8.4 Hz, 1H), 7.55 (br s, 1H), 7.15 (br s, 1H), 7.05-7.03 (m, 1H), 6.04 (s, 1H), 3.80 (s, 3H), 3.61 (br m, 1H), 2.40-2.38 (br m, 2H), 2.19-2.07 (m, 2H), 1.91-1.88 (m, 1H), 1.74-1.69 (m, 1H). MS (ESI): *m/z* 449.36 [M + H]⁺.

Compound 416

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (br s, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 8.08 (br s, 1H), 8.05 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.30 (br s, 1H), 7.15 (br m, 1H), 7.07-7.03 (m, 1H), 6.04 (m, 1H), 3.80 (s, 3H), 3.61-3.59 (m, 1H), 3.28-3.26 (m, 1H), 2.49-2.42 (m, 2H), 2.29-2.13 (m, 2H), 1.92-1.88 (m, 1H), 1.72 (br m, 1H). MS (ESI): *m/z* 449.38 [M + H]⁺.

Compound 416

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (br s, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 8.08 (br s, 1H), 8.05 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.30 (br s, 1H), 7.15 (br m, 1H), 7.07-7.03 (m, 1H), 6.04 (m, 1H), 3.80 (s, 3H), 3.61-3.59 (m, 1H), 3.28-3.26 (m, 1H), 2.49-2.42 (m, 2H), 2.29-2.13 (m, 2H), 1.92-1.88 (m, 1H), 1.72 (br m, 1H). MS (ESI): *m/z* 449.38 [M + H]⁺.

Compound 417

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.71 (br s, 1H), 8.51 (s, 1H), 8.18-8.13 (m, 2H), 7.94 (br s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.17 (br m, 1H), 6.98 (br m, 1H), 6.08 (s, 1H), 3.78-3.58 (m, 3H), 3.40 (br m, 1H), 3.19 (br m, 1H), 2.48-2.08 (m, 4H), 1.98-1.61 (m, 2H). MS (ESI): *m/z* 449.38 [M + H]⁺.

Compound 418

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.62 (br s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.11 (d, *J* = 1.7 Hz, 1H), 7.60 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.46-7.39 (m, 4H), 7.15 (dt, *J* = 8.4, 2.96 Hz, 1H), 4.32 (t, *J* = 6.1 Hz, 1H), 3.64-3.61 (m, 1H), 2.96-2.90 (m, 1H), 2.16-2.07 (m, 2H). MS (ESI): *m/z* 449.30 [M + H]⁺.

Compound 419

¹H NMR (400 MHz, DMSO-d₆): δ 10.29 (br s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.65-7.62 (m, 1H), 7.51-7.44 (m, 2H), 7.34 (br s, 2H), 7.25-7.18 (m, 1H), 7.10-7.04 (m, 1H), 4.34 (t, *J* = 5.3 Hz, 1H), 3.71-3.64 (m, 1H), 3.20-3.15 (m, 1H), 2.45-2.40 (m, 2H, merged in solvent residual signal), 2.17-2.00 (m, 2H). MS (ESI): 448.1 [M - H]⁻

Compound 420

¹H NMR (400 MHz, DMSO-d₆): δ 11.59 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 7.39 (br s, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 7.19-7.14 (m, 2H), 7.09-7.04 (m, 1H), 6.08 (s, 1H), 3.83 (s, 3H), 3.60 (br s, 1H), 3.27-3.22 (m, 1H), 2.42-2.38 (m, 2H), 2.19-2.07 (m, 2H), 1.92-1.88 (m, 1H), 1.75-1.60 (m, 1H). MS (ESI): *m/z* 450.4 [M + H]⁺

Compound 421

¹H NMR (400 MHz, DMSO-d₆): δ 11.94 - 11.11 (m, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 7.45 - 7.32 (m, 2H), 7.26 - 7.13 (m, 2H), 7.11 - 7.02 (m, 1H), 6.04 (s, 1H), 5.30 - 4.85 (m, 2H), 3.84 (s, 3H), 3.77 - 3.52 (m, 2H), 2.38 - 2.32 (m, 1H), 2.25 - 2.13 (m, 1H), 2.09 - 1.99 (m, 2H) MS (ESI): *m/z* 450.1 [M + H]⁺

Compound 422

¹H NMR (400 MHz, MeOD-*d*₄): δ 8.55 - 8.40 (m, 1H), 7.58 - 7.42 (m, 1H), 7.18 - 7.01 (m, 1H), 6.94 - 6.78 (m, 1H), 6.18 (s, 1H), 5.13 - 4.98 (m, 2H), 4.02 - 3.76 (m, 4H), 3.47 - 3.35 (m, 1H), 2.47 - 2.14 (m, 4H) MS (ESI): *m/z* 450.1 [M + H]⁺

Compound 423

¹H NMR (400 MHz, DMSO-d₆): δ 11.64 (br s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.42 (br s, 1H), 7.37 (d, *J* = 5.8 Hz, 1H), 7.21-7.12 (m, 2H), 6.74-6.68 (m, 1H), 6.00-5.96 (m, 1H), 3.82-3.58 (m, 5H), 2.41-2.35 (m, 2H), 2.30-2.11 (m, 2H), 2.10-2.00 (m, 1H), 1.91-1.77 (m, 1H). MS (ESI): *m/z* 450.4 [M + H]⁺

Compound 424

¹H NMR (400 MHz, DMSO-d₆): δ 11.59 (br s, 1H), 8.41 (d, *J* = 5.7 Hz, 1H), 7.41-7.36 (m, 3H), 7.21 (br s, 1H), 7.01-6.96 (m, 1H), 6.04 (s, 1H), 3.68 (br m, 4H), 2.40-2.37 (m, 2H), 2.28-2.00 (m, 2H), 1.89-1.86 (m, 1H), 1.71-1.66 (m, 1H). MS (ESI): *m/z* 450.40 [M + H]⁺

Compound 425

¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (br s, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.43 (br s, 1H), 7.35 (d, *J* = 5.6 Hz, 1H), 7.23 (br s, 1H), 6.94-6.93 (m, 2H), 6.06 (s, 1H), 3.72-3.40 (m, 5H), 2.43-2.37 (m, 2H), 2.20-2.08 (m, 3H), 1.97-1.90 (m, 1H). MS (ESI): *m/z* 450.30 [M + H]⁺

Compound 426

¹H NMR (400 MHz, DMSO-d₆): δ 11.63-11.60 (m, 1H), 8.41 (d, *J* = 5.5 Hz, 1H), 7.42 (br s, 1H), 7.36 (d, *J* = 5.8 Hz, 1H), 7.21-7.20 (m, 1H), 6.73-6.61 (m, 2H), 5.96-5.95 (m, 1H), 3.84

(s, 3H), 3.73-3.51 (m, 2H), 2.40-2.32 (m, 2H), 2.20-2.05 (m, 1H), 2.02-2.00 (m, 1H), 1.90-1.75 (m, 1H). MS (ESI): m/z 450.40 $[M + H]^+$

Compound 427

^1H NMR (400 MHz, DMSO- d_6): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.53 - 7.39 (m, 2H), 7.12 - 6.97 (m, 2H), 6.20 (s, 1H), 3.88 - 3.76 (m, 1H), 3.38 - 3.32 (m, 1H), 2.57 - 2.22 (m, 3H), 2.02 - 1.92 (m, 1H), 1.70 - 1.56 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 3H) MS (ESI): m/z 450.1 $[M + H]^+$

Compound 428

1H), 7.04 - 6.93 (m, 1H), 6.36 - 6.28 (m, 1H), 5.80 - 5.69 (m, 1H), 3.95 - 3.84 (m, 1H), 3.77 - 3.70 (m, 1H), 3.49 - 3.40 (m, 2H), 2.57 - 2.27 (m, 3H), 2.26 (d, $J = 1.6$ Hz, 3H), 2.23 - 2.21 (m, 1H), 2.05 - 1.97 (m, 1H), 1.87- 1.80 (m, 1H). MS (ESI): m/z 451.1 $[M + H]^+$

Compound 429

^1H NMR (400 MHz, DMSO- d_6): δ 11.70 (s, 1H), 8.41 (d, $J = 5.7$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.47 (d, $J = 1.8$ Hz, 1H), 7.41 (br s, 1H), 7.34 (d, $J = 6.4$ Hz, 2H), 7.20 (br s, 1H), 6.05 (s, 1H), 3.76-3.70 (m, 1H), 3.29 (br m, 1H), 2.45-2.42 (m, 2H), 2.22-2.19 (m, 2H), 2.00-1.90 (m, 1H), 1.75-1.59 (m, 1H). MS (ESI): m/z 452.30 $[M + H]^+$.

Compound 430

^1H NMR (400 MHz, DMSO- d_6): δ 10.81(br s, 1H), 8.52 (d, $J = 5.4$ Hz, 1H), 8.20 (d, $J = 1.8$ Hz, 1H), 7.72 (dd, $J = 5.4, 2.0$ Hz, 1H), 7.38 (br s, 2H), 7.00-6.96 (m, 1H), 6.47-6.44 (m, 1H), 4.63 (s, 1H), 3.78-3.76 (m, 1H), 3.68 (s, 3H), 3.30 (d, $J = 9.6$ Hz, 1H), 1.62 (d, $J = 7.4$ Hz, 1H), 1.54-1.51 (m, 1H), 1.07 (s, 3H), 1.01 (s, 3H). MS (ESI): m/z 453.30 $[M + H]^+$.

Compound 431

^1H NMR (400 MHz, DMSO- d_6): δ 10.22 (br s, 1H), 8.46 (d, $J = 5.5$ Hz, 1H), 8.03 (d, $J = 1.8$ Hz, 1H), 7.57 (dd, $J = 5.4, 2.0$ Hz, 1H), 7.24 (br s, 2H), 7.02-6.90 (m, 2H), 3.85-3.84 (m, 3H), 3.72-3.67 (m, 1H), 2.82-2.79 (m, 1H), 2.34-2.31 (m, 1H), 1.94-1.91 (m, 1H), 1.90-1.72 (m, 3H), 1.73-1.62 (m, 3H), 1.61-1.49 (m, 4H). MS (ESI): m/z 454.40 $[M + H]^+$

Compound 433

^1H NMR (400 MHz, DMSO- d_6): δ 10.47 (br s, 1H), 8.45 (d, $J = 5.4$ Hz, 1H), 8.01 (d, $J = 1.8$ Hz, 1H), 7.58 (dd, $J = 5.4, 2.0$ Hz, 1H), 7.34 (br s, 2H), 7.09-7.01 (m, 2H), 3.92-3.91 (m, 3H), 3.58-3.57 (m, 1H), 3.14-3.09 (m, 1H), 2.34-2.31 (m, 1H), 1.98-1.94 (m, 1H), 1.93-1.87 (m, 1H), 1.86-1.62 (m, 6H), 1.61-1.45 (m, 4H) Compound 434

^1H NMR (400 MHz, DMSO- d_6): δ 11.61 (br s, 1H), 8.41 (d, $J = 5.7$ Hz, 1H), 7.43-7.33 (m, 4H), 7.20 (br s, 1H), 6.09 (s, 1H), 3.75-3.70 (m, 1H), 3.36 (br m, 1H), 2.49-2.42 (m, 2H), 2.22-2.01 (m, 2H), 1.98-1.90 (m, 1H), 1.69-1.59 (m, 1H). MS (ESI): m/z 454.33 $[M + H]^+$

Compound 435

^1H NMR (400 MHz, DMSO- d_6): δ 11.63 (br s, 1H), 9.01 (s, 1H), 8.50 (d, $J = 5.8$ Hz, 1H), 7.36-7.35 (m, 2H), 6.81 (br s, 2H), 6.03 (s, 1H), 3.69 (br m, 4H), 3.18 (br m, 1H), 2.48-2.45 (m,

1H), 2.19-2.00 (m, 2H), 1.99-1.88 (m, 1H), 1.86-1.52 (m, 1H). MS (ESI): m/z 455.40 $[M + H]^+$.

Compound 436

^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 5.2$ Hz, 1H), 8.11 (s, 1H), 7.54 (d, $J = 4.4$ Hz, 1H), 7.12 – 7.07 (m, 2H), 3.89 (s, 3H), 3.27 – 3.19 (m, 3H), 3.13 – 3.10 (m, 1H), 3.01 – 2.98 (m, 1H), 2.45 (d, $J = 6.8$ Hz, 2H), 2.16 -2.09 (m, 2H), 1.71 - 1.62 (m, 2H), 1.05 (t, d, $J = 6.8$ Hz, 3H). MS (ESI): m/z 455.40 $[M + H]^+$

Compound 437

^1H NMR (400 MHz, DMSO- d_6): δ 12.28 - 11.79 (m, 1H), 8.39 (d, $J = 5.6$ Hz, 1H), 7.56 - 7.32 (m, 3H), 7.17 (s, 1H), 6.94 - 6.83 (m, 2H), 6.09 (d, $J = 8.8$ Hz, 1H), 3.82 - 3.68 (m, 1H), 3.60 - 3.45 (m, 1H), 3.29 - 3.22 (m, 1H), 2.55 - 2.50 (m, 1H), 2.46 - 2.37 (m, 2H), 2.26 - 2.12 (m, 3H), 2.05 - 1.94 (m, 3H), 1.83 - 1.71 (m, 2H), 1.66 - 1.52 (m, 1H). MS (ESI): m/z 456.2 $[M + H]^+$

Compound 438

^1H NMR (400 MHz, DMSO- d_6): δ 12.31 - 11.69 (m, 1H), 8.39 (d, $J = 4.8$ Hz, 1H), 7.59 - 7.30 (m, 3H), 7.17 (s, 1H), 6.96 - 6.79 (m, 2H), 6.17 - 6.01 (m, 1H), 3.75 - 3.65 (m, 1H), 3.60 - 3.44 (m, 1H), 3.29 - 3.23 (m, 1H), 2.55 - 2.50 (m, 1H), 2.43 - 2.41 (m, 2H), 2.27 - 2.13 (m, 3H), 2.03 - 1.94 (m, 3H), 1.82 - 1.72 (m, 2H), 1.64 - 1.53 (m, 1H). MS (ESI): m/z 456.2 $[M + H]^+$

Compound 440

^1H NMR (400 MHz, DMSO- d_6): δ 11.54 (s, 1H), 8.43 (d, $J = 5.6$ Hz, 1H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.39 (s, 1H), 7.24 - 7.16 (m, 2H), 7.14 - 7.05 (m, 1H), 5.97 (s, 1H), 3.76 (s, 3H), 3.73 - 3.64 (m, 1H), 3.22 - 3.12 (m, 1H), 2.23 - 2.11 (m, 2H), 2.09 - 2.01 (m, 1H), 1.94 - 1.83 (m, 1H), 1.58 - 1.46 (m, 1H), 0.91 (s, 9H). MS (ESI): m/z 456.2 $[M + H]^+$

Compound 441

^1H NMR (400 MHz, DMSO- d_6): δ 11.55 (s, 1H), 8.42 (d, $J = 5.6$ Hz, 1H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.39 (s, 1H), 7.24 - 7.16 (m, 2H), 7.14 - 7.06 (m, 1H), 5.97 (s, 1H), 3.76 (s, 3H), 3.73 - 3.64 (m, 1H), 3.23 - 3.13 (m, 1H), 2.24 - 2.11 (m, 2H), 2.05 (m, 1H), 1.95 - 1.84 (m, 1H), 1.58 - 1.46 (m, 1H), 0.92 (s, 9H). MS (ESI): m/z 456.2 $[M + H]^+$

Compound 442

^1H NMR (400 MHz, DMSO- d_6): δ 10.61 (s, 1H), 8.19 (s, 1H), 7.78-7.75 (m, 1H), 7.51-7.47 (m, 2H), 7.34-7.32 (m, 2H), 7.30-7.27 (m, 1H), 7.26-7.19 (m, 3H), 7.14-7.09 (m, 2H), 4.33-4.25 (m, 2H), 3.89 (s, 3H), 3.46-3.40 (m, 1H), 3.04-2.98 (m, 1H). MS (ESI): m/z 457.30 $[M + H]^+$.

Compound 443

¹H NMR (400 MHz, DMSO-d₆): 10.61 (br s, 1H), 8.19 (s, 1H), 7.78-7.76 (m, 1H), 7.51-7.48 (m, 2H), 7.34-7.30 (m, 3H), 7.28-7.19 (m, 3H), 7.16-7.09 (m, 2H), 4.34-4.26 (m, 2H), 3.89 (s, 3H), 3.46-3.40, 3.46-3.40 (m, 1H) MS (ESI): *m/z* 459.1 [M + H]⁺.

Compound 444

¹H-NMR (400 MHz, DMSO-d₆): δ 11.67 (s, 1H), 9.01 (s, 1H), 8.53 (d, *J* = 5.8 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 7.34-7.29 (m, 2H), 6.09 (s, 1H), 3.77-3.73 (m, 1H), 3.26 (br s, 1H), 2.63-2.57 (m, 1H), 2.51-2.46 (m, 1H), 2.22-2.06 (m, 2H), 2.06-1.96 (m, 1H), 1.74-1.64 (m, 1H), MS (ESI): *m/z* 459.30 [M + H]⁺.

Compound 446

¹H NMR (400 MHz, DMSO-d₆): δ 10.83 (br s, 1H), 8.54 (d, *J* = 5.4 Hz, 1H), 8.22-8.20 (m, 1H), 7.65-7.62 (m, 1H), 7.15-7.06 (m, 2H), 3.92-3.91 (m, 3H), 3.42-3.37 (m, 1H), 3.28 (s, 3H), 3.27-3.16 (m, 1H), 2.49-2.41 (m, 1H), 2.23-2.00 (m, 3H), 1.85-1.81 (m, 1H), 1.63-1.52 (m, 1H). MS (ESI): *m/z* 460.30 [M + H]⁺

Compound 447

¹H NMR (400 MHz, DMSO-d₆): δ 8.41 (d, *J* = 6.0 Hz, 1H), 7.43 - 7.29 (m, 2H), 7.28 - 7.03 (m, 2H), 6.75 (dd, *J* = 2.4, 11.2 Hz, 1H), 6.66 - 6.54 (m, 1H), 6.01 (s, 1H), 3.75 (s, 3H), 3.60 - 3.58 (m, 1H), 3.32 - 3.29 (m, 1H), 2.45 - 2.34 (m, 1H), 2.29 - 2.18 (m, 1H), 2.10 - 2.00 (m, 1H), 1.90 - 1.79 (m, 2H), 1.79 - 1.64 (m, 2H), 1.10 - 0.97 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 460.2 [M + H]⁺

Compound 448

¹H NMR (400 MHz, DMSO-d₆): δ 11.05 (br s, 1H), 8.42 (d, *J* = 6.0 Hz, 1H), 7.50 - 7.38 (m, 2H), 7.31 - 7.11 (m, 2H), 6.76 (dd, *J* = 2.4, 11.2 Hz, 1H), 6.66 - 6.57 (m, 1H), 6.04 (s, 1H), 3.74 (s, 3H), 3.68 - 3.53 (m, 1H), 3.42 - 3.34 (m, 1H), 2.48 - 2.32 (m, 1H), 2.30 - 2.19 (m, 1H), 2.14 - 2.00 (m, 1H), 1.97 - 1.74 (m, 3H), 1.74 - 1.63 (m, 1H), 1.01 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 460.3 [M + H]⁺

Compound 449

¹H NMR (400 MHz, DMSO-d₆): δ 11.38 (br s, 1H), 8.50 (d, *J* = 6.0 Hz, 1H), 7.40 (m, 1H), 7.37 (d, *J* = 6.0 Hz, 1H), 7.31 - 7.09 (m, 2H), 6.74 (br dd, *J* = 2.0, 11.2 Hz, 1H), 6.69 - 6.51 (m, 1H), 6.00 (s, 1H), 3.85 - 3.58 (m, 4H), 3.27 - 3.08 (m, 1H), 2.47 - 2.33 (m, 2H), 2.08 - 1.89 (m, 2H), 1.84 - 1.72 (m, 1H), 1.51 - 1.16 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H). MS (ESI): *m/z* 460.2 [M + H]⁺

Compound 450

¹H NMR (400 MHz, CD₃OD): δ 8.47 (d, *J* = 6.0 Hz, 1H), 7.52 (d, *J* = 6.0 Hz, 1H), 7.40 - 7.09 (m, 2H), 6.14 (s, 1H), 3.89 - 3.72 (m, 1H), 3.36 - 3.32 (m, 1H), 2.37 - 2.25 (m, 3H), 1.91 - 1.70 (m, 2H), 0.99 (s, 9H). MS (ESI): *m/z* 460.2 [M + H]⁺

Compound 451

^1H NMR (400 MHz, CD_3OD): δ 8.48 (d, $J = 6.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.39 - 7.15 (m, 2H), 6.14 (s, 1H), 3.94 - 3.97 (m, 1H), 3.29 - 3.19 (m, 1H), 2.40 - 2.19 (m, 3H), 2.10 - 1.99 (m, 1H), 1.75 - 1.57 (m, 1H), 0.99 (s, 9H). MS (ESI): m/z 460.2 $[\text{M} + \text{H}]^+$

Compound 452

^1H NMR (400 MHz, CD_3OD): δ 8.48 (d, $J = 6.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.37 - 7.16 (m, 2H), 6.15 (s, 1H), 3.89 - 3.74 (m, 1H), 3.36 - 3.31 (m, 1H), 2.39 - 2.23 (m, 3H), 1.92 - 1.71 (m, 2H), 1.00 (s, 9H). MS (ESI): m/z 460.2 $[\text{M} + \text{H}]^+$

Compound 452

^1H NMR (400 MHz, CD_3OD): δ 8.48 (d, $J = 6.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.37 - 7.16 (m, 2H), 6.15 (s, 1H), 3.89 - 3.74 (m, 1H), 3.36 - 3.31 (m, 1H), 2.39 - 2.23 (m, 3H), 1.92 - 1.71 (m, 2H), 1.00 (s, 9H). MS (ESI): m/z 460.2 $[\text{M} + \text{H}]^+$

Compound 453

^1H NMR (400 MHz, CD_3OD): δ 8.48 (d, $J = 6.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.19 (m, 1H), 6.15 (s, 1H), 3.94 - 3.87 (m, 1H), 3.29 - 3.20 (m, 1H), 2.39 - 2.19 (m, 3H), 2.11 - 2.04 (m, 1H), 1.67 - 1.65 (m, 1H), 1.00 (s, 9H). MS (ESI): m/z 460.2 $[\text{M} + \text{H}]^+$

Compound 454

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.29 (s, 1H), 7.99-7.98 (m, 1H), 7.58-7.55 (m, 1H), 7.46-7.40 (m, 2H), 7.32 (br s, 2H), 7.14-7.09 (m, 2H), 3.90 (s, 3H), 3.38 (t, $J = 8.8$ Hz, 1H), 3.16 (t, $J = 10.4$ Hz, 1H), 2.48-2.39 (m, 1H), 2.23-2.05 (m, 3H), 1.83-1.80 (m, 1H), 1.59 (br s, 1H). MS (ESI): m/z 459.20 $[\text{M}-\text{H}]^-$

Compound 455

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.79 (br s, 1H), 8.55 (d, $J = 5.6$ Hz, 1H), 8.13 (d, $J = 1.6$ Hz, 1H), 7.65 (dd, $J = 5.2, 1.6$ Hz, 1H), 7.13-7.05 (m, 2H), 3.91 (d, $J = 5.6$ Hz, 3H), 3.41-3.36 (m, 1H), 3.32-3.14 (m, 4H), 2.45-2.41 (m, 1H), 2.23-2.09 (m, 3H), 1.84-1.81 (m, 1H), 1.68-1.61 (m, 1H). MS (ESI): 461.30 $[\text{M} + \text{H}]^+$

Compound 456

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.54 (br s, 1H), 8.39 (d, $J = 5.6$ Hz, 1H), 7.39 (b s, 1H), 7.35 (d, $J = 5.6$ Hz, 1H), 7.18 (br s, 1H), 7.04 - 6.95 (m, 2H), 5.96 (s, 1H), 3.89 (s, 3H), 3.29 - 3.22 (m, 1H), 2.96 - 2.88 (m, 1H), 2.34 - 2.25 (m, 1H), 2.24 - 2.12 (m, 2H), 2.08 - 1.95 (m, 2H), 1.61 - 1.51 (m, 1H). MS (ESI): m/z 462.0 $[\text{M} + \text{H}]^+$

Compound 457

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.64 (br. s., 1H), 8.43 (d, $J = 5.6$ Hz, 1H), 7.45 (d, $J = 6.0$ Hz, 1H), 7.43 - 7.36 (m, 1H), 7.33 - 7.28 (m, 1H), 7.23 - 7.18 (m, 1H), 7.16 - 7.09 (m, 1H), 6.02 (s, 1H), 3.98 - 3.88 (m, 1H), 3.77 (d, $J = 1.6$ Hz, 3H), 3.68 - 3.58 (m, 1H), 2.40 -

2.29 (m, 2H), 2.21 - 2.14 (m, 1H), 1.99 - 1.92 (m, 1H), 1.65 - 1.60 (m, 1H), 1.53 - 1.49 (m, 1H) MS (ESI): m/z 462.0 [M + H]⁺

Compound 458

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.46 (br s, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.20 (br s, 1H), 7.14 - 7.09 (m, 1H), 7.07 - 6.98 (m, 1H), 5.84 (d, *J* = 1.2 Hz, 1H), 3.87 (d, *J* = 1.6 Hz, 3H), 3.28 - 3.19 (m, 1H), 2.94 - 2.83 (m, 1H), 2.45 - 2.37 (m, 1H), 2.15 - 1.80 (m, 5H) MS (ESI): m/z 462.0 [M + H]⁺

Compound 459

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.49 (br s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.21 (br s, 1H), 7.15 - 7.09 (m, 1H), 7.06 - 6.96 (m, 1H), 5.92 - 5.80 (m, 1H), 3.87 (d, *J* = 1.6 Hz, 3H), 3.28 - 3.19 (m, 1H), 2.95 - 2.84 (m, 1H), 2.45 - 2.36 (m, 1H), 2.14 - 1.81 (m, 5H) MS (ESI): m/z 462.0 [M + H]⁺

Compound 462

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.10 - 7.04 (m, 1H), 6.98 (q, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 3.60 - 3.43 (m, 1H), 3.42 - 3.34 (m, 1H), 2.53 - 2.33 (m, 2H), 2.24 (s, 3H), 2.16 - 2.07 (m, 1H), 2.00 - 1.78 (m, 4H), 1.08 (t, *J* = 7.6 Hz, 3H) MS (ESI): m/z 462.6 [M + H]⁺

Compound 462

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.10 - 7.04 (m, 1H), 6.98 (q, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 3.60 - 3.43 (m, 1H), 3.42 - 3.34 (m, 1H), 2.53 - 2.33 (m, 2H), 2.24 (s, 3H), 2.16 - 2.07 (m, 1H), 2.00 - 1.78 (m, 4H), 1.08 (t, *J* = 7.6 Hz, 3H) MS (ESI): m/z 462.6 [M + H]⁺

Compound 463

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 6.0 Hz, 1H), 7.20 - 7.08 (m, 1H), 6.69 (q, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 3.56 - 3.44 (m, 1H), 3.30 - 3.21 (m, 1H), 2.59 - 2.43 (m, 1H), 2.42 - 2.30 (m, 1H), 2.24 (s, 3H), 2.14 - 2.01 (m, 2H), 1.97 - 1.80 (m, 1H), 1.57 - 1.41 (m, 1H), 1.33 - 1.27 (m, 1H), 1.00 (t, *J* = 7.6 Hz, 3H) MS (ESI): m/z 462.2 [M + H]⁺

Compound 464

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.46 (d, *J* = 6.0 Hz, 1H), 7.20 - 7.10 (m, 1H), 6.99 (q, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 3.52 - 3.42 (m, 1H), 3.32 - 3.37 (m, 1H), 2.51 - 2.34 (m, 2H), 2.24 (s, 3H), 2.08 - 2.12 (m, 1H), 2.01 - 1.77 (m, 4H), 1.09 (t, *J* = 7.6 Hz, 3H) MS (ESI): m/z 462.2 [M + H]⁺

Compound 465

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.70 (s, 1H), 8.46 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.43 (s, 1H), 7.33 - 7.25 (m, 5H), 7.24 - 7.11 (m, 3H), 6.34 (s, 1H), 4.07 - 3.98 (m, 1H),

3.88 - 3.80 (m, 1H), 3.69 (d, $J = 2.0$ Hz, 3H), 3.43 (t, $J = 10.0$ Hz, 1H), 2.78 - 2.70 (m, 1H), 2.35 - 2.26 (m, 1H). MS (ESI): m/z 462.2 $[M + H]^+$

Compound 466

^1H NMR (400 MHz, CD_3OD): δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 5.6$ Hz, 1H), 7.14 - 6.99 (m, 1H), 6.92 - 6.79 (m, 1H), 6.22 (s, 1H), 3.89 (s, 3H), 3.79 - 3.59 (m, 1H), 3.29 - 3.24 (m, 1H), 2.54 - 2.43 (m, 1H), 2.42 - 2.19 (m, 2H), 1.94 - 1.87 (m, 1H), 1.79 - 1.55 (m, 1H), 1.11 (d, $J = 6.8$ Hz, 3H). MS (ESI): m/z 464.1 $[M + H]^+$

Compound 467

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.40 (d, $J = 5.6$ Hz, 1H), 7.56 - 7.32 (m, 2H), 7.31 - 7.02 (m, 3H), 6.04 (s, 1H), 3.73 (s, 3H), 3.55 - 3.47 (m, 1H), 3.24 - 3.15 (m, 1H), 2.44 - 2.16 (m, 3H), 2.01 - 1.78 (m, 2H), 0.69 (d, $J = 5.6$ Hz, 3H). MS (ESI): m/z 464.2 $[M + H]^+$

Compound 468

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.74 (s, 1H), 8.42 (d, $J = 5.6$ Hz, 1H), 7.51 - 7.31 (m, 1H), 7.48 - 7.31 (m, 1H), 7.20 (s, 1H), 7.07 - 6.95 (m, 2H), 6.20 (s, 1H), 3.91 (s, 3H), 3.64 - 3.52 (m, 1H), 2.47 - 2.38 (m, 2H), 2.37 - 2.20 (m, 2H), 2.19 - 2.07 (m, 1H), 0.81 (d, $J = 5.6$ Hz, 3H). MS (ESI): m/z 464.2 $[M + H]^+$

Compound 469

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.65 (br s, 1H), 8.40 (d, $J = 5.6$ Hz, 1H), 7.57 - 7.49 (m, 1H), 7.48 - 7.32 (m, 2H), 7.28 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.25 - 7.07 (m, 2H), 6.06 (s, 1H), 3.86 - 3.67 (m, 1H), 3.30 - 3.24 (m, 1H), 2.69 - 2.51 (m, 1H), 2.46 - 2.36 (m, 1H), 2.15 - 1.98 (m, 2H), 1.86 - 1.71 (m, 1H), 1.38 - 1.20 (m, 2H), 0.94 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 464.1 $[M + H]^+$

Compound 470

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.60 (br s, 1H), 8.43 (d, $J = 5.6$ Hz, 1H), 7.62 - 7.50 (m, 1H), 7.50 - 7.33 (m, 2H), 7.29 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.26 - 7.08 (m, 2H), 6.11 (s, 1H), 3.82 - 3.67 (m, 1H), 3.45 - 3.36 (m, 1H), 2.68 - 2.51 (m, 1H), 2.38 - 2.24 (m, 1H), 2.16 - 2.04 (m, 1H), 1.95 - 1.83 (m, 2H), 1.81 - 1.65 (m, 2H), 1.02 (t, $J = 7.2$ Hz, 3H). MS (ESI): m/z 464.2 $[M + H]^+$

Compound 471

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.63 (br s, 1H), 8.42 (d, $J = 5.6$ Hz, 1H), 7.61 - 7.51 (m, 1H), 7.49 - 7.33 (m, 2H), 7.29 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.25 - 7.09 (m, 2H), 6.09 (s, 1H), 3.81 - 3.66 (m, 1H), 3.50 - 3.39 (m, 1H), 2.64 - 2.52 (m, 1H), 2.37 - 2.25 (m, 1H), 2.17 - 2.02 (m, 1H), 1.95 - 1.82 (m, 2H), 1.80 - 1.64 (m, 2H), 1.02 (t, $J = 7.2$ Hz, 3H). MS (ESI): m/z 464.1 $[M + H]^+$

Compound 472

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br s, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.58 - 7.48 (m, 1H), 7.47 - 7.31 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.24 - 7.08 (m, 2H), 6.06 (s, 1H), 3.82 - 3.69 (m, 1H), 3.30 - 3.24 (m, 1H), 2.68 - 2.53 (m, 1H), 2.46 - 2.40 (m, 1H), 2.15 - 1.97 (m, 2H), 1.86 - 1.72 (m, 1H), 1.35 - 1.29 (m, 1H), 1.28 - 1.20 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* 464.1 [M + H]⁺

Compound 473

¹H NMR (400 MHz, DMSO-d₆): δ 10.67 (br s, 1H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.61 (dd, *J* = 5.4, 2.0 Hz, 1H), 7.40 (br s, 2H), 7.36-7.20 (m, 3H), 4.40 (t, *J* = 6.1 Hz, 1H), 3.75-3.70 (m, 1H), 3.30-2.98 (m, 1H), 2.56-2.54 (m, 1H), 2.20-2.16 (m, 2H). MS (ESI): *m/z* 465.00 [M + H]⁺

Compound 474

¹H NMR (400 MHz, DMSO-d₆): δ 10.48 (br s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.35 (br s, 2H), 7.10-7.07 (m, 2H), 3.88 (d, *J* = 1.2 Hz, 3H), 3.28-3.21 (m, 1H), 3.03-2.96 (m, 1H), 2.07-2.03 (m, 1H), 1.94-1.86 (m, 2H), 1.71-1.62 (m, 1H), 1.60-1.45 (m, 3H), 1.42-1.35 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H). MS (ESI) *m/z* 468.20 [M + H]⁺

Compound 475

¹H NMR (400 MHz, DMSO-d₆): δ 10.50 (br s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.35 (br s, 2H), 7.31-7.27 (m, 1H), 7.09-7.03 (m, 1H), 3.94-3.91 (m, 1H), 3.77 (d, *J* = 2.0 Hz, 3H), 2.98-2.93 (m, 1H), 1.86-1.74 (m, 4H), 1.61-1.48 (m, 2H), 1.29-1.25 (m, 1H), 1.23-1.07 (m, 1H), 0.92 (d, *J* = 0.8 Hz, 3H), 0.90 (d, *J* = 0.8 Hz, 3H). MS (ESI) *m/z* 468.20 [M + H]⁺

Compound 476

¹H NMR (400 MHz, DMSO-d₆): δ 10.50 (br s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.06 (s, *J* = 1.6 Hz, 1H), 7.58 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.33-7.27 (br m, 3H), 7.09-7.03 (m, 1H), 3.94-3.91 (m, 1H), 3.77 (d, *J* = 1.6 Hz, 3H), 2.98-2.93 (m, 1H), 1.86-1.74 (m, 4H), 1.59-1.48 (m, 2H), 1.29-1.23 (m, 1H), 1.18-1.09 (m, 1H), 0.92 (d, *J* = 0.8 Hz, 3H), 0.90 (d, *J* = 0.8 Hz, 3H). MS (ESI) *m/z* 468.20 [M + H]⁺

Compound 477

¹H NMR (400 MHz, DMSO-d₆): δ 10.61 (br s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 1.2 Hz, 1H), 7.63-7.61 (m, 1H), 7.36 (br s, 2H), 7.08-7.06 (m, 2H), 3.90 (s, 3H), 3.23-3.17 (m, 1H), 2.91-2.86 (m, 1H), 2.04-2.03 (m, 1H), 1.80-1.75 (m, 2H), 1.52 (br m, 1H), 1.37-1.17 (m, 4H), 0.90 (d, *J* = 4.4 Hz, 6H). MS (ESI) *m/z* 468.4 [M + H]⁺

Compound 478

¹H NMR (400 MHz, DMSO-d₆): δ 10.56 (br s, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.32 (br s, 2H), 7.11-7.02 (m, 2H), 3.89 (d, *J* = 1.2

Hz, 3H), 3.22-3.16 (m, 1H), 2.89-2.85 (m, 1H), 2.03-2.02 (m, 1H), 1.79-1.54 (m, 2H), 1.54-1.51 (m, 1H), 1.40-1.29 (m, 3H), 1.28-1.19 (m, 1H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.4$ Hz, 3H). MS (ESI) m/z 468.4 $[M + H]^+$

Compound 479

^1H NMR (400 MHz, CD_3OD): δ 8.48 (d, $J = 6.0$ Hz, 1H), 7.49 (d, $J = 6.0$ Hz, 1H), 7.12 - 7.05 (m, 2H), 6.26 (s, 1H), 4.03 - 3.96 (m, 1H), 3.75 - 3.63 (m, 1H), 2.59 - 2.17 (m, 5H), 0.98 - 0.91 (m, 3H) MS (ESI): m/z 468.1 $[M + H]^+$

Compound 480

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.50 (d, $J = 6.0$ Hz, 1H), 7.53 - 7.38 (m, 2H), 7.33 - 7.22 (m, 1H), 5.72 (br s, 1H), 4.33 - 4.28 (m, 1H), 3.66 - 3.52 (m, 1H), 2.83 - 2.52 (m, 2H), 2.40 - 2.26 (m, 1H), 2.24 - 2.10 (m, 2H), 0.82 (d, $J = 6.8$ Hz, 3H) MS (ESI): m/z 468.2 $[M + H]^+$

Compound 481

^1H NMR (400 MHz, CD_3OD) δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.30 - 7.24 (m, 1H), 7.19 (m, 1H), 6.21 (s, 1H), 3.88 - 3.78 (m, 1H), 3.37 (d, $J = 3.2$ Hz, 1H), 2.58 - 2.25 (m, 3H), 2.02 - 1.91 (m, 1H), 1.69 - 1.56 (m, 1H), 1.12 (d, $J = 6.4$ Hz, 3H). MS (ESI): m/z 468.4 $[M + H]^+$

Compound 482

^1H NMR (400 MHz, CD_3OD): δ 8.49 (d, $J = 6.0$ Hz, 1H), 7.50 (d, $J = 6.0$ Hz, 1H), 7.13 - 7.03 (m, 2H), 6.27 (s, 1H), 4.05 - 3.96 (m, 1H), 3.75 - 3.64 (m, 1H), 2.61 - 2.17 (m, 5H), 1.00 - 0.89 (m, 3H) MS (ESI): m/z 468.1 $[M + H]^+$

Compound 483

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.50 (d, $J = 6.0$ Hz, 1H), 7.11 - 7.01 (m, 1H), 6.92 - 6.80 (m, 1H), 6.22 (s, 1H), 3.92 (d, $J = 2.0$ Hz, 3H), 3.77 - 3.62 (m, 1H), 3.44 - 3.32 (m, 1H), 2.43 - 2.29 (m, 2H), 2.16 - 2.10 (m, 1H), 2.03 - 1.95 (m, 2H), 1.87 - 1.80 (m, 2H), 1.08 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 478.2 $[M + H]^+$

Compound 484

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.49 (d, $J = 6.0$ Hz, 1H), 7.14 - 7.03 (m, 1H), 6.92 - 6.81 (m, 1H), 6.22 (s, 1H), 3.93 (d, $J = 2.0$ Hz, 3H), 3.80 - 3.59 (m, 1H), 3.42 - 3.33 (m, 1H), 2.40 - 2.27 (m, 2H), 2.24 - 2.13 (m, 1H), 2.06 - 1.96 (m, 2H), 1.89 - 1.79 (m, 2H), 1.09 (t, $J = 7.6$ Hz, 3H)

Compound 485

^1H NMR (400 MHz, CD_3OD): δ 8.52 (d, $J = 6.0$ Hz, 1H), 7.59 (d, $J = 6.0$ Hz, 1H), 6.92 - 6.79 (m, 1H), 6.67 - 6.56 (m, 1H), 6.28 (s, 1H), 5.03 - 4.96 (m, 1H), 4.21 (dd, $J = 8.0, 10.0$ Hz, 1H), 3.79 (s, 3H), 3.44 - 3.33 (m, 2H), 2.78 - 2.70 (m, 1H), 2.40 - 2.26 (m, 1H) MS (ESI): m/z 469.1 $[M + H]^+$

Compound 486

¹H NMR (400 MHz, DMSO-d₆): δ 11.52 (br s, 1H), 10.09 (br s, 1H), 8.40 (d, *J* = 5.8 Hz, 1H), 7.39-7.35 (m, 2H), 7.19 (s, 1H), 6.94 (br m, 1H), 6.71-6.65 (m, 1H), 6.02 (s, 1H), 3.66-3.57 (m, 2H), 2.39-2.30 (m, 2H), 2.30-2.00 (m, 2H), 1.89-1.85 (m, 1H), 1.66 (br m, 1H). MS (ESI): *m/z* 436.40 [M + H]⁺.

Compound 487

¹H NMR (400 MHz, DMSO-d₆): δ 11.60 (br s, 1H), 8.42 (d, *J* = 5.7 Hz, 1H), 7.44-6.94 (m, 5H), 6.08 (s, 1H), 4.07-3.96 (m, 2H), 3.30-3.29 (m, 2H), 2.49-2.42 (m, 2H), 2.19-2.04 (m, 2H), 1.9-1.88 (m, 1H), 1.38 (t, *J* = 6.9 Hz, 3H). MS (ESI): *m/z* 464.05 [M + H]⁺.

Compound 488

¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.82-7.78 (m, 1H), 7.36 (d, *J* = 5.8 Hz, 1H), 7.13-7.04 (m, 2H), 6.06 (s, 1H), 3.83 (s, 3H), 3.60 (br m, 1H), 3.31-3.29 (m, 1H), 2.67 (d, *J* = 3.0 Hz, 3H), 2.47-2.33 (m, 2H), 2.20-2.07 (m, 1H), 1.69 (br m, 1H). MS (ESI): *m/z* 464.32 [M + H]⁺.

Compound 489

¹H NMR (400 MHz, DMSO-d₆): δ 11.54 (br s, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.39-7.00 (m, 6H), 6.04 (s, 1H), 3.62-3.56 (m, 1H), 2.39-1.88 (m, 5H), 1.70-1.61 (m, 1H). MS (ESI): *m/z* 486.30 [M+H]⁺.

Compound 490

¹H NMR (400 MHz, CD₃OD): δ 8.51 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 5.6 Hz, 1H), 6.86 - 6.73 (m, 1H), 6.62 - 6.51 (m, 1H), 6.33 (s, 1H), 4.86 - 4.82 (m, 1H), 4.24 - 4.17 (m, 1H), 3.96 (s, 3H), 3.46 - 3.34 (m, 2H), 2.88 - 2.78 (m, 1H), 2.22 - 2.11 (m, 1H)

Compound 491

¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (br s, 1H), 8.42 (d, *J* = 5.6 Hz, 1H), 7.51 - 7.30 (m, 2H), 7.19 (s, 1H), 7.11 - 6.92 (m, 2H), 6.19 (s, 1H), 3.67 - 3.50 (m, 1H), 2.46 - 2.37 (m, 2H), 2.36 - 2.20 (m, 2H), 2.19 - 2.05 (m, 1H), 0.81 (d, *J* = 5.6 Hz, 3H) MS (ESI): *m/z* 464.2 [M + H]⁺

Compound 492

¹H NMR (400 MHz, DMSO-d₆): δ 8.41 (d, *J* = 5.6 Hz, 1H), 7.51 - 7.31 (m, 2H), 7.29 - 7.01 (m, 3H), 6.05 (s, 1H), 3.74 (s, 3H), 3.57 - 3.47 (m, 1H), 3.23 - 3.16 (m, 1H), 2.47 - 2.18 (m, 3H), 2.02 - 1.78 (m, 2H), 0.69 (d, *J* = 5.6 Hz, 3H). MS (ESI): *m/z* 464.2 [M + H]⁺

Compound 493

¹H NMR (400 MHz, CD₃OD): δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.10 - 7.02 (m, 1H), 6.94 - 6.82 (m, 1H), 6.23 (s, 1H), 3.91 (s, 3H), 3.77 - 3.56 (m, 1H), 3.30 - 3.10 (m, 1H), 2.46 - 2.24 (m, 2H), 2.08 - 1.97 (m, 2H), 1.89 - 1.67 (m, 1H), 1.10 (s, 9H). MS (ESI): *m/z* 506.2 [M + H]⁺

Compound 494

¹H NMR (400 MHz, CD₃OD): δ 8.50 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 7.14 - 7.00 (m, 1H), 6.93 - 6.81 (m, 1H), 6.31 (s, 1H), 3.91 (s, 3H), 3.78 - 3.55 (m, 1H), 3.29 - 3.15 (m, 1H), 2.50 - 2.23 (m, 2H), 2.14 - 1.97 (m, 2H), 1.90 - 1.70 (m, 1H), 1.10 (s, 9H). MS (ESI): m/z 506.2 [M + H]⁺

Compound 495

¹H NMR (400 MHz, CD₃OD): δ 8.46 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 6.0 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.92 - 6.83 (m, 1H), 6.21 (s, 1H), 3.96 (d, J = 2.0 Hz, 3H), 3.82 - 3.70 (m, 1H), 3.41 - 3.37 (m, 1H), 2.58 - 2.34 (m, 2H), 2.23 - 2.13 (m, 2H), 1.98 - 1.85 (m, 1H), 1.21 (s, 9H). MS (ESI): m/z 506.2 [M + H]⁺

Compound 496

¹H NMR VT NMR AT 90° C (400 MHz, DMSO-d₆) δ 10.43 (s, 1H), 8.45 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.6 & 2.0 Hz, 1H), 7.08 - 6.98 (m, 4H), 4.50 (bs, 2H), 3.92 (s, 3H), 3.73 (s, 1H), 3.54 - 3.47 (m, 1H), 3.19 - 3.17 (m, 1H), 2.93 (s, 1H), 2.80 - 2.60 (m, 1H), 2.07 (s, 3H), 1.76 (d, J = 11.2 Hz, 1H), 1.51 (s, 1H). MS (ESI): m/z 469.40 [M + H]⁺

Compound 496

¹H NMR VT NMR AT 90° C (400 MHz, DMSO-d₆) δ 10.43 (s, 1H), 8.45 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 5.6 & 2.0 Hz, 1H), 7.08 - 6.98 (m, 4H), 4.50 (bs, 2H), 3.92 (s, 3H), 3.73 (s, 1H), 3.54 - 3.47 (m, 1H), 3.19 - 3.17 (m, 1H), 2.93 (s, 1H), 2.80 - 2.60 (m, 1H), 2.07 (s, 3H), 1.76 (d, J = 11.2 Hz, 1H), 1.51 (s, 1H). MS (ESI): m/z 469.40 [M + H]⁺

Compound 497

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 5.5, 2.0 Hz, 1H), 7.35 (br s, 2H), 7.14-7.06 (m, 2H), 3.91 (br m, 3H), 3.48-3.41 (m, 1H), 2.95-2.93 (m, 1H), 2.84-2.70 (m, 3H), 2.25-2.20 (m, 1H), 2.05-1.99 (m, 2H), 1.77-1.68 (m, 1H), 0.96 (d, J = 6.5 Hz, 6H). Compound 498

¹H NMR (400 MHz, DMSO-d₆): δ 10.51 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.73 (br s, 1H), 7.58 (dd, J = 5.4, 2.0 Hz, 1H), 7.37 (br s, 2H), 7.05-6.98 (m, 1H), 3.75 (br m, 3H), 3.57 (br s, 1H), 3.32-3.09 (m, 1H), 2.90-2.80 (m, 2H), 2.79-2.73 (m, 1H), 2.59-2.58 (m, 1H), 2.49-2.39 (m, 1H), 1.95-1.87 (m, 1H), 1.73-1.62 (m, 1H), 1.00-0.98 (m, 6H). MS (ESI): m/z 469.40 [M + H]⁺

Compound 499

¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (s, 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.60 (dd, J = 5.6 & 2.0 Hz, 2H), 7.37 (s, 2H), 7.11 - 7.06 (m, 2H), 3.90 (s, 3H), 3.22 (dt, J = 11.6 & 7.2 Hz, 1H), 3.14 - 3.04 (m, 2H), 2.86 - 2.78 (m, 2H), 2.34 - 2.25 (m, 2H), 1.73 (d, J = 9.6 Hz, 1H), 1.48 - 1.46 (m, 1H), 1.01 - 0.99 (m, 6H). MS (ESI): m/z 469.40 [M + H]⁺

Compound 500

¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (br s, 1H), 8.47 (d, *J* = 5.5 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 8.05 (d, *J* = 1.8 Hz, 1H), 7.76-7.59 (m, 1H), 7.37 (br s, 2H), 7.13-7.03 (m, 2H), 3.90 (br m, 3H), 3.27-3.21 (m, 1H), 3.20-3.10 (m, 1H), 3.09-3.03 (m, 1H), 2.85-2.78 (m, 2H), 2.34-2.25 (m, 2H), 1.74-1.71 (m, 1H), 1.49-1.145 (m, 1H), 1.01-0.99 (m, 6H). MS (ESI): *m/z* 469.40 [M + H]⁺

Compound 501

¹H NMR (400 MHz, DMSO-d₆): δ 10.53 (s, 1H), 7.77 (d, *J* = 5.4 Hz, 1H), 8.19 (brs, 1H), 7.66 (dd, *J* = 5.44, 2 Hz, 1H), 7.18 (s, 2H), 7.08-7.01 (m, 1H), 6.96-6.94 (m, 1H), 4.57 (brs, 1H), 3.99 (s, 3H), 3.41-3.15 (m, 7H), 1.28-1.26 (m, 6H). MS (ESI): *m/z* 470.30 [M + H]⁺.

Compound 502

¹H NMR (400 MHz, CD₃OD): δ 8.48 (d, *J* = 5.6 Hz, 1H), 7.58 (d, *J* = 5.6 Hz, 1H), 7.10 - 6.99 (m, 1H), 6.92 - 6.81 (m, 1H), 6.35 (d, *J* = 4.0 Hz, 1H), 3.91 (s, 3H), 3.67 - 3.54 (m, 1H), 3.45 - 3.35 (m, 4H), 2.80 - 2.68 (m, 2H), 2.51 - 2.44 (m, 1H), 2.33 - 2.21 (m, 2H), 2.00 - 1.96 (m, 1H). MS (ESI): *m/z* 484.0 [M + H]⁺

Compound 503

¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (br s, 1H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.69 (dd, *J* = 1.6, 5.6 Hz, 1H), 7.40 (br s, 2H), 7.26 - 7.09 (m, 2H), 3.86 (d, *J* = 1.2 Hz, 3H), 3.80 - 3.68 (m, 1H), 3.26 - 3.10 (m, 1H), 2.28 - 2.11 (m, 3H), 2.01 - 1.84 (m, 1H), 1.61 - 1.38 (m, 2H) MS (ESI): *m/z* 474.1 [M + H]⁺

Compound 504

¹H NMR (400 MHz, DMSO-d₆): δ 10.72 (br. s., 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.73 - 7.58 (m, 1H), 7.44 (s, 2H), 7.24 - 7.06 (m, 2H), 3.95 (s, 3H), 3.24 - 3.12 (m, 1H), 2.83 - 2.73 (m, 1H), 2.53 - 2.44 (m, 1H), 2.16 - 1.92 (m, 3H), 1.86 - 1.68 (m, 2H) MS (ESI): *m/z* 474.0 [M + H]⁺

Compound 505

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (br s, 1H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.13 (s, 1H), 7.71 - 7.65 (m, 1H), 7.39 (br s, 2H), 7.19 - 7.07 (m, 2H), 3.99 - 3.91 (m, 1H), 3.89 (s, 3H), 3.26 - 3.19 (m, 1H), 2.39 - 2.32 (m, 1H), 2.11 - 1.97 (m, 3H), 1.60 - 1.42 (m, 2H) MS (ESI): *m/z* 474.1 [M + H]⁺

Compound 506

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (br. s., 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.36 (s, 2H), 7.12 - 7.02 (m, 1H), 7.02 - 6.95 (m, 1H), 3.91 (s, 3H), 3.08 - 2.98 (m, 1H), 2.87 - 2.76 (m, 1H), 2.34 - 2.21 (m, 1H), 2.16 - 2.07 (m, 1H), 2.05 - 1.88 (m, 3H), 1.45 - 1.34 (m, 1H) MS (ESI): *m/z* 474.0 [M + H]⁺

Compound 507

¹H NMR (400 MHz, DMSO-d₆): δ 10.74 (br s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 1.6, 5.4 Hz, 1H), 7.39 (br s., 2H), 7.21 - 7.09 (m, 6H), 3.92 (s, 3H), 3.68 - 3.55 (m, 1H), 3.30 - 3.18 (m, 2H), 3.12 - 3.02 (m, 1H), 3.00 - 2.91 (m, 1H), 2.90 - 2.78 (m, 1H). MS (ESI): *m/z* 474.1 [M + H]⁺

Compound 508

¹H NMR (400 MHz, CD₃OD) δ 8.46 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.21 - 7.12 (m, 1H), 6.14 (s, 1H), 3.85 - 3.76 (m, 1H), 3.21 - 3.10 (m, 1H), 2.11 - 2.03 (m, 2H), 2.01 - 1.94 (m, 2H), 1.86 - 1.77 (m, 1H), 1.74 - 1.65 (m, 2H), 1.04 (s, 9H). MS (ESI): *m/z* 474.3 [M + H]⁺

Compound 509

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.21 - 7.12 (m, 1H), 6.14 (s, 1H), 3.84 - 3.77 (m, 1H), 3.20 - 3.10 (m, 1H), 2.12 - 2.04 (m, 2H), 2.03 - 1.93 (m, 2H), 1.88 - 1.77 (m, 1H), 1.74 - 1.65 (m, 2H), 1.04 (s, 9H). MS (ESI): *m/z* 474.2 [M + H]⁺

Compound 510

¹H NMR (400 MHz, DMSO-d₆): δ 8.58 (d, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.25 - 7.11 (m, 1H), 7.07 - 6.96 (m, 1H), 6.52 - 6.36 (m, 1H), 3.76 (s, 3H), 3.70 - 3.55 (m, 2H), 2.41 - 2.30 (m, 2H), 2.22 - 2.09 (m, 2H), 1.92 - 1.84 (m, 1H), 1.79 - 1.63 (m, 1H). MS (ESI): *m/z* 475.3 [M + H]⁺.

Compound 511

¹H NMR (400 MHz, DMSO-d₆): δ 10.63 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.10 - 7.92 (m, 1H), 7.55 (dd, *J* = 1.6, 5.6 Hz, 1H), 7.34 (br s, 1H), 7.19 - 6.94 (m, 2H), 4.01 - 3.83 (m, 3H), 3.20 - 3.03 (m, 2H), 2.44 - 2.31 (m, 1H), 2.28 - 2.07 (m, 2H), 2.03 - 1.68 (m, 2H), 0.77 - 0.60 (m, 3H). MS (ESI): *m/z* 476.1 [M + H]⁺

Compound 512

¹H NMR (400 MHz, DMSO-d₆): δ 10.94 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.40 (br s, 2H), 7.13 - 6.99 (m, 2H), 3.93 (d, *J* = 0.8 Hz, 3H), 3.68 - 3.58 (m, 1H), 3.51 - 3.45 (m, 1H), 2.47 - 2.17 (m, 3H), 2.17 - 2.00 (m, 2H), 0.83 - 0.69 (m, 3H). MS (ESI): *m/z* 476.1 [M + H]⁺

Compound 513

¹H NMR (400 MHz, DMSO-d₆): δ 10.58 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.10 - 7.95 (m, 1H), 7.56 (dd, *J* = 1.6, 5.6 Hz, 1H), 7.39 (br s, 2H), 7.23 - 6.88 (m, 2H), 4.00 - 3.84 (m, 3H), 3.29 - 3.01 (m, 2H), 2.47 - 2.35 (m, 1H), 2.27 - 2.09 (m, 2H), 2.00 - 1.72 (m, 2H), 0.75 - 0.61 (m, 3H). MS (ESI): *m/z* 476.1 [M + H]⁺

Compound 514

^1H NMR (400 MHz, DMSO- d_6): δ 10.74 - 10.61 (m, 1H), 8.48 (d, J = 5.6 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 2.0, 5.6 Hz, 1H), 7.43 - 7.29 (m, 2H), 7.14 - 7.03 (m, 2H), 3.90 (s, 3H), 3.52 - 3.40 (m, 1H), 3.22 - 3.11 (m, 1H), 2.48 - 2.40 (m, 1H), 2.32 - 2.05 (m, 2H), 1.84 - 1.70 (m, 1H), 1.51 - 1.30 (m, 1H), 0.98 (d, J = 6.4 Hz, 3H). Compound 515

^1H NMR (400 MHz, DMSO- d_6): δ 10.68 (s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.09 (s, 1H), 7.58 (d, J = 4.4 Hz, 1H), 7.37 (s, 2H), 7.17 - 6.99 (m, 2H), 3.88 (s, 3H), 3.55 - 3.41 (m, 1H), 3.22 - 3.10 (m, 1H), 2.47 - 2.40 (m, 1H), 2.32 - 2.04 (m, 2H), 1.85 - 1.69 (m, 1H), 1.50 - 1.30 (m, 1H), 0.97 (d, J = 6.4 Hz, 3H). MS (ESI): m/z 476.1 $[\text{M} + \text{H}]^+$

Compound 516

^1H NMR (400 MHz, DMSO- d_6): δ 9.64 (br s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.34 (br. s, 2H), 7.23 - 7.09 (m, 2H), 3.86 (s, 3H), 3.51 - 3.38 (m, 2H), 2.47 - 2.39 (m, 1H), 2.28 - 2.07 (m, 3H), 2.05 (s, 3H), 1.89 - 1.76 (m, 1H), 1.72 - 1.54 (m, 1H). MS (ESI): m/z 476.0 $[\text{M} + \text{H}]^+$

Compound 517

^1H NMR (400 MHz, DMSO- d_6): δ 11.44 (br s, 1H), 8.39 - 8.16 (m, 1H), 7.35 - 7.23 (m, 6H), 7.20 - 7.11 (m, 3H), 7.03 - 6.94 (m, 1H), 5.66 (s, 1H), 4.15 (m, 1H), 3.73 (s, 3H), 3.58 - 3.49 (m, 1H), 2.46 - 2.32 (m, 2H), 2.31 - 2.23 (m, 1H), 2.20 - 1.89 (m, 2H). MS (ESI): m/z 476.2 $[\text{M} + \text{H}]^+$

Compound 518

^1H NMR (400 MHz, DMSO- d_6): δ 11.44 (br s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.39 - 7.28 (m, 3H), 7.25 - 7.13 (m, 6H), 7.12 - 7.05 (m, 1H), 5.62 (s, 1H), 4.10 - 3.88 (m, 5H), 3.79 - 3.71 (m, 1H), 2.51 - 2.42 (m, 2H), 2.32 - 2.20 (m, 1H), 2.03 - 1.90 (m, 1H). MS (ESI): m/z 476.3 $[\text{M} + \text{H}]^+$

Compound 519

^1H NMR (400 MHz, DMSO- d_6) δ 11.51 (br s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.40 - 7.35 (m, 2H), 7.23 - 7.08 (m, 3H), 5.93 (s, 1H), 3.30 - 3.20 (m, 1H), 3.18 - 3.09 (m, 1H), 2.37 - 2.25 (m, 2H), 2.21 (d, J = 1.6 Hz, 3H), 2.07 (d, J = 12.8 Hz, 1H), 2.00 - 1.83 (m, 3H), 1.66 (q, J = 12.4 Hz, 1H), 1.52 - 1.33 (m, 2H). MS (ESI): m/z 480.0 $[\text{M} + \text{H}]^+$

Compound 520

^1H NMR (400 MHz, DMSO- d_6) δ (br s, 1H), 8.40 (d, J = 6.0 Hz, 1H), 7.40 - 7.35 (m, 2H), 7.22 - 7.08 (m, 3H), 5.92 (s, 1H), 3.30 - 3.22 (m, 1H), 3.19 - 3.07 (m, 1H), 2.36 - 3.24 (m, 2H), 2.21 (d, J = 1.6 Hz, 3H), 2.06 (d, J = 12.0 Hz, 1H), 1.99 - 1.83 (m, 3H), 1.66 (q, J = 12.4 Hz, 1H), 1.52 - 1.32 (m, 2H). MS (ESI): m/z 480.0 $[\text{M} + \text{H}]^+$

Compound 521

^1H NMR (400 MHz, DMSO- d_6) δ 11.41 (s, 1H), 8.40 (d, J = 6.0 Hz, 1H), 7.41 - 7.28 (m, 3H), 7.20 - 7.10 (m, 2H), 5.94 (s, 1H), 3.30 - 3.17 (m, 2H), 2.72 - 2.60 (m, 2H), 2.39 - 2.33

(m, 1H), 2.20 (d, $J = 1.6$ Hz, 3H), 2.15 - 2.04 (m, 1H), 1.92 - 1.77 (m, 3H), 1.71 - 1.63 (m, 1H), 1.62 - 1.50 (m, 1H). MS (ESI): m/z 480.0 $[M + H]^+$

Compound 522

^1H NMR (400 MHz, DMSO- d_6): δ 11.45 (br s, 1H), 8.40 (d, $J = 5.2$ Hz, 1H), 7.43 - 7.27 (m, 3H), 7.22 - 7.08 (m, 2H), 5.94 (s, 1H), 3.30 - 3.16 (m, 2H), 2.72 - 2.60 (m, 2H), 2.39 - 2.33 (m, 1H), 2.21 (d, $J = 1.6$ Hz, 3H), 2.15 - 2.03 (m, 1H), 1.92 - 1.73 (m, 3H), 1.71 - 1.63 (m, 1H), 1.61 - 1.50 (m, 1H). MS (ESI): m/z 480.0 $[M + H]^+$

Compound 523

^1H NMR (400 MHz, DMSO- d_6): δ 12.20 (s, 1H), 8.62 - 8.46 (m, 1H), 7.78 - 7.50 (m, 3H), 7.17 - 7.14 (m, 1H), 7.09 - 7.02 (m, 1H), 6.34 (s, 1H), 3.84 (s, 3H), 3.72 - 3.53 (m, 1H), 3.39 - 3.25 (m, 1H), 2.47 - 2.36 (m, 2H), 2.25 - 2.04 (m, 2H), 1.96 - 1.85 (m, 1H), 1.81 - 1.59 (m, 1H). MS (ESI): m/z 486.0 $[M + H]^+$

Compound 524

^1H NMR (400 MHz, DMSO- d_6): δ 8.47 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 1H), 7.32 - 7.24 (m, 1H), 7.24 - 7.13 (m, 1H), 6.22 (s, 1H), 3.89 - 3.73 (m, 1H), 3.39 - 3.32 (m, 1H), 2.58 - 2.47 (m, 1H), 2.47 - 2.33 (m, 1H), 2.18 - 2.02 (m, 2H), 1.96 - 1.89 (m, 1H), 1.59 - 1.46 (m, 1H), 1.36 - 1.28 (m, 1H), 1.01 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 482.2 $[M + H]^+$

Compound 525

^1H NMR (400 MHz, CD $_3$ OD): δ 8.54 (d, $J = 5.6$ Hz, 1H), 7.65 (d, $J = 5.6$ Hz, 1H), 7.04 (s, 1H), 6.92 - 6.80 (m, 1H), 6.29 (s, 1H), 3.92 (s, 3H), 3.66 - 3.53 (m, 1H), 3.43 (s, 3H), 3.29 - 3.16 (m, 1H), 2.85 - 2.67 (m, 1H), 2.54 - 2.45 (m, 1H), 2.39 - 2.15 (m, 3H), 2.12 - 2.01 (m, 1H). MS (ESI): m/z 485.3 $[M + H]^+$

Compound 526

^1H NMR (400 MHz, DMSO- d_6): δ 11.40 (br s, 1H), 8.38 (d, $J = 5.6$ Hz, 1H), 7.38 (s, 1H), 7.35 - 7.22 (m, 5H), 7.22 - 7.08 (m, 3H), 7.02 (q, $J = 8.8$ Hz, 1H), 5.66 (s, 1H), 4.26 - 4.12 (m, 1H), 3.71 (d, $J = 2.4$ Hz, 3H), 3.57 (m, 1H), 2.44 - 2.29 (m, 2H), 2.22 - 2.09 (m, 1H), 2.06 - 1.86 (m, 2H). MS (ESI): m/z 476.2 $[M + H]^+$

Compound 527

^1H NMR (400 MHz, DMSO- d_6): δ 8.46 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 1H), 7.19 - 6.71 (m, 2H), 6.23 (s, 1H), 3.90 (s, 3H), 3.78 - 3.51 (m, 1H), 3.29 - 3.07 (m, 1H), 2.53 - 2.25 (m, 2H), 2.15 - 1.97 (m, 2H), 1.95 - 1.88 (m, 1H), 1.75 - 1.46 (m, 1H), 1.41 - 1.25 (m, 1H), 1.00 (t, $J = 7.6$ Hz, 3H). MS (ESI): m/z 478.2 $[M + H]^+$

Compound 528

^1H NMR (400 MHz, DMSO- d_6): δ 11.48 (br s, 1H), 8.33 (d, $J = 4.8$ Hz, 1H), 7.34 - 7.19 (m, 3H), 7.18 - 7.05 (m, 6H), 7.03 - 6.95 (m, 1H), 5.58 (s, 1H), 4.05 - 3.79 (m, 5H), 3.73 - 3.63

(m, 1H), 2.44 - 2.39 (m, 1H), 2.25 - 2.15 (m, 1H), 2.03 - 1.82 (m, 2H). MS (ESI): m/z 476.3 [M + H]⁺

Compound 529

¹H NMR (400 MHz, DMSO-d₆): δ 10.49 (br s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 5.5, 2.0 Hz, 1H), 7.37 (br s, 2H), 7.29-7.26 (m, 1H), 7.25-7.05 (m, 1H), 3.86-3.89-3.88 (m, 3H), 3.32-3.25 (m, 1H), 3.14-3.04 (m, 1H), 2.45-2.33 (m, 1H), 2.03-1.99 (m, 1H), 1.88-1.83 (m, 1H), 1.67-1.48 (m, 7H), 1.48-1.39 (m, 2H), 1.39-1.30 (m, 1H), 1.30-1.16 (m, 1H). MS (ESI): m/z 480.39 [M + H]⁺

Compound 530

¹H NMR (400 MHz, DMSO-d₆): δ 10.53 (br s, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 5.5, 2.0 Hz, 1H), 7.37 (br s, 2H), 7.13-7.07 (m, 2H), 3.91-3.90 (m, 3H), 3.19-3.16 (m, 1H), 3.01-2.95 (m, 1H), 1.81-1.72 (m, 1H), 1.71-1.49 (m, 9H), 1.49-1.38 (m, 4H). MS (ESI): m/z 480.30 [M + H]⁺

Compound 531

¹H NMR (400 MHz, CD₃OD): δ 8.63 - 8.39 (m, 1H), 7.60 - 7.45 (m, 1H), 7.11 - 7.05 (m, 1H), 6.96 - 6.84 (m, 1H), 6.31 - 6.22 (m, 1H), 3.98 (d, J = 2.0 Hz, 3H), 3.82 - 3.72 (m, 1H), 3.46 - 3.39 (m, 1H), 2.62 - 2.38 (m, 2H), 2.25 - 2.16 (m, 2H), 1.98 - 1.88 (m, 1H), 1.23 (s, 9H). MS (ESI): m/z 506.2 [M + H]⁺

Compound 532

¹H NMR (400 MHz, DMSO-d₆): δ 11.60 (s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.49 - 7.38 (m, 4H), 7.35 (m, 2H), 7.30 - 7.19 (m, 3H), 7.18 - 7.10 (m, 1H), 6.09 (s, 1H), 4.04 - 3.91 (m, 1H), 3.77 (s, 3H), 3.63 - 3.47 (m, 2H), 2.41 - 2.32 (m, 1H), 2.29 - 2.15 (m, 2H), 2.15 - 1.87 (m, 1H). MS (ESI): m/z 476.2 [M + H]⁺

Compound 533

¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (br s, 1H), 8.51 - 8.38 (m, 1H), 7.47 (m, 1H), 7.45 - 7.32 (m, 6H), 7.28 - 7.19 (m, 2H), 7.18 - 7.11 (m, 1H), 6.04 (s, 1H), 3.88 (dt, J = 6.0, 11.2 Hz, 1H), 3.76 (s, 3H), 3.67 - 3.52 (m, 2H), 2.49 - 2.37 (m, 3H), 1.95 (q, J = 11.2 Hz, 1H). MS (ESI): m/z 476.2 [M + H]⁺

Compound 534

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (br s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.51 - 7.37 (m, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.31 - 7.17 (m, 3H), 7.17 - 7.09 (m, 1H), 6.08 (s, 1H), 3.98 (m, 1H), 3.77 (s, 3H), 3.63 - 3.53 (m, 1H), 2.39 - 2.32 (m, 1H), 2.26 - 2.15 (m, 2H), 2.13 - 1.86 (m, 1H). MS (ESI): m/z 476.2 [M + H]⁺

Compound 535

¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.43-7.40 (m, 2H), 7.32 (d, J = 5.8 Hz, 1H), 7.20 (br s, 1H), 7.08-7.04 (m, 2H), 6.14 (s, 1H), 3.50-3.43 (m,

1H), 3.35-3.23 (m, 1H), 2.47-2.36 (m, 2H), 2.32 (s, 3H), 2.25-2.10 (m, 2H), 1.99-1.89 (m, 1H), 1.65-1.56 (m, 1H). MS (ESI): m/z 482.30 [M + H]⁺

Compound 536

¹H NMR (400 MHz, CD₃OD): δ 8.48 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.24 - 7.12 (m, 2H), 7.04 - 6.85 (m, 2H), 6.22 (s, 1H), 4.06 - 3.92 (m, 1H), 3.61 - 3.47 (m, 1H), 3.36 - 3.32 (m, 2H), 3.21 - 2.98 (m, 2H). MS (ESI): m/z 484.1 [M + H]⁺

Compound 537

¹H NMR (400 MHz, CD₃OD): δ 8.47 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.34 - 7.26 (m, 1H), 7.24 - 7.13 (m, 2H), 7.00 - 6.89 (m, 2H), 6.22 (s, 1H), 4.06 - 3.95 (m, 1H), 3.58 - 3.49 (m, 1H), 3.37 - 3.32 (m, 2H), 3.19 - 2.96 (m, 2H). MS (ESI): m/z 484.1 [M + H]⁺

Compound 538

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (br s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 5.5, 2.0 Hz, 1H), 7.38 (br s, 2H), 7.06 (q, *J* = 9.2 Hz, 1H), 6.88-6.84 (m, 1H), 4.40 (s, 1H), 3.91 (s, 3H), 3.72-3.68 (m, 1H), 3.15-3.13 (m, 1H), 2.94-2.91 (m, 1H), 2.86-2.78 (m, 2H), 2.60-2.56 (m, 1H), 2.0 (br m, 2H), 1.84-1.67 (m, 4H), 1.60-1.51 (m, 2H). MS (ESI): m/z 546.05 [M - H]⁻

Compound 539

¹H NMR (400 MHz, CD₃OD): δ 8.47 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.34 - 7.27 (m, 1H), 7.24 - 7.14 (m, 2H), 6.98 - 6.89 (m, 2H), 6.22 (s, 1H), 4.08 - 3.96 (m, 1H), 3.57 - 3.48 (m, 1H), 3.30 - 3.29 (m, 2H), 3.22 - 3.02 (m, 2H). MS (ESI): m/z 484.1 [M + H]⁺

Compound 540

¹H-NMR (400 MHz, DMSO-d₆): δ 11.64 (s, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.42 (br s, 2H), 7.33-7.29 (m, 2H), 7.19 (br s, 1H), 6.07 (s, 1H), 3.79-3.74 (m, 1H), 3.37-3.29 (br m, 1H), 2.62-2.55 (m, 1H), 2.44-2.37 (m, 1H), 2.21-2.07 (m, 2H), 1.98-1.92 (m, 1H), 1.69-1.63 (m, 1H). MS (ESI): m/z 502.30 [M + H]⁺

Compound 541

¹H NMR (400 MHz, DMSO-d₆): δ 11.53 (s, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 5.6 Hz, 2H), 7.22 - 7.03 (m, 3H), 5.91 (s, 1H), 3.78 (s, 3H), 3.24 - 2.90 (m, 2H), 2.68 - 2.59 (m, 1H), 2.15 - 2.09 (m, 1H), 2.04 - 1.96 (m, 2H), 1.92 - 1.88 (m, 1H), 1.66 - 1.52 (m, 2H). MS (ESI): m/z 482.2 [M + H]⁺

Compound 542

¹H NMR (400 MHz, DMSO-d₆): δ 10.58 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.08 - 8.01 (m, 1H), 7.60 (d, *J* = 5.2 Hz, 1H), 7.35 (s, 2H), 7.12 - 7.02 (m, 2H), 3.90 (s, 3H), 3.16 - 3.13 (m, 1H), 2.93 - 2.87 (m, 1H), 2.02 - 1.97 (m, 1H), 1.88 - 1.64 (m, 10H), 1.42 - 1.34 (m, 1H), 1.16 - 1.10 (m, 1H). MS (ESI): m/z 560.4 [M + H]⁺

Compound 543

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.10 - 7.99 (m, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.34 (s, 2H), 7.12 - 7.00 (m, 2H), 3.90 (s, 3H), 3.17 - 3.15 (m, 1H), 2.93 - 2.87 (m, 1H), 2.02 - 1.98 (m, 1H), 1.90 - 1.58 (m, 10H), 1.44 - 1.36 (m, 1H), 1.16 - 1.08 (m, 1H) MS (ESI): *m/z* 560.4 [M + H]⁺

Compound 544

¹H NMR (400 MHz, DMSO-d₆): δ 11.64 (br s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.47 (br s, 1H), 7.40 (br m, 1H), 7.34 (d, *J* = 5.8 Hz, 1H), 7.19 (br m, 2H), 7.14 (s, 1H), 6.04 (s, 1H), 3.82 (s, 3H), 3.75 (br m, 1H), 2.43-2.38 (m, 2H), 2.19-2.14 (m, 2H), 2.06-2.03 (m, 1H), 1.93-1.90 (m, 1H), 1.63 (br m, 1H). MS (ESI): *m/z* 482.40 [M + H]⁺.

Compound 545

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H), 8.40 (d, *J* = 5.8 Hz, 1H), 7.57 (br s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.39 (br s, 1H), 7.33 (d, *J* = 5.8 Hz, 1H), 7.17 (br s, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.03 (s, 1H), 3.79 (br m, 4H), 2.49-2.39 (m, 2H), 2.19-1.91 (m, 4H), 1.68 (br m, 1H) MS (ESI): *m/z* 482.19 [M + H]⁺.

Compound 546

¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (br s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.39-7.34 (m, 3H), 7.17 (br s, 1H), 6.84-6.79 (m, 2H), 6.02 (s, 1H), 3.75 (s, 1H), 3.64 (br m, 1H), 2.49-2.37 (m, 2H), 2.22-1.99 (m, 3H), 1.87-1.85 (m, 1H), 1.66 (br m, 1H). MS (ESI): *m/z* 498.40 [M + H]⁺.

Compound 546

¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (br s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 7.39-7.34 (m, 3H), 7.17 (br s, 1H), 6.84-6.79 (m, 2H), 6.02 (s, 1H), 3.75 (s, 1H), 3.64 (br m, 1H), 2.49-2.37 (m, 2H), 2.22-1.99 (m, 3H), 1.87-1.85 (m, 1H), 1.66 (br m, 1H). MS (ESI): *m/z* 498.40 [M + H]⁺.

Compound 547

¹H NMR (400 MHz, DMSO-d₆): δ: 10.73 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.39 (s, 2H), 7.19 - 7.09 (m, 3H), 7.08 - 7.03 (m, 1H), 7.02 - 6.96 (m, 1H), 3.92 (s, 3H), 3.59 (s, 1H), 3.30 - 3.20 (m, 2H), 3.12 - 3.01 (m, 1H), 2.99 - 2.92 (m, 1H), 2.85 - 2.74 (m, 1H) MS (ESI): *m/z* 492.0 [M + H]⁺

Compound 548

¹H NMR (400 MHz, DMSO-d₆): δ: 10.73 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.39 (s, 2H), 7.23 (s, 1H), 7.19 - 7.09 (m, 2H), 7.04 - 6.95 (m, 2H), 3.93 (d, *J* = 0.8 Hz, 3H), 3.65 - 3.52 (m, 1H), 3.30 - 3.18 (m, 2H), 3.07 - 2.94 (m, 2H), 2.88 - 2.76 (m, 1H) MS (ESI): *m/z* 492.0 [M + H]⁺

Compound 549

^1H NMR (400 MHz, DMSO- d_6): δ 10.61 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.03 (d, $J = 2.0$ Hz, 1H), 7.60 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (s, 2H), 7.14 - 7.06 (m, 2H), 3.90 (d, $J = 0.8$ Hz, 3H), 3.26 - 3.22 (m, 1H), 3.02 - 2.93 (m, 1H), 2.59 - 2.54 (m, 1H), 2.28 - 2.19 (m, 1H), 2.00 - 1.92 (m, 1H), 1.89 - 1.80 (m, 1H), 1.65 - 1.45 (m, 3H) Compound 550

^1H NMR (400 MHz, DMSO- d_6): δ 10.62 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 8.03 (d, $J = 2.0$ Hz, 1H), 7.61 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (s, 2H), 7.15 - 7.05 (m, 2H), 3.90 (d, $J = 0.8$ Hz, 3H), 3.27 - 3.24 (m, 1H), 3.03 - 2.92 (m, 1H), 2.63 - 2.55 (m, 1H), 2.27 - 2.20 (m, 1H), 1.99 - 1.93 (m, 1H), 1.88 - 1.80 (m, 1H), 1.66 - 1.46 (m, 3H). MS (ESI): m/z 494.1 $[\text{M} + \text{H}]^+$

Compound 551

^1H NMR (400 MHz, DMSO- d_6): δ : 10.72 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.65 - 7.60 (m, 1H), 7.39 (s, 2H), 7.20 - 7.11 (m, 3H), 7.10 - 7.03 (m, 1H), 7.02 - 6.96 (m, 1H), 3.92 (s, 3H), 3.64 - 3.53 (m, 1H), 3.29 - 3.18 (m, 2H), 3.13 - 3.01 (m, 1H), 3.00 - 2.91 (m, 1H), 2.84 - 2.73 (m, 1H) MS (ESI): m/z 492.1 $[\text{M} + \text{H}]^+$

Compound 552

^1H NMR (400 MHz, DMSO- d_6): δ : 10.73 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.07 (d, $J = 2.0$ Hz, 1H), 7.62 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.39 (s, 2H), 7.19 - 7.09 (m, 3H), 7.08 - 7.03 (m, 1H), 7.02 - 6.96 (m, 1H), 3.92 (s, 3H), 3.59 (s, 1H), 3.30 - 3.20 (m, 2H), 3.12 - 3.01 (m, 1H), 2.99 - 2.92 (m, 1H), 2.85 - 2.74 (m, 1H) MS (ESI): m/z 492.0 $[\text{M} + \text{H}]^+$

Compound 553

^1H NMR (400 MHz, DMSO- d_6): δ : 10.72 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.69 - 7.56 (m, 1H), 7.39 (s, 2H), 7.27 - 7.20 (m, 1H), 7.18 - 7.11 (m, 2H), 7.04 - 6.94 (m, 2H), 3.93 (d, $J = 1.2$ Hz, 3H), 3.65 - 3.54 (m, 1H), 3.30 - 3.17 (m, 2H), 3.08 - 2.94 (m, 2H), 2.88 - 2.78 (m, 1H). MS (ESI): m/z 492.1 $[\text{M} + \text{H}]^+$

Compound 554

^1H NMR (400 MHz, DMSO- d_6): δ 10.53 (s, 1H), 8.46 (d, $J = 5.5$ Hz, 1H), 8.02 (d, $J = 1.2$ Hz, 1H), 7.63 (dd, $J = 5.3, 1.6$ Hz, 1H), 7.36 (br s, 2H), 7.10-7.05 (m, 2H), 3.89 (s, 3H), 3.21-3.14 (m, 1H), 3.08-3.03 (m, 1H), 1.93-1.90 (m, 1H), 1.74-1.71 (m, 1H), 1.54-1.51 (m, 5H), 1.50-1.35 (m, 5H), 1.34-1.08 (m, 4H). MS (ESI): m/z 494.20 $[\text{M} + \text{H}]^+$

Compound 555

^1H NMR (400 MHz, DMSO- d_6): δ 10.64 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.03 (d, $J = 2.0$ Hz, 1H), 7.61 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.36 (s, 2H), 7.15 - 6.99 (m, 2H), 3.89 (d, $J = 1.2$ Hz, 3H), 3.28 - 3.21 (m, 1H), 3.15 - 3.06 (m, 1H), 2.85 - 2.70 (m, 1H), 2.24 - 2.16 (m, 1H), 2.03 - 1.89 (m, 2H), 1.88 - 1.78 (m, 1H), 1.70 - 1.61 (m, 1H), 1.59 - 1.46 (m, 1H) MS (ESI): m/z 494.1 $[\text{M} + \text{H}]^+$

Compound 556

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.36 (s, 2H), 7.15 - 6.99 (m, 2H), 3.89 (d, *J* = 0.8 Hz, 3H), 3.27 - 3.13 (m, 2H), 2.25 - 2.18 (m, 1H), 2.07 - 1.99 (m, 1H), 1.76 - 1.54 (m, 4H), 1.17 (s, 3H) MS (ESI): *m/z* 508.1 [M + H]⁺

Compound 557

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.36 (br. s., 2H), 7.16 - 7.00 (m, 2H), 3.89 (d, *J* = 1.2 Hz, 3H), 3.29 - 3.11 (m, 2H), 2.27 - 2.16 (m, 1H), 2.06 - 1.97 (m, 1H), 1.76 - 1.52 (m, 4H), 1.17 (s, 3H) MS (ESI): *m/z* 508.1 [M + H]⁺

Compound 558

¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 7.38 (d, *J* = 5.6 Hz, 2H), 7.19 (s, 1H), 7.10 - 6.97 (m, 2H), 6.06 (s, 1H), 3.83 (d, *J* = 1.2 Hz, 3H), 3.30 - 3.08 (m, 2H), 2.92 - 2.77 (m, 1H), 2.22 - 2.02 (m, 3H), 1.99 - 1.87 (m, 1H), 1.80 - 1.58 (m, 2H) MS (ESI): *m/z* 482.2 [M + H]⁺

Compound 559

¹H NMR (400 MHz, DMSO-d₆): δ 10.53 (br s, 1H), 8.45 (d, *J* = 5.4 Hz, 1H), 8.08-8.05 (m, 1H), 7.63-7.57 (m, 1H), 7.36 (br s, 2H), 7.29-7.25 (m, 1H), 7.12-7.05 (m, 1H), 3.95-3.89 (m, 1H), 3.77 (s, 3H), 3.98-3.92 (m, 1H), 1.81-1.73 (m, 4H), 1.56-1.53 (m, 1H), 1.35-1.25 (m, 1H), 1.15-1.07 (m, 1H), 0.91(s, 9H). MS (ESI) *m/z* 482.40 [M + H]⁺

Compound 560

¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (br s, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 5.4, 2.0 Hz, 1H), 7.41 (br s, 2H), 7.05-6.98 (m, 1H), 6.87-6.83 (m, 1H), 3.97-3.96 (m, 3H), 3.51-3.48 (m, 1H), 3.37-3.33 (m, 1H), 3.22-3.17 (m, 1H), 2.49 (br m, 1H), 2.88-2.87 (m, 1H), 2.49-2.30 (m, 2H), 1.72-1.62 (m, 1H), 1.14 (m, 9H). MS (ESI): *m/z* 483.10 [M + H]⁺

Compound 561

¹H NMR (400 MHz, DMSO-d₆): δ 10.42 (br s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.10 (d, *J* = 1.4 Hz, 1H), 7.61 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.43-7.39 (m, 1H), 7.35 (br s, 1H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.07-6.98 (m, 3H), 6.79 (t, *J* = 7.2 Hz, 2H), 3.95-3.90 (m, 1H), 3.83 (br m, 3H), 3.69-3.66 (m, 1H), 3.61-3.56 (m, 1H), 3.40-3.36 (m, 1H), 3.28-3.27 (m, 1H), 3.04-3.00 (m, 1H), 2.05-2.03 (m, 1H), 1.97-1.94 (m, 1H). MS (ESI): *m/z* 503.40 [M + H]⁺

Compound 562

¹H NMR (400 MHz, DMSO-d₆): δ 10.42 (br s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.10 (d, *J* = 1.4 Hz, 1H), 7.61 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.43-7.39 (m, 1H), 7.35 (br s, 1H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.07-6.98 (m, 3H), 6.79 (t, *J* = 7.2 Hz, 2H), 3.95-3.90 (m, 1H), 3.83 (br m, 3H), 3.69-

3.66 (m, 1H), 3.61-3.56 (m, 1H), 3.40-3.36 (m, 1H), 3.28-3.27 (m, 1H), 3.04-3.00 (m, 1H), 2.05-2.03 (m, 1H), 1.97-1.94 (m, 1H). MS (ESI): m/z 503.40 $[M + H]^+$

Compound 563

^1H NMR (400 MHz, DMSO- d_6): δ 10.67 (br s, 1H), 8.47 (d, $J = 5.5$ Hz, 1H), 8.06 (d, $J = 1.8$ Hz, 1H), 7.61 (dd, $J = 5.4, 2.0$ Hz, 1H), 7.34 (br s, 2H), 7.13-7.04 (m, 2H), 3.89 (br m, 3H), 3.34 (br m, 1H), 3.31-3.19 (m, 1H), 3.10-3.08 (m, 1H), 3.07-2.98 (m, 1H), 2.24-2.15 (m, 2H), 1.77-1.74 (m, 1H), 1.49-1.39 (m, 1H), 1.07 (m, 9H). MS (ESI): m/z 483.10 $[M + H]^+$

Compound 564

^1H NMR (400 MHz, DMSO- d_6): δ 10.53 (br s, 1H), 8.49 (d, $J = 5.48$ Hz, 1H), 8.10 (d, $J = 1.84$ Hz, 1H), 7.69-7.66 (m, 1H), 7.38 (br s, 2H), 7.12-7.09 (m, 2H), 3.88 (s, 3H), 3.42-3.37 (m, 1H), 3.06-3.01 (m, 1H), 1.80-1.78 (m, 3H), 1.68-1.64 (m, 2H), 1.60-1.46 (m, 2H), 0.91 (s, 9H). MS (ESI) m/z 482.55 $[M + H]^+$

Compound 565

^1H NMR (400 MHz, DMSO- d_6): δ 10.67 (s, 1H), 8.51 (d, 1H, $J=5.4$ Hz), 8.14 (d, $J=1.4$ Hz, 1H), 7.62 (dd, $J = 5.44, 1.84$ Hz, 1H), 7.38 (s, 2H), 7.10-7.03 (m, 1H), 6.88-6.85 (m, 1H), 4.39 (brs, 1H), 3.74-3.70 (m, 1H), 3.31-3.18 (m, 3H), 3.07-3.03 (m, 1H), 2.92-2.90 (m, 2H), 2.76-2.72 (m, 1H). MS (ESI): m/z 510.40 $[M + H]^+$

Compound 566

^1H NMR (400 MHz, DMSO- d_6): δ 10.63 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.63 - 7.55 (m, 1H), 7.36 (br s, 2H), 7.11 - 7.02 (m, 2H), 3.89 (s, 3H), 3.49 - 3.42 (m, 1H), 2.92 - 2.83 (m, 1H), 2.04 - 1.93 (m, 2H), 1.91 - 1.80 (m, 3H), 1.77 - 1.72 (m, 1H), 1.71 - 1.54 (m, 4H), 1.52 - 1.44 (m, 1H), 1.40 - 1.23 (m, 4H), 1.18 - 1.08 (m, 1H), 0.87 - 0.74 (m, 2H) MS (ESI): m/z 508.2 $[M + H]^+$

Compound 567

^1H NMR (400 MHz, DMSO- d_6): δ 10.58 (s, 1H), 8.46 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 1.6$ Hz, 1H), 7.60 (dd, $J = 1.6, 5.6$ Hz, 1H), 7.36 (s, 2H), 7.14 - 6.99 (m, 2H), 3.89 (s, 3H), 3.30 - 3.21 (m, 1H), 2.85 - 2.73 (m, 1H), 2.13 - 2.05 (m, 1H), 1.88 - 1.82 (m, 1H), 1.76 - 1.51 (m, 7H), 1.39 - 1.28 (m, 1H), 1.22 - 1.05 (m, 6H), 1.01 - 0.88 (m, 2H) MS (ESI): m/z 508.2 $[M + H]^+$

Compound 568

^1H NMR (400 MHz, DMSO- d_6): δ 10.61 (s, 1H), 8.51 - 8.44 (m, 1H), 8.09 - 8.04 (m, 1H), 7.65 - 7.59 (m, 1H), 7.36 (s, 2H), 7.12 - 7.04 (m, 2H), 3.91 (s, 3H), 3.45 - 3.36 (m, 1H), 2.97 - 2.82 (m, 1H), 2.07 - 1.93 (m, 2H), 1.91 - 1.81 (m, 3H), 1.78 - 1.72 (m, 1H), 1.71 - 1.56 (m, 4H), 1.53 - 1.43 (m, 1H), 1.40 - 1.24 (m, 4H), 1.18 - 1.12 (m, 1H), 0.90 - 0.77 (m, 2H) MS (ESI): m/z 508.2 $[M + H]^+$

Compound 569

¹H NMR (400 MHz, DMSO-d₆): δ 10.57 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.06 - 8.05 (m, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.36 (s, 2H), 7.12 - 7.02 (m, 2H), 3.91 (s, 3H), 3.30 - 3.21 (m, 1H), 2.85 - 2.75 (m, 1H), 2.15 - 2.06 (m, 1H), 1.91 - 1.81 (m, 1H), 1.75 - 1.54 (m, 7H), 1.38 - 1.30 (m, 1H), 1.19 - 1.07 (m, 5H), 1.02 - 0.89 (m, 2H) MS (ESI): *m/z* 508.2 [M + H]⁺

Compound 570

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (s, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.77 - 7.52 (m, 1H), 7.37 (s, 2H), 7.19 - 7.03 (m, 2H), 3.92 (s, 3H), 3.65 - 3.52 (m, 1H), 2.97 - 2.86 (m, 1H), 1.97 - 1.79 (m, 3H), 1.69 - 1.37 (m, 4H), 0.92 (s, 9H) MS (ESI): *m/z* 482.1 [M + H]⁺

Compound 571

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.35 (br. s., 2H), 7.17 - 7.00 (m, 2H), 3.89 (s, 3H), 3.32 - 3.29 (m, 1H), 3.03 - 2.86 (m, 1H), 2.04 - 1.87 (m, 1H), 1.77 - 1.52 (m, 5H), 1.39 - 1.23 (m, 3H), 1.18 - 0.86 (m, 5H). MS (ESI): *m/z* 480.1 [M + H]⁺

Compound 572

¹H NMR (400 MHz, DMSO-d₆): δ 10.54 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.35 (s, 2H), 7.11 - 7.03 (m, 2H), 3.89 (s, 3H), 3.31 - 3.27 (m, 1H), 2.97 - 2.89 (m, 1H), 1.97 - 1.88 (m, 1H), 1.76 - 1.53 (m, 5H), 1.43 - 1.21 (m, 3H), 1.17 - 0.89 (m, 5H). MS (ESI): *m/z* 480.0 [M + H]⁺

Compound 573

¹H NMR (400 MHz, DMSO-d₆): δ 10.71 (br s, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 8.03 (d, *J* = 1.2 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.55 - 7.50 (m, 2H), 7.45 - 7.38 (m, 2H), 7.35 - 7.22 (m, 3H), 7.16 - 7.06 (m, 2H), 3.87 (s, 3H), 3.49 - 3.44 (m, 1H), 3.24 - 3.17 (m, 1H), 3.09 - 2.97 (m, 1H), 2.44 - 2.25 (m, 2H), 2.03 - 1.88 (m, 2H), 1.85 - 1.73 (m, 1H), 1.62 - 1.46 (m, 1H) MS (ESI): *m/z* 502.1 [M + H]⁺

Compound 574

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (br d, *J* = 6.8 Hz, 1H), 8.46 (dd, *J* = 2.0, 5.6 Hz, 1H), 8.09 - 8.01 (m, 1H), 7.67 - 7.58 (m, 1H), 7.36 (br s, 2H), 7.14 - 7.03 (m, 2H), 3.90 (d, *J* = 2.8 Hz, 3H), 3.29 - 3.15 (m, 1H), 2.95 - 2.80 (m, 1H), 2.26 - 2.06 (m, 1H), 1.94 - 1.71 (m, 5H), 1.65 - 1.45 (m, 6H), 1.36 - 1.20 (m, 2H), 1.16 - 1.02 (m, 2H) MS (ESI): *m/z* 494.1 [M + H]⁺

Compound 575

¹H NMR (400 MHz, DMSO-d₆): δ 10.60 (s, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.77 - 7.52 (m, 1H), 7.37 (s, 2H), 7.19 - 7.03 (m, 2H), 3.92 (s, 3H), 3.65 - 3.52 (m,

1H), 2.97 - 2.86 (m, 1H), 1.97 - 1.79 (m, 3H), 1.69 - 1.37 (m, 4H), 0.92 (s, 9H) MS (ESI): m/z 482.1 $[M + H]^+$

Compound 576

^1H NMR (400 MHz, DMSO- d_6): δ 10.59 (br s, 1H), 8.46 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 7.60 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.36 (br s, 2H), 7.14 - 7.01 (m, 2H), 3.90 (s, 3H), 3.29 - 3.22 (m, 1H), 2.87 - 2.75 (m, 1H), 2.13 - 2.04 (m, 1H), 1.95 - 1.88 (m, 1H), 1.82 - 1.63 (m, 3H), 1.62 - 1.40 (m, 6H), 1.33 - 1.22 (m, 1H), 1.19 - 0.98 (m, 4H) MS (ESI): m/z 494.1 $[M + H]^+$

Compound 577

^1H NMR (400 MHz, DMSO- d_6): δ 10.67 (br s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.64 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.39 - 7.25 (m, 6H), 7.22 - 7.15 (m, 2H), 7.13 - 7.04 (m, 1H), 3.92 (s, 3H), 3.55 - 3.42 (m, 1H), 3.03 - 2.90 (m, 1H), 2.86 - 2.76 (m, 1H), 2.25 - 2.14 (m, 1H), 2.03 - 1.92 (m, 1H), 1.88 - 1.72 (m, 2H), 1.69 - 1.53 (m, 2H) MS (ESI): m/z 502.1 $[M + H]^+$

Compound 578

^1H NMR (400 MHz, DMSO- d_6): δ 10.55 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.64 - 7.56 (m, 1H), 7.36 (br. s., 2H), 7.14 - 7.02 (m, 2H), 3.90 (s, 3H), 3.31 - 3.20 (m, 1H), 2.84 - 2.75 (m, 1H), 2.18 - 2.08 (m, 1H), 1.96 - 1.85 (m, 1H), 1.82 - 1.71 (m, 1H), 1.63 - 1.49 (m, 1H), 1.32 - 1.21 (m, 1H), 1.19 - 1.03 (m, 2H), 0.85 (s, 9H) MS (ESI): m/z 482.1 $[M + H]^+$

Compound 579

^1H NMR (400 MHz, DMSO- d_6): δ 10.56 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.65 - 7.58 (m, 1H), 7.36 (br.s., 2H), 7.17 - 6.95 (m, 2H), 3.91 (s, 3H), 3.31 - 3.22 (m, 1H), 2.84 - 2.74 (m, 1H), 2.18 - 2.07 (m, 1H), 1.96 - 1.85 (m, 1H), 1.79 - 1.71 (m, 1H), 1.63 - 1.49 (m, 1H), 1.32 - 1.22 (m, 1H), 1.19 - 1.03 (m, 2H), 0.85 (s, 9H) MS (ESI): m/z 482.1 $[M + H]^+$

Compound 580

^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (s, 1H), 10.51 (s, 1H), 8.51 (d, $J = 5.6$ Hz, 1H), 8.43 (d, $J = 5.6$ Hz, 1H), 8.09 (d, $J = 2.0$ Hz, 1H), 7.90 (s, 1H), 7.61 (d, $J = 4.4$ Hz, 1H), 7.53 - 7.50 (m, 3H), 7.44 (s, 2H), 7.39 - 7.31 (m, 3H), 7.14 - 7.10 (m, 2H), 4.90 (d, $J = 12.4$ Hz, 1H), 3.91 (s, 3H), 3.87 (s, 1H), 3.67 - 3.55 (m, 2H), 3.48 - 3.45 (m, 2H), 3.16 - 3.09 (m, 1H), 3.02 - 2.99 (m, 2H), 1.81 - 1.70 (m, 2H), 1.50 - 1.46 (m, 2H). MS (ESI): m/z 549.40 $[M + H]^+$

Compound 581

^1H NMR (400 MHz, DMSO- d_6) δ 10.81 (s, 1H), 8.48 (d, $J = 4.8$ Hz, 1H), 8.06 - 8.01 (m, 1H), 7.64 - 7.58 (m, 1H), 7.40 (s, 2H), 7.12 - 7.06 (m, 2H), 4.79 - 4.76 (m, 1H), 4.12 - 4.10 (m, 1H), 3.91 - 3.88 (m, 3H), 3.53 - 3.50 (m, 1H), 3.27 - 3.24 (m, 1H), 2.91 - 2.86 (m, 2H),

2.75 – 2.67 (m, 1H), 2.07 – 1.94 (m, 3H), 1.86 – 1.76 (m, 4H), 1.61 – 1.46 (m, 3H). MS (ESI): m/z 573.4 [M + H]⁺

Compound 582

¹H NMR (400 MHz, DMSO-d₆) δ 10.72 (s, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 5.6 & 2.0 Hz, 1H), 7.39 (s, 3H), 7.12 – 7.06 (m, 6H), 4.01 (d, *J* = 10.0 Hz, 1H), 3.92 (s, 3H), 3.73 (d, *J* = 12.0 Hz, 1H), 3.20 (dt, *J* = 11.6 & 8.0 Hz, 1H), 2.91 – 2.83 (m, 2H), 1.79 (d, *J* = 10.0 Hz, 1H), 1.67 – 1.64 (m, 1H). MS (ESI): m/z 521.40 [M + H]⁺

Compound 583

¹H NMR (400 MHz, DMSO-d₆) δ 10.74 (s, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 5.6 & 2.0 Hz, 1H), 7.39 (s, 2H), 7.23 – 7.11 (m, 3H), 7.04 – 6.99 (m, 1H), 6.82 – 6.76 (m, 1H), 3.93 (s, 3H), 3.75 (d, *J* = 12 Hz, 1H), 3.53 (d, *J* = 12 Hz, 1H), 3.44 (dt, *J* = 11.6 & 3.6 Hz, 1H), 3.26 (dt, *J* = 11.2 & 3.2 Hz, 1H), 3.00 – 2.88 (m, 2H), 1.83 – 1.70 (m, 2H). MS (ESI): m/z 539.40 [M + H]⁺

Compound 584

¹H NMR (400 MHz, DMSO-d₆) δ 10.74 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.59 (dd, *J* = 5.6 & 1.6 Hz, 1H), 7.37 (s, 2H), 7.25 – 7.20 (m, 2H), 1.15 – 7.11 (m, 2H), 7.03 – 6.99 (m, 1H), 3.96 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.42 – 3.38 (m, 2H), 3.28 – 3.25 (m, 2H), 2.95 (t, *J* = 10.8 Hz, 1H), 2.86 (t, *J* = 10 Hz, 1H), 1.84 – 1.71 (m, 2H). MS (ESI): m/z 539.40 [M + H]⁺

Compound 585

¹H NMR (400 MHz, DMSO-d₆): δ 10.62 (br s, 1H), 8.45 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.59 (dd, *J* = 5.5, 2.04 Hz, 1H), 7.50–7.45 (m, 1H), 7.36 (br s, 2H), 7.34–7.32 (m, 4H), 7.24–7.20 (m, 1H), 7.15–7.08 (m, 1H), 4.06 (t, *J* = 5.7 Hz, 1H), 3.81–3.80 (m, 3H), 3.19–3.13 (m, 1H), 2.80–2.74 (m, 1H), 2.28–2.15 (m, 1H), 2.07–2.00 (m, 1H), 1.96–1.87 (m, 2H), 1.66–1.52 (m, 2H). MS (ESI): m/z 502.30 [M + H]⁺

Compound 586

¹H NMR (400 MHz, DMSO-d₆): δ 10.48 (br s, 1H), 8.47–8.45 (m, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.64 (dd, *J* = 5.4, 2.0 Hz, 1H), 7.51–7.49 (m, 2H), 7.43–7.35 (m, 2H), 7.31 (br s, 2H), 7.25 (t, *J* = 7.28 Hz, 1H), 7.08–7.01 (m, 1H), 6.95–6.91 (m, 1H), 3.85 (br m, 3H), 3.38–3.32 (m, 1H), 3.29–3.26 (m, 1H), 3.00 (td, *J* = 11.6, 3.2 Hz, 1H), 2.49–2.44 (m, 1H), 2.28–2.24 (m, 1H), 2.12 (td, *J* = 12.9, 4.6 Hz, 1H), 2.01–1.94 (m, 1H), 1.65–1.61 (m, 1H), 1.53–1.44 (m, 1H). MS (ESI): m/z 502.30 [M + H]⁺

Compound 587

¹H NMR (400 MHz, DMSO-d₆): δ 10.78 (br s, 1H), δ 8.50 (d, *J* = 5.4 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 8.05–8.03 (m, 1H), 7.64 (dd, *J* = 5.5, 2.04 Hz, 1H), 7.55–7.50 (m, 1H), 7.37 (br s, 2H), 7.08 (q, *J* = 9.3 Hz, 1H), 6.92–6.85 (m, 2H), 6.64–6.61 (m, 1H), 4.45–4.42 (m, 1H), 4.34–

4.30 (m, 1H), 3.94 (s, 3H), 3.90-3.76 (m, 3H), 3.55-3.49 (m, 1H), 3.11-3.06 (m, 1H). MS (ESI): m/z 505.30 $[M + H]^+$

Compound 588

^1H NMR (400 MHz, DMSO- d_6): δ 10.64 (br s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.16 (d, $J = 1.6$ Hz, 1H), 7.63 (dd, $J = 5.5, 2.0$ Hz, 1H), 7.38 (br s, 2H), 7.06 (q, $J = 9.2$ Hz, 1H), 6.88-6.84 (m, 1H), 4.40 (s, 1H), 3.91 (s, 3H), 3.72-3.68 (m, 1H), 3.15-3.13 (m, 1H), 2.94-2.91 (m, 1H), 2.86-2.78 (m, 2H), 2.60-2.56 (m, 1H), 2.0 (br m, 2H), 1.84-1.67 (m, 4H), 1.60-1.51 (m, 2H). MS (ESI): m/z 546.05 $[M - H]^-$

Compound 589

^1H NMR (400 MHz, DMSO- d_6): δ 10.60 (br s, 1H), 8.45 (d, $J = 5.5$ Hz, 1H), 8.03 (d, $J = 1.8$ Hz, 1H), 7.60 (dd, $J = 5.5, 2.0$ Hz, 1H), 7.34-7.31 (m, 6H), 7.22-7.19 (m, 1H), 7.13-7.10 (m, 2H), 3.94 (br m, 3H), 3.40-3.37 (m, 1H), 3.08 (td, $J = 11.5, 2.4$ Hz, 1H), 2.80-2.74 (m, 1H), 2.18-2.14 (m, 1H), 1.91-1.76 (m, 3H), 1.75-1.52 (m, 2H). MS (ESI): m/z 502.30 $[M + H]^+$

Compound 590

^1H NMR (400 MHz, DMSO- d_6): δ 10.63 (br s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 7.60 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (br s, 2H), 7.18 - 7.06 (m, 2H), 3.92 (s, 3H), 3.44 - 3.39 (m, 1H), 2.94 - 2.82 (m, 1H), 2.72 - 2.58 (m, 1H), 2.22 - 2.13 (m, 1H), 2.07 - 1.97 (m, 1H), 1.92 - 1.81 (m, 1H), 1.76 - 1.61 (m, 1H), 1.52 - 1.34 (m, 2H). MS (ESI): m/z 494.0 $[M + H]^+$

Compound 591

^1H NMR (400 MHz, DMSO- d_6): δ 10.63 (br s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 7.60 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.37 (br s, 2H), 7.18 - 7.06 (m, 2H), 3.92 (s, 3H), 3.44 - 3.39 (m, 1H), 2.94 - 2.82 (m, 1H), 2.72 - 2.58 (m, 1H), 2.22 - 2.13 (m, 1H), 2.07 - 1.97 (m, 1H), 1.92 - 1.81 (m, 1H), 1.76 - 1.61 (m, 1H), 1.52 - 1.34 (m, 2H). MS (ESI): m/z 494.0 $[M + H]^+$

Compound 592

^1H NMR (400 MHz, DMSO- d_6): δ 10.51 (br. s., 1H), 8.63 - 8.57 (m, 2H), 7.44 (br. s., 2H), 7.19 - 7.05 (m, 2H), 3.90 (d, $J = 1.2$ Hz, 3H), 3.61 - 3.51 (m, 1H), 3.42 - 3.37 (m, 1H), 2.47 - 2.37 (m, 1H), 2.23 - 2.06 (m, 3H), 1.89 - 1.75 (m, 1H), 1.68 - 1.49 (m, 1H). MS (ESI): m/z 480.0 $[M + H]^+$

Compound 593

^1H NMR (400 MHz, DMSO- d_6) VT at 90° C δ 10.40 (s, 1H), 8.45 (d, $J = 5.6$ Hz, 1H), 8.00 (s, 1H), 7.57 (dd, $J = 5.6$ & 2.0 Hz, 1H), 7.08-6.98 (m, 4H), 4.65-4.63 (m, 1H), 4.42-4.40 (m, 1H), 4.10-4.09 (m, 1H), 3.91 (s, 3H), 3.61-3.60 (m, 1H), 3.50-3.48 (m, 1H), 3.06 - 3.04 (m, 1H), 1.92 - 1.89 (m, 1H), 1.66-1.63 (m, 1H). MS (ESI): m/z 523.40 $[M + H]^+$

Compound 594

¹H NMR (400 MHz, DMSO-d₆) δ 10.72 (s, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.38 (s, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.16 – 7.11 (m, 3H), 3.94 (s, 3H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.49 – 3.43 (m, 1H), 3.28 – 3.25 (m, 1H), 3.15 (t, *J* = 11.6 Hz, 1H), 2.99 (t, *J* = 12.4 Hz, 1H), 1.89 (d, *J* = 10.8 Hz, 1H), 1.79 – 1.76 (m, 1H). MS (ESI): *m/z* 528.40 [M + H]⁺

Compound 595

¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 1.2 Hz, 1H), 7.63 (dd, *J* = 5.2 & 2.0 Hz, 1H), 7.39 (s, 2H), 7.27 – 7.21 (m, 1H), 7.13 – 7.04 (m, 2H), 6.89 – 6.86 (m, 2H), 6.55 (t, *J* = 8.0 Hz, 1H), 4.19 (d, *J* = 11.6 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 1H), 3.51 – 3.46 (m, 1H), 3.16 – 3.11 (m, 1H), 3.00 – 2.93 (m, 3H), 1.76 (d, *J* = 10.8 Hz, 1H), 1.65 – 1.59 (m, 1H). MS (ESI): *m/z* 521.40 [M + H]⁺

Compound 596

¹H NMR (400 MHz, DMSO-d₆) δ 10.69 (s, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.60 (dd, *J* = 5.2 & 1.6 Hz, 1H), 7.37 (s, 2H), 7.19 – 7.12 (m, 2H), 7.07 – 6.99 (m, 3H), 3.94 (s, 3H), 3.44 – 3.38 (m, 1H), 3.28 – 3.24 (m, 1H), 3.17 – 3.10 (m, 1H), 3.02 (d, *J* = 10.4 Hz, 1H), 2.38 (s, 3H), 1.80 – 1.70 (m, 2H). MS (ESI): *m/z* 539.40 [M + H]⁺

Compound 597

¹H NMR (400 MHz, DMSO-d₆) δ 10.74 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 5.2 & 2.0 Hz, 1H), 7.38 (s, 2H), 7.14 – 7.09 (m, 3H), 7.04 – 6.98 (m, 2H), 3.93 (s, 3H), 3.77 – 3.73 (m, 1H), 3.53 – 3.50 (m, 1H), 3.43 (dd, *J* = 11.6 & 4.8 Hz, 1H), 3.33 – 3.27 (m, 1H), 3.04 – 2.98 (m, 2H), 1.82 – 1.75 (m, 2H). MS (ESI): *m/z* 539.40 [M + H]⁺

Compound 598

¹H NMR (400 MHz, DMSO-d₆): δ 10.93 (d, *J* = 5.4 Hz, 1H), 8.53 (d, *J* = 5.44 Hz, 2H), 8.38 – 8.32 (dd, *J* = 18.56, 1.8 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.22 – 6.97 (m, 2H), 3.92 (t, *J* = 1.72 Hz, 3H), 3.79 (t, *J* = 5.4 Hz, 2H), 3.48 (s, 3H), 3.46 – 3.37 (m, 1H), 3.22 – 3.19 (m, 1H), 2.49 – 2.46 (m, 3H & 1H merge with solvent peak), 2.24 – 2.06 (m, 3H), 1.84 (d, *J* = 13.4 Hz, 1H), 1.64 – 1.61 (m, 1H). MS (ESI): *m/z* 531.3 [M + H]⁺

Compound 599

¹H NMR (400 MHz, DMSO-d₆): δ 10.75 (s, 1H), 8.51 (d, *J* = 5.48 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 7.68 (dd, *J* = 5.48 Hz, *J* = 1.96 Hz, 1H), 7.38 (br s, 2H), 7.12 – 7.09 (m, 3H), 7.08 – 6.97 (m, 2H), 6.96 – 6.91 (m, 1H), 4.52 – 4.50 (m, 1H), 3.94 (s, 3H), 3.85 – 3.80 (m, 1H), 3.71 (dd, *J* = 12.36 Hz, *J* = 4.92 Hz, 1H), 3.47 (dd, *J* = 12.16 Hz, *J* = 3.4 Hz, 1H), 3.41 – 3.38 (m, 1H), 3.16 – 3.09 (m, 2H). MS (ESI): *m/z* 522.30 [M + H]⁺.

Compound 600

¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.04 (s, 1H), 7.70 – 7.60 (m, 4H), 7.37 (s, 3H), 7.16 (d, *J* = 7.6 Hz, 2H), 3.92 (s, 3H), 3.48 – 3.37 (m, 1H), 3.29

– 3.22 (m, 3H), 3.14 (t, $J = 10.8$ Hz, 1H), 3.05 (d, $J = 10.8$ Hz, 1H), 2.92 (t, $J = 11.6$ Hz, 1H), 1.83 (t, $J = 10.8$ Hz, 1H), 1.73 – 1.68 (m, 1H). MS (ESI): m/z 571.40 $[M + H]^+$

Compound 601

^1H NMR (400 MHz, DMSO- d_6) δ 10.71 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.04 (d, $J = 1.6$ Hz, 1H), 7.59 – 7.54 (m, 1H), 7.37 (s, 2H), 7.17 – 7.01 (m, 5H), 3.94 (s, 3H), 3.62 – 3.54 (m, 2H), 3.45 – 3.37 (m, 1H), 3.28 – 3.09 (m, 3H), 1.81 – 1.64 (m, 2H). MS (ESI): m/z 539.40 $[M + H]^+$

Compound 602

^1H NMR (400 MHz, DMSO- d_6) δ 10.64 (s, 1H), 8.44 (d, $J = 5.6$ Hz, 1H), 7.99 (d, $J = 1.6$ Hz, 1H), 7.57 (dd, $J = 5.2$ & 2.0 Hz, 1H), 7.35 (s, 2H), 7.11 – 7.02 (m, 2H), 3.87 (s, 3H), 3.26 – 3.19 (m, 1H), 3.13 (d, $J = 10.8$ Hz, 1H), 3.04 (dt, $J = 11.6$ & 3.6 Hz, 1H), 2.87 (d, $J = 11.2$ Hz, 1H), 2.72 – 2.66 (m, 3H), 2.46 – 2.38 (m, 2H), 2.04 – 1.92 (m, 2H), 1.70 (d, $J = 10.0$ Hz, 1H), 1.53 – 1.48 (m, 1H). MS (ESI): m/z 517.4 $[M + H]^+$

Compound 603

^1H NMR (400 MHz, DMSO- d_6) δ 10.73 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 1.6$ Hz, 1H), 7.58 (dd, $J = 7.6$ & 2.0 Hz, 1H), 7.43 (dd, $J = 8.4$ & 2.8 Hz, 1H), 7.37 (s, 2H), 7.32 – 7.30 (m, 1H), 7.21 – 7.10 (m, 3H), 3.94 (s, 3H), 3.51 (d, $J = 10$ Hz, 1H), 3.43 (dt, $J = 12$ & 4.4 Hz, 1H), 3.27 (d, $J = 3.2$ Hz, 1H), 3.02 (t, $J = 10.8$ Hz, 1H), 2.77 (t, $J = 9.6$ Hz, 1H), 1.86 – 1.70 (m, 2H). MS (ESI): m/z 555.3 $[M + H]^+$

Compound 604

^1H NMR (400 MHz, DMSO- d_6) δ 10.73 (s, 1H), 8.49 (d, $J = 5.6$ Hz, 1H), 8.15 (d, $J = 3.20$ Hz, 1H), 8.07 (s, 1H), 7.64 (dd, $J = 3.6$ & 1.6 Hz, 1H), 7.57 (t, $J = 7.2$ Hz, 1H), 7.39 (s, 2H), 7.10 – 7.02 (m, 2H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.66 (t, $J = 5.2$ Hz, 1H), 4.76 (d, $J = 10.8$ Hz, 1H), 4.43 (d, $J = 12.0$ Hz, 1H), 3.91 (s, 3H), 3.55 (t, $J = 10.0$ Hz, 1H), 3.05 – 2.95 (m, 3H), 1.77 (d, $J = 10.4$ Hz, 1H), 1.53 – 1.51 (m, 1H). MS (ESI): m/z 504.40 $[M + H]^+$

Compound 605

MS (ESI): m/z 493.4 $[M + H]^+$

Compound 606

^1H NMR (400 MHz, DMSO- d_6) δ 10.93 (s, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.22 (d, $J = 6.4$ Hz, 2H), 8.09 (s, 1H), 7.66 (dd, $J = 4.0$ & 1.6 Hz, 1H), 7.39 (s, 2H), 7.10 – 7.09 (m, 4H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.18 (d, $J = 12.8$ Hz, 1H), 3.91 (s, 3H), 3.64 – 3.57 (m, 1H), 3.22 – 3.10 (m, 3H), 1.80 (d, $J = 11.2$ Hz, 1H), 1.57 – 1.54 (m, 1H). MS (ESI): m/z 504.50 $[M + H]^+$

Compound 607

^1H NMR (400 MHz, DMSO- d_6): δ 10.65 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 7.72 (dd, $J = 2.0, 5.6$ Hz, 1H), 7.39 (br. s., 2H), 7.19 – 7.11 (m, 2H), 3.90 – 3.80 (m,

3H), 3.72 - 3.60 (m, 1H), 3.05 - 2.96 (m, 1H), 2.92 - 2.81 (m, 2H), 2.39 - 2.20 (m, 4H), 2.07 - 1.93 (m, 1H), 1.64 - 1.49 (m, 1H). MS (ESI): m/z 487.9 $[M + H]^+$

Compound 608

^1H NMR (400 MHz, DMSO- d_6) δ 10.77 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.42 (d, $J = 4.8$ Hz, 2H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.63 (dd, $J = 5.6$ & 2.0 Hz, 1H), 7.39 (s, 2H), 7.10 - 7.05 (m, 2H), 6.68 (t, $J = 4.8$ Hz, 1H), 5.07 (d, $J = 11.2$ Hz, 1H), 4.83 (d, $J = 12.8$ Hz, 1H), 3.92 (s, 3H), 3.59 (dt, $J = 11.60$ & 3.2 Hz, 1H), 3.11 - 2.97 (m, 3H), 1.80 (d, $J = 10.4$ Hz, 1H), 1.50 - 1.46 (m, 1H). MS (ESI): m/z 505.40 $[M + H]^+$

Compound 609

^1H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.08 (d, $J = 1.6$ Hz, 1H), 7.77 - 7.72 (m, 3H), 7.65 (dd, $J = 5.6$ & 2.0 Hz, 1H), 7.46 (dd, $J = 8.5$ & 2.0 Hz, 1H), 7.40 (s, 2H), 7.31 - 7.25 (m, 2H), 7.12 - 7.09 (m, 2H), 4.25 (d, $J = 10.8$ Hz, 1H), 4.01 (d, $J = 12.80$ Hz, 1H), 3.93 (s, 3H), 3.50 (dt, $J = 11.60$ & 3.6 Hz, 1H), 3.25 (dt, $J = 10.4$ & 2.8 Hz, 1H), 3.03 - 2.94 (m, 2H), 1.86 - 1.83 (m, 1H), 1.74 - 1.72 (m, 1H). MS (ESI): m/z 553.40 $[M + H]^+$

Compound 610

^1H NMR (400 MHz, DMSO- d_6) δ 10.74 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 1.6$ Hz, 1H), 7.60 (dd, $J = 5.2$ & 1.6 Hz, 1H), 7.38 (s, 2H), 7.18 - 7.10 (m, 5H), 7.02 - 7.00 (m, 1H), 3.93 (s, 3H), 3.70 (d, $J = 10.8$ Hz, 1H), 3.49 - 3.40 (m, 3H), 3.29 - 3.26 (m, 2H), 2.96 (t, $J = 11.2$ Hz, 1H), 2.88 (t, $J = 10.0$ Hz, 1H), 1.84 - 1.72 (m, 2H). MS (ESI): m/z 521.40 $[M + H]^+$

Compound 611

^1H NMR (400 MHz, DMSO- d_6) δ 10.80 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.90 (d, $J = 7.2$ Hz, 1H), 7.64 - 7.50 (m, 4H), 7.44 (t, $J = 7.60$ Hz, 1H), 7.40 (s, 2H), 7.28 - 7.14 (m, 3H), 3.97 (s, 3H), 3.65 (d, $J = 10.80$ Hz, 1H), 3.52 - 3.49 (m, 2H), 3.43 (d, $J = 12$ Hz, 1H), 3.11 (t, $J = 10.4$ Hz, 1H), 2.87 (t, $J = 11.6$ Hz, 1H), 2.00 - 1.89 (m, 2H). MS (ESI): m/z 553.60 $[M + H]^+$

Compound 612

^1H NMR (400 MHz, DMSO- d_6) δ 10.72 (s, 1H), 8.49 (d, $J = 4.6$ Hz, 1H), 8.06 (d, $J = 2.0$ Hz, 1H), 7.63 (dd, $J = 5.2$ & 2.0 Hz, 1H), 7.38 (s, 2H), 7.24 (t, $J = 8.8$ Hz, 2H), 7.12 - 7.04 (m, 4H), 6.80 (t, $J = 7.2$ Hz, 1H), 4.11 (d, $J = 10.80$ Hz, 1H), 3.92 (s, 3H), 3.83 (d, $J = 12.40$ Hz, 1H), 3.46 (dt, $J = 11.60$ & 3.2 Hz, 1H), 3.22 - 3.16 (m, 1H), 2.95 - 2.87 (m, 2H), 1.78 (d, $J = 10$ Hz, 1H), 1.66 - 1.66 (m, 1H). MS (ESI): m/z 501.50 $[M + H]^+$

Compound 613

^1H NMR (400 MHz, DMSO- d_6): δ 10.51 (br s, 1H), 8.47 (d, $J = 5.2$ Hz, 1H), 8.01 (d, $J = 1.6$ Hz, 1H), 7.60 (dd, $J = 1.6, 5.2$ Hz, 1H), 7.35 (br s, 2H), 7.16 - 7.04 (m, 2H), 3.93 (s, 3H), 3.39 - 3.33 (m, 1H), 3.07 - 2.94 (m, 1H), 2.03 - 1.75 (m, 3H), 1.74 - 1.66 (m, 1H), 1.57 - 1.45 (m, 1H), 1.44 - 1.31 (m, 3H). MS (ESI): m/z 488.1 $[M + H]^+$

Compound 614

¹H NMR (400 MHz, DMSO-d₆): δ 10.20 (br s, 1H), 8.10 (br s, 1H), 7.61-7.58 (m, 1H), 7.49-7.43 (m, 2H), 7.35-7.33 (br s, 3H), 7.35-7.28 (m, 2H), 6.87 (dt, J = 7.6, 1.8 Hz, 1H), 4.37 (t, J = 5.8 Hz, 1H), 3.82-3.76 (m, 1H), 3.16-3.12 (m, 1H), 2.43-2.23 (m, 2H), 2.15-2.07 (m, 2H). MS (ESI): *m/z* 480.20 [M + H]⁺.

Compound 615

¹H NMR (400 MHz, DMSO-d₆): δ 10.30 (br s, 1H), 8.17 (s, 1H), 7.73-7.72 (m, 1H), 7.49-7.46 (m, 2H), 7.34 (br s, 2H), 7.20-7.07 (m, 2H), 6.99-6.91 (m, 2H), 6.82-6.79 (m, 1H), 4.92 (d, J = 8.1 Hz, 1H), 3.70 (s, 3H), 3.55-3.48 (m, 1H), 3.42-3.40 (m, 1H), 3.20-3.14 (m, 1H). MS (ESI): *m/z* 475.30 [M - H]⁻.

Compound 616

¹H NMR (400 MHz, DMSO-d₆): δ 10.13 (br s, 1H), 7.89 (br m, 1H), 7.45-7.37 (m, 3H), 7.33 (br s, 2H), 7.20-7.18 (m, 1H), 7.03-6.88 (m, 3H), 6.51 (br s, 1H), 5.09 (d, J = 9.1 Hz, 1H), 3.85-3.79 (m, 4H), 3.50-3.44 (m, 1H), 3.14-3.07 (m, 1H). MS (ESI): *m/z* 375.20 [M - H]⁻.

Compound 617

¹H NMR (400 MHz, DMSO-d₆): δ 11.51 (br s, 1H), 8.41 (d, J = 5.1 Hz, 1H), 7.41-7.34 (m, 3H), 7.20 (br s, 1H), 6.87-6.86 (m, 1H), 6.83-6.81 (m, 1H), 6.04 (s, 1H), 3.66-3.62 (m, 4H), 3.29-3.25 (m, 1H), 2.45-2.40 (m, 2H), 2.20-2.04 (m, 2H), 1.93-1.89 (m, 1H), 1.65-1.56 (m, 1H). MS (ESI): *m/z* 448.30 [M + H]⁺.

Compound 618

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.37 (br. s., 2H), 7.16 - 6.99 (m, 2H), 3.91 (s, 3H), 3.24 - 3.15 (m, 1H), 3.14 - 3.05 (m, 1H), 2.20 - 2.08 (m, 1H), 1.83 - 1.76 (m, 2H), 1.74 - 1.64 (m, 1H), 1.60 - 1.45 (m, 3H), 1.13 (d, J = 7.2 Hz, 3H). MS (ESI): *m/z* 440.1 [M + H]⁺.

Compound 619

¹H NMR (400 MHz, CD₃OD) δ 8.44 (d, J = 5.6 Hz, 1H), 7.43 - 7.29 (m, 2H), 6.89 - 6.80 (m, 1H), 6.71 (d, J = 9.2 Hz, 1H), 6.29 (s, 1H), 3.40 - 3.33 (m, 2H), 2.80 - 2.65 (m, 1H), 2.50 - 2.36 (m, 3H), 2.31 - 2.08 (m, 2H), 2.00 - 1.80 (m, 2H), 1.63 - 1.41 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). MS (ESI): *m/z* 444.2 [M + H]⁺.

Compound 620

¹H NMR (400 MHz, DMSO-d₆) δ 11.50 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.45 - 7.35 (m, 2H), 7.18 (s, 1H), 7.15 - 7.05 (m, 2H), 5.91 (s, 1H), 3.30 - 3.27 (m, 1H), 3.04 - 2.98 (m, 1H), 2.21 (d, J = 2.0 Hz, 3H), 2.08 - 2.00 (m, 1H), 1.95 - 1.81 (m, 2H), 1.75 - 1.64 (m, 1H), 1.45 - 1.30 (m, 2H), 0.90 - 0.82 (m, 1H), 0.65 - 0.56 (m, 1H), 0.44 - 0.36 (m, 2H), 0.19 - 0.08 (m, 2H). MS (ESI): *m/z* 438.29 [M + H]⁺.

Compound 621

¹H NMR (400 MHz, DMSO-d₆) δ 11.73 (s, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 7.48 (d, *J* = 5.6 Hz, 1H), 7.40 (s, 1H), 7.18 (s, 1H), 7.15 - 7.06 (m, 2H), 5.90 (s, 1H), 3.30 - 3.28 (m, 1H), 3.09 - 2.98 (m, 1H), 2.21 (d, *J* = 1.6 Hz, 3H), 2.05 - 2.03 (m, 1H), 1.95 - 1.81 (m, 2H), 1.78 - 1.69 (m, 1H), 1.46 - 1.28 (m, 2H), 0.94 - 0.80 (m, 1H), 0.67 - 0.54 (m, 1H), 0.45 - 0.35 (m, 2H), 0.20 - 0.08 (m, 2H) MS (ESI): *m/z* 438.42 [M + H]⁺

Compound 622

¹H NMR (400 MHz, MeOD-d₄) δ 8.46 (d, *J* = 5.6 Hz, 1H), 7.43 (d, *J* = 4.0 Hz, 1H), 7.19 - 7.06 (m, 1H), 7.05 - 6.93 (m, 1H), 6.25 (s, 1H), 3.61 - 3.50 (m, 1H), 3.46 - 3.35 (m, 2H), 2.56 - 2.33 (m, 2H), 2.30 - 2.07 (m, 2H), 2.01 - 1.91 (m, 1H), 1.90 - 1.75 (m, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H) MS (ESI): *m/z* 462.2 [M + H]⁺

Compound 623

¹H NMR (400 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.37 (br. s., 2H), 7.16 - 6.99 (m, 2H), 3.91 (s, 3H), 3.24 - 3.15 (m, 1H), 3.14 - 3.05 (m, 1H), 2.20 - 2.08 (m, 1H), 1.83 - 1.76 (m, 2H), 1.74 - 1.64 (m, 1H), 1.60 - 1.45 (m, 3H), 1.13 (d, *J* = 7.2 Hz, 3H) MS (ESI): *m/z* 448.1 [M + H]⁺

Compound 624

¹H NMR (400 MHz, DMSO-d₆) δ 11.58 (br s, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 7.41 (br s, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.24 - 7.12 (m, 3H), 6.16 (s, 1H), 3.54 - 3.42 (m, 1H), 3.31 - 3.24 (m, 1H), 2.77 - 2.59 (m, 2H), 2.48 - 2.35 (m, 2H), 2.26 - 2.09 (m, 2H), 1.94 - 1.83 (m, 1H), 1.70 - 1.57 (m, 1H), 1.06 (t, *J* = 7.6 Hz, 3H) MS (ESI): *m/z* 440.1 [M + H]⁺

Compound 625

¹H NMR (400 MHz, CD₃OD): δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.45 (d, *J* = 6.0 Hz, 1H), 7.04 - 6.97 (m, 1H), 6.96 - 6.87 (m, 1H), 6.06 (s, 1H), 3.21 - 3.10 (m, 1H), 3.00 - 2.88 (m, 1H), 2.59 - 2.47 (m, 1H), 2.31 - 2.20 (m, 4H), 2.05 - 1.83 (m, 4H) MS (ESI): *m/z* 446.1 [M + H]⁺

Compound 626

¹H NMR (400 MHz, CD₃OD): δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.45 (d, *J* = 6.0 Hz, 1H), 7.04 - 6.98 (m, 1H), 6.96 - 6.88 (m, 1H), 6.06 (s, 1H), 3.22 - 3.10 (m, 1H), 3.02 - 2.87 (m, 1H), 2.61 - 2.48 (m, 1H), 2.30 - 2.19 (m, 4H), 2.07 - 1.81 (m, 4H) MS (ESI): *m/z* 446.1 [M + H]⁺

Compound 627

¹H NMR (400 MHz, CD₃OD): δ 8.43 (d, *J* = 6.0 Hz, 1H), 7.44 (d, *J* = 6.0 Hz, 1H), 7.17 - 7.09 (m, 1H), 6.99 - 6.92 (m, 1H), 6.21 (s, 1H), 3.37 - 3.31 (m, 1H), 3.27 - 3.18 (m, 1H), 2.23 (d, *J* = 2.0 Hz, 3H), 2.17 - 2.14 (m, 1H), 2.06 - 2.02 (m, 1H), 2.00 - 1.95 (m, 1H), 1.92 - 1.76 (m, 3H), 1.35 - 1.30 (m, 1H), 1.11 - 1.05 (m, 1H), 0.66 - 0.58 (m, 2H), 0.22 - 0.13 (m, 2H). MS (ESI): *m/z* 438.1 [M + H]⁺

Compound 628

¹H NMR (400 MHz, CD₃OD): δ 8.42 - 8.28 (m, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.14 - 7.11 (m, 1H), 6.97 - 6.86 (m, 1H), 6.23 (s, 1H), 3.42 - 3.30 (m, 1H), 3.30 - 3.22 (m, 1H), 2.23 (s, 3H), 2.16 - 2.12 (m, 1H), 2.06 - 2.01 (m, 1H), 1.98 - 1.95 (m, 1H), 1.89 - 1.76 (m, 3H), 1.34 - 1.31 (m, 1H), 1.09 - 1.03 (m, 1H), 0.64 - 0.57 (m, 2H), 0.18 - 0.15 (m, 2H). MS (ESI): m/z 438.0 [M + H]⁺

Compound 629

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.10 (br s, 1H), 8.40 (d, J = 5.5 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 7.38-7.26 (m, 2H), 7.15 (br s, 1H), 7.09-7.00 (m, 1H), 3.84-3.72 (m, 4H), 3.55 (br m, 1H), 2.58-2.53 (m, 1H), 2.22-2.19 (m, 4H), 2.11-1.89 (m, 3H), 0.88 (t, J = 7.32 Hz, 3H). MS (ESI): m/z 478.38 [M + H]⁺

Compound 630

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.43 (br s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.40-7.39 (m, 2H), 7.17 (br m, 2H), 7.04-7.02 (m, 1H), 5.93 (s, 1H), 3.80 (s, 3H), 3.16 (br m, 1H), 1.75-1.64 (m, 4H), 1.50 (br m, 2H), 1.12 (s, 3H), 1.00 (s, 3H). MS (ESI): m/z 442.41 [M + H]⁺

Compound 631

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.44 (br s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.38-7.41 (m, 2H), 7.17 (br m, 2H), 7.04-7.02 (m, 1H), 5.93 (s, 1H), 3.80 (s, 3H), 3.22-3.17 (br m, 1H), 1.75-1.68 (m, 4H), 1.64-1.50 (m, 2H), 1.12 (s, 3H), 0.85 (s, 3H). MS (ESI): m/z 442.41 [M + H]⁺

Compound 633

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.44 (br s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 2H), 7.23-7.09 (m, 3H), 5.97 (s, 1H), 3.25-3.15 (m, 2H), 2.25-2.15 (m, 3H), 1.80-1.60 (m, 3H), 1.60-1.45 (m, 3H), 1.12 (s, 3H), 1.01 (s, 3H). MS (ESI): m/z 426.10 [M + H]⁺

Compound 634

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.43 (br s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 2H), 7.23-7.09 (m, 3H), 5.97 (s, 1H), 3.25-3.15 (m, 2H), 2.25-2.15 (m, 3H), 1.80-1.60 (m, 3H), 1.55-1.45 (m, 3H), 1.12 (s, 3H), 1.01 (s, 3H). MS (ESI): m/z 426.15 [M + H]⁺

Compound 635

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.46 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.61-7.57 (m, 1H), 7.40-7.38 (m, 2H), 7.24 (dd, J = 8.8, 2.64 Hz, 1H), 7.16-7.11 (m, 2H), 5.89 (s, 1H), 3.43-3.37 (m, 1H), 3.24-3.17 (m, 1H), 1.59-1.68 (br m, 6H), 1.13 (s, 3H), 1.02 (s, 3H). MS (ESI): m/z 428.05 [M + H]⁺

Compound 636

¹H-NMR (400 MHz, DMSO-*d*₆): δ 11.46 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.61-7.57 (m, 1H), 7.39-7.38 (m, 2H), 7.24 (dd, J = 8.8, 2.6 Hz, 1H), 7.16-7.11 (m, 2H), 5.89 (s, 1H), 3.43-

3.41 (m, 1H), 3.24-3.18 (m, 1H), 1.57-1.71 (br m, 6H), 1.13 (s, 3H), 1.02 (s, 3H). MS (ESI): m/z 428.10 $[M + H]^+$.

Compound 637

^1H NMR (400 MHz, DMSO- d_6): δ 11.73 (br s, 1H), 8.39-8.35 (m, 2H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.57 (t, $J = 15.2$ Hz, 1H), 7.52 – 7.45 (m, 2H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.31-7.30 (m, 1H), 7.27 (br s, 1H), 7.08 (br s, 1H), 6.15 (s, 1H), 4.29-4.24 (m, 1H), 3.51 – 3.56 (m, 1H), 2.53 (br m, 1H), 2.49-2.10 (m, 4H), 2.07-2.02 (m, 1H), 1.73-1.66 (m, 1H). MS (ESI): m/z 434.15 $[M + H]^+$.

Compound 638

^1H NMR (400 MHz, DMSO- d_6): δ 11.54 (br s, 1H), 8.37 (br m, 1H), 7.52-7.49 (m, 1H), 7.37 (br m, 2H), 7.22 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.20-7.10 (m, 2H), 5.83 (s, 1H), 3.52-3.47 (m, 1H), 3.03-2.98 (m, 1H), 2.01-1.98 (m, 1H), 1.90-1.75 (m, 4H), 1.60-1.30 (m, 3H). MS (ESI): m/z 400.32 $[M + H]^+$.

Compound 639

^1H NMR (400 MHz, DMSO- d_6): δ 11.53 (br s, 1H), 8.37 (br m, 1H), 7.52-7.49 (m, 1H), 7.38 (d, $J = 5.2$ Hz, 1H), 7.22 (dd, $J = 8.8$ Hz, $J = 2.56$ Hz, 1H), 7.17-7.10 (m, 2H), 5.83 (s, 1H), 3.52-3.47 (m, 1H), 3.03-2.98 (m, 1H), 2.05-1.95 (m, 1H), 1.90-1.75 (m, 4H), 1.54-1.39 (m, 3H). MS (ESI): m/z 400.32 $[M + H]^+$.

Compound 640

^1H -NMR (400 MHz, DMSO- d_6): δ 11.43 (br s, 1H), 8.39 (d, $J = 5.8$ Hz, 1H), 7.40-7.37 (m, 3H), 7.16 (br s, 1H), 6.91-6.89 (m, 1H), 6.87-6.81 (m, 1H), 5.96 (s, 1H), 3.23-3.11 (m, 2H), 2.25 (s, 3H), 1.76-1.63 (m, 3H), 1.54-1.51 (m, 3H), 1.13 (s, 3H), 1.02 (s, 3H). MS (ESI): m/z 408.23 $[M + H]^+$.

Compound 641

^1H -NMR (400 MHz, DMSO- d_6): δ 11.43 (br s, 1H), 8.39 (d, $J = 5.8$ Hz, 1H), 7.48-7.37 (m, 3H), 7.16 (br s, 1H), 6.91-6.89 (m, 1H), 6.87-6.81 (m, 1H), 5.96 (s, 1H), 3.20-3.11 (m, 2H), 2.25 (s, 3H), 1.76-1.70 (m, 3H), 1.66-1.51 (m, 3H), 1.11 (s, 3H), 1.02 (s, 3H). MS (ESI): m/z 408.19 $[M + H]^+$.

Compound 643

^1H NMR (400 MHz, DMSO- d_6): δ 11.58 (s, 1H), 8.34 (br m 1H), 7.35-7.14 (m, 5H), 5.83 (s, 1H), 3.55-3.50 (m, 1H), 3.01 (br s, 1H), 2.01-1.98 (m, 1H), 1.90-1.65 (m, 4H), 1.52-1.46 (m, 2H), 1.41-1.34 (m, 1H). MS (ESI): m/z 418.12 $[M + H]^+$.

Compound 644

^1H NMR (400 MHz, DMSO- d_6) δ 11.62 (br s, 1H), 8.40 (d, $J = 6.0$ Hz, 1H), 7.42 (br s, 1H), 7.36 - 7.30 (m, 2H), 7.20 (br s, 1H), 6.96 - 6.89 (m, 1H), 6.88 - 6.82 (m, 1H), 6.18 (s, 1H),

3.48 - 3.40 (m, 2H), 2.94 - 2.87 (m, 1H), 2.83 - 2.76 (m, 1H), 2.64 - 2.58 (m, 2H), 2.25 (s, 3H), 1.91 - 1.84 (m, 1H), 1.81 - 1.68 (m, 1H) MS (ESI): m/z 448.2 $[M + H]^+$

Compound 647

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.41 (d, $J = 6.0$ Hz, 1H), 6.99 - 6.86 (m, 2H), 6.17 (s, 1H), 3.21 - 3.09 (m, 1H), 3.07 - 2.97 (m, 1H), 2.52 - 2.42 (m, 1H), 2.36 - 2.15 (m, 5H), 2.04 - 1.89 (m, 2H), 1.74 - 1.63 (m, 1H) MS (ESI): m/z 446.1 $[M + H]^+$

Compound 648

^1H NMR (400 MHz, CD_3OD): δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.41 (d, $J = 6.0$ Hz, 1H), 7.01 - 6.82 (m, 2H), 6.16 (s, 1H), 3.19 - 3.09 (m, 1H), 3.02 (dt, $J = 3.9, 11.1$ Hz, 1H), 2.51 - 2.41 (m, 1H), 2.36 - 2.15 (m, 5H), 2.05 - 1.91 (m, 2H), 1.74 - 1.62 (m, 1H) MS (ESI): m/z 446.1 $[M + H]^+$

Compound 649

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.43 (s, 1H), 8.38 (d, $J = 5.6$ Hz, 1H), 7.39 (d, $J = 4.0$ Hz, 2H), 7.30 - 7.24 (m, 1H), 7.19 (s, 1H), 6.89 - 6.78 (m, 2H), 5.89 (s, 1H), 3.13 - 3.01 (m, 1H), 2.99 - 2.88 (m, 1H), 2.44 - 2.37 (m, 1H), 2.28 (s, 3H), 2.18 - 2.04 (m, 2H), 1.98 - 1.85 (m, 2H), 1.76 - 1.66 (m, 1H). MS (ESI): m/z 428.3 $[M + H]^+$

Compound 650

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.42 (br s, 1H), 8.38 (d, $J = 5.6$ Hz, 1H), 7.39 (d, $J = 5.6$ Hz, 2H), 7.29 - 7.24 (m, 1H), 7.19 (br s, 1H), 6.91 - 6.80 (m, 2H), 5.89 (s, 1H), 3.11 - 3.01 (m, 1H), 2.99 - 2.89 (m, 1H), 2.45 - 2.35 (m, 1H), 2.29 (s, 3H), 2.18 - 2.02 (m, 2H), 2.00 - 1.84 (m, 2H), 1.71 (m, 1H). MS (ESI): m/z 428.3 $[M + H]^+$

Compound 651

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.51 (s, 1H), 8.38 (d, $J = 6.0$ Hz, 1H), 7.44 - 7.29 (m, 2H), 7.23 - 7.12 (m, 2H), 6.89 - 6.79 (m, 2H), 6.01 (s, 1H), 3.16 - 3.03 (m, 1H), 2.98 - 2.86 (m, 1H), 2.33 (s, 3H), 2.31 - 2.26 (m, 1H), 2.26 - 2.11 (m, 2H), 2.06 - 1.94 (m, 2H), 1.44 (t, $J = 13.2$ Hz, 1H). MS (ESI): m/z 428.4 $[M + H]^+$

Compound 652

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.18 (s, 1H), 8.38 (d, $J = 6.0$ Hz, 1H), 7.45 - 7.36 (m, 1H), 7.34 (d, $J = 5.6$ Hz, 1H), 7.26 - 7.10 (m, 2H), 6.88 - 6.80 (m, 2H), 6.02 (s, 1H), 3.15 - 3.04 (m, 1H), 2.98 - 2.86 (m, 1H), 2.33 (s, 3H), 2.31 - 2.26 (m, 1H), 2.26 - 2.13 (m, 2H), 2.09 - 1.95 (m, 2H), 1.44 (t, $J = 13.2$ Hz, 1H). MS (ESI): m/z 428.4 $[M + H]^+$

Compound 653

^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 8.43 (d, $J = 6.0$ Hz, 1H), 7.43 (d, $J = 5.6$ Hz, 1H), 7.24 - 7.14 (m, 1H), 6.78 - 6.65 (m, 2H), 6.06 (s, 1H), 3.07 - 2.90 (m, 2H), 2.64 - 2.52 (m, 1H), 2.30 (s, 3H), 2.22 - 2.13 (m, 1H), 1.99 - 1.79 (m, 2H), 1.26 - 1.10 (m, 2H), 0.85 - 0.75 (m, 1H), 0.49 - 0.40 (m, 1H) MS (ESI): m/z 392.2 $[M + H]^+$

Compound 654

¹H NMR (400 MHz, MeOD-d₄) δ 8.43 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 7.19 (dd, J = 6.4, 8.0 Hz, 1H), 6.77 - 6.63 (m, 2H), 6.06 (s, 1H), 3.06 - 2.89 (m, 2H), 2.63 - 2.51 (m, 1H), 2.30 (s, 3H), 2.22 - 2.13 (m, 1H), 1.99 - 1.79 (m, 2H), 1.25 - 1.09 (m, 2H), 0.85 - 0.74 (m, 1H), 0.49 - 0.40 (m, 1H) MS (ESI): *m/z* 392.3 [M + H]⁺

Compound 655

¹H NMR (400 MHz, MeOD-d₄) δ 8.43 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 7.08 (t, J = 6.8 Hz, 1H), 6.75 - 6.62 (m, 2H), 6.13 (s, 1H), 3.14 (dt, J = 5.2, 11.6 Hz, 1H), 2.85 (dt, J = 3.6, 11.6 Hz, 1H), 2.45 - 2.36 (m, 2H), 2.35 (s, 3H), 2.31 - 2.20 (m, 1H), 1.54 (t, J = 13.2 Hz, 1H), 1.30 - 1.09 (m, 2H), 0.87 - 0.73 (m, 1H), 0.35 (d, J = 4.8 Hz, 1H) MS (ESI): *m/z* 392.2 [M + H]⁺

Compound 656

¹H NMR (400 MHz, MeOD-d₄) δ 8.43 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 7.09 (t, J = 6.8 Hz, 1H), 6.76 - 6.62 (m, 2H), 6.13 (s, 1H), 3.14 (dt, J = 5.2, 11.6 Hz, 1H), 2.92 - 2.78 (m, 1H), 2.46 - 2.37 (m, 2H), 2.35 (s, 3H), 2.32 - 2.22 (m, 1H), 1.54 (t, J = 13.2 Hz, 1H), 1.31 - 1.10 (m, 2H), 0.86 - 0.74 (m, 1H), 0.36 (d, J = 4.8 Hz, 1H) MS (ESI): *m/z* 392.2 [M + H]⁺

Compound 657

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.43 - 7.35 (m, 1H), 6.93 - 6.84 (m, 1H), 6.82 - 6.73 (m, 1H), 6.06 (s, 1H), 3.41 - 3.35 (m, 1H), 2.92 - 2.81 (m, 1H), 2.27 (s, 3H), 2.23 - 2.10 (m, 2H), 1.98 - 1.89 (m, 2H), 1.79 - 1.63 (m, 2H) MS (ESI): *m/z* 428.3 [M + H]⁺

Compound 658

¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 5.6 Hz, 1H), 7.49 (d, J = 5.6 Hz, 1H), 7.45 - 7.37 (m, 1H), 6.93 - 6.83 (m, 1H), 6.81 - 6.72 (m, 1H), 6.06 (s, 1H), 3.41 - 3.34 (m, 1H), 2.95 - 2.84 (m, 1H), 2.27 (s, 3H), 2.21 - 2.09 (m, 2H), 1.98 - 1.88 (m, 2H), 1.78 - 1.60 (m, 2H) MS (ESI): *m/z* 428.7 [M + H]⁺

Compound 669

¹H NMR (400 MHz, CD₃OD) δ 8.43 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.23 - 7.05 (m, 1H), 7.04 - 6.88 (m, 1H), 6.16 (s, 1H), 3.29 - 3.20 (m, 1H), 3.22 - 2.93 (m, 1H), 2.70 - 2.66 (m, 2H), 2.17 - 2.04 (m, 1H), 2.00 - 1.76 (m, 4H), 1.33 - 1.22 (m, 2H), 1.10 (t, J = 7.6 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H) MS (ESI): *m/z* 426.2 [M + H]⁺

Compound 670

¹H NMR (400 MHz, CD₃OD) δ 8.43 (br d, J = 6.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.23 - 7.05 (m, 1H), 7.04 - 6.88 (m, 1H), 6.16 (s, 1H), 3.29 - 3.20 (m, 1H), 3.22 - 2.93 (m, 1H), 2.70 - 2.66 (m, 2H), 2.17 - 2.04 (m, 1H), 2.00 - 1.76 (m, 4H), 1.33 - 1.22 (m, 2H), 1.10 (t, J = 7.6 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H) MS (ESI): *m/z* 426.0 [M + H]⁺

Compound 671

¹H NMR (400 MHz, CD₃OD): δ 8.43 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 7.32 (dd, J = 6.0, 8.8 Hz, 1H), 6.85 - 6.77 (m, 1H), 6.71 (dd, J = 2.4, 10.0 Hz, 1H), 6.15 (s, 1H), 3.29 - 3.22 (m, 1H), 3.01 - 2.91 (m, 1H), 2.78 - 2.68 (m, 1H), 2.58 - 2.47 (m, 1H), 2.15 - 2.08 (m, 1H), 2.00 - 1.85 (m, 3H), 1.83 - 1.74 (m, 1H), 1.30 - 1.22 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H) MS (ESI): m/z 408.2 [M + H]⁺

Compound 672

¹H NMR (400 MHz, CD₃OD): δ 8.43 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.32 (dd, J = 6.0, 8.4 Hz, 1H), 6.87 - 6.76 (m, 1H), 6.71 (dd, J = 2.4, 10.0 Hz, 1H), 6.15 (s, 1H), 3.30 - 3.22 (m, 1H), 3.00 - 2.90 (m, 1H), 2.78 - 2.68 (m, 1H), 2.58 - 2.47 (m, 1H), 2.15 - 2.07 (m, 1H), 1.99 - 1.83 (m, 3H), 1.82 - 1.73 (m, 1H), 1.31 - 1.24 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H) MS (ESI): m/z 408.2 [M + H]⁺

Compound 676

¹H NMR (400 MHz, MeOD-d₄) δ 8.44 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.14 - 7.03 (m, 1H), 7.03 - 6.90 (m, 1H), 6.13 (s, 1H), 3.91 - 3.78 (m, 1H), 3.29 - 3.21 (m, 1H), 2.96 - 2.83 (m, 1H), 2.47 - 2.26 (m, 4H), 2.15 - 2.04 (m, 2H), 1.98 - 1.74 (m, 5H), 1.30 - 1.19 (m, 2H), 1.00 (d, J = 6.0 Hz, 3H) MS (ESI): m/z 452.4 [M + H]⁺

Compound 681

¹H NMR (400 MHz, DMSO-d₆) δ 11.57 (s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 7.41 (br s, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.23 - 7.14 (m, 3H), 6.14 (s, 1H), 3.91 - 3.80 (m, 1H), 3.30 - 3.20 (m, 1H), 2.66 - 2.51 (m, 1H), 2.44 - 2.36 (m, 1H), 2.26 - 2.09 (m, 2H), 2.02 - 1.94 (m, 1H), 1.68 - 1.57 (m, 2H), 1.14 - 1.06 (m, 2H), 0.68 - 0.54 (m, 2H)

Compound 682

¹H NMR (400 MHz, DMSO-d₆) δ 11.57 (br s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 7.42 (br s, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.25 - 7.14 (m, 3H), 6.14 (s, 1H), 3.90 - 3.80 (m, 1H), 3.31 - 3.22 (m, 1H), 2.64 - 2.53 (m, 1H), 2.45 - 2.34 (m, 1H), 2.26 - 2.09 (m, 2H), 2.03 - 1.94 (m, 1H), 1.69 - 1.57 (m, 2H), 1.16 - 1.06 (m, 2H), 0.69 - 0.54 (m, 2H) MS (ESI): m/z 460.3 [M + H]⁺

Compound 689

¹H-NMR (400 MHz, DMSO-d₆): δ 11.47 (br s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.45-7.38 (m, 4H), 7.17 (br s, 1H), 5.90 (s, 1H), 3.44-3.41 (m, 1H), 3.26-3.21 (m, 1H), 1.78-1.68 (m, 3H), 1.62-1.53 (m, 3H), 1.13 (s, 3H), 1.01 (s, 3H).

Compound 691

¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (br s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 7.48-7.44 (m, 2H), 7.31 (br s, 1H), 6.07 (s, 1H), 2.23-2.22 (m, 3H), 1.99-1.83 (m, 2H), 1.58-1.56 (m, 1H), 1.47-1.39 (m, 2H), 1.29-1.23 (m, 1H), 1.20 (s, 3H), 0.96 (s, 3H). MS (ESI): m/z 426.23 [M + H]⁺.

Compound 693

¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (br s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 7.48-7.44 (m, 2H), 7.31 (br s, 1H), 6.07 (s, 1H), 2.23-2.22 (m, 3H), 1.99-1.83 (m, 2H), 1.58-1.56 (m, 1H), 1.47-1.39 (m, 2H), 1.29-1.23 (m, 1H), 1.20 (s, 3H), 0.96 (s, 3H). MS (ESI): *m/z* 426.23 [M + H]⁺.

Compound 695

¹H NMR (400 MHz, DMSO-d₆): δ 11.48 (br s, 1H), 8.40 (d, J = 5.8 Hz, 1H), 7.44-7.43 (m, 2H), 7.40-7.10 (m, 2H), 6.73-7.00 (m, 1H), 6.61 (br m, 1H), 5.89 (s, 1H), 3.71 (s, 3H), 3.32 (br m, 2H), 1.70-1.55 (m, 4H), 1.55-1.40 (m, 2H), 1.11 (s, 3H), 0.99 (s, 3H). MS (ESI): *m/z* 424.26 [M + H]⁺.

Compound 697

¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (br s, 1H), 8.43 (d, J = 5.8 Hz, 1H), 7.47-7.46 (m, 2H), 7.29-7.23 (m, 2H), 6.71 (dd, J = 11.4, 2.4 Hz, 1H), 6.61 (br m, 1H), 5.92 (s, 1H), 3.72-3.63 (m, 4H), 2.82 (br s, 1H), 1.89-1.84 (m, 2H), 1.56-1.53 (m, 1H), 1.47-1.34 (m, 3H), 1.12 (s, 3H), 0.96 (s, 3H). MS (ESI): *m/z* 424.22 [M + H]⁺.

Compound 699

¹H NMR (400 MHz, DMSO-d₆): δ 11.42 (br s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.41-7.38 (m, 2H), 7.25 (dd, J = 28.8, 2.6 Hz, 1H), 7.15-7.09 (m, 2H), 5.89 (s, 1H), 3.69-3.63 (m, 1H), 2.94-2.88 (m, 1H), 1.96-1.85 (m, 2H), 1.59-1.41 (m, 3H), 1.40-1.32 (m, 1H), 1.13 (s, 3H), 0.94 (s, 3H). MS (ESI): *m/z* 428.10 [M + H]⁺.

Compound 701

¹H NMR (400 MHz, DMSO-d₆): δ 11.43 (br s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.40-7.38 (m, 2H), 7.31-7.27 (m, 1H), 7.16 (br s, 1H), 6.88-6.83 (m, 2H), 5.98 (s, 1H), 3.42-3.36 (m, 1H), 2.96-2.90 (m, 1H), 2.27 (s, 3H), 1.99-1.82 (m, 2H), 1.59-1.55 (m, 1H), 1.48-1.41 (m, 2H), 1.28-1.22 (m, 1H), 1.19 (s, 3H), 0.96 (s, 3H). MS (ESI): *m/z* 408.23 [M + H]⁺.

Compound 702

¹H NMR (400 MHz, DMSO-d₆): δ 11.43 (br s, 1H), 8.40 (d, J = 5.5 Hz, 1H), 7.40-7.37 (br m, 2H), 7.31-7.27 (m, 1H), 7.16 (br s, 1H), 6.88-6.83 (m, 2H), 5.98 (s, 1H), 3.42-3.37 (m, 1H), 2.96-2.91 (m, 1H), 2.28 (s, 3H), 1.96-1.82 (m, 2H), 1.59-1.55 (m, 1H), 1.48-1.41 (m, 2H), 1.28-1.22 (m, 1H), 1.19 (s, 3H), 0.96 (s, 3H). MS (ESI): *m/z* 408.17 [M + H]⁺.

Compound 711

¹H NMR (400 MHz, DMSO-d₆): δ 11.88 (br s, 1H), 8.48 (d, J = 5.4 Hz, 1H), 7.46 (d, J = 5.7 Hz, 1H), 7.20-7.00 (m, 2H), 6.12 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.58 (br m, 1H), 3.30-3.20 (m, 1H), 2.46-2.35 (m, 2H), 2.30-2.00 (m, 2H), 1.95-1.85 (m, 1H), 1.68 (br m, 1H). MS (ESI): *m/z* 465.05 [M + H]⁺.

Compound 712

¹H NMR (400 MHz, DMSO-d₆): δ 13.07 (br s, 1H), 11.80 (br s, 1H), 8.45 (d, J = 5.8 Hz, 1H), 7.41 (d, J = 5.8 Hz, 1H), 7.20-7.10 (m, 1H), 7.10-7.00 (m, 1H), 6.14 (s, 1H), 3.82 (s, 3H), 3.59 (br m, 1H), 3.31 (br m, 1H), 2.45-2.40 (m, 2H), 2.30-2.00 (m, 2H), 1.95-1.85 (m, 1H), 1.69 (br m, 1H). MS (ESI): m/z 451.05 [M + H]⁺

Compound 713

¹H NMR (400 MHz, DMSO-d₆): δ 11.74-11.68 (m, 1H), 8.45 (br m, 1H), 7.838-7.34 (m, 1H), 7.20-6.95 (m, 2H), 6.09-6.06 (m, 1H), 3.82-3.80 (m, 3H), 3.57 (br m, 1H), 3.24-3.20 (m, 1H), 2.92 (s, 3H), 2.41 (br m, 2H), 2.20-2.10 (m, 2H), 1.88 (br m, 1H), 1.73-1.65 (m, 1H). MS (ESI): m/z 478.05 [M + H]⁺

Compound 714

¹H NMR (400 MHz, CD₃OD): δ 8.43 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.31 (dd, J = 6.0, 8.4 Hz, 1H), 6.84 - 6.75 (m, 1H), 6.71 (dd, J = 2.8, 10.2 Hz, 1H), 6.17 (s, 1H), 3.51 - 3.41 (m, 1H), 3.04 - 2.93 (m, 1H), 2.80 - 2.68 (m, 1H), 2.60 - 2.48 (m, 1H), 2.27 - 2.15 (m, 1H), 2.10 - 2.00 (m, 1H), 1.93 - 1.69 (m, 5H), 1.29 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H). MS (ESI): m/z 408.2 [M + H]⁺

Compound 715

¹H NMR (400 MHz, CD₃OD): δ 8.44 (d, J = 6.0 Hz, 1H), 7.45 (d, J = 6.0 Hz, 1H), 7.32 (dd, J = 6.0, 8.4 Hz, 1H), 6.84 - 6.76 (m, 1H), 6.71 (dd, J = 2.4, 10.0 Hz, 1H), 6.18 (s, 1H), 3.52 - 3.42 (m, 1H), 3.03 - 2.92 (m, 1H), 2.79 - 2.69 (m, 1H), 2.60 - 2.48 (m, 1H), 2.26 - 2.17 (m, 1H), 2.10 - 2.00 (m, 1H), 1.95 - 1.68 (m, 5H), 1.29 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.6 Hz, 3H). MS (ESI): m/z 408.2 [M + H]⁺

Compound 716

¹H NMR (400 MHz, MeOD-d₄) δ 8.39 (d, J = 5.6 Hz, 1H), 7.56 - 7.27 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.02 (q, J = 8.8 Hz, 1H), 6.31 (s, 1H), 3.45 - 3.33 (m, 2H), 2.76 - 2.55 (m, 2H), 2.54 - 2.38 (m, 2H), 2.32 - 2.06 (m, 2H), 2.03 - 1.81 (m, 2H), 1.62 - 1.41 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). MS (ESI): m/z 462.2 [M + H]⁺

Compound 717

¹H NMR (400 MHz, MeOD-d₄) δ 8.45 (d, J = 6.0 Hz, 1H), 7.48 (d, J = 6.0 Hz, 1H), 7.13 - 7.07 (m, 1H), 7.00 - 6.90 (m, 1H), 6.14 (s, 1H), 3.63 - 3.55 (m, 1H), 3.43 - 3.38 (m, 1H), 3.09 - 2.97 (m, 1H), 2.26 - 2.16 (m, 1H), 2.12 - 2.00 (m, 1H), 1.96 - 1.87 (m, 2H), 1.84 - 1.74 (m, 2H), 1.72 - 1.64 (m, 1H), 1.35 - 1.28 (m, 6H), 1.21 (d, J = 6.4 Hz, 3H). MS (ESI): m/z 440.6 [M + H]⁺

Compound 718

¹H NMR (400 MHz, MeOD-d₄) δ 8.45 (d, J = 6.0 Hz, 1H), 7.48 (d, J = 6.0 Hz, 1H), 7.13 - 7.07 (m, 1H), 7.00 - 6.90 (m, 1H), 6.14 (s, 1H), 3.63 - 3.53 (m, 1H), 3.42 - 3.38 (m, 1H), 3.08 - 2.98 (m, 1H), 2.28 - 2.16 (m, 1H), 2.12 - 2.00 (m, 1H), 1.96 - 1.87 (m, 2H), 1.83 - 1.74 (m,

2H), 1.71 - 1.64 (m, 1H), 1.35 - 1.28 (m, 6H), 1.21 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 440.7 $[M + H]^+$

Compound 719

^1H NMR (400 MHz, CD_3OD) δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.21 - 7.09 (m, 1H), 7.07 - 6.86 (m, 1H), 6.18 (s, 1H), 3.53 - 3.36 (m, 1H), 3.04 - 2.93 (m, 1H), 2.76 - 2.62 (m, 2H), 2.29 - 2.17 (m, 1H), 2.15 - 2.00 (m, 1H), 1.95 - 1.69 (m, 5H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.13 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 426.3 $[M + H]^+$

Compound 720

^1H NMR (400 MHz, CD_3OD) δ 8.45 (d, $J = 6.0$ Hz, 1H), 7.47 (br d, $J = 6.0$ Hz, 1H), 7.22 - 7.08 (m, 1H), 7.05 - 6.89 (m, 1H), 6.19 (s, 1H), 3.50 - 3.38 (m, 1H), 3.04 - 2.93 (m, 1H), 2.76 - 2.62 (m, 2H), 2.29 - 2.17 (m, 1H), 2.16 - 2.01 (m, 1H), 1.93 - 1.68 (m, 5H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.13 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 426.0 $[M + H]^+$

Compound 721

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.42 (s, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 8.00 (s, 1H), 7.65 - 7.53 (m, 1H), 7.37 (s, 2H), 7.20 - 7.00 (m, 2H), 3.88 (s, 3H), 3.11 - 2.98 (m, 1H), 2.86 - 2.71 (m, 1H), 2.08 - 1.96 (m, 1H), 1.90 - 1.76 (m, 2H), 1.64 - 1.41 (m, 3H), 1.28 - 1.07 (m, 1H), 0.60 (d, $J = 6.4$ Hz, 3H) MS (ESI): m/z 440.1 $[M + H]^+$

Compound 722

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.42 (d, $J = 6.0$ Hz, 1H), 7.15 - 7.07 (m, 1H), 7.03 - 6.92 (m, 1H), 6.23 (s, 1H), 3.42 - 3.34 (m, 1H), 3.30 - 3.22 (m, 1H), 2.32 - 2.23 (m, 4H), 2.09 - 1.68 (m, 7H), 1.01 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 444.1 $[M + H]^+$

Compound 723

^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, $J = 6.0$ Hz, 1H), 7.42 (d, $J = 6.0$ Hz, 1H), 7.15 - 7.07 (m, 1H), 7.03 - 6.92 (m, 1H), 6.23 (s, 1H), 3.42 - 3.34 (m, 1H), 3.30 - 3.22 (m, 1H), 2.32 - 2.23 (m, 4H), 2.09 - 1.68 (m, 7H), 1.01 (t, $J = 7.6$ Hz, 3H) MS (ESI): m/z 444.1 $[M + H]^+$

Biological Example 1

Nav Inhibition Assay

[00349] Electrophysiology experiments were performed on Human Embryonic Kidney 293 cells (HEK) or Chinese hamster ovary cells (CHO) transfected with the full-length cDNA coding for the appropriate human Nav sodium channel α -subunit Nav 1.8. Similarly, experiments are performed on Human Embryonic Kidney 293 cells (HEK) or Chinese hamster ovary cells (CHO) transfected with the full-length cDNA coding for the appropriate human Nav sodium channel α -subunit, including Nav 1.7, Nav 1.6, Nav 1.5, and Nav 1.4.

[00350] Sodium currents were measured using the patch-clamp technique in the whole-cell configuration with a HEKA EPC 9 amplifier (HEKA Elektronik Dr. Schulze GmbH, Germany) or can be measured using an IonFlux 16 automated patch clamp system (Fluxion Biosciences, South San Francisco, USA) as previously described by Moran. *See*, Moran O, Picollo A, Conti F (2003) Tonic and phasic guanidinium toxin-block of skeletal muscle Na channels expressed in Mammalian cells, *Biophys J* 84(5):2999–3006. For manual patch-clamp experiments, borosilicate glass micropipettes (Sutter Instruments, Novato, CA) were pulled to a tip diameter yielding a resistance of 1.0–2.0 MΩ in the working solutions. The composition of intracellular solution was (in mM): CsF 125, EGTA 10, HEPES 10, NaCl 10, and the pH was adjusted to 7.2 with CsOH. The composition of extracellular solution was (in mM): NaCl 135, KCl 4.5, CaCl₂ 2, MgCl₂ 1, HEPES 10, and the pH was adjusted to 7.4 with NaOH. For human Nav 1.8, 0.3 – 1 μM tetrodotoxin (TTX) was added to the extracellular solution to inhibit native TTX-sensitive current. Peak currents were generally between 0.5–20 nA.

[00351] Lyophilized stock of each test article was stored at -20 °C, solubilized in DMSO (maximum final concentration 1%) and diluted to the desired concentration with the external solution prior to recording. Current measurements were recorded under continuous perfusion, controlled by syringe pump addition.

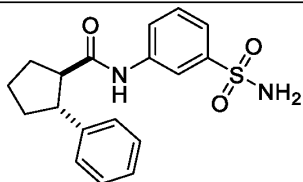
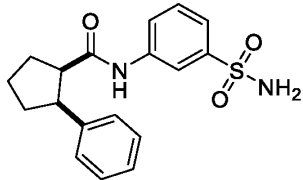
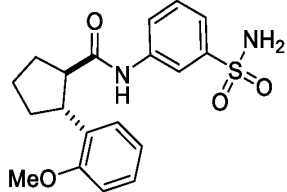
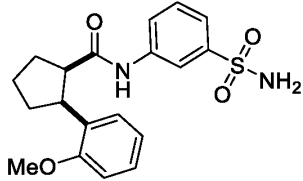
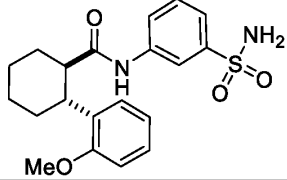
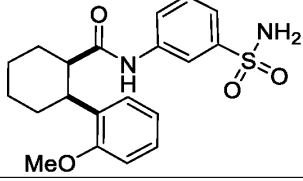
[00352] The output of the EPC 9 patch-clamp amplifier was filtered with a built-in low-pass, four-pole Bessel filter having a cutoff frequency of 10 kHz and sampled at 20–50 kHz. For both manual and automated recordings, the membrane was kept at a holding potential of between -120 and -80 mV. Pulse stimulation and data acquisition were controlled with the Pulse software (HEKA Elektronik Dr. Schulze GmbH, Germany) or the IonFlux software (Fluxion Biosciences, South San Francisco, USA). All measurements were performed at room temperature (about 20–22 °C). Recordings were made at least 5 min after establishing the whole-cell and voltage-clamp configuration to allow for stabilization of the voltage-dependent properties of the channels. Currents were elicited by 10–50 ms step depolarizations from a holding potential to a value between -40 and +10 mV. Peak currents after channel activation were recorded. These data were baseline-normalized, plotted against toxin concentration and analyzed in Microsoft Excel software. Data were fit to a four-parameter logistic equation with the Hill slope set to 1 to determine IC₅₀ values and expressed as mean.

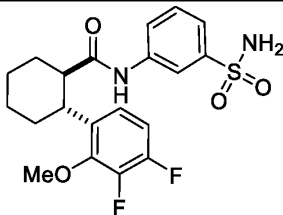
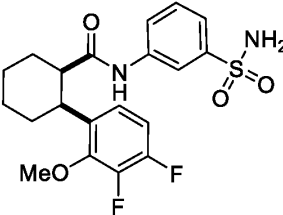
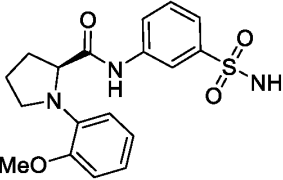
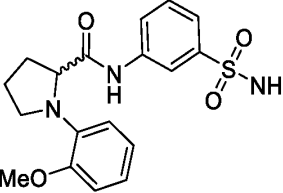
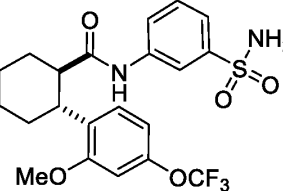
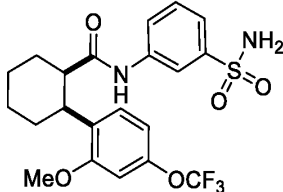
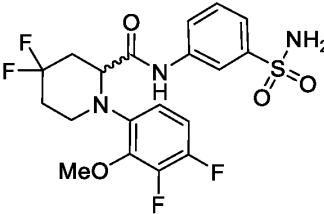
Table 1– Nav Isoform Potency and Selectivity

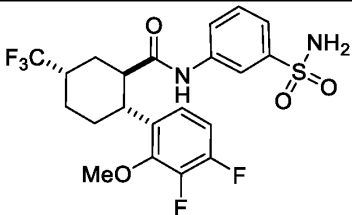
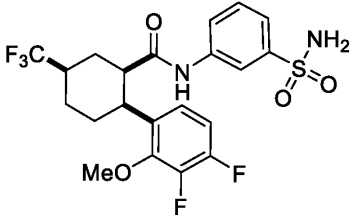
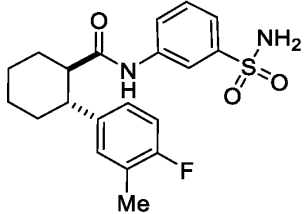
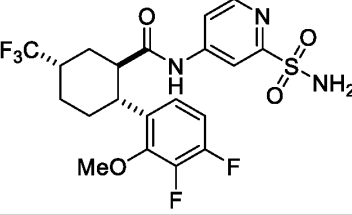
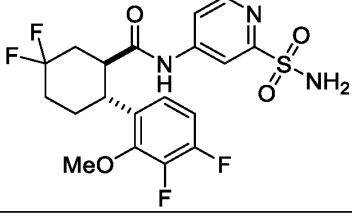
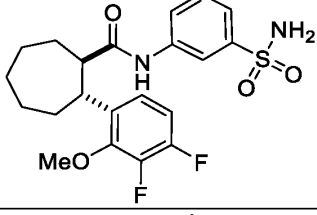
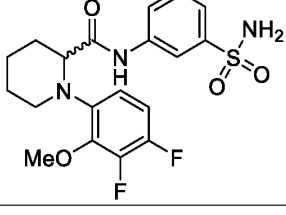
[00353] For Table 1, Column 1, all data were measured in HEK cells. Column 1 provides IC₅₀ data for Nav 1.8/β1 as measured using the manual patch-clamp technique in the whole-

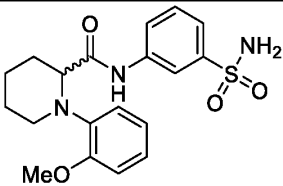
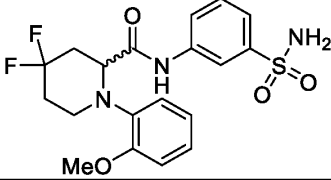
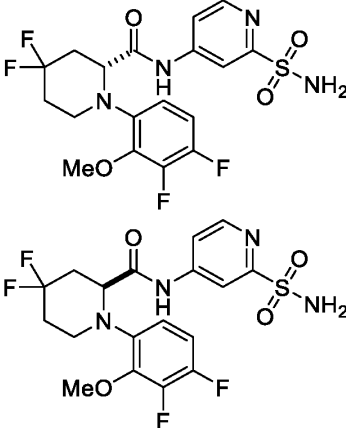
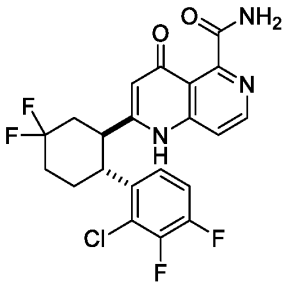
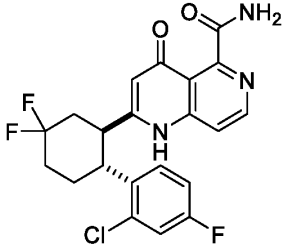
cell configuration with a HEKA EPC 9 amplifier, where +++ indicates an IC_{50} of less than or equal to 20 nM (nanomolar), ++ indicates an IC_{50} of greater than 20 nM but less than or equal to 100 nM, and + indicates an IC_{50} of greater than 100 nM but less than or equal to 1635 μ M. ND means not detectable. NT means not tested. For Table 1, Column 2, all data were measured in CHO cells. Column 2 provides IC_{50} data for Nav 1.8 / β 3 as measured using the SyncroPatch 384PE (Nanion Technologies, Livingston, NJ) automated patch clamp system. ND means not detectable. NT means not tested.

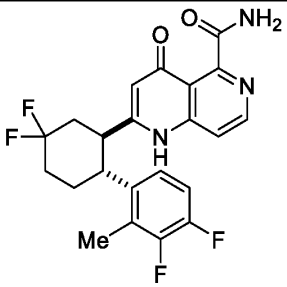
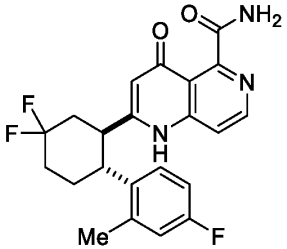
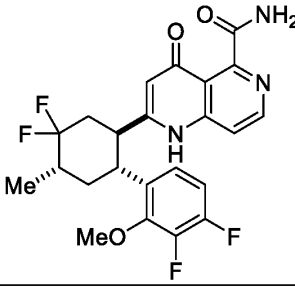
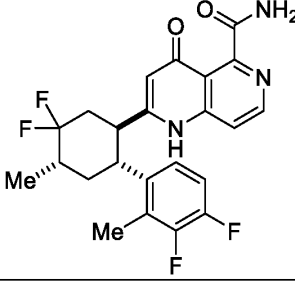
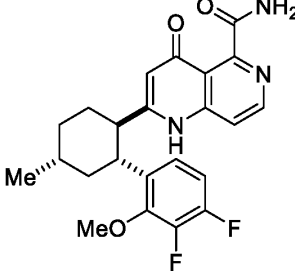
Table 1. Compounds

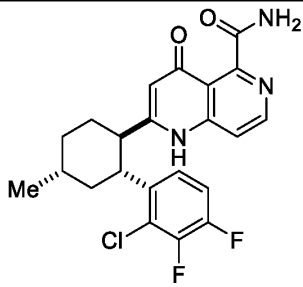
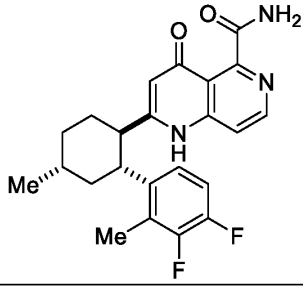
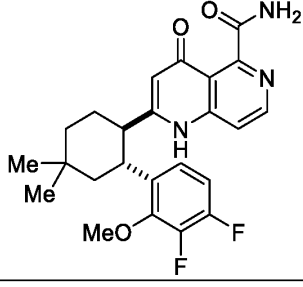
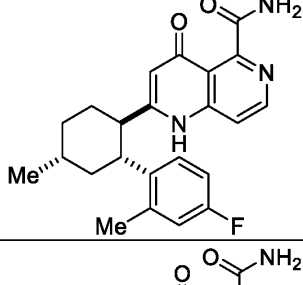
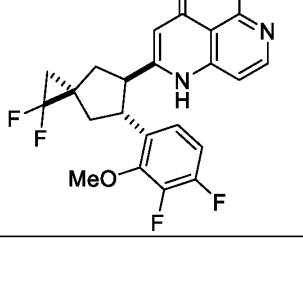
Compound No	Structure	Column 1	Column 2
1		NT	ND
3		NT	ND
5		NT	ND
7		NT	ND
9		NT	++
11		NT	ND

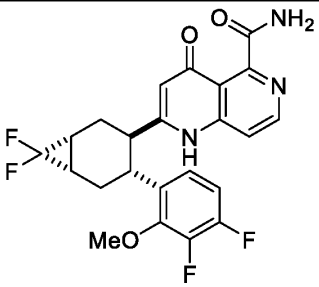
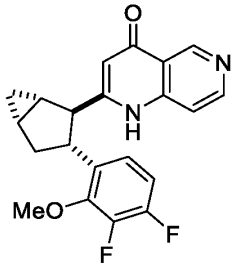
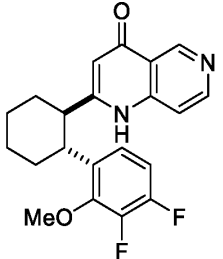
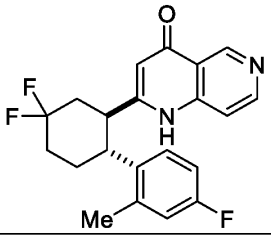
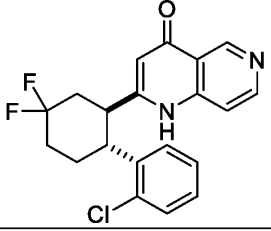
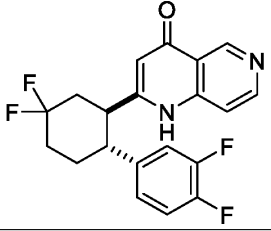
Compound No	Structure	Column 1	Column 2
13		+++	+++
15		NT	ND
17		NT	ND
18		NT	ND
19		NT	++
21		NT	++
23		+++	NT

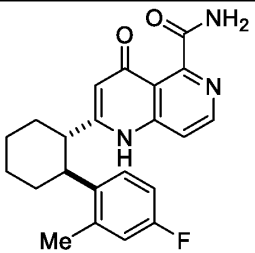
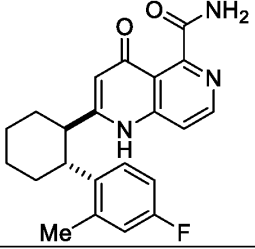
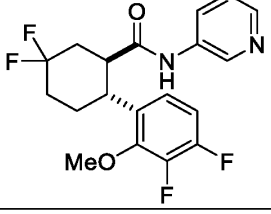
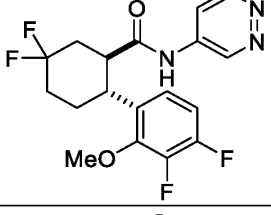
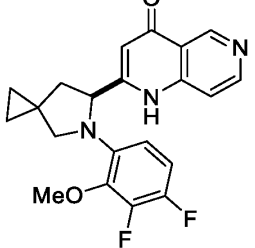
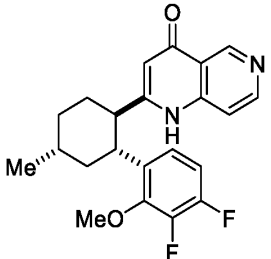
Compound No	Structure	Column 1	Column 2
24		+++	NT
26		NT	+
28		ND	NT
39		NT	+++
43		+++	NT
81		NT	+++
87		NT	++

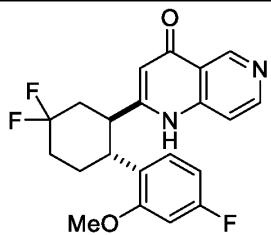
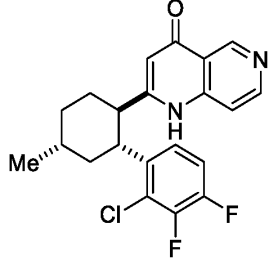
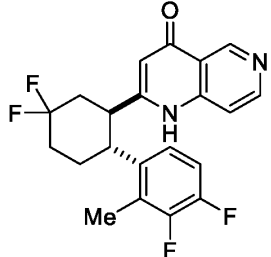
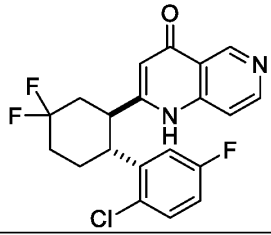
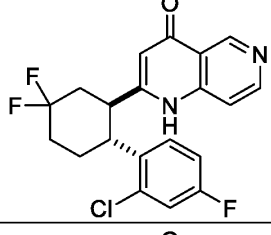
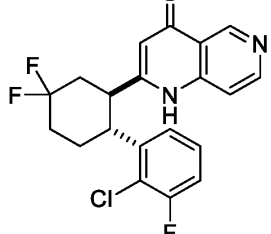
Compound No	Structure	Column 1	Column 2
88		NT	+
89		NT	+
163		NT	+++ (first-eluting compound) + (second-eluting compound)
184		++	+++
185		++	NT

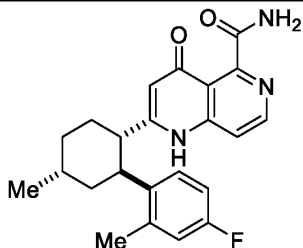
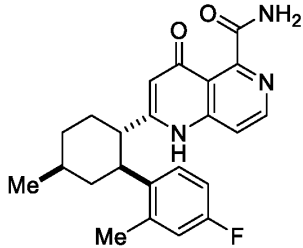
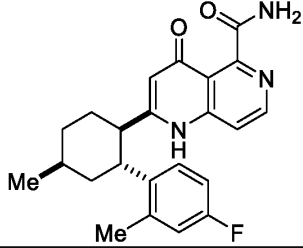
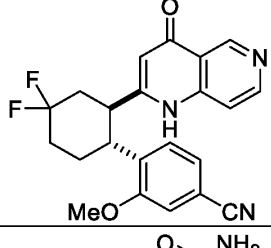
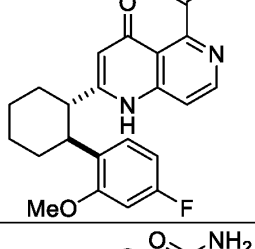
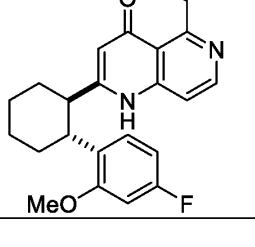
Compound No	Structure	Column 1	Column 2
186		++	+++
187		++	++
188		+++	+++
189		+++	+++
191		+++	+++

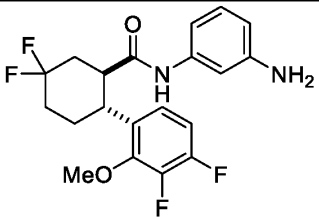
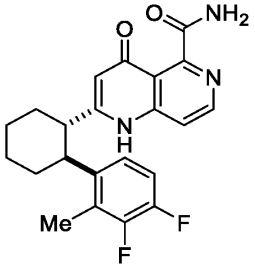
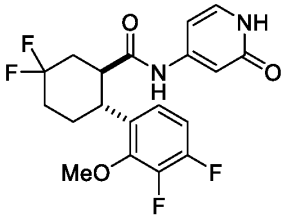
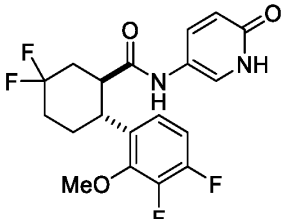
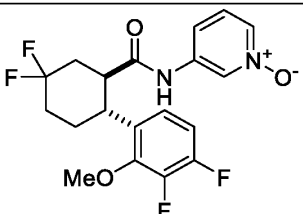
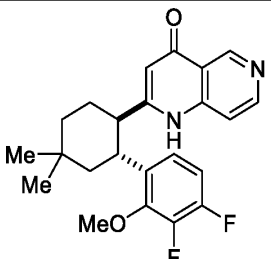
Compound No	Structure	Column 1	Column 2
192		+++	+++
193		+++	NT
194		NT	+++
205		+++	+++
209		+++	+++

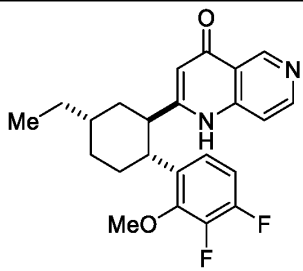
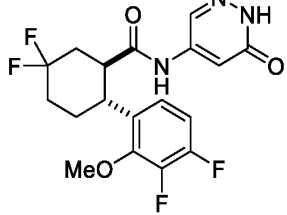
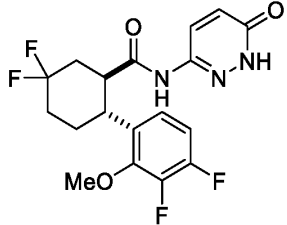
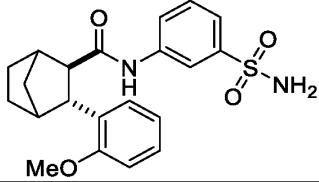
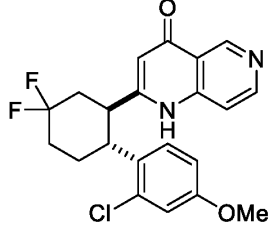
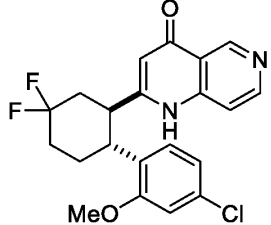
Compound No	Structure	Column 1	Column 2
210		++	+++
212		++	NT
213		++	NT
214		++	++
215		+	+
216		+	NT

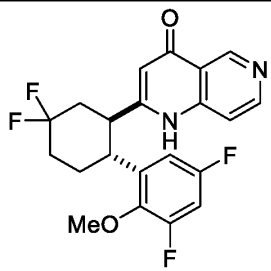
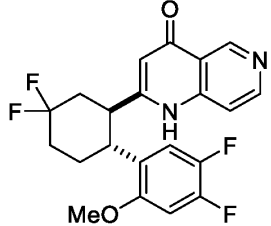
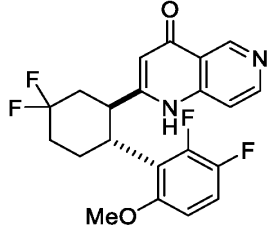
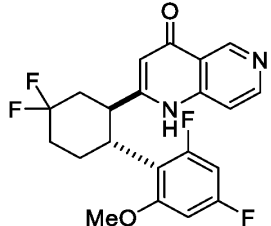
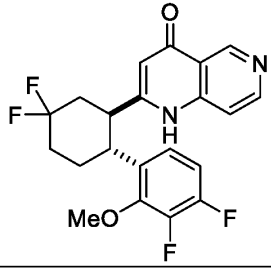
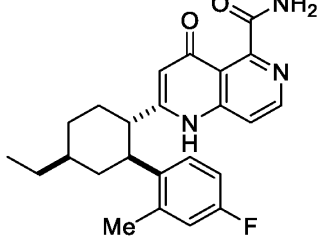
Compound No	Structure	Column 1	Column 2
217		NT	+
218		NT	++
219		+	NT
220		++	NT
221		+	NT
222		+++	NT

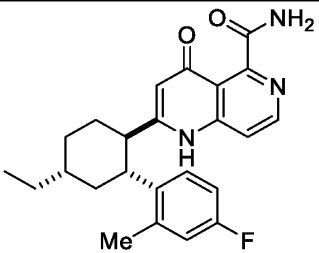
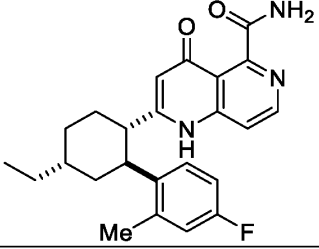
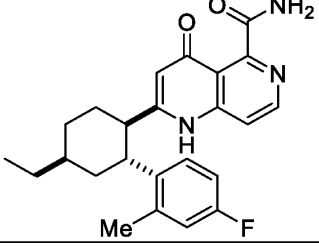
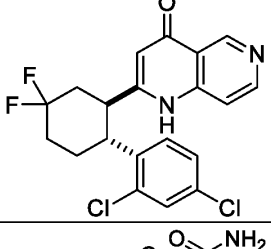
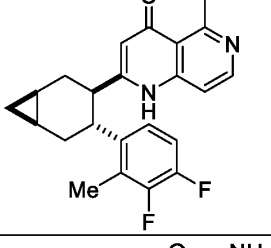
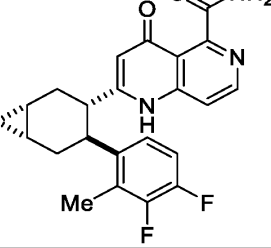
Compound No	Structure	Column 1	Column 2
223		++	NT
224		+++	NT
226		+++	NT
227		+	+
228		++	NT
229		+	NT

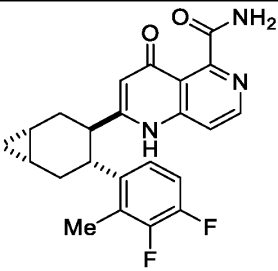
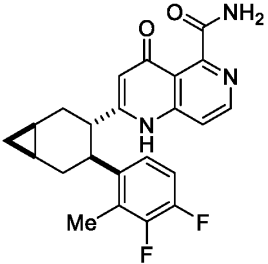
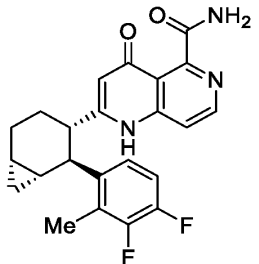
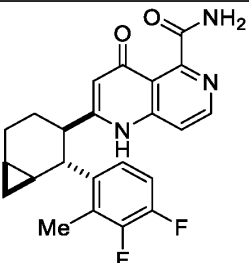
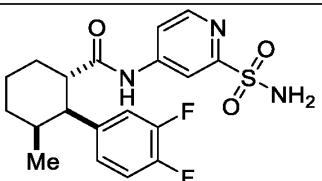
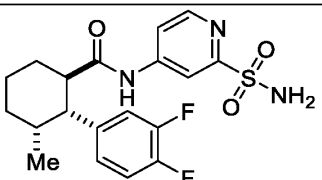
Compound No	Structure	Column 1	Column 2
230		ND	+
231		+	+
232		+++	+++
233		+	NT
234		NT	+
235		NT	+

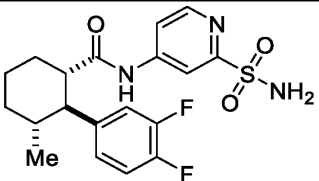
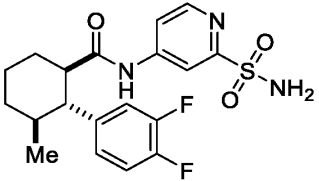
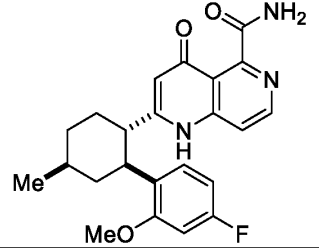
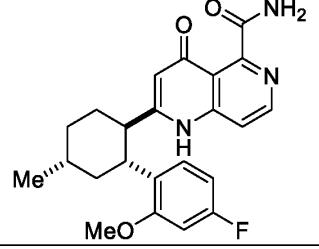
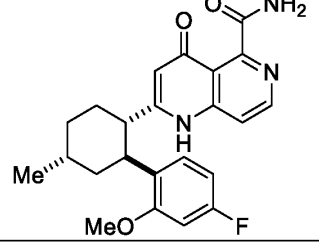
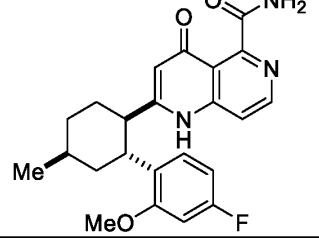
Compound No	Structure	Column 1	Column 2
236		+	NT
237		+	+
238		++	NT
239		+	NT
240		++	NT
241		+++	NT

Compound No	Structure	Column 1	Column 2
242		+++	NT
243		++	NT
244		+	NT
245		+	NT
246		+	NT
247		+	NT

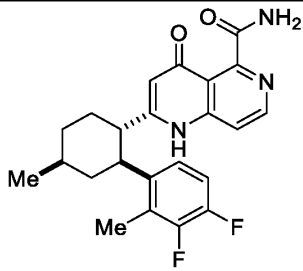
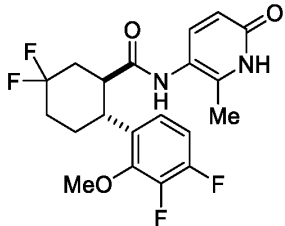
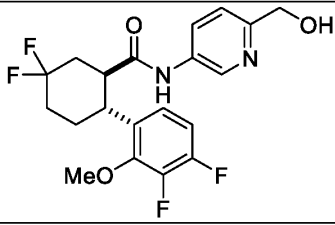
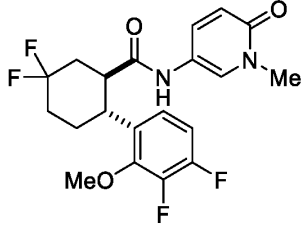
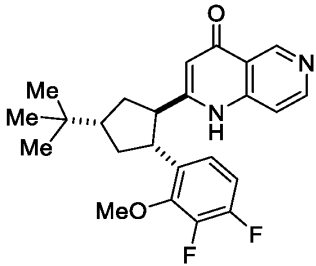
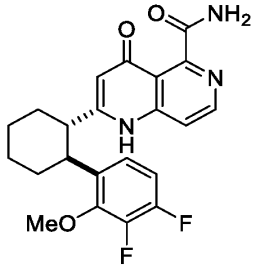
Compound No	Structure	Column 1	Column 2
248		ND	NT
249		+	NT
250		ND	NT
251		+	NT
252		+++	NT
253		+	+

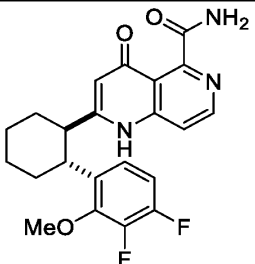
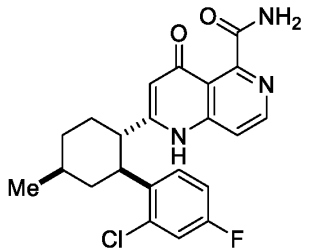
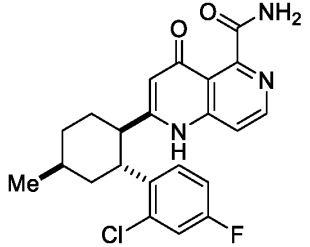
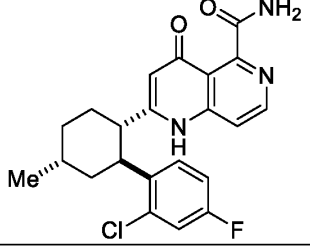
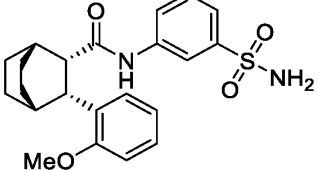
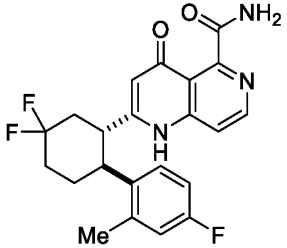
Compound No	Structure	Column 1	Column 2
254		+++	+++
255		ND	ND
256		+++	++
257		+	NT
258		+++	+++
259		+	+

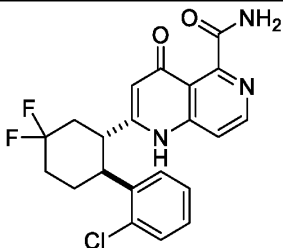
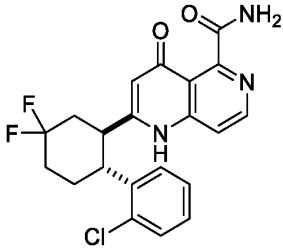
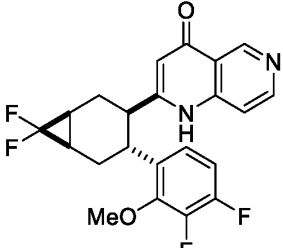
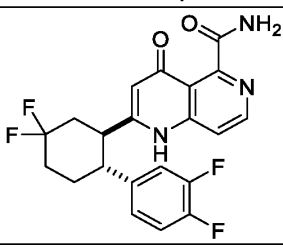
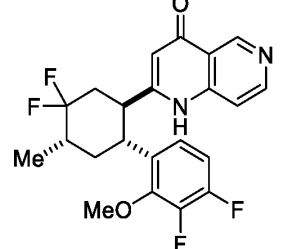
Compound No	Structure	Column 1	Column 2
260		+++	+++
261		+	+
262		+	+
263		+++	+++
264		+	NT
265		+++	NT

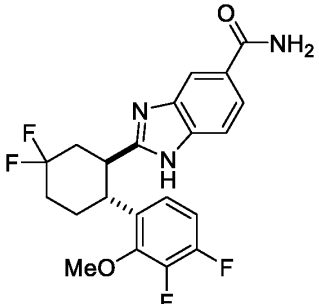
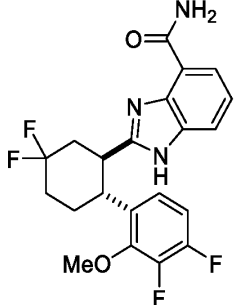
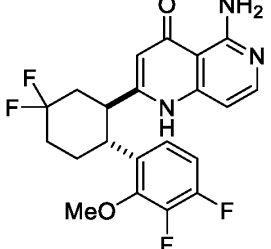
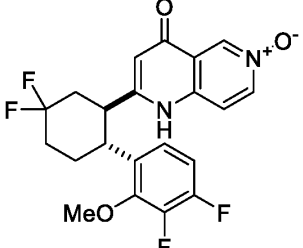
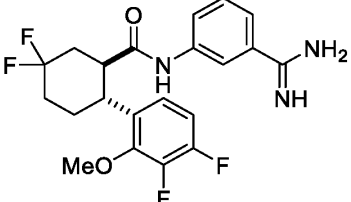
Compound No	Structure	Column 1	Column 2
266		+	NT
267		++	NT
268		+	NT
269		+++	NT
270		+	+
271		+++	++

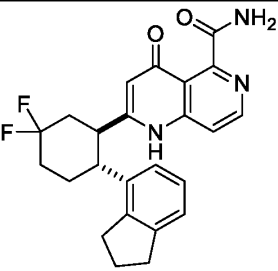
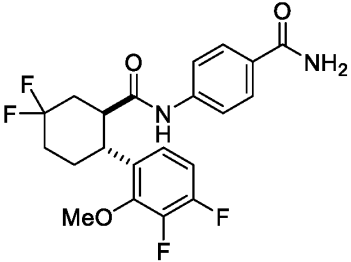
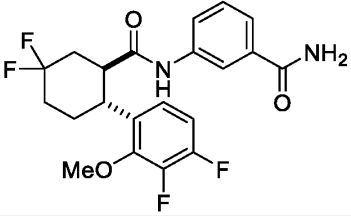
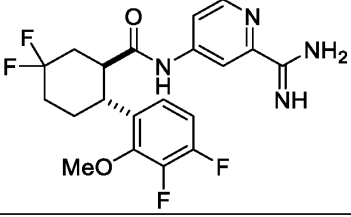
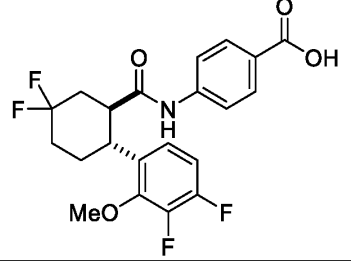
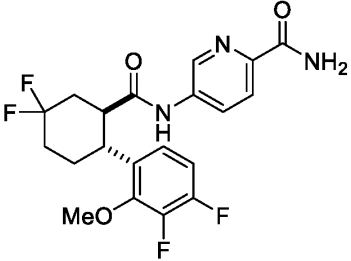
Compound No	Structure	Column 1	Column 2
272		++	NT
273		+++	NT
274		++	NT
275		+	+
276		+++	+++
277		ND	+

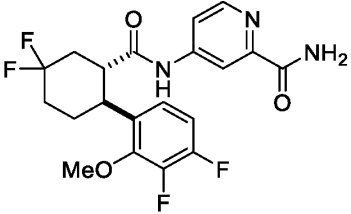
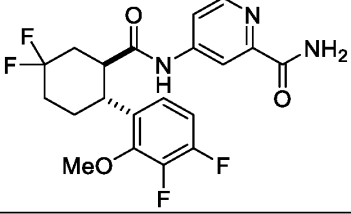
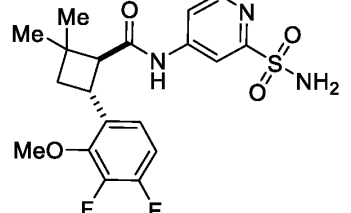
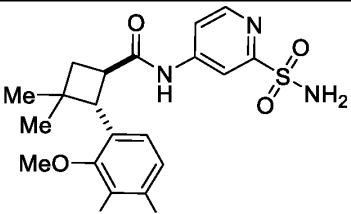
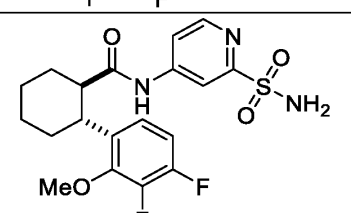
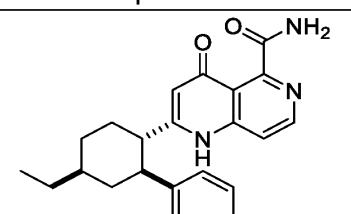
Compound No	Structure	Column 1	Column 2
278		++	+
279		ND	NT
280		+	NT
281		+	NT
282		+++	NT
283		+	+

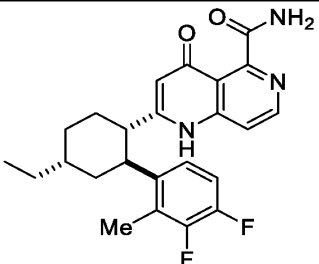
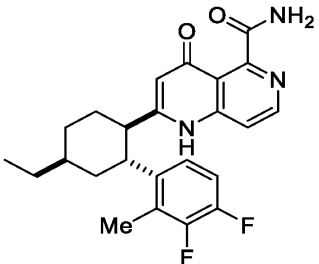
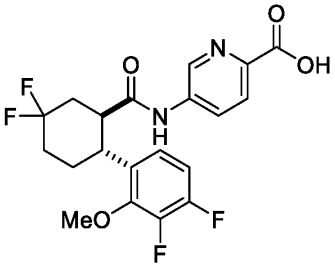
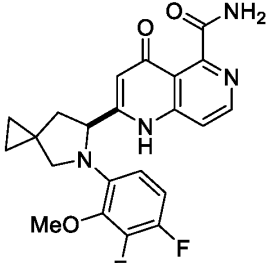
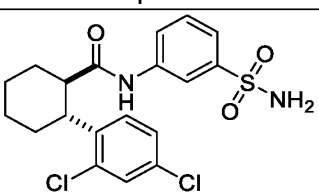
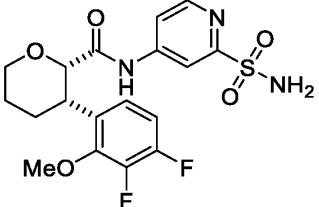
Compound No	Structure	Column 1	Column 2
284		+++	++
285		+	NT
286		+++	NT
287		ND	NT
288		+	NT
289		ND	NT

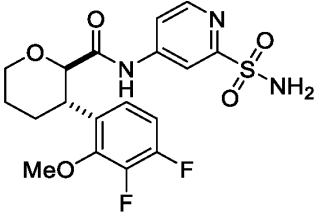
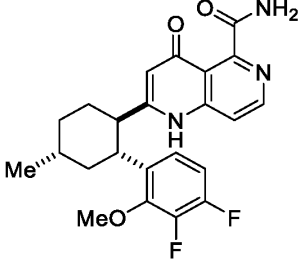
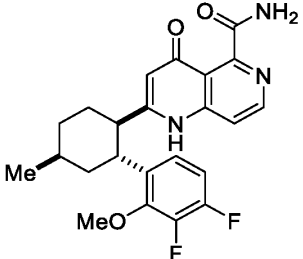
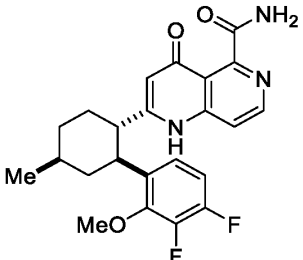
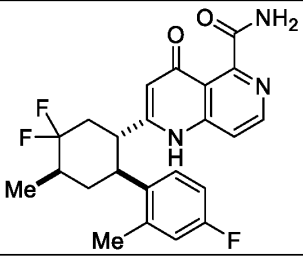
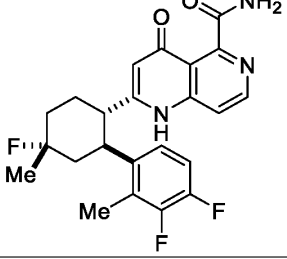
Compound No	Structure	Column 1	Column 2
291		ND	ND
292		+	+
293		++	NT
294		+	NT
295		+++	NT

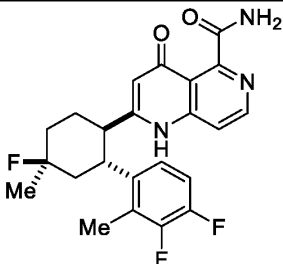
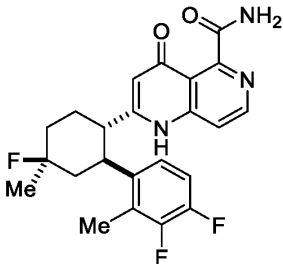
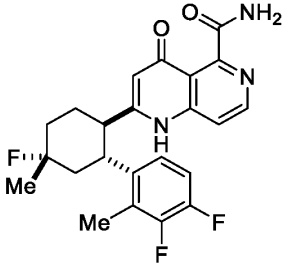
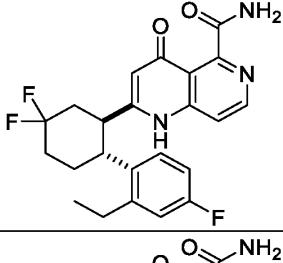
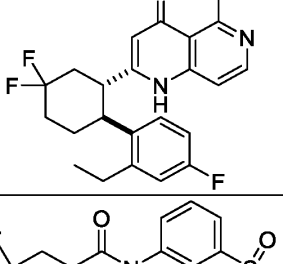
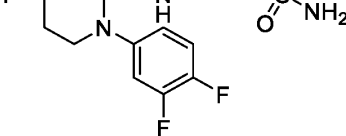
Compound No	Structure	Column 1	Column 2
296		+	NT
297		+	NT
298		++	NT
299		+	NT
300		+++	NT

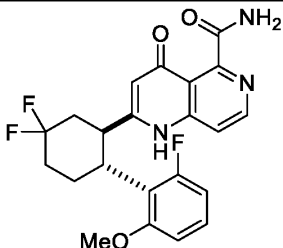
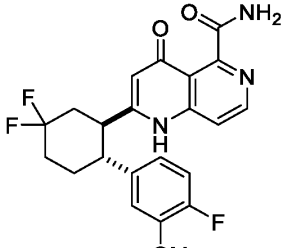
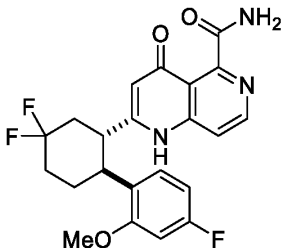
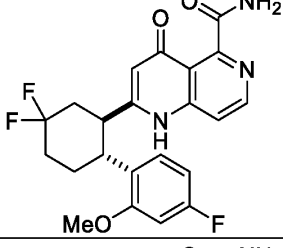
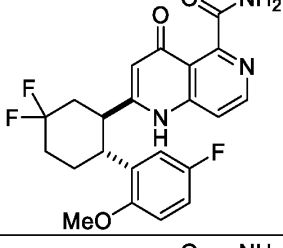
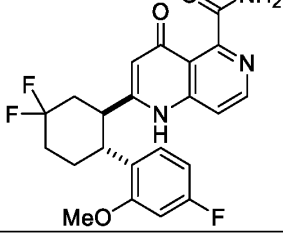
Compound No	Structure	Column 1	Column 2
301		++	NT
302		++	NT
303		++	NT
304		++	NT
305		+	NT
306		+	NT

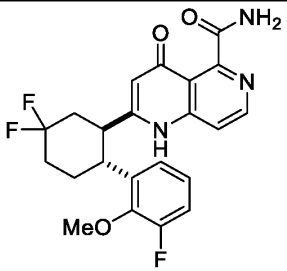
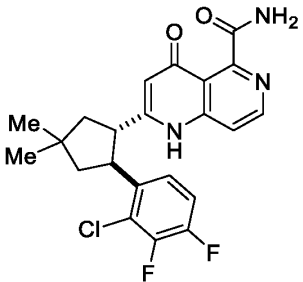
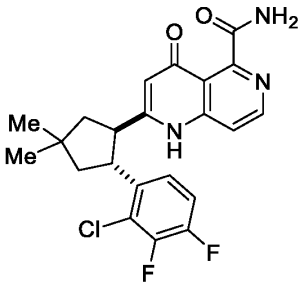
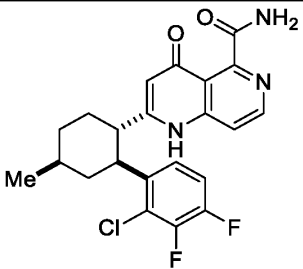
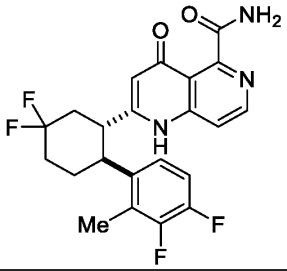
Compound No	Structure	Column 1	Column 2
307		ND	NT
308		+++	NT
309		+	NT
310		++	NT
311		+++	NT
312		++	++

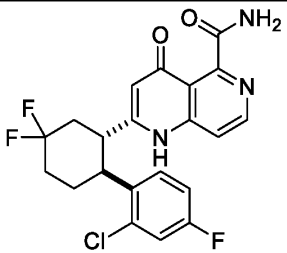
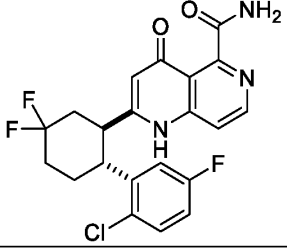
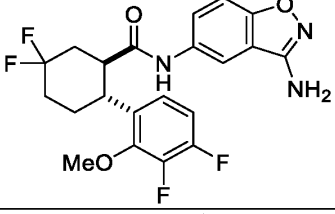
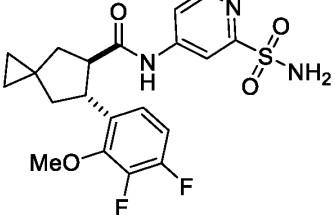
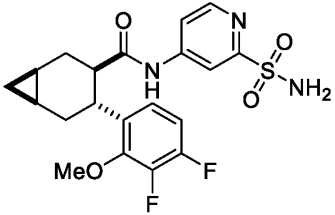
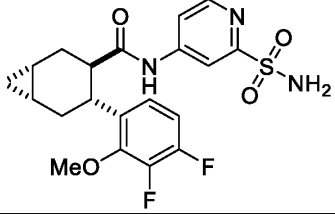
Compound No	Structure	Column 1	Column 2
313		+	+
314		+++	+++
315		+	NT
316		++	NT
317		ND	NT
318		+	NT

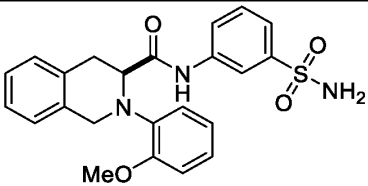
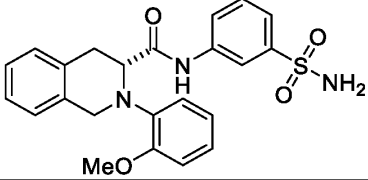
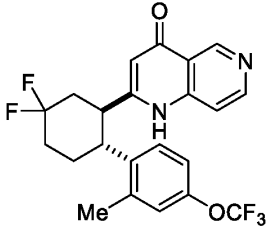
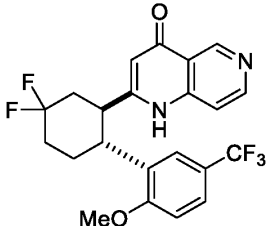
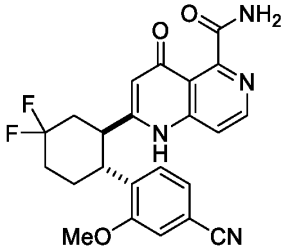
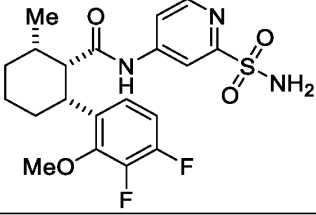
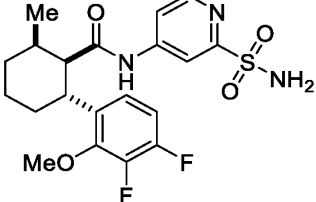
Compound No	Structure	Column 1	Column 2
319		+	NT
320		++	NT
321		++	+
322		+	+
323		++	NT
324		ND	+

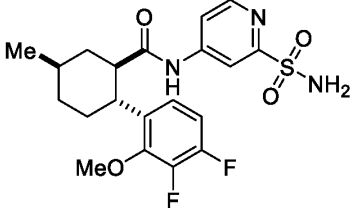
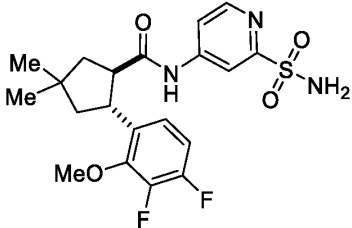
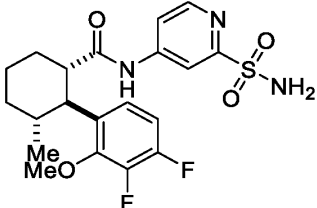
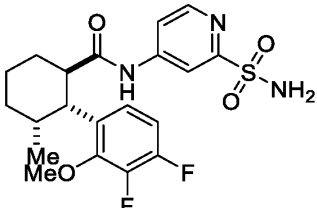
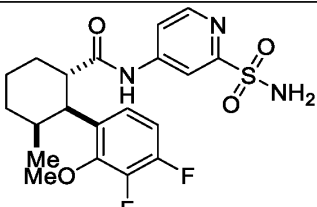
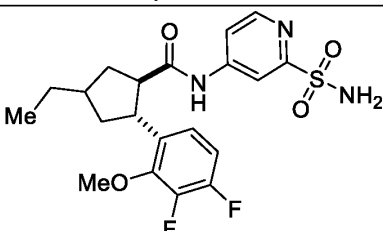
Compound No	Structure	Column 1	Column 2
325		+++	+++
326		ND	+
327		+++	++
328		+++	+++
329		ND	+
333		+	NT

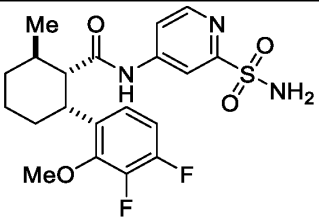
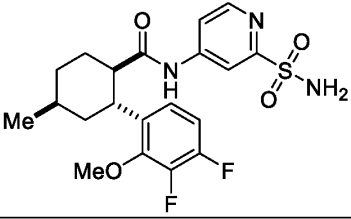
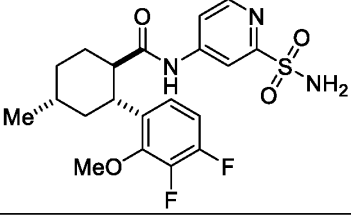
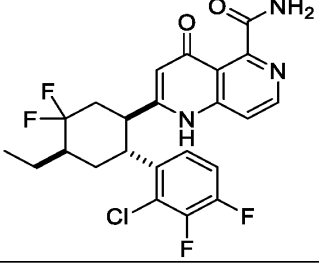
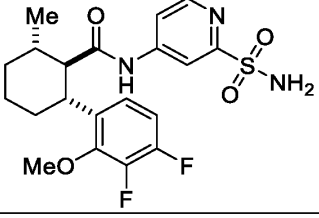
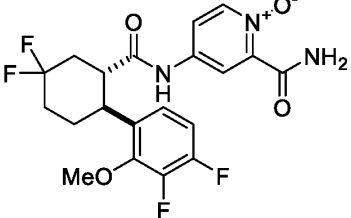
Compound No	Structure	Column 1	Column 2
334		ND	NT
335		+	NT
336		ND	NT
337		++	++
338		ND	NT
339		++	NT

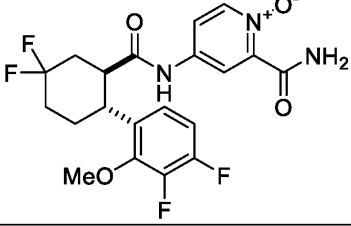
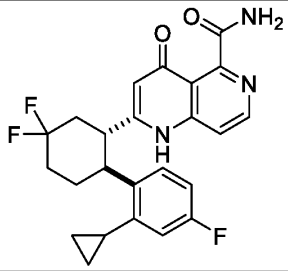
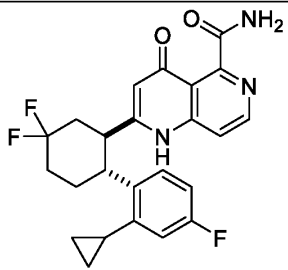
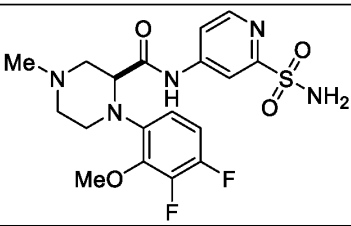
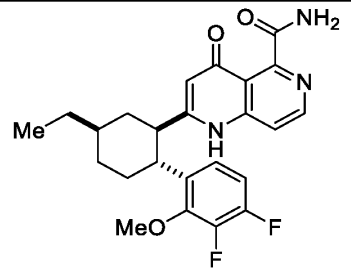
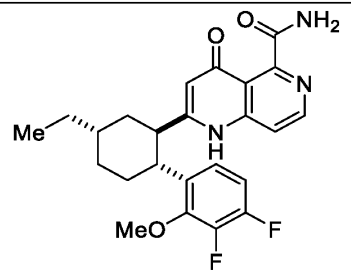
Compound No	Structure	Column 1	Column 2
340		++	NT
341		++	NT
342		+++	NT
344		+	+
345		ND	ND

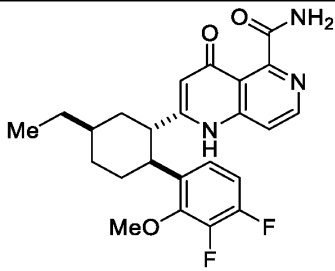
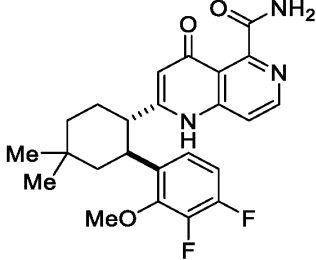
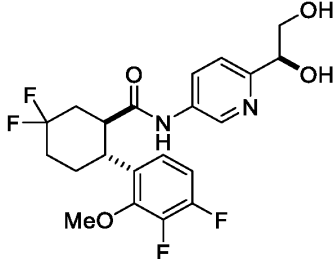
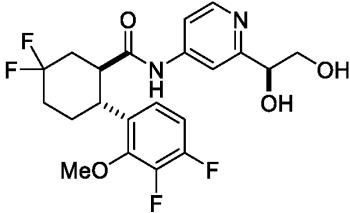
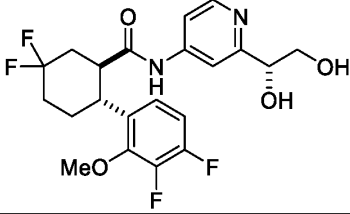
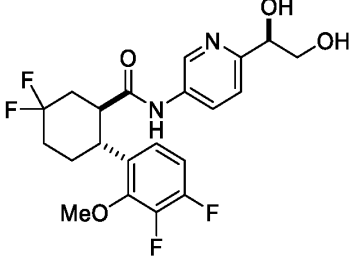
Compound No	Structure	Column 1	Column 2
348		ND	+
350		ND	ND
351		++	NT
352		+++	NT
353		+++	+++
354		+++	+++

Compound No	Structure	Column 1	Column 2
355		+	NT
356		+	NT
357		++	NT
358		ND	NT
359		ND	NT
360		ND	NT
361		+++	NT

Compound No	Structure	Column 1	Column 2
362		+++	NT
363		+++	NT
364		+	NT
365		+++	NT
366		+	NT
367		+++	NT

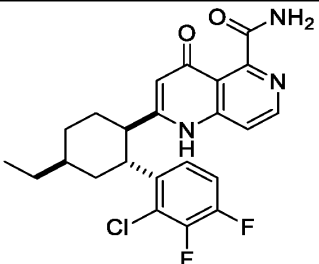
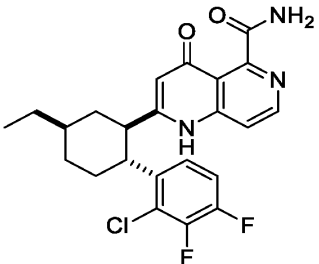
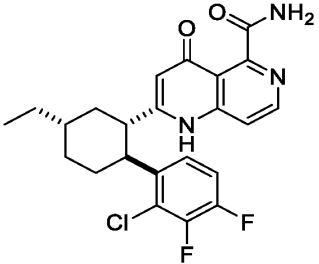
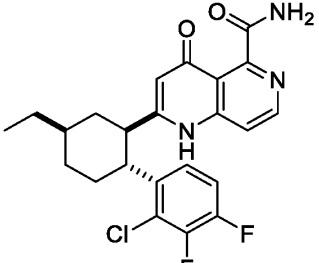
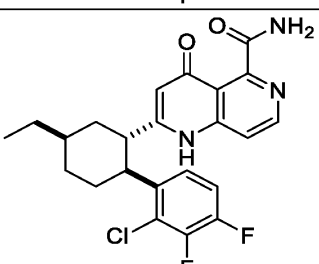
Compound No	Structure	Column 1	Column 2
368		+	NT
369		+++	NT
370		+++	NT
371		+++	NT
372		++	+
373		ND	NT

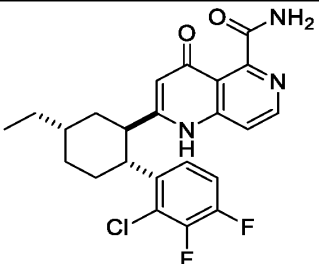
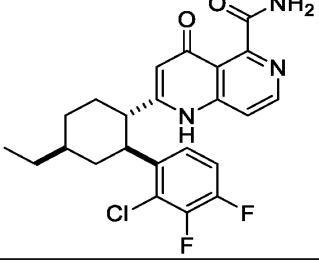
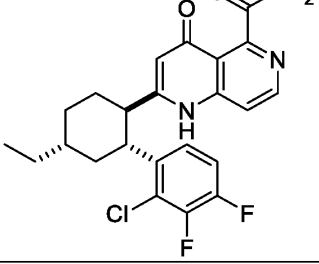
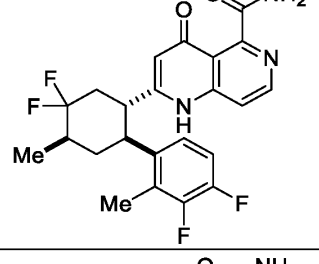
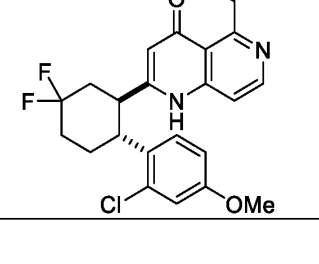
Compound No	Structure	Column 1	Column 2
374		++	NT
376		ND	+
377		++	++
379		ND	NT
381		++	NT
382		+++	NT

Compound No	Structure	Column 1	Column 2
383		++	NT
384		ND	NT
385		+	NT
386		++	NT
387		++	NT
388		+	NT

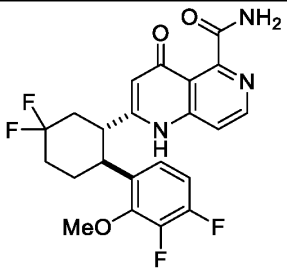
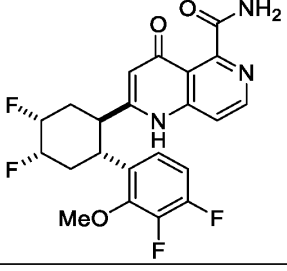
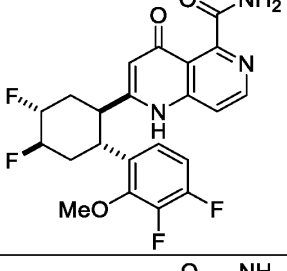
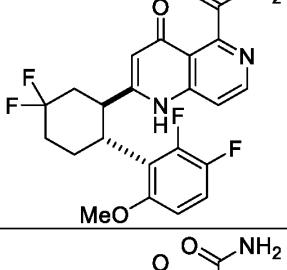
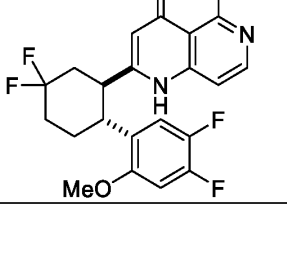
Compound No	Structure	Column 1	Column 2
389		+	NT
390		+	NT
392		++	NT
393		++	NT
394		++	++
395		+	+
396		+++	+++

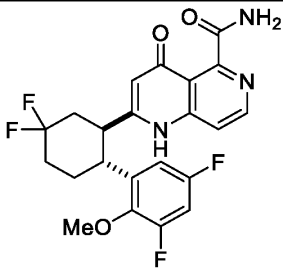
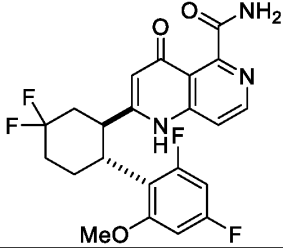
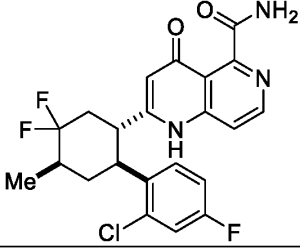
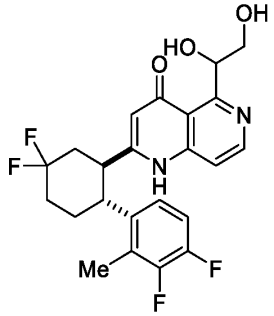
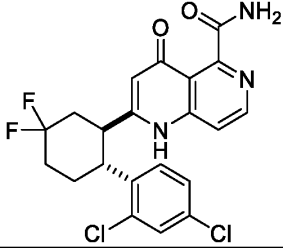
Compound No	Structure	Column 1	Column 2
397		+	NT
398		+++	NT
399		+	+
400		++	+
401		+	+
402		+	NT

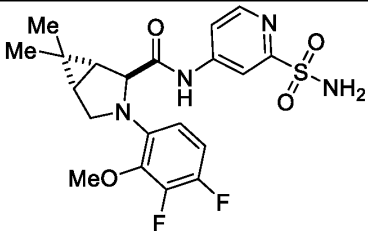
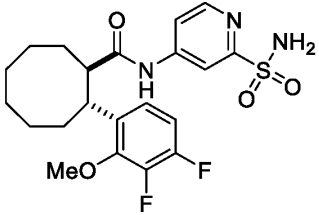
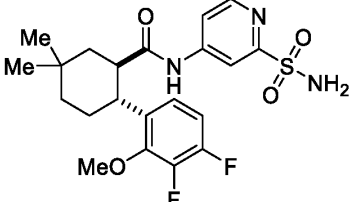
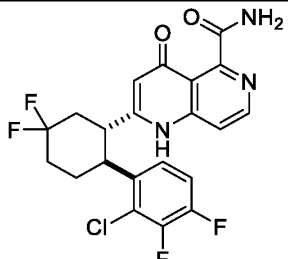
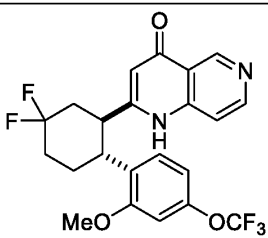
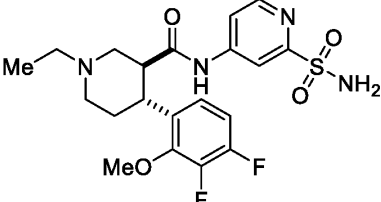
Compound No	Structure	Column 1	Column 2
403		++	NT
404		+	+
405		+	+
406		+	NT
407		++	++

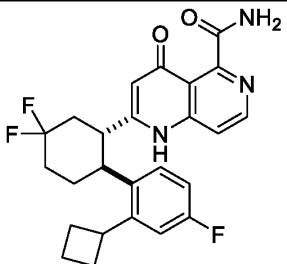
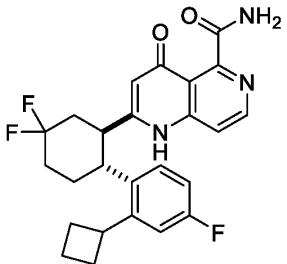
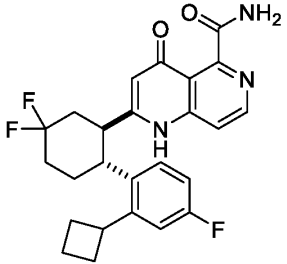
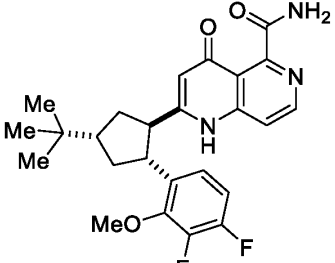
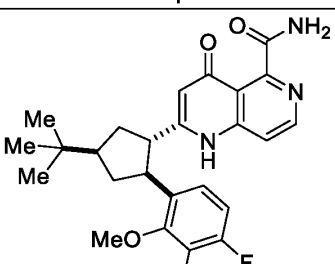
Compound No	Structure	Column 1	Column 2
408		+++	+++
409		+	NT
410		+++	NT
411		+	+
412		+	NT

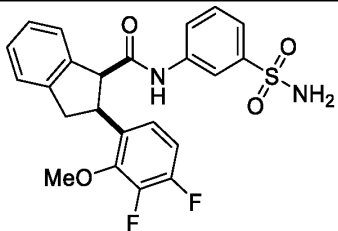
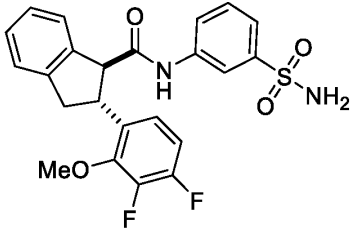
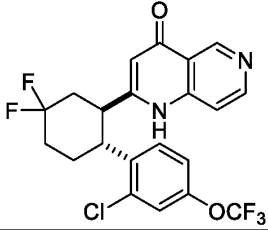
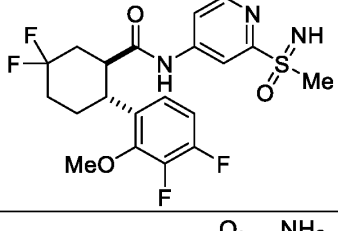
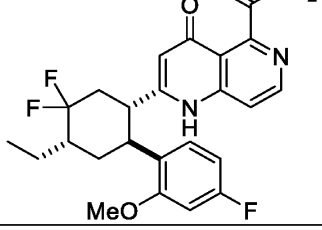
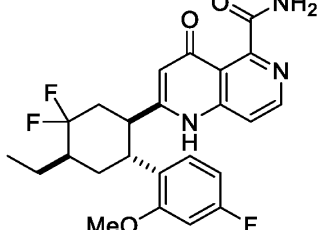
Compound No	Structure	Column 1	Column 2
413		+	NT
414		+	NT
416		+++	NT
417		ND	NT
418		+++	NT
419		+	NT

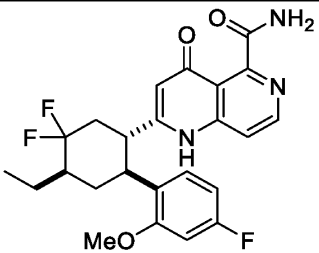
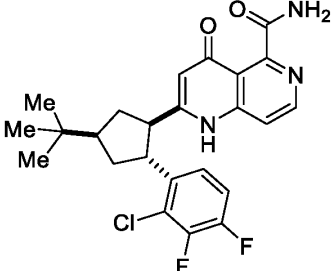
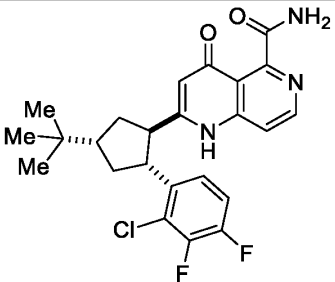
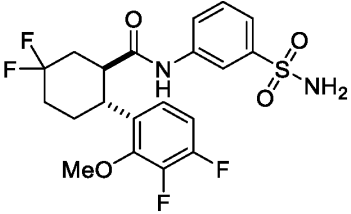
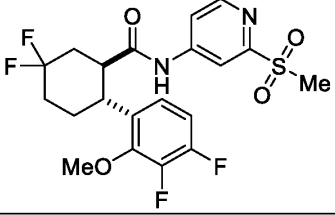
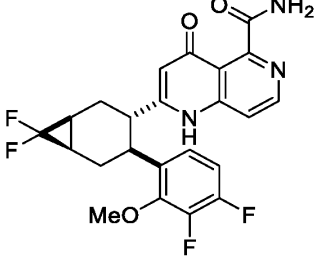
Compound No	Structure	Column 1	Column 2
420		+	NT
421		+	NT
422		+	NT
423		ND	NT
424		+	NT

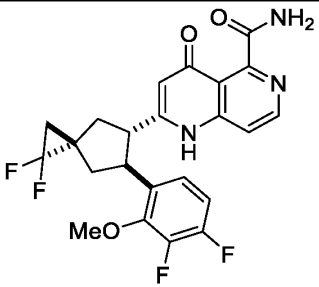
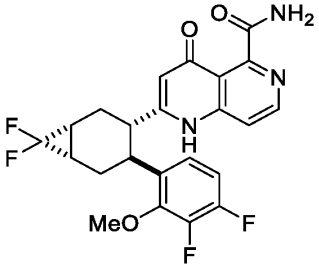
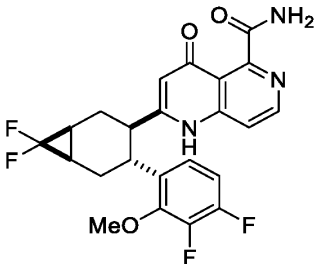
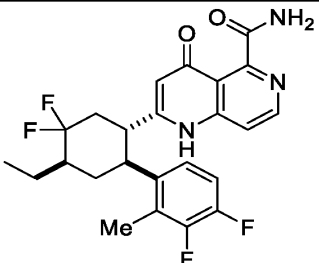
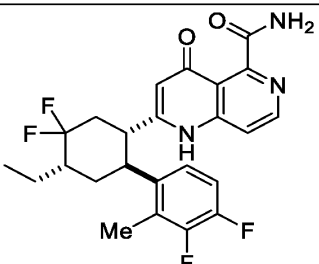
Compound No	Structure	Column 1	Column 2
425		ND	NT
426		+	NT
427		+	+
428		+++	NT
429		++	NT

Compound No	Structure	Column 1	Column 2
430		+++	NT
431		+++	NT
433		+++	NT
434		+	+
435		++	NT
436		+	NT

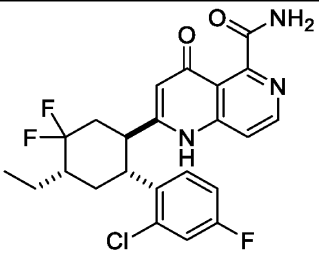
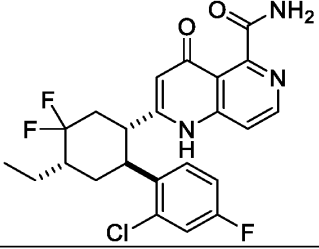
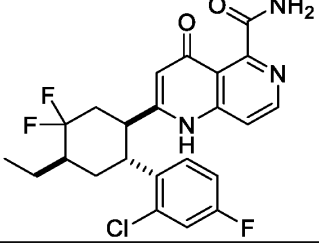
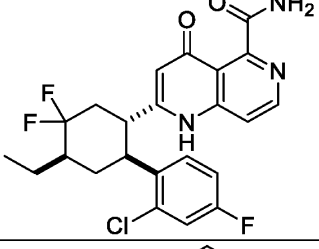
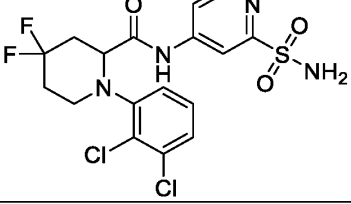
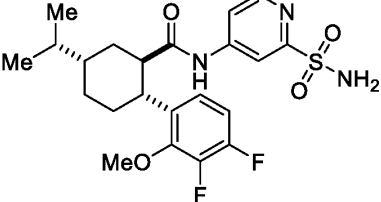
Compound No	Structure	Column 1	Column 2
437		ND	+
438		++	++
439		+++	NT
440		+++	+++
441		++	++

Compound No	Structure	Column 1	Column 2
442		++	NT
443		++	NT
444		++	NT
446		++	NT
447		NT	+
448		+++	NT

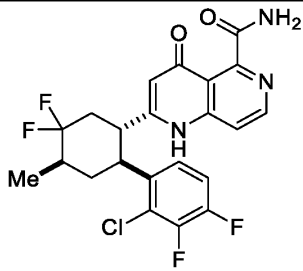
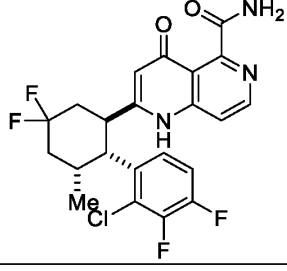
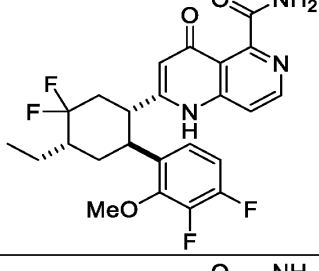
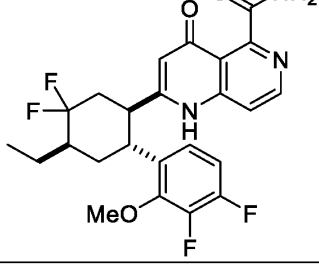
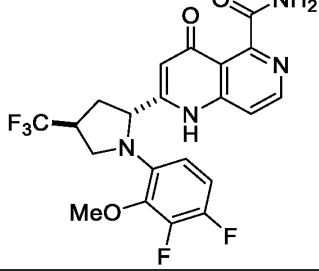
Compound No	Structure	Column 1	Column 2
449		NT	++
450		+++	NT
453		+++	NT
454		+++	NT
455		++	NT
456		ND	+

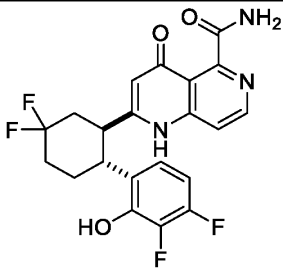
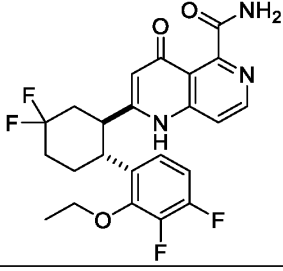
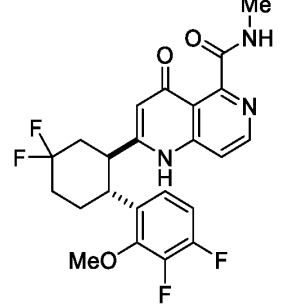
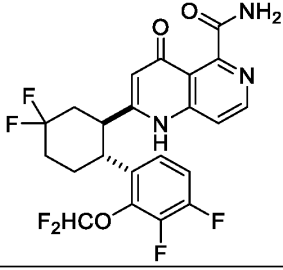
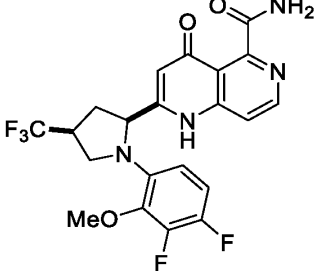
Compound No	Structure	Column 1	Column 2
457		+	NT
458		ND	NT
459		++	NT
462		++	+
463		+	NT

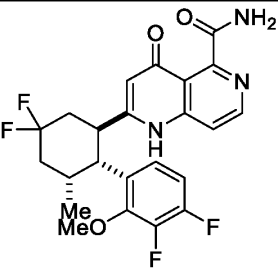
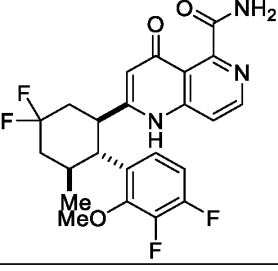
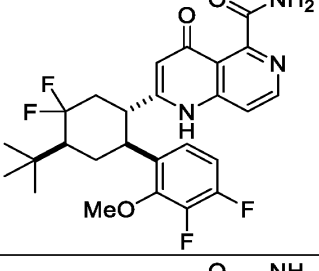
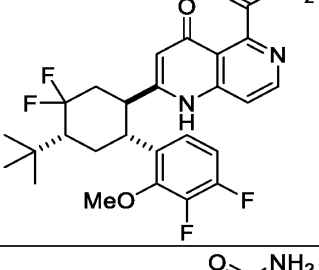
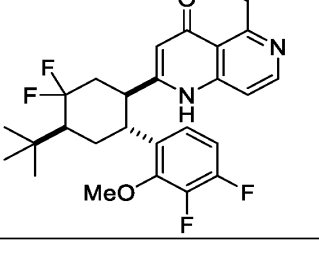
Compound No	Structure	Column 1	Column 2
464		+++	NT
465		++	NT
466		+	+
467		ND	NT
468		ND	+

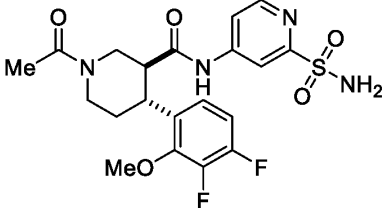
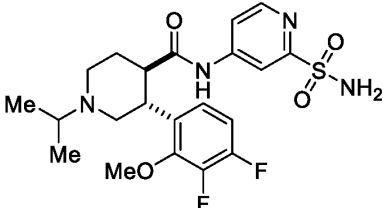
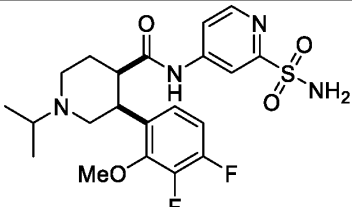
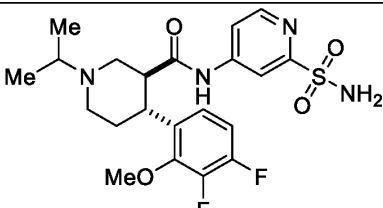
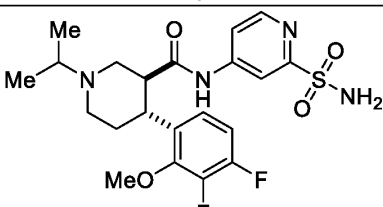
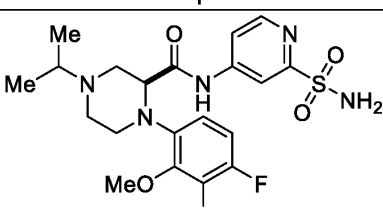
Compound No	Structure	Column 1	Column 2
469		+++	+++
470		ND	+
471		+++	+++
472		+	+
473		+++	NT
474		++	NT

Compound No	Structure	Column 1	Column 2
475		+	NT
476		ND	NT
477		+++	NT
478		+	NT
479		ND	NT
480		ND	NT

Compound No	Structure	Column 1	Column 2
481		+	NT
482		NT	+++
483		+	NT
484		+++	NT
485		ND	NT

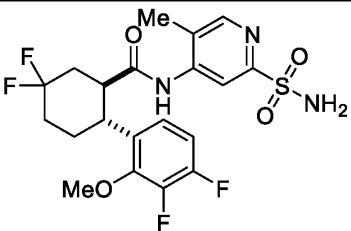
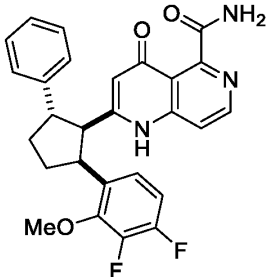
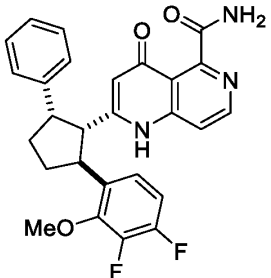
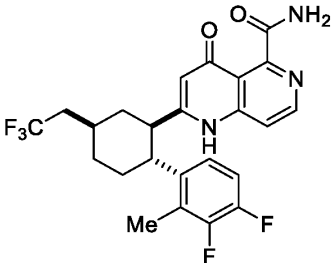
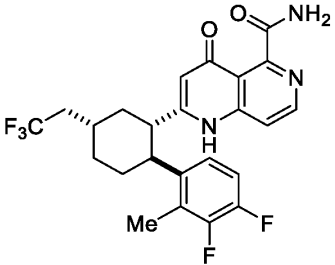
Compound No	Structure	Column 1	Column 2
486		+	+
487		+++	NT
488		NT	+
489		+++	NT
490		++	NT

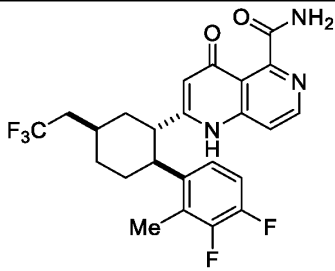
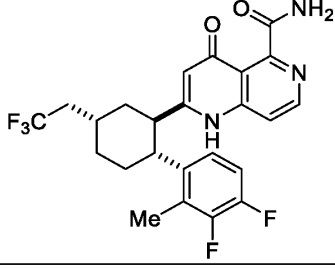
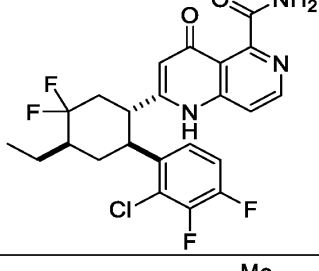
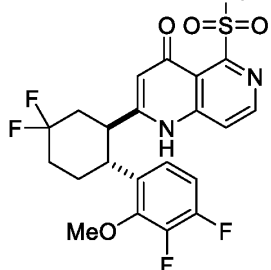
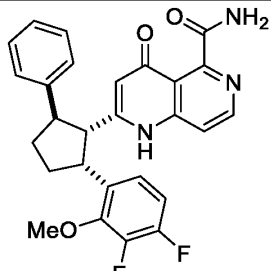
Compound No	Structure	Column 1	Column 2
491		+++	NT
492		+	NT
493		+++	NT
494		+++	NT
495		+++	NT

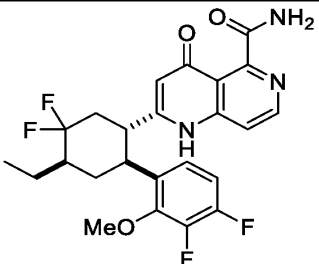
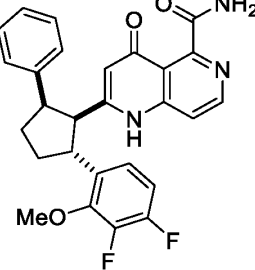
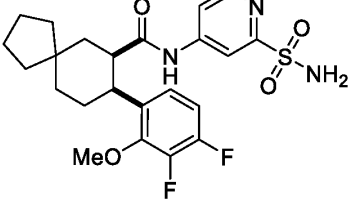
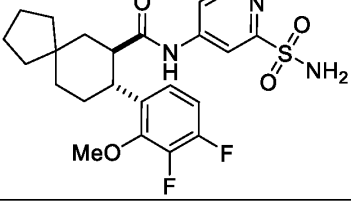
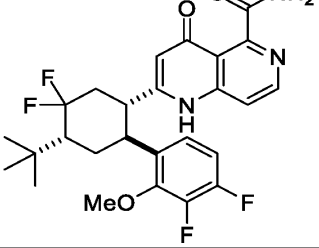
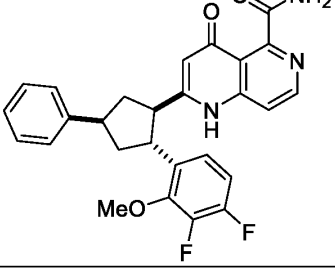
Compound No	Structure	Column 1	Column 2
496		+	NT
497		+	NT
498		ND	NT
499		+	NT
500		ND	NT
501		+	NT

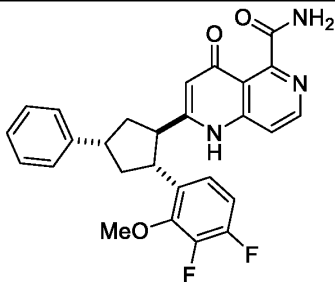
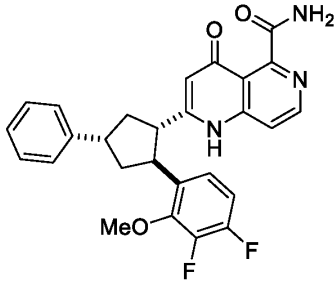
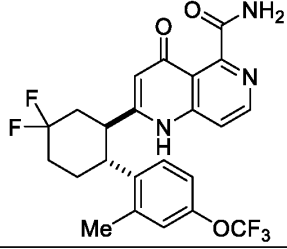
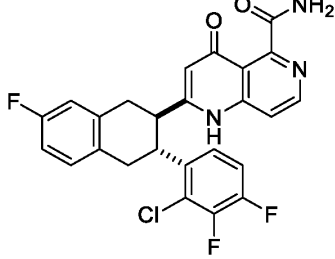
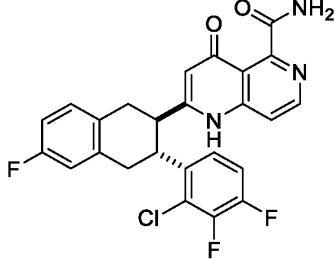
Compound No	Structure	Column 1	Column 2
502		+	NT
503		+++	NT
504		+++	+++
505		+++	NT
506		+++	+++
507		+++	NT

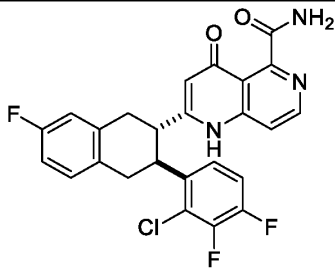
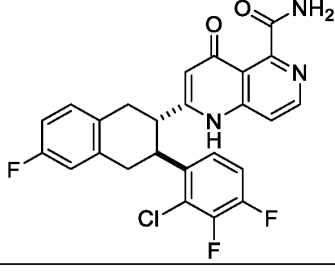
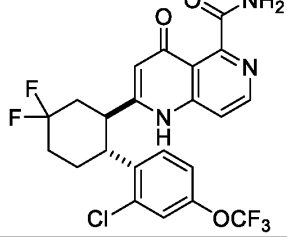
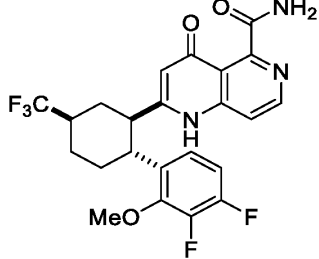
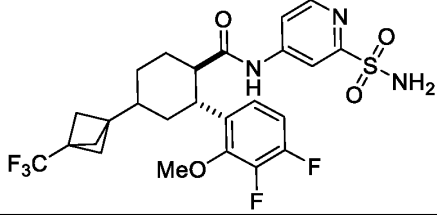
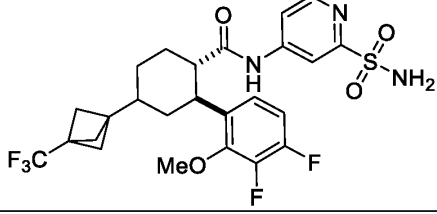
Compound No	Structure	Column 1	Column 2
510		+	NT
511		+++	NT
512		++	NT
513		+	NT
514		+++	NT
515		++	NT

Compound No	Structure	Column 1	Column 2
516		++	NT
517		ND	NT
518		ND	NT
519		+++	+++
520		ND	NT

Compound No	Structure	Column 1	Column 2
521		+	+
522		+++	+++
524		++	++
525		++	NT
526		ND	NT

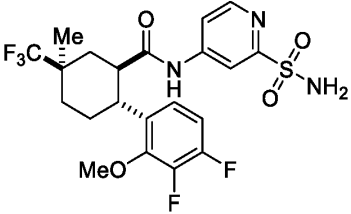
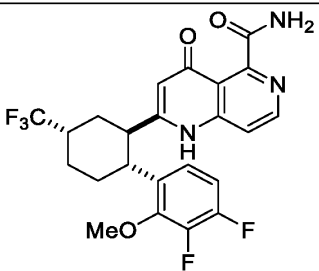
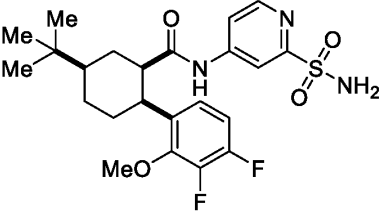
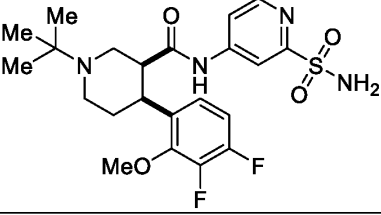
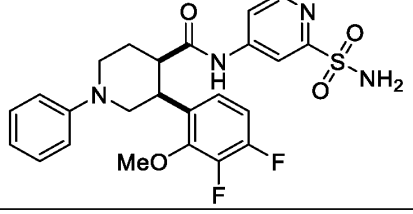
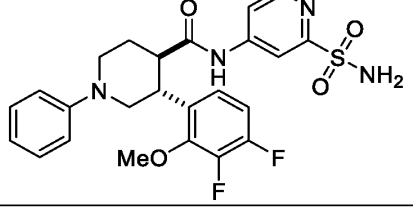
Compound No	Structure	Column 1	Column 2
527		+++	++
528		+	NT
529		++	NT
530		+++	NT
531		++	NT
532		+++	NT

Compound No	Structure	Column 1	Column 2
533		+++	NT
534		+	NT
535		++	NT
536		+++	+++
537		+++	NT

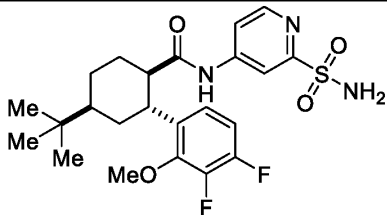
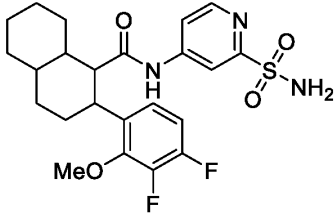
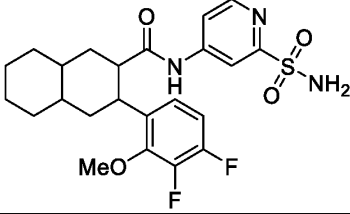
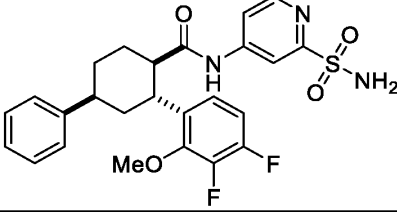
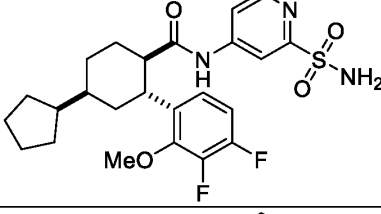
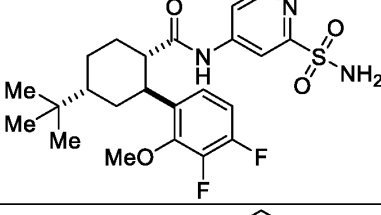
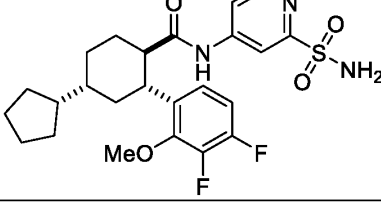
Compound No	Structure	Column 1	Column 2
538		+	+
539		++	NT
540		++	NT
541		+	NT
542		++	NT
543		+	NT

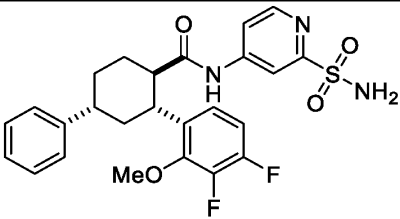
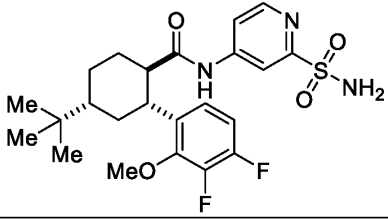
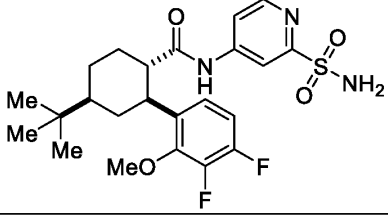
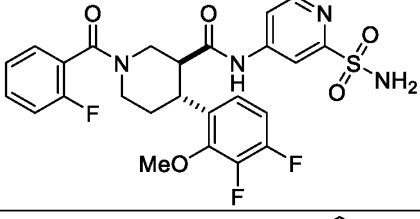
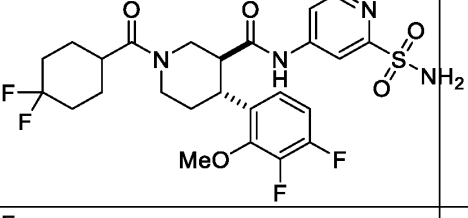
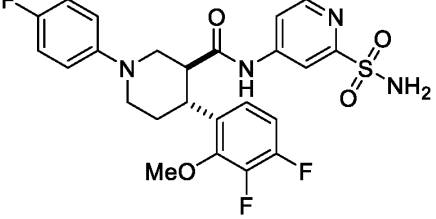
Compound No	Structure	Column 1	Column 2
544		+	NT
545		ND	NT
546		++	NT
547		++	NT
548		+++	NT
549		+	NT

Compound No	Structure	Column 1	Column 2
550		+++	+++
551		+++	+++
552		++	+
553		++	+
554		+++	NT
555		+++	NT
556		+	NT

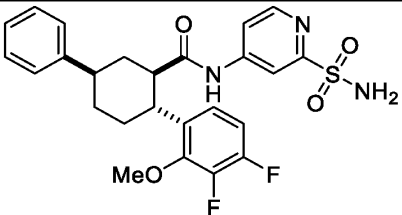
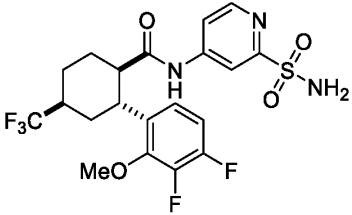
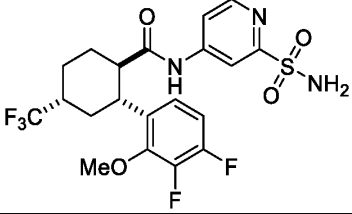
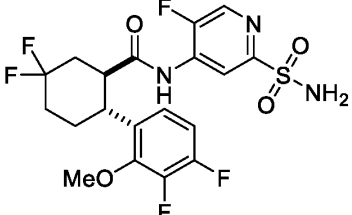
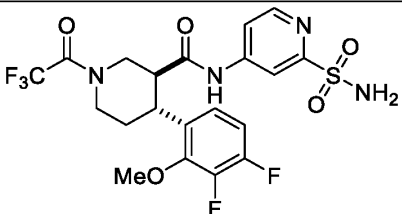
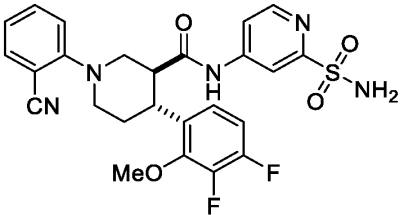
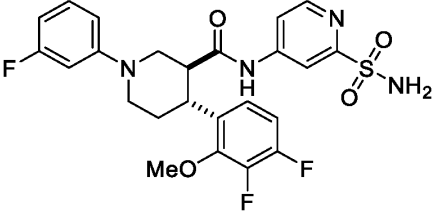
Compound No	Structure	Column 1	Column 2
557		+++	NT
558		++	NT
559		+	NT
560		ND	NT
561		+	NT
562		+++	NT

Compound No	Structure	Column 1	Column 2
563		ND	NT
564		+++	NT
565		++	NT
566		ND	NT
567		+	NT
568		+++	NT
569		+++	NT

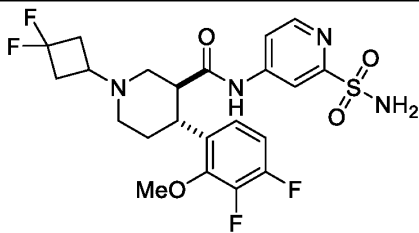
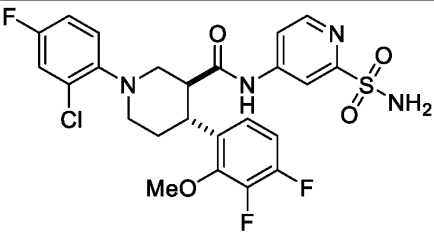
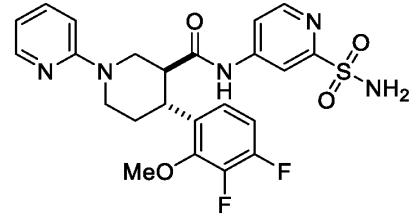
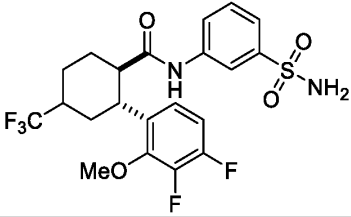
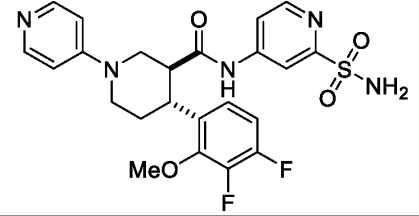
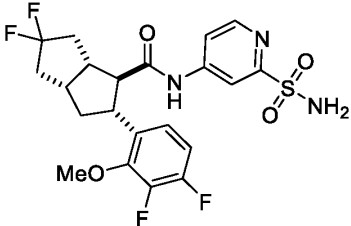
Compound No	Structure	Column 1	Column 2
570		+++	NT
571		++	NT
572		+++	NT
573		+++	NT
574		++	NT
575		++	NT
576		+++	NT

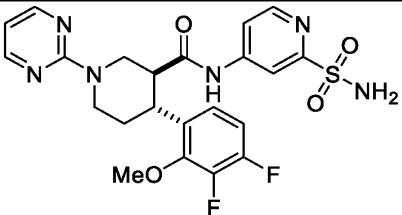
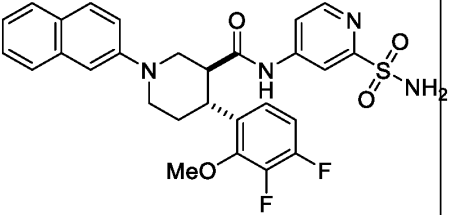
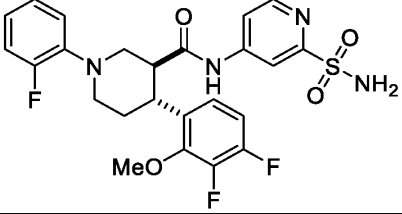
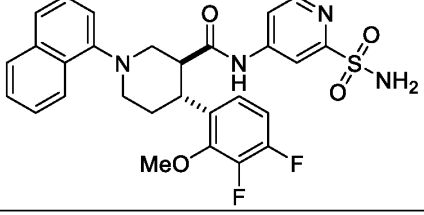
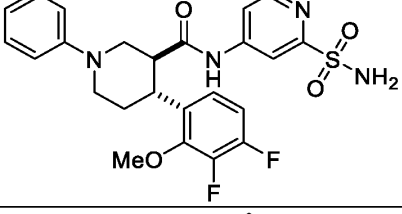
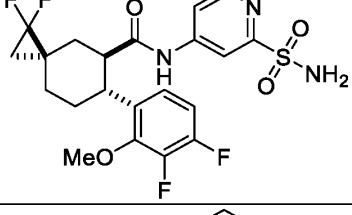
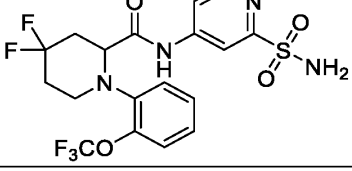
Compound No	Structure	Column 1	Column 2
577		+++	NT
578		+++	NT
579		+	NT
580		+	NT
581		+	NT
582		++	NT

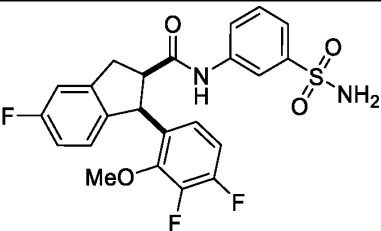
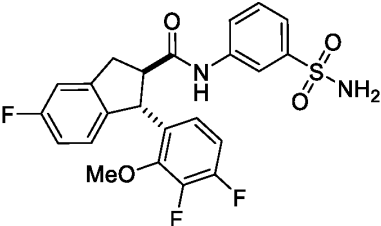
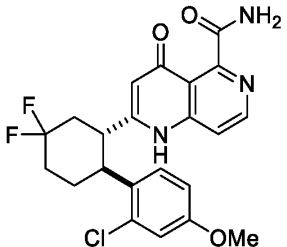
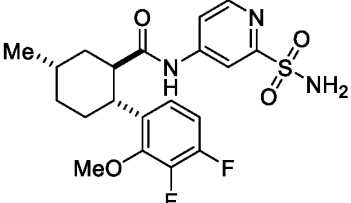
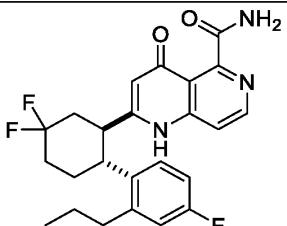
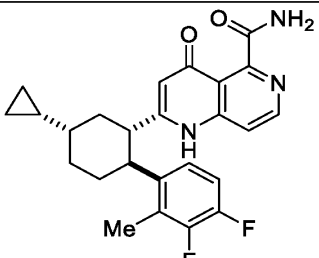
Compound No	Structure	Column 1	Column 2
583		++	NT
584		++	NT
585		+	NT
586		+	NT
587		+	NT
588		+	NT

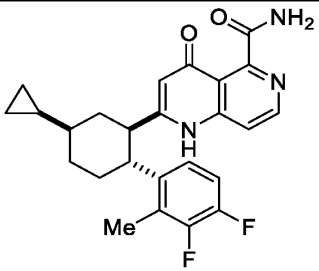
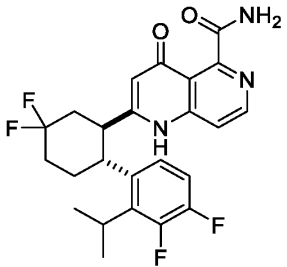
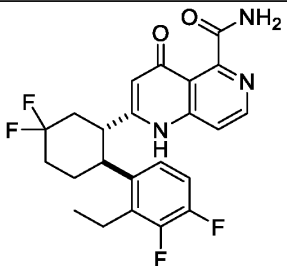
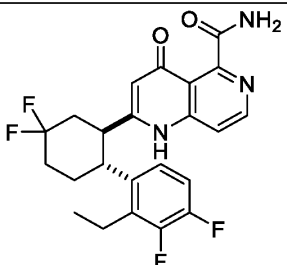
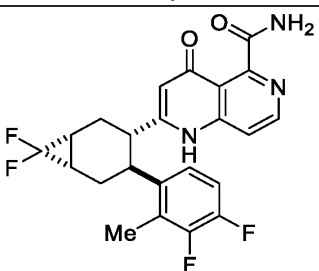
Compound No	Structure	Column 1	Column 2
589		++	NT
590		+++	NT
591		+++	NT
592		++	NT
593		++	NT
594		++	NT
595		++	NT

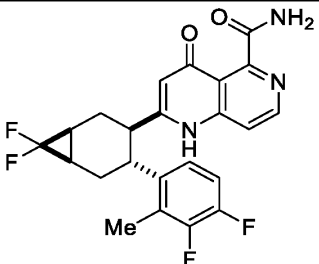
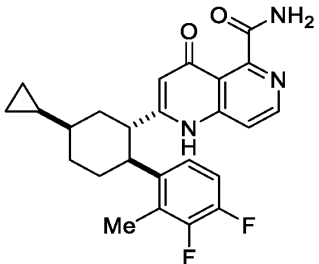
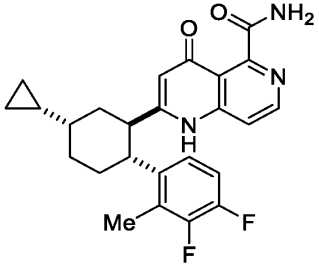
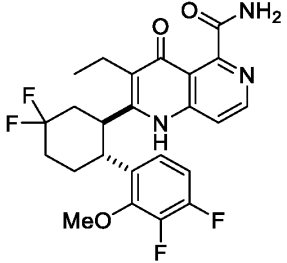
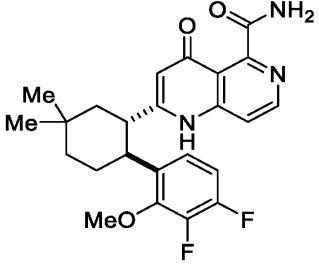
Compound No	Structure	Column 1	Column 2
596		++	NT
597		+++	NT
598		+++	NT
599		+	NT
600		++	NT
601		+	NT

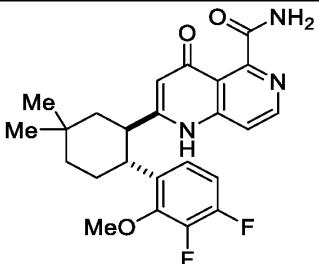
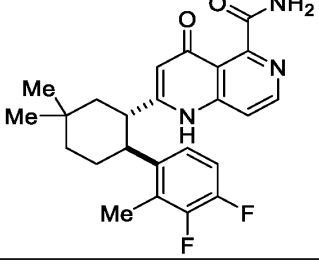
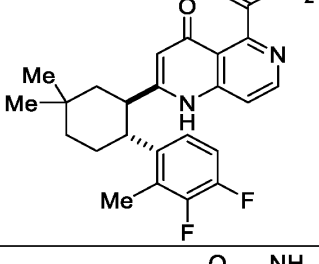
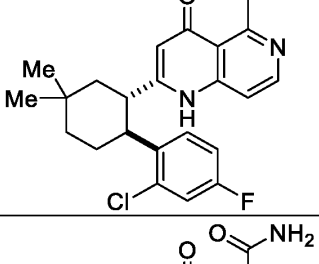
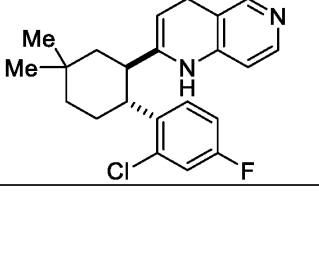
Compound No	Structure	Column 1	Column 2
602		+	NT
603		+++	NT
604		+	NT
605		ND	NT
606		ND	ND
607		+++	+++

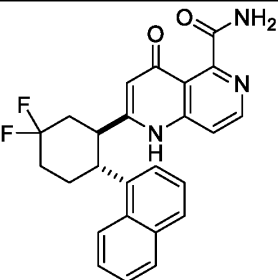
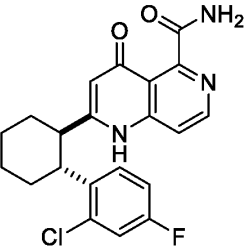
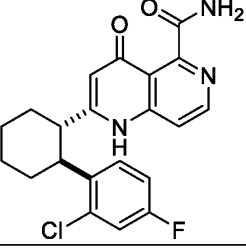
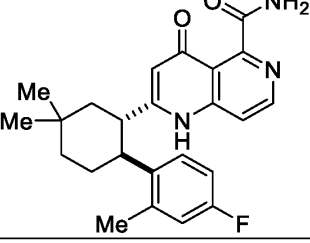
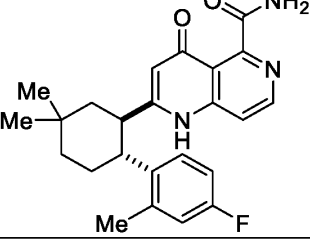
Compound No	Structure	Column 1	Column 2
608		+	NT
609		+	NT
610		++	NT
611		+	NT
612		+	NT
613		+++	NT
614		++	NT

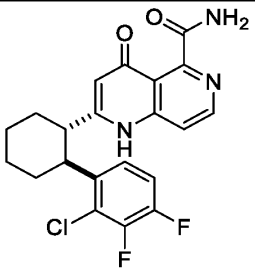
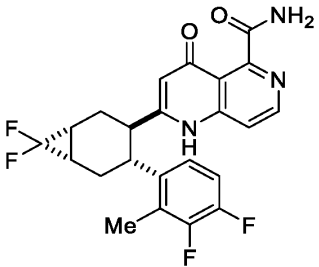
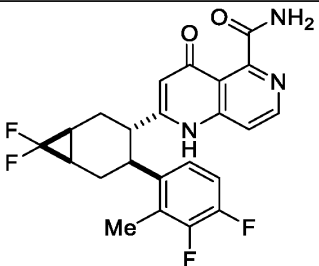
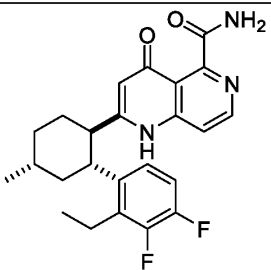
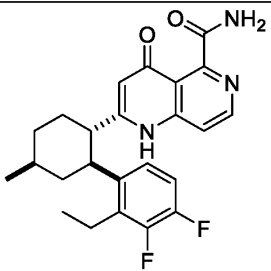
Compound No	Structure	Column 1	Column 2
615		++	NT
616		+	NT
617		+	NT
618		+++	NT
619		++	++
620		+	+

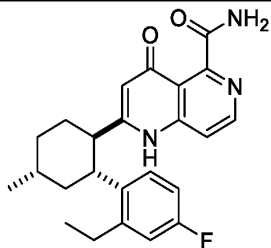
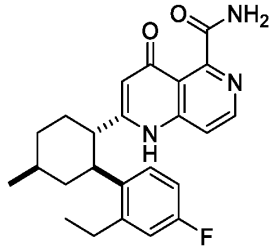
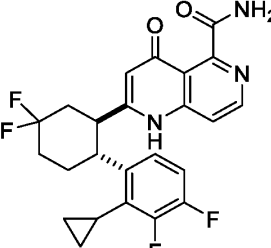
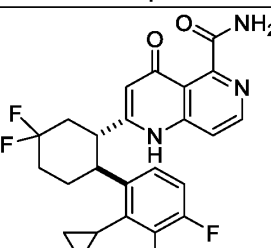
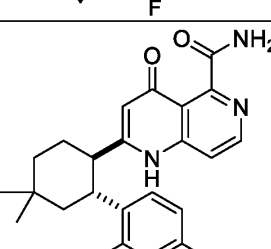
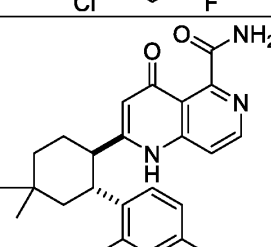
Compound No	Structure	Column 1	Column 2
621		+++	+++
622		+++	+++
623		ND	+
624		+++	+++
625		+	+

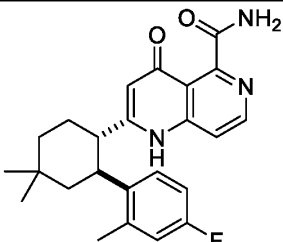
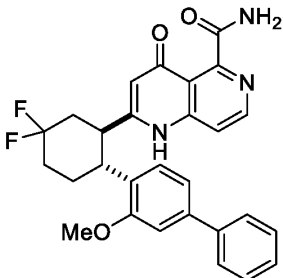
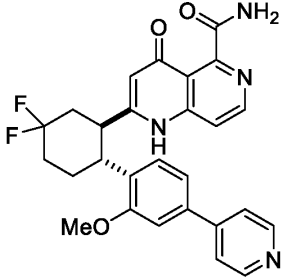
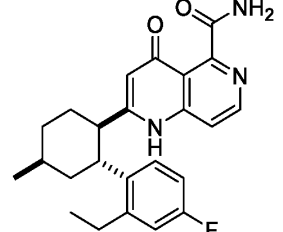
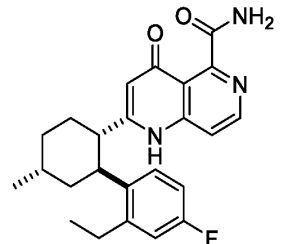
Compound No	Structure	Column 1	Column 2
626		+++	++
627		+	+
628		+++	+++
629		NT	+
630		NT	+

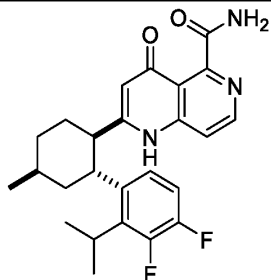
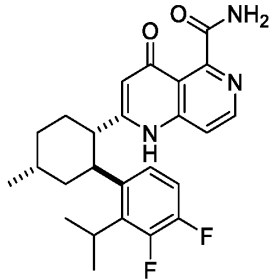
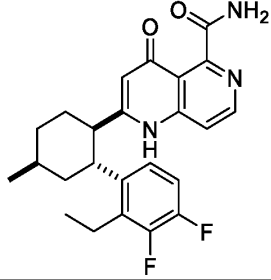
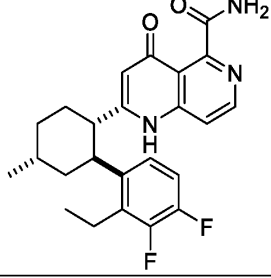
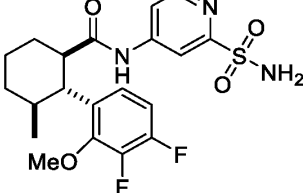
Compound No	Structure	Column 1	Column 2
631		NT	+++
633		NT	+
634		NT	+++
635		NT	+
636		NT	+++

Compound No	Structure	Column 1	Column 2
637		NT	+
638		NT	++
639		NT	ND
640		NT	+
641		NT	+++

Compound No	Structure	Column 1	Column 2
643		NT	ND
647		NT	+++
648		NT	+
669		NT	+++
670		NT	+

Compound No	Structure	Column 1	Column 2
671		NT	+++
672		NT	+
681		NT	+++
682		NT	+
699		NT	+++
701		NT	+++

Compound No	Structure	Column 1	Column 2
702		NT	+
709		NT	+
710		NT	+
714		NT	+++
715		NT	+

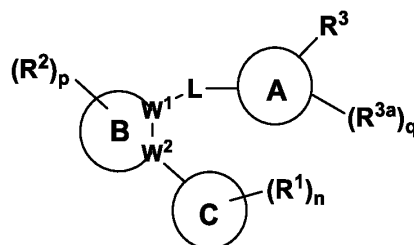
Compound No	Structure	Column 1	Column 2
717		NT	+++
718		NT	+
719		NT	+++
720		NT	+
721		+++	NT

[00354] All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application

were specifically and individually indicated to be incorporated by reference. While the claimed subject matter has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the claimed subject matter is limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I)

wherein

W^1 is CR^x ;

W^2 is CR^x or N;

each R^x is H or C_{1-3} alkyl;

L is a bond or is $-C(O)NH-$ where the nitrogen of $-C(O)NH-$ is attached to **ring A**;

ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 5- to 10-membered heterocyclic ring or N-oxide thereof;

ring B is a 3- to 11-membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

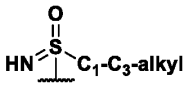
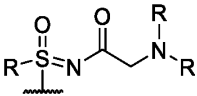
ring C is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where $(R^1)_n$ is substituted on any substitutable ring atom;

R^1 , independently in each instance, is selected from C_1 - C_6 alkyl, in some embodiments, methyl, ethyl, n-propyl, or isopropyl; halo, in some embodiments, fluoro, chloro, or bromo; C_1 - C_6 haloalkyl, in some embodiments, C_1 haloalkyl; cyano; aryl, in some embodiments, phenyl; C_3 - C_6 cycloalkyl, in some embodiments, cyclopropyl or cyclobutyl; C_1 - C_3 alkoxy, in some embodiments methoxy or ethoxy; deuterio- C_1 - C_3 alkoxy, in some embodiments, deuterio-methoxy; halo- C_1 - C_3 alkoxy, in some embodiments, halo- C_1 alkoxy or halo- C_2 alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C_2 - C_4 alkenyl, in some embodiments, vinyl; C_2 - C_4 alkynyl, in some embodiments, ethynyl; and hydroxy;

R^2 , independently in each instance, is selected from C_1 - C_6 alkyl, in some embodiments, methyl, ethyl, isopropyl, or tert-butyl; halo, in some embodiments, fluoro or chloro; C_1 - C_3 haloalkyl, in some embodiments, C_1 - C_2 haloalkyl; C_3 - C_6 cycloalkyl, in some

embodiments, cyclopropyl, cyclobutyl, or cyclopentyl; cyano; -C(O)C₁₋₆alkyl; -C(O)C₁₋₆haloalkyl; -C(O)C₃₋₆cycloalkyl; -C(O)aryl, and aryl, in some embodiments, phenyl or naphthyl; and 4- to 6-membered heteroaryl, in some embodiments, pyridinyl or pyrimidinyl; wherein the C₃₋₆cycloalkyl, aryl, and heteroaryl, each alone or as part of another group, are optionally substituted with 1, 2, or 3 **R**^{2a} groups independently selected from halo, -CN, C₁₋₆alkyl, and C₁₋₆haloalkyl

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁₋₆alkoxycarbonyl, C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, -C(=NH)NH₂, -C(O)N(R)₂, -S(O)₂NHR,

-S(O)₂C₁₋₆alkyl, , , C₁₋₆alkoxy, -NH₂, amino-C₁₋₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁₋₃alkyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl, and 5- to 6-membered heteroaryl wherein each **R** is independently selected from hydrogen, C₁₋₃alkyl, or C₃₋₅cycloalkyl; where the C₃₋₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁₋₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, oxo, halogen, C₁₋₃alkyl, or C₃₋₆cycloalkyl;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof; wherein the compound is not 1-methyl-2-(3-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)quinolin-4(1H)-one; 2-(3-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one; or 2-(3-(4-chlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1H)-one.

2. The compound of claim 1,

wherein

W¹ is CH;

W² is CH or N;

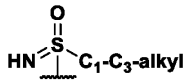
ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 5- to 10-membered heterocyclic ring or N-oxide thereof;

ring B is a 3- to 10-membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl;

R², independently in each instance, is selected from C₁-C₃ alkyl, in some embodiments, methyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,

-S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and wherein **R** is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

p is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

3. The compound of claim 2,
wherein

W¹ is CH;

W² is CH or N;

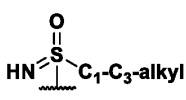
ring A is phenyl; a 5- to 10-membered heteroaryl or N-oxide thereof; or a 6- to 10-membered heterocyclic ring or N-oxide thereof;

ring B is a 3- to 10-membered cycloalkylene optionally fused to a benzo group or a 5- to 10-membered heterocycloalkylene ring optionally fused to a benzo group;

R¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl;

R², independently in each instance, is selected from C₁-C₃ alkyl, in some embodiments, methyl; halo, in some embodiments, fluoro or chloro; C₁-C₃ haloalkyl, in some embodiments, C₁-C₂ haloalkyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; and aryl, in some embodiments, phenyl;

R³ is selected from -H, -CN, halo, -OH, oxo, -B(OH)₂, -COOH, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl, -C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR,

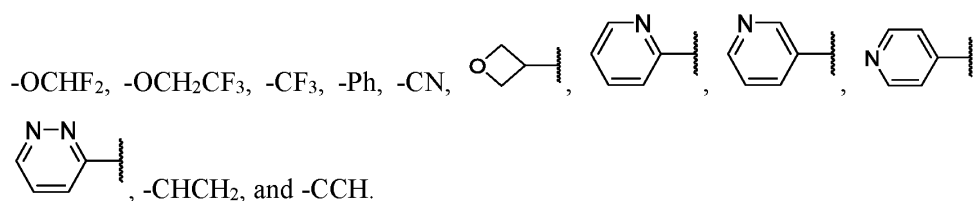
-S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, -NHC(O)C₁₋₃alkyl, -NHC(O)NH₂, -NHS(O)₂NH₂, -NHC(=NH)NH₂, halo-C₁-C₃alkyl, C₃-C₆-cycloalkyl, 3- to 6-membered heterocycloalkyl, and wherein **R** is hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl; where the C₃-C₆cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH₂; and wherein the alkyl in amino-C₁-C₆alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

p is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**¹, independently in each instance, is selected from methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -F, -Cl, -Br, -OMe, -OEt, -O-propyl, -OCD₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl, -CN, oxetanyl, pyridyl, pyridazinyl, -CHCH₂, -CCH, and hydroxy.
5. The compound of any one of claim 1-4, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**¹, independently in each instance, is selected from methyl, ethyl, propyl, cyclopropyl, -F, -Cl, -Br, -OMe, -OEt, -O-propyl, -OCD₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -CF₃, phenyl, -CN, oxetanyl, pyridyl, pyridazinyl, -CHCH₂, and -CCH.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**¹, independently in each instance, is selected from -Me, -Et, -CH(CH₃)₂, -F, -Cl, -Br, -OMe, -OEt, -OCH(CH₃)₂, -OCD₃, -OCF₃,

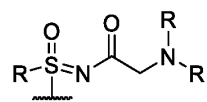


7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **n** is 1, 2, or 3; in some embodiments **n** is 1; in some embodiments **n** is 2; or in some embodiments **n** is 3.
8. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**², independently in each instance, is selected from -CH₃, -CH₂CH₃, -CH(CH₃)₂, C(CH₃)₃, -F, -CF₃, -CH₂CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyano, -C(O)C₁₋₆alkyl, -C(O)C₁₋₆haloalkyl, -C(O)cyclohexyl, -C(O)phenyl, phenyl, naphthyl, pyridinyl, and pyrimidinyl; wherein the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl (alone or as part of -C(O)cyclohexyl), phenyl (alone or as part of -C(O)phenyl), naphthyl, pyridinyl, and pyrimidinyl, are optionally substituted with 1, 2, or 3 **R**^{2a} groups independently selected from halo, -CN, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

9. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**², independently in each instance, is selected from -CH₃, -F, -CF₃, -CH₂CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl; in some embodiments, **R**², independently in each instance, is selected from halo and C₁-C₃ haloalkyl; wherein Ar is aryl, phenyl fused to **HET**, or phenyl fused to **CYC**, and where (**R**¹)_n is substituted on any substitutable ring atom; **R**¹, independently in each instance, is selected from C₁-C₆ alkyl, in some embodiments, methyl or propyl; halo, in some embodiments, fluoro, chloro, or bromo; C₁-C₃ haloalkyl, in some embodiments, C₁ haloalkyl; cyano; aryl, in some embodiments, phenyl; C₃-C₆ cycloalkyl, in some embodiments, cyclopropyl; C₁-C₃ alkoxy, in some embodiments methoxy; deuterio-C₁-C₃ alkoxy, in some embodiments, deuterio-methoxy; halo-C₁-C₃ alkoxy, in some embodiments, halo-C₁ alkoxy or halo-C₂ alkoxy; 5- to 6-membered heteroaryl, in some embodiments, pyridinyl, or pyridazinyl; 4- to 6-membered heterocyclic, in some embodiments, oxetanyl; C₂-C₄ alkenyl, in some embodiments, vinyl; and C₂-C₄ alkynyl, in some embodiments, ethynyl.

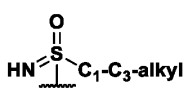
10. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **p** is 0, 1, or 2; in some embodiments **p** is 0; in some embodiments **p** is 1; or in some embodiments **p** is 2.

11. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**³ is not -H and **R**³ is selected from -CN, -OH, oxo, C₁-C₆ alkoxy, carbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl,

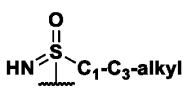


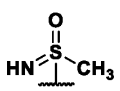
, C₁-C₆ alkoxy, -NH₂, amino-C₁-C₆alkyl, and 5- to 6-membered heteroaryl wherein each **R** is independently hydrogen, C₁-C₃ alkyl, or C₃-C₅cycloalkyl.

12. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**³ is not -H and **R**³ is selected from -CN, -OH, oxo, C₁-C₆ alkoxy, carbonyl, C₁-C₆ alkyl, hydroxy-C₁-C₆-alkyl,

-C(=NH)NH₂, -C(O)NH₂, -S(O)₂NHR, -S(O)₂C₁-C₆-alkyl, , C₁-C₆ alkoxy, -NH₂, and amino-C₁-C₆alkyl, and wherein **R** is hydrogen or C₃-C₅cycloalkyl; in some embodiments, **R**³ is selected from -CN, -OH, C₁-C₆ alkoxycarbonyl, -C(O)NH₂, -S(O)₂NH₂, -COOEt, and oxo.

13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**³ is selected from -CN, -OH, oxo, C₁-C₆

alkoxycarbonyl, -C(O)NH₂, -S(O)₂NH₂, -S(O)₂C₁-C₆-alkyl, , and C₁-C₆ alkoxy; in some embodiments, **R**³ is selected from -CN, -OH, oxo, -COOEt,

-C(O)NH₂, -S(O)₂NH₂, -S(O)₂CH₃, , and -OMe.

14. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **R**^{3a}, independently in each instance, is -H, halo, oxo, or C₁-C₃ alkyl; in some embodiments, **R**^{3a}, independently in each instance, is -H, -F, oxo, or -CH₃.

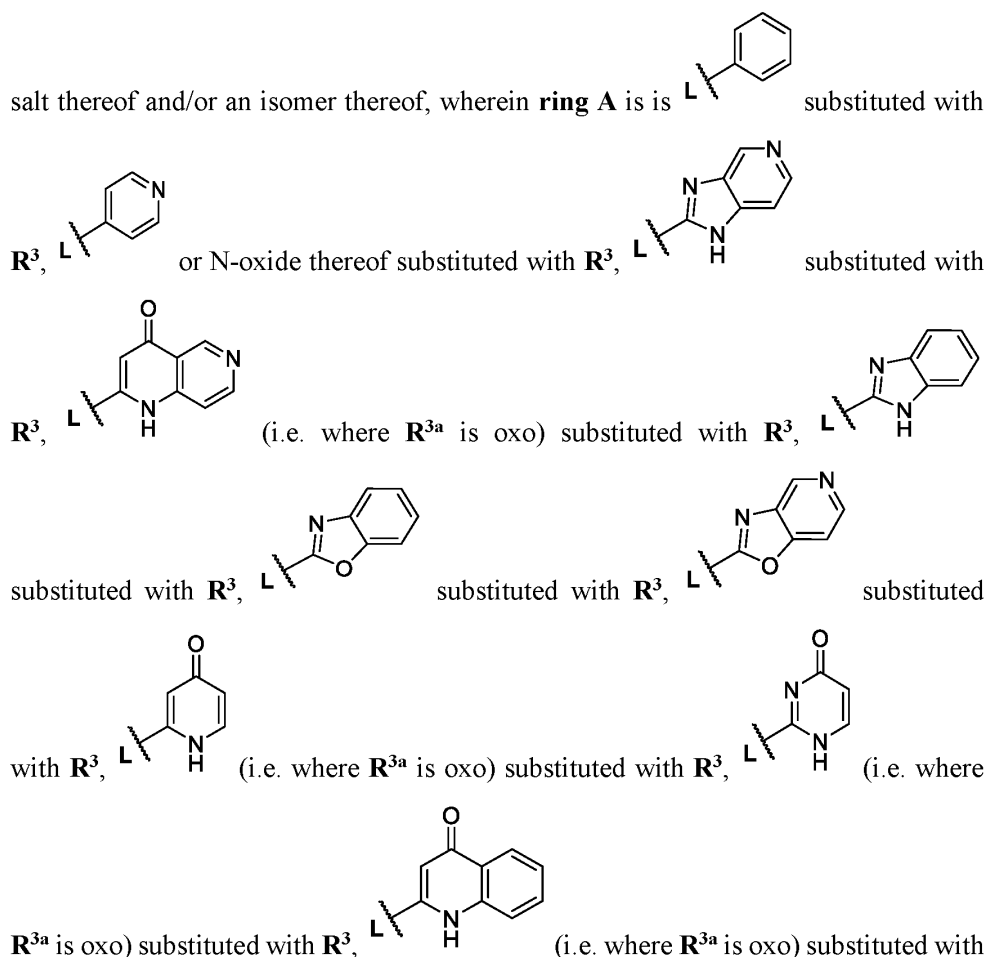
15. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **q** is 0, 1, or 2; in some embodiments **q** is 0; in some embodiments **q** is 1; or in some embodiments **q** is 2.

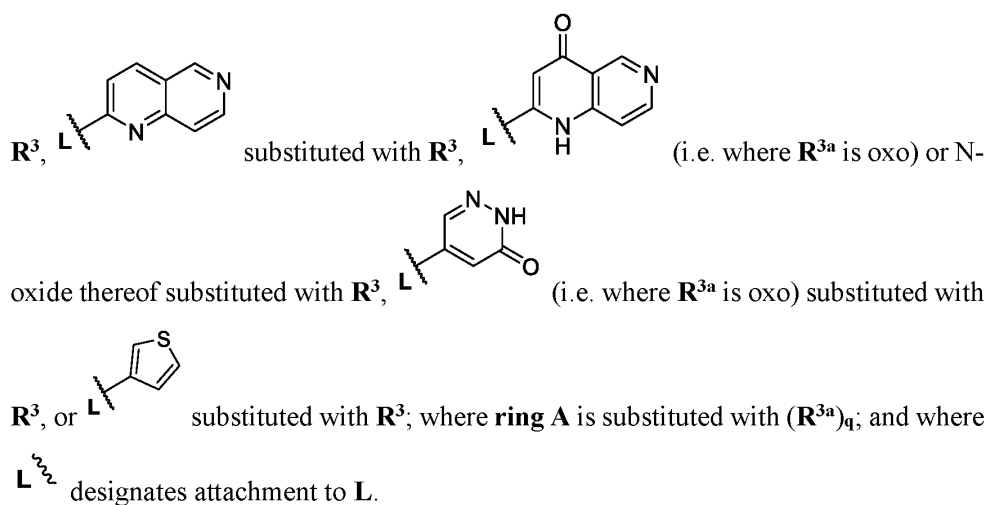
16. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **ring A** is phenyl substituted with **R**³, pyridyl or an N-oxide thereof substituted with **R**³, imidazopyridyl substituted with **R**³, benzimidazolyl substituted with **R**³, benzoxazolyl substituted with **R**³, benzoisoxazolyl substituted with **R**³, oxazolopyridinyl substituted with **R**³, pyridinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyrimidinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyridazinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, pyridazinyl substituted with **R**³, isoindolinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, indazolyl substituted with **R**³, indazolonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³, benzoisothiazolyl substituted with **R**³, quinolinonyl (i.e. where **R**^{3a} is oxo) substituted with **R**³,

naphthyridinonyl (i.e. where R^{3a} is oxo) or an N-oxide thereof substituted with R^3 ; thiophenyl substituted with R^3 , where **ring A** is substituted with $(R^{3a})_q$; in some embodiments, R^3 is not -H.

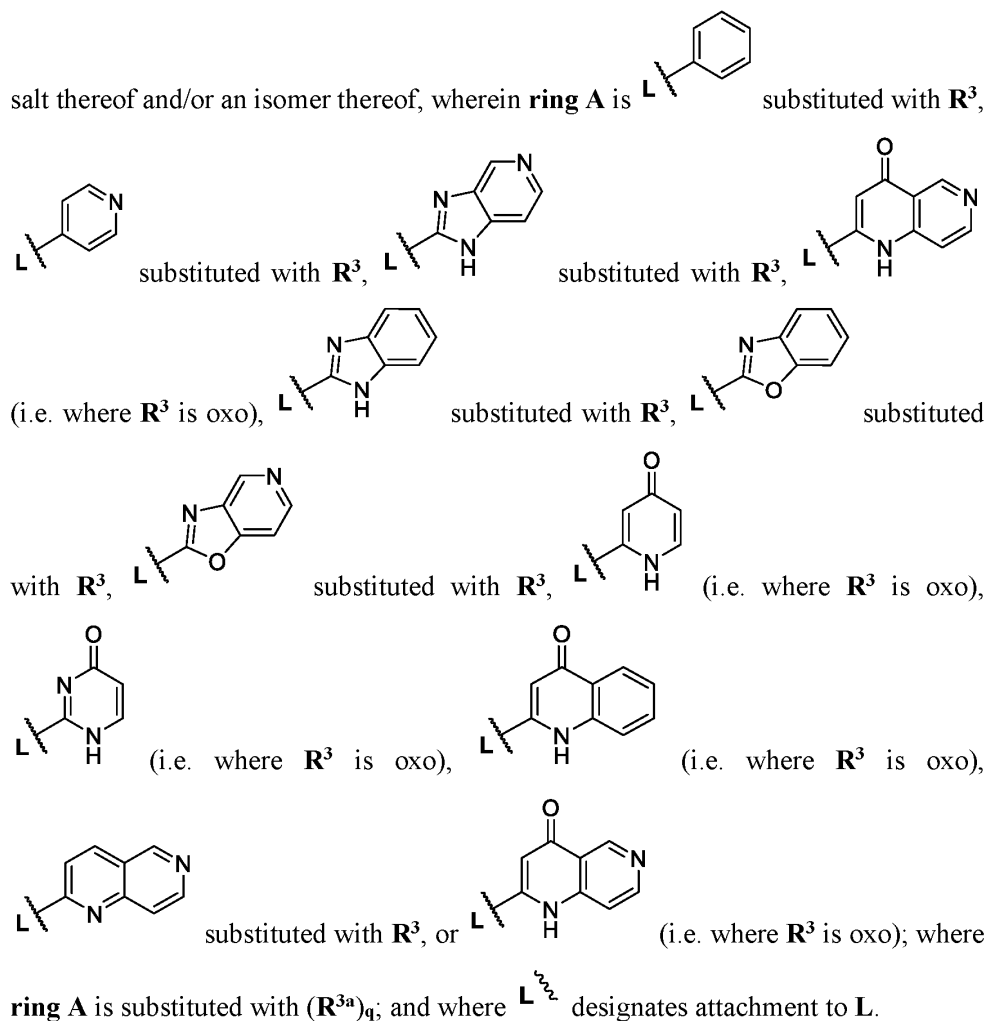
17. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **ring A** is phenyl substituted with R^3 , pyridyl substituted with R^3 , imidazopyridyl substituted with R^3 , benzimidazolyl substituted with R^3 , benzoxazolyl substituted with R^3 , oxazolopyridinyl substituted with R^3 , pyridinonyl (i.e. where R^3 is oxo), pyrimidinonyl (i.e. where R^3 is oxo), quinolinonyl (i.e. where R^3 is oxo), or naphthyridinonyl (i.e. where R^3 is oxo); where **ring A** is substituted with $(R^{3a})_q$; in some embodiments, R^3 is not -H.

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



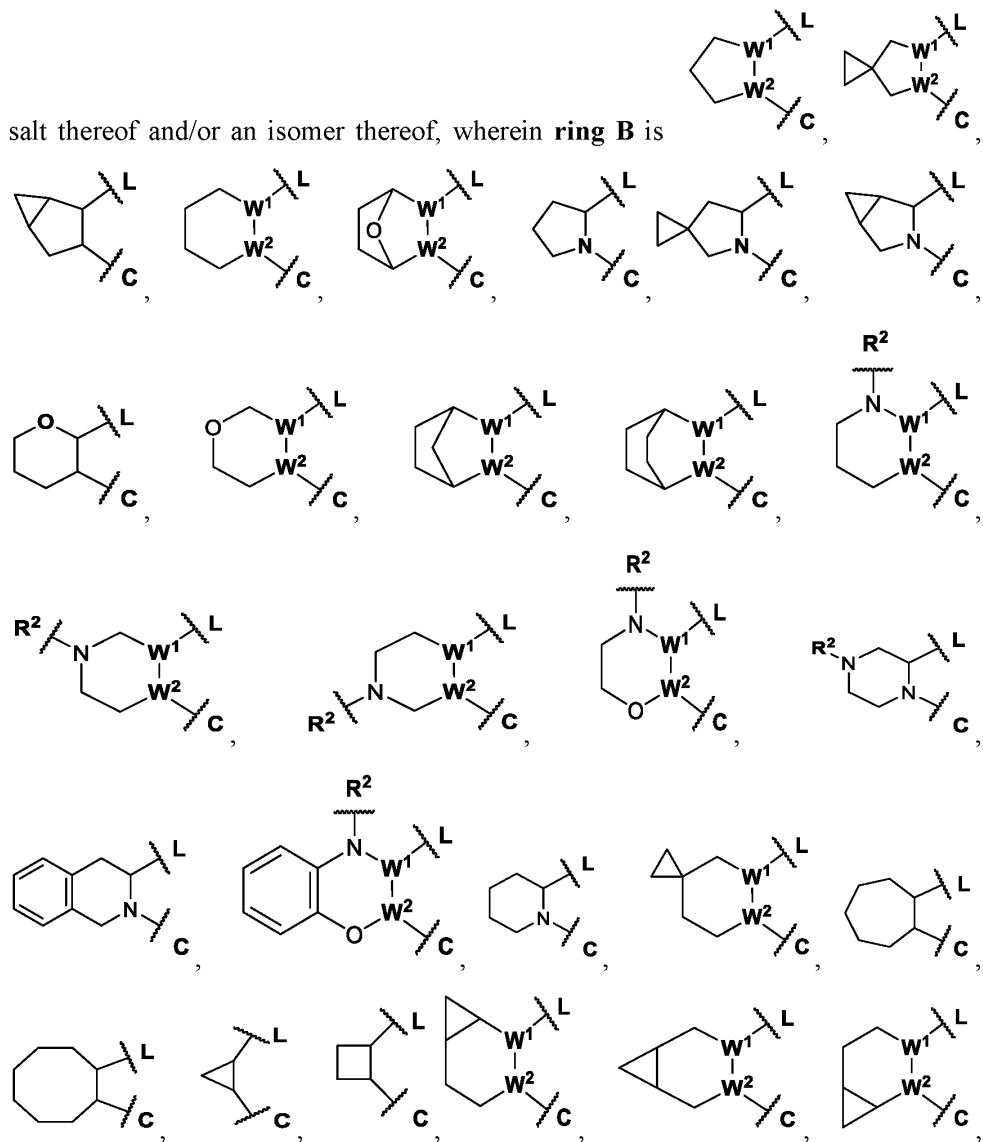


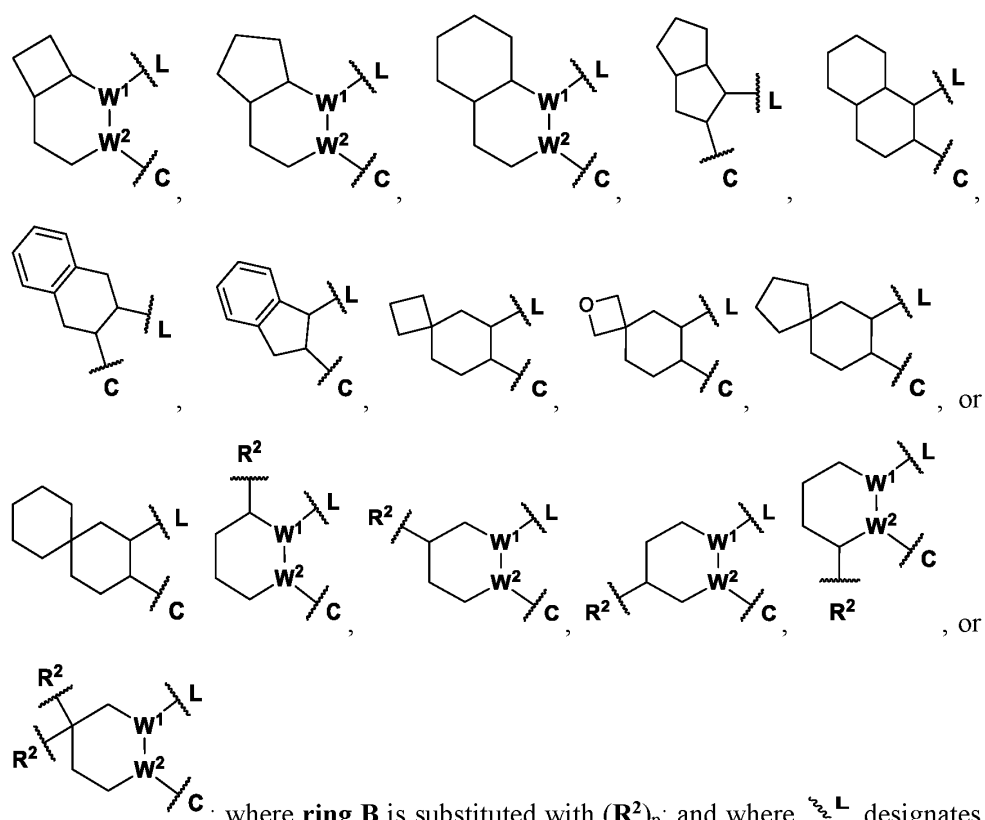
19. The compound of any one of the preceding claims, or a pharmaceutically acceptable



20. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **ring B** is a 3- to 11-membered cycloalkylene (in an embodiment, 3- to 10-membered cycloalkylene); or a 6-, 7-, or 10-membered heterocycloalkyl; where **ring B** is substituted with $(R^2)_p$.
21. The compound of any one of the preceding claims, or a pharmaceutically acceptable

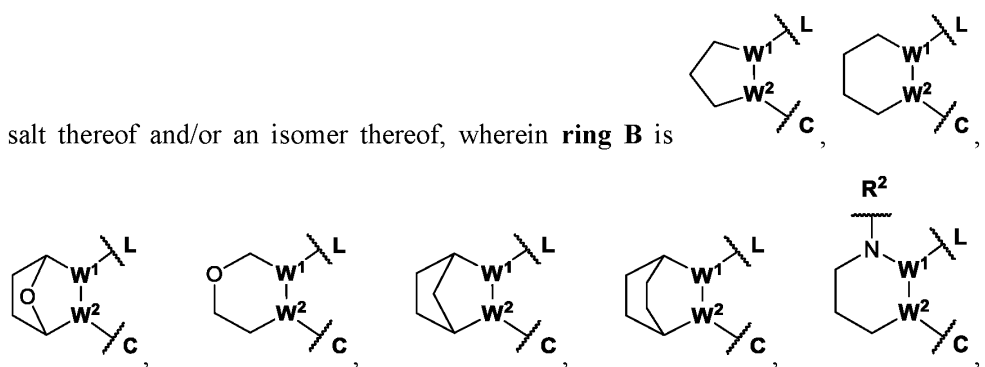
salt thereof and/or an isomer thereof, wherein **ring B** is

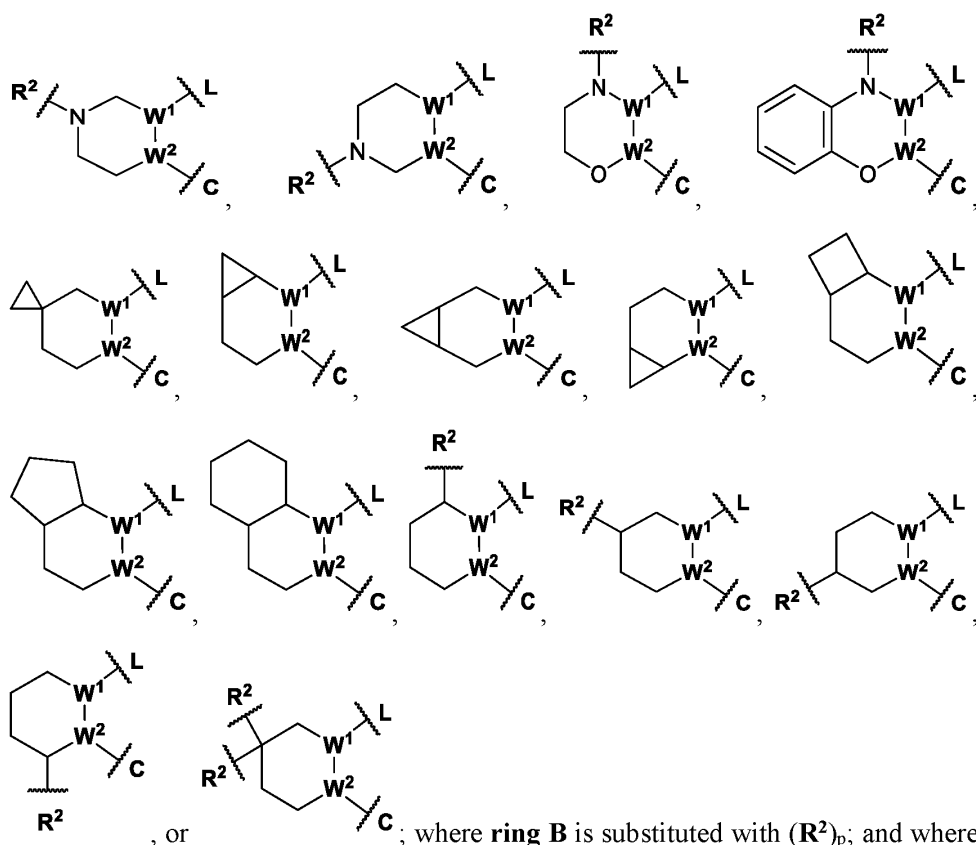




22. The compound of any one of the preceding claims, or a pharmaceutically acceptable

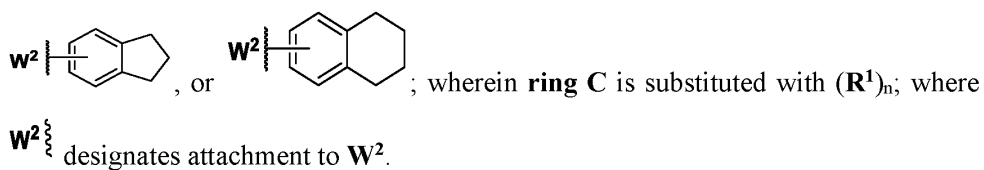
salt thereof and/or an isomer thereof, wherein **ring B** is



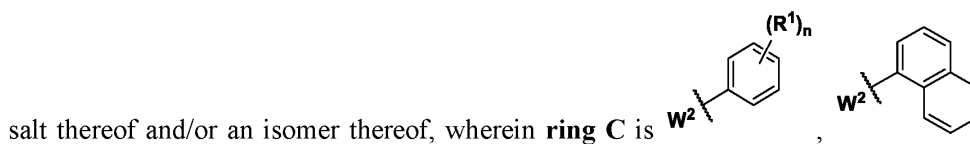


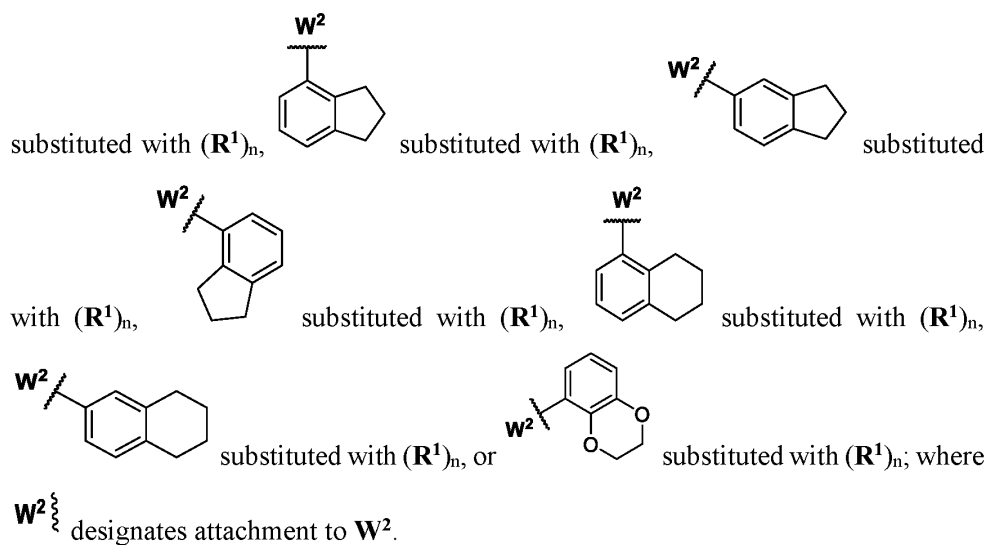
where **ring B** is substituted with $(R^2)_p$; and where L designates attachment to **L**, C designates attachment to **ring C**, and R^2 designates attachment to R^2 .

23. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **ring C** is 6- or 10-membered aryl,

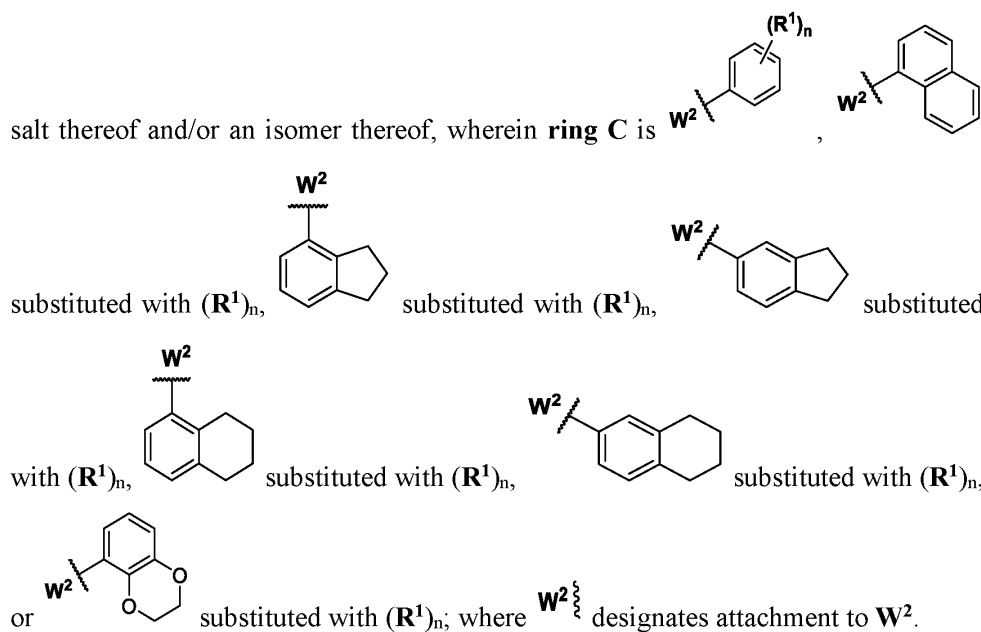


24. The compound of any one of the preceding claims, or a pharmaceutically acceptable





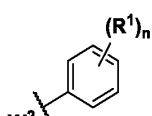
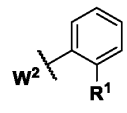
25. The compound of any one of the preceding claims, or a pharmaceutically acceptable

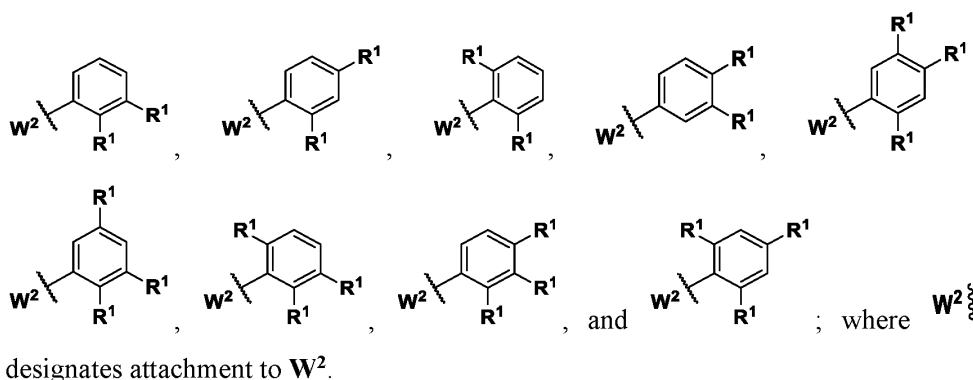


26. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein W^2 is CR^x .

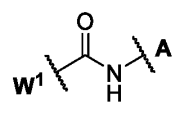
27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein W^2 is CH.

28. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **W**² is N.
29. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **W**¹ is CH.
30. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **n** is 0, 1, 2, or 3; **p** is 0, 1, 2, or 3; and **q** is 0 or 1.
31. The compound of any one of the preceding claims, or a pharmaceutically acceptable

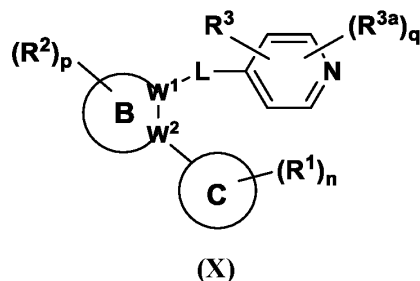
salt thereof and/or an isomer thereof, wherein when **ring C** is ; in some embodiments, **ring C** is selected from the group consisting of ,



32. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **L** is a bond.
33. The compound of any one of the preceding claims, or a pharmaceutically acceptable

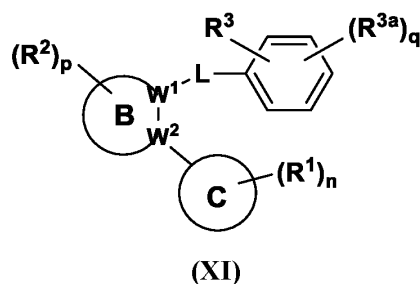
salt thereof and/or an isomer thereof, wherein **L** is ; where  indicates attachment to **W**¹, and  indicates attachment to **ring A**.

34. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (X):



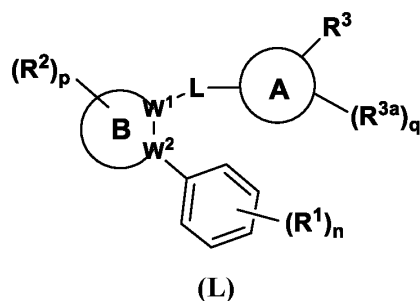
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

35. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (XI):



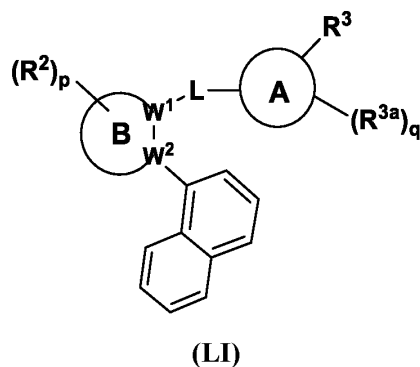
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

36. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (L):



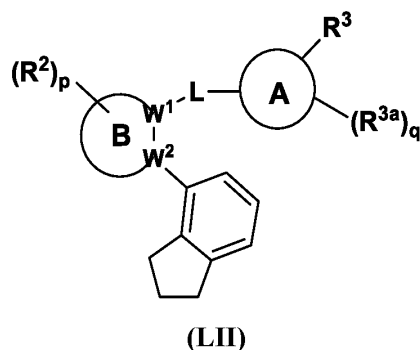
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

37. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LI):



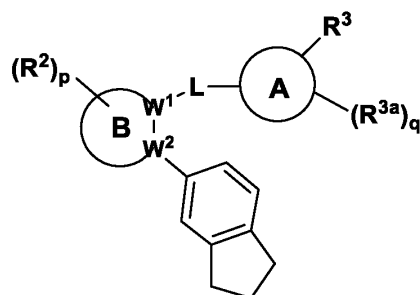
or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** naphthyl is substituted with $(R^1)_n$.

38. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LII):



or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** 2,3-dihydro-1H-inden-4-yl is substituted with $(R^1)_n$.

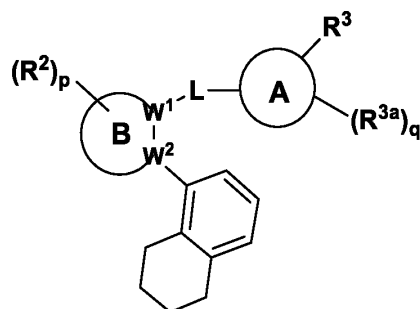
39. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LIII):



(LIII)

or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** 2,3-dihydro-1H-inden-5-yl is substituted with $(R^1)_n$.

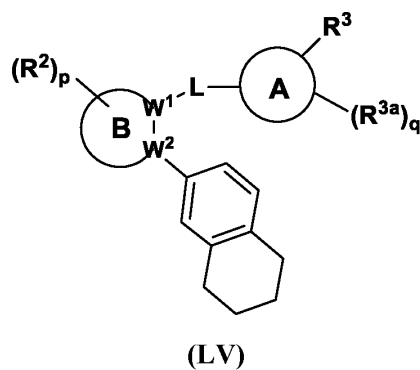
40. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LIV):



(LIV)

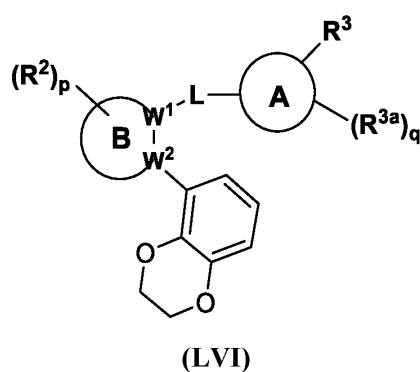
or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** 1,2,3,4-tetrahydronaphthalen-5-yl is substituted with $(R^1)_n$.

41. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LV):



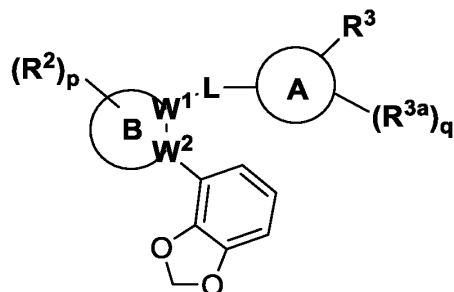
or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** 1,2,3,4-tetrahydronaphthalen-6-yl is substituted with $(R^1)_n$.

42. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LVI):



or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** 2,3-dihydrobenzo[b][1,4]dioxin-5-yl is substituted with $(R^1)_n$.

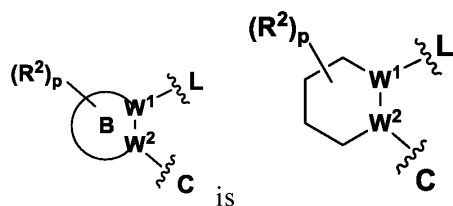
43. The compound of any one of claims 1 to 33, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (LVII):



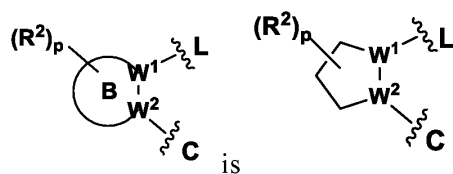
(LVII),

- or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein the **ring C** benzo[d][1,3]dioxole is substituted with $(R^1)_n$.

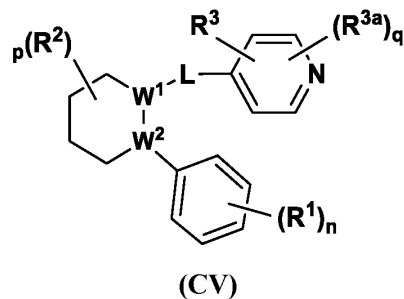
44. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein



45. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

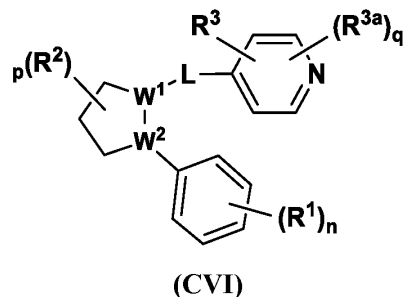


46. The compound of any one of claims 1 to 34 and 36, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (CV):



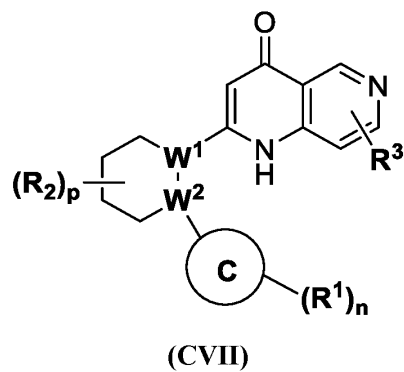
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

47. The compound of any one of claims 1 to 34 and 36, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (CVI):



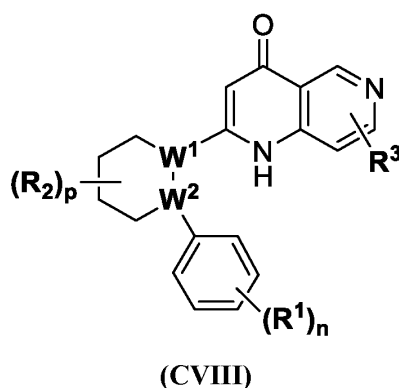
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

48. The compound of any one of claims 1 to 32, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (CVII):



or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

49. The compound of any one of claims 1 to 32, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, is a compound of Formula (CVIII):



or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

50. A compound of Table A-1, Table A-2, or Table A-3 or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

51. A pharmaceutical composition comprising the compound of any one of preceding claims, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, and a pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51, wherein the composition is an oral or injectable composition, optionally wherein the injectable composition is a subcutaneously injectable composition.

53. A method for the treatment of a condition associated with voltage-gated sodium channel function, including $Na_v1.8$, in a subject, comprising administering a therapeutically or prophylactically effective amount of the compound of any one of claims 1-50 or the pharmaceutical composition of claim 51 or 52.

54. The method of claim 53, wherein the subject is a human.

55. The method of claim 53 or 54, wherein the condition is pain or wherein the condition is associated with pain.

56. The method of claim 53 or 54, wherein the condition is pain.

57. The method of claim 53 or 54, wherein the condition is associated with pain.

58. The method of any one of claims 53-57, wherein the condition is selected from the group consisting of pain associated with erythromelalgia, pain associated with diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain

syndrome, pain associated with trigeminal neuralgia, pain associated with multiple sclerosis, pain associated with arthritis (including osteoarthritis), pain associated with postherpetic neuralgia, cancer pain, pain associated with cluster headache, pain associated with migraine, pain associated with sciatica, pain associated with endometriosis, pain associated with fibromyalgia, postsurgical pain, subacute pain, chronic pain, pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, pain associated with ocular surgery, pain associated with epilepsy, pain associated with Parkinson's disease, a mood disorder, psychosis, pain associated with amyotrophic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

59. The method of claim 53 or 54, wherein the condition is selected from the group consisting of acute pain, subacute pain, post-surgical pain, and ocular pain.
60. A method of inhibiting $NA_v1.8$ comprising contacting $NA_v1.8$ with a compound of any one of claims 1-50.