

IMIDAZOLE CONTAINING COMPOUNDS, DERIVATIVES THEREFORE, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Patent Application No. 63/498,049 filed April 25, 2023, U.S. Patent Application No. 63/515,229 filed July 24, 2023, U.S. Patent Application No. 63/550,274 filed February 6, 2024, U.S. Patent Application No. 63/550,228 filed February 6, 2024, and U.S. Patent Application No. 63/557,039 filed February 23, 2024, the disclosures of which are incorporated herein by reference in their entireties.

FIELD OF THE DISCLOSURE

The present disclosure describes novel alpha2 adrenergic receptor (α 2AR) agonists and uses thereof. In particular, the present disclosure describes novel imidazole containing compounds and their derivatives. These compounds can be useful as α 2AR agonists for the treatment or prevention of diseases thereof.

BACKGROUND OF THE DISCLOSURE

The alpha2 adrenergic receptor (α 2AR) family, as part of the G-protein-coupled receptors, plays a critical role for many central nervous system (CNS) biological functions. α 2ARs are key in modulating neurotransmitter release, thus influencing a spectrum of central physiological processes. Agonists targeting these receptors, such as clonidine and dexmedetomidine, have been successfully used to treat several conditions predominantly within the CNS. Related applications include treating hypertension, sedation in intensive care, and for problems like attention-deficit/hyperactivity disorder (ADHD) and agitation associated with schizophrenia or bipolar disorder.

Clonidine was first developed to manage hypertension. Later, clonidine was found to induce sedation by acting through the activation of central pre- and postsynaptic α 2AR in the locus coeruleus (LC), a nucleus in the medial dorsal pons, thereby inducing sedative effects. The later development and approval of dexmedetomidine for sedation, particularly in initially intubated and mechanically ventilated adult patients in intensive care settings, was attributed to its superior α 2AR selectivity and pharmacokinetic properties better suited for sedation.

Beyond its antihypertensive and sedation effects, clonidine has been approved for epidural use under the trade name Duraclon, marking a significant advancement in the

treatment of cancer pain. The analgesic mechanism is widely attributed to clonidine's diffusion into the spinal cord and activation of α_2 ARs in the dorsal horn, thereby attenuating pain transmission to higher CNS centers. This central action enables α_2 AR agonists to produce significant analgesic effects, making them an important method for managing pain.

However, the therapeutic application of α_2 AR agonists on analgesia comes with challenges, primarily due to the range of other biological adverse effects they can cause in CNS. Duraclon has been documented to induce centrally mediated sedation, hypotension, bradycardia, and depression of its applications, which persist throughout the analgesic treatment process. Such sedation effect significantly limits the dosages that can be administered safely. As a result, although α_2 AR agonists like clonidine and dexmedetomidine are considered important for pain treatment in both academic research and clinical settings, the sedation effect poses substantial hurdles to their widespread use in medical applications.

Therefore, it is desired to develop new classes of α_2 AR agonists that could provide substantial therapeutic benefits in pain management such as reduced sedation effect, thereby expanding the range of therapeutic alternatives to address the prevailing unmet medical needs.

BRIEF SUMMARY OF THE DISCLOSURE

In one general aspect, the present disclosure relates to methods of treating or preventing a disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective alpha2 adrenergic receptor (α_2 AR) agonist.

In some embodiments, the peripherally selective α_2 AR agonist activates at least one sub type of α_2 AR, particularly α_2A AR, α_2B AR, or α_2C AR.

In some embodiments, the peripherally selective α_2 AR agonist has a $K_{p,uu,brain}$ is lower than 0.05, 0.02, or 0.01.

In some embodiments, the disease is chosen from pain, rosacea, spasticity, and aging.

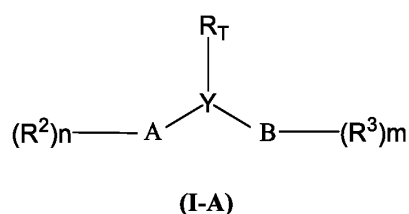
In some embodiments, the peripherally selective α_2 AR agonist causes reduced biological effects mediated by CNS, such as sedation, hypotension, and bradycardia, than treating with a non-peripherally selective α_2 AR agonist.

In another general aspect, the present disclosure provides a peripherally selective α_2 AR agonist that comprises an α_2 AR activation moiety covalently linked to a peripheral distribution moiety, and its uses in the treatment of a disease.

In another general aspect, the present disclosure relates to methods of treating or preventing a disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective $\alpha 2$ AR agonist, wherein the peripherally selective $\alpha 2$ AR agonist comprises an $\alpha 2$ AR activation moiety covalently linked to a peripheral distribution moiety.

In some embodiments, the peripherally selective $\alpha 2$ AR agonist causes less sedation than treating with a non-peripherally selective $\alpha 2$ AR agonist.

In another general aspect, the present disclosure relates to a compound of formula (I-A):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

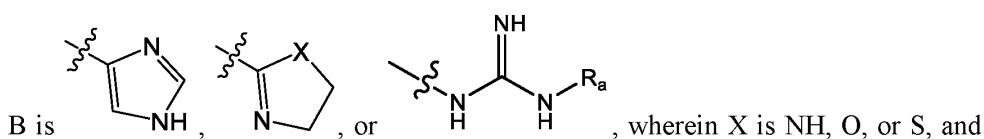
Y is $C(R^1)$, N, $-O-C$, $-C-NH-$, $-CH_2-C(O)-$, or $-CH=N-$;

when Y is $C(R^1)$, R^1 is chosen from H, D, and halogen;

when Y is $-O-C-$, the oxygen atom is connected to A, and the carbon atom is connected to both R_T and B; and

when Y is $-C-NH-$, the carbon atom is connected to both R_T and A, and the nitrogen atom is connected to B;

A is a ring chosen from phenyl, pyridinyl, thienyl, furyl, pyrrolyl, 4H-pyran, 4H-thiopyran, 1,2,3,4-tetrahydro-1-naphthyl, tetrahydrozoline, quinoxaliny, pyrimidinyl, and 2,1,3-benzothiadiazol;



n is 0, 1, 2, or 3;

each R^2 is independently chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, OR^4 , $-CN$, N_3 , NO_2 , $N(R^4)_2$, OR_4 , SR^4 , $C(O)R^4$, $SO_2N(R^4)_2$,

CH₂SR⁴; wherein the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R⁵;

R⁴ is chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, and the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R⁵;

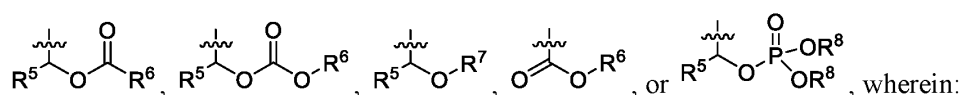
R⁵ is chosen from halogen, hydroxyl, -CN, -NO₂, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

alternatively, when A is a phenyl ring and two R² are substituted at adjacent positions of the phenyl ring, the two R² groups, with the carbon atoms they are connected to, form a ring that is fused to ring A to form a bicyclic ring, such as quinolinyl, indolyl, benzothienyl, benzofuryl, benzofuranyl, benzodioxolyl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, cinnolinyl, quinoxalinyl, or 1,2,4-benzotriazinyl;

m is 0, 1, 2, or 3;

each R³ is independently chosen from H, D, halogen, -OH, -SH, optionally substituted alkyl, optionally substituted heterocycle, and optionally substituted aryl;

alternatively, R³ is a group connected to the -NH of the imidazole ring, and R³ is of the formula of:



R⁵ is hydrogen or alkyl;

R⁶ is hydrogen, alkyl, cycloalkyl, or alkenyl;

R⁷ is an amino acid residue; and

R⁸ is alkyl or cycloalkyl;

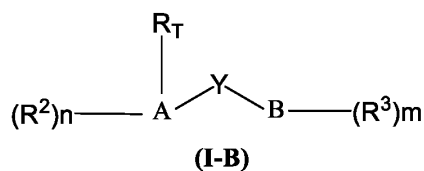
R_T is R_L-R_P, and R_P is optionally substituted with R_C, wherein:

R_L is a linker, wherein one end is connected to R_P and the other end is connected to Y;

R_P is a moiety that is connected to one end of R_L; and

R_C is a cap, which is a moiety that is connected to R_P.

In another general aspect, the present disclosure relates to a compound of formula (I-B):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y is a bond, CH(R¹), NH, -O-CH-, -C-NH-, -CH₂-C(O)-, or -CH=N-;

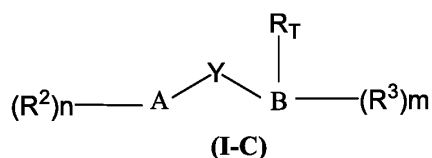
when Y is C(R¹), R¹ is chosen from H, D, and halogen;

when Y is -O-C-, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is -C-NH-, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R², n, R³, m, and R_T are defined as above in formula (I-A).

In another general aspect, the present disclosure relates to a compound of formula (I-C):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y is a bond, CH(R¹), NH, -O-CH-, -C-NH-, -CH₂-C(O)-, or -CH=N-;

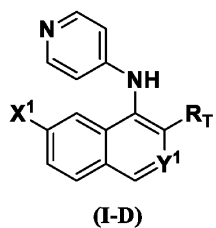
when Y is C(R¹), R¹ is chosen from H, D, and halogen;

when Y is -O-C-, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is -C-NH-, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R², n, R³, m, and R_T are defined as above in formula (I-A).

In another general aspect, the present disclosure relates to a compound of formula (I-D):



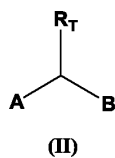
or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y¹ is CH, or N;

X¹ is chosen from H, D, and halogen;

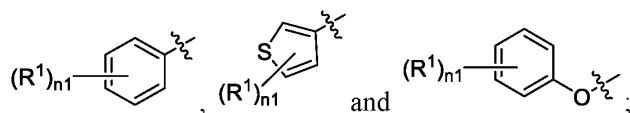
R_T is defined as above in formula (I-A).

In another general aspect, the present disclosure relates to a compound of formula (II):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

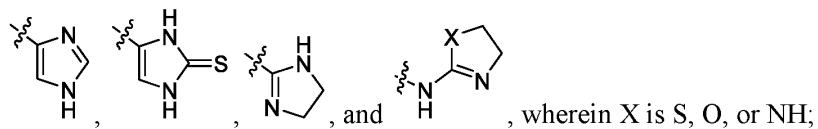
A is one chosen from:

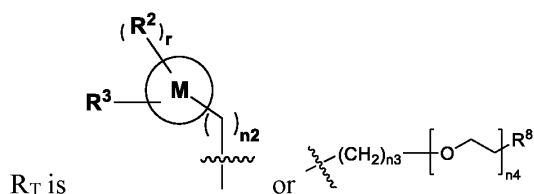


n₁ is 1 or 2;

each R¹ is independently chosen from hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and -COOH;

B is one chosen from:





ring M is C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, C₆₋₁₂ aryl, or C₁₋₁₂ heteroaryl, wherein the C₃₋₁₂ cycloalkyl or C₂₋₁₂ heterocyclyl is optionally fused with an aryl;

r is 1 or 2;

n₂ is 0, 1, or 2;

each R² is independently chosen from hydrogen, halogen, hydroxyl, and alkoxy;

R³ is chosen from CN, hydroxy, alkoxy, -C(O)-C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -SO₂-alkyl, -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-R^{3'}, -O-C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R^{4'}),

$\frac{1}{2} \text{O} \left[\text{CH}_2 \right]_m \text{R}^6$, -NH-R⁷, or $\frac{1}{2} \text{O} \left[\text{CH}_2 \text{OCH}_2 \right]_n \text{OCH}_3$; wherein one -CH₂- group in the -C₀₋₁₂ alkylene-R^{3'} is optionally replaced by oxygen atom or $\equiv$, the -C₀₋₁₂ alkylene-R^{3'} is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C₂₋₁₂ heterocyclyl and C₁₋₁₂ heteroaryl are each optionally substituted with one or more R^{4a};

R^{3'} is chosen from -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl;

each R^{4a} is independently chosen from hydroxy, alkyl, oxo, ketone, and -C₂₋₁₂ heterocyclyl;

each of R⁴ and R^{4'} is independently hydrogen, alkyl, alkoxy, -SO₂-N(R^{6a})_t, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or hydroxyalkyl, wherein the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

or R⁴ and R^{4'}, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S;

alternatively, when one R² is adjacent to R³, the R² and R³, together with the atoms that they are attached to, form a ring optionally substituted with one or more R^{4a};

R^5 is amino, alkylamino, C_{1-12} haloalkyl, $-C_{0-12}$ alkylene-OR^{6a}, $-C_{0-12}$ alkylene-N(R^{6a})_t, $-C_{0-12}$ alkylene-SR^{6a}, $-C_{0-12}$ alkylene-CN, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{2-12}$ alkenyl, or alkyl optionally substituted with cyano, amido, trialkylammonium, or thiolate; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ,

each R^{6a} is independently chosen from hydrogen, C_{1-12} alkyl, C_{1-12} alkoxy, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{6-12} aryl, and $-C_{0-12}$ alkylene- C_{1-12} heteroaryl; wherein each of the alkyl, C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl, is optionally substituted with one or more R^{4a} ;

R^6 is alkoxy, amino, sulfonamide, carbamide, or alkyl optionally substituted with cyano;

R^7 is hydrogen, alkyl, $-C_{0-12}$ alkylene-COOH, optionally substituted C_{3-12} cycloalkyl, C_{2-12} aryl, C_{1-12} heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, $-C_{0-12}$ alkylene-P(=O)(R⁴)(R^{4'}), $-C_{0-12}$ alkylene-N(R⁴)-C(=S)-R⁵, $-C(=S)-R^5$, or alkyl optionally substituted with cyano;

R^8 is alkoxy, amino, alkylamino, amide, sulfonamide, or carbamide;

n_3 is 0, 1, 2, 3, or 4;

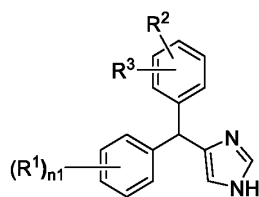
n_4 is 1, 2, 3, 4, 5, or 6;

t is 2 or 3;

m is 0, 1, 2, 3, 4, or 5; and

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

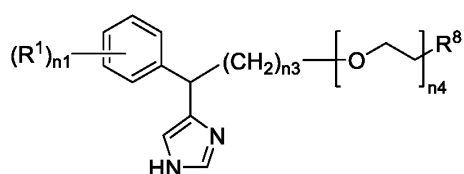
In some embodiments, the compound of formula (II) is a compound of formula (II-A):



(II-A), wherein R^1 , R^2 , R^3 , and n_1 are defined as above in formula

(II).

In some embodiments, the compound of formula (II) is a compound of formula (II-B):

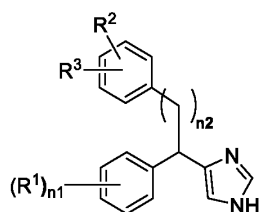


(II-B)

, wherein, R^1 , R^8 , n_1 , n_3 , and n_4 are defined

as above in formula (II).

In some embodiments, the compound of formula (II) is a compound of formula (II-C):



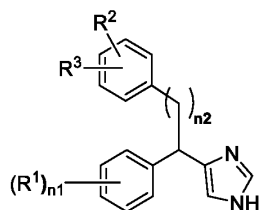
(II-C)

, wherein,

n_2 is 1 or 2; and

R^1 , R^2 , R^3 , and n_1 are defined as above in formula (II).

In some embodiments, the compound of formula (II) is a compound of formula (II-D):



(II-D)

wherein,

n_2 is 0 or 1;

R^3 is chosen from $-C(O)-NHR^4$, $-SO_2-NHR^4$, $-NH-C(O)-R^5$, and $-NH-SO_2-R^5$, and $-NH-R^7$;

R^4 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with trialkylammonium; wherein and each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

R^5 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with

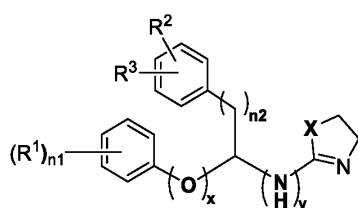
trialkylammonium; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

each R^{6a} is independently chosen from -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, and -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

R⁷ is C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴) (alkoxy), or -C₀₋₁₂ alkylene-N(R⁴)-C(=S)-R⁵; and

R¹, R², R^{4a}, and n1 and are defined as above in formula (II).

In some embodiments, the compound of formula (II) is a compound of formula (II-E):



(II-E), wherein

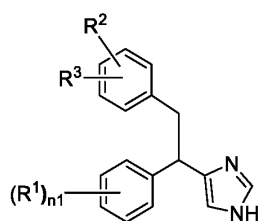
x is 0 or 1;

y is 0 or 1;

X is S, O, or NH; and

R¹, R², R³, n1, and n2 are defined as above in formula (II).

In some embodiments, the compound of formula (II) is a compound of formula (II-F):

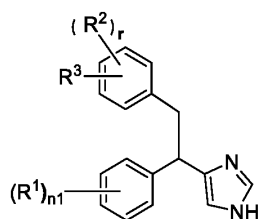


(II-F), wherein,

R² is adjacent to R³, and R² and R³, together with the carbon atoms that they are attached to, form a heterocycle optionally substituted with one or more R^{4a}; and

R¹, R^{4a}, and n1 are defined as above in formula (II).

In some embodiments, the compound of formula (II) is a compound of formula (II-G):



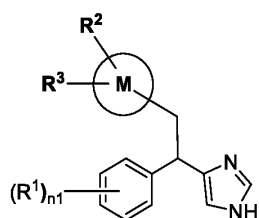
(II-G), wherein,

each R^2 is independently chosen from hydroxyl and alkoxy;

R^3 is chosen from hydroxy and alkoxy; and

R^1 , n_1 and r are defined as above in formula (II).

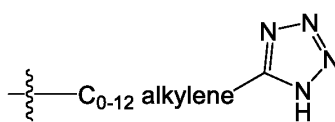
In some embodiments, the compound of formula (II) is a compound of formula (II-H):



(II-H), wherein,

M is C_{6-12} aryl or C_{1-12} heteroaryl;

R^3 is chosen from $-C_{0-12}$ alkylene-COOH, $-O-C_{0-12}$ alkylene-COOH, $-C_{0-12}$ alkylene- $P(O)(OH)_2$, $-C(O)-NH-SO_2-R^5$, $-C(O)-NH-C_{0-12}$ alkylene-COOH, $-NH-C_{0-12}$ alkylene-COOH,

$-SO_2-OH$, and ; wherein the $-C_{0-12}$ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino; and

R^1 , R^2 , and n_1 are defined as above in formula (II).

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure relates to the use of a compound as described herein or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, for treating or preventing a disease, including pain, glaucoma, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc. in a subject in need thereof.

Other features and advantages of the present disclosure are apparent from additional descriptions provided herein, including different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. Such examples do not limit the claimed disclosure. Based on the present disclosure, the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, aspects, features, and advantages of exemplary embodiments will become more apparent and may be better understood by referring to the following description taken in conjunction with the accompanying drawings.

FIGs. 1A-1H: PWT value of sham and SNI mouse model, vehicle and drug treatment groups at 1 hour after dosing.

FIG. 1A: 3 mg/mL pregabalin p.o.;

FIG. 1B: 1 mg/mL morphine s.c.;

FIG. 1C: 1 mg/mL compound 1-B p.o. and 10mg/mL compound 1-B p.o.;

FIG. 1D: 1 mg/mL compound 10-B p.o.;

FIG. 1E: 1 mg/mL compound 44-B p.o. and 1 mg/mL compound 45-B p.o.;

FIG. 1F: 1 mg/mL compound 46-B p.o. and 1 mg/mL compound 47-B p.o.;

FIG. 1G: 2 mg/mL compound 121 p.o. and 2 mg/mL compound 136 p.o.; and

FIG. 1H: 2 mg/mL compound 118 p.o. and 2 mg/mL compound 156 p.o.

FIGs. 2A-2D: PWT value of sham and bone cancer pain mouse model, vehicle and drug treatment groups at 1 hour after dosing.

FIG. 2A: 3 mg/mL pregabalin p.o.;

FIG. 2B: 1 mg/mL morphine s.c.;

FIG. 2C: 1 mg/mL compound 44-B p.o.; and

FIG. 2D: 20 mg/mL compound 1-B p.o. and : 20 mg/mL compound 44-B p.o.

FIGs. 3A-3C: PWT value of sham and post-surgery pain mouse model, vehicle and drug treatment groups at 1 hour after dosing.

FIG. 3A: 10 mg/mL compound 1-B p.o.;

FIG. 3B: 10 mg/mL compound 44-B p.o.; and

FIG. 3C: 3 mg/mL morphine s.c.

FIGs. 4A-4C: Body weight curve (FIG. 4A), tumor volume growth curve (FIG. 4B)), and tumor volume in day 17 (FIG. 4C) of mice in each group in subcutaneous colorectal cancer

syngeneic model MC38, including group 1 (control group, 0mg/kg, p.o., QD*Day0-17), group 2 (clonidine, 5mg/kg, p.o., QD*Day0-3; 2mg/kg, p.o., QD* Day4-17), group 3 (compound 1-B HCl, 5mg/kg, p.o., BID*Day0-17), and group 4 (compound 1-B HCl, 10mg/kg, p.o., BID*Day0-3; 5mg/kg, p.o., QD* Day4-17). Data is expressed as "average $\pm$ standard error".

FIGs. 5A-5B: Total distance travelled in 0-60 min of the test (FIG. 5A) for clonidine and compound 1-B HCl and the test (FIG. 5B) for clonidine, brimonidine tartrate and compound 44-B HCl. Data were expressed as Mean $\pm$ SEM (n=6). ***p<0.001 compared with Vehicle group, one-way ANOVA followed by Dunnutt's multiple comparisons.

FIGs. 6A-6D. Effects of clonidine and compound 44-B HCl compounds on rotarod test in C57BL/6 mice 30 min after administration (FIG. 6A). And its latency time at 30 min (FIG. 6B), 60 min (FIG. 6C), and 120 min (FIG. 6D).

DETAILED DESCRIPTION

Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is for the purpose of providing context for the disclosure. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to the disclosure.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the present disclosure pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification.

As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference (one or more) unless the context clearly dictates otherwise.

Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. For example, the phrase "at least A, B, and C" means that each of A, B, and C is present. The term "at least one of" preceding a series of elements is to be understood to refer to a single element in the series or any combination of two or more elements in the series. For example, the phrase "at least one of A, B, and C" means that only A is present, only B is present, only C is present, both A and B are present, both A and C are present, both B and C are present, or each of A, B, and C is present. Depending on

the context, “at least one of” preceding a series of elements can also encompass situations in which any one or more of the elements is present in greater than one instance, e.g., “at least one of A, B, and C” can also encompass situations in which A is present in duplicate alone or further in combination with any one or more of elements B and C.

As used herein, the conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and conjunctive options. For instance, where two elements are conjoined by “and/or,” a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to, conjunctively, the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or” as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or.”

Unless otherwise stated, any numerical value, such as a concentration or a concentration range described herein, are to be understood as being modified in all instances by the term “about.” Thus, a numerical value typically includes $\pm 10\%$ of the recited value. For example, the recitation of “10-fold” includes 9-fold and 11-fold. As used herein, the use of a numerical range expressly includes all possible permutations and combinations of subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

As used herein, “subject” means any animal, such as a mammal, particularly a human, to whom will be or has been treated by a method described herein. The term “mammal” as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, and non-human primates (NHPs), such as monkeys or apes, humans, etc.

The phrase “pharmaceutically acceptable salt(s)” means those salts of a compound of interest that are safe and effective for topical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in the specified compounds. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, carbonate, bicarbonate, acetate, lactate, salicylate, citrate, tartrate, propionate, butyrate, pyruvate, oxalate, malonate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate,

formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds used in the present disclosure can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, bismuth, and diethanolamine salts. For a review on pharmaceutically acceptable salts see Berge et al., 66 J. Pharm. Sci. 1-19 (1977), incorporated herein by reference.

As used herein, the term “alkyl” means a saturated, monovalent, unbranched or branched hydrocarbon chain. An alkyl group can be unsubstituted or substituted with one or more suitable substituents. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (e.g., n-propyl, isopropyl), butyl (e.g., n-butyl, isobutyl, tert-butyl), and pentyl (e.g., n-pentyl, isopentyl, neopentyl), etc. An alkyl group can have a specified number of carbon atoms. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular alkyl can contain. For example, “C₁ to C₁₀ alkyl” or “C₁₋₁₀ alkyl” is intended to include alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ alkyl” or “C₁₋₈ alkyl” denotes an alkyl having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

As used herein, the term “alkenyl” refers to an unbranched or branched hydrocarbon chain containing at least one carbon-carbon double bond. An alkenyl group can be unsubstituted or substituted with one or more suitable substituents. Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl). When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular alkenyl can contain. For example, “C₂ to C₁₀ alkenyl” or “C₂₋₁₀ alkenyl” is intended to include alkenyl groups having 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₂ to C₈ alkenyl” or “C₂₋₈ alkenyl” denotes an alkenyl having 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

As used herein, the term “alkynyl” refers to an unbranched or branched hydrocarbon chain containing at least one carbon-carbon triple bond. An alkynyl group can be unsubstituted or substituted with one or more suitable substituents. The term “alkynyl” also includes those groups having one triple bond and one double bond. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular alkynyl can contain. For example, “C₂ to C₁₀ alkynyl” or “C₂₋₁₀ alkynyl” is intended to include alkynyl groups having 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms.

Additionally, for example, “C₂ to C₈ alkynyl” or “C₂₋₈ alkynyl” denotes an alkynyl having 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

As used herein, the term “cycloalkyl” refers to any stable monocyclic or polycyclic saturated hydrocarbon ring system. A cycloalkyl group can be unsubstituted or substituted with one or more suitable substituents. A cycloalkyl group can have a specified number of carbon atoms. For example, “C₃ to C₆ cycloalkyl” or “C₃₋₆ cycloalkyl” includes cycloalkyl groups having 3, 4, 5, or 6 ring carbon atoms, i.e., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Polycyclic cycloalkyls include bridged, fused, and spiro ring structures in which all ring atoms are carbon atoms. A “spiro ring” is a polycyclic ring system in which two rings share one carbon atom, referred to as the “spiro atom,” which is typically a quaternary carbon atom. A “fused ring” is a polycyclic ring system in which two rings share two adjacent atoms, referred to as “bridgehead atoms,” i.e., the two rings share one covalent bond such that the bridgehead atoms are directly connected. A “bridged ring” is a polycyclic ring system in which two rings share three or more atoms separating the bridgehead atoms by a bridge containing at least one atom. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, phenyl, naphthyl, anthracenyl, phenanthryl, and the like. Aryl moieties are well known and described, for example, in Lewis, R. J., ed., *Hawley’s Condensed Chemical Dictionary*, 13th Edition, John Wiley & Sons, Inc., New York (1997). An aryl group can be substituted or unsubstituted with one or more suitable substituents. An aryl group can comprise a single ring structure (i.e., monocyclic) or multiple ring structures (i.e., polycyclic, e.g., bicyclic or tricyclic). For example, an aryl group can be a monocyclic aryl group, e.g., phenyl.

The term “heterocyclyl” includes stable monocyclic and polycyclic hydrocarbons that contain at least one heteroatom ring member, such as sulfur, oxygen, or nitrogen, wherein the ring structure is saturated or partially unsaturated, provided the ring system is not fully aromatic. A heterocyclyl group can be unsubstituted, or substituted with one or more suitable substituents at any one or more of the carbon atom(s) and/or nitrogen heteroatom(s) of the heterocyclyl. A heterocyclyl can comprise a single ring structure (i.e., monocyclic) or multiple ring structures (i.e., polycyclic, e.g., bicyclic). Polycyclic heterocyclyls include bridged, fused, and spiro ring structures in which at least one ring atom of at least one of the rings of the polycyclic ring system is a heteroatom, for instance oxygen, nitrogen, or sulfur, wherein

bridged, fused, and spiro rings are as defined above. A heterocyclyl ring can be attached to the parent molecule at any suitable heteroatom (typically nitrogen) or carbon atom of the ring. The term “4- to 9-membered monocyclic or bicyclic heterocyclyl” includes any four, five, six, seven, eight, or nine membered monocyclic or bicyclic ring structure containing at least one heteroatom ring member selected from oxygen, nitrogen, and sulfur, or independently selected from oxygen and nitrogen, optionally containing one to three additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, or independently selected from oxygen and nitrogen, wherein the ring structure is saturated or partially unsaturated, provided the ring structure is not fully aromatic.

In certain embodiments, the term “heterocyclyl” refers to 4-, 5-, 6-, or 7-membered monocyclic groups and 6-, 7-, 8-, or 9- membered bicyclic groups which have at least one heteroatom (O, S, or N) in at least one of the rings, wherein the heteroatom-containing ring(s) typically has 1, 2, or 3 heteroatoms, such as 1 or 2 heteroatoms, independently selected from O, S, and/or N, or independently selected from O and N. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular heterocycl can contain, in addition to the heteroatoms which that particular heterocycl can contain. For example, “C₁ to C₁₀ heterocycl” or “C₁₋₁₀ heterocycl” is intended to include heterocycl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ heterocycl” or “C₁₋₈ heterocycl” denotes a heterocycl having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

Examples of monocyclic heterocyclyl groups include, but are not limited to azetidiny, oxetany, tetrahydrofurany, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolany, dithiolany, piperidinyl, piperazinyl, dioxany, morpholinyl, azepany, oxepany, oxazepany (e.g., 1,4-oxazepany, 1,2-oxazepany) and the like. Examples of bicyclic heterocyclyl groups include, but are not limited to, 2-azabicyclo[2.2.1]heptany, 8-aza-bicyclo[3.2.1]octany, 2-aza-spiro[3.3]heptany, 3-azabicyclo[2.2.2]octany, 3-oxa-9-azabicyclo[3.3.1]nonany, 2-oxa-5-azabicyclo[2.2.1]heptany, 7-oxa-2-azaspiro[3.5]nonany, and 5-azaspiro[2.3]hexany and the like.

As used herein, the term “heteroaryl” includes stable monocyclic and polycyclic aromatic hydrocarbons that contain at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. A heteroaryl group can be unsubstituted or substituted with one or more suitable substituents. A heteroaryl can comprise a single ring structure (i.e., monocyclic) or

multiple ring structures (i.e., polycyclic, e.g., bicyclic or tricyclic). Each ring of a heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. Heteroaryl groups which are polycyclic, e.g., bicyclic or tricyclic must include at least one fully aromatic ring, but the other fused ring or rings can be aromatic or non-aromatic. For example, for a bicyclic heteroaryl, the fused rings completing the bicyclic group can contain only carbon atoms and can be saturated, partially saturated, or unsaturated. A heteroaryl can be attached to the parent molecule at any available nitrogen or carbon atom of any ring of the heteroaryl group. In some embodiments, the term “heteroaryl” refers to 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups which have at least one heteroatom (O, S, or N) in at least one of the rings, wherein the heteroatom-containing ring typically has 1, 2, or 3 heteroatoms, such as 1 or 2 heteroatoms, selected from O, S, and/or N. A heteroaryl group can be unsubstituted, or substituted with one or more suitable substituents at any one or more of the carbon atom(s) and/or nitrogen heteroatom(s) of the heteroaryl. The nitrogen and sulfur heteroatom(s) of a heteroaryl can optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_r$, wherein r is 0, 1 or 2).

When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular heteroaryl can contain, in addition to the heteroatoms which that particular heteraryl can contain. For example, “C₁ to C₁₀ heteroaryl” or “C₁₋₁₀ heteroaryl” is intended to include heteroaryl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ heteroaryl” or “C₁₋₈ heteroaryl” denotes a heteroaryl having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

Exemplary monocyclic heteroaryl groups include, but are not limited to, pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thiophenyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl. Exemplary bicyclic heteroaryl groups include, but are not limited to, indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridinyl, furopyridinyl, dihydroisoindolyl, and tetrahydroquinolinyl.

The term “alkoxy” as used herein refers to an –O-alkyl group, wherein alkyl is as defined above. An alkoxy group is attached to the parent molecule through a bond to an oxygen atom. An alkoxy group can have a specified number of carbon atoms. For example, “C₁ to C₁₀

alkoxy” or “C₁₋₁₀ alkoxy” is intended to include alkoxy groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₄ alkoxy” or “C₁₋₄ alkoxy” denotes an alkoxy having 1, 2, 3, or 4 carbon atoms. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy (e.g., n-propoxy, isopropoxy), butoxy (e.g., n-butoxy, isobutoxy, tert-butoxy), pentyloxy (e.g., n-pentyloxy, isopentyloxy, neopentyloxy), etc. An alkoxy group can be unsubstituted or substituted with one or more suitable substituents. Similarly, “alkylthio” or “thioalkoxy” represents an alkyl group as defined above attached to the parent molecule through a bond to a sulfur atom, for example, -S-methyl, -S-ethyl, etc. Representative examples of alkylthio include, but are not limited to, -SCH₃, -SCH₂CH₃, etc.

As used herein, the term “halogen” means fluorine, chlorine, bromine, or iodine. Correspondingly, the term “halo” means fluoro, chloro, bromo, and iodo.

“Haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon radicals substituted with one or more halogen atoms. “Fluorinated alkyl” or “fluoroalkyl” in particular refers to any alkyl group as defined above substituted with at least one fluoro atom, e.g., one to three fluoro atoms, such as one, two, or three fluoroatoms. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Suitable examples of fluoroalkyl in particular include, but are not limited to, -CF₃, -CHF₂, -CH₂CF₃, -CF₂CF₃, and the like.

The terms “hydroxy” and “hydroxyl” can be used interchangeably, and refer to -OH.

The term “carboxy” and “carboxyl” can be used interchangeably, and refers to -COOH.

The term “ester” refers to -COOR, wherein R is alkyl as defined above.

The term “cyano” refers to -CN.

The term “oxo” refers to a double bonded oxygen group, i.e., a substituent group of the formula =O.

The term “keto” refers to -C(O)R, wherein R is alkyl as defined above.

As used herein, the term “amino” refers to -NH₂. One or more hydrogen atoms of an amino group can be replaced by a substituent such as an alkyl group, which is referred to as an “alkylamino.” Alkylamino groups have one or both hydrogen atoms of an amino group replaced with an alkyl group and is attached to the parent molecule through a bond to the nitrogen atom of the alkylamino group. For example, alkylamino includes methylamino (-NHCH₃), dimethylamino (-N(CH₃)₂), -NHCH₂CH₃ and the like.

The term “aminoalkyl” as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more amino groups. For example, “C₁₋₄ aminoalkyl” is intended to include alkyl groups having 1, 2, 3, or 4 carbon atoms substituted with one or more amino groups. Aminoalkyl groups are attached to the parent molecule through a bond to a carbon atom of the alkyl moiety of the aminoalkyl group. Representative examples of aminoalkyl groups include, but are not limited to, -CH₂NH₂, -CH₂CH₂NH₂, and -CH₂CH(NH₂)CH₃.

As used herein, “amido” refers to -C(O)N(R)₂, wherein each R is independently an alkyl group (including both branched and straight-chain alkyl groups) or a hydrogen atom. Examples of amido groups include, but are not limited to, -C(O)NH₂, -C(O)NHCH₃, and -C(O)N(CH₃)₂.

The terms “hydroxyl-substituted alkyl,” “hydroxylalkyl” and “hydroxyalkyl” are used interchangeably, and refer to a branched or straight-chain aliphatic hydrocarbon group substituted with one or more hydroxyl groups. Hydroxyalkyl groups are attached to the parent molecule through a bond to a carbon atom of the alkyl moiety of the hydroxyalkyl group. A hydroxyalkyl group can have a specified number of carbon atoms. For example, “C₁ to C₁₀ hydroxyalkyl” or “C₁₋₁₀ hydroxyalkyl” is intended to include hydroxyalkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₄ hydroxylalkyl” or “C₁₋₄ hydroxyalkyl” denotes a hydroxyalkyl group having 1, 2, 3, or 4 carbon atoms. Examples of hydroxyalkyl include, but are not limited to, hydroxymethyl (-CH₂OH), hydroxyethyl (-CH₂CH₂OH), etc.

As used herein, “amide” refers to -N(R')C(O)R, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl. Examples of amide groups include, but are not limited to, -NHC(O)CH₃, -NHC(O)CH₂CH₃, and -N(CH₃)C(O)CH₃.

As used herein, “carbamide” refers to -N(R')C(O)N(R)₂, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl. Examples of carbamide groups include, but are not limited to, -NHC(O)NH₂, -NHC(O)NHCH₃ (methyl carbamide), and -NHC(O)NH(Ph).

As used herein, “sulfonamide” refers to -N(R')SO₂-R, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl. Examples of sulfonamide groups include, but are not limited to, -NHSO₂CH₃ (methyl sulfonamide), and -NH SO₂Ph.

In accordance with convention used in the art:



is used in structural formulas herein to depict the bond that is the point of attachment of a group, moiety or substituent to the core, backbone, or parent molecule structure.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom on the ring.

The term “substituted” as used herein with respect to any organic radical (e.g., alkyl, cycloalkyl, heteroaryl, aryl, heterocyclyl, etc.) means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that all normal valencies are maintained and that the substitution results in a stable compound. When a particular group is “substituted,” that group can have one or more substituents, such as from one to five substituents, one to three substituents, or one to two substituents, independently selected from the list of substituents. The term “independently” when used in reference to substituents, means that when more than one of such substituents is possible, such substituents can be the same or different from each other. Examples of suitable substituents include, but are not limited to, alkyl, halo, haloalkyl, alkoxy, amido, hydroxy, hydroxyalkyl, amino, carboxyl, ester, oxo, cyano and the like.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group can be optionally substituted with up to three R groups, and at each occurrence, R is selected independently from the definition of R.

The terms “optional” or “optionally” mean that the event or circumstance described can, but need not, occur, and such a description includes the situation in which the event or circumstance does or does not occur. For example, “optionally substituted heterocyclyl” means that a substituent group can be, but need not be, present, and such a description includes the situation of the heterocyclyl group being substituted by a suitable substituent and the heterocyclyl group not being substituted by any substituent.

One skilled in the art will recognize that in certain embodiments compounds described herein can have one or more asymmetric carbon atoms in their structure. As used herein, any chemical formulas with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g., R or S) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more

stereoisomers. Stereoisomers includes enantiomers and diastereomers. Enantiomers are stereoisomers that are non-super-imposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e., they are not related as mirror images, and occur when two or more stereoisomers of a compound have different configurations at one or more of the equivalent stereocenters and are not mirror images of each other. Substituent groups (e.g., alkyl, heterocyclyl, etc.) can contain stereocenters in either the R or S configuration.

Certain examples contain chemical structures that comprise (R) or (S) terminology. When (R) or (S) is used in the name of a compound or in the chemical representation of the compound, it is intended to mean that the compound is a single isomer at that stereocenter, with established absolute configuration of either (R) or (S).

Stereochemically pure isomeric forms can be obtained by techniques known in the art in view of the present disclosure. For example, diastereoisomers can be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers can be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers can also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereoselective reactions.

Compounds described herein can also form tautomers. The term “tautomer” refers to compounds that are interchangeable forms of a particular compound structure and that vary in the displacement of hydrogen atoms and electrons. Tautomers are constitutional isomers of chemical compounds that readily interconvert, usually resulting in relocation of a proton (hydrogen). Thus, two structures can be in equilibrium through the movement of pi electrons and an atom (usually hydrogen). All tautomeric forms and mixtures of tautomers of the compounds described herein are included with the scope of the present disclosure.

Compounds described herein can exist in solvated and unsolvated forms. The term “solvate” means a physical association, e.g., by hydrogen bonding, of a compound described herein with one or more solvent molecules. The solvent molecules in the solvate can be present in a regular arrangement and/or a non-ordered arrangement. The solvate can comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. “Solvate” encompasses both solution-phase and isolable solvates. Compounds described herein can form solvates with water (i.e., hydrates) or common organic solvents. Exemplary solvates include, but are not

limited to, hydrates, ethanlates, methanlates, and isopropanolates. Methods of solvation are generally known in the art.

Also included within the scope of the present disclosure are all isotopes of atoms occurring in the compounds described herein, including intermediates and final products. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C .

The present disclosure further includes isotopically-labeled compounds. An “isotopically-labeled” or “radio-labeled” compound is a compound of the present disclosure where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

As used herein, the name of a compound is intended to encompass all possible existing isomeric forms, including stereoisomers (e.g., enantiomers, diastereomers, racemate or racemic mixture, and any mixture thereof) of the compound.

In one general aspect, the present disclosure relates to methods of treating or preventing a disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective $\alpha 2\text{AR}$ agonist.

In some embodiments, the peripherally selective $\alpha 2\text{AR}$ agonist activates at least one sub type of $\alpha 2\text{AR}$, particularly $\alpha 2\text{A AR}$, $\alpha 2\text{B AR}$, or $\alpha 2\text{C AR}$.

In some embodiments, the disease is glaucoma, pain, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc.

In certain embodiments, the disease is chosen from pain, rosacea, spasticity, and aging.

In some embodiments, treating with the peripherally selective $\alpha 2\text{AR}$ agonist causes less sedation than treating with a non-peripherally selective $\alpha 2\text{AR}$ agonist, such as at similar or comparable dosage.

In some embodiments, the peripherally selective $\alpha 2\text{AR}$ agonist comprises an $\alpha 2\text{AR}$ activation moiety covalently linked to a peripheral distribution moiety.

In another general aspect, the present disclosure provides a peripherally selective $\alpha 2$ AR agonist that comprises an $\alpha 2$ AR activation moiety covalently linked to a peripheral distribution moiety, and its uses in the treatment or prevention of a disease.

In some embodiments, the disease is glaucoma, pain, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc.

In certain embodiments, the disease is pain.

Pain, as a complex and multidimensional sensory and emotional experience, poses a significant challenge to human health. It is not only an important symptom of physical diseases but also a key factor affecting the quality of life, causing great physical and mental distress to patients. Crucial components of pain are neuropathic pain and nociceptive pain. Neuropathic pain are caused by a lesion or disease of the somatosensory nervous system. Neuropathic pain can be divided into central neuropathic pain and peripheral neuropathic pain. Central neuropathic pain includes spinal cord injury, post-stroke pain, and MS pain, while peripheral neuropathic pain includes diabetic neuropathy, postherpetic neuralgia, HIV-associated pain, chemotherapy-induced peripheral neuropathy, and post-surgical neuropathic pain. Currently, first-line treatment drugs include Gabapentinoids, tricyclic antidepressants, and noradrenaline/serotonin uptake inhibitors. Although these drugs can relieve pain to some extent, the side effects of long-term use still cause a decrease in the quality of life of patients. Second-line treatment drugs, such as opiate receptor agonist, not only have side effects but also have a high addiction rate, which has caused many social impacts and cannot well address the demand for neuropathic pain drugs.

$\alpha 2$ AR agonists, such as clonidine and dexmedetomidine, are considered an important method for treating pain in academic research and clinical applications. Scientists have found that the intraspinal administration of $\alpha 2$ AR agonists can effectively relieve pain. However, the therapeutic benefits of $\alpha 2$ AR agonists are not without limitations. Existing $\alpha 2$ AR agonists are often associated with a range of biological reactions, including sedation, hypotension, bradycardia, drowsiness, dizziness, depression, bradycardia, orthostatic hypotension, constipation, nausea, gastric upset, dry mouth (xerostomia), dry nasal mucosa, impotence, fluid retention, edema, and pupil size. These other biological effects, especially sedation, set limits on the dosages that can be safely administered, thereby constraining the wide-scale utility of these drugs in long-term pain management. This not only affects the quality of life for patients but also restricts the applicability of these drugs for various types and levels of

pain symptoms. These biological effects, especially sedation, seriously impact the application of $\alpha 2$ AR agonists in the field of medical application.

Thus, there is a need to develop novel $\alpha 2$ AR agonist compounds for treating pain with reduced sedation. Our work seeks to make significant contributions to the field of pain management by offering not just more effective but also safer long-term non-opioid alternatives. The compounds and methods described herein can be useful for addressing such unmet need.

As used herein, “an effective amount” means an amount of a composition or compound that elicits a biological or medicinal response in a tissue system or subject that is being sought by a researcher, veterinarian, medical doctor or other professional, which can include alleviation of the symptoms of the disease, disorder, or condition being treated. An effective amount can vary depending upon a variety of factors, such as the physical condition of the subject, age, weight, health, etc.; and the particular disease, disorder, or condition to be treated. An effective amount can readily be determined by one of ordinary skill in the art in view of the present disclosure.

According to particular embodiments, an effective amount refers to the amount of a composition or compound described herein which is sufficient to activate $\alpha 2$ AR. In another particular embodiment, an effective amount refers to the amount of a composition or compound described herein which is sufficient to treat or prevent the disease or alleviate the symptoms associated with the disease.

In some embodiments, the pain is nociceptive pain, neuropathic pain such as peripheral neuropathic pain, or mixed pain.

In some embodiments, the neuropathic pain is cancer-associated pain, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, peripheral neuropathy, immune-mediated neuropathies, HIV-associated pain, post-stroke pain syndrome, phantom limb pain, chemotherapy-induced peripheral neuropathy, complex regional pain syndrome, and metabolic, endocrine, toxic neuropathies, chronic postsurgical pain, traumatic peripheral nerve injury, entrapment syndrome, heritable neuropathy, etc.

In some embodiments, the pain is post-surgery pain.

In some embodiments, the peripherally selective $\alpha 2$ AR agonist comprises an $\alpha 2$ AR activation moiety covalently linked to a peripheral distribution moiety.

In another general aspect, the present disclosure relates to methods of treating or preventing a disease in a subject in need thereof, the method comprising administering to the

subject a therapeutically effective amount of a peripherally selective $\alpha 2AR$ agonist, wherein the peripherally selective $\alpha 2AR$ agonist comprises an $\alpha 2AR$ activation moiety covalently linked to a peripheral distribution moiety.

In some embodiments, the disease is glaucoma, pain, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc.

In some embodiments, the disease is glaucoma or cancer.

In some embodiments, the disease is pain.

In some embodiments, the pain is nociceptive pain, neuropathic pain such as peripheral neuropathic pain, or mixed pain.

In some embodiments, the neuropathic pain is cancer-associated pain, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, peripheral neuropathy, immune-mediated neuropathies, HIV-associated pain, post-stroke pain syndrome, phantom limb pain, chemotherapy-induced peripheral neuropathy, complex regional pain syndrome, and metabolic, endocrine, toxic neuropathies, chronic postsurgical pain, traumatic peripheral nerve injury, entrapment syndrome, heritable neuropathy, etc.

In some embodiments, the pain is post-surgery pain.

In some embodiments, treating with the peripherally selective $\alpha 2AR$ agonist causes less side effects than treating with a non-peripherally selective $\alpha 2AR$ agonist, such as at similar or comparable dosage.

In some embodiments, treating with the peripherally selective $\alpha 2AR$ agonist causes no side effects.

The following embodiments apply to all general aspects described above.

In some embodiments, the side effect is sedation, decreasing heart rate, and decreasing blood pressure, particularly the side effect is sedation.

As used herein, the term “a non-peripherally selective $\alpha 2AR$ agonist” refers to a compound can be readily distributed into the CNS after being administered into a subject, binds to and activates $\alpha 2AR$ receptor in both the central nervous system (brain and spinal cord) and the peripheral nervous system. Examples of non-peripherally selective $\alpha 2AR$ agonists include, but not limited to, dexmedetomidine, and clonidine.

Without binding to the theory, if an $\alpha 2AR$ agonist binds to and activates $\alpha 2AR$ in the central nervous system, it can produce the above mentioned side effects in patients, such as sedation, decreased heart rate, blood pressure, depression, bradycardia, orthostatic

hypotension, constipation, nausea, gastric upset, dry mouth (xerostomia), dry nasal mucosa, impotence, fluid retention, edema, and pupil size.

As used herein, the term “a peripherally selective α 2AR agonist” refers to a compound that primarily exerts its effects outside of the central nervous system (CNS), typically because it is impeded by the blood-CNS barrier. Blood-CNS barrier, the physical barrier between blood and the CNS, safeguards the CNS from both toxic and pathogenic agents in the blood. The blood-CNS barrier comprises the blood-brain barrier, the blood-spinal cord barrier, and the blood-CSF (cerebrospinal fluid) barrier. By being largely impeded from entering the CNS, a compound may act on the rest of the body with less or no side-effects related to their effects on the brain or spinal cord. Examples of peripherally selective α 2AR agonists include, but not limited to, the compounds described herein, such as compounds of formula (I-A), (I-B), (I-C), (I-D), or (II), described herein.

The peripherally selective α 2AR agonist primarily binds to or activates α 2AR outside CNS, thus hereby producing less or no foregoing side effects, compared to the non-peripherally selective α 2AR agonists. The present invention satisfies an unmet need, and has developed a series of peripherally selective α 2AR agonists.

In some embodiments, the peripherally selective α 2AR agonist binds to α 2AR with a K_i ranging from 250nM to 1000nM, 50nM to 250nM, 10nM to 50nM, or less than 10nM. In some other embodiments, the peripherally selective α 2AR agonist activates α 2AR with an EC_{50} ranging from 250nM to 1000nM, 50nM to 250nM, 10nM to 50nM, or less than 10nM.

The non-peripherally selective α 2AR agonist and the peripherally selective α 2AR agonist can be differentiated in terms of blood-brain barrier (BBB) permeability. Drugs that specifically target the central nervous system (CNS) must first traverse the BBB. In contrast, peripherally selective drugs primarily exert their effects outside of CNS, largely because they are impeded by the blood-brain barrier (BBB). The blood-brain barrier (BBB) substantially limits the entry of these drugs into the central nervous system (CNS), leading to a predominance of the drug concentration outside the CNS compared to inside. Any methods known in the field can be used to measure a compound's BBB permeability. For example, one experimental measure of BBB permeability is K_p , which is the concentration of drug in the brain divided by concentration in the blood.

As used herein, “ K_p ”, or “B/P ratio”, refers to the ratio of the concentration of a compound in the brain and in the blood. K_p is often calculated as “logBB”, which refers to the logarithmic ratio of the concentration of a compound in the brain and in the blood. K_p is a

common numeric value for describing permeability across the blood-brain barrier. In some embodiments, a compound is considered “peripherally selective” if, upon administration to a subject, its K_p is lower than 0.4, 0.2, 0.1, 0.05, 0.02, or 0.01.

$K_{p,uu,brain}$ is another common numeric value for describing permeability across the blood-brain barrier. As used herein, “ $K_{p,uu,brain}$ ” or “ $K_{p,uu}$ ”, refers to the unbound brain-to-plasma partition coefficient. It represents the ability of a drug to cross the blood-brain barrier (BBB) after systemic administration. $K_{p,uu}$ provides a more accurate measure of distribution equilibrium between unbound fractions in brain and plasma.

Any methods known in the field can be used to measure $K_{p,uu,brain}$. One example of Area Under the Curve (AUC) method, which calculates the AUC of the unbound drug concentration-time profile in both brain and plasma after a single dose. Another example is Steady-State Concentrations, which uses the steady-state unbound concentrations of the drug in brain interstitial fluid ($C_{u,brain,ss}$) and in plasma ($C_{u,plasma,ss}$).

In some embodiments, a compound is considered “peripherally selective” if, upon administration to a subject, its $K_{p,uu,brain}$ is lower than 0.4, 0.2, 0.1, 0.05, 0.02, or 0.01. In some further embodiments, a compound is considered “peripherally selective” if, upon administration to a subject, its $K_{p,uu,brain}$ is lower than 0.05, 0.02, or 0.01.

In some embodiments, the peripherally selective $\alpha 2AR$ agonist comprises an $\alpha 2AR$ activation moiety that is covalently linked to a peripheral distribution moiety.

In certain embodiments, the $\alpha 2AR$ activation moiety is a non-peripherally selective $\alpha 2AR$ agonist or another peripherally selective $\alpha 2AR$ agonist.

In certain embodiments, the $\alpha 2AR$ activation moiety is an $\alpha 2AR$ agonist that is chosen from (R)-3-nitrobiphenylene, A-193080, ADX-415, AGN 192836, AGN-191103, AGN-197075, AGN-201781, AGN-241622, amitraz, Apraclonidine, AR-08, Bethanidine, Brimonidine, BRL-48962, Bromocriptine, Cirazoline, Clonidine, Detomidine, Detomidine carboxylic acid, Dexmedetomidine, Dipivefrin, DL-Methylephedrine, Droxidopa, Epinephrine, ergotamine, etilefrine, Etomidate, Fadolmidine, Guanabenz, Guanethidine, Guanfacine, Guanoxabenz, indanidine, Lofexidine, Medetomidine, mephentermine, Metamfetamine, metaraminol, methoxamine, Methyldopa, Methyldopate, Methyldopate hydrochloride, Methylnorepinephrine, mivazerol, Moxonidine, naphazoline, Norepinephrine, norfenefrine, octopamine, ODM-105, Oxymetazoline, Pergolide, phenylpropanolamine, Povafondine, propylhexedrine, Pseudoephedrine, Racepinephrine, rezatomidine, rilmenidine, romifidine,

syneprhine, talipexole, tasipimidine, Tiamenidine, Tizanidine, Xylazine, Xylometazoline, and a functional derivative thereof.

As used herein, the functional derivative of an α 2AR agonist refers to any compound that is derived from the α 2AR agonist by a chemical reaction. Examples of the derivatives include, but not limited to, acid or base salts, prodrugs, compounds containing protected functional groups such as hydroxyl, amino, carboxyl and carbonyl groups.

In certain embodiments, the α 2AR activation moiety is a non-peripherally selective α 2AR agonist, such as dexmedetomidine, brimonidine, and clonidine.

In certain embodiments, the α 2AR activation moiety is dexmedetomidine.

As used herein, the term “a peripheral distribution moiety” refers to a moiety that can increase or improve the peripheral selectivity of an α 2AR agonist. In some embodiments, the peripheral selectivity is increased or improved so that the α 2AR agonist is a peripherally selective α 2AR agonist.

According to the embodiments of the present disclosure, the peripheral distribution moiety can be the following chemical fragments:

- type A fragments; those that can increase the overall molecular polarity of the compound or reduce the overall lipophilicity of the compound;
- type B fragments: those that can increase the overall molecular weight or the molecular size of the compound; and
- type C fragments: those that comprises a substrate element of an efflux transporter.

In some embodiments, the peripheral distribution moiety is a type A fragment.

In certain embodiments, the type A fragment increases the total number of intermolecular hydrogen bond (H-bond) within the compound, such as H-bond donors and H-bond acceptors. In a preferred embodiment, the type A fragment is a H-bond donor.

In certain embodiments, the type A fragment increases the overall molecular polarity of the compound. For example, such type A fragments can comprise a polar functional group or a charged group. Examples of the polar functional group include, but not limited to, hydroxyl, amine, amide, sulfonamide, carboxyl, ether, imine, hydroxylamine, ester, aldehyde, ketone, nitro, phosphate, thioether, and sulfone groups. Examples of the charged group include, but not limited to, quaternary ammonium and organic acids such as carboxylic acids and sulfonic acids.

In certain embodiments, the type A fragment reduces the overall lipophilicity of the compound. Examples of such type A fragments include, but not limited to, alkyl or acyl that is added to a function group such as hydroxyl and amino.

In certain embodiments, the type A fragment is not tertiary amine or one that can help form an intramolecular H-bond.

In some embodiments, the peripheral distribution moiety is a type B fragment.

In certain embodiments, the type B fragment is a bulky group, which can increase the overall molecular weight and the molecular size of the compound. Examples of such type B fragments include, but not limited to, long alkyl chains, polyethylene glycol (PEG), large aromatic groups, and extra cyclic or heterocyclic groups.

In some embodiments, the peripheral distribution moiety is a type C fragment.

In certain embodiments, the type C fragment comprises a substrate element of an efflux transporter, wherein the efflux transporter is P-glycoprotein (P-gp) transporter, breast cancer resistance protein (BCRP) transporter, or multidrug resistance protein 2 (MRP2) transporter. As used herein, the term of “a substrate element of an efflux transporter” refers to a fragment that makes the compound to become a substrate of the efflux transporter. In other words, the term of “a substrate element of an efflux transporter” refers to a fragment of a substrate of the efflux transporter.

In certain embodiments, the type C fragment comprises a substrate element of P-gp.

Without binding to the theory, P-gp efflux is a significant limitation to BBB permeation. Any methods known in the filed can be used to determine whether a compound is a P-gp substrate. For example, the efflux ratio obtained from *in vitro* P-gp assay, MDCK-MDR1, can be used to identify the substrate of P-gp. A compound is considered as a P-gp substrate if its efflux ratio is greater than 2, 5, 8, 10, 50, or 100.

Alternatively, there are some rules for determining potential P-gp efflux substrates:

- the total number of N atom and O atom ($N+O$) ≥ 8 ;
- molecular weight (MW) > 400 ; and /or
- acid with $pK_a > 4$.

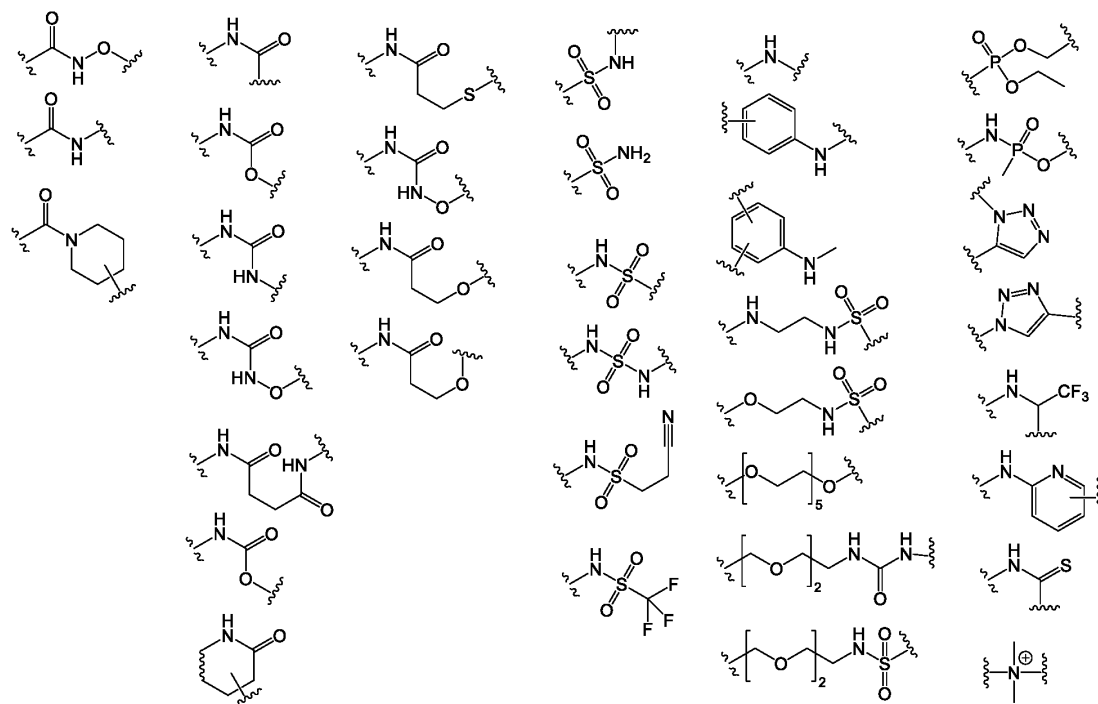
In contrast, if a compound has $N+O < 4$, $MW < 400$, and/or is a base with $pK_a < 8$, then it is a non-substrate of P-gp.

Certain structural modifications can improve P-gp efflux, such as removing steric hindrance to the hydrogen bond donating atoms by attachment of a bulky group or by

unmethylation the nitrogen atom, and improving hydrogen bonding potential by removal of an adjacent electron withdrawing group or by introducing the hydrogen bonding group such as amide.

In certain embodiments, the substrate element for P-gp contains one or more of the structural modifications described above.

In certain embodiments, the substrate element for P-gp is chosen from:



In certain embodiments, the type C fragment comprises a substrate element of BCPR transporter.

In certain embodiments, the type C fragment comprises a substrate element of MPR2 transporter.

In certain embodiments, the type C fragment does not comprise a substrate element of uptake transporter, such as LAT1, GLUT1, MCT1, CAT1, CNT2, OATP, PEPT1, PEPT2, and OCT.

In some embodiments, the peripheral distribution moiety reduces and/or minimizes brain exposure to a peripherally selective α 2AR agonist.

In certain embodiments, the peripheral distribution moiety decreases passive transcellular BBB permeability by increasing topological polar surface area (TPSA), increasing

molecule weight, increasing polarity, or adding hydrogen binding, especially hydrogen bond donor.

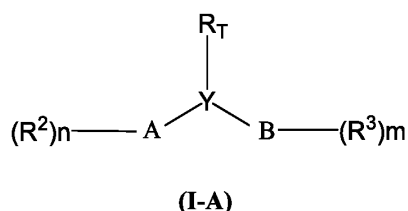
In certain embodiments, the peripheral distribution moiety introduces an acidic group to the peripherally selective $\alpha 2$ AR agonist.

In certain embodiments, the peripheral distribution moiety comprises a substrate element for P-gp, wherein the substrate element for P-gp increases P-gp efflux by increasing lipophilicity, increasing hydrogen bond acceptors, removing steric hindrance around hydrogen bond acceptors, or removing electron-withdrawing group adjacent to hydrogen bond acceptor.

In certain embodiments, the peripheral distribution moiety makes a compound to become a dual substrate for both P-gp and BCRP.

Compounds

In a general aspect, the present disclosure relates to a compound of formula (I-A):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

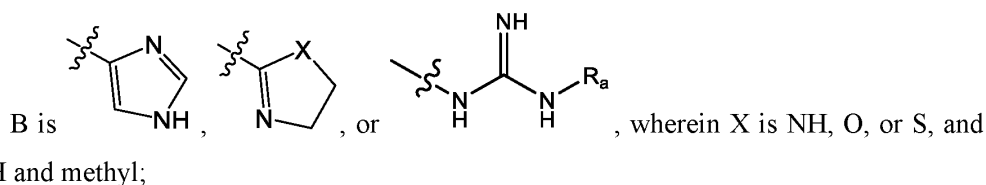
Y is $\text{C}(\text{R}^1)$, N, $-\text{O}-\text{C}$, $-\text{C}-\text{NH}-$, $-\text{CH}_2-\text{C}(\text{O})-$, or $-\text{CH}=\text{N}-$;

when Y is $\text{C}(\text{R}^1)$, R^1 is chosen from H, D, and halogen;

when Y is $-\text{O}-\text{C}-$, the oxygen atom is connected to A, and the carbon atom is connected to both R_T and B; and

when Y is $-\text{C}-\text{NH}-$, the carbon atom is connected to both R_T and A, and the nitrogen atom is connected to B;

A is a ring chosen from phenyl, pyridinyl, thienyl, furyl, pyrrolyl, 4H-pyran, 4H-thiopyran, 1,2,3,4-tetrahydro-1-naphthyl, tetrahydrozoline, quinoxaliny, pyrimidinyl, and 2,1,3-benzothiadiazol;



n is 0, 1, 2, or 3;

each R^2 is independently chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, OR^4 , $-CN$, N_3 , NO_2 , $N(R^4)_2$, OR_4 , SR^4 , $C(O)R^4$, $SO_2N(R^4)_2$, CH_2SR^4 ; wherein the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R^5 ;

R^4 is chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, and the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R^5 ;

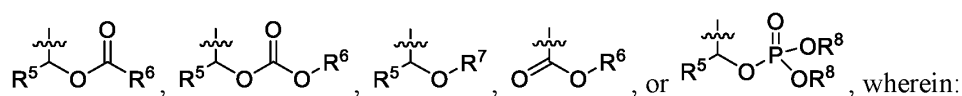
R^5 is chosen from halogen, hydroxyl, $-CN$, $-NO_2$, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

alternatively, when A is a phenyl ring and two R^2 are substituted at adjacent positions of the phenyl ring, the two R^2 groups, with the carbon atoms they are connected to, form a ring that is fused to ring A to form a bicyclic ring, such as quinolinyl, indolyl, benzothienyl, benzofuryl, benzofuranyl, benzodioxolyl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, cinnolinyl, quinoxalinyl, or 1,2,4-benzotriazinyl;

m is 0, 1, 2, or 3;

each R^3 is independently chosen from H, D, halogen, $-OH$, $-SH$, optionally substituted alkyl, optionally substituted heterocycle, and optionally substituted aryl;

alternatively, R^3 is a group connected to the $-NH$ of the imidazole ring, and R^3 is of the formula of:



R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, cycloalkyl, or alkenyl;

R^7 is an amino acid residue; and

R^8 is alkyl or cycloalkyl;

R_T is R_L - R_P , and R_P is optionally substituted with R_C , wherein:

R_L is a linker, wherein one end is connected to R_P and the other end is connected to Y;

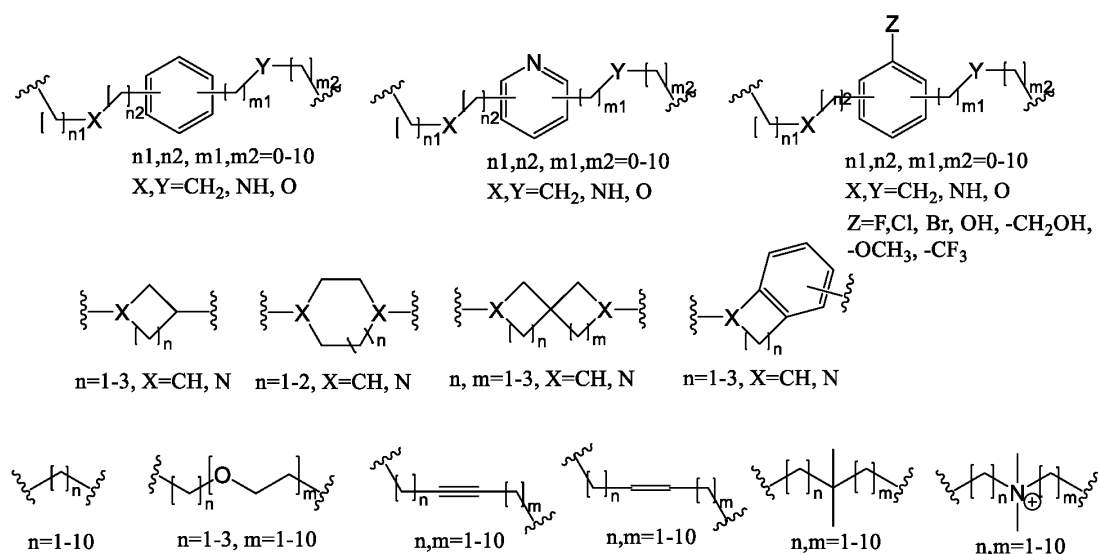
R_P is a moiety that is connected to one end of R_L ; and

R_C is a cap, which is a moiety that is connected to R_P .

As used herein, the term R_L is a moiety that covalently connects two functional groups or moieties within a single molecule. One end of R_L is connected to R_P and the other end of R_L is connected to Y. R_L can be any moiety that serves the linking function, such as the linkers used in proteolysis targeting chimeras (PROTACs) and non-cleavable linkers used in antibody-drug conjugates (ADCs). Examples of R_L include, but are not limited to, polyethylene glycol (PEG) and alkyl chains of varying lengths, glycols, alkynes, triazoles, saturated heterocycles such as piperazine and piperidine, thioethers, maleimidocaproyl linker.

In some embodiments, R_L is chosen from alkyl, polyethylene glycol, other glycol, cycloalkyl, heterocycle, aryl, and heteroaryl; wherein the cycloalkyl, heterocycle, aryl, or heteroaryl is optionally substituted with at least one substituent chosen from halogen, hydroxyl, alkyl, haloalkyl, alkoxy and hydroxyalkyl.

In certain embodiments, R_L is one selected from the followings:

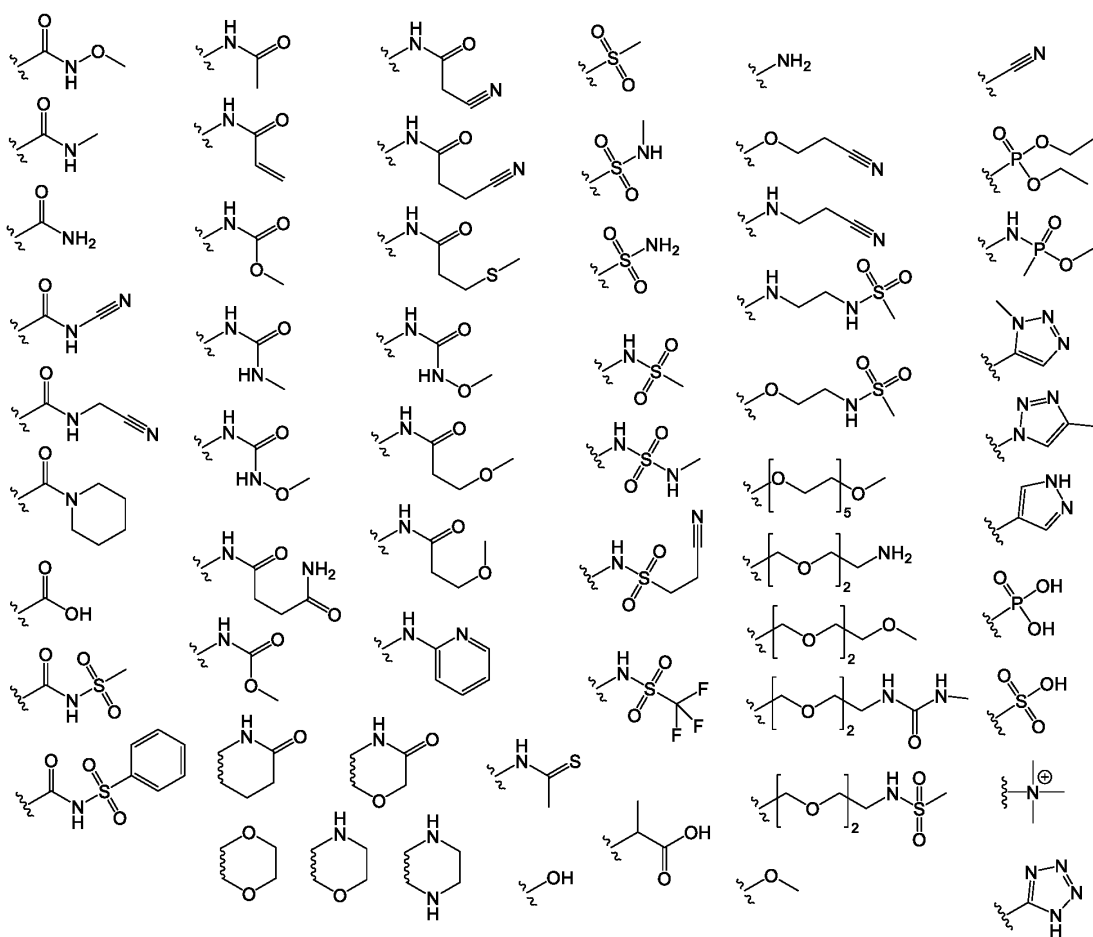


, or a combination of two or more thereof. When R_L is a combination of two or more the above fragments, the fragments can be connected in any order.

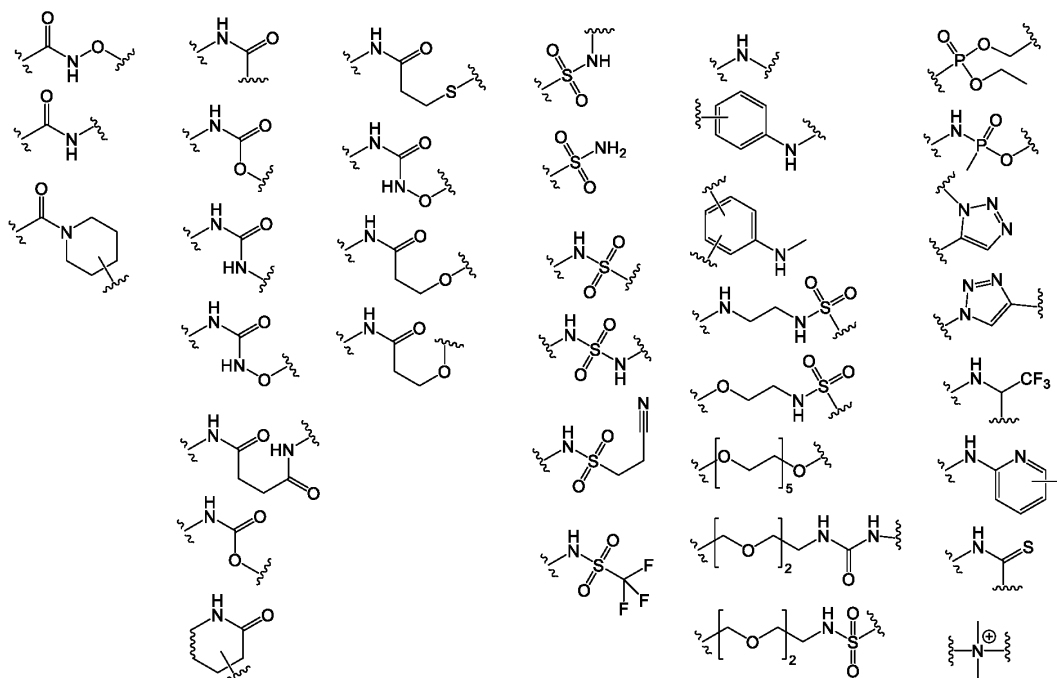
According to the embodiments of the present disclosure, R_P can be the following chemical moieties:

- those that can increase the overall molecular weight of the compound, such as bulky functional groups and additional molecular structures, including long alkyl chains, large aromatic groups, and extra cyclic structures like cyclohexane or cyclopentane rings;
- those that can increase the overall molecular polarity of the compound, such as hydroxyl, amine, amide, sulfonamide, ether, imine, hydroxylamine, ester, aldehyde, ketone, nitro, phosphate, thioether; and
- those that can bring charge to the compound, such as the functional groups that ionize at physiological pH, including carboxylic acid, quaternary ammonium and quaternary phosphonium.

In some embodiments, when R_P is not substituted with R_C , R_P is:



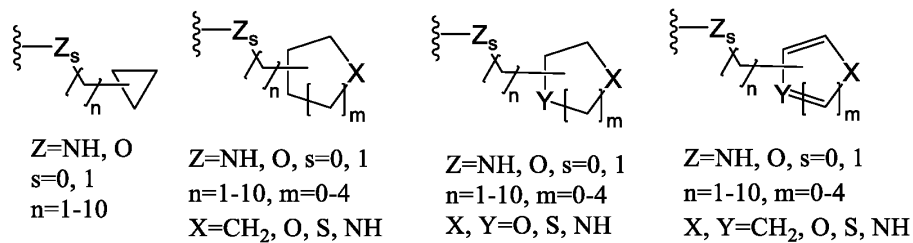
In some embodiments, when R_P is substituted with R_C , R_P is:



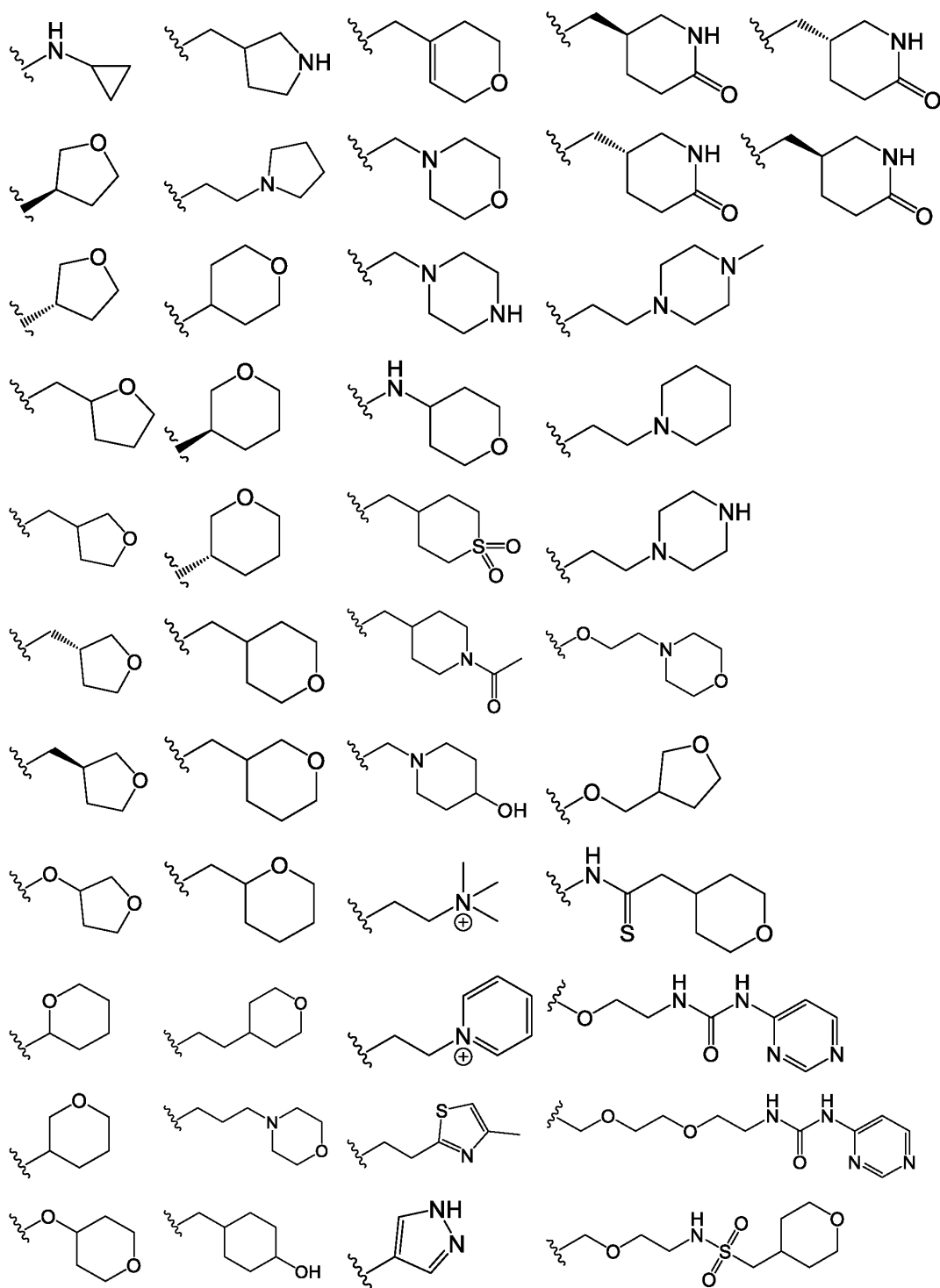
As used herein, the term R_C refers to a chemical moiety covalently attached to the end of R_P .

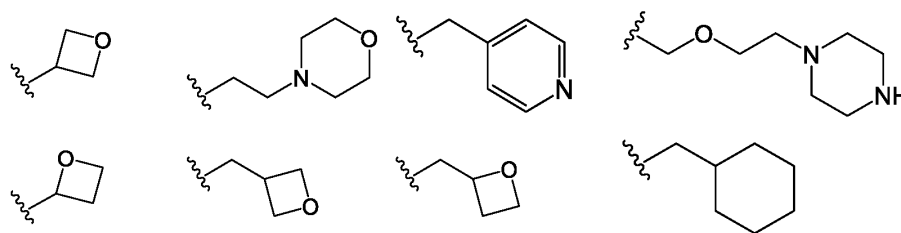
In some embodiments, R_C is chosen from $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-NH-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-NH-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-NH-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-O-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-O-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-O-C_{0-12}$ alkylene- C_{1-12} heteroaryl, and alkyl substituted with trialkylammonium, wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more substituents chosen from hydroxy, alkyl, oxo, and ketone.

In certain embodiments, R_C is:

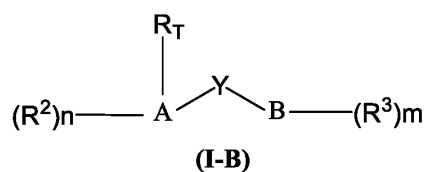


In certain embodiments, R_C is:





In another general aspect, the present disclosure relates to a compound of formula (I-B):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y is a bond, $\text{CH}(\text{R}^1)$, NH , $-\text{O}-\text{CH}-$, $-\text{C}-\text{NH}-$, $-\text{CH}_2-\text{C}(\text{O})-$, or $-\text{CH}=\text{N}-$;

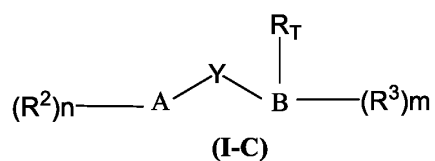
when Y is $\text{C}(\text{R}^1)$, R^1 is chosen from H, D, and halogen;

when Y is $-\text{O}-\text{C}-$, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is $-\text{C}-\text{NH}-$, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R^2 , n, R^3 , m, and R_T are defined as above in formula (I-A).

In another general aspect, the present disclosure relates to a compound of formula (I-C):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y is a bond, $\text{CH}(\text{R}^1)$, NH , $-\text{O}-\text{CH}-$, $-\text{C}-\text{NH}-$, $-\text{CH}_2-\text{C}(\text{O})-$, or $-\text{CH}=\text{N}-$;

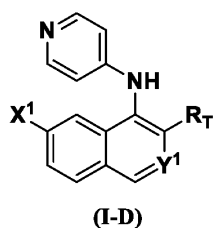
when Y is $\text{C}(\text{R}^1)$, R^1 is chosen from H, D, and halogen;

when Y is -O-C-, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is -C-NH-, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R^2 , R^3 , m, and R_T are defined as above in formula (I-A).

In another general aspect, the present disclosure relates to a compound of formula (I-D):



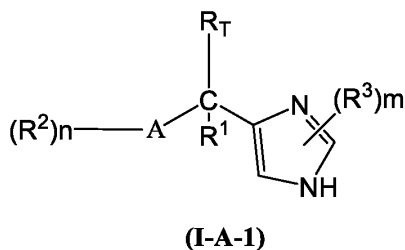
or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

Y^1 is CH, or N;

X^1 is chosen from H, D, and halogen; and

R_T is defined as above in formula (I-A).

In some embodiments, the compound of formula (I-A) has the formula (I-A-1):



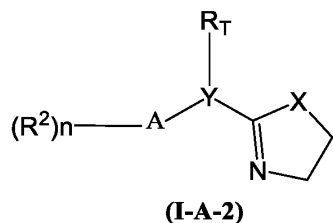
or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

R^1 is chosen from H, D, and halogen;

A is a ring chosen from phenyl, pyridinyl, thienyl, furyl, pyrrolyl, 4H-pyran, or 4H-thiopyran;

R^2 , n , R^3 , m, and R_T are defined as above in formula (I-A).

In some embodiments, the compound of formula (I-A) has the formula (I-A-2):

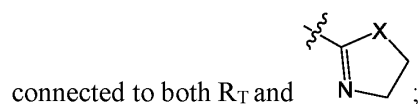


or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

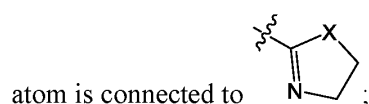
A is a ring chosen from phenyl, 1,2,3,4-tetrahydro-1-naphthyl, quinoxaliny, pyrimidinyl, and 2,1,3-benzothiadiazol;

Y is CH, N, -O-CH-, or -C-NH-;

when Y is -O-C-, the oxygen atom is connected to A, and the carbon atom is



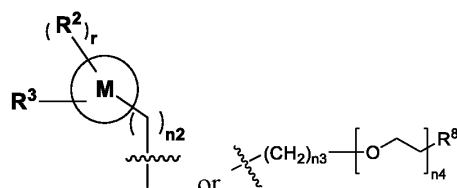
when Y is -C-NH-, the carbon atom is connected to both R_T and A, and the nitrogen



X is NH, O, or S; and

R^2 , n, and R_T are defined as above in formula (I-A).

In certain embodiments, when the compound of formula (I-A) has the formula (I-A-1)



or (I-A-2), R_T is

ring M is C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, C_{6-12} aryl, or C_{1-12} heteroaryl, wherein the C_{3-12} cycloalkyl or C_{2-12} heterocyclyl is optionally fused with an aryl;

r is 1 or 2;

n_2 is 0, 1, or 2;

each R^2 is independently chosen from hydrogen, halogen, hydroxyl, and alkoxy;

R^3 is chosen from CN, hydroxy, alkoxy, $-C(O)-C_{0-12}$ alkylene-CN, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-SO_2$ -alkyl, $-C(O)-NR^4R^4$, $-SO_2-NR^4R^4$, $-C_{0-12}$ alkylene- $R^{3'}$, $-O-C_{0-12}$ alkylene- $COOH$, $-C_{0-12}$ alkylene- $N(R^4)-C(O)-R^5$, $-C_{0-12}$ alkylene- $N(R^4)-SO_2-R^5$, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- $O-C_{0-12}$ alkylene- $N(R^4)-SO_2-R^5$, $-C_{0-12}$ alkylene- $P(=O)(R^4)(R^4)$, $\begin{array}{c} \text{O} \\ | \\ \text{---} \text{C} \text{---} \end{array} \text{---} \text{C}_m \text{---} R^6$, $-\text{NH}-R^7$, or $\begin{array}{c} \text{O} \\ | \\ \text{---} \text{C} \text{---} \end{array} \text{---} \text{C}_n \text{---} \text{O}-\text{CH}_3$; wherein one $-\text{CH}_2-$ group in the $-C_{0-12}$ alkylene- $R^{3'}$ is optionally replaced by oxygen atom or $\text{---} \equiv \text{---}$, the $-C_{0-12}$ alkylene- $R^{3'}$ is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C_{2-12} heterocyclyl and C_{1-12} heteroaryl are each optionally substituted with one or more R^{4a} ;

R^{3'} is chosen from -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂alkylene-COOH, -C₀₋₁₂alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂alkylene-N(R⁴)-SO₂-R⁵, C₀₋₁₂alkylene-C₁₋₁₂ heteroaryl;

each R^{4a} is independently chosen from hydroxy, alkyl, oxo, ketone, and -C₂₋₁₂ heterocyclyl;

each of R⁴ and R^{4'} is independently hydrogen, alkyl, alkoxy, -SO₂-N(R^{6a})_t, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or hydroxyalkyl, wherein the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

or R⁴ and R^{4'}, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S;

alternatively, when one R² is adjacent to R³, the R² and R³, together with the atoms that they are attached to, form a ring optionally substituted with one or more R^{4a};

R⁵ is amino, alkylamino, C₁₋₁₂ haloalkyl, -C₀₋₁₂ alkylene-OR^{6a}, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-SR^{6a}, -C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₂₋₁₂ alkenyl, or alkyl optionally substituted with cyano, amido, trialkylammonium, or thiolate; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

each R^{6a} is independently chosen from hydrogen, C₁₋₁₂ alkyl, C₁₋₁₂ alkoxy, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₆₋₁₂ aryl, and -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl, is optionally substituted with one or more R^{4a};

R^6 is alkoxy, amino, sulfonamide, carbamide, or alkyl optionally substituted with cyano;

R^7 is hydrogen, alkyl, $-C_{0-12}$ alkylene-COOH, optionally substituted C_{3-12} cycloalkyl, C_{2-12} aryl, C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- $N(R^4)$ -SO₂- R^5 , $-C_{0-12}$ alkylene-P(=O)(R^4)(R^4), $-C_{0-12}$ alkylene- $N(R^4)$ -C(=S)- R^5 , $-C(=S)$ - R^5 , or alkyl optionally substituted with cyano;

R^8 is alkoxy, amino, alkylamino, amide, sulfonamide, or carbamide;

n_3 is 0, 1, 2, 3, or 4;

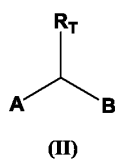
n_4 is 1, 2, 3, 4, 5, or 6;

t is 2 or 3;

m is 0, 1, 2, 3, 4, or 5; and

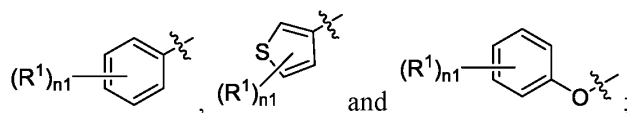
n is 0, 1, 2, 3, or 4.

In another general aspect, the present disclosure relates to a compound of formula (II):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, wherein,

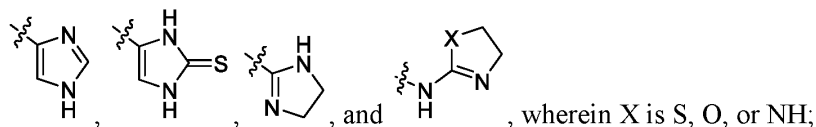
A is one chosen from:

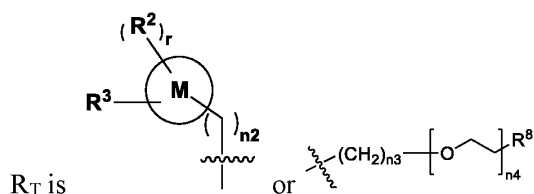


n_1 is 1 or 2;

each R^1 is independently chosen from hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and -COOH;

B is one chosen from:





ring M is C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, C₆₋₁₂ aryl, or C₁₋₁₂ heteroaryl, wherein the C₃₋₁₂ cycloalkyl or C₂₋₁₂ heterocyclyl is optionally fused with an aryl;

r is 1 or 2;

n_2 is 0, 1, or 2;

each R² is independently chosen from hydrogen, halogen, hydroxyl, and alkoxy;

R³ is chosen from CN, hydroxy, alkoxy, -C(O)-C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -SO₂-alkyl, -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-R^{3'}, -O-C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R^{4'}),

$\text{---O---} \left[\text{---CH}_2\text{---} \right]_m \text{---R}^6$, ---NH---R^7 , or $\text{---O---} \left[\text{---CH}_2\text{---O---} \right]_n \text{---CH}_3$; wherein one $\text{---CH}_2\text{---}$ group in the $\text{---C}_{0-12}\text{---}$ alkylene- $\text{R}^{3'}$ is optionally replaced by oxygen atom or $\text{---}\equiv\text{---}$, the $\text{---C}_{0-12}\text{---}$ alkylene- $\text{R}^{3'}$ is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C_{2-12} heterocyclyl and C_{1-12} heteroaryl are each optionally substituted with one or more R^{4a} ;

R^{3'} is chosen from -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl;

each R^{4a} is independently chosen from hydroxy, alkyl, oxo, ketone, and -C₂₋₁₂ heterocyclyl;

each of R⁴ and R^{4'} is independently hydrogen, alkyl, alkoxy, -SO₂-N(R^{6a})_t, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or hydroxyalkyl, wherein the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

or R⁴ and R⁴, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S;

alternatively, when one R² is adjacent to R³, the R² and R³, together with the atoms that they are attached to, form a ring optionally substituted with one or more R^{4a};

R^5 is amino, alkylamino, C_{1-12} haloalkyl, $-C_{0-12}$ alkylene-OR^{6a}, $-C_{0-12}$ alkylene-N(R^{6a})_t, $-C_{0-12}$ alkylene-SR^{6a}, $-C_{0-12}$ alkylene-CN, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{2-12}$ alkenyl, or alkyl optionally substituted with cyano, amido, trialkylammonium, or thiolate; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ,

each R^{6a} is independently chosen from hydrogen, C_{1-12} alkyl, C_{1-12} alkoxy, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{6-12} aryl, and $-C_{0-12}$ alkylene- C_{1-12} heteroaryl; wherein each of the alkyl, C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl, is optionally substituted with one or more R^{4a} ;

R^6 is alkoxy, amino, sulfonamide, carbamide, or alkyl optionally substituted with cyano;

R^7 is hydrogen, alkyl, $-C_{0-12}$ alkylene-COOH, optionally substituted C_{3-12} cycloalkyl, C_{2-12} aryl, C_{1-12} heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, $-C_{0-12}$ alkylene-P(=O)(R⁴)(R^{4'}), $-C_{0-12}$ alkylene-N(R⁴)-C(=S)-R⁵, $-C(=S)-R^5$, or alkyl optionally substituted with cyano;

R^8 is alkoxy, amino, alkylamino, amide, sulfonamide, or carbamide;

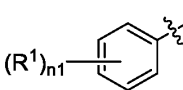
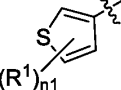
n_3 is 0, 1, 2, 3, or 4;

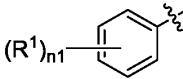
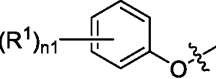
n_4 is 1, 2, 3, 4, 5, or 6;

t is 2 or 3;

m is 0, 1, 2, 3, 4, or 5; and

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

In some embodiments, A is  or .

In some embodiments, A is  or .

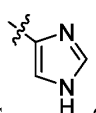
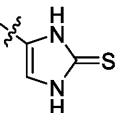
In some embodiments, R^1 is alkyl, such as methyl.

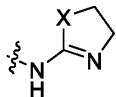
In some embodiments, R^1 is halogen, such as fluorine or chlorine.

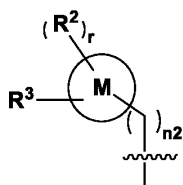
In some embodiments, R^1 is alkoxy, such as -OMe.

In some embodiments, R^1 is hydroxyl or -COOH or -CH₂OH.

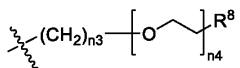
In some embodiments, R^1 is haloalkyl, such as trifluoromethyl or -CH₂CH₂F.

In some embodiment, B is  or .

In some embodiment, B is  or , wherein X is S, O, or NH.



In some embodiments, R_T is

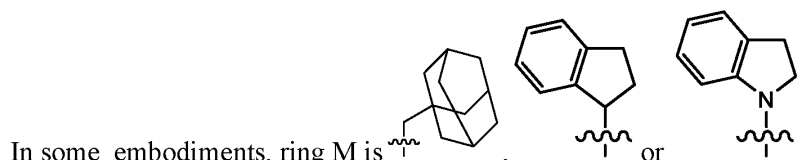


In some embodiments, R_T is

In some embodiments, ring M is C_{6-12} aryl or C_{1-12} heteroaryl.

In some embodiments, ring M is C_{3-12} cycloalkyl or C_{2-12} heterocyclyl, wherein the C_{3-12} cycloalkyl or C_{2-12} heterocyclyl is optionally fused with an aryl.

In some embodiments, ring M is phenyl, pyridinyl, pyrimidinyl, thiophenyl, cyclopentyl, or cyclohexyl.



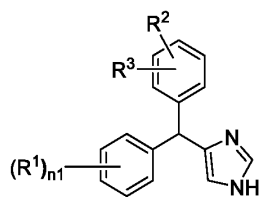
In some embodiments, R^2 is hydrogen.

In some embodiments, R^2 is hydroxyl.

In some embodiments, R^2 is halogen, such as fluorine or chlorine.

In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) is trifluoroacetate or hydrochloride.

In some embodiments, the compound of formula (II) is a compound of formula (II-A):



(II-A)

, wherein R^1 , R^2 , R^3 , and n_1 are defined as above in formula

(II).

In some embodiments, R^1 is halogen, haloalkyl, hydroxyl, alkyl, or $-COOH$.

In certain embodiments, R^1 is methyl, ethyl, hydroxyl, fluorine, chlorine, trifluoromethyl, $-\text{CH}_2\text{CH}_2\text{F}$, or $-\text{COOH}$.

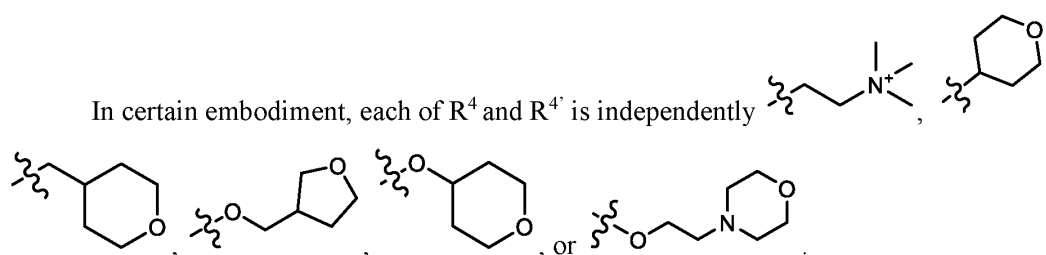
In some embodiments, n_1 is 2.

In some embodiments, R^2 is hydrogen, hydroxyl, or halogen.

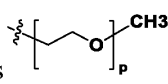
In certain embodiments, R^2 is fluorine or chlorine.

In some embodiments, R^3 is $-\text{C}(\text{O})-\text{NR}^4\text{R}^{4'}$ or $-\text{SO}_2-\text{NR}^4\text{R}^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, $-\text{C}_{0-12}$ alkylene- $\text{N}(\text{R}^{6a})_t$, $-\text{C}_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-\text{C}_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-\text{C}_{0-12}$ alkylene- C_{1-12} heteroaryl, $-\text{C}_{0-12}$ alkylene- OR^{6a} , or hydroxyalkyl, and the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} , wherein R^{4a} , R^{6a} , and t are defined as above.

In certain embodiments, each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, or hydroxyalkyl.

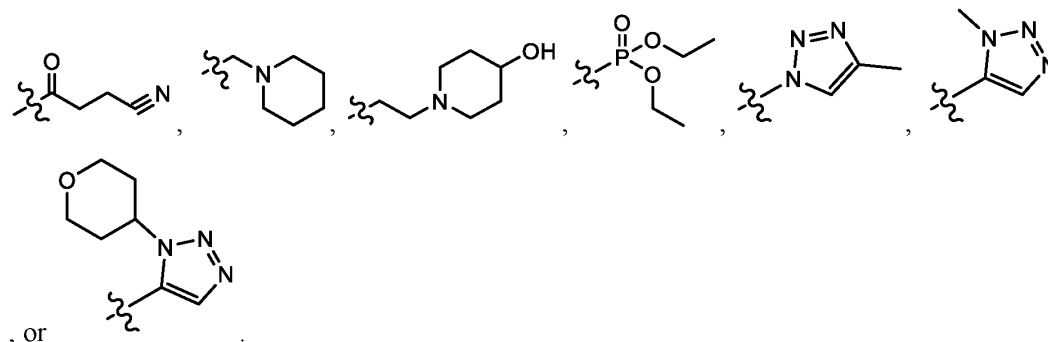


In certain embodiments, each of R^4 and $R^{4'}$ is independently hydroxyalkyl substituted

with alkoxy, such as , wherein p is 0, 1, 2, or 3, particularly p is 2.

In some embodiments, R^3 is $-\text{C}(\text{O})-\text{NR}^4\text{R}^{4'}$ or $-\text{SO}_2-\text{NR}^4\text{R}^{4'}$, wherein R^4 and $R^{4'}$, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S, particularly, R^4 and $R^{4'}$, together with the nitrogen atom that they are attached to, form a six-membered heterocycle.

In some embodiments, R³ is hydroxyl, -COOH, -CH(CH₃)-COOH, -CN,



In some embodiments, R³ is C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, or -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, wherein R⁴ is hydrogen or alkyl, and R⁵ is amino, alkylamino, C₁₋₁₂ haloalkyl, -C₀₋₁₂ alkylene-OR^{6a}, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-SR^{6a}, -C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₂₋₁₂ alkenyl, or alkyl optionally substituted with cyano or amido; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a}, wherein R^{4a}, R^{6a}, and t are defined as above.

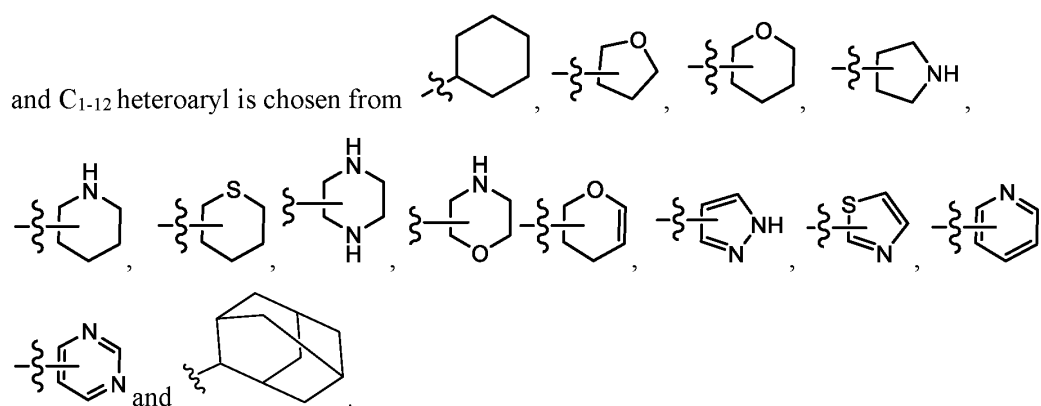
In certain embodiments, R⁵ is amino, alkylamino, alkoxy, alkyl, or -C₂₋₁₂ alkenyl.

In certain embodiments, R⁵ is alkyl substituted with cyano, such as -CH₂CN.

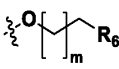
In certain embodiments, R⁵ is alkyl substituted with amido, such as -CH₂CH₃CONH₂.

In certain embodiments, R⁵ is alkyl substituted with alkoxy, trialkylammonium, or thiolate.

In certain embodiments, when R⁵ is -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, or -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl,

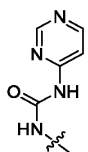


In certain embodiments, when each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is substituted with one or more R^{4a}, R^{4a} is hydroxyl, methyl, oxo, or -C(O)-Me.

In some embodiments, R³ is , wherein m is 0, 1, 2, 3, 4, or 5, and R⁶ is sulfonamide, carbamide, or alkyl optionally substituted with cyano.

In certain embodiments, R⁶ is sulfonamide of formula -N(R')SO₂-R, wherein each R and R' is independently chosen from hydrogen and alkyl, particularly R⁶ is -NHSO₂CH₃.

In certain embodiments, R⁶ is carbamide of formula -N(R')C(O)N(R)₂, wherein each R and R' is independently chosen from hydrogen, alkyl, and heteroaryl, particularly R⁶ is

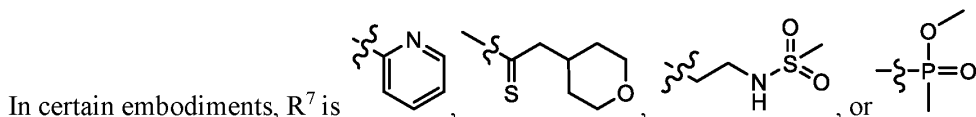


In certain embodiments, R⁶ is alkyl optionally substituted with cyano, such as C₁₋₄ alkyl optionally substituted with cyano, particularly C₁₋₄ alkyl substituted with cyano.

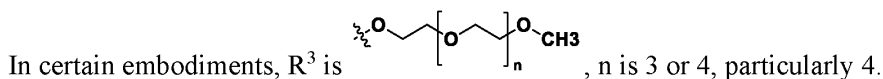
In certain embodiments, m is 1, 2, or 3, particularly 2.

In some embodiments, R³ is -NH-R⁷, wherein R⁷ is hydrogen, optionally substituted C₃₋₁₂ cycloalkyl, C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R^{4'}), -C₀₋₁₂ alkylene-N(R⁴)-C(=S)-R⁵, -C(=S)-R⁵, or alkyl optionally substituted with cyano; wherein R⁴, R^{4'} and R⁵ are defined as above.

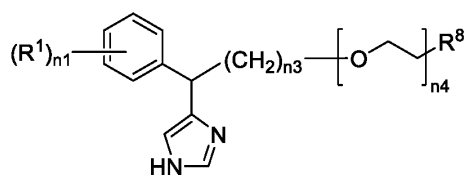
In certain embodiments, R⁷ is hydrogen.



In certain embodiments, R⁷ is alkyl optionally substituted with cyano, such as C₁₋₄ alkyl optionally substituted with cyano, particularly C₁₋₄ alkyl substituted with cyano.



In some embodiments, the compound of formula (II) is a compound of formula (II-B):



(II-B)

, wherein R^1 , R^8 , $n1$, $n3$, and $n4$ are defined

as above in formula (II).

In some embodiments, R^1 is hydrogen or alkyl, such as alkyl, particularly methyl.

In some embodiments, $n1$ is 2.

In some embodiments, $n3$ is 0, 1 or 3.

In some embodiments, $n4$ is 2, 3, or 5.

In some embodiments, R^8 is alkoxy, such as C_{1-4} alkoxy, particularly methoxy or ethoxy.

In some embodiments, R^8 is amino.

In some embodiments, R^8 is alkylamino, such as C_{1-4} alkylamino, particularly methylamino.

In some embodiments, R^8 is amide of formula $-N(R')C(O)R$, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl.

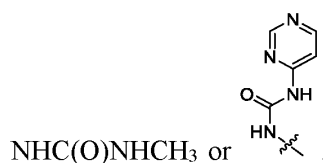
In some embodiments, R^8 is amide of formula $-N(R')C(O)R$, particularly R^8 is $-NHCOCH_3$.

In some embodiments, R^8 is sulfonamide of formula $-N(R')SO_2-R$, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl.

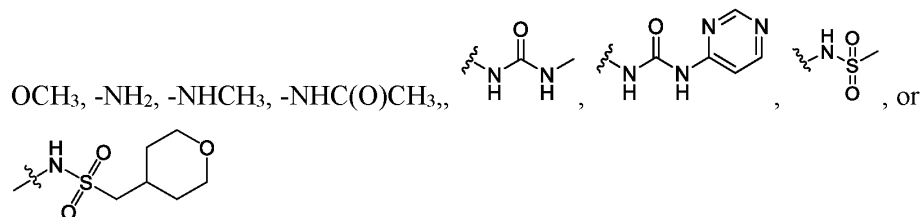
In certain embodiments, R^8 is sulfonamide of formula $-N(R')SO_2-R$, wherein each R and R' is independently chosen from hydrogen, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, and alkyl, particularly R^3 is $-NHSO_2CH_3$.

In some embodiments, R^8 is carbamide of formula $-N(R')C(O)N(R)_2$, wherein each R and R' is independently chosen from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl.

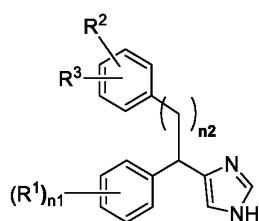
In certain embodiments, R^8 is carbamide of formula $-N(R')C(O)N(R)_2$, wherein each R and R' is independently chosen from hydrogen, alkyl, and heteroaryl, particularly R^3 is $-NHC(O)NHCH_3$ or



In some embodiments, when the compound is a compound of formula (II), R^8 is -



In some embodiments, the compound of formula (II) is a compound of formula (II-C):



(II-C), wherein,

n_2 is 1 or 2; and

R^1 , R^2 , R^3 , and n_1 are defined as above in formula (II).

In some embodiments, R^1 is alkyl, such as methyl.

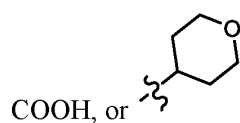
In some embodiments, n_1 is 2.

In some embodiments, n_2 is 1.

In some embodiments, R^2 is hydrogen or halogen.

In certain embodiments, R^2 is fluorine.

In some embodiments, R^3 is $-C(O)-NR^4R^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen, hydroxy, alkyl, alkoxy, $-SO_2-NHCH_3$, $-SO_2-NH-Ph$, $-CH_2-COOH$, $-CH_2-CH_2-$

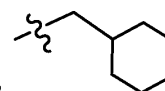


In some embodiments, R^3 is $-SO_2-NR^4R^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen, hydroxy, or $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl.

In some embodiments, R^3 is $-NH-C(O)-R^5$, $-N(CH_3)-C(O)-R^5$ or $-NH-SO_2-R^5$, wherein R^5 is alkyl, $-C_{0-12}$ alkylene-alkoxy, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene-NH- C_{1-12} alkyl, $-C_{0-12}$ alkylene-NH- C_{2-12} heterocyclyl, or $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl.

In certain embodiments, R^5 is alkyl, such as methyl.

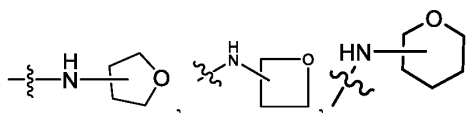
In certain embodiments, R^5 is $-C_{0-12}$ alkylene-alkoxy, such as $-CH_2-OCH_3$.



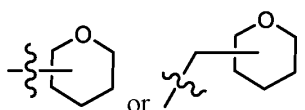
In certain embodiments, R^5 is $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, such as

In certain embodiments, R^5 is $-C_{0-12}$ alkylene-NH- C_{1-12} alkyl, such as $-NH-CH_3$.

In certain embodiments, R^5 is $-C_{0-12}$ alkylene-NH- C_{2-12} heterocyclyl, such as

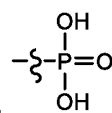


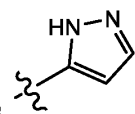
In certain embodiments, R^5 is $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, such as ,

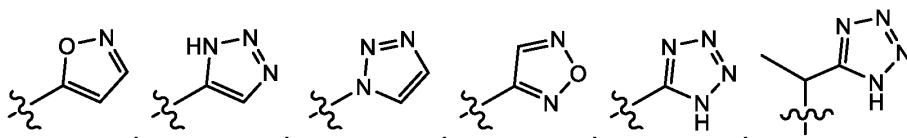


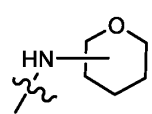
In some embodiments, R^3 is $-SO_2$ -alkyl, such as $-SO_2-CH_3$.

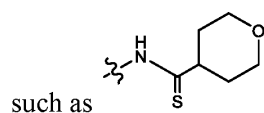
In some embodiments, R^3 is $-C_{0-12}$ alkylene-COOH, such as $-COOH$, $-CH_2-COOH$, $-C(Me)_2-COOH$, $-CH_2-CH_2-COOH$.

In some embodiments, R^3 is $-C_{0-12}$ alkylene- $P(=O)(R^4)(R^4)$, such as .

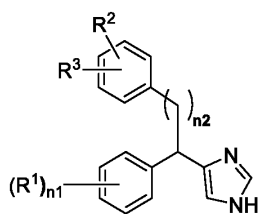
In some embodiments, R^3 is $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, such as ,



In some embodiments, R^3 is $-NH-R^7$, such as $-NH-CH_3$, , $-NH-C(=S)-R^5$



In some embodiments, the compound of formula (II) is a compound of formula (II-D):



(II-D)

wherein,

n_2 is 0 or 1;

R^3 is chosen from $-C(O)-NHR^4$, $-SO_2-NHR^4$, $-NH-C(O)-R^5$, and $-NH-SO_2-R^5$, and $-NH-R^7$;

R^4 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with trialkylammonium; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

R^5 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with trialkylammonium; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

each R^{6a} is independently chosen from $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, and $-C_{0-12}$ alkylene- C_{1-12} heteroaryl; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

R^7 is C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- $N(R^4)-SO_2-R^5$, $-C_{0-12}$ alkylene- $P(=O)(R^4)$ (alkoxy), or $-C_{0-12}$ alkylene- $N(R^4)-C(=S)-R^5$; and

R^1 , R^2 , R^{4a} , and n_1 are defined as above in formula (II).

In some embodiments, R^1 is alkyl, such as methyl.

In some embodiments, R^1 is alkoxy, such as $-OMe$.

In some embodiments, n_1 is 1.

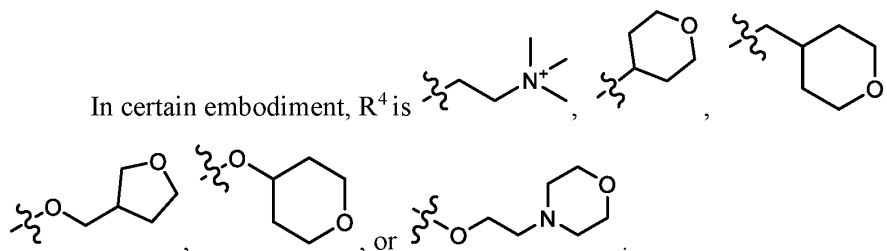
In some embodiments, n_1 is 2.

In some embodiments, n_2 is 0.

In some embodiments, n_2 is 1.

In some embodiments, R^2 is hydrogen or halogen.

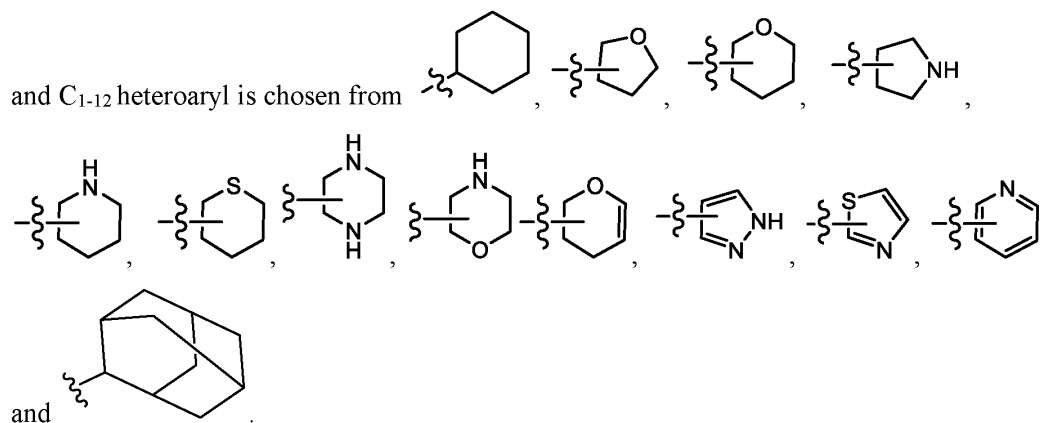
In some embodiments, R³ is -C(O)-NHR⁴ or -SO₂-NHR⁴, wherein R⁴ is -C₀₋₁₂ alkylene-NHR^{6a}, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or alkyl substituted with trialkylammonium; wherein and each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a}, wherein R^{4a} and R^{6a} are defined as above.



In some embodiments, R³ is -NH-C(O)-R⁵, or -NH-SO₂-R⁵, wherein R⁵ is -C₀₋₁₂ alkylene-NHR^{6a}, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or alkyl substituted with trialkylammonium; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a}, wherein R^{4a} and R^{6a} are defined as above.

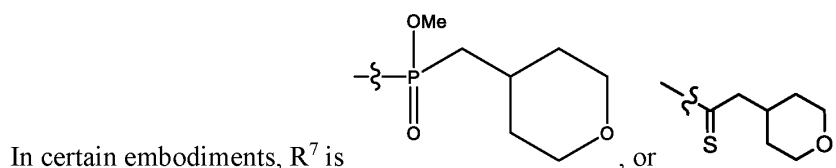
In certain embodiments, R⁵ is alkyl substituted with trialkylammonium.

In certain embodiments, when R⁵ is -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, or -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl,

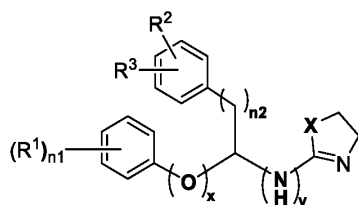


In certain embodiments, when each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is substituted with one or more R^{4a}, R^{4a} is hydroxyl, methyl, oxo, or -C(O)-Me.

In some embodiments, R³ is -NH-R⁷, wherein R⁷ is C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴) (alkoxy), or -C₀₋₁₂ alkylene-N(R⁴)-C(=S)-R⁵; wherein R⁴ and R⁵ are defined as above.



In some embodiments, the compound of formula (II) is a compound of formula (II-E):



(II-E), wherein

x is 0 or 1;

y is 0 or 1;

X is S, O, or NH; and

R^1 , R^2 , R^3 , n_1 , and n_2 are defined as above in formula (II).

In some embodiments, x is 0, y is 1, and X is S, O, or NH.

In some embodiments, x is 0 or 1, y is 0, and X is NH.

In some embodiments, each R^1 is independently chosen from hydrogen, halogen, alkoxy, and alkyl.

In certain embodiments, R^1 is methyl, chlorine, or methoxy.

In some embodiments, n_2 is 1.

In some embodiments, n_2 is 2.

In some embodiments, R^2 is hydrogen.

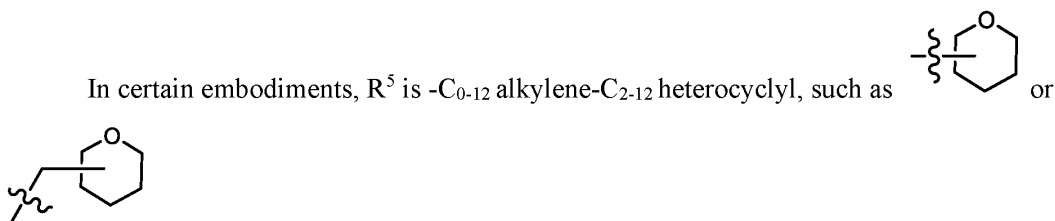
In some embodiments, R^3 is $-C(O)-NR^4R^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen or alkoxy.

In some embodiments, R^3 is $-SO_2-NR^4R^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen or alkyl.

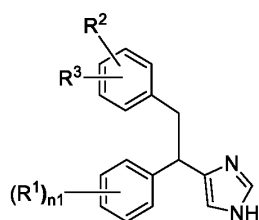
In some embodiments, R^3 is $-NH-C(O)-R^5$ or $-NH-SO_2-R^5$, wherein R^5 is alkyl or $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl.

In certain embodiments, R^5 is alkyl, such as methyl.

In certain embodiments, R^5 is $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, such as



In some embodiments, the compound of formula (II) is a compound of formula (II-F):



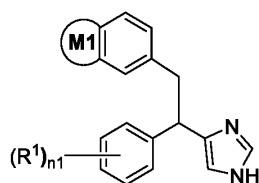
(II-F), wherein,

R^2 is adjacent to R^3 , and R^2 and R^3 , together with the carbon atoms that they are attached to, form a heterocycle optionally substituted with one or more R^{4a} ; and

R^1 , R^{4a} , and $n1$ are defined as above in formula (II).

In some embodiments, R^2 and R^3 , together with the carbon atoms that they are attached to, form a 5- or 6-membered heterocycle optionally substituted with one or more R^{4a} .

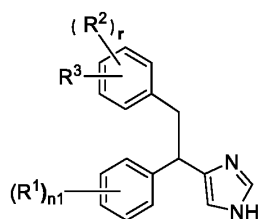
In some embodiments, the compound of formula (II-F) is a compound of formula (II-F-1):



(II-F-1), wherein M1 is a heterocycle optionally substituted with one or

more R^{4a} .

In some embodiments, the compound of formula (II) is a compound of formula (II-G):



(II-G), wherein,

each R^2 is independently chosen from hydroxyl and alkoxy;

R^3 is chosen from hydroxy and alkoxy; and

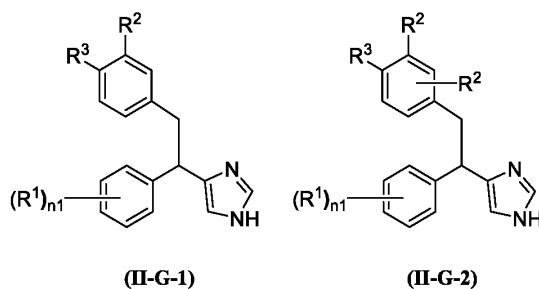
R^1 , n_1 and r are defined as above in formula (II).

In some embodiments, one R^2 is adjacent to R^3 .

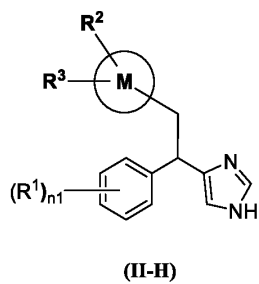
In some embodiments, each R^2 is independently chosen from hydroxyl and methoxy.

In some embodiments, R^3 is chosen from hydroxyl and methoxy.

In some embodiments, the compound of formula (II-G) is a compound of formula (II-G-1) of (II-G-2):



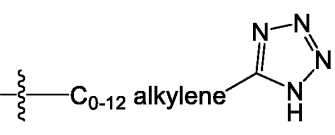
In some embodiments, the compound of formula (II) is a compound of formula (II-H):



(II-H), wherein,

M is C_{6-12} aryl or C_{1-12} heteroaryl;

R^3 is chosen from $-C_{0-12}$ alkylene-COOH, $-O-C_{0-12}$ alkylene-COOH, $-C_{0-12}$ alkylene-P(O)(OH)₂, $-C(O)-NH-SO_2-R^5$, $-C(O)-NH-C_{0-12}$ alkylene-COOH, $-NH-C_{0-12}$ alkylene-COOH,

-SO₂-OH, and ; wherein the -C₀₋₁₂ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino; and

R¹, R², and n1 are defined as above in formula (II).

In some embodiments, M is phenyl.

In some embodiments, M is pyridinyl.

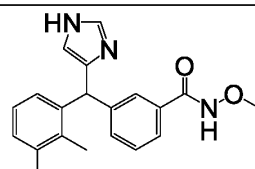
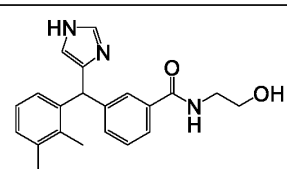
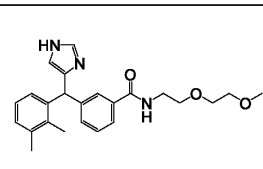
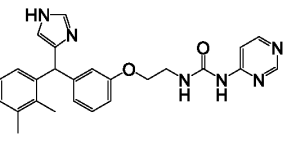
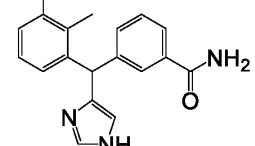
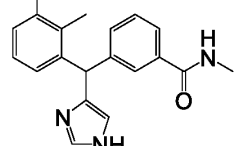
Exemplary compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) include, but are not limited to, the compounds described herein, and any tautomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof.

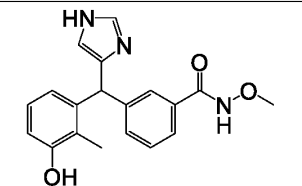
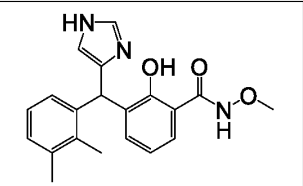
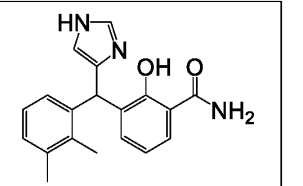
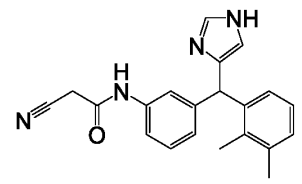
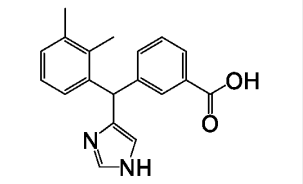
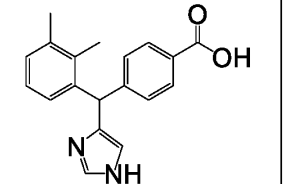
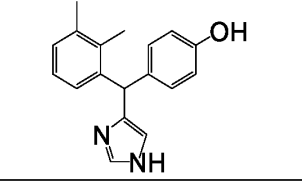
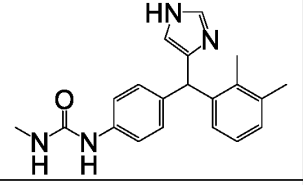
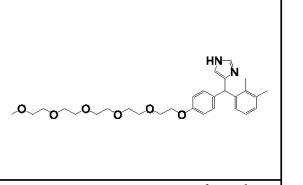
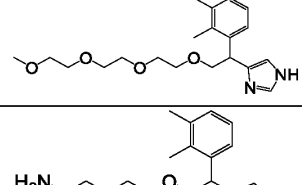
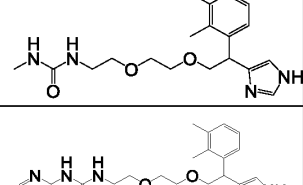
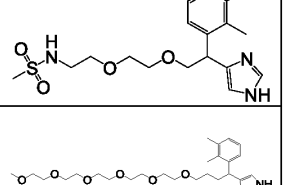
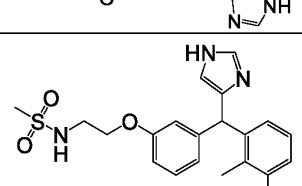
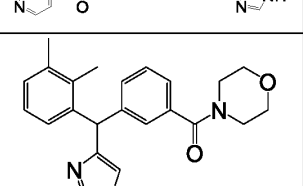
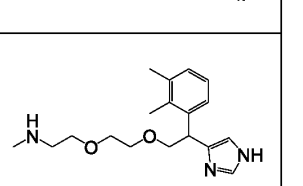
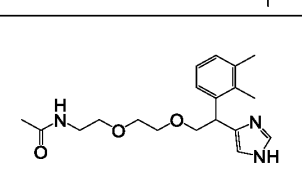
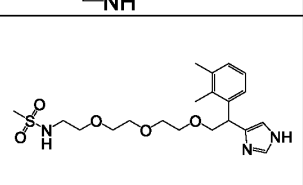
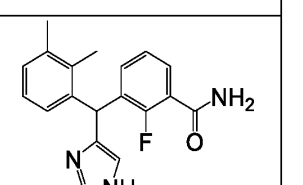
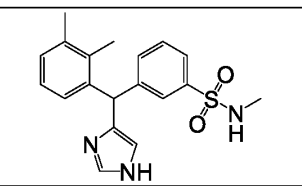
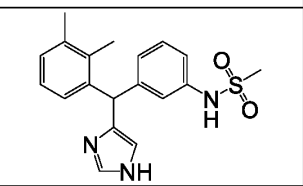
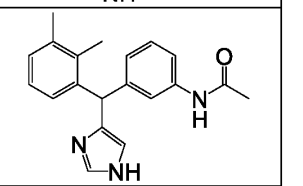
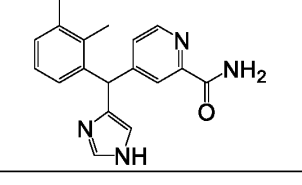
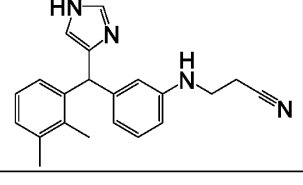
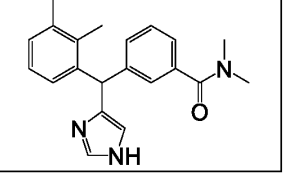
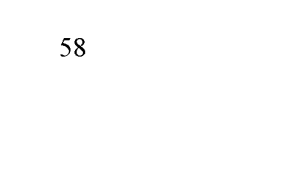
In particular embodiments, provided is a compound selected from Compounds 1-251, 401-403, 501-509, 601, and 602, or a tautomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof.

All possible combinations of the above-indicated embodiments of compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) and their tautomers, stereoisomers, pharmaceutically acceptable salts and solvates are considered to be embraced within the scope of the present disclosure.

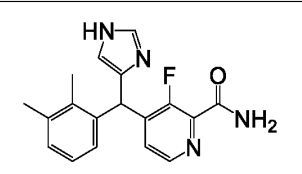
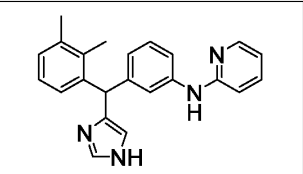
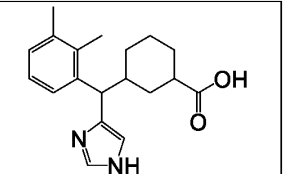
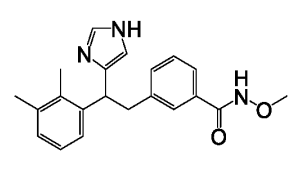
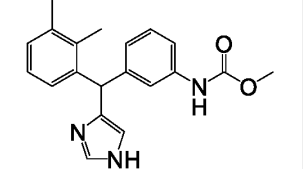
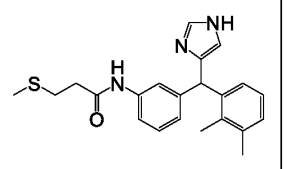
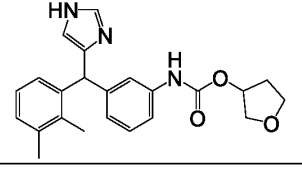
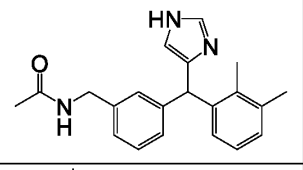
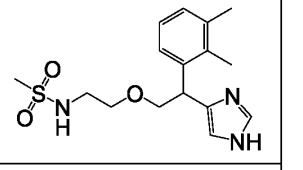
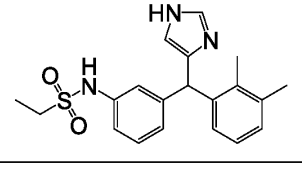
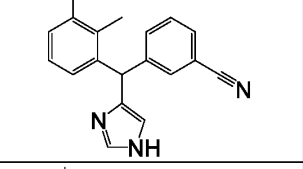
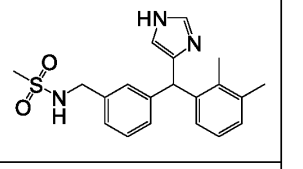
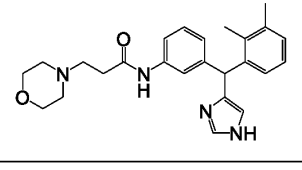
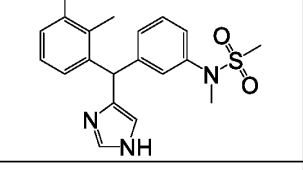
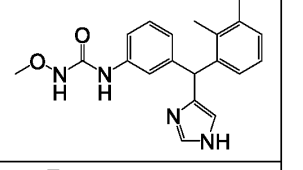
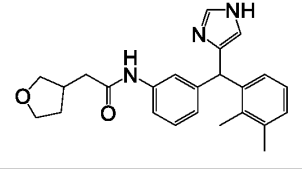
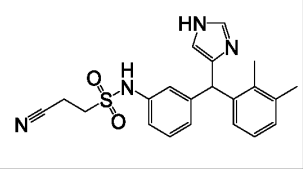
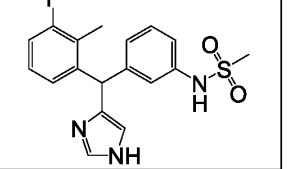
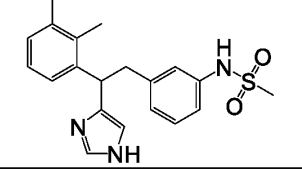
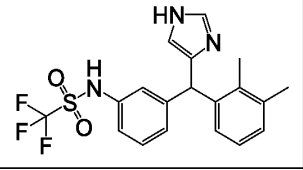
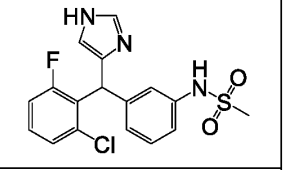
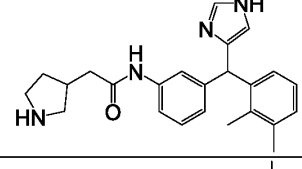
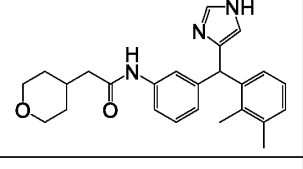
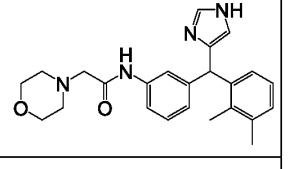
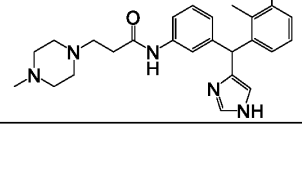
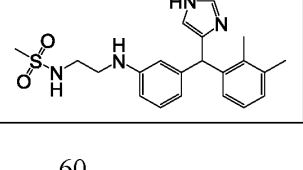
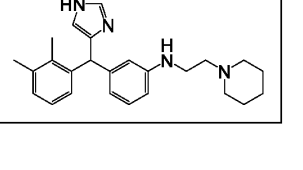
Exemplary compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) include, but are not limited to, the following compounds, and any tautomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof:

Table 1

No.	Structure	No.	Structure	No.	Structure
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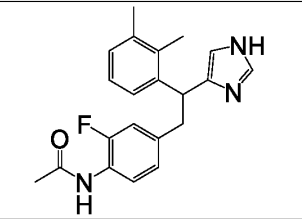
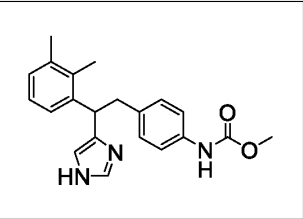
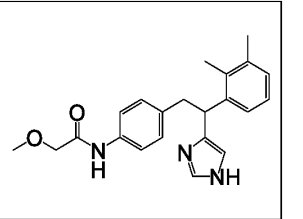
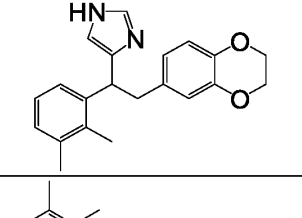
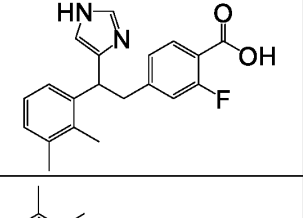
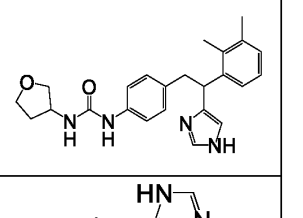
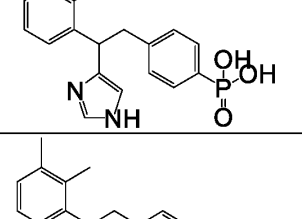
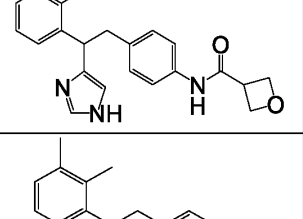
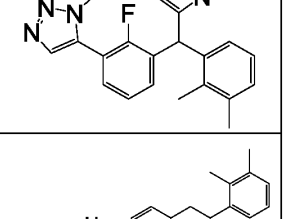
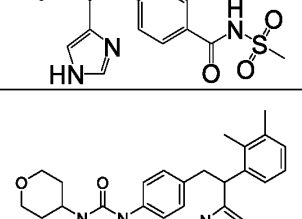
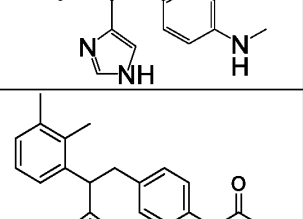
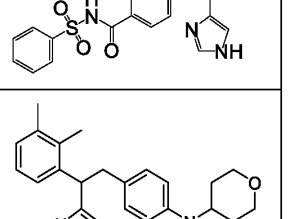
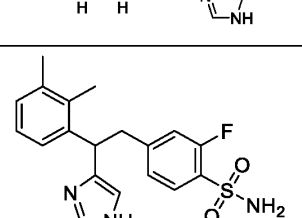
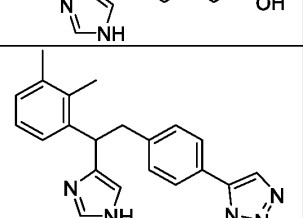
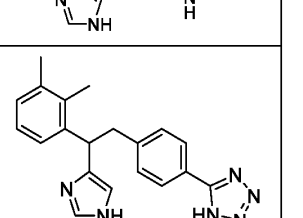
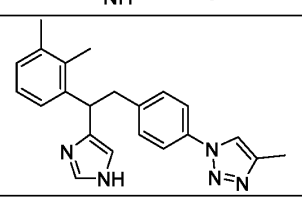
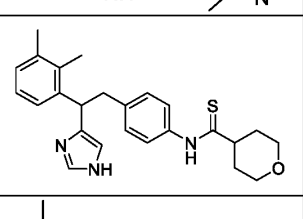
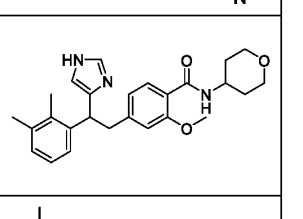
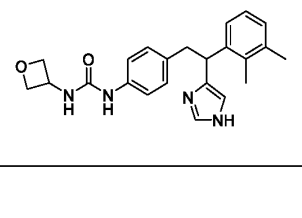
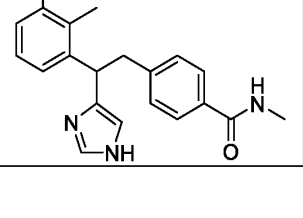
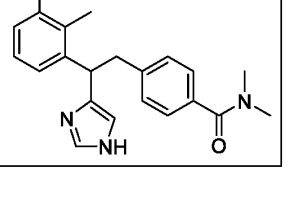
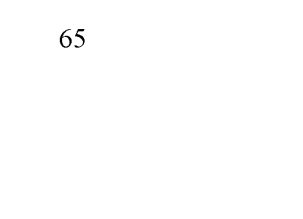
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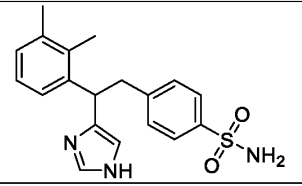
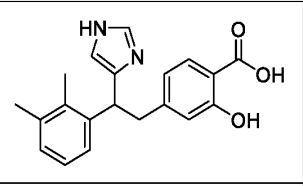
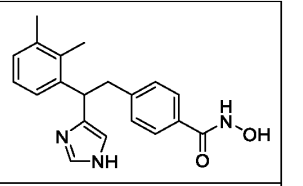
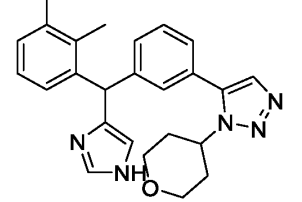
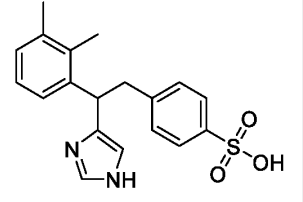
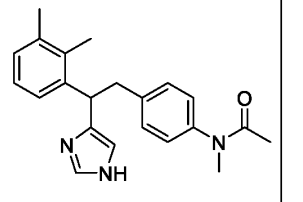
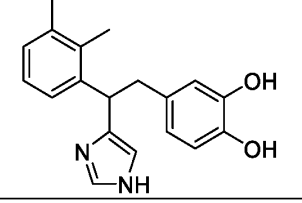
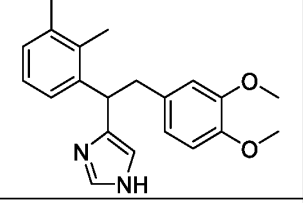
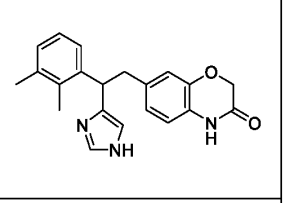
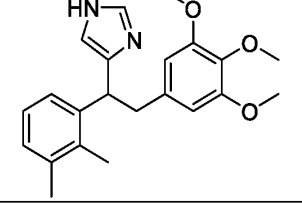
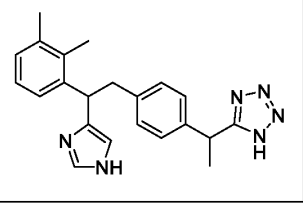
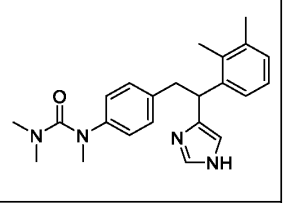
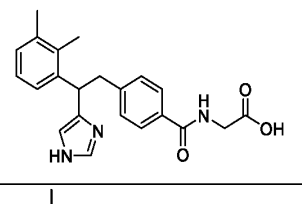
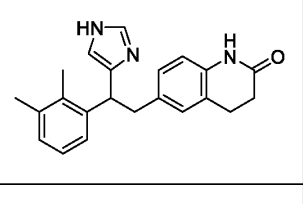
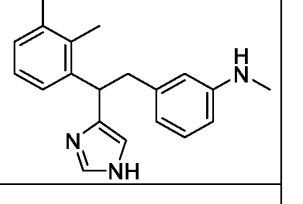
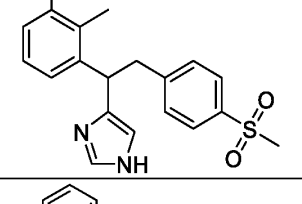
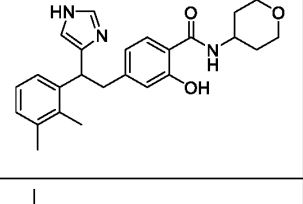
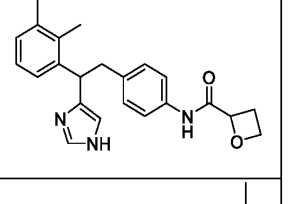
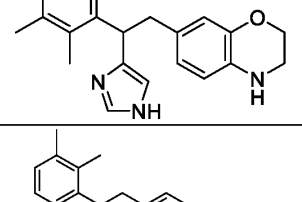
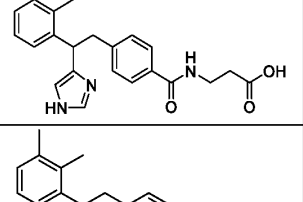
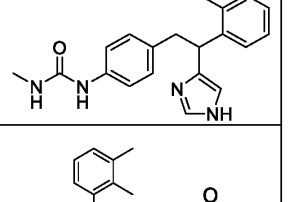
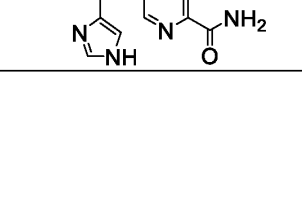
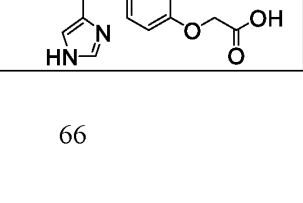
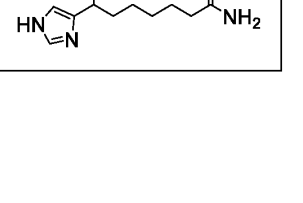
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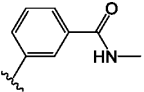
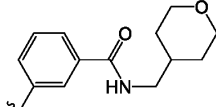
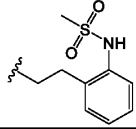
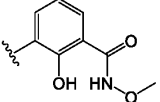
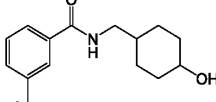
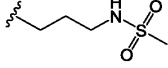
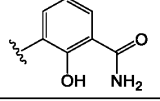
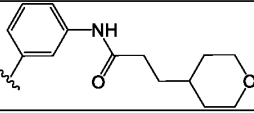
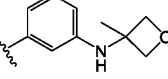
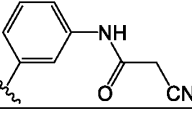
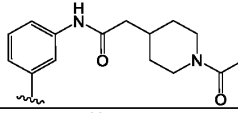
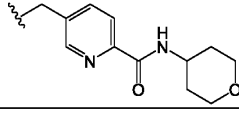
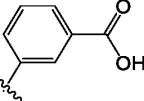
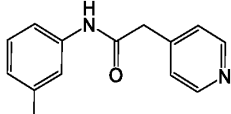
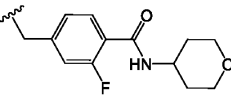
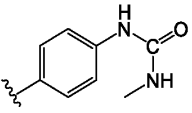
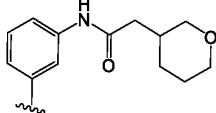
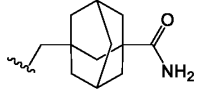
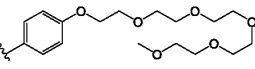
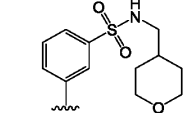
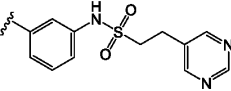
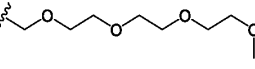
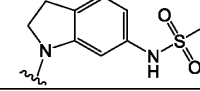
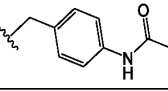
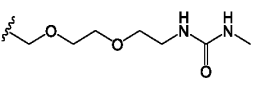
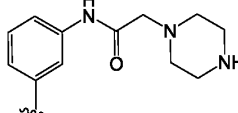
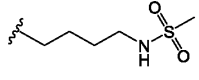
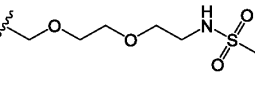
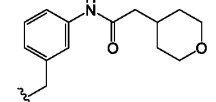
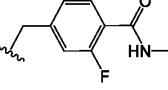
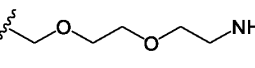
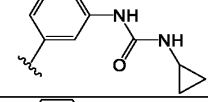
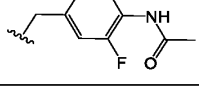
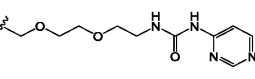
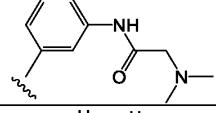
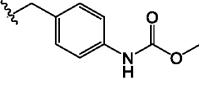
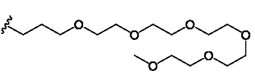
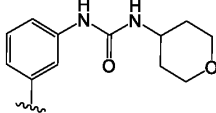
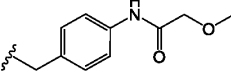
241		242		243	
244		245		246	
247		248		249	
250		251		401	
402		403		501	
502		503		504	
505		506		507	
508		509		510	
511		512		513	

514		515		516	
517		518		519	
520		601		602	

Exemplary R_T in formula (I-A), (I-B), (I-C), (I-D), or (II) include, but are not limited to, the following:

Table 1a. Exemplary R_T

No.	structure	No.	structure	No.	structure
1		93		178	
2		94		179	
3		95		180	
4		96		181	
5		97		182	

6		98		183	
8		99		184	
9		101		185	
10		102		186	
11		103		187	
14		104		188	
15		105		189	
16		106		190	
17		107		191	
18		108		192	
19		109		193	
20		110		194	
21		111		195	

22		112		196	
23		114		197	
24		116		198	
25		117		199	
26		119		200	
27		121		201	
28		120		202	
29		122		203	
30		123		204	
31		124		205	
32		125		206	
33		126		207	
37		127		208	

38		128		209	
39		129		210	
40		130		211	
41		131		212	
42		133		213	
43		134		214	
48		136		215	
50		137		216	
51		138		217	
53		139		218	
54		141		219	
55		142		220	
56		143		221	

57		144		222	
58		145		223	
59		146		224	
60		147		225	
61		148		226	
62		149		227	
63		150		228	
64		151		229	
65		152		230	
66		153		231	
67		154		232	
68		155		233	

69		156		234	
70		157		235	
71		158		236	
72		159		237	
73		160		238	
74		161		239	
76		162		240	
77		163		241	
79		164		242	
80		165		243	
81		166		245	
82		167		246	
83		168		247	

84		169		248	
85		170		249	
86		171		250	
87		172		251	
88		173			
89		174			
90		175			
91		176			
92		177			

Methods of Preparation

Compounds described herein can be prepared by any number of processes as described generally below and more specifically illustrated by the exemplary compounds which follow in the Examples section herein. The compounds provided herein as prepared in the processes described below can be synthesized in the form of mixtures of stereoisomers (e.g., enantiomers, diastereomers), including racemic mixtures of enantiomers, which can be separated from one another using art-known resolution procedures, for instance including liquid chromatography using a chiral stationary phase. Additionally or alternatively, stereochemically pure isomeric

forms of the compounds described herein can be derived from the corresponding stereochemically pure isomeric forms of the appropriate starting materials, intermediates, or reagents. For example, if a specific stereoisomer is desired, the compound can be synthesized by stereospecific methods of preparation, which typically employ stereochemically pure starting materials or intermediate compounds.

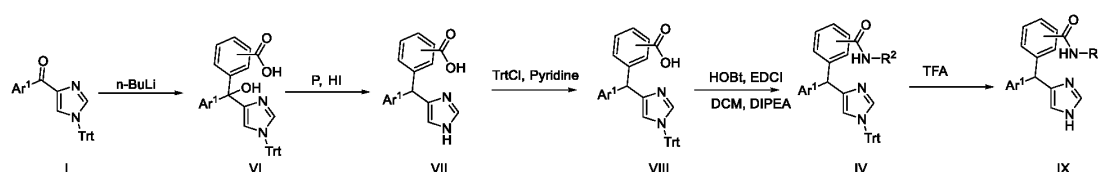
Pharmaceutically acceptable salts of compounds described herein can be synthesized from the parent compound containing an acidic or basic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate acid or base in water or in an organic solvent, or in a mixture of the two. Examples of suitable organic solvents include, but are not limited to, ether, ethyl acetate (EtOAc), ethanol, isopropanol, or acetonitrile.

By way of illustration, but not as a limitation, compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) described herein can be prepared according to the following general preparation procedures shown in Scheme 1 as well as the examples shown in the present disclosure. One of ordinary skill in the art will recognize that, to obtain various compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) as described herein, starting materials can be suitably selected so that the ultimately desired substituent groups will be carried through (i.e., be stable over the course of the synthesis) the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in place of the ultimately desired substituent, a suitable group that may be carried through (i.e., be stable over the course of the synthesis) the reaction scheme and replaced as appropriate with the desired substituent.

If no temperature or temperature range is stated, it is to be understood that the reaction is to be conducted at room temperature.

When isomerically pure samples are desired, isomeric mixtures of compounds synthesized according to Scheme 1 can be separated by chiral supercritical fluid chromatography (SFC) or high performance liquid chromatography (HPLC).

Scheme 1:



Compositions

In one aspect, provided is a pharmaceutical composition comprising a compound of formula (I-A), (I-B), (I-C), (I-D), or (II) or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, as described herein.

Compositions can also comprise a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier is non-toxic and should not interfere with the efficacy of the active ingredient. Pharmaceutically acceptable carriers can include one or more excipients such as binders, disintegrants, swelling agents, suspending agents, emulsifying agents, wetting agents, lubricants, flavorants, sweeteners, preservatives, dyes, solubilizers and coatings. The precise nature of the carrier or other material can depend on the route of administration, e.g., intramuscular, intradermal, subcutaneous, oral, intravenous, cutaneous, intramucosal (e.g., gut), intranasal or intraperitoneal routes. For liquid injectable preparations, for example, suspensions and solutions, suitable carriers and additives include water, glycols, oils, alcohols, preservatives, coloring agents and the like. For solid oral preparations, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. For nasal sprays/inhalant mixtures, the aqueous solution/suspension can comprise water, glycols, oils, emollients, stabilizers, wetting agents, preservatives, aromatics, flavors, and the like as suitable carriers and additives.

Compositions can be formulated in any manner suitable for administration to a subject to facilitate administration and improve efficacy, including, but not limited to, oral (enteral) administration and parenteral injections. The parenteral injections include intravenous injection or infusion, subcutaneous injection, intradermal injection, and intramuscular injection. Compositions can also be formulated for other routes of administration including transmucosal, ocular, rectal, long acting implantation, sublingual administration, under the tongue, from oral mucosa bypassing the portal circulation, inhalation, or intranasal.

The form of the pharmaceutical compositions, the route of administration, the dosage and the regimen depend upon the condition to be treated, such as the severity of the illness, the age, weight, and sex of the patient. Pharmaceutical compositions can be formulated for different modes of administration such as for topical, oral, intranasal, parenteral, intraocular, intravenous, intramuscular, or subcutaneous administration.

In yet another aspect, provided is a method of preparing a pharmaceutical composition comprising combining a compound of formula (I-A), (I-B), (I-C), (I-D), or (II), or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, with at least one pharmaceutically acceptable carrier. Pharmaceutical compositions can be prepared by any method known in the art in view of the present disclosure, and one of ordinary skill in the art will be familiar with such techniques used to prepare pharmaceutical compositions. For example, a pharmaceutical composition according to the present disclosure can be prepared by mixing a compound of formula (I-A), (I-B), (I-C), (I-D), or (II), with one or more pharmaceutically acceptable carriers according to conventional pharmaceutical compounding techniques, including but not limited to, conventional admixing, dissolving, granulating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Methods of Use

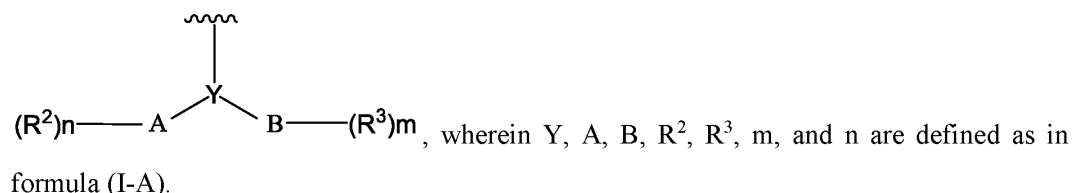
In one general aspect, provided are methods of treating or preventing pain in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective $\alpha 2AR$ agonist, wherein treating with the peripherally selective $\alpha 2AR$ agonist causes less side effects than treating with a non-peripherally selective $\alpha 2AR$ agonist, such as at similar or comparable dosage.

In some embodiments, the peripherally selective $\alpha 2AR$ agonist comprises an $\alpha 2AR$ activation moiety covalently linked to a peripheral distribution moiety.

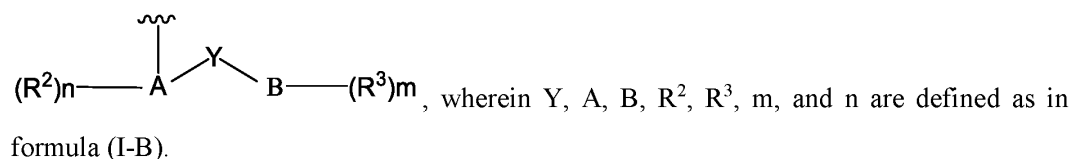
In another general aspect, provided are methods of treating or preventing a disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective $\alpha 2AR$ agonist, wherein the peripherally selective $\alpha 2AR$ agonist comprises an $\alpha 2AR$ activation moiety covalently linked to a peripheral distribution moiety.

The following embodiments apply to the above two general aspects of methods of use.

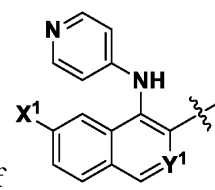
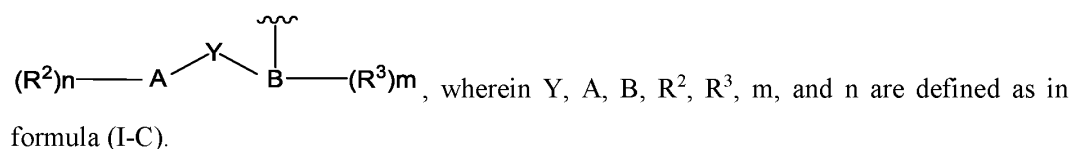
In some embodiments, the $\alpha 2AR$ activation moiety has formula of



In some embodiments, the $\alpha 2AR$ activation moiety has formula of

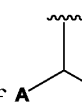


In some embodiments, the $\alpha 2AR$ activation moiety has formula of



In some embodiments, the $\alpha 2AR$ activation moiety has formula of

wherein X^1 and Y^1 are defined as in formula (I-D).



In some embodiments, the $\alpha 2AR$ activation moiety has formula of

A and B are defined as in formula (II).



In some embodiments, the peripheral distribution moiety has formula of

R_T is defined as in formula (I-A).



In some embodiments, the peripheral distribution moiety has formula of

R_T is defined as in formula (II).

In another general aspect, provided are methods of activating $\alpha 2AR$ and methods of treating or preventing a disease in a subject, using the compounds described herein or the composition containing the compounds with one or more acceptable pharmaceutical carriers, describe herein.

In some embodiments, the compounds of formula (I-A), (I-B), (I-C), (I-D), or (II) can be useful for activating $\alpha 2AR$.

In some embodiments, provided is a method of activating $\alpha 2AR$ in a subject in need thereof, comprising administering to the subject a compound or composition described herein, e.g., administering an effective amount of a compound or composition described herein.

In some embodiments, provided is a method of treating or preventing a disease in human or in animal.

In some embodiments, provided is a method of treating or preventing a disease in a subject in need thereof, comprising administering to the subject a compound or composition described herein, e.g., administering an effective amount of a compound or composition described herein.

In some embodiments, the disease is glaucoma, pain, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc.

In some embodiments, the disease is pain.

In some embodiments, the pain is nociceptive pain, neuropathic pain such as peripheral neuropathic pain, or mixed pain. Examples of peripheral neuropathic pain include, but not limited to diabetic neuropathy, postherpetic neuralgia, HIV-associated pain, chemotherapy-induced peripheral neuropathy, and post-surgical neuropathic pain.

In some embodiments, the compounds and pharmaceutical compositions described herein cause less side effects when treating pain, such as sedation, decreasing heart rate, and decreasing blood pressure in the treated subject.

In certain embodiments, the compounds and pharmaceutical compositions described herein do not cause sedative response in the treated subject.

EXAMPLES

The following examples are to further illustrate the nature of the present disclosure. It should be understood that the following examples do not limit the disclosure and the scope of the present disclosure is to be determined by the appended claims.

Methods of Synthesis

Unless indicated otherwise, the abbreviations for chemical reagents and synthesis conditions have their ordinary meaning known in the art as follows:

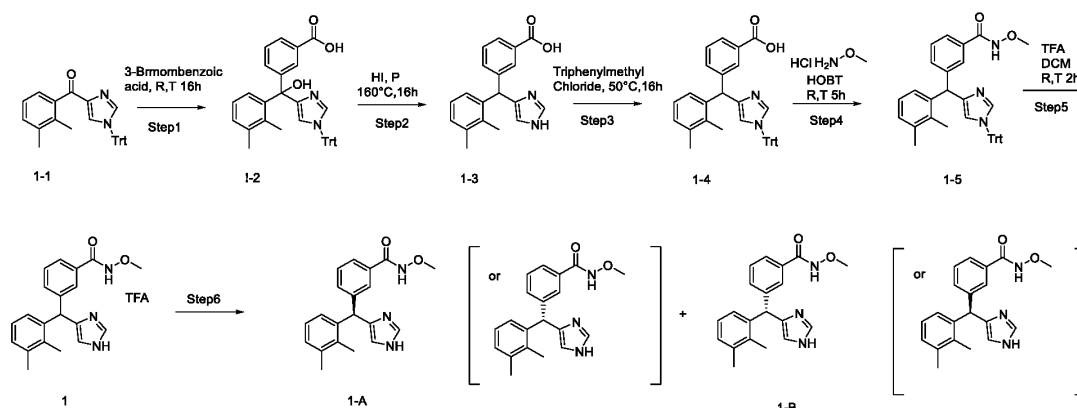
“ACN” refers to acetonitrile;

“LDA” refers to lithium diisopropyl amide;

“EA” or “EtOAc” refers to ethyl acetate;

“PE” refers to petroleum ether;
“r.t.” and “rt” refer to room temperature;
“THF” refers to tetrahydrofuran;
“DIPEA” refers to diisopropylethylamine;
“DCM” refers to dichloromethane;
“HOBT” refers to hydroxybenzotriazole;
“TLC” refers to thin layer chromatography;
“TLC” refers to thin layer chromatography;
“DMF” refers to dimethylformamide;
“h” refers to hours;
“min” refers to minutes;
“EDCI” refers to 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide;
“DMAP” refers to 4-Dimethylaminopyridine;
“Prep-HPLC” refers to preparative high performance liquid chromatography;
“DPPF” refers to 1,1'-Bis(diphenylphosphino)ferrocene; and
“NCS” refers to N-chlorosuccinimide.
“TEA” refers to triethylamine.
“TES” refers to triethyl silane.
“Trt” refers to trityl group or triphenylmethyl group.
“MeOH” refers to methanol.
“EtOH” refers to ethanol.
“t-BuXphos” refers to tert-butyl-Xantphos
“TMAI” refers to trimethylaluminum
“Xantphos” refers to 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
“Pd(PPh₃)₄” refers to tetrakis(triphenylphosphine)palladium(0)

Example 1. Synthesis of Compound 1



Step 1: 400mL THF and 36g (0.18mol, 4.0eq) of 3-bromobenzoic acid were added into a 500mL reaction flask. Following cooling to -65°C , 135mL (4mol/L, 0.428mol, 7.5eq) of n-Butyllithium was added. The mixture was stirred at -65°C for 2 hours before 20g (0.057mol, 1.0eq) of compound 1-1 and an additional 400mL of THF were introduced. After stirring at -65°C for 30 minutes, the mixture was allowed to warm to room temperature over 16 hours. Completion was confirmed by LC-MS, and 270mL of saturated ammonium chloride was added. The organic phase was then separated, vacuum concentrated, and the residue was column chromatographed (DCM-DCM: MeOH=92:8) to yield 13g of compound 1-2, with a 40.4% yield.

Step 2: 150 ml of 55% HI, 7.5g (13.3mmol, 1.0eq) of compound 1-2, and 4.1g (133mmol, 10.0eq) of red phosphorus were added into a 200 mL sealing tube. The mixture was stirred at 160°C for 16 hours until LC-MS indicated completion. Following vacuum concentration, the residue was collected to produce 7.3g of compound 1-3, achieving a 100% yield.

Step 3: 240 ml of pyridine, 12.1g (39.5mmol, 1.0eq) of compound 1-3, and 55.1g (197.5mmol, 3.0eq) of triphenylmethyl chloride were added to a 50mL reaction flask. The mixture was stirred at 50°C for 2 hours until LC-MS confirmed completion. After vacuum concentration, the residue underwent column chromatography (DCM-DCM:MeOH=92:8) to obtain 4.5g of compound 1-4, with a 20.8% yield.

Step 4: 52ml DCM, and then 1.3g (2.37mmol, 1.0eq) of compound 1-4, 594mg (7.11mmol, 3.0eq) of methoxyammonium chloride, 2.45g (18.96mmol, 8.0eq) of DIPEA, 640mg (4.74mmol, 2.0eq) of HOBT, and 999mg (5.21mmol, 2.2eq) of EDCI were added to a 100 mL

reaction flask. The mixture was stirred at room temperature for 5 hours until LC-MS confirmed the reaction's completion. After vacuum concentration, the residue was purified by column chromatography (DCM-DCM:MeOH=91:9) to yield 900mg of compound 1-5, with a yield of 65.8%.

Step 5: 18mL DCM and 900mg (1.56mmol, 1.0eq) of compound 1-5, along with 9mL of TFA, were added to a 50mL reaction flask. The reaction was stirred at room temperature for 2 hours until LC-MS showed completion. Following vacuum concentration, the residue underwent column chromatography to yield 670 mg of compound 1, achieving a 98.5% yield.

¹H NMR: (400 MHz DMSO) δ 14.33 (s, 2H), 11.79 (s, 1H), 9.00 (d, J = 0.9 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.17 – 7.06 (m, 2H), 6.94 (s, 1H), 6.70 (d, J = 7.2 Hz, 1H), 5.91 (s, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).

LC-MS: [M-TFA+1]⁺ = 336.2

Step 6: Compound 1 was separated by chiral HPLC to afford compound 1-A and compound 1-B. A column with the dimensions 30×250 mm packed with CHIRALPAK® IG (10 μ m particle size) was used as the chiral stationary phase. A mixture of 60% volume mobile phase A and 40% volume mobile phase B was used as the mobile phase.

*Mobile phase A: Hexane+0.2% NH₃ in MeOH

*Mobile phase B: EtOH+0.2% NH₃ in MeOH

The operation conditions were as follows:

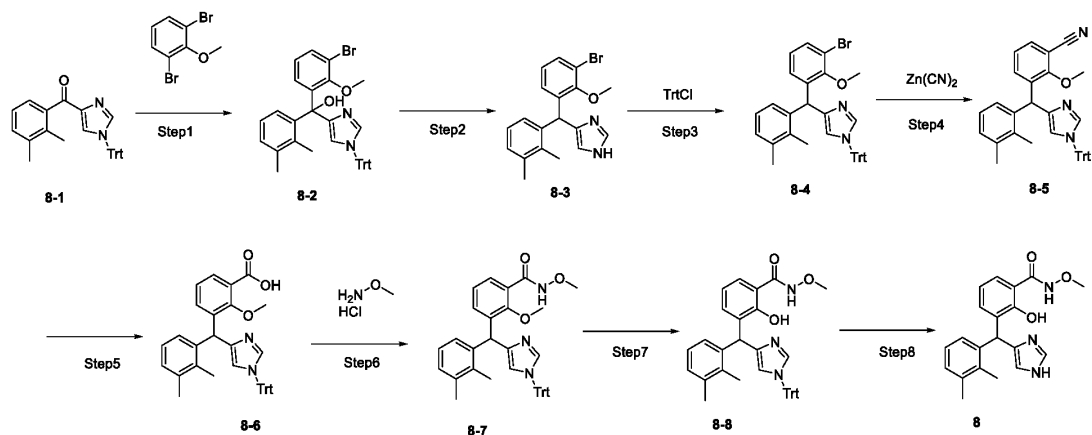
Temperature: Ambient temperature

Flow rate: 25mL/min

Detection: UV 214nm

500mg of compound 1 was separated on the column. The first eluting enantiomer (compound 1-A) with a retention time of 4.18min was isolated from the eluent with an enantiomeric excess of 100% in 80% yield. The second eluting enantiomer (compound 1-B) with a retention time of 5.83min was isolated from the eluent with an enantiomeric excess of 99.2% in 81% yield.

In this application, the naming convention for separated enantiomers is systematic. "A" denotes the first eluting product from the chromatography, and "B" indicates the second. For compounds where chirality leads to four distinct products, they are labeled as "A," "B," "C," and "D," based on their elution order. Consequently, if a compound is named as X, the separated products would be systematically named "X-A," "X-B," "X-C," and "X-D."

Example 2. Synthesis of Compound 8

Step 1: 200mL of THF and 9.10 g (34.1mmol, 1.5eq) of 2,6-dibromo-1-methoxybenzene were added in a 500mL three-necked round bottom flask under nitrogen atmosphere. At 0°C, 27mL (34.1mmol, 1.5eq) of isopropylmagnesium chloride lithium chloride complex was introduced. The mixture was stirred for 6 hours at 0°C before adding 10g (22.7mmol, 1eq) of compound 8-1, still under 0°C. Stirring continued for 16 hours at room temperature (25°C). Then, it was poured into water, washed with ethyl acetate, dried using Na₂SO₄, and fast silica gel column purification yielded 11.3g of compound 8-2 (79%).

Step 2: A 250mL three-necked round bottom flask received 113ml of DCM, 11.3 g (18mmol, 1.0eq) of compound 8-2, HSiEt₃ (21g, 180mmol, 10eq), and TFA (21g, 180mmol, 10eq) under nitrogen at 0°C. It was stirred until reaching room temperature over 16 hours. Concentration under vacuum produced compound 8-3 (17g, crude).

Step 3: 17 g (18mmol, 1.0eq) of compound 8-3, TrtCl (12.6g, 45mmol, 2.5eq), 170ml of DCM and Et₃N (9.1 g, 90mmol, 5eq) were mixed in a 500ml three-necked round bottom flask under nitrogen. After stirring for 16 hours at 25°C, completion was confirmed by LC-MS. The product was processed similarly to previous steps to yield 7.1 g of compound 8-4 (64%).

Step 4: 100ml of DMF, 6 g (9.8mmol, 1.0eq) of compound 8-4, Zn(CN)₂ (1.26g, 10.8mmol, 1.1eq), and Pd(PPh₃)₄ (1.26g, 1.1mmol, 0.11eq) were added under nitrogen to a 250ml three-necked round bottom flask. After stirring at 120°C for 2 hours, LC-MS confirmed completion. Following the standard work-up, 5.1 g of compound 8-5 (93%) was obtained.

Step 5: 60ml of EtOH, 2 g (3.6mmol, 1.0eq) of compound 8-5, and 12mL of 30% KOH were added under nitrogen into a 100ml single-mouth flask. The mixture was refluxed for 72 hours. After concentration under vacuum and subsequent work-up, 1.9 g of compound 8-6 (91%) was purified.

Step 6: 20ml of DCM, 1g (1.73mmol, 1.0eq) of compound 8-6, EDCI (0.432g, 2.25mmol, 1.3eq), DIPEA (0.893g, 6.92mmol, 4eq), HOBt (0.234g, 1.73mmol, 1.0eq), and methoxyammonium chloride (0.174g, 2.08mmol, 1.2eq) were combined in a 100mL single-mouth flask under nitrogen. Stirred for 16 hours at 25°C and then processed as before, this yielded 0.43 g of compound 8-7 (41%).

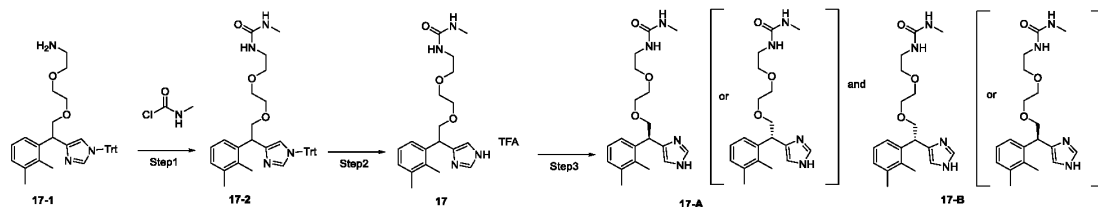
Step 7: 10ml of DCM, 0.430 g (0.71mmol, 1eq) of compound 8-7, and BBr₃ (0.435 g, 1.775mmol, 2.5eq) were mixed in a 25ml single-mouth flask at 0°C under nitrogen. Stirring continued for 3 hours at 0°C until LC-MS indicated completion, proceeding directly to the next step.

Step 8: The mixture from Step 7 and 10ml of MeOH were added to a 50ml single-mouth flask under nitrogen. Heated to reflux for 16 hours, completion was verified by LC-MS. After concentration under vacuum and further purification steps, including the addition of 10mL saturated NaHCO₃ solution and washing with ethyl acetate, drying over Na₂SO₄, and purification using Liquid Phase Method, 39mg of compound 8 was obtained, marking a 16% yield.

¹H NMR: (400 MHz DMSO) δ 12.25 (s, 3H), 7.57 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 6.98 (dt, J = 15.0, 6.6 Hz, 3H), 6.79 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 6.37 (s, 1H), 5.87 (s, 1H), 3.35 (s, 1H), 2.22 (s, 3H), 2.08 (s, 3H).

LC-MS: $[M+1]^+=352.2$

Example 3. Synthesis of Compound 17



Step 1: a 10ml single-mouth flask was initially charged under N₂ at 0°C with 4ml of DCM,

180mg (0.33mmol, 1eq) of compound 17-1, 110mg (1.00mmol, 3eq) of TEA, and 47mg (0.5mmol, 1.5eq) of methylaminoformyl chloride. The reaction mixture, after being allowed to reach 25°C, was stirred for 16 hours. Once LC-MS confirmed the reaction's completion, it was concentrated under vacuum and then purified using a fast silica gel column, resulting in 150mg of compound 17-2 at a 75% yield.

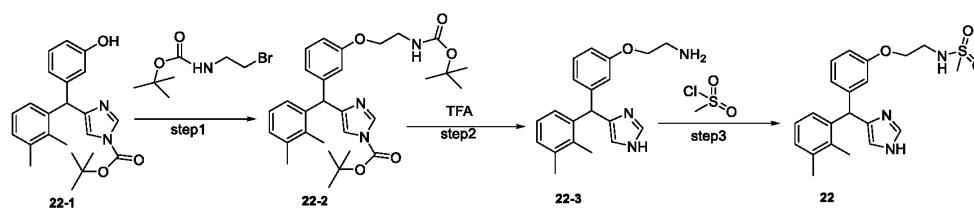
Step 2: 3ml of DCM, 150mg (0.25mmol, 1eq) of compound 17-2, and 1.5ml of TFA were added to a 10ml single-mouth flask under N₂ at 25°C. After stirring for 2 hours and confirmation of completion by LC-MS, the reaction mixture was vacuum concentrated and subjected to purification through a fast silica gel column, yielding 33mg of compound 17, which corresponds to a 28% yield.

Step 3: 438mg of compound 17 underwent separation using a chiral column, leading to the collection of compound 17-A (133mg), which after preparative liquid chromatography with a neutral method yielded 101mg (Yield = 23.06%), and compound 17-B (133mg), which also resulted in 101mg after similar purification, with a yield of 23.06%.

¹H NMR: (400 MHz CDCl₃) δ 8.66 (s, 1H), 7.19 – 7.02 (m, 2H), 6.96 (d, J = 7.2 Hz, 1H), 6.68 (s, 1H), 5.93 (s, 1H), 4.61 (dd, J = 9.3, 4.1 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.84 – 3.77 (m, 1H), 3.65 (ddd, J = 17.3, 13.3, 7.2 Hz, 5H), 3.46 – 3.31 (m, 2H), 2.66 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H).

LC-MS: [M-TFA+1]⁺=361.3

Example 4. Synthesis of Compound 22



Step 1: a 50mL three-necked flask received 10ml ACN, 300mg (0.793mmol, 1eq) of compound 22-1, 335mg (1.58mmol, 2eq) of tert-butyl N-(2-bromoethyl)carbamate, and 387mg (1.189mmol, 1.5eq) of Cs₂CO₃. The mixture was stirred at 60°C for 12 hours. Upon completion, as indicated by LC-MS, it was poured into water and extracted with EtOAc. The organic layer was dried over Na₂SO₄, vacuum concentrated, and yielded 300mg of compound 22-2 as a white solid, which was carried forward without further purification, yielding 72.5%.

Step 2: 300mg of compound 22-2, 10ml DCM, and 5ml TFA were added to a 50mL three-necked flask. This mixture was stirred at room temperature (25°C) for 12 hours. LC-MS confirmed completion; the mixture was then diluted with water, adjusted to pH 10, and extracted with DCM. The organic phase was dried over Na₂SO₄, vacuum concentrated, and the resulting residue was column chromatographed on silica gel to obtain 85mg of compound 22-3 as a yellow solid, with a yield of 45.9%.

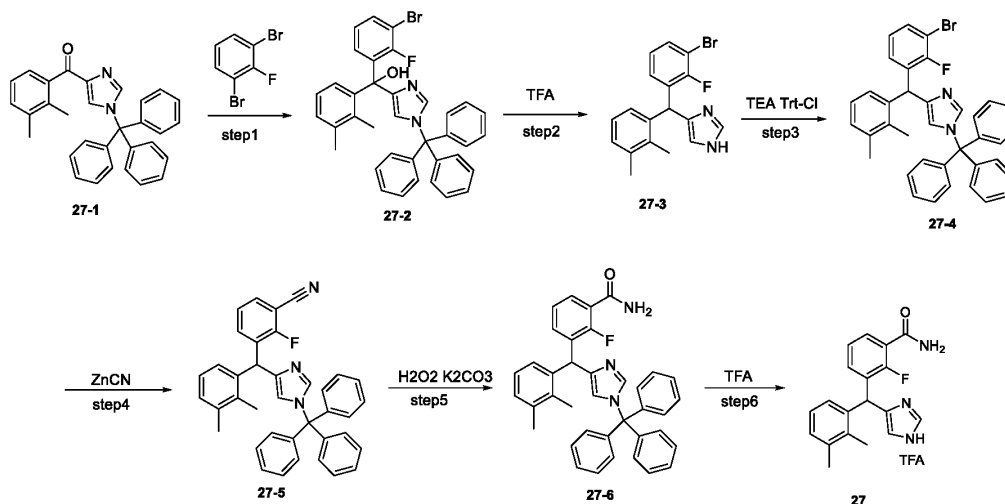
Step 3: a 10ml three-necked flask was charged with 5ml DMF, 75mg (0.233mmol, 1eq) of compound 22-3, 75mg (0.583mmol, 2.5eq) of DIPEA, and 29mg (0.257mmol, 1.1eq) of methanesulfonyl chloride. Stirring continued at 25°C for 2 hours until LC-MS analysis confirmed the reaction's completion. The mixture was then diluted with water, extracted with EA, and the organic phase was dried over Na₂SO₄ and vacuum concentrated. Purification by silica gel column chromatography yielded 14mg of compound 22 as a white solid, achieving a 13.2% yield.

Overall yield = 4.4%.

LC-MS: [M+1]⁺=400.2

¹H NMR (400 MHz, DMSO) δ 13.46 (s, 1H), 8.27 (s, 1H), 7.24 (dd, *J* = 13.6, 5.7 Hz, 2H), 7.04 (d, *J* = 11.2 Hz, 2H), 6.93 – 6.49 (m, 5H), 5.68 (s, 1H), 3.96 (s, 2H), 3.29 (d, *J* = 4.5 Hz, 2H), 2.91 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H).

Example 5. Synthesis of Compound 27



Step 1: In a 50mL reaction flask, 10mL of THF and 860mg (3.39mmol, 1.5eq) of 1,3-dibromo-2-fluorobenzene were combined and cooled to -65°C. Next, 1.4mL (3.39mmol,

1.5eq) of n-butyllithium was added. The mixture was stirred at this temperature for 2 hours before adding 1g (2.26mmol, 1eq) of compound 27-1 and another 10mL of THF. It was stirred for an additional 30 minutes at -65°C, then allowed to warm to room temperature over 16 hours. Completion was verified by LC-MS, and 20mL of saturated ammonium chloride was added. The organic phase was then separated, concentrated under vacuum, and purified via column chromatography, yielding 600mg of compound 27-2 with a yield of 43%.

Step 2: A 50mL three-necked flask was charged with 600mg (0.971mmol, 1eq) of compound 27-2, 1.1g (9.71mmol, 10eq) of triethylsilane, and 1.1g (9.71mmol, 10eq) of TFA. The mixture was stirred at 25°C for 1 hour. Upon completion, confirmed by LC-MS, it was poured into water, adjusted to pH=10, extracted with EA, dried over Na₂SO₄, and concentrated under vacuum. Purification via column chromatography on silica gel led to the isolation of 170mg of compound 27-3 as a yellow solid, yielding 48.7%.

Step 3: Into a 25mL reaction flask, 10ml of DMF, 170mg (0.473mmol, 1eq) of compound 27-3, 158g (0.568mmol, 1.2eq) of triphenylmethyl chloride, and 96mg (0.946mmol, 2eq) of TEA were added. The mixture was stirred at 25°C for 12 hours until LC-MS indicated the reaction had completed. After pouring into water, extracting with EA, drying over Na₂SO₄, and concentrating, the crude was purified by column chromatography, yielding 220mg of compound 27-4 with a 77.3% yield.

Step 4: A 25mL reaction flask was prepared with 10ml DMF, 170mg (0.283mmol, 1eq) of compound 27-4, 100mg (0.848mmol, 3eq) of ZnCN, and 98mg (0.0848mmol, 0.3eq) of tetrakis(triphenylphosphine)palladium. Stirring was conducted at 150°C for 30 minutes in a microwave. After completion, confirmed by LC-MS, the mixture was worked up and purified by column chromatography to yield 130mg of compound 27-5, an 84% yield.

Step 5: To a 25mL reaction flask, 10mL of DMSO and 110mg (0.201mmol, 1eq) of compound 27-5 were added and cooled to 0°C. Then, 3ml of 30% H₂O₂ was added, and the mixture was stirred at 0°C for 1 hour. Following LC-MS confirmation of completion, water was added, and the organic phase was separated and concentrated under vacuum. Column chromatography purification yielded 100mg of compound 27-6, an 88.1% yield.

Step 6: In a 25mL three-port flask, 10ml of DCM and 110mg of compound 27-6 were combined, and 5ml of TFA was added at 0°C. The mixture was allowed to reach room temperature naturally and stirred for 2 hours. Completion was indicated by LC-MS. The

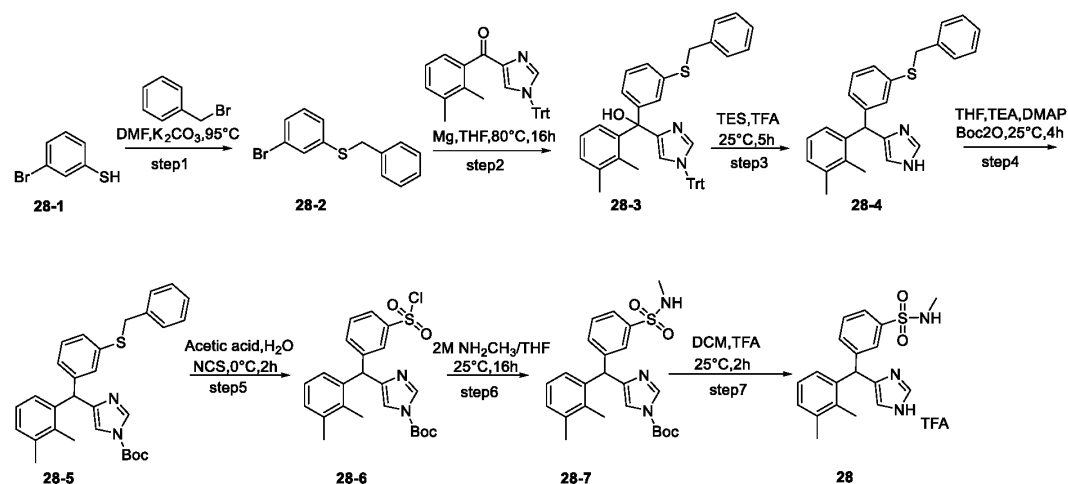
mixture was then concentrated under reduced pressure, and the residue was purified by TLC to obtain 25mg of compound 27 as a white solid, with a yield of 29.4%.

Overall yield = 3.5%.

LC-MS: $[M-C_2HF_3O_2+1]^+=324.2$

1H NMR (400 MHz, DMSO) δ 14.36 (s, 5H), 8.97 (s, 3H), 7.77 (s, 3H), 7.64 (s, 3H), 7.60 (t, $J = 6.7$ Hz, 3H), 7.24 (t, $J = 7.7$ Hz, 3H), 7.15 (d, $J = 7.3$ Hz, 3H), 7.13 – 6.98 (m, 9H), 6.71 (d, $J = 7.5$ Hz, 3H), 6.01 (s, 3H), 2.27 (s, 9H), 2.12 (s, 9H)

Example 6. Synthesis of Compound 28



Step 1: In a 500ml reaction flask, 220ml DMF, 24.5g (0.13mol, 1eq) of compound 28-1, 26.6g (0.16mol, 1.2eq) of benzyl bromide, and 21.5g (1.2mol, 1.2eq) of K_2CO_3 were combined. The mixture was heated to 95°C for 16 hours. GC-MS confirmed the reaction's completion. After filtration and concentration, column chromatography purification yielded 32g of compound 28-2 with an 88.5% yield.

Step 2: Into a 25ml reaction flask, 5ml THF, 185mg (7.6mmol, 2.1eq) of magnesium chips, and 2g (7.2mmol, 2.0eq) of compound 28-2 were added. The mixture was stirred at 65°C for 1 hour before cooling to room temperature for the next step. A 50mL reaction flask received 20mL THF and 1.59g (3.6mmol, 1.0eq) of (2,3-Dimethylphenyl)-[1-(trityl)-1H-imidazol-4-yl]methanone. The previously prepared Grignard reagent was added, and the reaction was heated to 80°C for 16 hours. Completion was verified by LC-MS. After quenching with 10mL water, extraction with EA, and drying with Na_2SO_4 , the mixture was concentrated. Column chromatography purification yielded 1.6g of compound 28-3, a 69.2% yield.

Step 3: A 100mL reaction flask was charged with 14mL DCM, 1.4g (2.18mmol, 1.0eq) of compound 28-3, and 2.53g (21.8mmol, 10eq) of TES. After cooling to 0°C, 2.48g (21.8mmol, 10eq) of TFA was added. The mixture was warmed to 25°C for 5 hours, then concentrated under vacuum after LC-MS confirmed completion. The residue was column chromatographed to yield 500mg of compound 28-4, a 68.4% yield.

Step 4: In a 5mL reaction flask, 2mL THF, 100mg (0.29mmol, 1.0eq) of compound 28-4, 7mg (0.06mmol, 0.2eq) of DMAP, 94mg (0.43mmol, 1.5eq) of Boc₂O, and 44mg (0.43mmol, 1.5eq) of TEA were mixed. The reaction was held at 25°C for 4 hours, confirmed by LC-MS. After vacuum concentration, the residue was purified by column chromatography, yielding 120mg of compound 28-5, an 85.5% yield.

Step 5: A 10mL reaction flask was loaded with 1.5mL acetic acid, 0.5ml water, and 120mg (0.25mmol, 1.0eq) of compound 28-5. After chilling to 0°C, 165mg (1.24mmol, 5eq) of NCS was added. The mixture was stirred at 0°C for 2 hours until LC-MS confirmed completion, then moved to the next step without purification. The yield was recorded as 100%.

Step 6: To a 50mL reaction flask, 10mL of 2M NH₂CH₃/THF was added and cooled to 0°C before introducing the crude compound 28-6. Stirring proceeded at 25°C for 16 hours, as evidenced by LC-MS. After concentration under vacuum, the mixture was purified by column chromatography to yield 40mg of compound 28-7, a 40% yield.

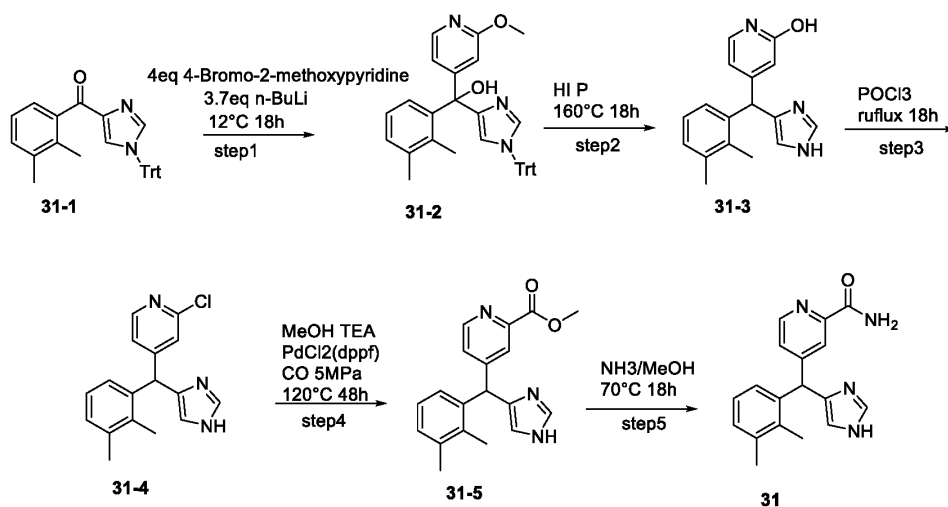
Step 7: In a 5mL reaction flask, 1mL DCM and 40mg (0.088mmol, 1.0eq) of compound 28-7 were combined. The mixture was cooled to 0°C before adding 0.5ml TFA, then allowed to warm to 25°C for 2 hours, completion shown by LC-MS. The concentrated mixture was purified through prep-HPLC to obtain 14mg of compound 28, with a yield of 44.8%.

Overall yield=6.4%.

LC-MS: [M+1-TFA]⁺= 356.1

¹H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.01 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.46 (dt, *J* = 17.1, 6.3 Hz, 2H), 7.12 (dt, *J* = 15.1, 7.4 Hz, 2H), 6.95 (s, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 2.37 (d, *J* = 4.9 Hz, 3H), 2.26 (s, 3H), 2.12 (s, 3H).

Example 7. Synthesis of Compound 31



Step 1: Into a 250mL three-port reaction bottle, 120ml of THF, 5.08g (27.15mmol, 4.0eq) of 4-bromo-2-methoxypyridine, and 10mL of 2.5N n-butyl lithium in n-hexane (25.1mmol, 3.7eq) were added dropwise at -65°C. The solution was maintained at -65°C for 1 hour before adding 3g (6.79mmol, 1eq) of compound 31-1. After another 0.5 hours at -65°C, the reaction was left to proceed overnight at room temperature. Completion was verified by LC-MS. The reaction was quenched with 100ml of saturated ammonium chloride, and the organic layer was separated and concentrated. The residue was mixed with 50mL DCM, stirred for 5 minutes, filtered, and dried with an infrared lamp to yield 2.88g of compound 31-2 (77% yield).

Step 2: A 50ml closed tank received 20ml of 57 wt.% HI, 2.35g (4.599mmol, 1.0eq) of compound 31-2, and 1.43g (45.99mmol, 10eq) of red phosphorus. Stirred at 160°C overnight and checked by LC-MS for completion, the mixture was cooled to room temperature and concentrated to yield 5g of crude compound 31-3 (100% yield).

Step 3: Compound 31-3 (1g, crude) and 15mL of POCl₃ were added to a 5mL reaction flask. After refluxing overnight and verifying completion with LC-MS, the mixture was cooled, concentrated under vacuum, and the residue was neutralized to pH=8 with saturated sodium bicarbonate. Extraction with 40mL EA (three times), drying with anhydrous sodium sulfate, and concentration provided 174mg of compound 31-4 via column chromatography (30% yield).

Step 4: Into a 200mL high-pressure reactor, 174mg (0.586mmol, 1eq) of compound 31-4, 10 mL of MeOH, 296mg (2.93mmol, 5eq) of TEA, and 48mg (0.0586mmol, 0.1eq) of

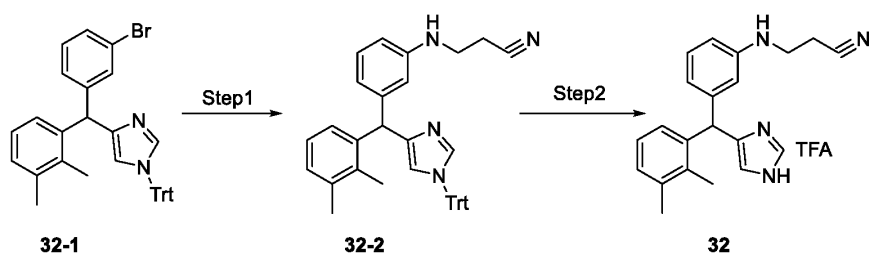
$\text{PdCl}_2(\text{dppf})$ were introduced. The reaction, under 5MPa of carbon monoxide at 120°C for 48 hours, left 5% of the starting material, as shown by LC-MS. After filtration and concentration, 270mg of compound 31-5 was isolated by column chromatography (100% yield).

Step 5: A 50mL closed tank was charged with 100mg (0.312mmol, 1eq) of compound 31-5 and 5mL of MeOH/ NH_3 (15M/L). The mixture was stirred at 68°C overnight, cooled to room temperature, concentrated under vacuum, and then purified to obtain 10mg of compound 31 through pre-HPLC (10% yield).

LC-MS: $[\text{M}+1]^+=307.2$

^1H NMR (400 MHz, DMSO) δ 12.53 (s, 1H), 8.52 (d, $J = 4.7$ Hz, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.35 (d, $J = 3.8$ Hz, 1H), 7.10 – 7.00 (m, 2H), 6.81 (d, $J = 7.2$ Hz, 1H), 6.66 (s, 1H), 5.80 (s, 1H), 2.24 (s, 3H), 2.11 (s, 3H).

Example 8. Synthesis of Compound 32



Step 1: Into the bottom of a 50mL single-mouth flask, 300mg (0.51mmol, 1eq) of compound 32-1, 108mg (1.54mmol, 3eq) of 2-cyanoethylamine, 213mg (1.54mmol, 3eq) of K_2CO_3 , 47mg (0.051mmol, 0.1eq) of $\text{Pd}_2(\text{dba})_3$, and 55mg (0.10mmol, 0.2eq) of brettphos were added. The mixture was stirred under nitrogen at 120°C for 1 hour. The completion of the reaction was indicated by TLC. The mixture was then transferred into 100mL of water and extracted three times with 50mL of ethyl acetate. After washing the organic layer with 50mL of brine, it was dried over Na_2SO_4 and concentrated under vacuum to yield 1g of a crude yellow oil. This was purified via column chromatography (Petroleum Ether: Ethyl Acetate = 1:0 to 1:1) to obtain 216mg of compound 32-2 as a yellow powder, resulting in a yield of 73.36%.

Step 2: A 50mL single-mouth flask was charged with 200mg (0.35mmol, 1eq) of compound 32-2, 5mL of dichloromethane, and 1mL of trifluoroacetic acid. The mixture was stirred at room temperature for 1 hour, with TLC confirming the reaction's completion. The solution

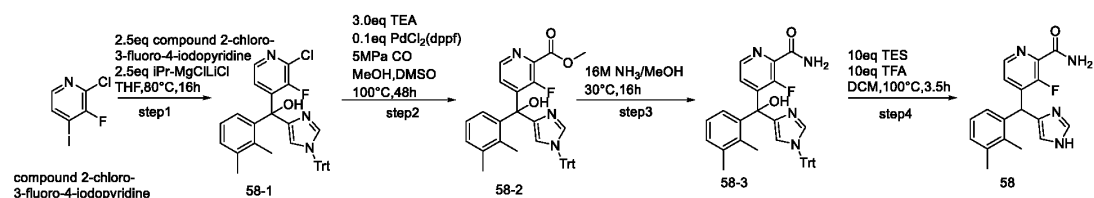
was then vacuum-concentrated, and the crude product was subjected to column chromatography (Dichloromethane: Methanol = 1:0 to 90:10) to produce 120mg of compound 32. Further purification by preparative HPLC yielded 93mg of compound 32 as a yellow powder, with an overall yield of 59.92%.

Overall yield=43.96%.

LC-MS: $[M+1]^+ = 331.2$.

¹H NMR (400 MHz, DMSO) δ 14.18 (s, 2H), 8.91 (s, 1H), 7.15 – 7.01 (m, 3H), 6.90 (s, 1H), 6.70 (d, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 8.0$ Hz, 1H), 6.41 (s, 1H), 6.36 (d, $J = 7.6$ Hz, 1H), 5.97 (s, 1H), 5.65 (s, 1H), 3.49 – 3.13 (m, 5H), 2.67 (t, $J = 6.5$ Hz, 2H), 2.25 (s, 3H), 2.13 (s, 3H). Y=59.92%. Total yield=43.96%.

Example 9. Synthesis of Compound 58



Step 1: In a 100mL reaction flask, 40mL of THF and 4g (15.5mmol, 2.5eq) of 2-chloro-3-fluoro-4-iodopyridine were added. After cooling the mixture to 0°C, 12mL (15.5mmol, 2.5eq) of iPr-MgClLiCl was introduced. The reaction was stirred at 0°C for 3 hours, then 1.16g (2.63mmol, 1.0eq) of 2,3-dimethylphenyl[1-(trityl)-1H-imidazol-4-yl]methanone was added and the reaction was stirred at 80°C for 16 hours. Following completion, confirmed by LC-MS, the reaction was quenched with 40mL water and extracted with EA. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography to yield 2.6g of compound 58-1, achieving a 29.3% yield.

Step 2: To a 200mL high-pressure reactor, 1g (1.74mmol, 1.0eq) of 58-1, 40 mL of MeOH, 40mL of DMSO, 530mg (5.24mmol, 3.0eq) of TEA, and 148mg (0.17mmol, 0.1eq) of PdCl₂(dppf) were added. The mixture was reacted with carbon monoxide at 5MPa and 100 °C for 48 hours, with LC-MS indicating 5% remaining raw material. After concentration, the residue was purified by column chromatography to yield 53mg of compound 58-2, a 51.2% yield.

Step 3: A 50mL sealed tube received 25mL of 16M NH₃/MeOH and 530mg (0.89mmol, 1.0eq) of compound 58-2. Stirred at 30°C for 16 hours until LC-MS confirmed completion, the

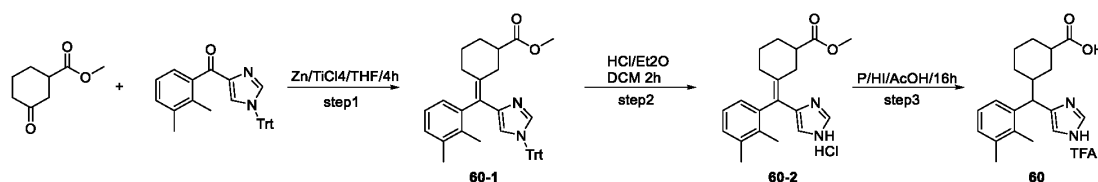
residue was then purified by column chromatography to yield 360mg of compound 58-3, a 67.8% yield.

Step 4: Into a 10mL reaction flask, 3mL DCM, 100mg (0.17mmol, 1.0eq) of compound 58-3, and 195mg (1.7mmol, 10eq) of TES were added. After cooling to 0°C, 191mg (1.7mmol, 10eq) of TFA was introduced. The reaction was then warmed to 100°C for 3.5 hours. LC-MS showed completion, and after concentration under vacuum, the residue was purified by prep-HPLC to yield 16mg of compound 58, with a 28.8% yield.

LC-MS: $[M + 1]^+ = 325.2$

¹H NMR (400 MHz, CD₃OD) δ 8.36 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 0.9 Hz, 1H), 7.13 (dt, J = 22.7, 10.1 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.53 (s, 1H), 6.05 (s, 1H), 2.32 (s, 3H), 2.21 (s, 3H).

Example 10. Synthesis of Compound 60



Step 1: Into a 100mL three-necked flask, 29mL of THF and 2.9g (43.9mmol, 7.5eq) of zinc were added. This mixture was cooled to -10°C under a nitrogen atmosphere while stirring. Then, 4.1g (21.6mmol, 3.7eq) of titanium tetrachloride was added dropwise at -10°C. The reaction mixture was stirred at 70°C for 16 hours, followed by the addition of 950mg (6.08mol, 1.04eq) of methyl 3-oxocyclohexanecarboxylate and 2.6g (5.85mol, 1eq) of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone. Stirring continued for 4 hours at 80°C. Completion was confirmed by LC-MS. The reaction was then diluted with 100mL of water and 100mL of EA, filtered, and the filtrate was extracted with EA. After washing with brine and drying over Na₂SO₄, the organic layers were concentrated under reduced pressure to yield 950mg of compound 60-1 as crude, with a 50% yield.

Step 2: To a 25mL three-necked flask, 10mL of DCM and 0.5g (1.54mmol, 1eq) of compound 60-1, along with 10mL of HCl/Et₂O, were added. The mixture was stirred at room temperature for 3 hours. LC-MS indicated the reaction was complete. Concentrating under reduced pressure yielded 400mg of compound 60-2 as crude, with a 100% yield.

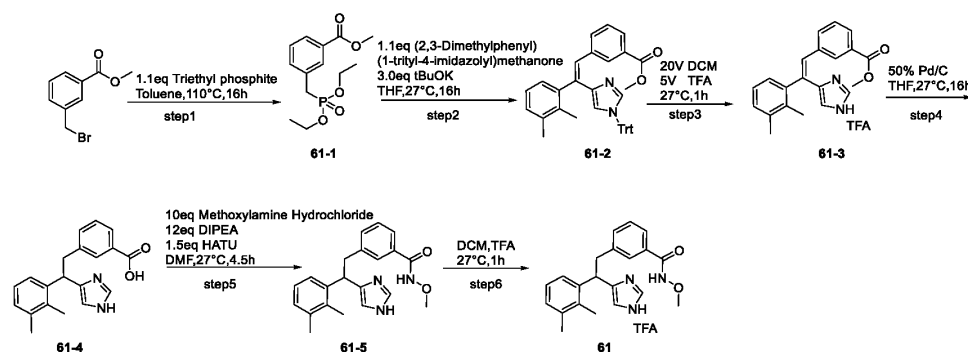
Step 3: A 250mL three-necked flask received 1.2mL of AcOH, 0.9mL of hydriodic acid (55%-58%), 50mg (0.15mmol, 1.0eq) of compound 60-2, and 167mg (5.4mmol, 35eq) of phosphorus. The reaction mixture was stirred at 100°C for 16 hours. Completion was confirmed by LC-MS. The mixture was then added to water, adjusted to pH=7, and extracted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to obtain 70mg of crude. Purification by liquid chromatography yielded 6mg of compound 60, with a 10% yield.

Overall yield: 5%

LC-MS: [M-TFA-1]⁻=311.2

¹H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 12.02 (s, 1H), 9.02 – 8.89 (m, 1H), 7.75 – 7.56 (m, 1H), 7.13 (ddt, J = 22.9, 16.8, 9.0 Hz, 3H), 4.26 – 4.06 (m, 1H), 2.28 – 2.08 (m, 8H), 1.91 – 0.73 (m, 8H).

Example 11. Synthesis of Compound 61



Step 1: A 50mL reaction flask received 20mL toluene, 3.8g (16.7mmol, 1.0eq) of methyl 3-(bromomethyl)benzoate, and 3.04g (18.3mmol, 1.1eq) of triethyl phosphite. The mixture was stirred at 110°C for 16 hours. Upon completion, confirmed by LC-MS, the solution was concentrated. The residue underwent column chromatography, yielding 5.3g of compound 61-1 with a 99% yield.

Step 2: Into a 100mL reaction flask, 40mL THF, 2g (7.0mmol, 1.0eq) of compound 61-1, and 3.4g (7.7mmol, 1.1eq) of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone were combined and cooled to 0°C before adding 2.35g (21mmol, 3.0eq) of potassium tert-butoxide. After stirring at 27°C for 16 hours and confirmation of completion by LC-MS, the solution was concentrated and purified by column chromatography to yield 1.03g of compound 61-2, a 26.3% yield.

Step 3: A 25mL reaction flask was charged with 10mL DCM and 500mg of compound 61-2, followed by the addition of 2.5mL TFA. The reaction mixture was stirred at 27°C for 1 hour. LC-MS indicated completion, and after concentration, the residue was purified by column chromatography to yield 240mg of compound 61-3, an 84.5% yield.

Step 4: In a 10mL reaction flask, 3mL THF, 240mg of compound 61-3, and 120mg (50%) of Pd/C were added. Stirred at 27°C for 16 hours and confirmed by LC-MS, the solution was filtered. The organic phase was concentrated, and the residue was purified by column chromatography to yield 150mg of compound 61-4, a 62.1% yield.

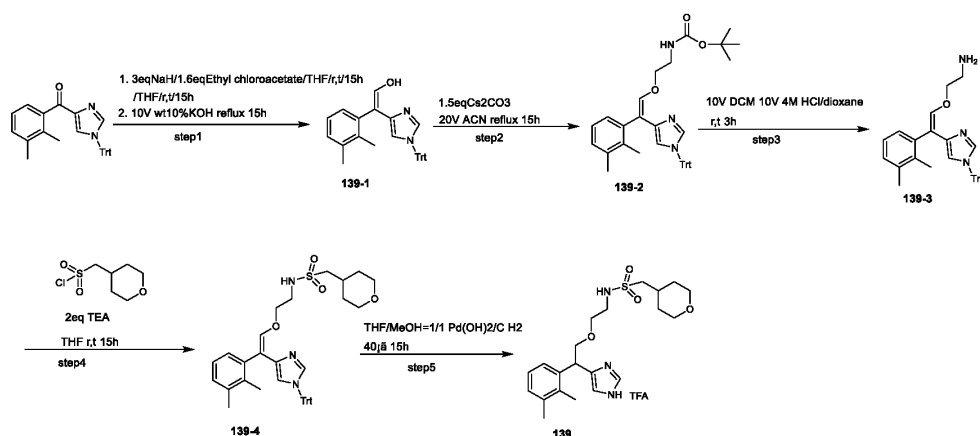
Step 5: To a 10mL reaction flask, 3mL DMF, 80mg (0.25mmol, 1.0eq) of compound 61-4, 209mg (2.5mmol, 10eq) of methoxyammonium chloride, cooled to 0°C, then 386mg (3mmol, 12eq) of DIPEA and 142mg (0.37mmol, 1.5eq) of HATU were added. Stirred at 27°C for 4.5 hours, LC-MS showed 40% remaining raw material. The mixture was concentrated under vacuum to yield 160mg of compound 61-5, achieving a 100% yield.

Step 6: A 10mL reaction flask was prepared with 1mL DCM and 160mg of compound 61-5, and 0.5mL TFA was added. Stirred at 27°C for 1 hour, completion was confirmed by LC-MS. After concentration under vacuum, the residue was purified by prep-HPLC to yield 25mg of compound 61, a 15.3% yield. Overall yield: 2.1%.

LC-MS: $[M - C_2HF_3O_2 + 1]^+ = 350.2$

¹H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 11.69 (s, 1H), 8.96 (d, J = 0.9 Hz, 1H), 7.61 (d, J = 4.6 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.31 (t, J = 6.4 Hz, 2H), 7.07 (dt, J = 12.8, 4.6 Hz, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.70 (s, 3H), 3.39 (d, J = 8.5 Hz, 1H), 3.19 (dd, J = 13.8, 7.3 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).

Example 12. Synthesis of Compound 139



Step 1: In a 100ml single-mouth flask, 50ml of THF, 5g (11.29mmol, 1.0eq) of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone, 2.3g (18.1mmol, 1.6eq) of ethyl chloroacetate, and 1.35g (33.9mmol, 3eq, 60% wt) of NaH were combined under a nitrogen atmosphere. The mixture was stirred at 25°C for 16 hours, confirmed complete by LC-MS, and concentrated under vacuum. After adding 50ml of 10% KOH, it was stirred for another 16 hours at 100°C, then worked up and purified via a fast silica gel column to yield 3.4g of 139-1, with a 65.9% yield.

Step 2: A 100mL three-necked flask received 60ml of ACN, 3.2g (7.01mmol, 1eq) of 139-1, 3.14g (14.02mmol, 2eq) of CAS 39684-80-5, and 3.42g (10.51mmol, 1.5eq) of Cs_2CO_3 . Stirred at 60°C for 12 hours and confirmed complete by LC-MS, the reaction was worked up and purified to give 930mg of 139-2, a 22.1% yield.

Step 3: To a 25mL three-necked flask was added 300mg of 139-2, 3ml of DCM, and 3ml of 4M HCl in dioxane. After stirring at 25°C for 3 hours and confirmation of completion by LC-MS, the reaction was neutralized to pH=10, extracted, and purified to yield 130mg of 139-3 as a white solid, a 52% yield.

Step 4: A 25mL three-necked flask was charged with 5ml of THF, 130mg (0.260mmol, 1eq) of 139-3, 40mg (0.390mmol, 1.5eq) of TEA, and 57mg (0.286mmol, 1.1eq) of (Tetrahydro-2H-pyran-4-yl)methanesulfonyl chloride (CAS 264608-29-9). Stirred at 25°C for 18 hours and verified complete by LC-MS, the mixture was worked up and purified to give 80mg of 139-4 as a white solid, yielding 46.5%.

Step 5: 139-4 (80mg) was combined with $\text{Pd}(\text{OH})_2/\text{C}$ (80mg), 5mL of methanol, and 5mL of THF, stirred at 40°C for 18 hours under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated, mixed with 10mL of DCM and 5mL of TFA, stirred for ten

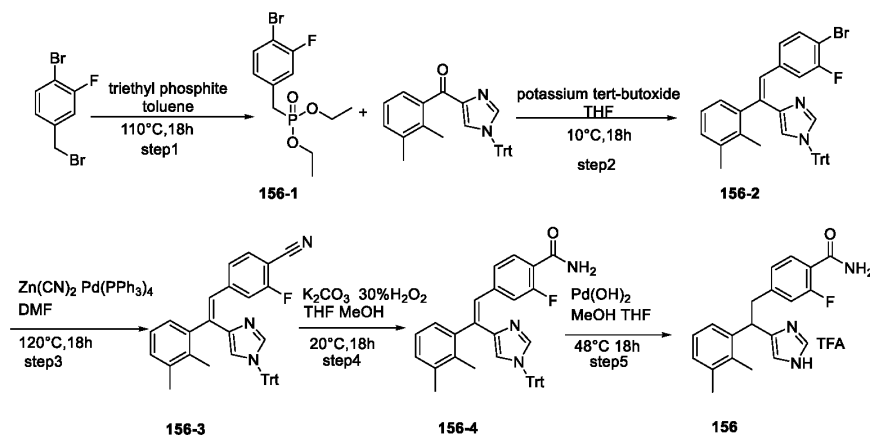
minutes, and dried. The residue was purified by preparative HPLC to yield 30mg of 139 as a white solid, with a 46.3% yield.

Overall yield=1.63%.

LC-MS: $[M-C_2HF_3O_2+1]^+=422.2$

¹H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 9.00 (s, 1H), 7.58 (s, 1H), 7.21 – 6.95 (m, 3H), 6.86 (d, $J = 7.5$ Hz, 1H), 4.65 (dd, $J = 8.2, 5.3$ Hz, 1H), 3.90 (t, $J = 9.3$ Hz, 1H), 3.78 (dd, $J = 16.0, 8.9$ Hz, 3H), 3.50 (d, $J = 5.1$ Hz, 2H), 3.28 (t, $J = 11.2$ Hz, 2H), 3.09 (dd, $J = 11.1, 5.4$ Hz, 2H), 2.92 (d, $J = 6.3$ Hz, 2H), 2.28 (s, 6H), 2.00 (d, $J = 4.4$ Hz, 1H), 1.72 (d, $J = 12.9$ Hz, 2H), 1.28 (qd, $J = 12.2, 4.1$ Hz, 2H).

Example 13. Synthesis of Compound 156



Step 1: A 50mL reaction flask was charged with 25mL of toluene, 5g (0.0188mmol, 1.0eq) of 3-fluoro-4-bromobenzyl bromide, and 3.44g (0.0207mmol, 1.1eq) of triethyl phosphite. Stirred at 110°C for 18 hours, completion was confirmed by LC-MS. The reaction mixture was concentrated and the residue was purified by column chromatography to yield 5.69g of compound 156-1, with a 93.4% yield.

Step 2: To a 50mL reaction flask, 20mL of THF, 1g (3.08mmol, 1.0eq) of compound 156-1, and 1.36g (3.08mmol, 1.0eq) of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone were added and cooled to 0°C. Then, 1.04g (9.24mmol, 3.0eq) of potassium tert-butoxide was introduced. After stirring at 10°C for 18 hours and confirmation of completion by LC-MS, the reaction was filtered, concentrated, and the residue was purified by column chromatography to yield 1.31g of 156-2, a 69.5% yield.

Step 3: A 10mL reaction flask received 5mL of DMF, 500mg (0.817mmol, 1.0eq) of 156-2, 192mg (1.634mmol, 2.0eq) of zinc cyanide, and 95mg (0.0817mmol, 0.1eq) of Pd(PPh₃)₄. Stirred at 120°C for 18 hours, TLC indicated 50% of the raw materials remained. The mixture was diluted with 40mL of ice water, extracted three times with 20mL of EA, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by column chromatography yielded 220mg of 156-3, an 83.5% yield.

Step 4: Into a 5mL reaction flask, 1.5mL of THF, 1.5mL of MeOH, 110mg (0.197mmol, 1.0eq) of 156-3, 54mg (0.394mmol, 2.0eq) of K₂CO₃, and 45mg (0.394mmol, 2.0eq) of 30% H₂O₂ were combined under nitrogen. The mixture was stirred overnight at 20°C for 18 hours. Following completion, confirmed by LC-MS, the mixture was poured into 10mL of water, extracted three times with 10mL of EA, dried over Na₂SO₄, and concentrated under vacuum. Purification by column chromatography yielded 77mg of 156-4, a 67.7% yield.

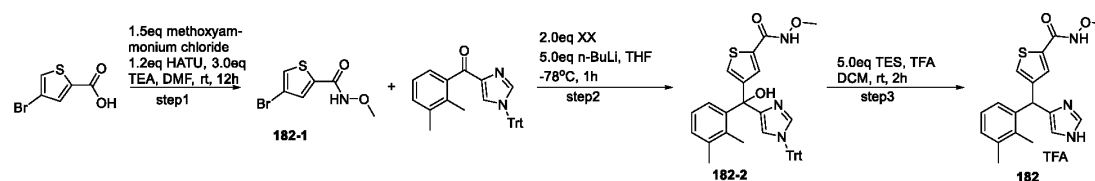
Step 5: In a 5mL reaction flask, 3mL of MeOH:THF (1:1), 90mg (0.156mmol, 1.0eq) of 156-4, and 87mg of Pd(OH)₂ were stirred at 48°C overnight under a hydrogen environment. LC-MS confirmed the reaction's completion. The reaction was filtered, concentrated, and the crude product was further processed with 2mL of DCM and 0.5mL of TFA, stirred for 0.5 hours, then concentrated. Purification by pre-HPLC yielded 41mg of compound 156, with a 58.3% yield.

Overall yield: 21.4%

LC-MS: [M-C₂H₃O₂+1]⁺=338.2

¹H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.97 (s, 1H), 7.65 – 7.48 (m, 4H), 7.09 (dt, J = 14.4, 7.2 Hz, 5H), 4.78 (t, J = 7.9 Hz, 1H), 3.42 (dd, J = 13.9, 8.5 Hz, 1H), 3.22 (dd, J = 13.9, 7.3 Hz, 1H), 2.23 (s, 3H), 2.16 (s, 3H).

Example 14. Synthesis of Compound 182



Step 1: In a 50mL flask, 20mL DMF, 2g (9.66mmol, 1.0eq) of 4-bromo-2-thiophenecarboxylic acid, 2.93g (28.98mmol, 3.0eq) of TEA, and 1.21g (14.49mmol, 1.5eq) of methoxyammonium chloride were combined. After adding 4.41g (11.59mmol, 1.2eq) of HATU, the mixture was stirred at room temperature for 12 hours. Following completion,

confirmed by LC-MS, the reaction was quenched with water and extracted with ethyl acetate. After drying over Na_2SO_4 and filtration, the concentrate was purified by column chromatography (PE:EA=67:33) to yield 1.25g of 182-1 as a white solid, a 54.8% yield.

Step 2: In a 25mL three-necked flask, 598mg (2.53mmol, 2.0eq) of 182-1 was dissolved in 6mL THF and cooled to -80°C under nitrogen. n-BuLi (2.5M, 2.5mL, 6.33mmol, 5.0eq) was added, stirred for 40 minutes, then a mixture of 560mg (1.27mmol, 1.0eq) of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone in 6mL THF was introduced. After stirring for 1 hour and quenching with water, the mixture was warmed and extracted with ethyl acetate. The organic phase was dried, filtered, and concentrated, then purified by column chromatography (DCM:MeOH=90:10) and further recrystallized with PE:MTBE=2:1 to yield 67mg of 182-2 as a light yellow solid, an 8.8% yield.

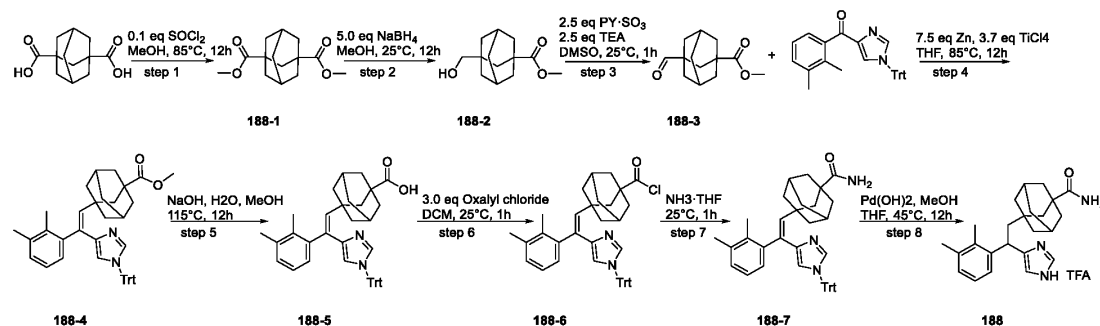
Step 3: A 10mL flask received 1mL DCM, 1mL TFA, 65mg (0.11mmol, 1.0eq) of 182-2, and 38mg (0.33mmol, 3.0eq) of TES. After stirring for 2 hours, confirmed complete by LC-MS, the mixture was concentrated and purified by preparative HPLC to afford 20mg of 182 as a white solid, yielding 42.1%.

Overall yield=2.03%.

LC-MS: $[\text{M}-\text{C}_2\text{H}_3\text{O}_2+1]^+=342.1$

^1H NMR (400 MHz, DMSO) δ 14.36 (s, 2H), 11.75 (s, 1H), 9.06 (s, 1H), 7.46 (s, 2H), 7.12 (p, $J = 7.4$ Hz, 3H), 6.75 (d, $J = 7.3$ Hz, 1H), 5.88 (s, 1H), 3.67 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H).

Example 15. Synthesis of Compound 188



Step 1: Thionyl chloride (0.582mL, 8.03mol, 0.1eq) was added to a methanol solution of adamantane-1,3-dicarboxylic acid (18g, 80.27mmol, 1.0eq) at 0°C . Stirred at 85°C for 12 hours, the reaction completion was confirmed by LC-MS. The concentrated mixture was diluted with water (50mL), neutralized to pH=8 with saturated NaHCO_3 , extracted with ethyl

acetate (30mL×3), dried, and concentrated to yield 20g of 188-1 as a white solid (100% yield).

Step 2: 188-1 (20g, 79.27mmol, 1.0eq) was dissolved in methanol (350mL), and NaBH₄ (14.99g, 0.39mol, 5.0eq) was added at 0°C. After stirring at 25°C for 12 hours and confirming the completion, the reaction was concentrated, diluted with ethyl acetate, extracted with water, dried, and purified to obtain 5g of 188-2 as a white solid (11.7% yield).

Step 3: DMSO (50mL), 188-2 (4g, 17.83mmol, 1.0eq), PySO₃ (7.1g, 44.58mmol, 2.5eq), and TEA (4.51g, 44.58mmol, 2.5eq) were added to a 250mL flask. Stirred at 25°C for an hour and verified by LC-MS, the mixture was processed and purified to yield 2g of 188-3 as a white solid (51.3% yield).

Step 4: In a 50mL flask, THF (20mL) was combined with Zn (1.1g, 16.87mmol, 7.5eq) and TiCl₄ (1.58g, 8.32mmol, 3.7eq) at -70°C, followed by 188-3 (500mg, 2.25mmol, 1.0eq) and a specified compound in THF. Stirred at 80°C for 2 hours, the reaction was completed, worked up, and purified to yield 270mg of 188-4 as a yellow solid (19.1% yield).

Step 5: 188-4 (200mg) was reacted with NaOH (5mL, 8M) in methanol at 20°C, heated to 115°C for 12 hours, cooled, adjusted to pH=4, extracted, and concentrated to yield 80mg of 188-5 as a yellow solid (40.8% yield).

Step 6: 188-5 (60mg, 0.096mmol, 1.0eq) was mixed with oxalyl dichloride (36.92mg, 0.291mmol, 3.0eq) in DCM (1mL) at 0°C, stirred at 15°C for an hour, concentrated to yield 60mg of 188-6 as a white solid (100% yield), and used directly in the next step.

Step 7: 188-6 (60mg) was dissolved in THF (0.5 mL) and treated with NH₃·THF (8mL) at 0°C, stirred at 15°C for an hour, concentrated to yield 60mg of 188-7 as a white solid (100% yield), and used directly in the next step.

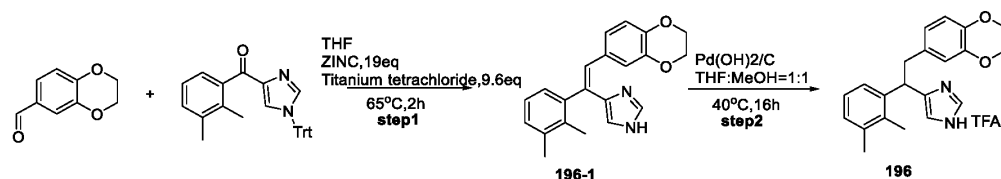
Step 8: 188-7 (60mg) was combined with Pd(OH)₂ (60mg) in MeOH:THF (16mL, 1:1), stirred at 45°C under hydrogen, concentrated, treated with DCM (1mL) and TFA (0.5mL), concentrated, and purified to yield 20mg of 188 as a white solid (43.4% yield).

Overall yield=0.2%.

LC-MS: [M-C₂H₃O₂+1]⁺=378.2

¹H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 8.96 (s, 1H), 7.66 (s, 1H), 7.03 (t, J = 6.2 Hz, 3H), 6.89 (s, 1H), 6.67 (s, 1H), 4.53 (dd, J = 8.5, 3.6 Hz, 1H), 2.27 (d, J = 16.9 Hz, 6H), 2.06 (dd, J = 14.4, 9.0 Hz, 1H), 1.95 (s, 2H), 1.68 – 1.21 (m, 13H).

Example 16. Synthesis of Compound 196



Step 1: Zinc (5.6g, 0.085mol, 19eq) was added to a solution of THF (20mL), followed by dropwise addition of TiCl_4 (8.2g, 0.043mol, 9.6eq) at 0°C. The reaction was then heated and refluxed at 70°C for 1 hour. After cooling to 30°C, a THF solution containing 2,3-dihydrobenzo[1,4]dioxin-6-carbaldehyde (1.8g, 0.0108mol, 2.4eq) and (2,3-Dimethylphenyl)(1-trityl-4-imidazolyl)methanone (2g, 0.0045mol, 1eq) was introduced and refluxed at 65°C for 2 hours under nitrogen. Completion was confirmed by LC-MS. The reaction was quenched with water, extracted with ethyl acetate, dried, and concentrated. Purification via column chromatography yielded 2.1g of 196-1 as a white solid (100% yield).

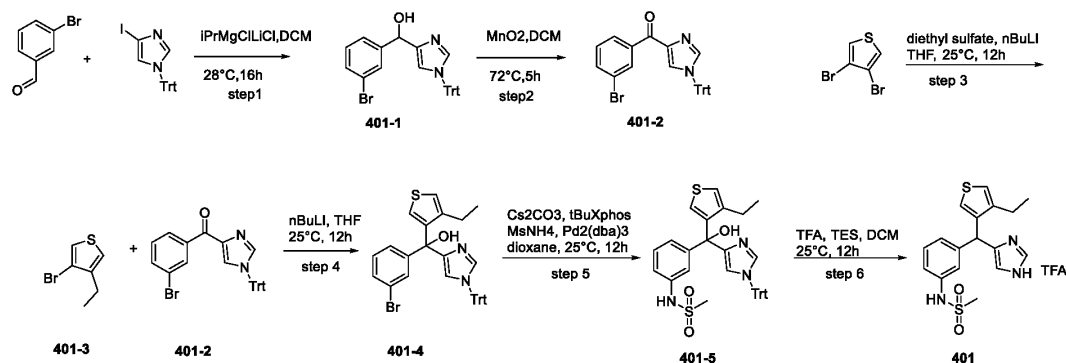
Step 2: 196-1 (100mg, 0.37mmol, 1eq) was combined with $\text{Pd}(\text{OH})_2/\text{C}$ (100mg) in a THF:MeOH (1:1) solution and stirred at 40°C for 16 hours under hydrogen. Following LC-MS confirmation of completion, the reaction was filtered and concentrated to give a crude product. DCM (2mL) and TFA (1mL) were added to the crude, which was then concentrated and purified by preparative HPLC to yield 12mg of 196 as a white solid (9.7% yield).

Overall yield = 9.7%

LCMS: $[\text{M}-\text{C}_2\text{HF}_3\text{O}_2+1]^+=335.2$

^1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 8.94 (s, 1H), 7.59 (s, 1H), 7.13 – 6.99 (m, 3H), 6.67 (dd, $J = 7.5, 4.9$ Hz, 2H), 6.59 (dd, $J = 8.2, 1.6$ Hz, 1H), 4.64 (t, $J = 7.7$ Hz, 1H), 4.16 (s, 4H), 3.22 (dd, $J = 13.9, 8.8$ Hz, 1H), 3.01 (dd, $J = 13.9, 6.8$ Hz, 1H), 2.23 (s, 3H), 2.15 (s, 3H).

Example 17. Synthesis of Compound 401



Step 1: In a 100mL flask, 50mL of dichloromethane and 4-Iodo-1-trityl-1H-imidazole (11.8g, 0.027mol, 1.0eq) were combined. After cooling the mixture to 0°C, iPrMgClLiCl (1.3mol/L, 20.7mL, 0.027mol, 1.0eq) was added. The mixture was stirred at 0°C for 2 hours, then 3-Bromobenzaldehyde (5g, 0.027mol, 1.0eq) was introduced. Stirring continued at 28°C for 16 hours until LC-MS confirmed the reaction's completion. After cooling back to 0°C and quenching with 44mL of saturated ammonium chloride, the organic layer was separated, concentrated, and purified via column chromatography using ethyl acetate to yield 7.1g of 401-1, achieving a 53% yield.

Step 2: Into a 200mL high-pressure tube, 180mL of dichloromethane, compound 401-1 (6.1g, 12.35mmol, 1.0eq), and MnO₂ (6.44g, 74.1mmol, 6.0eq) were added. The mixture was stirred at 72°C for 5 hours. Completion was verified by LC-MS, and the mixture was then filtered to yield 5.6g of compound 401-2, achieving an 83.9% yield.

Step 3: A 1L reaction vessel was charged with 500 mL of diethyl ether and 20g (82.67mmol, 1eq) of 3,4-Dibromothiophene (Cas: 3141-26-2). Upon cooling to -78°C, 36.37mL (90.94mmol, 1.1eq) of n-BuLi was added dropwise. The mixture was stirred at -78°C for 30 minutes before 14.02g (90.94mmol, 1.1eq) of diethyl sulfate was added dropwise. Stirring continued at 25°C for 5 hours until LC-MS confirmed the reaction's completion. After adding 25mL of aqueous ammonia, the organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to yield 10g of compound 401-3, achieving a 63.3% yield.

Step 4: Into a 50 mL reaction flask, 5mL of THF and 387.28mg (2.03mmol, 2eq) of 401-3 were introduced. Cooled to -78°C, 0.81mL (2.03mmol, 2eq) of n-BuLi was added dropwise. After stirring at -78°C for 30 minutes, a solution of 500mg (1.01mmol, 1.0eq) of 401-2 in 5mL of THF was added. The reaction was then stirred at 25°C for 12 hours, as indicated by LC-MS completion. The mixture was diluted with 20mL water and the aqueous phase was extracted with EA (3 times, 5mL each), the organic layers were combined, washed with brine (3 times, 5mL each), dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography purified the crude to yield 400mg of compound 401-4, a 65.2% yield.

Step 5: To a 25mL flask, 7mL of dioxane, 340mg (0.561mmol, 1.0eq) of 401-4, 64.08mg (0.67mmol, 1.2eq) of MsNH₄, 10.28mg (0.011mmol, 0.02eq) of Pd₂(dba)₃, 9.54mg (0.022mmol, 0.04eq) of tBuxphos, and 365.85mg (1.12mmol, 2eq) of Cs₂CO₃ were added. The mixture was stirred at 100°C for 5 hours. After confirmation of completion by LC-MS, it

was concentrated under vacuum and purified via column chromatography to obtain 100mg of compound 401-5, yielding 35.2%.

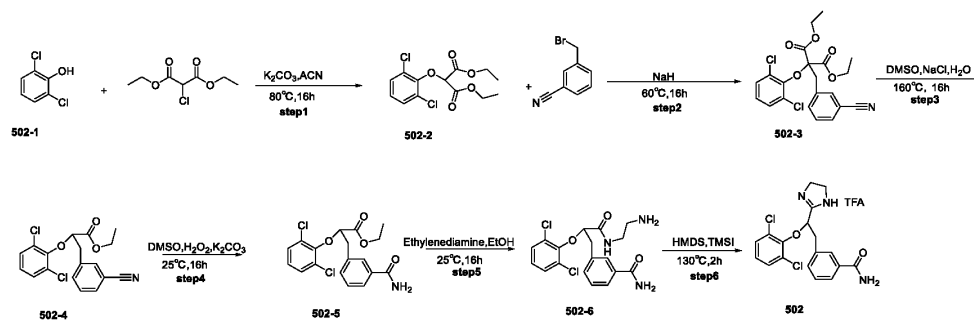
Step 6: A 5mL flask was prepared with 1mL DCM, 0.1mL TFA, 0.3mL TES, and 100mg (1.0eq) of 401-5. The mixture was stirred at 25°C for 2 hours, as shown by LC-MS completion. After concentration under vacuum, pre-HPLC purification yielded 10mg of compound 401, a 17.2% yield.

Overall yield = 2.5%

LCMS: $[M-C_2HF_3O_2+1]^+=362.1$

¹H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.79 (s, 1H), 9.06 (d, $J = 0.7$ Hz, 1H), 7.34 (dd, $J = 10.3, 5.4$ Hz, 1H), 7.25 (d, $J = 3.0$ Hz, 1H), 7.17 – 7.11 (m, 1H), 7.06 (s, 2H), 6.99 – 6.92 (m, 2H), 5.58 (s, 1H), 2.97 (s, 3H), 2.46 – 2.37 (m, 1H), 2.35 – 2.23 (m, 1H), 1.08 (t, $J = 7.4$ Hz, 3H).

Example 18. Synthesis of Compound 502



Step 1: A 500mL three-necked flask was loaded with 250mL of ACN, 25g (0.15mol, 1eq) of 502-1, 31.5g (0.16mol, 1.05eq) of diethyl chloromalonate, and 43g (0.31mol, 2eq) of K_2CO_3 . The reaction mixture was refluxed at 80°C overnight. After completion was confirmed by LC-MS, the mixture was concentrated under vacuum and purified via silica gel column chromatography to yield 40g of 502-2. The yield was 83%.

Step 2: In a 1L three-necked flask, 250mL of DMF and 8g (0.21mol, 1.5eq, 60%) of NaH were combined and cooled to 0°C. Then, 40g (0.125mol, 1eq) of 502-2 dissolved in 100mL of DMF was added at 0°C and stirred for 1 hour. Next, 30g (0.154mol, 1.1eq) of 3-(bromomethyl)benzonitrile in 100mL of DMF was added at 0°C, and the mixture was stirred at 58°C overnight. After completion (confirmed by LC-MS), the reaction was quenched with

water, extracted with EA, dried over Na₂SO₄, and concentrated. Purification by silica gel column chromatography yielded 36g of 502-3 with a 64% yield.

Step 3: A 500mL three-necked flask received 300mL of DMSO, 36g (0.08mol, 1eq) of 502-3, 9g (0.15mol, 2eq) of NaCl, and 11g (0.3mol, 4eq) of H₂O. The mixture was stirred at 150°C overnight. LC-MS indicated the reaction was incomplete. The mixture was worked up similarly to previous steps and purified to yield 25g of 502-4 with an 86% yield.

Step 4: To a 500mL three-necked flask, 200mL of DMSO, 20g (0.055mol, 1eq) of 502-4, 13g (0.11mol, 2eq) of H₂O₂, and 15g (0.11mol, 2eq) of K₂CO₃ were added. The mixture was stirred at room temperature overnight and purified after standard work-up to yield 8g of 502-05. The yield was 38%.

Step 5: A 100mL three-necked flask was charged with 40mL of EtOH, 8g (0.021mol, 1eq) of 502-5, and 12.6g (0.21mol, 10eq) of ethylenediamine. The mixture was stirred at room temperature overnight and purified to yield 7g of 502-6 with an 84% yield.

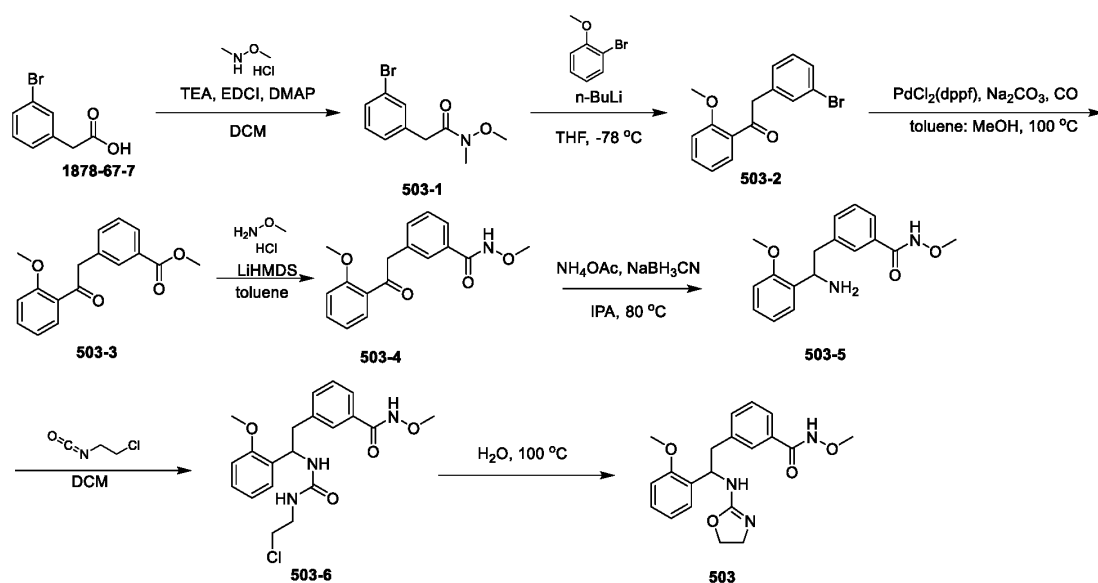
Step 6: To a 25mL single-necked flask, 1g (2.53mmol, 1eq) of 502-6, 7.5mL of HMDS, and 0.5mL of TMSI were added. The mixture was stirred at 130°C overnight, concentrated under vacuum, then added to 2mL DCM and 1mL TFA, stirred for 1 hour at room temperature, and concentrated. Purification yielded 10mg of 502 with a final yield of 1%.

Overall yield = 0.15%

LCMS: [M-C₂HF₃O₂+1]⁺=378.0

¹H NMR (400 MHz, DMSO) δ 10.45 (s, 2H), 7.98 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.43 (dt, J = 14.9, 7.6 Hz, 3H), 7.26 (t, J = 8.1 Hz, 1H), 5.23 (t, J = 7.1 Hz, 1H), 3.81 (dd, J = 14.5, 6.8 Hz, 4H), 3.60 (d, J = 7.7 Hz, 1H), 3.50 (d, J = 5.7 Hz, 1H).

Example 19. Synthesis of Compound 503



Step 1: Into a 500mL three-necked flask, 250mL of ACN, 25g (0.15mol, 1eq) of (3-bromophenyl)acetic acid, 31.5g (0.16mol, 1.05eq) of diethyl chloromalonate, and 43g (0.31mol, 2eq) of K₂CO₃ were added. The mixture was refluxed overnight at 80°C. Following LC-MS confirmation of completion, it was concentrated and purified via silica gel chromatography, eluting with EtOAc/PE from 1/20 to 1/10 to yield 20g of 2-(3-bromophenyl)-N-methoxy-N-methylacetamide (503-1) as a yellow oil, with a 73.60% yield.

Step 2: A solution of 1-bromo-2-methoxybenzene (28.99g, 155mmol) in dry THF (150mL) was cooled to -78°C, to which n-BuLi (2.5M in hexane, 62mL, 155mmol) was added dropwise. After stirring at -78°C for 30 minutes, a solution of 503-1 (20g, 77.5mmol) in dry THF (100mL) was added dropwise. The solution was then allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with saturated NH₄Cl solution, extracted with EtOAc, and purified via silica gel chromatography, eluting with EtOAc/PE at 1/50 to yield 10g of 2-(3-bromophenyl)-1-(2-methoxyphenyl)ethenone (503-2) as a yellow oil, with a 40.13% yield.

Step 3: A solution of 503-2 (1.5g, 4.9mmol), PdCl₂(dppf) (360mg, 0.49mmol), and sodium carbonate (1.04g, 9.8mmol) in toluene:MeOH (10mL, 1:1 ratio) was heated at 100°C for 3 days under CO atmosphere. The reaction was diluted with water, extracted with EtOAc, and purified via silica gel chromatography, eluting with EtOAc/PE from 1% to 10%, to yield 700mg of methyl 3-[2-(2-methoxyphenyl)-2-oxoethyl]benzoate (503-3) as a yellow oil, with a 46.94% yield.

Step 4: To a solution of methyl 3-[2-(2-methoxyphenyl)-2-oxoethyl]benzoate (600mg, 2.1mmol) and O-methylhydroxylamine hydrochloride (264.38mg, 3.16mmol) in toluene (8mL), LiHMDS (1M, 8.4mL, 8.441mmol) was added and stirred at 25°C for 3 hours. After dilution with aqueous NH₄Cl and extraction with EtOAc, the product was purified via silica gel chromatography, eluting with DCM/MeOH at 1/20, to yield 400mg of N-methoxy-3-[2-(2-methoxyphenyl)-2-oxoethyl]benzamide (503-4) as a yellow oil, with a 60.45% yield.

Step 5: A solution of N-methoxy-3-[2-(2-methoxyphenyl)-2-oxoethyl]benzamide (400mg, 1.3364mmol) and NH₄OAc (1.545g, 20.046mmol) in IPA (8.0mL) was stirred at 25°C for 30 minutes before adding NaBH₃CN (335.92mg, 5.34mmol) and heated at 80°C for 3 hours. After adjusting the pH to 8 with 2M NaOH, the mixture was extracted with DCM and purified via silica gel chromatography, eluting with MeOH/DCM at 1/10, to yield 320mg of 3-[2-amino-2-(2-methoxyphenyl)ethyl]-N-methoxybenzamide (503-5) as a white solid, with a 71.75% yield.

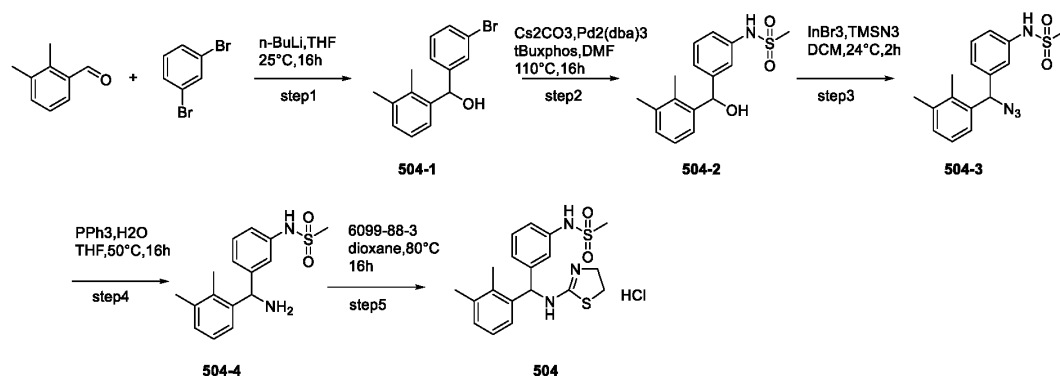
Step 6: To a solution of 3-[2-amino-2-(2-methoxyphenyl)ethyl]-N-methoxybenzamide (300mg, 0.9988mmol, 1eq) in DCM:DMF (5.0mL, 10:1 ratio), 1-chloro-2-isocyanatoethane (421.59mg, 3.9952mmol) was stirred at 25°C for 6 hours. After dilution with water and extraction with DCM, the combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Without further purification, the crude product (250mg, 46.26% yield) was obtained as a yellow oil.

Step 7: To a solution of 3-(2-([(2-chloroethyl)carbamoyl]amino))-2-(2-methoxyphenyl)ethyl]-N-methoxybenzamide (200mg, 0.4927mmol) in water (5.0mL), the mixture was heated at 100°C for 3 hours. After cooling to room temperature, the mixture was purified by Biotage using a C18 column, eluting with 5% to 95% MeCN/H₂O containing 0.1% NH₄OH, to afford 48.25mg of 3-[2-(4,5-dihydro-1,3-oxazol-2-ylamino)-2-(2-methoxyphenyl)ethyl]-N-methoxybenzamide (503) as a white solid, with a 24.65% yield. Overall yield = 11.40%

LCMS (ESI): m/z found 370.10 [M + H]⁺.

[M+1]⁺ = 370.10

¹H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 7.66 (s, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.34 (dt, J = 18.4, 7.6 Hz, 3H), 7.21 (t, J = 8.0 Hz, 1H), 6.93 (dd, J = 16.8, 8.4 Hz, 3H), 5.06 (d, J = 6.4 Hz, 1H), 4.02 (t, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.38 (t, J = 8.4 Hz, 2H), 2.89 (dd, J = 13.6, 4.0 Hz, 1H), 2.75 (dd, J = 13.6, 10.0 Hz, 1H).

Example 20. Synthesis of Compound 504

Step 1: In a 250mL flask, 100mL of THF and 13.1g (0.056mol, 1.5eq) of 1,3-dibromobenzene were combined. After cooling to -78°C , 22.4mL (0.056mol, 1.5eq) of 2.5M n-BuLi was added. Stirred at -78°C for 1 hour, then a solution of 5g (0.0373mol, 1.0eq) of 2,3-dimethylbenzaldehyde in 10mL THF was introduced. The reaction continued at -78°C for another hour before warming to room temperature overnight. Post-completion, verified by LC-MS, the reaction was quenched with 25mL saturated ammonium chloride and the organic layer was separated, dried over Na_2SO_4 , concentrated under vacuum, and purified via column chromatography (PE:EA=85:15) to yield 8.6g of 504-1, a 77.8% yield

Step 2: A 50mL flask was charged with 20mL DMF, 1g (3.45mmol, 1.0eq) of 504-1, 492mg (5.175mmol, 1.5eq) of MsNH_2 , 2.25g (6.9mmol, 2.0eq) of Cs_2CO_3 , 316mg (0.345mmol, 0.1eq) of $\text{Pd}_2(\text{dba})_3$, and 293mg (0.69mmol, 0.2eq) of tBuxphos. Stirred at 110°C for 16 hours and completion confirmed by LC-MS, the reaction was quenched with ice water, extracted with EA, and dried over Na_2SO_4 . Purification by column chromatography (PE:EA=1:1) yielded 180mg of 504-2, a 17% yield.

Step 3: To a 5mL flask, 1.5mL DCM, 134mg (0.439mmol, 1.0eq) of 504-2, 76mg (0.659mmol, 1.5eq) of TMSN_3 , and 31mg (0.0878mmol, 0.2eq) of InBr_3 were added. Stirred at 17°C for 2 hours, completion confirmed by LC-MS, concentrated under vacuum and purified by column chromatography (PE:EA=68:32) to yield 105mg of 504-3, a 72.4% yield.

Step 4: A 5mL flask received 1.5mL THF, 0.3mL water, 144mg (0.436mmol, 1.0eq) of 504-3, and 229mg (0.87mmol, 2.0eq) of PPh_3 . Stirred at 50°C for 16 hours, completion confirmed by LC-MS, concentrated under vacuum and purified by TLC (DCM:MeOH=20:1) to yield 62mg of 504-4, a 46.7% yield.

Step 5: To a 5mL flask, 1mL dioxane, 52mg (0.171mmol, 1.0eq) of 504-4, and 60mg (0.5mmol, 2.9eq) of 2-chloroethyl isothiocyanate were added. Stirred at 80°C for 16 hours,

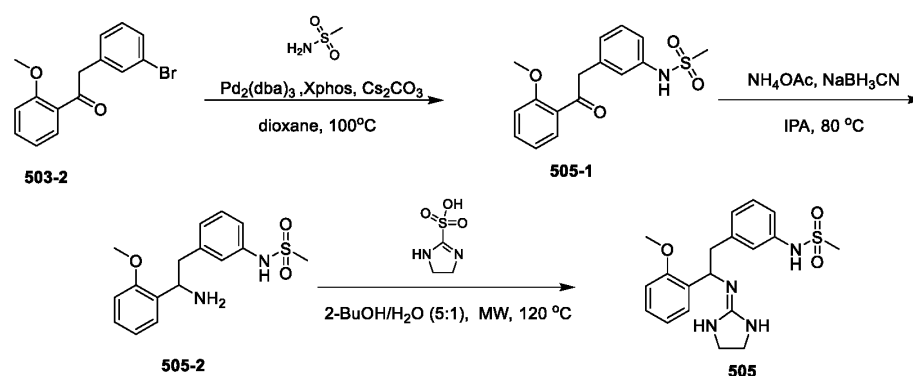
completion confirmed by LC-MS, concentrated under vacuum and purified by pre-HPLC to yield 3.3mg of compound 504, a 5% yield.

Overall yield: 2.2%

LCMS: $[M-HCl+1]^+=390.1$

¹H NMR (400 MHz, MeOD) δ 7.40 (t, $J = 7.9$ Hz, 1H), 7.27 – 7.20 (m, 2H), 7.17 (t, $J = 7.6$ Hz, 2H), 7.00 (dd, $J = 23.2, 7.5$ Hz, 2H), 6.16 (s, 1H), 4.02 (t, $J = 7.5$ Hz, 2H), 3.65 (t, $J = 7.6$ Hz, 2H), 2.95 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H).

Example 21. Synthesis of Compound 505



Step 1: A solution of 2-(3-bromophenyl)-1-(2-methoxyphenyl)ethanone (503-2, 2.0g, 6.6mmol), methanesulfonamide (0.75g, 7.92mmol), Pd(OAc)₂ (150mg, 0.663mmol), Xantphos (0.76g, 1.32mmol), and Cs₂CO₃ (4.30g, 13.20mmol) in dioxane (20.0ml) was heated at 100°C for 16 hours under nitrogen. After cooling, it was diluted with aqueous NH₄Cl and extracted with EtOAc. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel chromatography (MeOH/DCM, 1% to 10%) yielded N-{3-[2-(2-methoxyphenyl)-2-oxoethyl]phenyl}methanesulfonamide (505-1, 400mg, 16.17% yield) as a yellow oil.

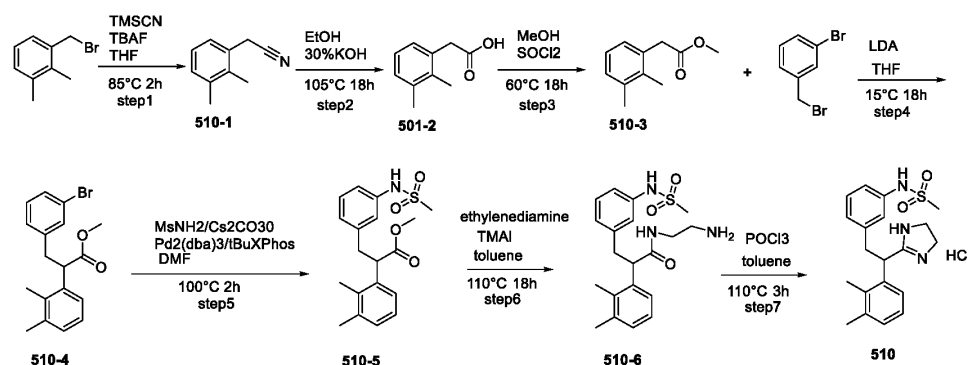
Step 2: A mixture of N-{3-[2-(2-methoxyphenyl)-2-oxoethyl]phenyl}methanesulfonamide (400mg, 0.5323mmol) and NH₄OAc (1.448g, 18.785mmol) in isopropanol (8.0ml) was stirred at 25°C for 0.5 hour, then NaBH₃CN (314.80mg, 5.0096mmol) was added and the mixture was heated at 80°C for 4.5 hours. After cooling, the mixture was filtered through celite and concentrated. It was purified by preparative TLC (EtOAc/PE, 1/3) to obtain N-{3-[2-amino-2-(2-methoxyphenyl)ethyl]phenyl}methanesulfonamide (505-2, 240mg, 53.82% yield) as a yellow oil.

Step 3: A solution of N-{3-[2-amino-2-(2-methoxyphenyl)ethyl]phenyl}methanesulfonamide (505-2, 160mg, 0.4994mmol) and 4,5-dihydro-1H-imidazole-2-sulfonic acid (224.96mg, 1.4982mmol) in butanol:water (5:1 ratio, 3.0ml) was heated at 120°C for 2 hours in a microwave reactor. After cooling, the mixture was concentrated, diluted with water, and extracted with EtOAc. The organic phases were combined, washed with brine, dried over sodium sulfate, concentrated, and purified by Biotage using a C18 column (eluting with 10% to 95% MeCN/H₂O, containing 0.1% TFA) to yield N-{3-[2-(imidazolidin-2-ylideneamino)-2-(2-methoxyphenyl)ethyl]phenyl}methanesulfonamide (505, 8.38mg, 4.31% yield) as a white solid.

LCMS: [M+1]⁺=388.38

¹H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.74 (d, J = 9.2 Hz, 1H), 8.31 (s, 1H), 7.67 (s, 1H), 7.33 – 7.16 (m, 3H), 7.11 (s, 1H), 7.03 (dd, J = 17.2, 8.4 Hz, 3H), 6.94 (t, J = 7.6 Hz, 1H), 4.96-4.90 (m, 1H), 3.88 (s, 3H), 3.48 (s, 5H), 3.09 (dd, J = 13.6, 4.8 Hz, 1H), 2.94 – 2.87 (m, 4H).

Example 22. Synthesis of Compound 510



Step 1: In a 100mL flask, 20mL of ACN, 2g (0.01mol, 1.0eq) of 2,3-Dimethylbenzyl bromide, 2g (0.02mmol, 2.0eq) of TMSCN, and 20mL (0.05mmol, 2.0eq) of TBAF in THF were combined and refluxed for 1.5 hours. After LC-MS confirmation of completion, the mixture was concentrated and purified by column chromatography (PE:EA=85:15) to yield 1.42g of 510-1, a 97.9% yield.

Step 2: In a 100mL flask, 28mL of ethanol and 5.7mL of 30% KOH solution were added to 1.42g (0.0098mol, 1.0eq) of 510-1. The mixture was refluxed for 18 hours, concentrated, diluted with 20mL water, adjusted to pH=2 with 6M HCl, filtered, and dried to yield 1.35g of 510-2 as a solid, an 84.0% yield.

Step 3: A 50mL flask received 15mL of methanol and 1.3g (0.008mol, 1.0eq) of 510-2, cooled to 0°C, then 1.89g (0.0159mol, 1.5eq) of SOCl₂ was added. The reaction was stirred at 60°C for 18 hours, concentrated, and purified by column chromatography (PE:EA=68:32) to yield 1.37g of 510-3, a 96.2% yield.

Step 4: In a 25mL bottle, 10mL of THF, 497mg (2.81mmol, 1.0eq) of 510-3 were cooled to -80°C under nitrogen. LDA (3.37mL, 3.37mmol, 1.2eq) was added, followed by 731mg (2.95mmol, 1.05eq) of 823-78-9 in 2mL THF. The mixture was warmed to room temperature overnight, quenched, and purified by column chromatography to yield 670mg of 510-4, a 68.9% yield.

Step 5: A 50mL bottle received 10mL of DMF, 570mg (1.65mmol, 1.0eq) of 510-4, 1.07g (3.3mmol, 2.0eq) of Cs₂CO₃, 235mg (2.47mmol, 1.5eq) of methanesulfonamide, 151mg (0.165mmol, 0.1eq) of Pd₂(dba)₃, and 141mg (0.33mmol, 0.2eq) of t-BuXphos. Stirred at 105°C for 2 hours under nitrogen, the reaction was worked up and purified to yield 600mg of 510-5, an 85.7% yield.

Step 6: In a 10mL bottle, 5mL of toluene, 200mg (0.554mmol, 1.0eq) of 510-5, 166.5mg (2.77mmol, 5.0eq) of ethylenediamine, and TMAI (1.39mL, 2.77mmol, 5.0eq) were stirred at 110°C overnight. After cooling and working up, the crude was purified to yield 29mg of 510-6, a 13.5% yield.

Step 7: A 5mL bottle received 1mL of toluene and 29mg (0.0745mmol, 1.0eq) of 510-6, then 57mg (0.37mmol, 5.0eq) of POCl₃ was added. Stirred at 110°C for 3 hours, the mixture was filtered and purified to yield 3.6mg of 510, an 11.9% yield.

LC-MS= [M-HCl+1]⁺= 372.2

¹H NMR (400 MHz, DMSO) δ 9.98 (s, 2H), 7.35 (d, J = 7.1 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.15 (dd, J = 18.1, 7.2 Hz, 2H), 7.09 – 7.00 (m, 2H), 6.95 (d, J = 7.4 Hz, 1H), 4.44 (t, J = 7.5 Hz, 1H), 3.78 (s, 4H), 3.46 – 3.40 (m, 1H), 3.07 (dd, J = 13.4, 7.1 Hz, 1H), 2.90 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H).

Other compounds were synthesized similarly as the above compounds. The characterization data of compounds are listed in the Table 2 below.

Table 2

#	¹ H-NMR and MS
1	LC-MS:[M-TFA+1] ⁺ =336.2, ¹ H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 11.79 (s, 1H), 9.00 (d, J = 0.9 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.17 – 7.06 (m, 2H), 6.94 (s, 1H), 6.70 (d, J = 7.2 Hz, 1H), 5.91 (s, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).

1-A	$[M+1]^+=336.2$, 1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 11.71 (s, 1H), 7.61 (s, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.05 – 6.95 (m, 2H), 6.79 (d, J = 7.0 Hz, 1H), 6.44 (s, 1H), 5.65 (s, 1H), 3.67 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H).
1-B	$[M-HCl+1]^+=336.2$, 1H NMR (400 MHz, DMSO) δ 14.60 (s, 2H), 11.93 (s, 1H), 9.13 (d, J = 1.1 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.61 (s, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.18 – 7.05 (m, 2H), 7.00 (s, 1H), 6.72 (d, J = 7.1 Hz, 1H), 5.95 (s, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
2	$[M-TFA+1]^+=350.2$, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 9.03 (s, 1H), 8.48 (t, J = 5.5 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.11 (dt, J = 15.1, 7.4 Hz, 2H), 6.94 (s, 1H), 6.70 (d, J = 7.4 Hz, 1H), 5.90 (s, 1H), 4.73 (s, 1H), 3.49 (t, J = 6.2 Hz, 2H), 3.30 (q, J = 6.0 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H).
3	$[M-TFA+1]^+=408.3$, 1H NMR (400 MHz, DMSO) δ 14.35 (s, 1H), 9.03 (s, 1H), 8.55 (t, J = 5.5 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.69 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.11 (dt, J = 15.1, 7.4 Hz, 2H), 6.95 (s, 1H), 6.70 (d, J = 7.4 Hz, 1H), 5.90 (s, 1H), 3.54 – 3.49 (m, 4H), 3.44 – 3.41 (m, 4H), 3.22 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
4	$[M+1]^+=443.2$, 1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 9.68 (s, 1H), 8.67 (s, 1H), 8.46 (d, J = 5.9 Hz, 1H), 7.93 (d, J = 36.3 Hz, 1H), 7.56 (d, J = 4.7 Hz, 2H), 7.18 (s, 1H), 6.98 (s, 2H), 6.72 (d, J = 8.9 Hz, 4H), 6.37 (d, J = 94.6 Hz, 1H), 5.58 (d, J = 38.0 Hz, 1H), 3.97 (s, 2H), 3.51 (d, J = 5.0 Hz, 2H), 2.22 (s, 3H), 2.11 (s, 3H).
5	LC-MS: $[M-TFA+1]^+=306.2$, 1H NMR (400 MHz, DMSO) δ 14.29 (s, 2H), 8.97 (s, 1H), 7.99 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.70 (s, 1H), 7.43 (dd, J = 14.7, 6.6 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.18 – 7.02 (m, 2H), 6.93 (s, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.88 (s, 1H), 2.26 (s, 3H), 2.13 (s, 3H).
5-A	LC-MS: $[M+1]^+=306.2$, 1H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 7.92 (s, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.59 (s, 1H), 7.31 (dt, J = 25.6, 7.6 Hz, 3H), 7.00 (q, J = 7.7 Hz, 2H), 6.79 (d, J = 6.8 Hz, 1H), 6.42 (s, 1H), 5.64 (s, 1H), 2.23 (s, 3H), 2.11 (s, 3H).
5-B	LC-MS: $[M+1]^+=306.2$, 1H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 7.92 (s, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.59 (s, 1H), 7.31 (dt, J = 25.9, 7.6 Hz, 3H), 7.00 (q, J = 7.7 Hz, 2H), 6.79 (d, J = 6.7 Hz, 1H), 6.42 (s, 1H), 5.64 (s, 1H), 2.23 (s, 3H), 2.11 (s, 3H).
6	LC-MS: $[M-TFA+1]^+=320.2$, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.01 (s, 1H), 8.45 (d, J = 4.5 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.66 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.17 – 7.05 (m, 2H), 6.94 (s, 1H), 6.70 (d, J = 7.3 Hz, 1H), 5.89 (s, 1H), 2.76 (d, J = 4.5 Hz, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
7	$[M+1]^+=338.2$, 1H NMR (400 MHz, DMSO) δ 14.09 (s, 2H), 11.78 (s, 1H), 9.45 (s, 1H), 8.82 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.98 (t, J = 7.9 Hz, 1H), 6.88 (s, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.31 (d, J = 7.6 Hz, 1H), 5.77 (s, 1H), 3.68 (s, 3H), 2.02 (s, 3H).
8	1H NMR (400 MHz, DMSO) δ 12.25 (s, 3H), 7.57 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 6.98 (dt, J = 15.0, 6.6 Hz, 3H), 6.79 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 6.37 (s, 1H), 5.87 (s, 1H), 3.35 (s, 1H), 2.22 (s, 3H), 2.08 (s, 3H), $[M+1]^+=352.2$.
9	1H NMR (400 MHz, DMSO) δ 13.74 (s, 1H), 11.82 (s, 1H), 8.46 (s, 1H), 7.95 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.22 – 6.83 (m, 3H), 6.77 (t, J = 7.7 Hz, 2H), 6.40 (s, 1H), 5.87 (s, 1H), 2.22 (s, 3H), 2.09 (s, 3H), $[M+1]^+=322.2$.
10	LC-MS: $[M-C_2HFO_2+1]^+=345.2$, 1H NMR (400 MHz, DMSO) δ 13.33 (s, 2H), 10.27 (s, 1H), 8.19 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.35 – 7.18 (m, 2H), 7.05 (dd, J = 19.4, 7.0 Hz, 2H), 6.89 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 6.7 Hz, 1H), 6.58 (s, 1H), 5.70 (s, 1H), 3.84 (s, 2H), 2.24 (s, 3H), 2.10 (s, 3H).
10-A	LC-MS: $[M+1]^+=345.2$, 1H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 10.20 (s, 1H), 7.57 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.27 – 7.17 (m, 2H), 6.99 (q, J = 7.5 Hz, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 6.1 Hz, 1H), 6.42 (s, 1H), 5.56 (s, 1H), 3.82 (s, 2H), 2.22 (s, 3H), 2.11 (s, 3H).
10-B	LC-MS: $[M+1]^+=345.2$, 1H NMR (400 MHz, DMSO) δ 11.87 (s, 1H), 10.20 (s, 1H), 7.57 (s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.29 – 7.16 (m, 2H), 6.99 (q, J = 7.3 Hz, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.79 (s, 1H), 6.42 (s, 1H), 5.56 (s, 1H), 3.83 (s, 2H), 2.22 (s, 3H), 2.09 (d, J = 12.3 Hz, 3H).
11	LC-MS: $[M-TFA+1]^+=307.2$, 1H NMR (400 MHz, DMSO) δ 14.05 (s, 2H), 8.79 (s, 1H), 7.87 (d, J = 6.5 Hz, 1H), 7.74 (s, 1H), 7.60 – 7.37 (m, 2H), 7.10 (d, J = 13.8 Hz, 2H), 6.87 (s, 1H), 6.71 (d, J = 6.5 Hz, 1H), 5.92 (s, 1H), 2.26 (s, 3H), 2.12 (s, 3H).
12	LC-MS: $[M+1]^+=307.36$, 1H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.58 (s, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.07 – 6.94 (m, 2H), 6.79 (d, J = 6.8 Hz, 1H), 6.44 (s, 1H), 5.66 (s, 1H), 2.23 (s, 3H), 2.11 (s, 3H).
13	$[M+1]^+=279.2$, 1H NMR (400 MHz, DMSO) δ 11.21 (d, J = 18.6 Hz, 1H), 7.96 – 7.74 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 6.40 (d, J = 25.1 Hz, 2H), 6.08 – 5.85 (m, 2H), 5.53 (dt, J = 19.2, 9.6 Hz, 1H), 4.41 – 4.24 (m, 1H), 4.10 (dd, J = 27.9, 21.9 Hz, 1H), 3.64 (s, 2H), 3.51 (s, 12H), 3.43 – 3.35 (m, 4H), 3.16 (dd, J = 19.1, 5.7 Hz, 5H), 2.99 (d, J = 6.1 Hz, 2H), 2.81 (dt, J = 21.6, 10.8 Hz, 1H), 2.59 (s, 1H), 2.07 (s, 2H), 1.66 (s, 3H), 1.56 – 1.37 (m, 3H), 1.31 (dd, J = 15.0, 6.7 Hz, 2H), $[M+1]^+=352.2$.
14	LC-MS: $[M+1]^+=335.41$, 1H NMR (400 MHz, DMSO) δ 11.77 (t, J = 46.3 Hz, 1H), 8.64 (d, J = 38.2 Hz, 1H), 7.55 (s, 1H), 7.39 – 7.22 (m, 2H), 6.98 (t, J = 15.2 Hz, 4H), 6.89 – 6.60 (m, 1H), 6.52 – 6.07 (m, 2H), 5.50 (d, J = 37.5 Hz, 1H), 2.62 (d, J = 4.4 Hz, 3H), 2.22 (s, 3H), 2.10 (s, 3H).
15	$[M+1]^+=513.3$, 1H NMR (400 MHz, DMSO) δ 11.84 (s, 1H), 7.56 (s, 1H), 7.00 (dd, J = 14.8, 8.2 Hz, 4H), 6.85 (d, J = 8.6 Hz, 2H), 6.76 (s, 1H), 6.36 (s, 1H), 5.53 (s, 1H), 4.11 – 3.98 (m, 2H), 3.80 – 3.67 (m, 2H), 3.64 – 3.55 (m, 2H), 3.56 – 3.45 (m, 12H), 3.42 (dd, J = 5.9, 3.5 Hz, 2H), 3.23 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H).

16	LCMS=[M-TFA+1] ⁺ =363.3, ¹ H NMR (400 MHz, DMSO) δ 14.17 (s, 6H), 8.83 (s, 4H), 7.47 (s, 4H), 7.16 – 6.98 (m, 8H), 6.89 (d, J = 7.3 Hz, 4H), 4.64 (dd, J = 8.3, 5.5 Hz, 4H), 3.91 (t, J = 9.2 Hz, 4H), 3.77 (dd, J = 9.8, 5.5 Hz, 4H), 3.60 – 3.54 (m, 8H), 3.52 – 3.47 (m, 32H), 3.42 – 3.40 (m, 9H), 3.23 (s, 13H), 2.27 (s, 24H).
17	¹ H NMR (400 MHz, CDCl ₃) δ 8.66 (s, 1H), 7.19 – 7.02 (m, 2H), 6.96 (d, J = 7.2 Hz, 1H), 6.68 (s, 1H), 5.93 (s, 1H), 4.61 (dd, J = 9.3, 4.1 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.84 – 3.77 (m, 1H), 3.65 (ddd, J = 17.3, 13.3, 7.2 Hz, 5H), 3.46 – 3.31 (m, 2H), 2.66 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H). [M-TFA+1] ⁺ =361.3
17-A	¹ H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 7.74 (s, 1H), 7.12 – 6.94 (m, 3H), 6.87 (s, 1H), 5.97 – 5.70 (m, 2H), 4.48 (t, J = 7.1 Hz, 1H), 3.97 – 3.84 (m, 1H), 3.84 – 3.70 (m, 1H), 3.51 (d, J = 5.0 Hz, 2H), 3.45 (t, J = 4.3 Hz, 2H), 3.31 (t, J = 5.7 Hz, 2H), 3.09 (q, J = 5.6 Hz, 2H), 2.52 (d, J = 4.9 Hz, 3H), 2.23 (d, J = 7.1 Hz, 6H). [M+1] ⁺ =361.3
17-B	¹ H NMR (400 MHz, DMSO) δ 14.04 (s, 2H), 8.77 (s, 1H), 7.44 (s, 1H), 7.14 – 6.97 (m, 2H), 6.89 (d, J = 7.1 Hz, 1H), 6.00 – 5.69 (m, 2H), 4.72 – 4.47 (m, 1H), 3.90 (t, J = 9.1 Hz, 1H), 3.76 (dd, J = 9.8, 5.6 Hz, 1H), 3.62 – 3.52 (m, 2H), 3.49 (dt, J = 8.9, 4.0 Hz, 2H), 3.32 (t, J = 5.8 Hz, 3H), 3.11 (dd, J = 11.6, 5.8 Hz, 2H), 2.52 (d, J = 4.6 Hz, 3H), 2.26 (d, J = 2.8 Hz, 6H). [M-TFA+1] ⁺ =361.3
18	[M+1] ⁺ =382.2 ¹ H NMR (400 MHz, DMSO) δ 14.12 (s, 2H), 8.85 (s, 1H), 7.49 (s, 1H), 7.10 – 6.99 (m, 3H), 6.88 (d, J = 7.3 Hz, 1H), 4.63 (dd, J = 8.3, 5.6 Hz, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.76 (dd, J = 9.8, 5.5 Hz, 1H), 3.58 (dt, J = 13.5, 4.1 Hz, 2H), 3.50 (t, J = 4.5 Hz, 2H), 3.41 (t, J = 5.8 Hz, 2H), 3.06 (q, J = 5.8 Hz, 2H), 2.87 (s, 3H), 2.26 (s, 6H).
18-A	¹ H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 7.83 (s, 1H), 7.07 – 6.96 (m, 4H), 6.91 (s, 1H), 4.49 (t, J = 7.0 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.77 (dd, J = 9.6, 6.9 Hz, 1H), 3.56 – 3.50 (m, 2H), 3.48 (d, J = 4.9 Hz, 2H), 3.40 (t, J = 5.7 Hz, 2H), 3.05 (q, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.23 (d, J = 6.5 Hz, 6H). [M+1] ⁺ =382.2
18-B	¹ H NMR (400 MHz, DMSO) δ 13.26 (s, 2H), 8.36 (d, J = 60.9 Hz, 1H), 7.25 (s, 1H), 7.04 (t, J = 7.4 Hz, 3H), 6.93 (d, J = 7.2 Hz, 1H), 4.57 (t, J = 6.9 Hz, 1H), 3.91 (t, J = 9.0 Hz, 1H), 3.76 (dd, J = 9.8, 6.2 Hz, 1H), 3.54 (t, J = 8.5 Hz, 2H), 3.50 (d, J = 4.4 Hz, 2H), 3.41 (t, J = 5.7 Hz, 2H), 3.06 (q, J = 5.7 Hz, 2H), 2.87 (s, 3H), 2.25 (d, J = 3.8 Hz, 6H). [M-TFA+1] ⁺ =382.2
19	LC-MS: [M-2TFA+1] ⁺ =304.2, ¹ H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 8.85 (s, 1H), 7.80 (s, 3H), 7.48 (s, 1H), 7.13 – 7.00 (m, 2H), 6.89 (d, J = 7.3 Hz, 1H), 4.63 (dd, J = 8.0, 5.8 Hz, 1H), 3.91 (t, J = 9.1 Hz, 1H), 3.77 (dd, J = 9.8, 5.7 Hz, 1H), 3.62 – 3.57 (m, 2H), 3.53 (dd, J = 9.8, 4.8 Hz, 4H), 2.94 (d, J = 4.9 Hz, 2H), 2.26 (d, J = 2.7 Hz, 6H).
20	¹ H NMR (400 MHz, DMSO) δ 11.77 (s, 1H), 9.68 (s, 1H), 8.69 (s, 1H), 8.46 (d, J = 5.9 Hz, 1H), 7.74 (s, 1H), 7.64 – 7.42 (m, 2H), 6.97 (s, 2H), 6.75 (s, 1H), 4.45 (s, 1H), 3.93 (s, 1H), 3.80 (t, J = 8.2 Hz, 1H), 3.53 (s, 2H), 3.50 (s, 2H), 3.42 (t, J = 5.1 Hz, 2H), 3.27 (d, J = 5.1 Hz, 2H), 2.21 (d, J = 7.0 Hz, 6H), 1.24 (s, 2H). [M+1] ⁺ =425.2
21	¹ H NMR (400 MHz, DMSO) δ 7.47 (s, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.02 – 6.90 (m, 2H), 6.78 (s, 1H), 4.33 (s, 1H), 4.16 – 4.04 (m, 1H), 4.01 (t, J = 5.3 Hz, 2H), 3.70 – 3.57 (m, 2H), 3.56 – 3.44 (m, 14H), 3.45 – 3.39 (m, 2H), 3.36 (t, J = 6.5 Hz, 2H), 3.24 (s, 3H), 3.19 (t, J = 7.1 Hz, 1H), 2.22 (d, J = 8.4 Hz, 6H), 2.09 – 1.92 (m, 1H), 1.88 – 1.68 (m, 1H), 1.47 – 1.27 (m, 2H). [M+1] ⁺ =479.3
22	[M+1] ⁺ =400.2, ¹ H NMR (400 MHz, DMSO) δ 13.46 (s, 1H), 8.27 (s, 1H), 7.24 (dd, J = 13.6, 5.7 Hz, 2H), 7.04 (d, J = 11.2 Hz, 2H), 6.93 – 6.49 (m, 5H), 5.68 (s, 1H), 3.96 (s, 2H), 3.29 (d, J = 4.5 Hz, 2H), 2.91 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H).
23	LC-MS=[M-C ₂ HF ₃ O ₂ +1] ⁺ =376.2, ¹ H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.90 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.18 – 7.04 (m, 3H), 6.92 (s, 1H), 6.70 (d, J = 7.4 Hz, 1H), 5.88 (s, 1H), 3.44 (d, J = 102.9 Hz, 8H), 2.26 (s, 3H), 2.12 (s, 3H).
24	LC-MS=[M+1-TFA] ⁺ =318.2, ¹ H NMR (400 MHz, DMSO) δ 14.43 (s, 2H), 9.00 (s, 1H), 8.52 (s, 2H), 7.56 (s, 1H), 7.13 – 7.01 (m, 2H), 6.87 (d, J = 7.2 Hz, 1H), 4.66 (dd, J = 7.9, 5.7 Hz, 1H), 3.91 (t, J = 9.1 Hz, 1H), 3.77 (dd, J = 9.8, 5.5 Hz, 1H), 3.63 – 3.50 (m, 6H), 3.05 (s, 2H), 2.54 (s, 3H), 2.27 (s, 6H).
25	LC-MS=[M+1-TFA] ⁺ =346.2, ¹ H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.92 (s, 1H), 7.87 (s, 1H), 7.51 (s, 1H), 7.12 – 7.01 (m, 2H), 6.88 (d, J = 7.3 Hz, 1H), 4.64 (dd, J = 8.0, 5.6 Hz, 1H), 3.90 (t, J = 9.2 Hz, 1H), 3.76 (dd, J = 9.8, 5.4 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.48 (t, J = 4.4 Hz, 2H), 3.35 (t, J = 5.9 Hz, 2H), 3.15 (q, J = 5.8 Hz, 2H), 2.26 (s, 6H), 1.78 (s, 3H).
26	¹ H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 8.97 (s, 1H), 7.55 (s, 1H), 7.05 (dt, J = 19.1, 5.9 Hz, 3H), 6.86 (d, J = 7.3 Hz, 1H), 4.65 (dd, J = 8.2, 5.4 Hz, 1H), 3.90 (t, J = 9.2 Hz, 1H), 3.76 (dd, J = 9.8, 5.4 Hz, 1H), 3.60 – 3.54 (m, 2H), 3.53 – 3.47 (m, 6H), 3.44 (t, J = 5.8 Hz, 2H), 3.07 (q, J = 5.8 Hz, 2H), 2.89 (s, 3H), 2.27 (s, 6H). [M-C ₂ HF ₃ O ₂ +1] ⁺ =426.2
27	LCMS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =324.2, ¹ H NMR (400 MHz, DMSO) δ 14.36 (s, 5H), 8.97 (s, 3H), 7.77 (s, 3H), 7.64 (s, 3H), 7.60 (t, J = 6.7 Hz, 3H), 7.24 (t, J = 7.7 Hz, 3H), 7.15 (d, J = 7.3 Hz, 3H), 7.13 – 6.98 (m, 9H), 6.71 (d, J = 7.5 Hz, 3H), 6.01 (s, 3H), 2.27 (s, 9H), 2.12 (s, 9H).
28	LC-MS=[M+1-TFA] ⁺ =356.1, ¹ H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.01 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.46 (dt, J = 17.1, 6.3 Hz, 2H), 7.12 (dt, J = 15.1, 7.4 Hz, 2H), 6.95 (s, 1H), 6.68 (d, J = 7.4 Hz, 1H), 2.37 (d, J = 4.9 Hz, 3H), 2.26 (s, 3H), 2.12 (s, 3H).
29	LC-MS=[M-C ₂ HF ₃ O ₂ +1] ⁺ =356.1, ¹ H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.75 (s, 1H), 9.01 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.95 (s, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 5.81 (s, 1H), 2.96 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
30	LC-MS=[M-C ₂ HF ₃ O ₂ +1] ⁺ =320.1, ¹ H NMR (400 MHz, DMSO) δ 14.36 (s, 2H), 9.95 (s, 1H), 9.06 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.35 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.10 (dt, J = 15.0, 7.3 Hz, 2H), 6.96 (s, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 5.78 (s, 1H), 2.26 (s, 3H), 2.13 (s, 3H), 1.99 (s, 3H).

31	LC-MS=[M+1] ⁺ =307.2, 1H NMR (400 MHz, DMSO) δ 12.53 (s, 1H), 8.52 (d, J = 4.7 Hz, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.35 (d, J = 3.8 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.81 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 5.80 (s, 1H), 2.24 (s, 3H), 2.11 (s, 3H).
32	[M+1] ⁺ =331.2, 1H NMR (400 MHz, DMSO) δ 14.18 (s, 2H), 8.91 (s, 1H), 7.15 – 7.01 (m, 3H), 6.90 (s, 1H), 6.70 (d, J = 7.2 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.41 (s, 1H), 6.36 (d, J = 7.6 Hz, 1H), 5.97 (s, 1H), 5.65 (s, 1H), 3.49 – 3.13 (m, 5H), 2.67 (t, J = 6.5 Hz, 2H), 2.25 (s, 3H), 2.13 (s, 3H). Y=59.92%. Total yield=43.96%.
33	[M-CF ₃ COOH+1] ⁺ =334.2 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 8.98 (s, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.18 (s, 1H), 7.16 – 7.03 (m, 2H), 6.93 (s, 1H), 6.70 (d, J = 7.4 Hz, 1H), 5.89 (s, 1H), 2.94 (s, 3H), 2.85 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
34	[M-C ₂ HF ₃ O ₂ +1] ⁺ =306.2, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.05 (d, J = 1.2 Hz, 1H), 7.80 (s, 1H), 7.53 (dt, J = 7.9, 3.6 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.17 – 7.04 (m, 2H), 6.89 (dt, J = 6.9, 3.5 Hz, 1H), 6.80 (s, 1H), 6.66 – 6.57 (m, 2H), 2.25 (s, 3H), 2.07 (d, J = 6.5 Hz, 3H).
35	LC-MS=[M-C ₂ HF ₃ O ₂ +1] ⁺ =376.1, 1H NMR (400 MHz, DMSO) δ 14.46 (s, 2H), 11.84 (s, 1H), 9.10 (d, J = 0.9 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.67 (dd, J = 8.1, 1.3 Hz, 1H), 7.60 (s, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.11 (s, 1H), 7.03 (dd, J = 7.8, 1.2 Hz, 1H), 6.06 (s, 1H), 3.69 (s, 3H).
36	LCMS:[M-C ₂ HF ₃ O ₂ +1] ⁺ =356.2/358.1, 1H NMR (400 MHz, DMSO) δ 14.45 (s, 2H), 11.83 (s, 1H), 9.08 (d, J = 5.9 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.60 (s, 1H), 7.51 – 7.42 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.02 (s, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.96 (d, J = 5.6 Hz, 1H), 3.69 (s, 3H), 2.29 (s, 3H).
37	[M-C ₂ HF ₃ O ₂ +1] ⁺ =319.3, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.00 (s, 1H), 7.57 (s, 1H), 7.15 – 6.96 (m, 2H), 6.86 (d, J = 7.4 Hz, 1H), 4.69 – 4.62 (m, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.76 (dd, J = 9.7, 5.2 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.52 – 3.45 (m, 4H), 3.43 – 3.37 (m, 2H), 3.23 (s, 3H), 2.27 (s, 6H).
38	[M-2HF ₃ O ₂ +1] ⁺ =340.1, 1H NMR (400 MHz, DMSO) δ 14.41 (s, 2H), 9.08 (d, J = 1.2 Hz, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.43 – 7.33 (m, 2H), 7.13 (dt, J = 11.6, 7.4 Hz, 2H), 6.98 – 6.90 (m, 2H), 6.64 (d, J = 7.4 Hz, 1H), 6.08 (s, 1H), 2.31 – 2.24 (m, 3H), 2.09 (s, 3H).
39	[M+1] ⁺ =278.2, 1H NMR (400 MHz, DMSO) δ 7.55 (d, J = 1.0 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.90 (t, J = 7.7 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.38 (dd, J = 6.0, 3.1 Hz, 2H), 6.33 (s, 1H), 6.27 (d, J = 7.6 Hz, 1H), 5.40 (s, 1H), 4.94 (s, 1H), 2.23 (s, 3H), 2.11 (s, 3H).
40	[M-C ₂ HF ₃ O ₂ +1] ⁺ =368.2, 1H NMR (400 MHz, DMSO) δ 14.45 (s, 2H), 9.03 (s, 1H), 7.37 (s, 1H), 7.27 (dd, J = 6.3, 2.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.05 (t, J = 5.9 Hz, 1H), 5.87 (s, 1H), 3.59 (s, 4H), 3.45 (t, J = 5.8 Hz, 2H), 3.09 (q, J = 5.8 Hz, 2H), 2.88 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H).
41	[M-C ₂ HF ₃ O ₂ +1] ⁺ =363.2, 1H NMR (400 MHz, DMSO) δ 14.44 (s, 2H), 10.20 (s, 1H), 9.07 (s, 1H), 7.86 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 15.4, 7.5 Hz, 2H), 7.13 – 7.00 (m, 2H), 6.88 – 6.59 (m, 2H), 6.01 (s, 1H), 3.97 (s, 2H), 2.25 (d, J = 18.4 Hz, 3H), 2.14 (s, 3H).
42	[M-C ₂ HF ₃ O ₂ +1] ⁺ =377.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.95 (s, 1H), 9.07 (d, J = 1.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.40 (s, 1H), 7.32 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 6.9 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.75 (s, 1H), 6.67 (d, J = 7.1 Hz, 1H), 5.78 (s, 1H), 2.47 (d, J = 6.7 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H).
43	[M-C ₂ HF ₃ O ₂ +1] ⁺ =359.2, 1H NMR (400 MHz, DMSO) δ 14.35 (s, 2H), 10.12 (s, 1H), 9.07 (d, J = 1.1 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.40 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 6.7 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.0 Hz, 1H), 5.80 (s, 1H), 2.74 – 2.61 (m, 4H), 2.26 (s, 3H), 2.13 (s, 3H).
43-A	[M+1] ⁺ =359.2, 1H NMR (400 MHz, MeOD) δ 7.65 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.26 (dd, J = 9.8, 5.6 Hz, 2H), 7.05 (d, J = 7.3 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.38 (s, 1H), 5.68 (s, 1H), 2.79 – 2.65 (m, 4H), 2.29 (s, 3H), 2.17 (s, 3H).
43-B	[M+1] ⁺ =359.2, 1H NMR (400 MHz, MeOD) δ 7.65 (s, 1H), 7.61 – 7.51 (m, 1H), 7.25 (dd, J = 9.8, 5.8 Hz, 2H), 7.05 (d, J = 7.2 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.38 (s, 1H), 5.68 (s, 1H), 2.79 – 2.67 (m, 4H), 2.29 (s, 3H), 2.17 (s, 3H).
44-A	[M+1] ⁺ =356.2, 1H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 9.64 (s, 1H), 7.58 (d, J = 1.0 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.08 – 6.96 (m, 4H), 6.87 (d, J = 7.7 Hz, 1H), 6.79 (s, 1H), 6.43 (s, 1H), 5.55 (s, 1H), 2.93 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H).
44-B	[M+1] ⁺ =356.2, 1H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 9.64 (s, 1H), 7.58 (d, J = 1.0 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.08 – 6.96 (m, 4H), 6.87 (d, J = 7.7 Hz, 1H), 6.79 (s, 1H), 6.43 (s, 1H), 5.55 (s, 1H), 2.93 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H).
45-A	[M+1] ⁺ =324.1, 1H NMR (400 MHz, DMSO) δ 11.99 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 1.0 Hz, 1H), 7.57 (s, 1H), 7.50 (td, J = 7.3, 1.8 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 6.6 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.51 (s, 1H), 5.84 (s, 1H), 2.24 (s, 3H), 2.12 (s, 3H).
45-B	[M+1] ⁺ =324.2, 1H NMR (400 MHz, DMSO) δ 12.00 (s, 1H), 7.71 (s, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.57 (s, 1H), 7.50 (td, J = 7.3, 1.8 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 6.5 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.51 (s, 1H), 5.84 (s, 1H), 2.24 (s, 3H), 2.12 (s, 3H).
46-A	[M+1] ⁺ =400.2, 1H NMR (400 MHz, DMSO-D ₂ O) δ 7.58 (d, J = 0.9 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.11 – 6.86 (m, 2H), 6.74 (dd, J = 26.0, 7.5 Hz, 3H), 6.64 (s, 1H), 6.44 (s, 1H), 5.56 (s, 1H), 3.93 (t, J = 5.3 Hz, 2H), 3.27 (t, J = 5.3 Hz, 2H), 2.89 (s, 3H), 2.20 (s, 3H), 2.09 (s, 3H).
46-B	[M+1] ⁺ =400.2, 1H NMR (400 MHz, DMSO-D ₂ O) δ 7.58 (s, 1H), 7.20 (t, J = 7.7 Hz, 1H), 6.98 (d, J = 8.5 Hz, 2H), 6.73 (dd, J = 26.9, 7.4 Hz, 3H), 6.62 (s, 1H), 6.44 (s, 1H), 5.56 (s, 1H), 3.26 (t, J = 5.2 Hz, 2H), 2.89 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H).

47-A	[M+1] ⁺ =356.1, 1H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 7.61 (d, J = 4.3 Hz, 2H), 7.57 (s, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.07 – 6.97 (m, 2H), 6.67 (d, J = 113.4 Hz, 2H), 5.72 (s, 1H), 2.37 (d, J = 5.0 Hz, 3H), 2.24 (s, 3H), 2.12 (s, 3H).
47-B	[M+1] ⁺ =356.1, 1H NMR (400 MHz, DMSO) δ 7.61 (dd, J = 9.5, 4.4 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.10 – 6.92 (m, 2H), 6.72 (s, 1H), 6.47 (s, 1H), 5.71 (s, 1H), 2.34 (s, 3H), 2.20 (s, 3H), 2.10 – 2.07 (m, 3H).
48	LCMS: [M-C2HF3O2+1] ⁺ =332.2, 1H NMR (400 MHz, DMSO) δ 14.58 (s, 1H), 9.48 (s, 1H), 9.08 (s, 1H), 7.21 – 6.99 (m, 4H), 6.74 – 6.59 (m, 3H), 6.53 (s, 1H), 5.72 (s, 1H), 4.42 (t, J = 6.5 Hz, 2H), 3.18 (t, J = 6.5 Hz, 2H), 2.25 (s, 3H), 2.11 (s, 3H).
49	[M-C2HF3O2+1] ⁺ =308.2, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 11.79 (s, 1H), 9.04 (s, 1H), 7.72 – 7.60 (m, 2H), 7.51 – 7.22 (m, 7H), 7.15 (s, 1H), 5.74 (s, 1H), 3.69 (s, 3H).
50	LC-MS= [M-C2HF3O2+1] ⁺ =338.0, 1H NMR (400 MHz, DMSO) δ 14.43 (s, 2H), 9.75 (s, 1H), 9.07 (d, J = 1.2 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.17 – 7.06 (m, 4H), 6.69 (dd, J = 13.1, 7.0 Hz, 2H), 6.00 (s, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H).
51	LC-MS= [M-C2HF3O2+1] ⁺ =374.0, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 9.68 (s, 1H), 9.08 (d, J = 1.2 Hz, 1H), 7.39 (td, J = 7.9, 1.3 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.09 (dd, J = 13.2, 5.6 Hz, 2H), 6.78 (dd, J = 10.5, 4.0 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.00 (s, 1H), 3.03 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H).
52	[M-C2HF3O2+1] ⁺ = 390.2, 1H NMR (400 MHz, DMSO) δ 14.43 (s, 1.5H), 11.83 (s, 1H), 9.09 (d, J = 0.9 Hz, 1H), 7.70 (t, J = 6.7 Hz, 2H), 7.62 (s, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.02 (s, 1H), 6.05 (s, 1H), 3.69 (s, 3H), 2.34 (d, J = 7.0 Hz, 3H).
53	[M-C2HF3O2+1] ⁺ =354.2, 1H NMR (400 MHz, DMSO) δ 14.39 (s, 2H), 11.58 (s, 1H), 9.07 (s, 1H), 7.48 – 7.39 (m, 1H), 7.38 – 7.26 (m, 2H), 7.17 – 7.06 (m, 2H), 6.97 (s, 1H), 6.68 (d, J = 7.3 Hz, 1H), 5.93 (s, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 2.12 (s, 3H).
54	[M-C2HF3O2+1] ⁺ = 390.2, 1H NMR (400 MHz, DMSO) δ 14.43 (s, 1.5H), 11.83 (s, 1H), 9.09 (d, J = 0.9 Hz, 1H), 7.70 (t, J = 6.7 Hz, 2H), 7.62 (s, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.02 (s, 1H), 6.05 (s, 1H), 3.69 (s, 3H), 2.34 (d, J = 7.0 Hz, 3H).
54	[M-C2HF3O2+1] ⁺ =354.2, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 11.65 (s, 1H), 9.05 (s, 1H), 7.55 (t, J = 6.5 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.10 (dd, J = 16.2, 8.9 Hz, 3H), 6.71 (d, J = 7.5 Hz, 1H), 6.01 (s, 1H), 3.70 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H).
55	LCMS: [M-C2HF3O2+1] ⁺ =418.1, 1H NMR (400 MHz, DMSO) δ 8.95 (d, J = 1.2 Hz, 1H), 7.10 (ddd, J = 15.2, 10.7, 7.4 Hz, 4H), 6.99 (s, 1H), 6.65 (t, J = 12.9 Hz, 1H), 6.48 (dd, J = 8.8, 5.2 Hz, 1H), 5.96 (s, 1H), 4.08 (t, J = 5.3 Hz, 2H), 3.33 (t, J = 5.2 Hz, 2H), 2.92 (s, 3H), 2.24 (s, 3H), 2.09 (s, 3H).
56	[M+1] ⁺ =307.1, 1H NMR (400 MHz, DMSO) δ 11.94 (s, 1H), 8.06 – 7.78 (m, 3H), 7.63 (d, J = 20.5 Hz, 2H), 7.40 (dd, J = 6.7, 1.9 Hz, 1H), 7.14 – 6.89 (m, 3H), 6.61 (s, 1H), 5.83 (s, 1H), 2.20 (d, J = 22.4 Hz, 6H).
57	[M+1] ⁺ =357.1, 1H NMR (400 MHz, DMSO) δ 11.93 (s, 1H), 10.81 (s, 1H), 8.06 (s, 1H), 7.61 (s, 1H), 7.14 – 6.93 (m, 2H), 6.93 – 6.48 (m, 4H), 5.56 (s, 1H), 3.20 (s, 3H), 2.26 (s, 3H), 2.10 (s, 3H).
58	[M+1] ⁺ = 325.2, 1H NMR (400 MHz, CD3OD) δ 8.36 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 0.9 Hz, 1H), 7.13 (dt, J = 22.7, 10.1 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.53 (s, 1H), 6.05 (s, 1H), 2.32 (s, 3H), 2.21 (s, 3H).
59	[M+1] ⁺ =355.15, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 1H), 9.27 (s, 1H), 9.08 (s, 1H), 8.08 (d, J = 4.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.34 (s, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.16 – 7.06 (m, 2H), 7.02 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.71 (d, J = 7.2 Hz, 1H), 5.78 (s, 1H), 2.27 (s, 3H), 2.16 (s, 3H).
60	[M-TFA-1] ⁻ =311.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 12.02 (s, 1H), 9.02 – 8.89 (m, 1H), 7.75 – 7.56 (m, 1H), 7.13 (ddt, J = 22.9, 16.8, 9.0 Hz, 3H), 4.26 – 4.06 (m, 1H), 2.28 – 2.08 (m, 8H), 1.91 – 0.73 (m, 8H).
61	[M-C2HF3O2+1] ⁺ = 350.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 11.69 (s, 1H), 8.96 (d, J = 0.9 Hz, 1H), 7.61 (d, J = 4.6 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.31 (t, J = 6.4 Hz, 2H), 7.07 (dt, J = 12.8, 4.6 Hz, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.70 (s, 3H), 3.39 (d, J = 8.5 Hz, 1H), 3.19 (dd, J = 13.8, 7.3 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).
62	[M-C2HF3O2+1] ⁺ =336.2, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 9.67 (s, 1H), 9.06 (d, J = 0.8 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.96 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.77 (s, 1H), 3.63 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
63	[M-C2HF3O2+1] ⁺ =380.1, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 9.99 (s, 1H), 9.05 (d, J = 0.9 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.95 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.1 Hz, 1H), 5.78 (s, 1H), 2.70 (t, J = 7.0 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.25 (d, J = 10.4 Hz, 3H), 2.13 (s, 3H), 2.06 (s, 3H).
64	[M-C2HF3O2+1] ⁺ =392.2, 1H NMR (400 MHz, DMSO) δ 14.29 (s, 2H), 9.74 (s, 1H), 9.06 (d, J = 1.1 Hz, 1H), 7.34 (dd, J = 20.1, 15.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.19 – 7.03 (m, 2H), 6.96 (s, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.2 Hz, 1H), 5.76 (s, 1H), 5.21 (dd, J = 6.0, 4.4 Hz, 1H), 4.02 – 3.64 (m, 5H), 3.47 (s, 18H), 2.55 – 2.46 (m, 7H), 2.26 (s, 3H), 2.23 – 1.97 (m, 4H), 1.97 – 1.80 (m, 1H), 1.44 – 1.11 (m, 1H), 0.01 (s, 1H).

65	[M-C2HF3O2+1] ⁺ =334.2, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.06 (d, J = 1.1 Hz, 1H), 8.34 (t, J = 5.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.15 – 6.99 (m, 4H), 6.94 (s, 1H), 6.69 (d, J = 7.2 Hz, 1H), 5.81 (s, 1H), 4.26 – 4.16 (m, 2H), 2.26 (s, 3H), 2.14 (s, 3H), 1.84 (s, 3H).
66	[M-C2HF3O2+1] ⁺ =338.1, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 9.00 (d, J = 1.1 Hz, 1H), 7.58 (s, 1H), 7.07 (dt, J = 12.0, 7.0 Hz, 3H), 6.87 (d, J = 7.5 Hz, 1H), 4.66 (dd, J = 8.5, 5.3 Hz, 1H), 3.91 (t, J = 9.3 Hz, 1H), 3.76 (dd, J = 9.8, 5.3 Hz, 1H), 3.51 (d, J = 2.1 Hz, 2H), 3.09 (q, J = 5.8 Hz, 2H), 2.83 (s, 3H), 2.28 (s, 6H).
67	[M-C2HF3O2+1] ⁺ =370.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.80 (s, 1H), 9.07 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.17 – 7.05 (m, 3H), 7.02 (s, 1H), 6.97 (s, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 5.81 (s, 1H), 3.05 (q, J = 7.3 Hz, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 1.15 (t, J = 7.3 Hz, 3H).
68	[M-C2HF3O2+1] ⁺ =288.2, 1H NMR (400 MHz, DMSO) δ 14.39 (s, 2H), 9.06 (d, J = 0.9 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.18 – 7.08 (m, 2H), 7.03 (s, 1H), 6.69 (d, J = 7.3 Hz, 1H), 5.96 (s, 1H), 2.27 (s, 3H), 2.12 (s, 3H).
69	[M-C2HF3O2+1] ⁺ =370.1, 1H NMR (400 MHz, DMSO) δ 14.38 (s, 2H), 9.07 (d, J = 1.1 Hz, 1H), 7.56 (t, J = 6.3 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.15 – 7.06 (m, 3H), 6.94 (s, 1H), 5.83 (s, 1H), 4.13 (d, J = 6.3 Hz, 2H), 2.80 (s, 3H), 2.26 (s, 3H), 2.14 (s, 3H).
70	[M-C4H2F6O4+1] ⁺ =419.2, 1H NMR (400 MHz, DMSO+D2O) δ 8.98 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.16 – 7.02 (m, 2H), 6.89 (d, J = 3.9 Hz, 2H), 6.64 (d, J = 7.4 Hz, 1H), 5.77 (s, 1H), 3.95 (s, 2H), 3.30 (dd, J = 62.3, 55.3 Hz, 6H), 2.78 (t, J = 7.1 Hz, 2H), 2.24 (s, 3H), 2.11 (s, 3H).
71	[M-C2HF3O2+1] ⁺ =370.1, 1H NMR (400 MHz, DMSO) δ 14.39 (s, 2H), 9.08 (d, J = 1.1 Hz, 1H), 7.46 – 7.33 (m, 2H), 7.27 (s, 1H), 7.17 – 7.05 (m, 3H), 6.96 (s, 1H), 6.70 (d, J = 7.2 Hz, 1H), 5.87 (s, 1H), 3.21 (s, 3H), 2.92 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H).
72	[M-C2HF3O2+1] ⁺ =351.2, 1H NMR (400 MHz, D2O) δ 8.56 (s, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 10.3 Hz, 2H), 7.02 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.80 (s, 1H), 6.70 (d, J = 7.7 Hz, 1H), 5.81 (s, 1H), 3.62 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H).
73	[M-C2HF3O2+1] ⁺ = 390.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.96 (s, 1H), 9.07 (d, J = 0.9 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.79 (d, J = 8.1 Hz, 1H), 3.75 (dd, J = 8.8, 3.4 Hz, 1H), 3.72 – 3.65 (m, 2H), 3.30 (dd, J = 8.2, 6.4 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.42 – 2.32 (m, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 2.00 (dtd, J = 12.9, 7.7, 5.5 Hz, 1H), 1.51 (td, J = 14.5, 7.1 Hz, 1H).
73-A	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.95 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.3 Hz, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.85 – 3.67 (m, 2H), 3.63 (q, J = 7.6 Hz, 1H), 3.38 – 3.21 (m, 1H), 2.59 – 2.52 (m, 1H), 2.43 – 2.31 (m, 2H), 2.27 (s, 3H), 2.14 (s, 3H), 2.00 (td, J = 12.8, 7.6 Hz, 1H), 1.51 (dq, J = 14.4, 7.2 Hz, 1H).
73-B	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.95 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.1, 7.4 Hz, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.75 (ddd, J = 13.4, 11.6, 6.7 Hz, 2H), 3.63 (dd, J = 15.3, 7.5 Hz, 1H), 3.35 – 3.25 (m, 1H), 2.42 – 2.33 (m, 2H), 2.27 (s, 3H), 2.14 (s, 3H), 2.00 (td, J = 12.9, 7.6 Hz, 1H), 1.51 (dq, J = 14.4, 7.2 Hz, 1H).
74	[M-C2HF3O2+1] ⁺ =395.1, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 10.08 (s, 1H), 9.07 (d, J = 1.0 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 14.5 Hz, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 5.82 (s, 1H), 3.45 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.26 (s, 3H), 2.11 (d, J = 14.5 Hz, 3H).
75	[M-C2HF3O2+1] ⁺ =360.1, 1H NMR (400 MHz, DMSO) δ 14.36 (s, 2H), 9.79 (s, 1H), 9.08 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.25 (dd, J = 14.2, 7.6 Hz, 1H), 7.15 (t, J = 8.1 Hz, 2H), 7.03 (d, J = 10.8 Hz, 2H), 6.93 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 5.82 (s, 1H), 2.97 (s, 3H), 2.14 (s, 3H).
76	[M-C2HF3O2+1] ⁺ =370.1, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 9.64 (s, 1H), 8.97 (s, 1H), 7.62 (s, 1H), 7.18 (t, J = 8.1 Hz, 1H), 7.07 (dt, J = 10.8, 6.6 Hz, 3H), 6.95 (dd, J = 18.4, 7.0 Hz, 3H), 4.67 (t, J = 7.8 Hz, 1H), 3.37 (dd, J = 13.7, 8.2 Hz, 1H), 3.12 (dd, J = 13.7, 7.5 Hz, 1H), 2.83 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H).
77	[M-C2HF3O2+1] ⁺ = 410.1, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 1.5H), 9.07 (s, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.19 – 7.01 (m, 5H), 6.92 (s, 1H), 6.65 (d, J = 7.3 Hz, 1H), 5.86 (s, 1H), 2.26 (s, 3H), 2.11 (s, 3H).
78	[M-C2HF3O2+1] ⁺ =380.0, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 9.81 (s, 1H), 9.08 (s, 1H), 7.52 – 7.43 (m, 2H), 7.38 – 7.26 (m, 2H), 7.21 – 7.15 (m, 2H), 7.11 (s, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.06 (s, 1H), 2.97 (s, 3H).
79	[M-C2HF3O2+1] ⁺ =389.2, 1H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 9.03 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.37 (s, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.15 – 7.04 (m, 2H), 6.93 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 5.77 (s, 1H), 3.36 (dd, J = 11.4, 7.3 Hz, 1H), 3.27 – 3.18 (m, 1H), 3.15 – 3.04 (m, 1H), 2.79 (dd, J = 11.2, 8.9 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.49 – 2.39 (m, 2H), 2.25 (s, 3H), 2.15 – 2.02 (m, 4H), 1.54 (dq, J = 13.0, 8.8 Hz, 1H).
80	[M-C2HF3O2+1] ⁺ =433.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.92 (s, 1H), 9.06 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.17 – 7.05 (m, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.78 (s, 1H), 3.81 (dd, J = 11.2, 2.7 Hz, 2H), 3.28 (t, J = 10.9 Hz, 2H), 2.26 (s, 3H), 2.21 (d, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.96 (ddd, J = 11.2, 7.4, 3.8 Hz, 1H), 1.55 (d, J = 11.6 Hz, 2H), 1.21 (qd, J = 12.2, 4.3 Hz, 2H).
81	[M-C2HF3O2+1] ⁺ =405.2, 1H NMR (400 MHz, DMSO) δ 14.40 (s, 1H), 10.56 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.17 – 7.05 (m, 2H), 7.03 – 6.90 (m, 2H), 6.67 (d, J = 7.4 Hz, 1H), 5.84 (s, 1H), 4.03 (s, 2H), 3.84 (s, 4H), 3.24 (s, 4H), 2.26 (s, 3H), 2.13 (s, 3H).

82	[M-C2HF3O2+1] ⁺ =432.2, 1H NMR (400 MHz, DMSO) δ 14.41 (s, 2H), 10.07 (s, 1H), 9.08 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.1, 7.3 Hz, 2H), 6.94 (s, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.54 – 2.86 (m, 10H), 2.76 (s, 3H), 2.57 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H).
83	[M-C2HF3O2+1] ⁺ =399.2, 1H NMR (400 MHz, DMSO) δ 14.29 (s, 2H), 9.05 (s, 1H), 7.14 – 7.05 (m, 4H), 6.95 (s, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 9.4 Hz, 1H), 6.39 (s, 1H), 6.34 (d, J = 7.6 Hz, 1H), 5.66 (s, 1H), 3.13 – 3.03 (m, 4H), 2.88 (s, 3H), 2.26 (s, 3H), 2.14 (s, 3H).
84	[M-C2HF3O2+1] ⁺ =417.2, 1H NMR (400 MHz, DMSO) δ 9.01 (d, J = 1.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.37 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.10 (dt, J = 15.1, 7.4 Hz, 2H), 6.90 (d, J = 9.8 Hz, 2H), 6.65 (d, J = 7.4 Hz, 1H), 5.78 (s, 1H), 3.40 (d, J = 12.0 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 11.2 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.11 (s, 3H), 1.81 (d, J = 14.3 Hz, 2H), 1.72 – 1.54 (m, 3H), 1.39 (t, J = 12.1 Hz, 1H).
85	[M-C2HF3O2+1] ⁺ =344.2, 1H NMR (400 MHz, DMSO) δ 14.35 (s, 2H), 9.05 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.78 (s, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.19 – 7.07 (m, 2H), 6.96 (s, 1H), 6.69 (d, J = 7.3 Hz, 1H), 5.96 (s, 1H), 3.47 – 3.34 (m, 2H), 2.71 (t, J = 6.6 Hz, 2H), 2.25 (s, 3H), 2.11 (s, 3H).
86	[M-C2HF3O2+1] ⁺ =426.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.89 (s, 1H), 9.07 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.4 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.91 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 5.82 (s, 1H), 3.82 – 3.75 (m, 1H), 3.71 – 3.66 (m, 1H), 3.61 (dd, J = 7.4, 1.9 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.23 – 3.13 (m, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 2.08 – 1.85 (m, 1H), 1.65 – 1.41 (m, 1H).
87	[M-C2HF3O2+1] ⁺ =372.2, 1H NMR (400 MHz, DMSO) δ 14.35 (s, 2H), 9.84 (s, 1H), 9.08 (d, J = 1.0 Hz, 1H), 8.19 (s, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.17 – 7.06 (m, 2H), 7.00 (s, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 7.1 Hz, 1H), 5.81 (s, 1H), 2.27 (s, 3H), 2.16 (s, 3H).
88	[M-C2HF3O2+1] ⁺ =433.2, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 10.05 (s, 2H), 9.05 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.37 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.93 (s, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.96 (s, 2H), 3.55 (s, 4H), 3.19 – 2.91 (m, 4H), 2.43 – 2.34 (m, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.98 – 1.87 (m, 2H).
89	[M-C2HF3O2+1] ⁺ =403.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 10.19 (s, 1H), 9.49 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.33 (dd, J = 15.6, 7.7 Hz, 2H), 7.19 – 7.05 (m, 2H), 6.92 (d, J = 9.4 Hz, 2H), 6.66 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.40 (d, J = 6.1 Hz, 4H), 3.05 (d, J = 7.3 Hz, 2H), 2.77 (t, J = 7.1 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 2.01 (s, 2H), 1.87 (dd, J = 7.3, 4.8 Hz, 2H).
90	[M-C2HF3O2+1] ⁺ =418.2, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 10.12 (s, 1H), 9.00 (d, J = 60.9 Hz, 3H), 7.56 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.19 – 7.05 (m, 2H), 6.94 (s, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.80 (s, 1H), 3.13 (d, J = 88.2 Hz, 10H), 2.63 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H).
91	[M-C2HF3O2+1] ⁺ =435.2, 1H NMR (400 MHz, DMSO) δ 9.02 (d, J = 0.9 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.17 – 7.05 (m, 2H), 6.93 (s, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.91 (s, 1H), 4.29 – 4.16 (m, 2H), 4.00 (s, 2H), 3.74 (s, 2H), 3.50 (s, 2H), 3.47 – 3.42 (m, 2H), 3.22 (d, J = 7.1 Hz, 2H), 2.25 (s, 3H), 2.11 (s, 3H).
92	[M-C2HF3O2+1] ⁺ =312.2, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 8.97 (d, J = 0.8 Hz, 1H), 7.65 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.12 – 6.99 (m, 2H), 6.62 (s, 1H), 4.12 (d, J = 10.6 Hz, 1H), 2.25 (d, J = 4.1 Hz, 6H), 2.14 (dd, J = 22.9, 11.7 Hz, 1H), 2.03 (t, J = 10.0 Hz, 1H), 1.80 – 1.65 (m, 2H), 1.45 (dd, J = 31.5, 12.5 Hz, 2H), 1.31 – 1.13 (m, 2H), 1.02 – 0.85 (m, 2H).
93	[M-C2HF3O2+1] ⁺ =396.2, 1H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 7.58 (s, 1H), 7.05 (dd, J = 7.3, 5.8 Hz, 2H), 6.98 – 6.89 (m, 1H), 4.53 (t, J = 7.5 Hz, 1H), 3.51 – 3.47 (m, 2H), 3.44 (dd, J = 7.2, 4.1 Hz, 4H), 3.34 (dd, J = 10.5, 4.9 Hz, 1H), 3.29 – 3.20 (m, 1H), 3.07 (t, J = 5.7 Hz, 2H), 2.90 (s, 3H), 2.28 (dd, J = 17.4, 4.5 Hz, 7H), 2.05 (td, J = 13.5, 6.0 Hz, 1H).
94	[M-C2HF3O2+1] ⁺ =455.2, 1H NMR (400 MHz, DMSO) δ 14.36 (s, 1H), 10.11 (s, 1H), 9.08 (d, J = 1.0 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 7.4 Hz, 1H), 5.82 (s, 1H), 3.69 (s, 4H), 3.52 (s, 2H), 3.13 (d, J = 111.8 Hz, 6H), 2.26 (s, 3H), 2.13 (s, 3H).
95	[M-C2HF3O2+1] ⁺ =406.2, 1H NMR (400 MHz, DMSO) δ 9.04 (d, J = 1.2 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.96 (s, 1H), 6.68 (d, J = 7.3 Hz, 1H), 5.90 (s, 1H), 3.87 – 3.80 (m, 1H), 3.72 (ddd, J = 13.7, 12.6, 7.2 Hz, 3H), 3.64 – 3.55 (m, 2H), 3.52 – 3.50 (m, 1H), 2.25 (s, 3H), 2.12 (s, 3H), 2.01 – 1.91 (m, 1H), 1.58 (td, J = 13.4, 7.1 Hz, 1H).
96	[M-C2HF3O2+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.93 (s, 1H), 9.07 (d, J = 1.1 Hz, 1H), 7.56 (t, J = 7.0 Hz, 1H), 7.42 (d, J = 11.7 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.18 – 7.01 (m, 2H), 6.96 (s, 1H), 6.85 (dd, J = 7.5, 3.8 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 5.78 (s, 1H), 3.81 (d, J = 11.2 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.30 (td, J = 11.0, 2.5 Hz, 1H), 2.42 (dd, J = 14.2, 8.2 Hz, 1H), 2.33 (dd, J = 13.8, 4.3 Hz, 1H), 2.26 (s, 3H), 2.13 (s, 3H), 1.80 – 1.71 (m, 1H), 1.60 (d, J = 12.5 Hz, 1H), 1.52 – 1.36 (m, 3H), 1.28 – 1.15 (m, 1H).
97	[M-C2HF3O2+1] ⁺ =384.2, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 9.67 (s, 1H), 9.01 (d, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.12 – 7.02 (m, 3H), 7.02 – 6.95 (m, 2H), 6.92 (d, J = 7.7 Hz, 1H), 4.35 (t, J = 7.4 Hz, 1H), 2.96 (s, 3H), 2.57 (dd, J = 8.9, 5.1 Hz, 1H), 2.47 (s, 1H), 2.36 (d, J = 8.6 Hz, 1H), 2.26 (s, 3H), 2.16 – 2.02 (m, 4H).
98	[M-C2HF3O2+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.36 (s, 2H), 9.08 (d, J = 1.1 Hz, 1H), 8.52 (t, J = 5.7 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.17 – 7.06 (m, 2H), 6.96 (s, 1H), 6.69 (d, J = 7.3 Hz, 1H), 5.90 (s, 1H), 3.84 (dd, J = 11.3, 2.6 Hz, 2H), 3.25 (t, J = 10.9 Hz, 2H), 3.13 (t, J = 6.4 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.77 (ddt, J = 14.9, 7.7, 3.8 Hz, 1H), 1.56 (d, J = 11.5 Hz, 2H), 1.18 (q, J = 12.1, 4.4 Hz, 2H).

98-A	[M+1] ⁺ =404.2, 1H NMR (400 MHz, MeOD) δ 7.68 (d, J = 4.1 Hz, 2H), 7.63 (s, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.00 (dd, J = 14.2, 6.7 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.40 (s, 1H), 5.77 (s, 1H), 3.95 (dd, J = 11.2, 3.2 Hz, 2H), 3.40 (dd, J = 19.1, 7.6 Hz, 2H), 3.25 (d, J = 7.0 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.89 (ddd, J = 15.2, 7.5, 3.6 Hz, 1H), 1.67 (d, J = 12.9 Hz, 2H), 1.42 – 1.19 (m, 3H).
98-B	[M+1] ⁺ =404.2, 1H NMR (400 MHz, MeOD) δ 7.66 (t, J = 12.4 Hz, 3H), 7.40 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.11 – 6.97 (m, 2H), 6.73 (d, J = 7.6 Hz, 1H), 6.39 (s, 1H), 5.77 (s, 1H), 3.95 (dd, J = 11.2, 3.0 Hz, 2H), 3.41 (t, J = 11.2 Hz, 2H), 3.25 (d, J = 6.9 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.93 – 1.83 (m, 1H), 1.67 (d, J = 12.8 Hz, 2H), 1.37 – 1.28 (m, 3H).
99	[M – C ₂ HF ₃ O ₂ +1] ⁺ =418.2, 1H NMR (400 MHz, DMSO) δ 9.01 (s, 1H), 7.51 (d, J = 6.6 Hz, 1H), 7.41 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.10 (dt, J = 15.1, 7.3 Hz, 2H), 6.95 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 5.76 (s, 1H), 3.68 (d, J = 20.5 Hz, 1H), 3.35 – 3.24 (m, 1H), 2.25 (s, 3H), 2.16 (t, J = 7.0 Hz, 1H), 2.12 (s, 4H), 1.78 (d, J = 8.7 Hz, 2H), 1.59 (dd, J = 37.0, 9.9 Hz, 3H), 1.39 (dd, J = 18.5, 8.5 Hz, 3H), 1.14 – 1.04 (m, 1H), 0.95 (q, J = 12.9 Hz, 1H).
100-A	[M+1] ⁺ =319.1, 1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 8.71 (s, 1H), 8.15 (s, 1H), 7.48 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.98 – 6.96 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.82 (s, 1H), 6.46 – 6.43 (m, 1H), 5.65 (s, 1H), 4.26 (d, J = 10.4 Hz, 1H), 3.79 – 3.74 (m, 1H), 2.78 – 2.67 (m, 1H), 2.61 – 2.55 (m, 1H), 2.19 (s, 3H), 1.98 – 1.92 (m, 1H), 1.89 (s, 3H), 1.85 – 1.75 (m, 1H).
100-B	[M+1] ⁺ =319.1, 1H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 8.81 (s, 1H), 8.15 (s, 1H), 7.54 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 6.4 Hz, 2H), 6.85 (s, 1H), 6.48 – 6.46 (m, 1H), 5.87 – 5.86 (m, 1H), 4.15 – 4.12 (m, 1H), 4.03 – 3.92 (m, 1H), 2.69 – 2.63 (m, 1H), 2.60 – 2.55 (m, 1H), 2.22 (s, 6H), 1.91 – 1.80 (m, 1H), 1.47 – 1.34 (m, 1H).
101	[M – C ₂ HF ₃ O ₂ +1] ⁺ =418.3, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.91 (s, 1H), 9.07 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.4 Hz, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.78 (s, 1H), 3.82 (dd, J = 11.0, 3.2 Hz, 2H), 3.25 (t, J = 11.2 Hz, 2H), 2.31 – 2.23 (m, 5H), 2.13 (s, 3H), 1.50 (ddd, J = 19.0, 15.8, 9.5 Hz, 5H), 1.14 (qd, J = 12.4, 4.2 Hz, 2H).
102	[M – C ₂ HF ₃ O ₂ +1] ⁺ =445.3, 1H NMR (400 MHz, DMSO) δ 9.96 (s, 1H), 9.04 (s, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.40 (s, 2H), 7.28 (t, J = 7.9 Hz, 2H), 7.10 (dt, J = 15.1, 7.4 Hz, 4H), 6.95 (s, 2H), 6.84 (d, J = 7.6 Hz, 2H), 6.66 (d, J = 7.5 Hz, 2H), 5.77 (s, 2H), 4.30 (d, J = 13.1 Hz, 2H), 3.76 (d, J = 13.2 Hz, 2H), 2.99 (t, J = 12.0 Hz, 2H), 2.47 (s, 2H), 2.25 (s, 6H), 2.20 (d, J = 7.0 Hz, 4H), 2.12 (s, 6H), 1.97 (s, 8H), 1.64 (t, J = 14.8 Hz, 4H), 1.18 – 1.05 (m, 2H), 0.98 (dt, J = 12.0, 8.6 Hz, 2H).
103	[M – C ₂ HF ₃ O ₂ +1] ⁺ =397.2, 1H NMR (400 MHz, DMSO) δ 14.36 (s, 1H), 10.37 (s, 1H), 9.07 (s, 1H), 8.68 (d, J = 5.5 Hz, 2H), 7.64 (d, J = 5.4 Hz, 2H), 7.55 (d, J = 8.1 Hz, 1H), 7.39 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.10 (dt, J = 15.1, 7.4 Hz, 2H), 6.97 – 6.86 (m, 2H), 6.66 (d, J = 7.4 Hz, 1H), 5.80 (s, 1H), 3.85 (s, 2H), 2.26 (s, 3H), 2.12 (s, 3H).
104	[M – C ₂ HF ₃ O ₂ +1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.93 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.39 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.4 Hz, 2H), 6.97 (s, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.72 (dd, J = 9.2, 5.8 Hz, 2H), 3.30 (td, J = 10.8, 2.6 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.26 (s, 3H), 2.21 – 2.07 (m, 5H), 2.01 – 1.90 (m, 1H), 1.77 (d, J = 9.4 Hz, 1H), 1.60 – 1.40 (m, 2H), 1.27 – 1.13 (m, 1H).
105	[M – C ₂ HF ₃ O ₂ +1] ⁺ =440.2, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.09 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 5.9 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.45 (d, J = 7.7 Hz, 1H), 7.20 – 7.06 (m, 2H), 6.97 (s, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.01 (s, 1H), 3.80 – 3.74 (m, 3H), 3.16 (t, J = 11.2 Hz, 2H), 2.56 (dd, J = 11.9, 6.3 Hz, 2H), 2.27 (s, 3H), 2.10 (d, J = 17.5 Hz, 3H), 1.48 (dd, J = 20.5, 9.5 Hz, 3H), 1.07 – 0.92 (m, 2H).
106	[M – C ₂ HF ₃ O ₂ +1] ⁺ =397.2, 1H NMR (400 MHz, DMSO) δ 14.40 (s, 2H), 9.34 (s, 1H), 9.09 (s, 1H), 7.49 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.42 (d, J = 7.8 Hz, 1H), 6.13 (s, 1H), 6.00 (s, 1H), 3.35 (q, J = 8.7 Hz, 1H), 3.07 (dd, J = 15.7, 9.0 Hz, 1H), 2.89 (dd, J = 15.4, 6.9 Hz, 2H), 2.80 (s, 3H), 2.30 (s, 3H), 2.17 (d, J = 10.9 Hz, 3H).
107	[M – C ₂ HF ₃ O ₂ +1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.41 (s, 2H), 9.95 (s, 1H), 9.08 (s, 1H), 8.73 (s, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.45 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.1, 7.4 Hz, 2H), 6.95 (s, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 5.80 (s, 1H), 3.35 (s, 2H), 3.17 (s, 4H), 2.84 (s, 4H), 2.26 (s, 3H), 2.13 (s, 3H).
108	[M – C ₂ HF ₃ O ₂ +1] ⁺ =418.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 9.83 (s, 1H), 8.97 (s, 1H), 7.62 (s, 1H), 7.49 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.05 (dd, J = 9.1, 4.9 Hz, 3H), 6.83 (d, J = 7.5 Hz, 1H), 4.68 (t, J = 7.7 Hz, 1H), 3.86 – 3.81 (m, 2H), 3.38 – 3.23 (m, 3H), 3.09 (dd, J = 13.9, 6.9 Hz, 1H), 2.22 (d, J = 6.0 Hz, 5H), 2.16 (s, 3H), 1.97 (ddd, J = 11.3, 7.6, 4.0 Hz, 1H), 1.57 (d, J = 12.1 Hz, 2H), 1.23 (qd, J = 12.3, 4.2 Hz, 2H).
109	[M+1] ⁺ =361.1, 1H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 8.22 – 8.19 (m, 1H), 7.55 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.14 – 7.03 (m, 2H), 7.01 – 6.95 (m, 2H), 6.78 – 6.76 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.40 (s, 1H), 6.25 – 6.24 (m, 1H), 5.49 (s, 1H), 2.47 – 2.46 (m, 1H), 2.22 (s, 3H), 2.11 (s, 3H), 0.66 – 0.52 (m, 2H), 0.44 – 0.25 (m, 2H).
110	[M+1] ⁺ =362.9, 1H NMR (400 MHz, DMSO) δ 11.83 (d, J = 30.0 Hz, 1H), 9.62 (d, J = 21.4 Hz, 1H), 7.56 (s, 2H), 7.38 (s, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.0 Hz, 2H), 6.79 (dd, J = 36.8, 28.4 Hz, 2H), 6.37 (d, J = 92.8 Hz, 1H), 5.55 (d, J = 37.8 Hz, 1H), 3.00 (s, 2H), 2.23 (d, J = 7.0 Hz, 9H), 2.12 (s, 3H).
111	[M – C ₂ HF ₃ O ₂ +1] ⁺ =405.2, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 9.04 (s, 1H), 8.43 (s, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 7.8 Hz, 2H), 7.16 – 7.04 (m, 2H), 6.96 (s, 1H), 6.69 (dd, J = 16.0, 7.5 Hz, 2H), 6.22 (d, J = 7.6 Hz, 1H), 5.74 (s, 1H), 3.80 (dd, J = 8.2, 3.4 Hz, 2H), 3.68 – 3.57 (m, 1H), 3.37 – 3.32 (m, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.74 (d, J = 11.1 Hz, 2H), 1.35 (td, J = 14.9, 4.3 Hz, 2H).

112	LC-MS= [M-C2HF3O2+1] ⁺ =454.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 9.76 (s, 1H), 8.99 (d, J = 0.8 Hz, 1H), 7.62 (s, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.10 – 7.00 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 4.67 (t, J = 7.8 Hz, 1H), 3.82 – 3.75 (m, 2H), 3.37 (dd, J = 13.8, 8.1 Hz, 1H), 3.26 (t, J = 11.4 Hz, 2H), 3.12 (dd, J = 13.7, 7.6 Hz, 1H), 2.87 (d, J = 6.3 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H), 2.06 – 1.96 (m, 1H), 1.70 – 1.60 (m, 2H), 1.30 – 1.16 (m, 2H).
112 -A	LC-MS= [M +1] ⁺ =454.2, 1H NMR (400 MHz, DMSO) δ 11.79 (d, J = 47.0 Hz, 1H), 9.69 (s, 1H), 7.49 (s, 1H), 7.20 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.03 – 6.88 (m, 4H), 6.85 (d, J = 7.2 Hz, 1H), 6.74 (s, 1H), 4.48 (s, 1H), 3.79 (d, J = 11.4 Hz, 2H), 3.26 (t, J = 11.7 Hz, 2H), 3.04 (dd, J = 13.7, 7.7 Hz, 1H), 2.84 (t, J = 10.8 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 2.01 (dd, J = 9.4, 5.6 Hz, 1H), 1.64 (t, J = 12.0 Hz, 2H), 1.28 – 1.15 (m, 2H).
112 -B	LC-MS= [M +1] ⁺ =454.2, 1H NMR (400 MHz, DMSO) δ 11.73 (s, 1H), 9.69 (s, 1H), 7.49 (s, 1H), 7.19 (s, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.04 – 6.88 (m, 4H), 6.85 (d, J = 7.3 Hz, 1H), 6.74 (s, 1H), 4.48 (s, 1H), 3.84 – 3.71 (m, 2H), 3.26 (t, J = 11.7 Hz, 2H), 3.04 (dd, J = 13.7, 7.6 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 2.08 – 1.94 (m, 1H), 1.64 (t, J = 11.6 Hz, 2H), 1.31 – 1.15 (m, 2H).
113	[M-C2HF3O2+1] ⁺ =408.2, 1H NMR (400 MHz, DMSO) δ 14.38 (s, 2H), 9.95 (s, 1H), 9.09 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (dt, J = 14.0, 7.8 Hz, 2H), 7.15 (t, J = 8.9 Hz, 1H), 7.04 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 5.79 (s, 1H), 3.81 (dd, J = 11.2, 2.6 Hz, 2H), 3.28 (t, J = 10.9 Hz, 2H), 2.25 – 2.10 (m, 5H), 1.96 (ddd, J = 11.2, 7.3, 3.8 Hz, 1H), 1.55 (d, J = 11.3 Hz, 2H), 1.21 (qd, J = 12.3, 4.3 Hz, 2H).
114	[M-C2HF3O2+1] ⁺ =360.2, 1H NMR (400 MHz, DMSO) δ 14.49 (s, 2H), 9.70 (s, 1H), 9.07 (s, 1H), 7.51 – 7.40 (m, 2H), 7.33 – 7.23 (m, 2H), 7.17 – 7.06 (m, 2H), 6.97 (s, 1H), 6.69 (d, J = 7.4 Hz, 1H), 5.87 (s, 1H), 4.24 (s, 2H), 3.28 (s, 2H), 2.83 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.78 (s, 2H), 1.73 – 1.55 (m, 3H), 1.34 (d, J = 10.5 Hz, 1H).
115	[M-C2HF3O2+1] ⁺ =372.1, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.77 (s, 1H), 9.07 (s, 1H), 7.41 – 7.26 (m, 2H), 7.22 – 7.10 (m, 2H), 7.00 (d, J = 16.8 Hz, 2H), 6.91 (d, J = 7.7 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.82 (s, 1H), 5.21 (d, J = 53.4 Hz, 1H), 4.51 (s, 2H), 2.97 (s, 3H), 2.15 (s, 3H).
116	[M+1] ⁺ =414.1, 1H NMR (400 MHz, DMSO) δ 7.63 (s, 1H), 7.29-7.21 (m, 2H), 7.12 (s, 1H), 7.04-6.95 (m, 3H), 6.68 (d, J = 7.6 Hz, 1H), 6.32 (s, 1H), 5.68 (s, 1H), 4.49 (s, 2H), 3.53 (t, J = 5.2 Hz, 2H), 3.23 (t, J = 5.6 Hz, 2H), 2.85 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H).
117	[M-C2HF3O2+1] ⁺ =452.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.97 (s, 1H), 9.07 (d, J = 1.0 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.97 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.15 (dd, J = 18.4, 7.9 Hz, 2H), 3.00 (d, J = 12.5 Hz, 2H), 2.28 (d, J = 8.9 Hz, 5H), 2.21 – 2.07 (m, 4H), 2.00 (d, J = 12.6 Hz, 2H), 1.66 (q, J = 11.6 Hz, 2H).
118	[M-C2HF3O2+1] ⁺ =374.1, 1H NMR (400 MHz, DMSO) δ 14.38 (s, 2H), 9.79 (s, 1H), 9.09 (d, J = 1.1 Hz, 1H), 7.35 (dd, J = 16.1, 8.0 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 7.14 (dt, J = 13.8, 6.9 Hz, 1H), 7.02 (d, J = 6.2 Hz, 2H), 6.91 (t, J = 7.6 Hz, 2H), 5.87 (s, 1H), 5.57 (q, J = 11.0 Hz, 1H), 5.45 (q, J = 11.1 Hz, 1H), 2.97 (s, 3H), 2.25 (d, J = 11.4 Hz, 3H).
119	[M-C2HF3O2+1] ⁺ =440.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.86 (s, 1H), 9.08 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.20 – 7.04 (m, 3H), 6.94 (dd, J = 19.3, 6.6 Hz, 3H), 6.64 (d, J = 7.5 Hz, 1H), 5.82 (s, 1H), 3.79 – 3.75 (m, 2H), 3.23 (t, J = 11.7 Hz, 2H), 2.97 (d, J = 6.3 Hz, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 2.06 – 1.94 (m, 1H), 1.63 (t, J = 11.1 Hz, 2H), 1.29 – 1.15 (m, 2H).
120	[M-C2HF3O2+1] ⁺ =402.2, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 10.00 (s, 1H), 9.07 (d, J = 0.9 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.18 – 7.05 (m, 2H), 6.98 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 5.59 (s, 1H), 4.02 (s, 2H), 3.66 (t, J = 5.5 Hz, 2H), 2.99 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 2.05 (s, 2H).
121	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO+D2O) δ 9.02 (d, J = 1.1 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.16 – 7.06 (m, 2H), 6.93 (s, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.89 (s, 1H), 3.92 (ddd, J = 29.2, 18.1, 8.0 Hz, 3H), 3.36 (t, J = 11.1 Hz, 2H), 2.24 (s, 3H), 2.11 (s, 3H), 1.75 – 1.68 (m, 2H), 1.56 (qd, J = 11.9, 4.2 Hz, 2H).
121 -A	LC-MS: [M +1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 8.73 (s, 1H), 8.31 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.69 (s, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.17 (s, 1H), 7.13 – 7.02 (m, 3H), 6.82 (s, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.85 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, J = 9.0 Hz, 2H), 3.37 (s, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 1.73 (d, J = 10.1 Hz, 2H), 1.57 (qd, J = 12.0, 4.4 Hz, 2H).
121 -B	LC-MS: [M +1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 8.26 (d, J = 7.7 Hz, 1H), 7.68 (dd, J = 13.3, 8.6 Hz, 3H), 7.36 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.78 (d, J = 7.1 Hz, 1H), 6.43 (s, 1H), 5.66 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, J = 9.6 Hz, 2H), 3.37 (s, 2H), 2.24 (s, 3H), 2.12 (s, 3H), 1.73 (d, J = 10.4 Hz, 2H), 1.63 – 1.53 (m, 2H).
122 -A	[M-C2HF3O2+1] ⁺ =417.3, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.97 (d, J = 19.3 Hz, 1H), 9.08 (d, J = 0.9 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 20.3 Hz, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.18 – 7.04 (m, 2H), 6.97 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.19 (d, J = 11.8 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.30 (dd, J = 17.6, 10.6 Hz, 5H), 2.22 – 2.04 (m, 6H), 1.84 – 1.73 (m, 1H), 1.45 (dq, J = 13.0, 8.4 Hz, 1H).
122 -B	[M-C2HF3O2+1] ⁺ =417.3, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.97 (d, J = 19.3 Hz, 1H), 9.08 (d, J = 0.9 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 20.3 Hz, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.18 – 7.04 (m, 2H), 6.97 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.79 (s, 1H), 3.19 (d, J = 11.8 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.30 (dd, J = 17.6, 10.6 Hz, 5H), 2.22 – 2.04 (m, 6H), 1.84 – 1.73 (m, 1H), 1.45 (dq, J = 13.0, 8.4 Hz, 1H).

123	[M-C2HF3O2+1] ⁺ =419.2, 1H NMR (400 MHz, DMSO) δ 14.49 (s, 2H), 10.63 (s, 1H), 9.73 (s, 1H), 9.08 (s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.37 (dd, J = 9.4, 6.3 Hz, 2H), 7.17 – 7.06 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.94 (s, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.84 (s, 1H), 5.06 (s, 1H), 4.08 (s, 2H), 3.92 (s, 1H), 3.45 (s, 1H), 3.29 (s, 2H), 3.09 (s, 1H), 2.26 (s, 3H), 2.13 (s, 3H), 1.93 (d, J = 6.0 Hz, 2H), 1.71 (s, 2H).
124	[M-C2HF3O2+1] ⁺ =422.2, 1H NMR (400 MHz, DMSO) δ 14.38 (s, 2H), 9.07 (s, 1H), 8.43 (t, J = 5.6 Hz, 1H), 7.53 (t, J = 6.4 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.07 (ddd, J = 22.1, 14.3, 7.4 Hz, 3H), 6.71 (d, J = 7.4 Hz, 1H), 6.02 (s, 1H), 3.85 (dd, J = 11.3, 2.6 Hz, 2H), 3.26 (t, J = 11.0 Hz, 2H), 3.19 – 3.07 (m, 2H), 2.28 (s, 3H), 2.12 (s, 3H), 1.75 (ddd, J = 11.1, 7.7, 3.9 Hz, 1H), 1.58 (d, J = 12.6 Hz, 2H), 1.19 (qd, J = 12.2, 4.4 Hz, 2H).
124 -B	LC-MS: [M+1] ⁺ =422.2, 1H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.42 (t, J = 6.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.11 – 6.98 (m, 3H), 6.76 (d, J = 7.4 Hz, 1H), 6.56 (s, 1H), 5.85 (s, 1H), 3.88 – 3.77 (m, 2H), 3.23 (d, J = 11.2 Hz, 2H), 3.11 (t, J = 6.3 Hz, 2H), 2.24 (s, 3H), 2.11 (s, 3H), 1.82 – 1.69 (m, 1H), 1.57 (d, J = 12.4 Hz, 2H), 1.17 (qd, J = 12.4, 4.5 Hz, 2H).
124 -A	LC-MS: [M+1] ⁺ =422.2, 1H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.45 (t, J = 6.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.14 – 6.99 (m, 3H), 6.79 – 6.66 (m, 2H), 5.89 (s, 1H), 3.90 – 3.77 (m, 2H), 3.24 (d, J = 11.3 Hz, 2H), 3.12 (t, J = 6.3 Hz, 2H), 2.25 (s, 3H), 2.09 (d, J = 16.2 Hz, 3H), 1.75 (dd, J = 9.0, 5.4 Hz, 1H), 1.58 (d, J = 12.6 Hz, 2H), 1.18 (qd, J = 12.2, 4.1 Hz, 2H).
125	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 2H), 9.49 (s, 1H), 9.07 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 6.3 Hz, 1H), 7.13 (d, J = 6.3 Hz, 2H), 7.07 (dd, J = 15.4, 7.7 Hz, 2H), 6.94 (s, 1H), 5.81 (s, 1H), 5.03 (s, 1H), 3.64 (d, J = 10.5 Hz, 1H), 3.51 (d, J = 11.8 Hz, 1H), 3.35 (d, J = 11.6 Hz, 1H), 3.25 (d, J = 8.4 Hz, 2H), 3.16 (d, J = 11.7 Hz, 1H), 3.04 – 2.89 (m, 3H), 2.26 (s, 3H), 2.13 (s, 3H), 1.97 (d, J = 12.4 Hz, 1H), 1.90 – 1.71 (m, 2H), 1.56 (dd, J = 23.4, 10.1 Hz, 1H).
126	[M-C2HF3O2+1] ⁺ =399.2, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.09 (d, J = 1.0 Hz, 1H), 7.74 – 7.59 (m, 1H), 7.59 – 7.46 (m, 2H), 7.46 – 7.35 (m, 1H), 7.13 (dt, J = 15.1, 7.4 Hz, 2H), 6.96 (s, 1H), 6.66 (d, J = 7.4 Hz, 1H), 6.00 (s, 1H), 4.03 – 3.89 (m, 4H), 2.26 (s, 3H), 2.11 (s, 3H), 1.28 – 1.08 (m, 6H).
127	LC-MS: [M-C2HF3O2+1] ⁺ = 371.1, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.67 (s, 1H), 9.07 (d, J = 0.8 Hz, 1H), 7.28 (dt, J = 13.3, 6.3 Hz, 2H), 7.17 – 7.05 (m, 3H), 6.96 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 5.76 (s, 1H), 2.43 (d, J = 4.9 Hz, 3H), 2.26 (s, 3H), 2.13 (s, 3H).
128	[M-C2HF3O2+1] ⁺ =335.2, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 9.06 (d, J = 1.1 Hz, 1H), 8.58 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.20 (dd, J = 13.9, 6.1 Hz, 2H), 7.14 – 7.04 (m, 2H), 6.96 (s, 1H), 6.68 (t, J = 7.6 Hz, 2H), 6.02 (d, J = 4.2 Hz, 1H), 5.73 (s, 1H), 2.59 (d, J = 3.7 Hz, 3H), 2.25 (s, 3H), 2.13 (s, 3H).
129	[M-C2HF3O2+1] ⁺ =332.2, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 10.18 (s, 1H), 9.07 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.47 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.17 – 7.06 (m, 2H), 6.99 (s, 1H), 6.91 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.40 (dd, J = 16.9, 10.1 Hz, 1H), 6.23 (dd, J = 17.0, 1.8 Hz, 1H), 5.81 (s, 1H), 5.74 (dd, J = 10.1, 1.8 Hz, 1H), 2.27 (s, 3H), 2.14 (s, 3H).
130 -A	[M+1] ⁺ =362.2, 1H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 7.53 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 3.91 (d, J = 10.2 Hz, 1H), 3.07 – 2.94 (m, 1H), 2.78 (s, 3H), 2.23 (d, J = 1.7 Hz, 6H), 2.14 (dd, J = 23.6, 12.8 Hz, 1H), 1.88 (d, J = 11.2 Hz, 1H), 1.64 (t, J = 14.8 Hz, 2H), 1.50 (d, J = 12.4 Hz, 1H), 1.27 – 1.16 (m, 1H), 1.13 – 1.00 (m, 1H), 0.88 – 0.68 (m, 2H).
130 -B	[M+1] ⁺ =362.2, 1H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 7.51 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.99 (dd, J = 15.4, 7.7 Hz, 2H), 6.92 (d, J = 7.2 Hz, 1H), 6.86 (s, 1H), 3.91 (d, J = 10.3 Hz, 1H), 3.05 (dd, J = 18.6, 15.0 Hz, 1H), 2.82 (s, 3H), 2.22 (d, J = 5.3 Hz, 6H), 2.18 – 2.10 (m, 1H), 1.84 (dd, J = 27.2, 11.6 Hz, 2H), 1.59 (d, J = 12.7 Hz, 1H), 1.32 (d, J = 12.5 Hz, 1H), 1.10 (dt, J = 22.1, 11.6 Hz, 2H), 0.89 (dd, J = 23.9, 11.9 Hz, 1H), 0.65 (dd, J = 23.1, 11.1 Hz, 1H).
131	[M-C2HF3O2+1] ⁺ =467.1, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.99 (s, 1H), 9.08 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 6.2 Hz, 3H), 7.10 – 7.03 (m, 2H), 6.99 (s, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 5.82 (s, 1H), 3.57 – 3.47 (m, 2H), 3.33 – 3.24 (m, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H).
132	[M-C2HF3O2+1] ⁺ =406.2, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.92 (s, 1H), 9.06 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.30 (ddd, J = 22.5, 12.2, 4.8 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.93 (dt, J = 7.5, 6.8 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 5.81 (s, 1H), 3.81 (dd, J = 11.2, 2.7 Hz, 2H), 3.76 (s, 3H), 3.28 (t, J = 10.9 Hz, 2H), 2.21 (d, J = 7.1 Hz, 2H), 1.96 (ddd, J = 11.1, 7.3, 3.9 Hz, 1H), 1.55 (d, J = 11.5 Hz, 2H), 1.21 (qd, J = 12.1, 4.3 Hz, 2H).
133	[M-C2HF3O2+1] ⁺ =342.1, 1H NMR (400 MHz, DMSO) δ 14.39 (s, 2H), 9.08 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.65 (s, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.47 – 7.33 (m, 3H), 7.23 – 7.07 (m, 2H), 6.96 (s, 1H), 6.70 (d, J = 7.5 Hz, 1H), 5.98 (s, 1H), 2.28 (s, 3H), 2.15 (s, 3H).
134	[M-C2HF3O2+1] ⁺ =440.2, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 9.76 (s, 1H), 8.98 (s, 1H), 7.60 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.13 – 7.03 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 4.68 (t, J = 7.8 Hz, 1H), 3.89 (dd, J = 11.4, 3.0 Hz, 2H), 3.37 (dd, J = 13.7, 8.3 Hz, 1H), 3.23 (t, J = 11.6 Hz, 2H), 3.12 (dd, J = 14.0, 7.2 Hz, 2H), 2.22 (s, 3H), 2.14 (s, 3H), 1.77 (d, J = 12.2 Hz, 2H), 1.60 (dt, J = 11.9, 8.2 Hz, 2H).
135	[M-C2HF3O2+1] ⁺ =358.1, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 9.75 (s, 1H), 9.06 (s, 1H), 7.32 (dd, J = 12.4, 7.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 9.4 Hz, 2H), 7.01 (s, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.93 – 6.86 (m, 2H), 5.82 (s, 1H), 3.76 (s, 3H), 2.97 (s, 3H).
136	[M-C2HF3O2+1] ⁺ =370.1, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 9.61 (s, 1H), 8.97 (s, 1H), 7.62 (s, 1H), 7.07 (dt, J = 12.6, 8.6 Hz, 7H), 4.67 (t, J = 7.8 Hz, 1H), 3.33 (dd, J = 13.7, 8.3 Hz, 1H), 3.09 (dd, J = 13.7, 7.4 Hz, 1H), 2.92 (s, 3H), 2.21 (s, 3H), 2.09 (s, 3H).

136 -A	LC-MS: [M+1] ⁺ =370.2, 1H NMR (400 MHz, DMSO) δ 11.78 (s, 1H), 9.51 (s, 1H), 7.50 (s, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.10 – 6.89 (m, 6H), 6.76 (s, 1H), 4.48 (t, J = 7.6 Hz, 1H), 3.35 (s, 1H), 3.30 (s, 1H), 3.01 (dd, J = 13.7, 7.4 Hz, 3H), 2.19 (s, 3H), 2.12 (s, 3H).
136 -B	LC-MS: [M+1] ⁺ =370.2, 1H NMR (400 MHz, DMSO) δ 11.72 (s, 1H), 9.52 (s, 1H), 7.50 (s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.10 – 6.91 (m, 6H), 6.76 (s, 1H), 4.48 (t, J = 7.6 Hz, 1H), 3.31 (s, 1H), 3.01 (dd, J = 13.7, 7.4 Hz, 1H), 2.90 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H).
137 -A	[M-C2HF3O2+1] ⁺ =396.2, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 9.31 (s, 1H), 9.01 (s, 1H), 7.74 (s, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 17.1, 8.0 Hz, 2H), 7.06 (d, J = 7.2 Hz, 1H), 6.92 (dd, J = 8.0, 1.6 Hz, 1H), 6.07 (s, 1H), 4.48 (d, J = 10.8 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.80 – 2.70 (m, 1H), 2.61 (s, 3H), 2.17 (s, 4H), 1.82 (s, 4H).
137 -B	[M-C2HF3O2+1] ⁺ =396.2, 1H NMR (400 MHz, DMSO) δ 14.32 (d, J = 34.6 Hz, 2H), 9.48 (s, 1H), 9.04 (s, 1H), 7.68 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.08 (d, J = 7.4 Hz, 1H), 6.99 (dd, J = 8.0, 1.4 Hz, 1H), 6.32 (s, 1H), 4.30 (d, J = 11.3 Hz, 1H), 4.04 (dd, J = 12.9, 5.6 Hz, 1H), 2.90 – 2.77 (m, 4H), 2.75 – 2.66 (m, 1H), 2.23 (d, J = 16.0 Hz, 6H), 2.02 (dd, J = 13.0, 8.1 Hz, 1H), 1.61 – 1.48 (m, 1H).
138	[M-C2HF3O2+1] ⁺ =420.2, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 13.74 (d, J = 23.1 Hz, 1H), 9.15 – 8.89 (m, 2H), 7.87 (d, J = 6.9 Hz, 1H), 7.22 – 6.99 (m, 2H), 6.99 – 6.80 (m, 3H), 6.68 (d, J = 7.4 Hz, 1H), 6.01 (s, 1H), 3.92 – 3.74 (m, 2H), 3.23 (dt, J = 12.4, 8.7 Hz, 4H), 2.26 (s, 3H), 2.07 (s, 3H), 1.93 – 1.73 (m, 1H), 1.59 (d, J = 12.3 Hz, 2H), 1.20 (qt, J = 35.5, 17.7 Hz, 2H).
139	[M-C2HF3O2+1] ⁺ =422.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 9.00 (s, 1H), 7.58 (s, 1H), 7.21 – 6.95 (m, 3H), 6.86 (d, J = 7.5 Hz, 1H), 4.65 (dd, J = 8.2, 5.3 Hz, 1H), 3.90 (t, J = 9.3 Hz, 1H), 3.78 (dd, J = 16.0, 8.9 Hz, 3H), 3.50 (d, J = 5.1 Hz, 2H), 3.28 (t, J = 11.2 Hz, 2H), 3.09 (dd, J = 11.1, 5.4 Hz, 2H), 2.92 (d, J = 6.3 Hz, 2H), 2.28 (s, 6H), 2.00 (d, J = 4.4 Hz, 1H), 1.72 (d, J = 12.9 Hz, 2H), 1.28 (qd, J = 12.2, 4.1 Hz, 2H).
140	[M-C2HF3O2+1] ⁺ =356.2, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.77 (s, 1H), 9.09 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 4.5 Hz, 2H), 7.24 – 7.17 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.01 (s, 2H), 6.89 (t, J = 7.4 Hz, 2H), 5.82 (s, 1H), 2.96 (s, 3H), 2.71 – 2.55 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H).
141	[M-C2HF3O2] ⁺ =391.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 10.20 (s, 1H), 8.92 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.32 (t, J = 7.7 Hz, 2H), 7.10 (dt, J = 15.0, 7.5 Hz, 2H), 6.97 – 6.79 (m, 2H), 6.68 (d, J = 7.3 Hz, 1H), 5.78 (s, 1H), 3.61 (t, J = 7.6 Hz, 2H), 3.07 (s, 9H), 2.85 (t, J = 7.4 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H).
142	[M-C2HF3O2+1] ⁺ =454.2, 1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 7.61 – 7.49 (m, 3H), 7.47 – 7.35 (m, 2H), 7.07 (dt, J = 14.6, 7.7 Hz, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.78 (d, J = 8.4 Hz, 2H), 3.48 (dd, J = 13.9, 7.2 Hz, 1H), 3.22 (dt, J = 23.8, 10.1 Hz, 3H), 2.43 (d, J = 6.5 Hz, 2H), 2.17 (s, 3H), 2.04 (s, 3H), 1.49 (t, J = 14.8 Hz, 3H), 1.11 – 0.95 (m, 2H).
143	[M-C2HF3O2] ⁺ =411.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 10.14 (s, 1H), 9.16 – 8.98 (m, 3H), 8.60 (t, J = 7.8 Hz, 1H), 8.15 (t, J = 6.9 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 17.6, 9.7 Hz, 2H), 7.17 – 7.03 (m, 2H), 6.97 – 6.83 (m, 2H), 6.63 (t, J = 12.2 Hz, 1H), 5.78 (s, 1H), 4.87 (t, J = 6.2 Hz, 2H), 3.12 (t, J = 6.3 Hz, 2H), 2.26 (s, 3H), 2.14 – 2.08 (m, 3H).
144	[M-C2F3O2] ⁺ =391.2, 1H NMR (400 MHz, DMSO) δ 14.43 (s, 2H), 9.08 (s, 1H), 8.87 (t, J = 5.4 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.19 – 7.06 (m, 2H), 6.94 (s, 1H), 6.69 (d, J = 7.5 Hz, 1H), 5.93 (s, 1H), 3.66 (d, J = 5.8 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 3.13 (s, 9H), 2.27 (s, 3H), 2.10 (d, J = 18.2 Hz, 3H).
145	[M-C2F3O2+1] ⁺ =406.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 11.58 (s, 1H), 9.07 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.12 (dt, J = 15.1, 7.4 Hz, 2H), 6.97 (s, 1H), 6.70 (d, J = 7.4 Hz, 1H), 5.91 (s, 1H), 4.06 (s, 1H), 3.88 – 3.82 (m, 2H), 3.37 (t, J = 9.2 Hz, 2H), 2.27 (s, 3H), 2.13 (s, 3H), 1.89 (d, J = 10.6 Hz, 2H), 1.55 (d, J = 8.9 Hz, 2H).
146	[M+1] ⁺ =336.1, 1H NMR (400 MHz, DMSO) δ 14.42 (s, 1H), 9.36 (s, 1H), 9.09 (d, J = 0.8 Hz, 1H), 7.96 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.16 – 7.06 (m, 4H), 6.88 (d, J = 7.2 Hz, 1H), 6.74 (d, J = 6.8 Hz, 1H), 5.90 (s, 1H), 2.53 (d, J = 4.4 Hz, 3H), 2.26 (s, 3H), 2.16 (s, 3H).
147	[M+1] ⁺ =363.80, 1H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 7.55 – 7.43 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.16–7.08 (m, 2H), 6.96 – 6.82 (m, 2H), 6.68 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.59 (t, J = 6.0 Hz, 2H), 3.22 (s, 3H), 2.53 – 2.49 (m, 2H), 2.26 (s, 3H), 2.14 (s, 3H).
148	[M+1] ⁺ =377.80, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 9.92 (s, 1H), 9.06 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.14–7.06 (m, 2H), 6.96 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.2 Hz, 1H), 5.77 (s, 1H), 3.32 (t, J = 6.4 Hz, 2H), 3.21 (s, 3H), 2.34 – 2.29 (m, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.80 – 1.72 (m, 2H).
149	[M+1] ⁺ =390.1, 1H NMR (400 MHz, MeOD) δ 7.62 (s, 1H), 7.52 – 7.50 (m, 1H), 7.24 – 7.20 (m, 2H), 7.03 – 7.01 (m, 1H), 6.98 – 6.95 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.70 – 6.68 (m, 1H), 6.35 (s, 1H), 5.65 (s, 1H), 3.99 – 3.95 (m, 2H), 3.47 – 3.41 (m, 2H), 2.61 – 2.53 (m, 1H), 2.27 (s, 3H), 2.15 (s, 3H), 1.85 – 1.78 (m, 2H), 1.75 – 1.69 (m, 2H).
150	[M-C2HF3O2+1] ⁺ =358.1, 1H NMR (400 MHz, DMSO) δ 14.35 (s, 2H), 9.49 (d, J = 124.3 Hz, 1H), 9.06 (s, 1H), 7.82 – 7.45 (m, 3H), 7.15 (d, J = 7.4 Hz, 1H), 7.08 (dd, J = 15.2, 7.7 Hz, 1H), 7.05 – 6.91 (m, 3H), 6.67 (d, J = 7.6 Hz, 1H), 6.06 (s, 1H), 2.27 (s, 3H), 2.11 (d, J = 10.4 Hz, 3H).
151 -A	[M-C2HF3O2+1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 10.05 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.1, 7.4 Hz, 2H), 6.97 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.90 (t, J = 8.2 Hz, 1H), 3.78 – 3.66 (m, 3H), 3.11 (p, J = 7.6 Hz, 1H), 2.27 (s, 3H), 2.14 (s, 3H), 2.04 (dd, J = 14.3, 7.1 Hz, 2H).

151 -B	[M-C2HF3O2+1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 10.05 (s, 1H), 9.06 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.97 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.4 Hz, 1H), 5.79 (s, 1H), 3.90 (t, J = 8.2 Hz, 1H), 3.77 – 3.67 (m, 3H), 3.16 – 3.05 (m, 1H), 2.27 (s, 3H), 2.14 (s, 3H), 2.04 (dd, J = 14.4, 7.2 Hz, 2H).
152	[M-C2HF3O2+1] ⁺ =407.2, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 11.55 (s, 1H), 9.08 (s, 1H), 8.06 – 7.86 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.38 (s, 1H), 7.18 – 7.05 (m, 2H), 6.96 (d, J = 7.3 Hz, 1H), 6.07 (s, 1H), 4.12 (dd, J = 8.5, 4.3 Hz, 1H), 3.91 – 3.86 (m, 2H), 3.38 (t, J = 9.4 Hz, 2H), 2.25 (d, J = 7.5 Hz, 6H), 1.89 (d, J = 12.3 Hz, 2H), 1.58 (d, J = 9.1 Hz, 2H).
153	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 8.97 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.09 (dt, J = 15.1, 7.4 Hz, 2H), 6.92 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 5.76 (s, 1H), 4.21 – 3.99 (m, 1H), 3.76 – 3.72 (m, 1H), 3.57 (dd, J = 14.6, 7.5 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.24 (s, 3H), 2.11 (s, 3H), 1.96 (td, J = 12.4, 6.6 Hz, 1H), 1.88 – 1.71 (m, 2H), 1.48 (td, J = 15.5, 7.6 Hz, 1H).
154 -A	[M-C2HF3O2+1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 11.34 (s, 1H), 9.01 (s, 1H), 7.74 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 6.3 Hz, 2H), 7.10 – 7.05 (m, 1H), 6.39 (s, 1H), 4.50 (d, J = 10.3 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.61 (s, 3H), 3.05 (dt, J = 16.3, 8.1 Hz, 1H), 2.90 – 2.76 (m, 1H), 2.27 – 2.17 (m, 1H), 2.13 (s, 3H), 1.98 – 1.87 (m, 1H), 1.65 (s, 3H).
154 -B	[M-C2HF3O2+1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 11.57 (s, 1H), 9.05 (s, 1H), 7.71 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 6.86 (s, 1H), 4.36 (d, J = 10.9 Hz, 1H), 4.09 (t, J = 11.3 Hz, 1H), 3.66 (s, 3H), 2.95 – 2.84 (m, 1H), 2.82 – 2.75 (m, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 2.03 (td, J = 15.9, 8.1 Hz, 1H), 1.64 – 1.52 (m, 1H).
155 -A	[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 14.31 (s, 2H), 9.96 (s, 1H), 9.07 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.3 Hz, 2H), 6.96 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.78 (s, 1H), 3.92 (d, J = 11.3 Hz, 1H), 3.80 (d, J = 10.6 Hz, 1H), 3.41 – 3.24 (m, 2H), 2.58 (t, J = 10.8 Hz, 1H), 2.27 (s, 3H), 2.13 (s, 3H), 1.90 (d, J = 11.8 Hz, 1H), 1.61 (ddd, J = 40.6, 24.3, 12.0 Hz, 3H).
155 -B	LCMS=[M-C2HF3O2+1] ⁺ =390.2, 1H NMR (400 MHz, DMSO) δ 14.32 (s, 2H), 9.96 (s, 1H), 9.07 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.16 – 7.03 (m, 2H), 6.96 (s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.78 (s, 1H), 3.91 (d, J = 12.4 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.31 (ddd, J = 16.4, 13.4, 6.4 Hz, 2H), 2.63 – 2.54 (m, 1H), 2.27 (s, 3H), 2.13 (s, 3H), 1.90 (d, J = 12.1 Hz, 1H), 1.73 – 1.43 (m, 3H).
156	LC-MS=[M-C2HF3O2+1] ⁺ =338.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.97 (s, 1H), 7.65 – 7.48 (m, 4H), 7.09 (dt, J = 14.4, 7.2 Hz, 5H), 4.78 (t, J = 7.9 Hz, 1H), 3.42 (dd, J = 13.9, 8.5 Hz, 1H), 3.22 (dd, J = 13.9, 7.3 Hz, 1H), 2.23 (s, 3H), 2.16 (s, 3H).
156 -A	LC-MS: [M+1] ⁺ =338.2, 1H NMR (400 MHz, MeOD) δ 7.62 (t, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.08 – 6.95 (m, 3H), 6.90 (d, J = 12.5 Hz, 1H), 6.73 (s, 1H), 4.63 (t, J = 7.8 Hz, 1H), 3.49 (dd, J = 13.4, 7.0 Hz, 1H), 3.21 (dd, J = 13.7, 8.6 Hz, 1H), 2.22 (s, 3H), 2.10 (s, 3H).
156 -B	LC-MS: [M+1] ⁺ =338.2, 1H NMR (400 MHz, CDCl ₃) δ 7.91 (t, J = 8.2 Hz, 1H), 7.53 (d, J = 11.1 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (ddd, J = 21.4, 15.4, 7.7 Hz, 3H), 6.81 (d, J = 13.1 Hz, 1H), 6.68 – 6.52 (m, 2H), 5.72 (s, 1H), 4.56 (t, J = 7.6 Hz, 1H), 3.57 (dd, J = 13.7, 7.7 Hz, 1H), 3.20 (dd, J = 13.7, 7.6 Hz, 1H), 2.24 (s, 3H), 2.10 (s, 3H).
157	[M-C2HF3O2+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 9.79 (s, 1H), 8.95 (s, 1H), 7.58 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.14 – 7.01 (m, 5H), 4.68 (t, J = 7.8 Hz, 1H), 3.90 (d, J = 11.0 Hz, 2H), 3.42 – 3.24 (m, 3H), 3.09 (dd, J = 13.8, 7.2 Hz, 1H), 2.56 (dd, J = 13.1, 7.8 Hz, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 1.63 (ddd, J = 17.5, 10.7, 3.6 Hz, 4H).
157 -A	LC-MS: [M-HCl+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 8.87 (s, 1H), 7.53 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.13 – 7.01 (m, 5H), 4.69 (t, J = 7.8 Hz, 1H), 3.89 (d, J = 11.2 Hz, 2H), 3.33 (ddd, J = 22.1, 12.6, 6.2 Hz, 3H), 3.10 (dd, J = 13.7, 7.5 Hz, 1H), 2.57 (d, J = 20.7 Hz, 1H), 2.18 (d, J = 30.3 Hz, 6H), 1.72 – 1.55 (m, 4H).
157 -B	LC-MS: [M-HCl+1] ⁺ =404.3, 1H NMR (400 MHz, DMSO) δ 14.45 (s, 2H), 9.89 (s, 1H), 8.97 (s, 1H), 7.59 – 7.38 (m, 3H), 7.18 – 7.00 (m, 5H), 4.69 (t, J = 7.7 Hz, 1H), 3.89 (d, J = 11.0 Hz, 2H), 3.33 (dd, J = 13.5, 7.0 Hz, 3H), 3.08 (dd, J = 13.7, 7.0 Hz, 1H), 2.65 – 2.55 (m, 1H), 2.19 (d, J = 22.6 Hz, 6H), 1.71 – 1.55 (m, 4H).
158	[M-C2HF3O2+1] ⁺ =440.2, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 9.75 (s, 1H), 8.97 (s, 1H), 7.62 (s, 1H), 7.17 – 6.92 (m, 7H), 4.66 (t, J = 7.8 Hz, 1H), 3.89 (dd, J = 11.1, 3.3 Hz, 2H), 3.38 – 3.16 (m, 4H), 3.07 (dd, J = 13.6, 7.6 Hz, 1H), 2.21 (s, 3H), 2.07 (s, 3H), 1.81 (d, J = 12.2 Hz, 2H), 1.62 (qd, J = 12.4, 4.5 Hz, 2H).
159	[M+1] ⁺ =370.1, 1H NMR (400 MHz, DMSO) δ 14.44 (s, 2H), 9.07 (d, J = 1.2 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.13-7.05 (m, 2H), 6.98 (d, J = 10.4 Hz, 2H), 6.80 (s, 1H), 6.67 (d, J = 7.2 Hz, 2H), 5.75 (s, 1H), 3.49 (dd, J = 11.2, 6.4 Hz, 3H), 2.26 (s, 3H), 2.13 (s, 3H), 1.44 (dd, J = 16.8, 8.0 Hz, 3H).
160	[M+1] ⁺ =344.43, 1H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 8.46 (s, 1H), 7.70 – 7.61 (m, 2H), 7.60 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.86 (s, 1H), 6.51 (s, 1H), 5.72 (s, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.15 (s, 3H).
161	[M+1] ⁺ =419.90, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 2H), 11.54 (s, 1H), 9.07 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.16 – 7.06 (m, 3H), 7.00 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 5.85 (s, 1H), 3.86 – 3.78 (m, 2H), 3.27 (t, J = 11.2 Hz, 2H), 2.65 (d, J = 7.2 Hz, 2H), 2.26 (s, 3H), 2.15 (s, 3H), 1.58 (d, J = 12.8 Hz, 2H), 1.24 (m, 2H).
162	[M+1] ⁺ =426.9, 1H NMR (400 MHz, MeOD) δ 8.91 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.18 – 7.16 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.00 (s, 1H), 3.77 – 3.74 (m, 2H), 3.25 – 3.19 (m, 2H), 3.17 – 3.11 (m, 1H), 2.31 (s, 3H), 2.18 (s, 3H), 1.49 – 1.46 (m, 2H), 1.43 – 1.27 (m, 2H).

163	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =320.2, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 8.96 (s, 1H), 7.87 (s, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.61 (s, 1H), 7.25 (t, J = 13.1 Hz, 3H), 7.15 – 7.02 (m, 3H), 4.75 (t, J = 7.8 Hz, 1H), 3.42 (dd, J = 13.7, 8.4 Hz, 1H), 3.20 (dd, J = 13.7, 7.4 Hz, 1H), 2.22 (s, 3H), 2.13 (s, 3H).
164	[M+1] ⁺ =344.43, 1H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.64 (s, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 7.2 Hz, 1H), 6.42 (s, 1H), 5.80 (s, 1H), 3.97 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H).
165	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =418.3, 1H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 9.81 (s, 1H), 8.95 (s, 1H), 7.59 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.16 – 6.97 (m, 5H), 4.67 (t, J = 7.7 Hz, 1H), 3.82 (dd, J = 11.2, 2.4 Hz, 2H), 3.29 (t, J = 10.9 Hz, 3H), 3.09 (dd, J = 13.8, 7.1 Hz, 1H), 2.21 (d, J = 9.2 Hz, 5H), 2.15 (s, 3H), 1.96 (ddd, J = 11.2, 7.3, 3.9 Hz, 1H), 1.56 (d, J = 12.2 Hz, 2H), 1.22 (qd, J = 12.3, 4.2 Hz, 2H).
166	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =426.2, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 9.76 (d, J = 7.4 Hz, 1H), 9.00 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.91 (d, J = 11.9 Hz, 2H), 6.66 (d, J = 7.7 Hz, 1H), 5.79 (s, 1H), 4.17 – 4.08 (m, 1H), 3.57 (ddd, J = 22.3, 15.0, 7.7 Hz, 2H), 3.21 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.98 (s, 1H), 1.82 – 1.71 (m, 2H), 1.55 (dd, J = 16.7, 10.1 Hz, 1H).
167	[M+1] ⁺ =454.2, 1H NMR (400 MHz, DMSO) δ 14.33 (s, 1H), 9.05 (s, 1H), 7.70 (dd, J = 8.0, 4.4 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.00 – 6.92 (m, 2H), 6.81 – 6.75 (m, 1H), 6.72 – 6.63 (m, 2H), 5.74 (s, 1H), 3.74 (dd, J = 13.6, 8.4 Hz, 2H), 3.50 (dd, J = 11.2, 6.4 Hz, 3H), 3.21 (m, 2H), 2.26 (s, 3H), 2.12 (d, J = 2.8 Hz, 3H), 1.86 – 1.57 (m, 5H), 1.17 (m, 2H).
168	[M+1] ⁺ =377.20, 1H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 7.49 (s, 1H), 6.98 (m, 4H), 6.73 (s, 1H), 4.41 (t, J = 6.8 Hz, 1H), 3.05 (s, 1H), 2.98 – 2.89 (m, 2H), 2.88 (s, 3H), 2.82 (d, J = 11.6 Hz, 1H), 2.67 – 2.62 (m, 1H), 2.23 (s, 6H), 2.07 – 1.99 (m, 2H), 1.74 (d, J = 11.2 Hz, 2H), 1.40 – 1.23 (m, 3H).
169	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =418.3, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 9.81 (s, 1H), 8.94 (s, 1H), 7.59 (s, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.07 (t, J = 7.6 Hz, 5H), 4.67 (t, J = 7.7 Hz, 1H), 3.82 (d, J = 11.1 Hz, 1H), 3.68 (s, 1H), 3.35 – 3.26 (m, 2H), 3.08 (dd, J = 13.8, 7.1 Hz, 1H), 2.43 (dd, J = 14.1, 8.1 Hz, 1H), 2.32 (dd, J = 14.1, 4.8 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.77 (d, J = 10.1 Hz, 1H), 1.61 (d, J = 12.6 Hz, 1H), 1.50 – 1.38 (m, 3H), 1.23 (t, J = 11.7 Hz, 1H).
170	LCMS=[M-C ₂ HF ₃ O ₂ +1] ⁺ =440.3, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 9.63 (s, 1H), 9.07 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.45 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.3 Hz, 2H), 6.98 (s, 1H), 6.81 (d, J = 7.7 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 5.77 (s, 1H), 2.62 (s, 1H), 2.27 (s, 3H), 2.19 (s, 2H), 2.15 (s, 3H), 2.08 (s, 2H), 1.89 (s, 1H), 1.79 (q, J = 12.6 Hz, 5H), 1.70 (s, 2H), 1.53 (d, J = 12.0 Hz, 2H).
171	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 9.84 (s, 1H), 8.95 (s, 1H), 7.59 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 6.9 Hz, 5H), 4.67 (t, J = 7.8 Hz, 1H), 3.79 (t, J = 7.6 Hz, 1H), 3.72 (dd, J = 7.9, 5.5 Hz, 1H), 3.66 – 3.61 (m, 1H), 3.30 (dd, J = 15.6, 8.8 Hz, 2H), 3.09 (dd, J = 13.8, 7.2 Hz, 1H), 2.55 (dd, J = 13.6, 6.3 Hz, 1H), 2.39 – 2.33 (m, 2H), 2.22 (s, 3H), 2.14 (s, 3H), 2.00 (td, J = 12.8, 7.6 Hz, 1H), 1.52 (dq, J = 14.4, 7.3 Hz, 1H).
172	[M-C ₂ HF ₃ O ₂ +1] ⁺ =426.2, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 9.76 (d, J = 7.6 Hz, 1H), 9.02 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.18 – 7.06 (m, 3H), 7.00 (s, 1H), 6.97 – 6.86 (m, 2H), 6.66 (d, J = 7.5 Hz, 1H), 5.80 (s, 1H), 4.12 (p, J = 6.2 Hz, 1H), 3.63 – 3.54 (m, 2H), 3.21 (d, J = 4.9 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.99 (dd, J = 11.8, 6.2 Hz, 1H), 1.76 (dd, J = 13.9, 7.1 Hz, 2H), 1.62 – 1.47 (m, 1H).
173	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =440.2, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.69 (s, 1H), 9.08 (s, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.4 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.94 (dd, J = 18.0, 11.3 Hz, 3H), 6.66 (d, J = 7.5 Hz, 1H), 5.80 (s, 1H), 3.77 – 3.58 (m, 2H), 3.31 – 3.06 (m, 3H), 2.26 (s, 3H), 2.13 (s, 3H), 1.71 (s, 1H), 1.58 (d, J = 13.1 Hz, 1H), 1.48 – 1.09 (m, 4H).
174	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 12.17 (s, 1H), 8.96 (s, 1H), 7.64 (s, 1H), 7.17 – 7.01 (m, 7H), 4.69 (t, J = 7.7 Hz, 1H), 3.60 (q, J = 7.0 Hz, 1H), 3.34 (dd, J = 13.9, 8.6 Hz, 1H), 3.10 (dd, J = 13.9, 7.0 Hz, 1H), 2.21 (s, 3H), 2.11 (s, 3H), 1.31 (d, J = 7.1 Hz, 3H).
174 -A	LC-MS: [M+1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 7.50 (s, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.05 (dd, J = 19.6, 8.1 Hz, 4H), 6.98 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 6.8 Hz, 1H), 6.75 (s, 1H), 4.51 (t, J = 7.7 Hz, 1H), 3.44 (q, J = 7.0 Hz, 1H), 3.32 (dd, J = 13.9, 8.4 Hz, 1H), 3.00 (dd, J = 14.0, 6.9 Hz, 1H), 2.17 (d, J = 18.9 Hz, 6H), 1.25 (d, J = 7.1 Hz, 3H).
174 -B	LC-MS: [M+1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 7.50 (s, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.06 (dd, J = 17.5, 8.1 Hz, 4H), 7.00 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 6.75 (s, 1H), 4.52 (t, J = 7.5 Hz, 1H), 3.45 (q, J = 7.2 Hz, 1H), 3.32 (dd, J = 13.6, 8.3 Hz, 1H), 3.01 (dd, J = 14.0, 7.0 Hz, 1H), 2.17 (d, J = 19.2 Hz, 6H), 1.25 (d, J = 7.1 Hz, 3H).
174 -C	LC-MS: [M+1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 7.51 (s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.06 (dd, J = 18.2, 8.0 Hz, 4H), 6.99 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 4.53 (t, J = 7.7 Hz, 1H), 3.44 (dd, J = 14.1, 7.0 Hz, 1H), 3.31 (dd, J = 13.9, 8.0 Hz, 1H), 3.01 (dd, J = 14.0, 7.1 Hz, 1H), 2.17 (d, J = 18.2 Hz, 6H), 1.25 (d, J = 7.1 Hz, 3H).
174 -D	LC-MS: [M+1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 7.50 (s, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.06 (dd, J = 22.6, 8.1 Hz, 4H), 6.99 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 4.52 (t, J = 7.6 Hz, 1H), 3.41 (q, J = 7.1 Hz, 1H), 3.31 (dd, J = 13.8, 8.1 Hz, 1H), 3.01 (dd, J = 13.9, 7.1 Hz, 1H), 2.17 (d, J = 17.8 Hz, 6H), 1.24 (d, J = 7.1 Hz, 3H).
175	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =321.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.96 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.14 – 7.04 (m, 3H), 4.76 (t, J = 7.8 Hz, 1H), 3.45 (dd, J = 13.6, 8.4 Hz, 1H), 3.23 (dd, J = 13.7, 7.4 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).

175 -A	LC-MS: [M+1] ⁺ =321.2, 1H NMR (400 MHz, DMSO) δ 12.42 (s, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.62 (s, 1H), 7.27 – 7.17 (m, 3H), 7.04 – 6.91 (m, 2H), 6.82 (s, 1H), 4.56 (t, J = 7.7 Hz, 1H), 3.44 (dd, J = 13.5, 8.1 Hz, 1H), 3.14 (dd, J = 13.6, 7.3 Hz, 1H), 2.19 (s, 3H), 2.14 (s, 3H).
175 -B	LC-MS: [M+1] ⁺ =321.2, 1H NMR (400 MHz, DMSO) δ 11.95 (s, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.50 (s, 1H), 7.22 (d, J = 8.0 Hz, 3H), 7.03 – 6.89 (m, 2H), 6.75 (s, 1H), 4.54 (t, J = 7.6 Hz, 1H), 3.44 (dd, J = 13.6, 8.2 Hz, 1H), 3.13 (dd, J = 13.7, 7.3 Hz, 1H), 2.19 (s, 3H), 2.14 (s, 3H).
176	LC-MS: [M-C2HF3O2+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 9.82 (s, 1H), 8.95 (s, 1H), 7.59 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.08 (t, J = 7.4 Hz, 5H), 4.67 (t, J = 7.8 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.76 (dd, J = 14.3, 7.3 Hz, 1H), 3.59 (dd, J = 14.6, 7.5 Hz, 1H), 3.30 (dd, J = 13.7, 8.5 Hz, 1H), 3.09 (dd, J = 13.8, 7.2 Hz, 1H), 2.47 (d, J = 7.5 Hz, 1H), 2.40 (dd, J = 14.0, 5.7 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.98 (dt, J = 12.0, 6.5 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.52 (td, J = 15.8, 7.5 Hz, 1H).
177	LC-MS: [M-C2HF3O2+1] ⁺ =404.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.96 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.59 (s, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.09 (dt, J = 10.4, 7.4 Hz, 3H), 4.76 (t, J = 7.8 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.87 (d, J = 10.0 Hz, 2H), 3.40 (dt, J = 22.2, 9.6 Hz, 3H), 3.22 (dd, J = 13.7, 7.6 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 1.72 (d, J = 12.7 Hz, 2H), 1.55 (qd, J = 12.2, 4.2 Hz, 2H).
178	[M-C2HF3O2+1] ⁺ =402.2, 1H NMR (400 MHz, DMSO) δ 14.30 (s, 2H), 9.86 (s, 1H), 9.07 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 15.0, 7.4 Hz, 2H), 6.97 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 5.78 (s, 1H), 2.27 (s, 3H), 2.15 (d, J = 6.1 Hz, 5H), 1.78 – 1.56 (m, 6H), 1.17 (tt, J = 23.8, 12.0 Hz, 3H), 0.94 (q, J = 11.0 Hz, 2H).
179	LC-MS: [M+1] ⁺ =412.2, 1H NMR (400 MHz, DMSO) δ 11.74 (s, 1H), 8.36 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.22 (s, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.74 (s, 1H), 4.53 (t, J = 7.4 Hz, 1H), 4.31 (tt, J = 21.2, 7.1 Hz, 3H), 4.09 (dd, J = 8.3, 3.5 Hz, 2H), 3.45 (dd, J = 13.3, 7.7 Hz, 1H), 3.16 (dd, J = 13.4, 8.1 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H).
180	[M-C2HF3O2+1] ⁺ =389.2, 1H NMR (400 MHz, DMSO) δ 14.28 (s, 2H), 9.06 (s, 1H), 8.44 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.16 – 7.04 (m, 2H), 6.96 (s, 1H), 6.70 (dd, J = 11.2, 7.8 Hz, 2H), 5.73 (s, 1H), 3.41 – 3.33 (m, 4H), 2.27 (s, 3H), 2.15 (s, 3H), 1.56 (d, J = 4.6 Hz, 2H), 1.47 (d, J = 3.8 Hz, 4H).
181	[M-C2HF3O2+1] ⁺ =416.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 9.75 (s, 1H), 8.96 (s, 1H), 7.60 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.8 Hz, 5H), 4.67 (t, J = 7.8 Hz, 1H), 3.29 (dd, J = 13.7, 8.6 Hz, 1H), 3.08 (dd, J = 13.8, 7.1 Hz, 1H), 2.22 (s, 3H), 2.14 (d, J = 5.9 Hz, 5H), 1.77 – 1.59 (m, 6H), 1.19 (dq, J = 23.7, 12.0 Hz, 3H), 1.01 – 0.89 (m, 2H).
182	1H NMR (400 MHz, DMSO) δ 14.36 (s, 2H), 11.75 (s, 1H), 9.06 (s, 1H), 7.46 (s, 2H), 7.12 (p, J = 7.4 Hz, 3H), 6.75 (d, J = 7.3 Hz, 1H), 5.88 (s, 1H), 3.67 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), [M-C2HF3O2+1] ⁺ =342.1
183	[M+1] ⁺ =384.1, 1H NMR (400 MHz, MeOD) δ 8.76 (s, 1H), 7.51 (s, 1H), 7.33 – 7.27 (m, 1H), 7.25 – 7.23 (m, 3H), 7.08 – 7.07 (m, 2H), 7.00 – 6.92 (m, 1H), 4.48 (t, J = 6.8 Hz, 1H), 2.97 (s, 3H), 2.94 – 2.86 (m, 1H), 2.83 – 2.73 (m, 1H), 2.50 – 2.35 (m, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 2.21 – 2.12 (m, 1H).
184	[M+1] ⁺ =322.8, 1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.05 – 7.02 (m, 1H), 7.00 – 6.97 (m, 2H), 6.71 (s, 1H), 4.28 (t, J = 7.8 Hz, 1H), 3.09 – 2.98 (m, 2H), 2.86 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.18 – 2.09 (m, 1H), 1.99 – 1.90 (m, 1H), 1.62 – 1.44 (m, 2H).
185	1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 9.04 (s, 1H), 7.15 – 7.02 (m, 3H), 6.97 (s, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H), 6.24 (d, J = 7.9 Hz, 1H), 6.05 (s, 1H), 5.67 (s, 1H), 4.51 (dd, J = 10.7, 5.8 Hz, 2H), 4.33 (d, J = 5.6 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.45 (s, 3H). LC-MS: [M-C2HF3O2+1] ⁺ =348.2.
186	LC-MS: [M-C2HF3O2+1] ⁺ =405.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.97 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.10 (dt, J = 12.2, 7.1 Hz, 3H), 4.75 (t, J = 7.8 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.85 (d, J = 11.2 Hz, 2H), 3.50 (dd, J = 13.7, 8.0 Hz, 1H), 3.42 – 3.23 (m, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.74 – 1.59 (m, 4H).
187	LC-MS: [M-C2HF3O2+1] ⁺ =422.2, 1H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 8.96 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.17 – 7.02 (m, 5H), 4.78 (t, J = 7.8 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.84 (d, J = 11.2 Hz, 2H), 3.46 – 3.32 (m, 3H), 3.22 (dd, J = 13.9, 7.4 Hz, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 1.73 (d, J = 11.0 Hz, 2H), 1.50 (qd, J = 12.1, 4.3 Hz, 2H).
188	LC-MS: [M-C2HF3O2+1] ⁺ =378.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 8.96 (s, 1H), 7.66 (s, 1H), 7.03 (t, J = 6.2 Hz, 3H), 6.89 (s, 1H), 6.67 (s, 1H), 4.53 (dd, J = 8.5, 3.6 Hz, 1H), 2.27 (d, J = 16.9 Hz, 6H), 2.06 (dd, J = 14.4, 9.0 Hz, 1H), 1.95 (s, 2H), 1.68 – 1.21 (m, 13H).
189	LC-MS: [M-C2HF3O2+1] ⁺ =448.2, 1H NMR (400 MHz, DMSO) δ 14.10 (s, 2H), 9.92 (s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.64 (s, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.18 – 6.98 (m, 4H), 6.90 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 7.1 Hz, 1H), 5.77 (s, 1H), 3.53 – 3.43 (m, 2H), 2.98 (t, J = 7.1 Hz, 2H), 2.23 (s, 3H), 2.10 (s, 3H).
190	LC-MS: [M-C2HF3O2+1] ⁺ =334.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 9.84 (s, 1H), 8.95 (s, 1H), 7.60 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 10.8 Hz, 5H), 4.66 (t, J = 7.8 Hz, 1H), 3.29 (dd, J = 13.7, 8.5 Hz, 1H), 3.07 (dd, J = 13.7, 7.1 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H), 1.99 (s, 3H).
191	[M+1] ⁺ =336.15, 1H NMR (400 MHz, DMSO) δ 12.13 (s, 1H), 8.15 (s, 1H), 7.50 (s, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.90 (t, J = 6.0 Hz, 1H), 6.72 (s, 1H), 4.15 (t, J = 7.6 Hz, 1H), 2.92 – 2.84 (m, 2H), 2.83 (s, 3H), 2.22 (d, J = 4.8 Hz, 6H), 2.05 – 1.95 (m, 1H), 1.85 – 1.70 (m, 1H), 1.50 – 1.39 (m, 2H), 1.29 – 1.15 (m, 2H).
192	LC-MS: [M-C2HF3O2+1] ⁺ =352.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.96 (s, 1H), 8.11 (s, 1H), 7.60 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.16 – 7.02 (m, 5H), 4.77 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.7, 8.5 Hz, 1H), 3.21 (dd, J = 13.8, 7.3 Hz, 1H), 2.74 (d, J = 4.3 Hz, 3H), 2.22 (s, 3H), 2.15 (s, 3H).

193	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =352.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 9.62 (s, 1H), 8.96 (s, 1H), 7.65 (dd, J = 21.2, 12.9 Hz, 2H), 7.06 (dd, J = 12.2, 8.4 Hz, 4H), 6.92 (d, J = 8.2 Hz, 1H), 4.71 (t, J = 7.7 Hz, 1H), 3.33 (dd, J = 13.6, 8.7 Hz, 1H), 3.12 (dd, J = 13.7, 7.2 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H).
194	LC-MS: [M+1] ⁺ =350.2, 1H NMR (400 MHz, DMSO) δ 11.76 (s, 1H), 9.46 (s, 1H), 7.48 (s, 1H), 7.20 (dd, J = 19.1, 7.8 Hz, 3H), 7.06 – 6.89 (m, 4H), 6.73 (s, 1H), 4.46 (t, J = 7.6 Hz, 1H), 3.62 (s, 3H), 3.31 – 3.23 (m, 1H), 2.98 (dd, J = 13.7, 7.4 Hz, 1H), 2.18 (s, 3H), 2.13 (s, 3H).
195	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =364.3, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 9.65 (s, 1H), 8.95 (s, 1H), 7.60 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 6.8 Hz, 5H), 4.67 (t, J = 7.7 Hz, 1H), 3.95 (s, 2H), 3.36 – 3.27 (m, 4H), 3.09 (dd, J = 13.7, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H).
196	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =335.2, 1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 8.94 (s, 1H), 7.59 (s, 1H), 7.13 – 6.99 (m, 3H), 6.67 (dd, J = 7.5, 4.9 Hz, 2H), 6.59 (dd, J = 8.2, 1.6 Hz, 1H), 4.64 (t, J = 7.7 Hz, 1H), 4.16 (s, 4H), 3.22 (dd, J = 13.9, 8.8 Hz, 1H), 3.01 (dd, J = 13.9, 6.8 Hz, 1H), 2.23 (s, 3H), 2.15 (s, 3H).
197	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =339.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 13.14 (s, 1H), 8.96 (d, J = 1.2 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 7.60 (s, 1H), 7.16 – 7.00 (m, 5H), 4.77 (t, J = 7.9 Hz, 1H), 3.44 (dd, J = 13.8, 8.5 Hz, 1H), 3.23 (dd, J = 13.8, 7.4 Hz, 1H), 2.21 (s, 3H), 2.13 (d, J = 8.1 Hz, 3H).
198	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =405.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 8.95 (d, J = 1.0 Hz, 1H), 8.31 (s, 1H), 7.60 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.10 – 6.87 (m, 5H), 6.44 (d, J = 6.8 Hz, 1H), 4.64 (t, J = 7.8 Hz, 1H), 4.15 (dd, J = 6.2, 2.9 Hz, 1H), 3.78 – 3.67 (m, 3H), 3.44 (dd, J = 8.9, 3.5 Hz, 1H), 3.26 (dd, J = 13.8, 8.5 Hz, 1H), 3.04 (dd, J = 13.8, 7.1 Hz, 1H), 2.22 (s, 3H), 2.13 (s, 3H), 2.11 – 2.04 (m, 1H), 1.77 – 1.59 (m, 1H).
199	LC-MS: [M+1] ⁺ =357.2, 1H NMR (400 MHz, DMSO) δ 7.82 (s, 1H), 7.46 (dd, J = 12.6, 8.0 Hz, 2H), 7.23 – 7.13 (m, 3H), 7.06 – 6.90 (m, 3H), 4.58 (t, J = 7.8 Hz, 1H), 3.39 (dd, J = 13.7, 8.5 Hz, 1H), 3.10 (dd, J = 13.8, 7.0 Hz, 1H), 2.20 (s, 3H), 2.16 (s, 3H).
200	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 9.85 (s, 1H), 8.94 (d, J = 1.1 Hz, 1H), 7.59 (s, 1H), 7.43 (t, J = 9.2 Hz, 2H), 7.13 – 7.00 (m, 5H), 4.74 – 4.58 (m, 5H), 3.96 – 3.86 (m, 1H), 3.30 (dd, J = 13.8, 8.5 Hz, 1H), 3.08 (dd, J = 13.8, 7.2 Hz, 1H), 2.21 (s, 3H), 2.14 (d, J = 7.8 Hz, 3H).
201	[M+1] ⁺ =362.17, 1H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.06 – 6.98 (m, 2H), 6.83 (s, 1H), 6.61 (s, 1H), 5.86 (s, 1H), 3.93 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H).
202	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =364.3, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 9.65 (s, 1H), 8.95 (s, 1H), 7.60 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 6.8 Hz, 5H), 4.67 (t, J = 7.7 Hz, 1H), 3.95 (s, 2H), 3.36 – 3.27 (m, 4H), 3.09 (dd, J = 13.7, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H).
203	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =306.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.95 (d, J = 1.2 Hz, 1H), 7.59 (s, 1H), 7.13 – 7.01 (m, 3H), 6.96 (d, J = 8.2 Hz, 2H), 6.59 (d, J = 6.7 Hz, 2H), 4.62 (t, J = 7.8 Hz, 1H), 3.23 (dd, J = 13.9, 8.5 Hz, 1H), 3.02 (dd, J = 13.8, 7.1 Hz, 1H), 2.67 (s, 3H), 2.21 (s, 3H), 2.13 (s, 3H).
204	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =460.2, 1H NMR (400 MHz, DMSO) δ 14.03 (s, 2H), 8.94 (t, J = 6.0 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.71 (dd, J = 11.1, 4.8 Hz, 3H), 7.63 (t, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.11 – 7.02 (m, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.42 (dd, J = 13.8, 8.3 Hz, 2H), 3.21 (dd, J = 13.8, 7.5 Hz, 1H), 2.20 (s, 3H), 2.12 (d, J = 9.4 Hz, 3H).
205	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =419.3, 1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 8.95 (d, J = 1.2 Hz, 1H), 8.31 (s, 1H), 7.59 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.13 – 6.92 (m, 5H), 6.22 (d, J = 7.6 Hz, 1H), 4.64 (t, J = 7.8 Hz, 1H), 3.80 (dt, J = 11.3, 3.3 Hz, 2H), 3.62 (qd, J = 10.7, 5.5 Hz, 1H), 3.36 (td, J = 11.4, 2.1 Hz, 2H), 3.26 (dd, J = 13.8, 8.5 Hz, 1H), 3.04 (dd, J = 13.8, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 1.75 (d, J = 10.3 Hz, 2H), 1.44 – 1.27 (m, 2H).
206	LC-MS: [M-C ₂ HF ₃ O ₂ -1] ⁻ =333.1, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 8.95 (d, J = 1.0 Hz, 1H), 7.62 (s, 1H), 7.12 – 7.01 (m, 7H), 4.69 (t, J = 7.8 Hz, 1H), 3.48 (s, 2H), 3.34 – 3.30 (m, 1H), 3.10 (dd, J = 13.9, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H).
207	LC-MS: [M+1] ⁺ =376.3, 1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 7.57 (s, 1H), 7.13 (d, J = 7.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.0 Hz, 1H), 6.84 – 6.75 (m, 3H), 6.40 (d, J = 8.4 Hz, 2H), 5.19 (s, 1H), 4.41 (t, J = 7.6 Hz, 1H), 3.83 (dd, J = 8.2, 3.3 Hz, 2H), 3.36 (td, J = 11.4, 1.9 Hz, 3H), 3.17 (dd, J = 13.8, 8.0 Hz, 1H), 2.87 (dd, J = 13.8, 7.2 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 1.81 (d, J = 12.7 Hz, 2H), 1.39 – 1.18 (m, 2H).
208	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =374.2, 1H NMR (400 MHz, DMSO) δ 14.27 (s, 2H), 8.96 (d, J = 1.0 Hz, 1H), 7.71 – 7.53 (m, 4H), 7.26 (d, J = 11.2 Hz, 1H), 7.10 (tdd, J = 9.0, 7.1, 2.4 Hz, 4H), 4.79 (t, J = 7.9 Hz, 1H), 3.45 (dd, J = 13.8, 8.5 Hz, 1H), 3.25 (dd, J = 13.8, 7.4 Hz, 1H), 2.22 (s, 3H), 2.15 (s, 3H).
209	[M+1] ⁺ =358.2, 1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.57 (s, 1H), 7.37 – 7.30 (m, 2H), 7.26 – 7.23 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H), 4.65 (t, J = 7.6 Hz, 1H), 4.03 (s, 3H), 3.51 (dd, J = 13.6, 6.8 Hz, 1H), 3.22 (dd, J = 13.6, 8.8 Hz, 1H), 2.21 (s, 3H), 2.09 (s, 3H).
210	[M+1] ⁺ =345.17, 1H NMR (400 MHz, MeOD) δ 8.41 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.10 (s, 1H), 7.10 – 7.06 (m, 1H), 7.05 – 7.02 (m, 1H), 4.74 (t, J = 8.0 Hz, 1H), 3.47 (dd, J = 13.6, 7.6 Hz, 1H), 3.25 (dd, J = 13.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.08 (s, 3H).
211	[M+1] ⁺ =358.1, 1H NMR (400 MHz, MeOD) δ 8.78 (d, J = 1.2 Hz, 1H), 8.19 (s, 1H), 7.65 – 7.63 (d, J = 8.5 Hz, 2H), 7.48 (s, 1H), 7.27 – 7.25 (m, 2H), 7.14 – 7.02 (m, 3H), 4.84 – 4.79 (m, 2H), 3.56 – 3.51 (m, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 2.05 (s, 3H).
212	[M+1] ⁺ =420.2, 1H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.51 – 7.49 (m, 2H), 7.14 – 7.12 (m, 1H), 7.04 – 6.99 (m, 3H), 6.96 – 6.94 (m, 1H), 6.76 (s, 1H), 4.59 (t, J = 8.0 Hz, 1H), 4.02 – 3.98 (m, 2H), 3.52 – 3.46 (m, 2H), 3.44 – 3.39

	(m, 1H), 3.15 – 3.10 (m, 1H), 2.98 – 2.87 (m, 1H), 2.21 (s, 3H), 2.14 – 2.05 (m, 2H), 2.04 (s, 3H), 1.70 – 1.67 (m, 2H).
213	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =434.3, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 8.96 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.74 – 7.50 (m, 2H), 7.21 – 6.98 (m, 3H), 6.98 – 6.73 (m, 2H), 4.76 (t, J = 7.9 Hz, 1H), 4.08 – 3.89 (m, 1H), 3.89 – 3.67 (m, 5H), 3.39 (ddd, J = 11.3, 5.5, 2.0 Hz, 3H), 3.19 (dd, J = 13.7, 7.6 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 1.76 (d, J = 10.3 Hz, 2H), 1.51 (qd, J = 11.9, 4.3 Hz, 2H).
214	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =391.2, 1H NMR (400 MHz, DMSO) δ 14.40 (s, 2H), 11.10 (d, J = 503.9 Hz, 1H), 8.96 (d, J = 1.1 Hz, 1H), 7.59 (s, 1H), 7.20 (dd, J = 27.6, 7.8 Hz, 4H), 7.15 – 6.96 (m, 3H), 4.85 (t, J = 8.8 Hz, 1H), 4.72 (dd, J = 15.9, 8.1 Hz, 1H), 4.66 (dd, J = 8.5, 5.3 Hz, 1H), 4.38 – 4.17 (m, 1H), 3.53 (ddd, J = 24.8, 11.8, 3.2 Hz, 2H), 3.39 (dd, J = 13.9, 8.3 Hz, 1H), 3.16 (dd, J = 13.9, 7.4 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).
215	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =334.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.95 (d, J = 1.2 Hz, 1H), 8.32 (d, J = 4.5 Hz, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.61 (s, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.12 – 7.01 (m, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.41 (dd, J = 13.7, 8.3 Hz, 1H), 3.19 (dd, J = 13.7, 7.5 Hz, 1H), 2.74 (d, J = 4.5 Hz, 3H), 2.20 (s, 3H), 2.11 (s, 3H).
216	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =348.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.96 (d, J = 0.9 Hz, 1H), 7.64 (s, 1H), 7.20 (dd, J = 23.5, 8.1 Hz, 4H), 7.10 – 7.01 (m, 3H), 4.72 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.7, 8.3 Hz, 1H), 3.16 (dd, J = 13.7, 7.5 Hz, 1H), 2.90 (d, J = 37.8 Hz, 6H), 2.20 (s, 3H), 2.09 (s, 3H).
217	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =356.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.95 (d, J = 0.9 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.60 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.28 (s, 2H), 7.13 – 7.02 (m, 3H), 4.76 (t, J = 7.9 Hz, 1H), 3.47 – 3.41 (m, 1H), 3.23 (dd, J = 13.8, 7.4 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H).
218	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =337.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 3H), 11.20 (s, 1H), 8.95 (d, J = 1.2 Hz, 1H), 7.72 – 7.51 (m, 2H), 7.24 – 7.01 (m, 3H), 6.86 – 6.63 (m, 2H), 4.75 (t, J = 7.9 Hz, 1H), 3.36 (dd, J = 13.8, 8.6 Hz, 1H), 3.16 (dd, J = 13.8, 7.2 Hz, 1H), 2.19 (d, J = 22.4 Hz, 6H).
219	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =336.2, 1H NMR (400 MHz, DMSO) δ 14.16 (s, 2H), 11.12 (s, 1H), 8.94 (d, J = 23.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 3H), 7.23 (d, J = 8.2 Hz, 2H), 7.10 – 7.02 (m, 3H), 4.73 (t, J = 7.8 Hz, 1H), 3.44 – 3.40 (m, 1H), 3.18 (dd, J = 13.8, 7.3 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).
220	LC-MS: [M+1] ⁺ = 414.15, 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.11 (s, 1H), 7.07 – 7.05 (m, 1H), 7.02 – 6.98 (m, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.41 (s, 1H), 5.81 (s, 1H), 4.42 – 4.32 (m, 1H), 4.03 – 3.90 (m, 2H), 3.27 – 3.23 (m, 2H), 2.30 (s, 3H), 2.28 – 2.21 (m, 2H), 2.19 (s, 3H), 1.77 – 1.74 (m, 2H).
221	[M-C ₂ HF ₃ O ₂ +1] ⁺ =357.1, 1H NMR (400 MHz, DMSO) δ 14.12 (d, J = 25.5 Hz, 2H), 8.93 (s, 1H), 7.61 (s, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.18 – 7.02 (m, 5H), 4.79 – 4.64 (m, 1H), 3.34 (dd, J = 13.8, 9.1 Hz, 1H), 3.14 (dd, J = 13.8, 6.7 Hz, 1H), 2.21 (d, J = 16.4 Hz, 6H).
222	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =348.3, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.97 (s, 1H), 7.66 (s, 1H), 7.31 – 6.81 (m, 7H), 4.70 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.3, 7.9 Hz, 1H), 3.24 – 2.96 (m, 4H), 2.18 (s, 3H), 2.04 (s, 3H), 1.75 (d, J = 51.6 Hz, 3H).
223	[M-C ₂ HF ₃ O ₂ +1] ⁺ =309.2, 1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.53 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.81 – 6.67 (m, 2H), 6.61 (dd, J = 8.2, 1.6 Hz, 1H), 6.56 (d, J = 1.5 Hz, 1H), 4.45 (t, J = 7.6 Hz, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 3.28 (d, J = 7.7 Hz, 1H), 2.98 (dd, J = 13.6, 7.7 Hz, 1H), 2.18 (s, 3H), 2.10 (s, 3H).
224	[M+1] ⁺ =337.2, 1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.53 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.81 – 6.67 (m, 2H), 6.61 (dd, J = 8.2, 1.6 Hz, 1H), 6.56 (d, J = 1.5 Hz, 1H), 4.45 (t, J = 7.6 Hz, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 3.28 (d, J = 7.7 Hz, 1H), 2.98 (dd, J = 13.6, 7.7 Hz, 1H), 2.18 (s, 3H), 2.10 (s, 3H).
225	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =348.2, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 10.61 (s, 1H), 8.95 (s, 1H), 7.60 (s, 1H), 7.13 – 6.98 (m, 3H), 6.81 – 6.65 (m, 3H), 4.66 (t, J = 7.8 Hz, 1H), 4.50 (s, 2H), 3.26 (dd, J = 13.9, 8.7 Hz, 1H), 3.04 (dd, J = 13.9, 7.0 Hz, 1H), 2.22 (s, 3H), 2.15 (s, 3H).
226	LC-MS: [M+1] ⁺ =367.2, 1H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 7.58 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.83 (s, 1H), 6.30 (s, 2H), 4.47 (t, J = 7.6 Hz, 1H), 3.61 (s, 6H), 3.57 (s, 3H), 3.38 (d, J = 33.0 Hz, 1H), 2.98 (dd, J = 13.5, 7.9 Hz, 1H), 2.18 (s, 3H), 2.07 (s, 3H).
227	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =373.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.94 (s, 1H), 7.62 (s, 1H), 7.14 – 7.01 (m, 7H), 4.67 (t, J = 6.3 Hz, 1H), 4.48 (q, J = 7.0 Hz, 1H), 3.33 (dd, J = 13.8, 8.5 Hz, 1H), 3.08 (dd, J = 13.8, 6.7 Hz, 1H), 2.19 (d, J = 5.2 Hz, 3H), 2.07 (d, J = 4.9 Hz, 3H), 1.61 (d, J = 7.2 Hz, 3H).
228	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =377.3, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 8.96 (s, 1H), 7.63 (s, 1H), 7.18 – 6.96 (m, 5H), 6.87 (d, J = 8.3 Hz, 2H), 4.66 (t, J = 7.8 Hz, 1H), 3.34 (dd, J = 13.6, 7.9 Hz, 1H), 3.08 (dd, J = 13.5, 7.9 Hz, 1H), 3.00 (s, 3H), 2.55 (s, 6H), 2.18 (s, 3H), 2.06 (s, 3H).
229	[M-C ₂ HF ₃ O ₂ -1] ⁺ =376.2, 1H NMR (400 MHz, DMSO) δ 14.20 (s, 2H), 8.95 (s, 1H), 8.74 (t, J = 5.9 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.15 – 7.01 (m, 3H), 4.75 (t, J = 7.9 Hz, 1H), 3.42 (dd, J = 13.7, 8.4 Hz, 1H), 3.21 (dd, J = 13.7, 7.4 Hz, 1H), 2.21 (s, 3H), 2.13 (s, 3H).
230	LC-MS: [M+1] ⁺ =346.15, 1H NMR (400 MHz, DMSO) δ 14.13 (s, 1H), 9.99 (s, 1H), 8.95 (s, 1H), 7.62 (s, 1H), 7.05 (dd, J = 17.2, 7.2 Hz, 3H), 6.96 – 6.88 (m, 2H), 6.66 (d, J = 4.0 Hz, 1H), 4.64 (t, J = 6.0 Hz, 1H), 3.26 – 3.20 (m, 1H), 3.03 (dd, J = 12.8, 6.0 Hz, 1H), 2.79 – 2.73 (m, 2H), 2.41 – 2.36 (m, 2H), 2.22 (s, 3H), 2.14 (s, 3H).

231	LC-MS: [M+1] ⁺ = 306.15, 1H NMR (400 MHz, MeOD) δ 7.53 (s, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.93 (dd, J = 14.4, 6.4 Hz, 2H), 6.74 (s, 1H), 6.43 – 6.38 (m, 2H), 6.29 (s, 1H), 4.57 (t, J = 7.6 Hz, 1H), 3.33 – 3.32 (m, 1H), 3.02 (dd, J = 13.2, 8.4 Hz, 1H), 2.62 (s, 3H), 2.21 (s, 3H), 2.05 (s, 3H).
232	LC-MS: [M-C2HF3O2+1] ⁺ = 355.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.95 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.61 (s, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.16 – 7.01 (m, 3H), 4.78 (t, J = 7.8 Hz, 1H), 3.49 (dd, J = 13.8, 8.4 Hz, 1H), 3.27 (dd, J = 13.8, 7.4 Hz, 1H), 3.16 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H).
233	LC-MS: [M-C2HF3O2+1] ⁺ = 420.2, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 12.63 (s, 1H), 8.96 (d, J = 0.9 Hz, 1H), 8.51 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 14.8 Hz, 1H), 7.57 (s, 1H), 7.27 – 6.94 (m, 3H), 6.83 – 6.58 (m, 2H), 4.74 (t, J = 7.9 Hz, 1H), 4.06 – 3.97 (m, 1H), 3.87 (d, J = 9.7 Hz, 2H), 3.45 – 3.26 (m, 3H), 3.14 (dd, J = 13.8, 7.4 Hz, 1H), 2.22 (s, 3H), 2.16 (s, 3H), 1.80 – 1.68 (m, 2H), 1.58 (qd, J = 12.2, 4.4 Hz, 2H).
234	LCMS: [M-C2HF3O2+1] ⁺ = 376.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 9.78 (s, 1H), 8.95 (s, 1H), 7.63 – 7.52 (m, 3H), 7.07 (dt, J = 9.1, 6.6 Hz, 5H), 5.04 (dd, J = 8.9, 6.6 Hz, 1H), 4.63 (tt, J = 8.7, 6.8 Hz, 3H), 3.31 (dd, J = 13.8, 8.5 Hz, 1H), 3.10 (dd, J = 13.8, 7.2 Hz, 1H), 2.94 (tt, J = 10.9, 8.7 Hz, 1H), 2.58 (ddd, J = 15.3, 11.0, 6.7 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H).
235	LC-MS: [M-C2HF3O2+1] ⁺ = 334.2, 1H NMR (400 MHz, DMSO) δ 14.18 (s, 2H), 8.95 (s, 1H), 7.59 (s, 1H), 7.15 – 6.93 (m, 3H), 6.46 (d, J = 7.6 Hz, 2H), 6.40 (d, J = 7.8 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.04 (dd, J = 9.3, 5.0 Hz, 2H), 3.28 – 3.18 (m, 2H), 3.13 (dd, J = 13.9, 9.0 Hz, 1H), 2.93 (dd, J = 14.0, 6.6 Hz, 1H), 2.24 (d, J = 7.4 Hz, 3H), 2.16 (d, J = 7.6 Hz, 3H).
236	LCMS: [M-C2HF3O2+1] ⁺ = 390.1, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.95 (s, 1H), 8.42 (t, J = 5.4 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.59 (s, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.11 – 7.03 (m, 3H), 4.74 (t, J = 7.9 Hz, 1H), 3.40 (dd, J = 12.3, 5.4 Hz, 3H), 3.20 (dd, J = 13.7, 7.4 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H).
237	LC-MS: [M-C2HF3O2+1] ⁺ = 349.2, 1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 8.95 (d, J = 0.9 Hz, 1H), 8.42 (s, 1H), 7.59 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.11 – 7.02 (m, 3H), 6.98 (d, J = 8.4 Hz, 2H), 6.01 (s, 1H), 4.64 (t, J = 7.7 Hz, 1H), 3.25 (dd, J = 13.8, 8.6 Hz, 1H), 3.04 (dd, J = 13.8, 7.1 Hz, 1H), 2.63 (t, J = 13.9 Hz, 3H), 2.22 (s, 3H), 2.13 (s, 3H).
238	LC-MS: [M-C2HF3O2+1] ⁺ = 321.2, 1H NMR (400 MHz, DMSO) δ 14.29 (s, 2H), 8.97 (d, J = 0.8 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.03 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.73 (dd, J = 8.0, 2.0 Hz, 1H), 7.64 (s, 1H), 7.58 (s, 1H), 7.10 (dt, J = 11.8, 7.3 Hz, 3H), 4.76 (t, J = 7.9 Hz, 1H), 3.49 (dd, J = 13.7, 8.0 Hz, 1H), 3.26 (dd, J = 13.7, 7.9 Hz, 1H), 2.19 (s, 3H), 2.07 (s, 3H).
239	[M-HCl-1] ⁻ = 349.1, 1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 7.55 (s, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.02 – 6.91 (m, 4H), 6.78 (s, 1H), 6.69 (d, J = 8.6 Hz, 2H), 4.55 (s, 2H), 4.46 (t, J = 7.6 Hz, 1H), 3.31 – 3.25 (m, 1H), 2.97 (dd, J = 13.8, 7.2 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H).
240	LC-MS: [M+1] ⁺ = 300.1, 1H NMR (400 MHz, MeOD) δ 7.55 - 7.51 (m, 1H), 7.04 - 6.95 (m, 3H), 6.67 (s, 1H), 4.25 (t, J = 7.6 Hz, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 2.15 (t, J = 7.6 Hz, 2H), 2.11 - 2.02 (m, 1H), 1.93 - 1.82 (m, 1H), 1.62 - 1.52 (m, 2H), 1.40 - 1.25 (m, 4H).
241	LC-MS: [M+1] ⁺ = 359.5, 1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.21 - 7.16 (m, 3H), 7.06 - 7.01 (m, 1H), 6.99 - 6.95 (m, 1H), 6.77 (s, 1H), 4.64 (t, J = 7.6 Hz, 1H), 4.38 (s, 3H), 3.50 (dd, J = 13.6, 7.2 Hz, 1H), 3.20 (dd, J = 13.6, 8.4 Hz, 1H), 2.20 (s, 3H), 2.06 (s, 3H).
242	LC-MS: [M-C2HF3O2+1] ⁺ = 405.2, 1H NMR (400 MHz, DMSO) δ 14.26 (s, 2H), 10.35 (s, 1H), 8.97 (d, J = 1.0 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.54 (dd, J = 8.6, 2.2 Hz, 1H), 7.07 (ddd, J = 11.7, 5.5, 3.7 Hz, 3H), 4.69 (t, J = 7.9 Hz, 1H), 3.88 (dd, J = 10.3, 2.6 Hz, 2H), 3.41 – 3.24 (m, 3H), 3.12 (dd, J = 13.9, 7.6 Hz, 1H), 2.71 (td, J = 10.7, 4.8 Hz, 1H), 2.21 (s, 3H), 2.11 (s, 3H), 1.71 – 1.56 (m, 4H).
243	LC-MS: [M-C2HF3O2+1] ⁺ = 375.2, 1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 8.96 (d, J = 0.9 Hz, 1H), 7.61 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.06 (td, J = 9.3, 5.3 Hz, 5H), 4.67 (t, J = 7.8 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.43 – 3.35 (m, 2H), 3.30 (dd, J = 13.8, 8.6 Hz, 1H), 3.08 (dd, J = 13.8, 7.1 Hz, 1H), 2.73 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H).
244	LC-MS: [M-C2HF3O2+1] ⁺ = 306.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.96 (s, 1H), 7.87 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.65 (s, 1H), 7.34 – 7.24 (m, 2H), 7.20 (d, J = 8.1 Hz, 3H), 7.16 – 7.06 (m, 2H), 4.64 (t, J = 7.8 Hz, 1H), 3.43 (dd, J = 13.5, 8.1 Hz, 1H), 3.21 (dd, J = 13.5, 7.8 Hz, 1H), 2.20 (s, 3H).
245	LC-MS: [M-C2HF3O2+1] ⁺ = 419.3, 1H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 8.95 (s, 1H), 8.19 (s, 1H), 7.60 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.05 (ddd, J = 19.5, 13.6, 8.1 Hz, 5H), 5.00 – 4.80 (m, 1H), 4.66 (t, J = 7.8 Hz, 1H), 3.91 (td, J = 8.5, 4.8 Hz, 1H), 3.70 – 3.52 (m, 3H), 3.27 (dd, J = 13.8, 8.6 Hz, 1H), 3.06 (dd, J = 13.8, 7.1 Hz, 1H), 2.83 (s, 3H), 2.22 (s, 3H), 2.18 – 2.04 (m, 4H), 1.80 (qd, J = 13.3, 8.1 Hz, 1H).
246	LC-MS: [M-C2HF3O2+1] ⁺ = 333.2, 1H NMR (400 MHz, DMSO) δ 14.25 (s, 2H), 8.96 (s, 1H), 7.57 (s, 1H), 7.10 – 6.99 (m, 3H), 6.61 (s, 1H), 6.48 (d, J = 21.4 Hz, 2H), 4.62 (t, J = 7.5 Hz, 1H), 3.29 (s, 4H), 3.21 – 3.14 (m, 1H), 2.97 (dd, J = 13.9, 6.7 Hz, 1H), 2.23 (s, 3H), 2.18 (s, 3H).
247	LC-MS: [M+1] ⁺ = 352.05, 1H NMR (400 MHz, MeOD) δ 7.54 (d, J = 0.8 Hz, 1H), 7.40 (dd, J = 12.4, 2.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.86 (t, J = 8.4 Hz, 1H), 6.78 (s, 1H), 4.64 (t, J = 8.0 Hz, 1H), 3.39 (dd, J = 13.6, 7.6 Hz, 1H), 3.09 (dd, J = 13.6, 8.4 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H).
248	LC-MS: [M+1] ⁺ = 335.25, 1H NMR (400 MHz, MeOD) δ 8.80 (d, J = 1.2 Hz, 1H), 7.94 – 7.93 (m, 1H), 7.73 – 7.71 (m, 1H), 7.67 – 7.63 (m, 1H), 7.49 (s, 1H), 7.14 – 7.06 (m, 3H), 4.80 – 4.76 (m, 1H), 3.55 – 3.51 (m, 1H), 3.29 – 3.22 (m, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 2.02 (s, 3H).
249	LC-MS: [M+1] ⁺ = 350.85, 1H NMR (400 MHz, MeOD) δ 7.53 (s, 1H), 7.05 – 6.95 (m, 3H), 6.68 (s, 1H), 4.26 (t, J = 7.6 Hz, 1H), 2.99 (t, J = 6.8 Hz, 2H), 2.88 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.14 – 2.04 (m, 1H), 1.92 – 1.85 (m, 1H), 1.52 – 1.47 (m, 2H), 1.43 – 1.37 (m, 2H), 1.36 – 1.28 (m, 2H).

250	LC-MS: [M+1] ⁺ = 406.20, 1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.04-6.96 (m, 3H), 6.69 (s, 1H), 4.26 (t, J = 7.6 Hz, 1H), 4.00 (dd, J = 11.2, 4.0 Hz, 2H), 3.39 (td, J = 12.0, 1.6 Hz, 2H), 3.20-3.13 (m, 1H), 3.02 (t, J = 7.2 Hz, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.14 – 2.04 (m, 1H), 1.93-1.84 (m, 3H), 1.79-1.69 (m, 2H), 1.60 – 1.52 (m, 2H), 1.42-1.33 (m, 2H).
251	LC-MS: [M-C2HF3O2-1] ⁻ = 361.2, 1H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 7.60 (s, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.14 – 7.04 (m, 5H), 4.70 (t, J = 7.7 Hz, 1H), 3.33 (dd, J = 13.9, 8.4 Hz, 1H), 3.09 (dd, J = 14.0, 7.1 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 1.42 (s, 6H).
401	[M-C2HF3O2+1] ⁺ = 362.1, 1H NMR (400 MHz, DMSO) δ 14.37 (s, 2H), 9.79 (s, 1H), 9.06 (d, J = 0.7 Hz, 1H), 7.34 (dd, J = 10.3, 5.4 Hz, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.06 (s, 2H), 6.99 – 6.92 (m, 2H), 5.58 (s, 1H), 2.97 (s, 3H), 2.46 – 2.37 (m, 1H), 2.35 – 2.23 (m, 1H), 1.08 (t, J = 7.4 Hz, 3H).
402	LC-MS: [M-C2HF3O2+1] ⁺ = 362.1, 1H NMR (400 MHz, DMSO) δ 14.39 (s, 2H), 9.79 (s, 1H), 9.11 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 10.8 Hz, 2H), 6.97 (s, 1H), 6.92 (d, J = 7.7 Hz, 1H), 5.68 (s, 1H), 2.97 (s, 3H), 2.08 (s, 3H), 1.92 (s, 3H).
403	[M-C2F3O2+1] ⁺ = 348, 1H NMR (400 MHz, DMSO) δ 14.34 (s, 2H), 9.76 (d, J = 16.2 Hz, 1H), 9.07 (s, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 5.7 Hz, 2H), 6.95 (dd, J = 12.3, 5.3 Hz, 2H), 5.57 (s, 1H), 2.97 (s, 3H), 2.01 (s, 3H).
501	[M-HCl+1] ⁺ = 412.1, 1H NMR (400 MHz, DMSO) δ 9.61 (s, 2H), 7.34 (dd, J = 24.5, 16.5 Hz, 3H), 7.09 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.04 (dd, J = 11.1, 3.8 Hz, 1H), 3.86 (s, 4H), 3.61 (dd, J = 12.6, 3.8 Hz, 2H), 3.30 – 3.22 (m, 1H), 2.78 (s, 3H).
502	[M-C2HF3O2+1] ⁺ = 378.0, 1H NMR (400 MHz, DMSO) δ 10.45 (s, 2H), 7.98 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.43 (dt, J = 14.9, 7.6 Hz, 3H), 7.26 (t, J = 8.1 Hz, 1H), 5.23 (t, J = 7.1 Hz, 1H), 3.81 (dd, J = 14.5, 6.8 Hz, 4H), 3.60 (d, J = 7.7 Hz, 1H), 3.50 (d, J = 5.7 Hz, 1H).
503	[M+1] ⁺ = 370.10, 1H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 7.66 (s, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.34 (dt, J = 18.4, 7.6 Hz, 3H), 7.21 (t, J = 8.0 Hz, 1H), 6.93 (dd, J = 16.8, 8.4 Hz, 3H), 5.06 (d, J = 6.4 Hz, 1H), 4.02 (t, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.38 (t, J = 8.4 Hz, 2H), 2.89 (dd, J = 13.6, 4.0 Hz, 1H), 2.75 (dd, J = 13.6, 10.0 Hz, 1H).
504	[M-HCl+1] ⁺ = 390.1, 1H NMR (400 MHz, MeOD) δ 7.40 (t, J = 7.9 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.17 (t, J = 7.6 Hz, 2H), 7.00 (dd, J = 23.2, 7.5 Hz, 2H), 6.16 (s, 1H), 4.02 (t, J = 7.5 Hz, 2H), 3.65 (t, J = 7.6 Hz, 2H), 2.95 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H).
505	[M+1] ⁺ = 388.38, 1H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.74 (d, J = 9.2 Hz, 1H), 8.31 (s, 1H), 7.67 (s, 1H), 7.33 – 7.16 (m, 3H), 7.11 (s, 1H), 7.03 (dd, J = 17.2, 8.4 Hz, 3H), 6.94 (t, J = 7.6 Hz, 1H), 4.96-4.90 (m, 1H), 3.88 (s, 3H), 3.48 (s, 5H), 3.09 (dd, J = 13.6, 4.8 Hz, 1H), 2.94 – 2.87 (m, 4H).
506	[M+1] ⁺ = 389.70, 1H NMR (400 MHz, DMSO-D2O) δ 7.70 (s, 1H), 7.62 (dd, J = 8.6, 1.7 Hz, 1H), 7.39 (dd, J = 15.1, 8.1 Hz, 5H), 7.27 (d, J = 6.7 Hz, 1H), 5.03 – 4.98 (m, 1H), 4.77 (s, 0H), 3.94 – 3.82 (m, 1H), 3.82 (s, 4H), 3.51 (dd, J = 14.0, 7.2 Hz, 2H), 3.25 (dd, J = 14.8, 8.2 Hz, 2H).
507	[M-HCl+1] ⁺ = 438.2, 1H NMR (400 MHz, MeOD) δ 7.58 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.1 Hz, 2H), 6.16 (s, 1H), 4.02 (t, J = 7.5 Hz, 2H), 3.94 (dd, J = 11.2, 3.4 Hz, 2H), 3.65 (t, J = 7.4 Hz, 2H), 3.44 (td, J = 11.9, 1.8 Hz, 2H), 2.37 – 2.27 (m, 5H), 2.18 (s, 3H), 2.08 (dd, J = 14.8, 7.6, 3.7 Hz, 1H), 1.67 (dd, J = 12.9, 1.6 Hz, 2H), 1.38 (qd, J = 12.2, 4.4 Hz, 2H).
508	[M-HCl+1] ⁺ = 372.1, 1H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 10.22 (t, J = 227.4 Hz, 2H), 7.79 – 7.66 (m, 2H), 7.55 – 7.42 (m, 2H), 7.42 – 7.32 (m, 1H), 7.21 – 6.88 (m, 3H), 6.21 (d, J = 162.9 Hz, 1H), 4.01 – 3.86 (m, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.61 – 3.47 (m, 2H).
509	[M+1] ⁺ = 390.10, 1H NMR (400 MHz, DMSO) δ 9.60 (s, 1H), 8.22 (d, J = 18.8 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.25-7.19 (m, 2H), 7.13 (s, 1H), 7.06 – 6.99 (m, 1H), 6.96 (dd, J = 13.1, 8.0 Hz, 3H), 6.1-6.85 (m, 1H), 5.06 (dd, J = 9.2, 4.4 Hz, 1H), 4.27 – 4.09 (m, 2H), 3.82 (s, 3H), 3.48 (t, J = 8.8 Hz, 2H), 2.94 (s, 3H), 2.88 (s, 1H), 2.80 – 2.70 (m, 1H).
510	LC-MS: [M-HCl+1] ⁺ = 372.2, 1H NMR (400 MHz, DMSO) δ 9.98 (s, 2H), 7.35 (d, J = 7.1 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.15 (dd, J = 18.1, 7.2 Hz, 2H), 7.09 – 7.00 (m, 2H), 6.95 (d, J = 7.4 Hz, 1H), 4.44 (t, J = 7.5 Hz, 1H), 3.78 (s, 4H), 3.46 – 3.40 (m, 1H), 3.07 (dd, J = 13.4, 7.1 Hz, 1H), 2.90 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H).
511	[M+1] ⁺ = 383.9, 1H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 7.65 (s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.45 – 7.24 (m, 4H), 7.07 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 5.17 (s, 1H), 3.73 – 3.61 (m, 5H), 3.10 (t, J = 7.2 Hz, 2H), 2.85 (qd, J = 14.0, 7.2 Hz, 2H), 2.21 (s, 3H), 2.16 (s, 3H).
512	[M+1] ⁺ = 423.8, 1H NMR (400 MHz, MeOD) δ 7.74 (d, J = 37.2 Hz, 1H), 7.62 (dd, J = 10.4, 8.8 Hz, 2H), 7.54 – 7.38 (m, 4H), 5.33 (d, J = 6.4 Hz, 1H), 5.19 (s, 1H), 3.87 (d, J = 11.2 Hz, 1H), 3.82 (s, 3H), 3.73 (dd, J = 18.8, 8.0 Hz, 1H), 3.47 (dd, J = 13.2, 5.6 Hz, 2H), 3.12 (t, J = 12.4 Hz, 1H).
513	[M+1] ⁺ = 387.05, 1H NMR (400 MHz, MeOD) δ 8.54 – 8.46 (m, 1H), 7.97 (d, J = 23.2 Hz, 1H), 7.44 – 7.31 (m, 2H), 7.26 (d, J = 7.2 Hz, 1H), 7.10 – 6.93 (m, 2H), 5.36 – 5.24 (m, 1H), 5.06-5.01 (m, 0H), 3.90 (d, J = 3.2 Hz, 2H), 3.88 – 3.84 (m, 2H), 3.82 (d, J = 3.2 Hz, 3H), 3.54 – 3.45 (m, 2H), 3.30-3.28 (m, 3H).
514	[M-HCl+1] ⁺ = 440.1, 1H NMR (400 MHz, DMSO-D2O) δ 7.59 – 7.47 (m, 2H), 7.40 – 7.29 (m, 2H), 7.17 – 6.90 (m, 4H), 6.07 (d, J = 139.2 Hz, 1H), 3.91 (t, J = 7.5 Hz, 2H), 3.80 (d, J = 10.3 Hz, 5H), 3.54 (t, J = 7.5 Hz, 2H), 3.27 (t, J = 11.3 Hz, 2H), 2.22 (d, J = 7.1 Hz, 2H), 1.95 (ddd, J = 11.0, 7.3, 3.9 Hz, 1H), 1.54 (d, J = 12.6 Hz, 2H), 1.22 (qd, J = 12.3, 4.2 Hz, 2H).

515	[M-HCl+1] ⁺ =490.1, 1H NMR (400 MHz, DMSO-D ₂ O) δ 7.29 (dt, J = 28.1, 7.6 Hz, 3H), 7.14 – 6.89 (m, 5H), 5.01 (d, J = 137.5 Hz, 1H), 3.77 (dd, J = 42.7, 34.7 Hz, 7H), 3.43 (s, 2H), 3.27 (t, J = 11.0 Hz, 2H), 3.20 – 2.86 (m, 4H), 2.06 (d, J = 4.4 Hz, 1H), 1.68 (d, J = 11.9 Hz, 2H), 1.26 (q, J = 11.6 Hz, 2H).
516	[M-HCl+1] ⁺ =428.0, 1H NMR (400 MHz, DMSO) δ 10.52 (s, 2H), 9.82 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.34 – 7.18 (m, 3H), 7.11 (dd, J = 18.0, 7.8 Hz, 2H), 5.16 (t, J = 7.0 Hz, 1H), 3.82 (td, J = 9.6, 3.6 Hz, 4H), 3.57 – 3.43 (m, 2H), 2.98 (s, 3H).
517	LC-MS: [M-HCl+1] ⁺ =412.2, 1H NMR (400 MHz, DMSO) δ 11.58 (m, 1H), 10.71 – 9.43 (m, 2H), 7.79 – 6.87 (m, 6H), 5.06 (ddd, J = 163.0, 84.2, 66.5 Hz, 1H), 3.97 – 3.28 (m, 13H), 3.11 – 2.73 (m, 2H), 1.81 (d, J = 162.4 Hz, 2H).
518	LC-MS: [M-HCl+1] ⁺ = 372.2, 1H NMR (400 MHz, DMSO) δ 10.20 (s, 2H), 9.72 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.22 – 7.05 (m, 6H), 4.45 (t, J = 7.8 Hz, 1H), 3.78 (s, 4H), 3.42 – 3.37 (m, 1H), 3.06 (dd, J = 13.7, 7.3 Hz, 1H), 2.94 (d, J = 9.4 Hz, 3H), 2.22 (s, 3H), 2.09 (s, 3H).
519	[M-C ₂ HF ₃ O ₂ +1] ⁺ =428.0, 1H NMR (400 MHz, DMSO) δ 10.48 (s, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.53 (t, J = 7.9 Hz, 4H), 7.45 (d, J = 5.0 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 5.29 (t, J = 6.8 Hz, 1H), 3.83 (dd, J = 15.0, 6.7 Hz, 4H), 3.56 (ddd, J = 30.5, 14.0, 6.9 Hz, 2H), 2.38 (d, J = 4.9 Hz, 3H).
520	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =284.1/286.1, 1H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 8.30 (s, 2H), 7.60 (dt, J = 8.9, 4.4 Hz, 1H), 7.54 – 7.44 (m, 2H), 4.49 (s, 2H), 3.65 (s, 4H), 3.59 (dd, J = 5.5, 3.6 Hz, 2H), 3.49 (dd, J = 5.7, 3.5 Hz, 2H), 3.27 (s, 3H).
601	[M +1] ⁺ =294.1, 1H NMR (400 MHz, DMSO) δ 11.49 (s, 1H), 8.73 (s, 1H), 8.04 (t, J = 6.0 Hz, 3H), 7.94 (t, J = 7.4 Hz, 2H), 7.66 – 7.53 (m, 3H), 6.44 (d, J = 4.9 Hz, 2H), 3.49 (s, 3H).
602	[M+1] ⁺ =455.3 1H NMR (400 MHz, DMSO) δ 13.79 (s, 1H), 10.73 (s, 1H), 8.36 (d, J = 7.0 Hz, 1H), 8.02 (ddd, J = 25.7, 14.2, 7.8 Hz, 3H), 7.77 – 7.63 (m, 2H), 7.56 (p, J = 6.7 Hz, 2H), 7.45 (dd, J = 6.9, 2.3 Hz, 1H), 5.96 (dd, J = 6.9, 2.2 Hz, 1H), 3.72 – 3.59 (m, 2H), 3.43 (tq, J = 8.6, 4.3 Hz, 16H), 3.22 (s, 3H), 3.00 (dt, J = 13.7, 6.9 Hz, 1H), 2.86 (dt, J = 13.4, 6.6 Hz, 1H).

Biological Assays

Example 1. α₂AAR FLIPR assay

This experimental protocol involved cell seeding and a FLIPR assay using the α₂AAR (α₂A-adrenergic receptor) cell line hosted in HEK293 cells. The growth media used is DMEM (11965-092, Gibco) supplemented with 10% FBS (FSP500, Excell), 300μg/mL G418 (10131-027, Gibco), and 2μg/mL Blasticidin S HCl (BS) (A11139-03, Gibco). On Day 1, the cell seeding process started with the removal of the culture medium, followed by rinsing the cells with DPBS (21-031-CVC, Corning). Cells were then treated with 0.05% EDTA-Trypsin (25300-062, Gibco), incubated at 37°C for 1-2 minutes, and monitored under an inverted microscope. The cells were detached, resuspended in growth media, and centrifuged at room temperature at 1000 rpm for 5 minutes. After discarding the supernatant, the cell pellet was resuspended in growth media to a concentration of 10 × 10⁵ cells per mL. This suspension was added to 384-well plates (19-Jul-38, Greiner) at 20 μL per well and incubated overnight at 37°C in 5% CO₂.

On Day 2, the FLIPR assay began with the preparation of the assay buffer comprising 20 mM HEPES (15630-106, Invitrogen), 1× HBSS (14025-076, Invitrogen), and 0.5% BSA (B2064, Sigma). A 250 mM Probenecid solution was prepared in this buffer. The Fluo-4 Direct™ Loading Buffer was made by dissolving Fluo-4 Direct™ crystals (F10471,

Invitrogen) in the FLIPR Assay Buffer and adding Probenecid. The buffer was then vortexed and allowed to stand for over 5 minutes, shielded from light. For the FLIPR procedure, testing compounds for agonist activity were serially diluted and transferred to a 384-well compound plate (25-Jan-39, Greiner). The cell plate was then treated with 2× Fluo-4 Direct™ loading buffer and incubated for 50 minutes at 37 °C in a 5% CO₂ atmosphere, followed by 10 minutes at room temperature. Subsequently, the FLIPR assay buffer was added to the compound plate, which is then centrifuged.

The cell plate was analyzed in the FLIPR Tetra+ System for fluorescence signals. For the agonist test, reference compounds were added to the cell plates, and fluorescence was measured. The “Max-Min” calculation began from Read 1 to the maximum allowed. The data were analyzed using Prism software to calculate activation percentage for agonists and inhibition percentage for antagonists. The results were then fitted using specific models to determine EC₅₀ for agonists.

The experimental protocol utilized various reagents and apparatus, including Penicillin/Streptomycin (100×) (SV30010, Hyclone), Poly-L-lysine hydrobromide (P1399, Sigma), and different types of 384-well plates such as the 384-Well PP 2.0 Microplate (PP-0200, LABCYTE) and 384 well Low Dead Volume Microplate (LP-0200, LABCYTE). The use of specific reference compounds like UK14304 was also integral to the assay.

Example 2. α 2AAR binding assay

The α 2AR Binding Assay was conducted using a stable HEK293 cell line, specifically constructed by WuXi AppTec for targeting α 2AAR. This assay primarily focused on the binding activity of the radioligand [3H]-RX 821002 (PerkinElmer, NET1153250UC) to α 2AAR, with the membrane concentration set at 0.5 µg/well and the radioligand concentration at 0.5 nM. Essential equipment for this assay includes Unifilter-96 GF/C filter plates (Perkin Elmer, 6005174), 96 well conical polypropylene plates (Agilent, 5042-1385), TopSeal-A sealing film (Perkin Elmer, 6050185), a MicroBeta2 reader (CNLL0153, Perkin Elmer, 1310887), and a cell harvester (UNIFILTER-96, Perkin Elmer, 1951369), all procured from Perkin Elmer. Both the assay and wash buffers consist of 50 mM Tris-HCl at a pH of 7.4 (Tris base, Sigma, T1503-1KG).

The procedure initiated with the preparation of test compounds and a reference compound, yohimbine (Sigma, Y3125), through an 8-point 4-fold serial dilution, transferring 1 µL of each to the assay plate. The assay involved adding 100 µL of membrane stocks

(0.5 µg/well) and 100 µL 0.5 nM of [3H]-RX 821002 to each well. After sealing, the plates were agitated at room temperature for one hour. Subsequently, the Unifilter-96 GF/C filter plates were pre-soaked with 0.3% PEI (Sigma, P3143) for at least half an hour. The reaction mixtures were then filtered and washed four times with cold wash buffer using a Perkin Elmer Cell harvester. Post-filtration, the plates were dried at 50 °C for one hour. The next step involved sealing the bottom of the filter plate wells with Perkin Elmer Unifilter-96 backing seal tape and adding 50 µL of MicroScint-O cocktail (PerkinElmer, 6013611) to each well. The top of the plates was then sealed with TopSeal-A sealing film. The trapped 3H was quantified using a Perkin Elmer MicroBeta2 Reader. The inhibition rate was calculated using the formula: %Inhibition = $(1 - (\text{Assay well Average_LC}) / (\text{Average_HC} - \text{Average_LC})) \times 100\%$. Finally, the data were analyzed with Prism 5.0 software, employing the “log (inhibitor) vs. response -- Variable slope” model for data fitting. This comprehensive process ensured precise assessment of the binding affinity of compounds to the α2AAR.

The result of the α2AAR FLIPR assay and binding assay result are listed in Table 3 below.

Table 3 α2A AR agonist activity (EC50) and affinity (Ki)

Compound name	racemate/enantiomer	α2A agonist activity (EC50, nM)	α2A affinity (Ki, nM)	Compound name	racemate/enantiomer	α2A agonist activity (EC50, nM)	α2A affinity (Ki, nM)
1	-	C	C	133	-	B	B
1	-A	E		134	-	B	A
1	-B	B	C	135	-		C
2	-	B		136	-	A	A
3	-	B		136	-A	E	
4	-	C		136	-B	A	A
5	-	B		137	-A		C
5	-A	E		137	-B		E
5	-B	B	B	138	-	B	A
6	-	B		139	-	B	B
7	-	D		140	-		C
8	-	B		141	-	C	B
9	-	B		142	-	B	A
10	-	B		143	-	C	B
10	-A	E		144	-		C
10	-B	B	B	145	-	B	A
11	-	D		146	-	B	B

12	-	E		147	-	B	B
13	-	E		148	-	B	B
14	-	E		149	-	B	B
15	-	E		150	-	C	
16	-	B		151	-A	B	B
17	-	B		151	-B	B	
17	-A	E		152	-	B	A
17	-B	B	B	153	-	B	B
18	-	B		154	-A		D
18	-A	D		154	-B	E	
18	-B	B	B	155	-A	B	B
19	-	C		155	-B	B	
20	-	B	C	156	-	A	A
21	-	E		156	-A		E
22	-	B	B	156	-B	A	A
23	-	D		157	-	A	A
24	-	D		157	-A	E	
25	-	C		157	-B	B	A
26	-	B	C	158	-	B	A
27	-	B	A	159	-	B	B
28	-	B	B	160	-	B	B
29	-	B	A	161	-	B	A
30	-	C	C	162	-	B	A
31	-	B	C	163	-	B	A
32	-	C	C	164	-	B	B
33	-	C		165	-	A	A
34	-	E		166	-	B	B
35	-	C		167	-	B	B
36	-	C		168	-	C	
37	-	C		169	-	A	A
38	-	B		170	-	C	
39	-	C		171	-	A	A
40	-		E	172	-	B	
41	-		C	173	-	B	
42	-		C	174	-	B	C
43	-	B	B	174	-A	E	
43	-A		E	174	-B	B	B
43	-B	B	B	174	-C	D	
44	-A		D	174	-D	B	B
44	-B	B	A	175	-	B	D
45	-A		E	175	-A		E

45	-B	B	A	175	-B	B	C
46	-A		E	176	-	A	A
46	-B	A	B	177	-	A	B
47	-A		D	178	-	B	
47	-B	B	B	179	-	A	A
48	-		E	180	-	B	B
49	-		E	181	-	C	A
50	-	C	C	182	-		C
51	-	C	B	183	-		D
52	-	D		184	-		D
53	-		D	185	-	C	
54	-	B	B	186	-	B	B
55	-	B	B	187	-	B	A
56	-	B	B	188	-		E
57	-		D	189	-		B
58	-		C	190	-	B	A
59	-	C		191	-		C
60	-		D	192	-	B	A
61	-	B	B	193	-	B	A
62	-		C	194	-	B	A
63	-	B	B	195	-	B	A
64	-	B	B	196	-	C	A
65	-		C	197	-	B	C
66	-		D	198	-	B	A
67	-	B	B	199	-		E
68	-		C	200	-	B	A
69	-		C	201	-	B	A
70	-	B	B	202	-	C	C
71	-		B	203	-	C	A
72	-	B	B	204	-	C	C
73	-	B	B	205	-	B	A
73	-A	B	A	206	-	C	C
73	-B	B		207	-	B	A
74	-	C	B	208	-	A	A
75	-		C	209	-	B	A
76	-	C	A	210	-	C	B
77	-		D	211	-	B	A
78	-		D	212	-	B	A
79	-	C	B	213	-	A	A
80	-	B	A	214	-	B	A
81	-	B	A	215	-	A	A

82	-		E	216	-	A	A
83	-		C	217	-	A	A
84	-	B	A	218	-	B	C
85	-	C	B	219	-	A	A
86	-	B	A	220	-	A	A
87	-		C	221	-	B	B
88	-	C	B	222	-	B	B
89	-	C	B	223	-	B	A
90	-	C	C	224	-	A	A
91	-		C	225	-	A	A
92	-		E	226	-	A	A
93	-		D	227	-	B	B
94	-	C	C	228	-	A	A
95	-	B	A	229	-	B	C
96	-	B	A	230	-	B	A
97	-		C	231	-	B	B
98	-A		D	232	-	A	A
98	-B	A	A	233	-	B	B
99	-	B	B	234	-	B	A
100	-A		A	235	-	B	A
100	-B		C	236	-	B	C
101	-	B	B	237	-	B	A
102	-	B	B	238	-		C
103	-	B	B	239	-	B	C
104	-	B	A	240	-		D
105	-	B	A	241	-	B	B
106	-		C	242	-	B	C
107	-		C	243	-	A	A
108	-	B	A	244	-	C	C
109	-	B	B	245	-	A	A
110	-		C	246	-	B	B
111	-	B	B	247	-	B	A
112	-	B	A	248	-	B	C
112	-A		D	249	-		C
112	-B	B	A	250	-		C
113	-		C	251	-	B	C
114	-		E	401	-	B	A
115	-		D	402	-		D
116	-		B	403	-	C	
117	-	A	B	501	-		D
118	-	B	B	502	-		C

119	-	B	A	503	-	C	A
120	-	A	A	504	-		C
121	-	A	B	505	-	C	A
121	-A	E		506	-	C	A
121	-B	A	A	507	-		B
122	-A	B	B	508	-		D
122	-B		C	509	-	C	A
123	-	B	A	510	-		C
124	-	B	A	511	-		A
124	-A		D	512	-		A
124	-B	B	A	513	-		A
125	-		B	514	-		C
126	-	B	A	515	-	C	A
127	-		B	516	-	C	C
128	-		C	517	-		B
129	-		C	518	-		C
130	-A		E	519	-	C	B
130	-B		D	520	-		D
131	-		B	601	-	C	
132	-		C	602	-	C	

A: <10nM

B: 10nM-50nM

C: 50nM-250nM

D: 250nM-1000nM

E: >1000nM

Example 3. MDR1-MDCK Permeability Assay

MDR1-MDCK II cells (obtained from Piet Borst at the Netherlands Cancer Institute) were seeded onto Polycarbonate membranes (PC) in 96-well insert systems at 3.33×10^5 cells/mL until to 4-7 days for confluent cell monolayer formation.

Selected $\alpha 2AR$ agonist from table 3s were diluted with the transport buffer (HBSS with 10.0 mM Hepes, pH7.4) from DMSO stock solution to a concentration of 2 μ M (DMSO<1%) and applied to the apical or basolateral side of the cell monolayer. Digoxin was used as a positive control for the P-glycoprotein (P-gp) substrate, while clonidine, dexmedetomidine, faldomedine and brimonidine were used as negative control. Permeation of the test compounds from A to B direction and/or B to A direction was determined in duplicate. Digoxin was tested at 10.0 μ M from A to B direction and B to A direction in duplicate. The plate was incubated for 2.5 hours in CO₂ incubator at 37.0 $\pm$ 1.0°C, with 5.0%

CO₂ at saturated humidity without shaking. In addition, the efflux ratio of each compound was also determined. Test and reference compounds were quantified by LC/MS/MS analysis based on the peak area ratio of analyte/IS.

After transport assay, lucifer yellow rejection assay was applied to determine the cell monolayer integrity. Buffers were removed from both apical and basolateral chambers, followed by the addition of 75 µL of 100 µM lucifer yellow in transport buffer and 250 µL transport buffer in apical and basolateral chambers, respectively. The plate was incubated for 30 minutes at 37.0°C with 5.0% CO₂ and 95.0% relative humidity without shaking. After 30 minutes incubation, 20 µL of lucifer yellow samples were taken from the apical sides, followed by the addition of 60 µL of transport Buffer. And then 80 µL of lucifer yellow samples were taken from the basolateral sides. The relative fluorescence unit (RFU) of lucifer yellow was measured at 425/528 nm (excitation/emission) with an Envision plate reader.

The apparent permeability coefficient P_{app} (cm/s) was calculated using the equation:

$$P_{app} = (dCr/dt) \times V_r / (A \times C_0)$$

wherein dCr/dt is the cumulative concentration of compound in the receiver chamber as a function of time (µM/s); V_r is the solution volume in the receiver chamber (0.075 mL on the apical side, 0.25 mL on the basolateral side); A is the surface area for the transport, i.e. 0.143 cm² for the area of the monolayer; and C₀ is the initial concentration in the donor chamber (µM).

The efflux ratio was calculated using the equation:

$$\text{Efflux Ratio} = P_{app}(\text{BA}) / P_{app}(\text{AB})$$

The results of the MDR1-MDCK permeability assay are listed in Table 4 below.

Table 4 Efflux ratio of P-gp from MDCK-MDR1 assay

compound name	racemate / enantiomer	Efflux ratio	compound name	racemate / enantiomer	Efflux ratio
Digoxin		13.74	109		94.75
Clonidine		0.71	111		172.99
Dexmedetomidine		0.64	112		58.40
Fadolmidine		0.80	118		25.26
Brimonidine		0.83	121	-B	30.89
1	-B	51.02	124	-B	10.26
5	-B	33.20	136	-B	7.69
18	-B	27.47	138		7.85
44	-B	41.00	141		2.61
45	-B	14.02	156	-B	2.86

46	-B	34.01	157	-B	10.85
47	-B	18.17	158		23.66
55		26.39	163		9.08
56		11.51	165		14.79
64		24.33	186		3.38
67		28.97	187		2.60
72		32.93	190		4.91
73		96.13	200		27.73
74		93.45	205		61.80
80		112.12	208		8.88
81		62.48	213		4.92
95		102.22	214		56.11
98		82.58	215		4.77
99		140.52	216		3.21
101		103.83	217		17.52
103		149.19	219		26.89
105		65.78	401		22.02
108		72.22			

Example 4. *in vivo* drug distribution

The binding affinity of various compounds to plasma proteins was evaluated, including clonidine HCl, dexmedetomidine HCl, 1-B HCl, and 44-B HCl, with warfarin serving as a control. The experiment utilized a HT-Dialysis plate (HTD 96 b) and a dialysis membrane with a molecular weight cutoff of 12-14 kDa. The plasma was derived from male C57BL/6J mice, treated with EDTA-K2 as an anticoagulant. The experimental procedure commenced with plasma thawing under cold tap water, followed by centrifugation at 3220 ×g for 5 minutes to eliminate clots, and pH adjustment to 7.4 ± 0.1 .

Dialysis membranes were initially hydrated in ultra-pure water for about one hour and then treated in a 20:80 ethanol-water mixture for 20 minutes. These prepared membranes could be used immediately or stored at 2-8°C for up to a month. Membranes were rinsed in ultra-pure water before use.

Test and control compounds were prepared at a 400 µM concentration by diluting stock solutions with DMSO. Working solutions were further diluted to create 2 µM loading matrix solutions, which were thoroughly mixed. In the assay, 50 µL aliquots of these solutions were dispensed in triplicate into a Sample Collection Plate, balanced with blank PBS to a final volume of 100 µL per well. A stop solution containing acetonitrile, tolbutamide, and labetalol was added, and samples were mixed and cooled at 2 to 8°C.

During the dialysis, 100 μ L aliquots from the loading matrix were placed in the dialysis well's donor side, matched with an equal volume of PBS on the receiver side, and incubated at 37°C for 4 hours. Post-dialysis, samples from both sides were collected, balanced to 100 μ L with corresponding blank fluids, treated with stop solution, vortexed, and centrifuged to prepare for LC-MS/MS analysis.

Data analysis involved calculating the percentages of Unbound, Bound, and Recovery of the compounds post-dialysis. %Unbound was calculated as the ratio of the compound's peak area on the receiver side to its internal standard, reflecting the fraction that crossed the membrane. %Bound was the complement of %Unbound, representing the fraction retained on the donor side. %Recovery was determined from the peak area ratios on both sides of the membrane, assessing the dialysis efficiency in retaining the compound. These metrics provided insights into the compound's free, bound, and recoverable quantities, elucidating its behavior in the dialysis system. The plasma protein binding ratio result is shown in Table 5.

Table 5. The plasma protein binding ratio

Sample Name	%Unbound (n = 3)	SD	%Bound	%Recovery (n = 3)	SD
Clonidine HCl	70.8	4.8	29.2	93.2	3.7
Dexmedetomidine HCl	6.8	0.2	93.2	88.9	1.8
1-B HCl	5.1	0.3	94.5	88.8	3.5
44-B HCl	6.4	0.8	93.6	86.7	7.0
Warfarin	2.3	0.1	97.7	82.7	2.2

The binding affinity of various compounds to brain proteins was evaluated including clonidine HCl, dexmedetomidine HCl, 1-B HCl, and 44-B HCl, with propranolol serving as a control. The initial preparation of the dialysis membrane involved thawing brain homogenate in a water bath at room temperature and subsequently heating it at 37°C for 10 minutes. The dialysis setup utilized was from HT Dialysis LLC, featuring a HT-Dialysis plate (Model HTD 96 b) and a dialysis membrane with a molecular weight cutoff of 12-14 kDa.

The membrane underwent a comprehensive pretreatment which included hydration in ultra-pure water at room temperature for approximately one hour. This was followed by separation and immersion in a 20:80 ethanol:water solution for about 20 minutes. After this

treatment, the membranes were either used immediately or stored at 2-8°C for up to one month, with a final rinse in ultra-pure water prior to experimental use.

For compound preparation, test and control substances were first dissolved to create 400µM working solutions by mixing 4µL of stock solution with 96µL of DMSO. These working solutions were then further diluted to 2µM in a blank matrix by combining 3µL of the prepared solution with 597µL of matrix, ensuring thorough mixing.

During the assay, 50µL aliquots of the 2µM compound-matrix mixture were dispensed in triplicate into a Sample Collection Plate. Each aliquot was paired with an equal volume of blank PBS to standardize the total volume to 100µL per well at a 1:1 matrix to PBS ratio. A stop solution comprising 500µL of acetonitrile with tolbutamide and labetalol at 250nM each was added to stabilize the samples at T0. The samples were then shaken at 800 rpm for 10 minutes and stored at 2-8°C.

The dialysis procedure included assembling the dialysis device according to the manufacturer's specifications, loading the matrix aliquots into the donor side of the dialysis wells, and conducting the dialysis under a humidified atmosphere with 5% CO₂ at 37°C for 4 hours.

Post-dialysis, 50 µL samples were collected from both the receiver and donor sides into new 96-well plates. Volumes were adjusted to 100 µL by adding an equivalent amount of the opposite blank matrix or PBS. The samples were prepared for LC-MS/MS analysis after thorough vortexing and centrifugation. Blank control samples were prepared and processed similarly to mirror the test conditions.

Data analysis involved calculating the percentages of undiluted unbound and bound fractions, and recovery of the compounds. The %Undiluted Unbound was determined using the formula: $\%Undiluted\ Unbound = 100 \times 1/D / ((1 / (F/T) - 1) + 1/D)$, where D is the dilution factor (10). %Undiluted Bound was derived as 100 - %Undiluted Unbound. %Recovery was calculated using: $\%Recovery = 100 \times (F + T) / T_0$, with F and T representing the peak area ratios of the compound to the internal standard on the receiver and donor sides respectively, after 4 hours of incubation. The brain protein binding result is shown in Table 6

Table 6: The brain protein binding result

Sample Name	%Undiluted Unbound (n = 3)	SD	%Undiluted Bound (n = 3)	%Recovery (n = 3)	SD
Clonidine HCl	23.0	5.4	77.0	105.2	1.3
Dexmedetomidine HCl	6.3	0.9	93.7	93.8	2.7
1-B HCl	5.1	0.3	94.9	88.8	3.5
44-B HCl	2.4	0.3	97.6	88.6	3.7
Propranolol	2.6	0.2	97.4	108.6	1.8

Male C57BL/6J mouse was used in the *in vivo* distribution assay. The sample of brain, spinal cord and serum were collected for the drug distribution calculation.

Before commencing the study, the mice were acclimated to the test facility for at least 3 days. During this period, their general health was assessed by veterinary staff or other authorized personnel. The mice were housed in groups of up to four per cage in polysulfone cages, using either certified aspen shaving bedding or corncob bedding. This bedding was regularly tested for environmental contaminants by the manufacturer. The facility's environment was carefully controlled to maintain a temperature range of 20-26°C, relative humidity between 40 to 70%, and a 12-hour light/12-hour dark cycle, although this cycle can be interrupted for study-related activities. Temperature and humidity were continuously monitored by the Vawasala ViewLinc Monitoring system.

For dosing, an appropriate amount of the compounds was accurately weighed and mixed with a suitable volume of vehicle to achieve a clear solution. This process may require vortexing or sonication in a water bath. The animals were dosed within four hours of formulation preparation. Samples from each formulation were then collected for dose validation using either LC/UV or LC-MS/MS analysis.

Oral gavage was employed for dosing following the facility's SOPs, with the dose volume based on the animal's body weight measured on the morning of the dosing day. Compounds such as 5 mg/kg Clonidine HCl, 5 mg/kg dexmedetomidine HCl, 5 mg/kg and 80 mg/kg compound 1-B, and 5 mg/kg and 80 mg/kg compound 44-B were administered in a 20% HP- β -CD solution in water, with sample collections scheduled at 0.5, 1, 2, and 8 hours post-dosing.

Blood collections were performed from the saphenous vein or another suitable site, with approximately 0.1 mL collected per time point into pre-chilled commercial EDTA-K2

tubes. The samples were kept on wet ice until centrifugation at 4°C and 3,200 g for 10 minutes. The plasma was then transferred into pre-labeled 96-well plates or polypropylene tubes, quick-frozen over dry ice, and stored at -60°C or lower until LC-MS/MS analysis.

The brain and spinal cord tissues were harvested immediately, washed with cold saline, dried, and weighed. These samples were homogenized in a cold 15 mM PBS (pH 7.4):MeOH=2:1 solution at a 1:9 tissue-to-buffer ratio. The homogenates were split into two aliquots: one for immediate LC-MS/MS analysis and one stored at -70±10 °C as a backup. This comprehensive method ensures the detailed and standardized collection and analysis of pharmacokinetic data in a controlled and scientifically rigorous manner.

We calculated AUC ratio from the equation $\text{AUC ratio} = \text{Tissue AUC}_{0-\text{last}} / \text{plasma AUC}_{0-\text{last}}$. $\text{LogBB} = \log_{10}(\text{brain AUC}_{0-\text{last}} / \text{plasma AUC}_{0-\text{last}})$, $\text{LogSB} = \log_{10}(\text{brain AUC}_{0-\text{last}} / \text{spinal cord AUC}_{0-\text{last}})$, $\text{Kp} = \text{brain AUC}_{0-\text{last}} / \text{plasma AUC}_{0-\text{last}}$ and $\text{Kp}_{\text{uu, brain}} = \text{AUC}_{\text{b,u}} / \text{AUC}_{\text{p,u}} = \text{AUC}_{\text{brain}} / \text{AUC}_{\text{plasma}} \times (\text{fu}_{\text{brain}} / \text{fu}_{\text{plasma}})$. The *in vivo* drug distribution result is shown in Table 7

Table 7: the *in vivo* drug distribution

Compounds	dosage	Brain /plasma, Kp	Spinal cord /plasma	logBB	logSB	Kp, uu, brain
Clonidine HCl	5 mg/kg	2.27	1.78	0.356	0.252	0.739
Dexmedetomidine HCl	5 mg/kg	1.26	1.14	0.101	0.133	1.17
1-B HCl	5 mg/kg	below detection limit*				
	80 mg/kg	0.0598	0.0153	-1.22	-0.732	0.032
44-B HCl	5 mg/kg	below detection limit*				
	80 mg/kg	0.0334	0.0511	-1.48	-1.29	0.013

* drug in brain and spinal cord is below the detection limit (DL). DL=10ng/mL. The distribution parameters are not available

Example 5. Efficacy study on spared nerve injury in mice

50 male C57BL/6 mice weighing between 20-30 g were subjected to spared nerve injury (SNI) surgery, of which 6 mice were as sham surgery and the others were of SNI surgery. A few days after SNI surgery, all animals were subjected to mechanical allodynia test to obtain baseline paw withdrawal threshold (PWT). The qualified mice baseline PWT <

0.6 g were randomly assigned to different groups (Vehicle group and test articles groups) based on baseline PWT and 6 sham mice as Sham group for evaluating efficacy of the test compounds, 8 mice in each group.

The animals were acclimated to the environment for 3-7 days after arriving at the animal facility. Three days before 1st mechanical allodynia test, the animals were habituated to the test environment for 15 minutes per day.

Aseptic techniques were employed by all surgeons, and all surgical instruments, including scissors, sharp forceps, scalpels, sterile cotton pads, needles, and metal clips, were sterilized prior to surgery. The animals were anesthetized with Zoletil 50 (50 mg/kg, 2.5 mL/kg, i.p.) and Xylazine Hydrochloride (8 mg/kg, 2.5 mL/kg, i.p.), with a toe pinch used to ensure full anesthesia before incision, and ophthalmic ointment applied to the rodents' eyes to prevent drying of the corneas. The fur on the posterior thigh was closely shaved, and the surgical area's skin was swabbed with three rounds of alternating Betadine and 70% ethanol, then allowed to dry. An incision was made on the lateral surface of the thigh, cutting through the biceps femoris muscle to expose the sciatic nerve and its terminal branches: the sural, common peroneal, and tibial nerves, with the common peroneal and tibial nerves being cut, leaving the sural nerve intact. The wound was closed in layers, with the skin sutured. Surgical instruments were cleaned and sterilized using a glass bead sterilizer post-operation. The animals recovered from anesthesia on a warm pad, were injected with 1 mL sterile saline subcutaneously to prevent dehydration, and returned to their home cage once fully awake and mobile.

On day 11, the animals were individually placed in plastic enclosures with mesh bottoms, allowing full paw access. For three consecutive days, mice were acclimated for 15 minutes each day. Mechanical allodynia baseline measurements were performed on day 14. Animals not exhibiting allodynia ($PWT > 0.6$ g) were excluded, leaving 24 qualified animals ($PWT < 0.6$ g) who were then randomly divided into three groups based on their baseline PWT, in addition to 6 sham mice forming a Sham group, totaling four groups with 6-8 mice each.

The administration route for the therapeutic intervention for compounds 1-B with a dosage from 1 mg/mL to 20 mg/mL, and 10-B, 44-B, 45-B, 46-B, 47-B, 121, 136, 118, 156 and 175 was oral (p.o.) with a dosage of 1 mg/mL, while the ones for 1 mg/kg morphine via s.c. and 3mg/kg pregabalin via p.o. as positive control, which were prepared in a 20% HP- β -CD solution. 1-B, 10-B, 44-B 45-B, 46-B and 47-B are the active enantiomer of 1, 10, 44, 45,

46, 47, respectively, while 121, 136, 118, and 156 are racemate. The solution was vortexed to ensure thorough mixing until homogeneous. The dosage administered to the mice was 10 ml/kg.

Mechanical allodynia tests were conducted on the left hind paw of mice, which were individually placed in plastic enclosures with mesh bottoms for full paw access and acclimated for 15 minutes prior to testing. Following acclimation, the mid-plantar hind paw was probed using a series of eight Von Frey filaments with logarithmically incremental stiffness: 0.02 g (2.36), 0.04 g (2.44), 0.07 g (2.83), 0.16 g (3.22), 0.4 g (3.61), 0.6 g (3.84), 1 g (4.08), and 1.4 g (4.17). The filaments were applied perpendicularly to the paw's plantar surface with enough force to slightly buckle against it, maintaining contact for 6-8 seconds. Tests were spaced by 5-second intervals to ensure clear resolution of any response to the prior stimulus, with a sharp withdrawal or flinching upon filament removal indicating a positive response. Ambulatory reactions were deemed ambiguous, prompting a repeat of the stimulus. Testing began with the 0.16 g (3.22) filament, adjusting the force of subsequent filaments up or down depending on the mouse's response, following the Dixon up-down method. The maximum force used was the 1.4 g (4.17) filament, with the criteria for a positive response being a distinct withdrawal of the paw or flinching immediately after the filament's removal.

Data were presented in Prism 8.0 (Graph Pad Software, Inc.) by one-way ANOVA or two-way ANOVA followed by Dunnett's or Tukey's multiple comparison or by t test followed by two-tailed comparison test. The results are demonstrated by Figs. 1A-1H.

Example 7. Efficacy on bone cancer pain model in mice

Animals were acclimatized to the environment for 3-7 days upon arrival at the facility. Male C3H/He mice were anesthetized with a combination of Zoletil 50 (50 mg/kg) and Xylazine Hydrochloride (8 mg/kg) administered via intraperitoneal injection, and positioned supinely. The right hind limb was shaved and sterilized. A minimal incision was made on the right hind leg to sever the patellar ligaments and expose the condyles of the distal femur. The proximal femur was perforated using a 0.3 mL syringe needle. A 10 μ L suspension containing 2×10^4 NCTC-2472 cells (suspended in a pellet formed from 2 mL of cell stock by centrifugation at 1000 rpm for 4 minutes, washed twice with 2 mL PBS, and resuspended in PBS at a concentration of 2×10^6 cells/mL) was slowly injected into the intramedullary cavity of the femur. Control group animals received a 10 μ L PBS injection (day 0). Animals were

subsequently acclimatized to the testing environment for an additional three days before baseline PWT measurements were initiated.

On day 14, baseline measurements for mechanical allodynia were conducted. Animals not exhibiting allodynia ($PWT > 0.6$ g) were excluded. The remaining qualified animals were then randomly assigned into four groups based on their baseline PWT values as outlined in section 5.1. The animals received a single injection of test compounds, including pregabalin 3mg/kg p.o., morphine 1mg/kg s.c., 44-B 1mg/kg p.o., as well as a group for 1-B 20mg/kg p.o. and 44-B 20mg/kg p.o. at a dose of 10 mL/kg based on body weight, and mechanical allodynia tests were performed at various time points post-administration as dictated by different experimental requirements with sham group and vehicle group. Each mouse was placed in a separate plastic enclosure with a mesh floor to freely access the paws and allowed to acclimate for 15 minutes prior to testing. Mechanical allodynia tests were conducted and analyzed as described in SNI model in example 6. The results are demonstrated by Figs. 2A-2D.

Example 8. Evaluation of the efficacy in post-surgery pain model in mice

Upon arrival at the facility, the animals were adaptively fed for 3 to 7 days. Additionally, for three days preceding the surgical procedures, all animals were placed in the test environment and acclimated daily for at least 15 minutes.

Aseptic techniques were rigorously applied by all surgeons. All surgical tools—including scissors, sharp forceps, scalpels, sterile cotton pads, needles, and metal clips—were sterilized prior to use. Animals were anesthetized using Zoletil 50 (50 mg/kg, 2.5 mL/kg, intraperitoneal) and Xylazine Hydrochloride (8 mg/kg, 2.5 mL/kg, intraperitoneal). A toe pinch confirmed deep anesthesia before any incisions were made. Ophthalmic ointment was applied to the animals' eyes to prevent corneal drying. The plantar aspect of the left hind paw was cleansed with three rounds of alternating Betadine and 70% ethanol applications, allowing the surface to air-dry. A 0.5-mm longitudinal incision was then made through the skin and fascia from 2 mm proximal to the heel towards the toes. The plantar muscle was longitudinally incised while preserving the origin and insertion points. Hemostasis was achieved with gentle pressure, and the skin was closed with two mattress sutures. Post-surgery, all surgical instruments were cleaned and re-sterilized using a glass bead sterilizer. Animals were allowed to recover from anesthesia on a heated recovery pad and were

hydrated with 1 mL of sterile saline orally to prevent dehydration. Once fully awake and mobile, the animals were returned to their home cages.

On the first day post-surgery, all animals, including those in the Naive group, were assessed for mechanical allodynia using a Touch-Test Sensory Evaluator. Surgical animals not displaying allodynia (PWT > 0.6 g) were excluded, leaving only 24 qualified surgical animals who were randomly assigned into three groups based on their baseline PWT, forming a total of four groups including the Naive group.

Animals were administered test compounds: morphine at 3 mg/mL s.c., 1-B HCl at 10 mg/mL p.o. and 44-B HCl at 10 mg/mL p.o., all at a dosage of 10 mL/kg based on body weight. Animals in the Naive group were also assessed but received no treatment.

Mechanical allodynia tests were conducted and analyzed as described in SNI model in example 6. The results are demonstrated by Figs. 3A-3C.

Example 9. *in vivo* Efficacy Study in the Treatment of Subcutaneous Colorectal Cancer Syngeneic Model MC38 in Female C57BL6/J Mice

The objective of this study is to evaluate the *in vivo* efficacy study of test articles in the Treatment of Subcutaneous Colorectal Cancer Syngeneic Model MC38 in Female C57BL6/J mice. The mice are *Mus musculus* C57BL6/J, female, supplied by Beijing HFK Bioscience Co. LTD, with an average age of 6-8 weeks. The cage is polysulfone IVC cage, with a temperature 20-26°C and humidity 40 - 70%. The light cycle is 12 hours light and 12 hours dark. The mice is feed by a diet of standard rodent chow, irradiated, ad libitum. The water is autoclaved filtered RO (reverse osmosis) softened, filtered water, ad libitum.

Clonidine and compound 1-B HCl were used as control and test articles, respectively, and the study is designed according to the following table. Due to the poor state of mice caused by high dose, the dose of clonidine in G2 group and 1-B HCl in G4 group was adjusted from 5mg/mL to 2mg/mL and 10mg/kg to 5mg/kg, respectively, starting from Day 4. The detailed design and formulation is in Table 8.

Table 8. Study design and formulation

Group	No. of mice	Treatment	Dose Level (mg/kg)	Dosing Solution (mg/mL)	Dosing Volume (μL/g)	ROA	Dosing Frequency & Duration
1	6	Vehicle	--	--	10	p.o.	QD×Day0~Day17
2	6	Clonidine	5	0.5	10	p.o.	QD×Day0~Day3

			2*	0.2	10	p.o.	QD×Day4~Day17
3	6	1-B HCl	5	0.5	10	p.o.	BID×Day0~Day17
4	6	1-B HCl	10	1	10	p.o.	BID×Day0~Day3
			5*	0.5	10	p.o.	QD×Day4~Day17

*dosage adjusted on day 4

The MC38 cancer cells were maintained *in vitro* with DMEM medium supplemented with 10% fetal bovine serum and 50µg/mL Hygromycin B at 37°C in an atmosphere of 5% CO₂ in air. The cells in exponential growth phase were harvested and quantitated by cell counter before tumor inoculation. Each mouse was inoculated subcutaneously at the right rear flank region with MC38 tumor cells (1×10^6) in 0.1 mL of PBS mixed with PBS for tumor development. The randomization started when the mean tumor size reached approximately 121.36 mm³. 30 mice were enrolled in the study. All animals were randomly allocated to 5 study groups, 6 mice in each group. Randomization was performed based on “Matched distribution” method. The date of randomization was denoted as day 0.

The treatment was initiated on the same day of randomization (day 0) per study design. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss (Body weights were measured twice per week after randomization), eye/hair matting and any other abnormalities. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured twice per week after randomization in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: “ $V = (L \times W \times W)/2$ ”, where V was tumor volume, L was tumor length (the longest tumor dimension) and W was tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using StudyDirector™ software (version 3.1.399.19).

The body weights of all animals were monitored throughout the study and animals were euthanized if they lose over 20% of their body weight relative to the weight on the day of randomization. Meanwhile, the individual mouse was euthanized if its tumor volume exceeds 3000 mm³. To deter cannibalization, any animal exhibiting an ulcerated or necrotic tumor were separated immediately and singly housed and monitored daily before the animal was euthanized or until tumor regression was completed. The mouse was euthanized rapidly

if a) tumor ulcerates, and the ulceration diameter was greater than 5 mm, or pus or necrosis observed, and b) tumor burden, including metastasis, compromises animal's normal physiologic performances, e.g., orientation, access to food or water, etc.

The body weight between randomization grouping is shown in FIG. 4A. The tumor growth of each treatment group and control group is shown in FIG. 4B. In day 17, the mice were sacrificed and the tumors were removed and measured. The data are shown in FIG. 4C. The tumor growth inhibition (TGI) and T/C were calculated based on the tumor size data of day 17, which is the last dosing day of the treatment. The Tumor volume were shown as the mean $\pm$ SEM, while the $T/C\% = \text{tumor volume of treatment group} / \text{tumor volume of control group} \times 100\%$. The $TGI\% = (1 - T/C) \times 100\%$. The pharmacodynamic analysis result is shown in Table 9.

Table 9: Pharmacodynamic analysis of each group in Subcutaneous Colorectal Cancer Syngeneic Model MC38

Group	D17			
	Tumor volume (mm ³) (mean $\pm$ SEM)	TGI (%)	T/C (%)	P Value (Compared with control group)
G1	2478.07 $\pm$ 439.10	--	--	--
G2	766.52 $\pm$ 147.17	72.62%	27.38	<0.05
G3	1009.16 $\pm$ 258.31	62.32%	37.68	<0.05
G4	996.54 $\pm$ 270.05	62.86%	37.14	<0.05

Example 10. Spontaneous Locomotor Activity in Mice

The study evaluated the effects of clonidine, brimonidine tartrate, compound 1-B HCl, compound 44-B HCl on spontaneous locomotor activity in male C57BL/6 mice. Initially, mice were acclimatized to the testing environment for 8 hours the day before the experiment, followed by at least 2 hours of habituation on the day of the test. The mice were then grouped randomly based on their body weight into six per group, ensuring a balanced distribution for the administration of the drug, which was dissolved in 20% HP- β -CD in water. On the test day, in one test, clonidine at a dose of 1mg/kg and compound 1-B HCl at concentrations of 1mg/kg, 10mg/kg, and 20mg/kg were freshly prepared and administered orally at a volume of 10mL/kg. In another test, clonidine at a dose of 1mg/kg, brimonidine tartrate at a dose of 1mg/kg and compound 44-B HCl at a dose of 1mg/kg were freshly prepared and administered orally at a volume of 10mL/kg.

The locomotor activity was monitored by placing the mice in the center of a test box, with a video tracking system measuring the distance traveled every 5 minutes for 60 minutes. The testing began at T=0 minutes, immediately after administering the vehicle or compounds, and concluded at T=60 minutes. For data analysis, Prism 8.3.0 software was utilized, employing Two-way ANOVA followed by Bonferroni's multiple comparison test to analyze distance variations across different time points and One-way ANOVA followed by Dunnett's multiple comparisons test for assessing the total distance covered by the groups. A significance level of $p < 0.05$ was established for determining significant differences. As demonstrated in FIG. 5, no significant sedation was observed after the treatment of compound 1-B HCl at 1mg/kg, 10mg/kg and 20mg/kg in the first assay and compound 44-B HCl at 1mg/kg in the second assay, while 1mg/kg of clonidine in the first assay and 1mg/kg brimonidine tartrate in the second assay leads to a significant sedation. The total distance between 0 to 60 minutes of the two tests is shown in Fig 5A and 5B.

Example 11. The effects on motor function in mice

Upon arrival at the facility, the animals were acclimated for one week. The day before the rotarod training commenced, mice were randomly assigned to groups based on their body weight to ensure homogeneity across the groups in terms of weight before any treatment was administered.

Rotarod training occurred two days prior to the testing phase. On the first training day, the mice underwent three trials on the rotarod at a speed of 6 rpm, each lasting 120 seconds, with 30-minute intervals between trials. If a mouse fell off before completing 120 seconds, it was immediately placed back on the rotarod to complete the training duration. The following day, the training consisted of a single trial at the same speed of 6 rpm but extended to 300 seconds. Mice that fell before the 300-second mark were similarly returned to the rotarod to ensure they reached the full training time.

On the test day, treatments were administered orally to the mice at a dosage volume of 10 mL/kg based on their body weight. The treatments included a vehicle, clonidine (1 mg/kg), and 44-B HCl at three dosages (1 mg/kg, 10 mg/kg, and 20 mg/kg). The time of compound administration was designated as time zero.

The rotarod test was conducted at 30, 60, and 120 minutes post-administration, with each session lasting 300 seconds at a speed of 6 rpm. The primary measure was the latency time

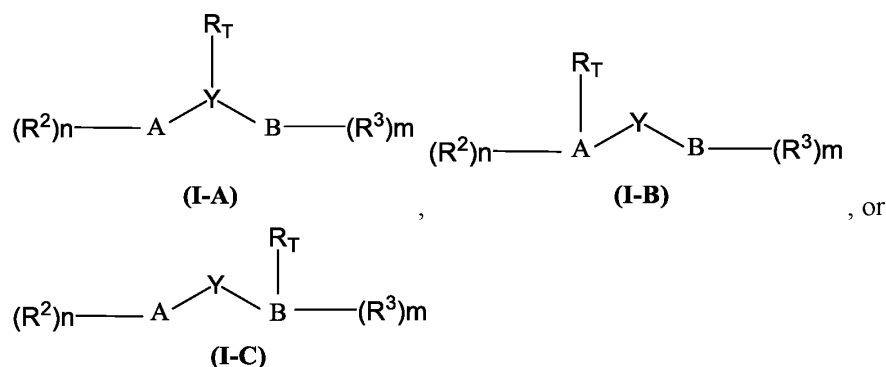
until a mouse fell from the rotarod, which served as an indicator of the compounds' effects on motor function.

Data were recorded in Microsoft Excel and subsequently analyzed using GraphPad Prism. Statistical significance was assessed with a threshold P-value of less than 0.05, indicating meaningful differences between treatment groups.

The detailed analysis method is described as follows. Initially, the data are assessed for normal distribution and homogeneity of variance. If the data adhere to both normal distribution and homogeneity of variance, a T-test is applied for comparisons involving two data sets, and a one-way ANOVA is utilized for analyses involving multiple data sets. In cases where the data exhibit normal distribution but heterogeneity of variance, Welch's T-test is used for two data sets, and a nonparametric test is employed for multiple data sets. If the data do not fit a normal distribution, the Mann-Whitney test is applied for two data sets, and the Kruskal-Wallis test is used for multiple data sets. The results are displayed in Fig. 6A to 6D.

CLAIMS

1. A compound of formula (I-A), (I-B), or (I-C):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

in formula (I-A),

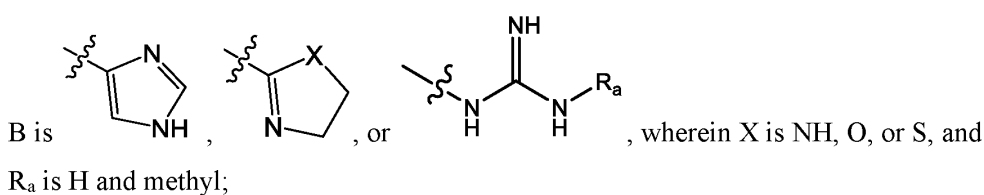
Y is C(R¹), N, -O-C-, -C-NH-, -CH₂-C(O)-, or -CH=N-;

when Y is C(R¹), R¹ is chosen from H, D, and halogen;

when Y is -O-C-, the oxygen atom is connected to A, and the carbon atom is connected to both R_T and B; and

when Y is -C-NH-, the carbon atom is connected to both R_T and A, and the nitrogen atom is connected to B;

A is a ring chosen from phenyl, pyridinyl, thienyl, furyl, pyrrolyl, 4H-pyran, 4H-thiopyran, 1,2,3,4-tetrahydro-1-naphthyl, tetrahydrozoline, quinoxaliny, pyrimidinyl, and 2,1,3-benzothiadiazol;



n is 0, 1, 2, or 3;

each R² is independently chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, OR⁴, -CN, N₃, NO₂, N(R⁴)₂, OR₄, SR⁴, C(O)R⁴, SO₂N(R⁴)₂, CH₂SR⁴; wherein the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl,

cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R^5 ;

R^4 is chosen from H, D, halogen, alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl, and the alkyl, alkenyl, alkynyl, alkoxy, ester, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclolalkyl is optionally substituted with one or more R^5 ;

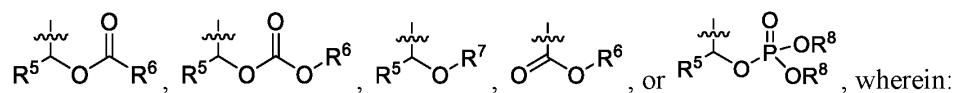
R^5 is chosen from halogen, hydroxyl, -CN, -NO₂, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

alternatively, when two R^2 are substituted at adjacent positions of the phenyl ring, the two R^2 groups, with the carbon atoms they are connected to, form a ring that is fused to ring A to form a bicyclic ring, such as quinolinyl, indolyl, benzothienyl, benzofuryl, benzofuranyl, benzodioxolyl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, cinnolinyl, quinoxaliny, or 1,2,4-benzotriazinyl;

m is 0, 1, 2, or 3;

each R^3 is independently chosen from H, D, halogen, -OH, -SH, optionally substituted alkyl, optionally substituted heterocycle, and optionally substituted aryl;

alternatively, R^3 is a group connected to the -NH of the imidazole ring, and R^3 is of the formula of:



R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, cycloalkyl, or alkenyl;

R^7 is an amino acid residue; and

R^8 is alkyl or cycloalkyl;

R_T is R_L-R_P , and R_P is optionally substituted with R_C , wherein:

R_L is a linker, wherein one end is connected to R_P and the other end is connected to Y;

R_P is a moiety that is connected to one end of R_L ; and

R_C is a cap, which is a moiety that is connected to R_P ;

in formula (I-B),

Y is a bond, $\text{CH}(\text{R}^1)$, NH , $-\text{O}-\text{CH}-$, $-\text{C}-\text{NH}-$, $-\text{CH}_2-\text{C}(\text{O})-$, or $-\text{CH}=\text{N}-$;

when Y is $\text{C}(\text{R}^1)$, R^1 is chosen from H, D, and halogen;

when Y is $-\text{O}-\text{C}-$, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is $-\text{C}-\text{NH}-$, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R^2 , n, R^3 , m, and R_T are defined as above in formula (I-A); and

in formula (I-C),

Y is a bond, $\text{CH}(\text{R}^1)$, NH , $-\text{O}-\text{CH}-$, $-\text{C}-\text{NH}-$, $-\text{CH}_2-\text{C}(\text{O})-$, or $-\text{CH}=\text{N}-$;

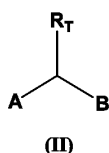
when Y is $\text{C}(\text{R}^1)$, R^1 is chosen from H, D, and halogen;

when Y is $-\text{O}-\text{C}-$, the oxygen atom is connected to A, and the carbon atom is connected to B;

when Y is $-\text{C}-\text{NH}-$, the carbon atom is connected to A, and the nitrogen atom is connected to B; and

A, B, R^2 , n, R^3 , m, and R_T are defined as above in formula (I-A).

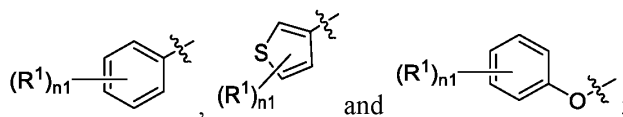
2. A compound of formula (II):



or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

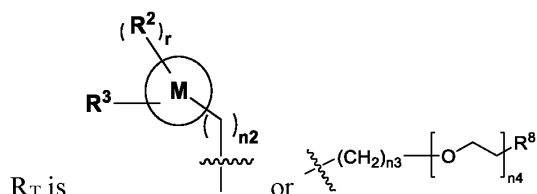
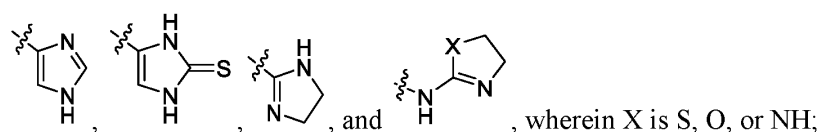
A is one chosen from:



n_1 is 1 or 2;

each R^1 is independently chosen from hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-\text{COOH}$;

B is one chosen from:



ring M is C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, C₆₋₁₂ aryl, or C₁₋₁₂ heteroaryl, wherein the C₃₋₁₂ cycloalkyl is optionally fused with an aryl;

r is 1 or 2;

n₂ is 0, 1, or 2;

each R² is independently chosen from hydrogen, halogen, hydroxyl, and alkoxy;

R³ is chosen from CN, hydroxy, alkoxy, -C(O)-C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -SO₂-alkyl, -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-R^{3'}, -O-C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R^{4'}),

; wherein one -CH₂- group in the -C₀₋₁₂ alkylene-R^{3'} is optionally replaced by oxygen atom or $\equiv$, the -C₀₋₁₂ alkylene-R^{3'} is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C₂₋₁₂ heterocyclyl and C₁₋₁₂ heteroaryl are each optionally substituted with one or more R^{4a};

R^{3'} is chosen from -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, and C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl;

each R^{4a} is independently chosen from hydroxy, alkyl, oxo, ketone, and -C₂₋₁₂ heterocyclyl;

each of R⁴ and R^{4'} is independently hydrogen, alkyl, alkoxy, -SO₂-N(R^{6a})_t, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or hydroxyalkyl, wherein the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

or R^4 and $R^{4'}$, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S;

alternatively, when one R^2 is adjacent to R^3 , the R^2 and R^3 , together with the atoms that they are attached to, form a ring optionally substituted with one or more R^{4a} ;

R^5 is amino, alkylamino, C_{1-12} haloalkyl, $-C_{0-12}$ alkylene-OR^{6a}, $-C_{0-12}$ alkylene-N(R^{6a})_t, $-C_{0-12}$ alkylene-SR^{6a}, $-C_{0-12}$ alkylene-CN, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{2-12}$ alkenyl, or alkyl optionally substituted with cyano, amido, trialkylammonium, or thiolate; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

each R^{6a} is independently chosen from hydrogen, C_{1-12} alkyl, C_{1-12} alkoxy, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{6-12} aryl, and $-C_{0-12}$ alkylene- C_{1-12} heteroaryl; wherein each of the alkyl, C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl, is optionally substituted with one or more R^{4a} ;

R^6 is alkoxy, amino, sulfonamide, carbamide, or alkyl optionally substituted with cyano;

R^7 is hydrogen, alkyl, $-C_{0-12}$ alkylene-COOH, optionally substituted C_{3-12} cycloalkyl, C_{2-12} aryl, C_{1-12} heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, $-C_{0-12}$ alkylene-P(=O)(R⁴)(R^{4'}), $-C_{0-12}$ alkylene-N(R⁴)-C(=S)-R⁵, $-C(=S)-R^5$, or alkyl optionally substituted with cyano;

R^8 is alkoxy, amino, alkylamino, amide, sulfonamide, or carbamide;

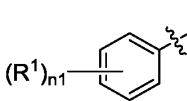
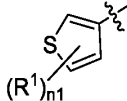
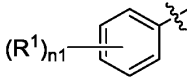
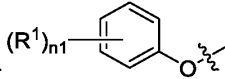
n_3 is 0, 1, 2, 3, or 4;

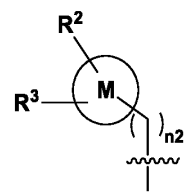
n_4 is 1, 2, 3, 4, 5, or 6;

t is 2 or 3;

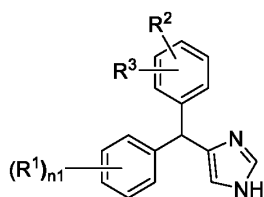
m is 0, 1, 2, 3, 4, or 5; and

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

3. The compound of claim 2, wherein A is  or .
4. The compound of claim 2, wherein A is  or .
5. The compound of any one of claims 2-4, wherein R^1 is alkyl or halogen.
6. The compound of any one of claims 2-5, wherein n_1 is 2.



7. The compound of any one of claims 2-6, wherein R_T is
8. The compound of any one of claims 2-7, wherein M is C_{6-12} aryl or C_{1-12} heteroaryl, such as phenyl, thiophenyl, pyrimidinyl, or pyridinyl.
9. The compound of any one of claims 2-8, wherein M is C_{3-12} cycloalkyl or C_{2-12} heterocyclyl, such as cyclopentyl, cyclohexyl or pyrrolidinyl, wherein the C_{3-12} cycloalkyl or C_{2-12} heterocyclyl is optionally fused with an aryl.
10. The compound of any one of claims 2-9, wherein R^2 is hydrogen or halogen.
11. The compound of any one of claims 2-10, wherein the pharmaceutically acceptable salt is trifluoroacetate or hydrochloride.
12. The compound of claim 2, being a compound of formula (II-A):



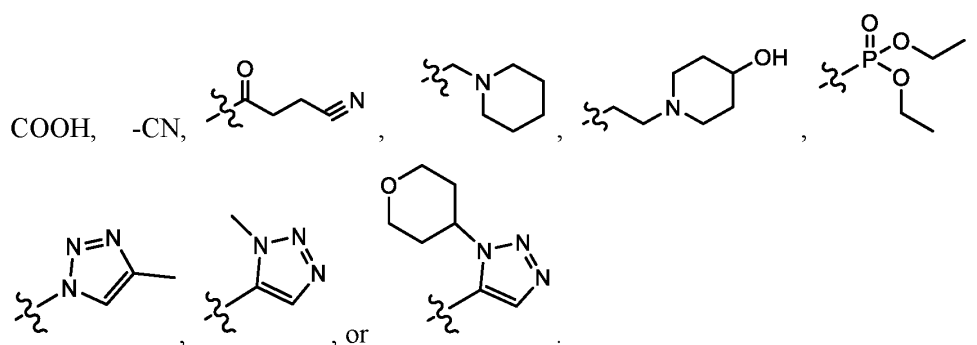
(II-A), wherein R^1 , R^2 , R^3 , and $n1$ are defined as in claim 2.

13. The compound of claim 12, wherein R^1 is halogen, haloalkyl, hydroxyl, alkyl, or $-COOH$.
14. The compound of claim 12 or 13, wherein $n1$ is 2.
15. The compound of any one of claims 12-14, wherein R^2 is hydrogen, hydroxyl, or halogen.
16. The compound of any one of claims 12-15, wherein R^3 is $-C(O)-NR^4R^{4'}$ or $-SO_2-NR^4R^{4'}$, wherein each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, $-C_{0-12}$ alkylene- $N(R^{6a})$, $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or hydroxyalkyl, and the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C_{3-12}

cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a}.

17. The compound of any one of claims 12-15, wherein R³ is C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, or -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, wherein R⁴ is hydrogen or alkyl, and R⁵ is amino, alkylamino, C₁₋₁₂ haloalkyl, -C₀₋₁₂ alkylene-OR^{6a}, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-SR^{6a}, -C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₂₋₁₂ alkenyl, or alkyl optionally substituted with cyano or amido; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a}.

18. The compound of any one of claims 12-15, wherein R³ is hydroxyl, -COOH, -CH(CH₃)-

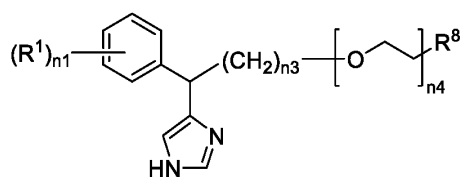


19. The compound of any one of claims 12-15, wherein R³ is $\text{--}[\text{O}(\text{CH}_2)_m\text{CH}_2\text{R}^6]_m$, m is 0, 1, 2, 3, 4, or 5, and R⁶ is sulfonamide, carbamide, or alkyl optionally substituted with cyano.

20. The compound of any one of claims 12-15, wherein R³ is -NH-R⁷, and R⁷ is hydrogen, optionally substituted C₃₋₁₂ cycloalkyl, C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R⁴'), -C₀₋₁₂ alkylene-N(R⁴)-C(=S)-R⁵, -C(=S)-R⁵, or alkyl optionally substituted with cyano.

21. The compound of any one of claims 12-15, wherein R³ is $\text{--}[\text{O}(\text{CH}_2)_n\text{CH}_2\text{OCH}_3]_n$, n is 3 or 4, particularly 4.

22. The compound of claim 2, being a compound of formula (II-B):



(II-B)

, wherein R^1 , R^8 , $n1$, $n3$, and $n4$ are defined

as in claim 2.

23. The compound of claim 22, wherein R^8 is $-OCH_3$, $-NH_2$, $-NHCH_3$, $-NHC(O)CH_3$, sulfonamide, or carbamide.

24. The compound of claim 23, wherein the sulfonamide is or .

25. The compound of claim 23, wherein the carbamide is or .

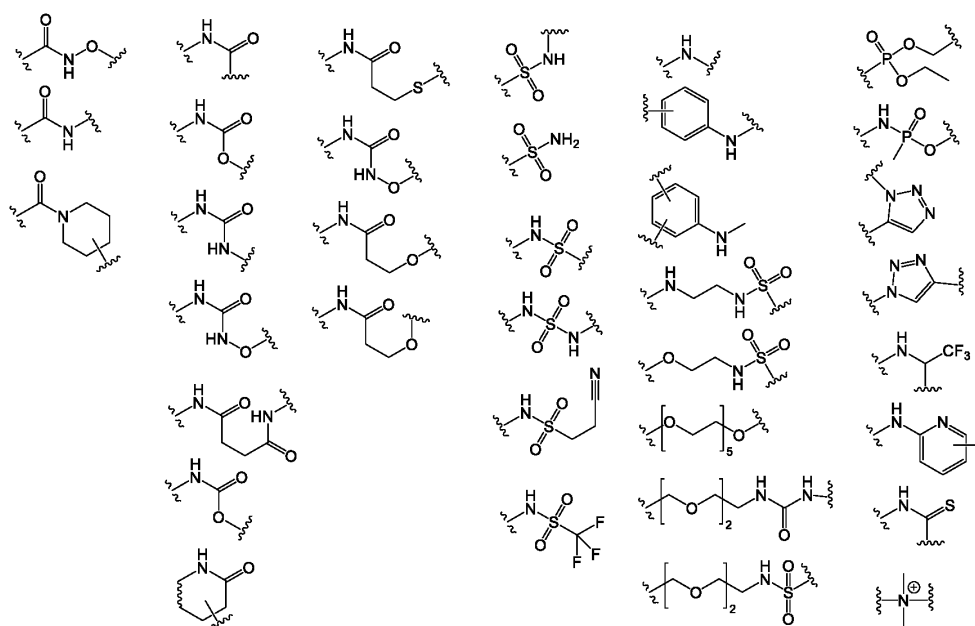
26. A compound chosen from Compounds 1-251, 401-403, 501-519, 601, and 602.

or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof.

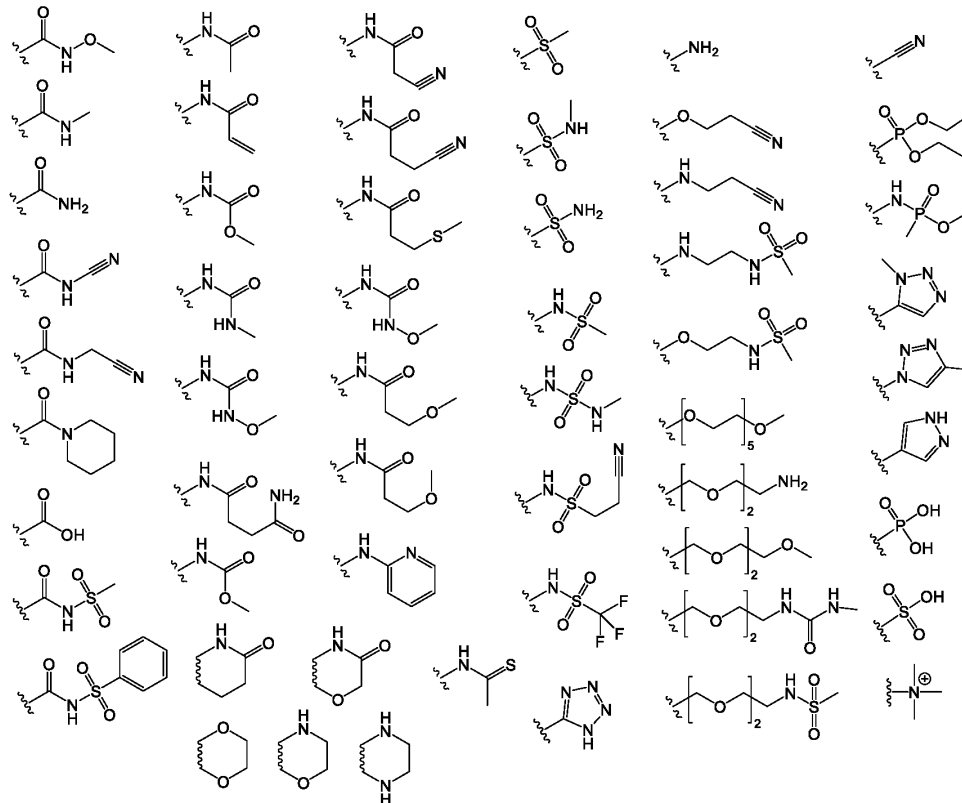
27. A pharmaceutical composition comprising the compound of any one of preceding claims, and a pharmaceutically acceptable carrier.
28. A method of treating or preventing a disease in a subject in need thereof, the method comprising administering to the subject the compound of any one claims 1-26 or the pharmaceutical composition of claim 27.
29. The method of claim 28, wherein the disease is pain, glaucoma, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, or cancer.
30. A method of activating alpha2 adrenergic receptor (α_2AR) in a subject in need thereof, the method comprising administering to the subject the compound of any one claims 1-26 or the pharmaceutical composition of claim 27.
31. A method of treating or preventing pain in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peripherally selective alpha2 adrenergic receptor (α_2AR) agonist.

32. The method of claim 31, wherein the peripherally selective α 2AR agonist has a K_p ,uu,brain is lower than 0.05, 0.02, or 0.01.
33. The method of claim 31 or 32, wherein the disease is neuropathic pain, nociceptive pain or mixed pain.
34. The method of any one of claims 31-33, wherein treating with the peripherally selective α 2AR agonist causes less sedation than treating with a non-peripherally selective α 2AR agonist.
35. The method of any one of claims 31-34, wherein the peripherally selective α 2AR agonist comprises an α 2AR activation moiety covalently linked to a peripheral distribution moiety.
36. The method of claim 31, wherein the α 2AR activation moiety is an α 2AR agonist.
37. The method of claim 36, wherein the α 2AR activation moiety is an α 2AR agonist chosen from (R)-3-nitrobiphenylene, A-193080, ADX-415, AGN 192836, AGN-191103, AGN-197075, AGN-201781, AGN-241622, amitraz, Apraclonidine, AR-08, Bethanidine, Brimonidine, BRL-48962, Bromocriptine, Cirazoline, Clonidine, Detomidine, Detomidine carboxylic acid, Dexmedetomidine, Dipivefrin, DL-Methylephedrine, Droxidopa, Epinephrine, ergotamine, etilefrine, Etomidate, Fadolmidine, Guanabenz, Guanethidine, Guanfacine, Guanoxabenz, indanidine, Lofexidine, Medetomidine, mephentermine, Metamfetamine, metaraminol, methoxamine, Methyldopa, Methyldopate, Methyldopate hydrochloride, Methylnorepinephrine, mivazerol, Moxonidine, naphazoline, Norepinephrine, norfenefrine, octopamine, ODM-105, Oxymetazoline, Pergolide, phenylpropanolamine, Povafonidine, propylhexedrine, Pseudoephedrine, Racepinephrine, rezatomidine, rilmenidine, romifidine, synephrine, talipexole, tasipimidine, Tiamenidine, Tizanidine, Xylazine, Xylometazoline, and a functional derivative thereof.
38. The method of claim 36 or 37, wherein the α 2AR activation moiety is dexmedetomidine.
39. The method of any one of claims 35-38, wherein the peripheral distribution moiety comprises a substrate element for an active efflux transporter.

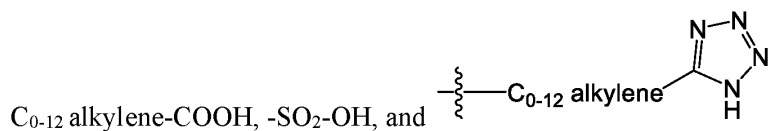
40. The method of claim 39, wherein the active efflux transporter is P-glycoprotein (P-gp).
41. The method of claim 40, wherein the substrate element is a fragment of a P-gp substrate, and the P-gp substrate has an efflux ratio of greater than 2, 5, 8, 10, 50, or 100.
42. The method of claim 39 or 40, wherein the substrate element for P-glycoprotein (P-gp) is chosen from:



, and

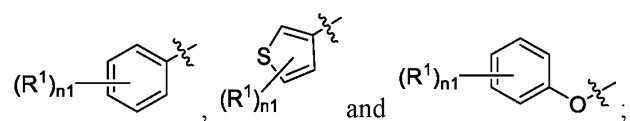


43. The method of claim 39, wherein the active efflux transporter is breast cancer resistance protein (BCRP) transporter.
44. The method of claim 39, wherein the active efflux transporter is multidrug resistance protein 2 (MRP2) transporter.
45. The method of any one of claim 35-38, wherein the peripheral distribution moiety comprises a structure chosen from: $-C_{0-12}$ alkylene-COOH, $-O-C_{0-12}$ alkylene-COOH, $-C_{0-12}$ alkylene-P(O)(OH)₂, $-C(O)-NH-SO_2-R^5$, $-C(O)-NH-C_{0-12}$ alkylene-COOH, $-NH-C_{0-12}$ alkylene-COOH, $-SO_2-OH$, and



46. The method of claim 35, wherein the $\alpha 2AR$ activation moiety has formula **A** **B**,
wherein,

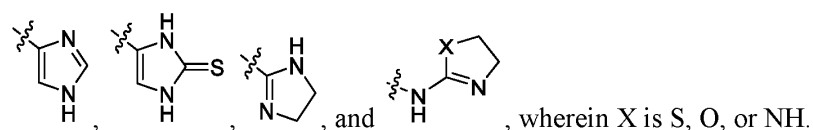
A is one chosen from:



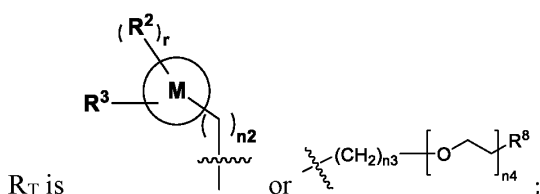
n_1 is 1 or 2;

each R¹ is independently chosen from hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and -COOH;

B is chosen from:



47. The method of claim 35, wherein the peripheral distribution moiety has formula , wherein,



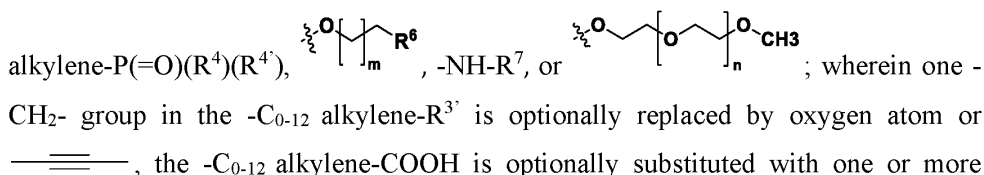
ring M is C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, C₆₋₁₂ aryl, or C₁₋₁₂ heteroaryl, wherein the C₃₋₁₂ cycloalkyl or C₂₋₁₂ heterocyclyl is optionally fused with an aryl;

r is 1 or 2;

n_2 is 0, 1, or 2;

each R² is independently chosen from hydrogen, halogen, hydroxyl, and alkoxy;

R³ is chosen from CN, hydroxy, alkoxy, -C(O)-C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -SO₂-alkyl, -C(O)-NR⁴R⁴, -SO₂-NR⁴R⁴, -C₀₋₁₂ alkylene-R³, -O-C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-O-C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂



substitutes chosen from amino and alkylamino, and the C₂₋₁₂ heterocyclyl and C₁₋₁₂ heteroaryl are each optionally substituted with one or more R^{4a};

R^{3'} is chosen from -C(O)-NR⁴R^{4'}, -SO₂-NR⁴R^{4'}, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R⁴)-C(O)-R⁵, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl;

each R^{4a} is independently chosen from hydroxy, alkyl, oxo, ketone, and -C₂₋₁₂ heterocyclyl;

each of R⁴ and R^{4'} is independently hydrogen, alkyl, alkoxy, -SO₂-N(R^{6a})_t, -C₀₋₁₂ alkylene-COOH, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-OR^{6a}, or hydroxyalkyl, wherein the hydroxyalkyl is optionally substituted with alkoxy; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

or R⁴ and R^{4'}, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms chosen from O, N, and S;

alternatively, when one R² is adjacent to R³, the R² and R³, together with the atoms that they are attached to, form a ring optionally substituted with one or more R^{4a};

R⁵ is amino, alkylamino, C₁₋₁₂ haloalkyl, -C₀₋₁₂ alkylene-OR^{6a}, -C₀₋₁₂ alkylene-N(R^{6a})_t, -C₀₋₁₂ alkylene-SR^{6a}, -C₀₋₁₂ alkylene-CN, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, -C₂₋₁₂ alkenyl, or alkyl optionally substituted with cyano, amido, trialkylammonium, or thiolate; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

each R^{6a} is independently chosen from hydrogen, C₁₋₁₂ alkyl, C₁₋₁₂ alkoxy, -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclyl, -C₀₋₁₂ alkylene-C₆₋₁₂ aryl, and -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl; wherein each of the alkyl, C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl, is optionally substituted with one or more R^{4a};

R⁶ is alkoxy, amino, sulfonamide, carbamide, or alkyl optionally substituted with cyano;

R⁷ is hydrogen, alkyl, -C₀₋₁₂ alkylene-COOH, optionally substituted C₃₋₁₂ cycloalkyl, C₂₋₁₂ aryl, C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R^{4'}), -C₀₋₁₂ alkylene-N(R⁴)-C(=S)-R⁵, -C(=S)-R⁵, or alkyl optionally substituted with cyano;

R⁸ is alkoxy, amino, alkylamino, amide, sulfonamide, or carbamide;

n₃ is 0, 1, 2, 3, or 4;

n₄ is 1, 2, 3, 4, 5, or 6;

t is 2 or 3;

m is 0, 1, 2, 3, 4, or 5; and

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

48. A process for making a peripheral acting α 2AR agonist, the process comprising covalently linking a non-peripherally selective α 2AR agonist to a peripheral distribution moiety.