

CROSS-REFERENCE TO RELATED APPLICATION

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higher CNS centers. This central action enables $\alpha 2$ AR agonists to produce significant analgesic effects, making them an important method for managing pain.

However, the therapeutic application of $\alpha 2$ AR agonists on analgesia comes with challenges, primarily due to the range of other biological adverse effects they can cause in CNS.

5 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 $\alpha 2$ AR agonists such as clonidine and dexmedetomidine are considered important for pain treatment in both academic research and clinical settings, the sedation effect poses

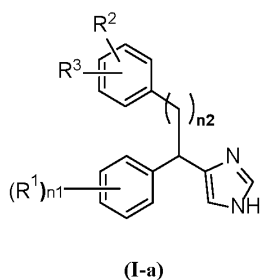
10 substantial hurdles to their widespread use in medical applications.

Therefore, it is desired to develop new classes of $\alpha 2$ 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.

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BRIEF SUMMARY OF THE DISCLOSURE

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



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

20 each R^1 is independently selected from the group consisting of hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-COOH$;

R^2 is selected from the group consisting of hydrogen, halogen, and hydroxyl;

R^3 is selected from the group consisting of $-C(O)-NHR^4$, $-SO_2-NHR^4$, $-NH-C(O)-R^5$, and $-NH-SO_2-R^5$, and $-NH-R^7$;

25 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-C₃₋₁₂ cycloalkyl, $-C_{0-12}$ alkylene-C₂₋₁₂ heterocyclyl, $-C_{0-12}$ alkylene-C₁₋₁₂ 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};

5 each R^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and ketone;

each R^{6a} is independently selected from the group consisting of $-C_{0-12}$ alkylene-C₃₋₁₂ cycloalkyl, $-C_{0-12}$ alkylene-C₂₋₁₂ heterocyclyl, and $-C_{0-12}$ alkylene-C₁₋₁₂ heteroaryl; wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is optionally substituted with one or
10 more R^{4a};

R^7 is C₁₋₁₂ heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, $-C_{0-12}$ alkylene-P(=O)(R⁴) (alkoxy), or $-C_{0-12}$ alkylene-C(=S)-R⁵;

n1 is 1 or 2; and

n2 is 0 or 1.

15 In some embodiments, R¹ is alkyl, such as methyl.

In some embodiments, n1 is 2.

In some embodiments, n2 is 1.

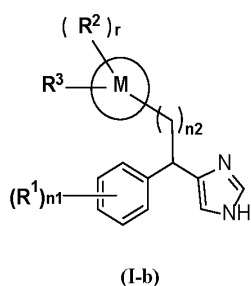
In some embodiments, R² is hydrogen or halogen.

In some embodiments, R³ is $-C(O)-NHR^4$ or $-SO_2-NHR^4$, wherein R⁴ is $-C_{0-12}$ alkylene-NHR^{6a}, $-C_{0-12}$ alkylene-C₃₋₁₂ cycloalkyl, $-C_{0-12}$ alkylene-C₂₋₁₂ heterocyclyl, $-C_{0-12}$ alkylene-C₁₋₁₂ 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
20 more R^{4a}, wherein R^{4a} and R^{6a} are defined as above.

In some embodiments, R³ is $-NH-C(O)-R^5$, or $-NH-SO_2-R^5$, wherein R⁵ is $-C_{0-12}$ alkylene-NHR^{6a}, $-C_{0-12}$ alkylene-C₃₋₁₂ cycloalkyl, $-C_{0-12}$ alkylene-C₂₋₁₂ heterocyclyl, $-C_{0-12}$ alkylene-C₁₋₁₂ 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}, wherein R^{4a} and R^{6a} are defined as above.

In some embodiments, R³ is $-NH-R^7$, wherein R⁷ is C₁₋₁₂ heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, or $-C_{0-12}$ alkylene-N(R⁴)-C(=S)-R⁵; wherein R⁴ and R⁵ are defined as above.
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In one 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,

each R^1 is independently selected from the group consisting of hydrogen, halogen,
5 haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-COOH$;

ring M is C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, C_{6-12} aryl, or C_{1-12} heteroaryl;

R^2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, haloalkyl,
and haloalkoxy;

R^3 is selected from the group consisting of $-C_{0-12}$ alkylene- $COOH$, $-C_{1-12}$ heteroaryl, $-C_{0-12}$
10 alkylene- $P(=O)(R^4)(R^{4'})$, and $-(SO_2)_{0-1}-NH-C_{0-12}$ alkylene- $COOH$; wherein the $-C_{0-12}$ alkylene- $COOH$ is optionally substituted with one or more substitutes chosen from amino and alkylamino,
and the C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

each R^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and
ketone;

15 each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, $-C_{0-12}$ alkylene- $N(R^{6a})_t$, $-C_{0-12}$ 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, wherein 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} ;

20 or R^4 and $R^{4'}$, together with the nitrogen atom that they are attached to, form a heterocycle comprising one or more heteroatoms selected from the group consisting of O, N, and S;

each R^{6a} is independently selected from the group consisting of 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, 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,
25 is optionally substituted with one or more R^{4a} ;

n_1 is 1 or 2;

n_2 is 1 or 2;

$r = 0, 1, \text{ or } 2$; and

t is 2 or 3.

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

In some embodiments, $n1$ is 2.

In some embodiments, M is C_{6-12} aryl or C_{1-12} heteroaryl, such as phenyl, thiophenyl,
5 pyrimidinyl, pyridinyl, or naphthyl.

In some embodiments, M is C_{3-12} cycloalkyl or C_{2-12} heterocyclyl, such as cyclopentyl, cyclohexyl, pyrrolidinyl, indolinyl, or 2,3-dihydro-1H-indenyl.

In some embodiments, $n2$ is 1.

In some embodiments, R^2 is hydrogen, halogen, alkyl, hydroxy, haloalkyl, or haloalkoxy.

10 In some embodiments, R^3 is $-C_{0-12}$ alkylene-COOH, and the $-C_{0-12}$ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino.

In some embodiments, R^3 is $-C_{1-12}$ heteroaryl that is optionally substituted with one or more R^{4a} .

In some embodiments, R^3 is $-C_{0-12}$ alkylene- $P(=O)(R^4)(R^{4'})$, such as $-P(O)(OH)_2$.

15 In some embodiments, R^3 is $-(SO_2)_{0-1}-NH-C_{0-12}$ alkylene-COOH, such as $-NH-CH_2-COOH$, or $-SO_2-NH-(CH_2)_2-COOH$.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein or a stereoisomer, tautomer, pharmaceutically
20 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 disease, including glaucoma, analgesia, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, cancer, etc. in a subject in need
25 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 invention. Based on the present disclosure, the skilled artisan
30 can identify and employ other components and methodology useful for practicing the present disclosure.

DETAILED DESCRIPTION OF THE DISCLOSURE

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
5 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 this invention
10 pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein.

It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference 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
20 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
25 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 combined 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
30 first. A third option refers to 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
5 includes all possible 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, to whom will be or has been treated by a method described herein. The term “mammal” as used herein, encompasses any
10 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
15 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,
20 maleate, gentisinate, fumarate, gluconate, glucuronate, 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 application 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
25 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),
30 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 a 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, “C₁ to C₁₀ alkenyl” or “C₁₋₁₀ alkenyl” is intended to include alkenyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ alkenyl” or “C₁₋₈ alkenyl” denotes an alkenyl having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

As used herein, the term “alkynyl” refers to a 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, “C₁ to C₁₀ alkynyl” or “C₁₋₁₀ alkynyl” is intended to include alkynyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ alkynyl” or “C₁₋₈ alkynyl” denotes an alkynyl having 1, 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. Examples of monocyclic heterocyclyl groups include, but are not limited to azetidiny, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, piperazinyl, dioxanyl, morpholinyl, azepanyl, oxepanyl, oxazepanyl (e.g., 1,4-oxazepanyl, 1,2-oxazepanyl) and the like. Examples of bicyclic heterocyclyl groups include, but are not limited to, 2-aza-bicyclo[2.2.1]heptanyl, 8-aza-bicyclo[3.2.1]octanyl,

2-aza-spiro[3.3]heptanyl, 3-azabicyclo[2.2.2]octanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 7-oxa-2-azaspiro[3.5]nonanyl, and 5-azaspiro[2.3]hexanyl 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→O and S(O)_r, wherein r is 0, 1 or 2).

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
5 (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.

10 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
15 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.

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

The term “carboxy” 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
25 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
30 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), hydroxylethyl (-CH₂CH₂OH), etc.

As used herein, “amide” refers to -N(R')C(O)R, wherein each R and R' is independently selected from the group consisting of 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 selected from the group consisting of 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 selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl. Examples of carbamide 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
5 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
10 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
15 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 subsequently can, but need not, occur, and such a description includes the situation in which the
20 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
25 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
30 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,
5 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
10 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
15 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
20 are included with the scope of the application.

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 of the application 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
25 either a stoichiometric or nonstoichiometric amount of the solvent molecules. “Solvate” encompasses both solution-phase and isolable solvates. Compounds of the application can form solvates with water (i.e., hydrates) or common organic solvents. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

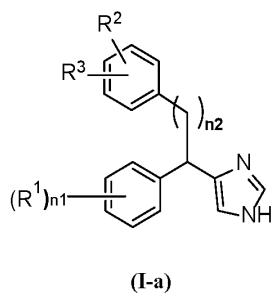
Also included within the scope of the application are all isotopes of atoms occurring in the
30 compounds described herein, including intermediates and final products. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation,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

The present disclosure further includes isotopically-labeled compounds described herein. 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.

Compounds

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



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

wherein,

each R^1 is independently selected from the group consisting of hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-COOH$;

R^2 is selected from the group consisting of hydrogen, halogen, and hydroxyl;

R^3 is selected from the group consisting of $-C(O)-NHR^4$, $-SO_2-NHR^4$, $-NH-C(O)-R^5$, 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^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and ketone;

each R^{6a} is independently selected from the group consisting of $-C_{0-12}$ 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- $C(=S)-R^5$;

$n1$ is 1 or 2; and

$n2$ is 0 or 1.

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

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

In some embodiments, R^1 is halogen, such as F.

In some embodiments, $n1$ is 1.

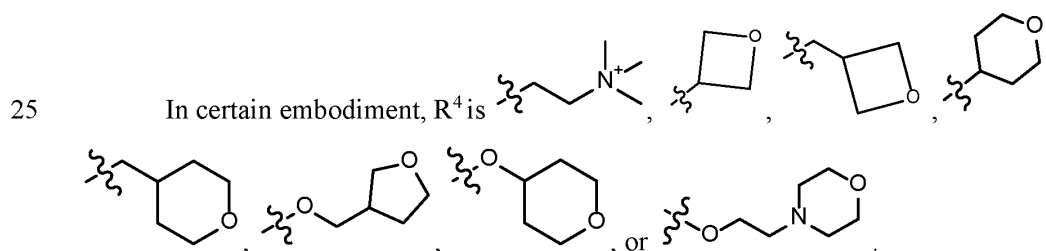
In some embodiments, $n1$ is 2.

In some embodiments, $n2$ is 0.

In some embodiments, $n2$ is 1.

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

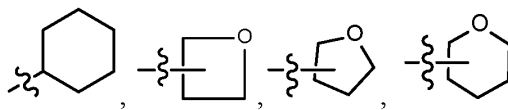
In some embodiments, R^3 is $-C(O)-NHR^4$ or $-SO_2-NHR^4$, wherein R^4 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with trialkylammonium; 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} , wherein R^{4a} and R^{6a} are defined as above.

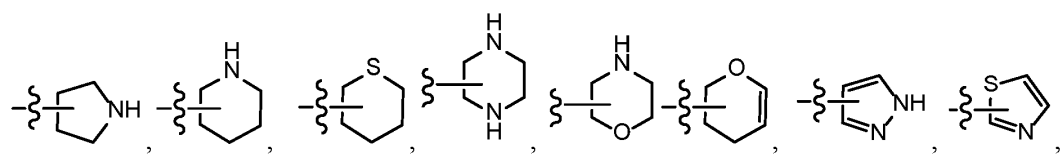


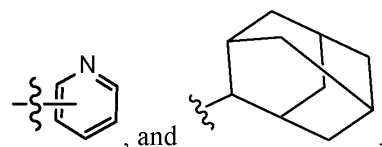
In some embodiments, R^3 is $-NH-C(O)-R^5$, or $-NH-SO_2-R^5$, wherein R^5 is $-C_{0-12}$ alkylene- NHR^{6a} , $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, $-C_{0-12}$ alkylene- OR^{6a} , or alkyl substituted with trialkylammonium; 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} , wherein R^{4a} and R^{6a} are defined as above.

In certain embodiments, R^5 is alkyl substituted with trialkylammonium.

In certain embodiments, when R^5 is $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, or $-C_{0-12}$ alkylene- C_{1-12} heteroaryl, the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12}

heteroaryl is selected from the group consisting of ,

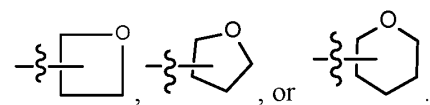
5 , ,

, and .

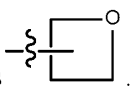
In certain embodiments, R^5 is alkyl substituted with trialkylammonium.

In certain embodiments, when R^5 is $-C_{0-12}$ alkylene-NHR^{6a}, R^{6a} is $-C_{0-12}$ alkylene- C_{3-12}

cycloalkyl or $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl. In further embodiments, R^{6a} is ,

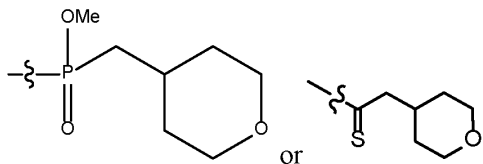
10 , or .

In certain embodiments, when R^5 is $-C_{0-12}$ alkylene-OR^{6a}, R^{6a} is $-C_{0-12}$ alkylene- C_{2-12}

heterocyclyl such as .

15 In certain embodiments, when each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is substituted with one or more R^{4a}, R^{4a} is hydroxyl, methyl, oxo, or $-C(O)-Me$.

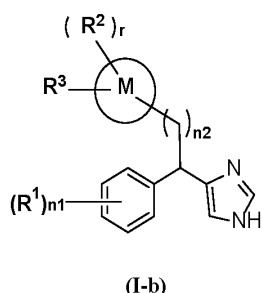
In some embodiments, R³ is $-NH-R^7$, wherein R⁷ is C_{1-12} heteroaryl, $-C_{0-12}$ alkylene-N(R⁴)-SO₂-R⁵, $-C_{0-12}$ alkylene-P(=O)(R⁴) (alkoxy), or $-C_{0-12}$ alkylene-C(=S)-R⁵; wherein R⁴ and R⁵ are defined as above.



In certain embodiments, R⁷ is

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

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



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

5 wherein,

each R^1 is independently selected from the group consisting of hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-COOH$;

ring M is C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, C_{6-12} aryl, or C_{1-12} heteroaryl;

10 R^2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, haloalkyl, and haloalkoxy;

R^3 is selected from the group consisting of $-C_{0-12}$ alkylene- $COOH$, $-C_{1-12}$ heteroaryl, $-C_{0-12}$ alkylene- $P(=O)(R^4)(R^{4'})$, and $-(SO_2)_{0-1}-NH-C_{0-12}$ alkylene- $COOH$; wherein the $-C_{0-12}$ alkylene- $COOH$ is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

15 each R^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and ketone;

20 each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, $-C_{0-12}$ alkylene- $N(R^{6a})_t$, $-C_{0-12}$ 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, wherein 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} ;

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

25 each R^{6a} is independently selected from the group consisting of 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, 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} ;

n_1 is 1 or 2;

n₂ is 1 or 2;

r = 0, 1, or 2; and

t is 2 or 3.

5 In some embodiments, R¹ is alkyl, such as methyl.

In some embodiments, R¹ is haloalkyl, such as -CH₂F.

In some embodiments, n₁ is 1.

In some embodiments, n₁ is 2.

10 In some embodiments, ring M is C₆₋₁₂ aryl or C₁₋₁₂ heteroaryl, such as phenyl, thiophenyl, pyrimidinyl, pyridinyl, or naphthyl.

In certain embodiments, ring M is monocyclic C₆₋₁₂ aryl or monocyclic C₁₋₁₂ heteroaryl, such as phenyl or pyridinyl.

In certain embodiments, ring M is bicyclic C₆₋₁₂ aryl such as naphthyl or bicyclic C₁₋₁₂ heteroaryl.

15 In some embodiments, ring M is C₃₋₁₂ cycloalkyl or C₂₋₁₂ heterocyclyl, such as cyclopentyl, cyclohexyl, pyrrolidinyl, indolinyl, or 2,3-dihydro-1H-indenyl.

In certain embodiments, ring M is monocyclic C₃₋₁₂ cycloalkyl or monocyclic C₂₋₁₂ heterocyclyl, such as cyclopentyl or cyclohexyl.

20 In certain embodiments, ring M is bicyclic C₃₋₁₂ cycloalkyl or bicyclic C₂₋₁₂ heterocyclyl, such as 2,3-dihydro-1H-indenyl or indolinyl.

In some embodiments, n₂ is 1.

In some embodiments, n₂ is 2.

In some embodiments, R² is hydrogen, halogen, hydroxy, alkyl, haloalkyl, or haloalkoxy.

In certain embodiments, R² is hydrogen.

25 In certain embodiments, R² is halogen, such as F and Cl.

In certain embodiments, R² is hydroxy.

In certain embodiments, R² is alkyl, such as methyl.

In certain embodiments, R² is haloalkyl, such as -CF₃.

In certain embodiments, R² is haloalkoxy, such as -OCF₃.

30 In some embodiments, r is 0, or r is 1 and R² is hydrogen.

In some embodiments, r is 1, and R² is hydroxyl or halogen.

In some embodiments, r is 1, and R² is alkyl, haloalkyl, or haloalkoxy.

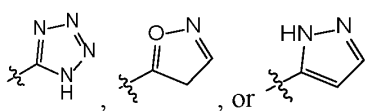
In some embodiments, r is 2. In certain embodiments, each R² is independently alkyl or halogen.

In some embodiments, at least one R^2 is alkyl, haloalkyl, or haloalkoxy.

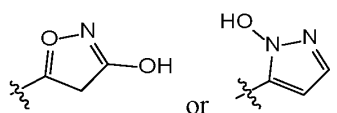
In some embodiments, R^3 is $-C_{0-12}$ alkylene-COOH, wherein the $-C_{0-12}$ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino.

In certain embodiments, R^3 is -COOH, $-\text{CH}_2\text{-COOH}$, $-\text{CH}(\text{CH}_3)\text{-COOH}$, $-\text{C}(\text{CH}_3)_2\text{-COOH}$, $-\text{CH}(\text{NH}_2)\text{-COOH}$, or $-\text{CH}(\text{NHCH}_3)\text{-COOH}$.

In some embodiments, R^3 is $-C_{1-12}$ heteroaryl that is optionally substituted with one or more R^{4a} .

In certain embodiments, R^3 is $-C_{1-12}$ heteroaryl, such as , or

In certain embodiments, R^3 is $-C_{1-12}$ heteroaryl substituted with one or more hydroxy,

such as .

In some embodiments, R^3 is $-C_{0-12}$ alkylene- $\text{P}(=\text{O})(\text{R}^4)(\text{R}^{4'})$, such as $-\text{P}(\text{O})(\text{OH})_2$.

In some embodiments, R^3 is $-(\text{SO}_2)_{0-1}\text{-NH-}C_{0-12}$ alkylene-COOH, such as $-\text{NH-CH}_2\text{-COOH}$, or $-\text{SO}_2\text{-NH-(CH}_2)_2\text{-COOH}$.

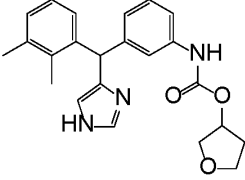
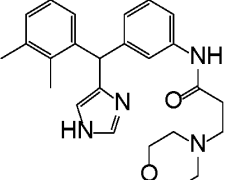
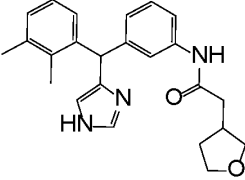
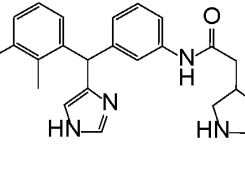
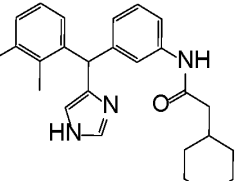
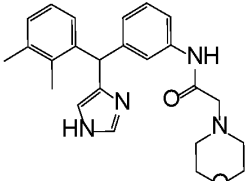
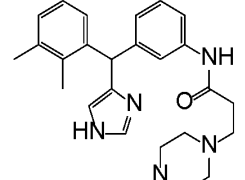
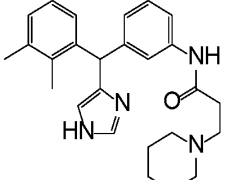
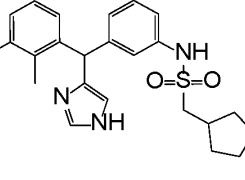
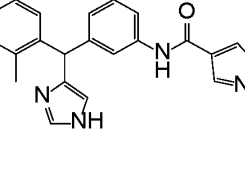
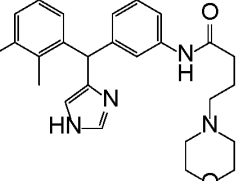
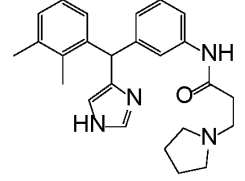
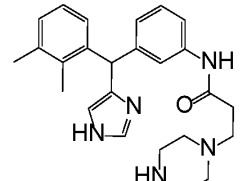
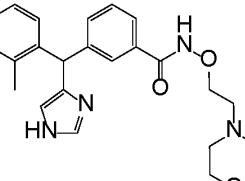
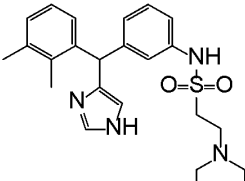
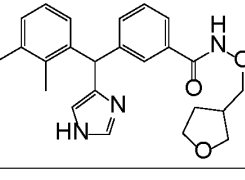
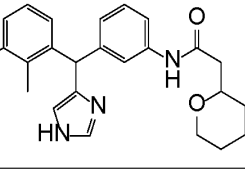
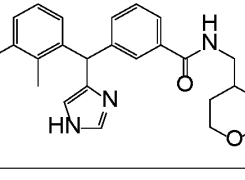
In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I-b) is trifluoroacetate or hydrochloride.

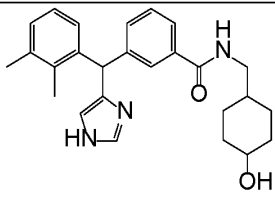
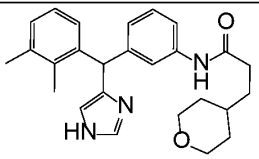
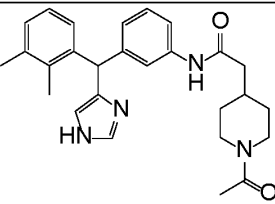
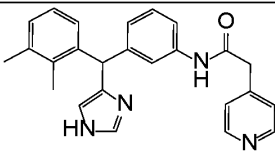
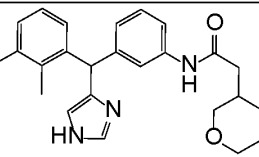
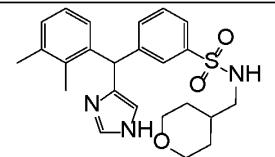
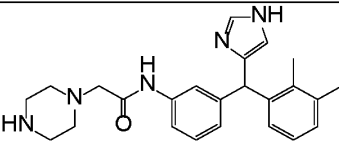
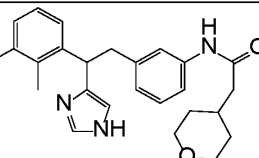
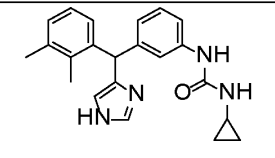
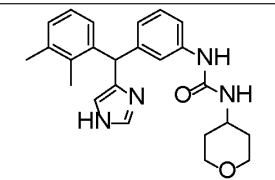
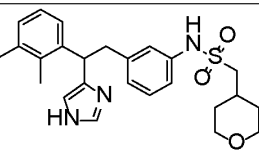
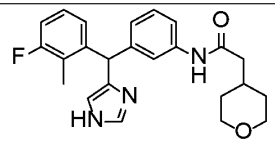
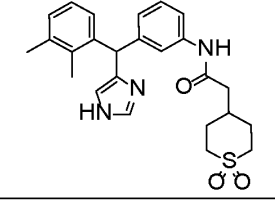
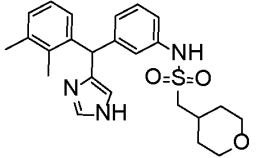
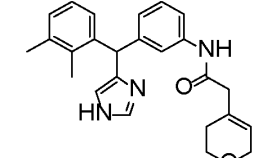
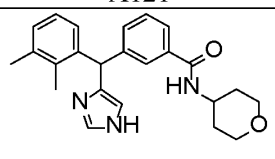
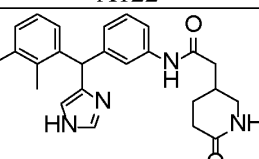
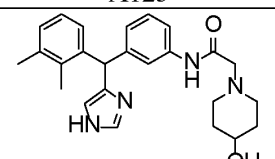
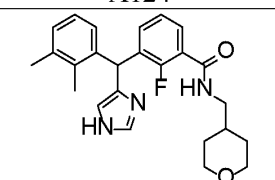
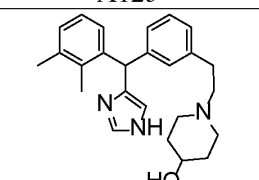
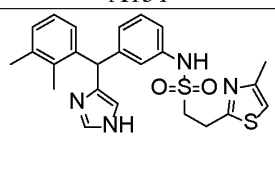
Exemplary compounds of formula (I-a) or formula (I-b) include, but are not limited to, the compounds described in this application, and any tautomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof.

All possible combinations of the above-indicated embodiments of compounds of formula (I-a) or formula (I-b) and their tautomers, stereoisomers, pharmaceutically acceptable salts and solvates are considered to be embraced within the scope of this application.

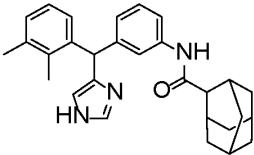
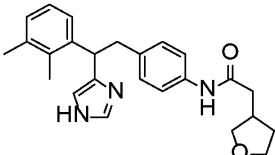
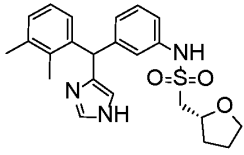
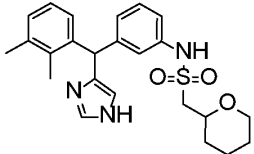
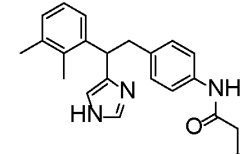
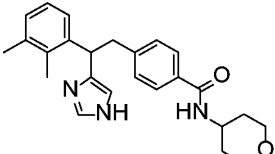
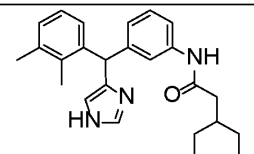
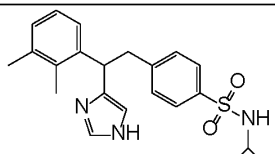
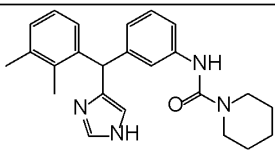
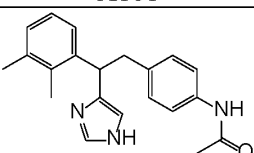
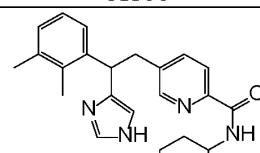
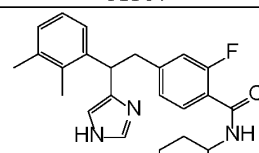
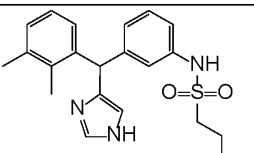
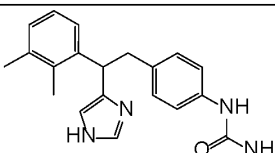
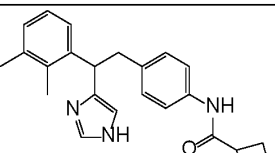
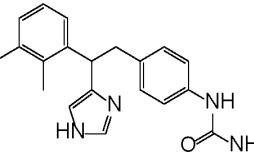
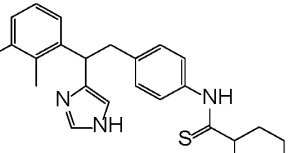
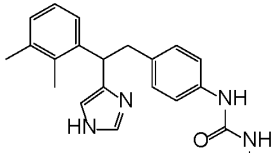
Exemplary compounds of formula (I-a) or formula (I-b) include, but are not limited to, the following compounds, and any tautomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof:

Table 1

A64	A70	A73
		
A79	A80	A81
		
A82	A84	A86
		
A87	A88	A89
		
A90	A91	A94
		
A95	A96	A98
		

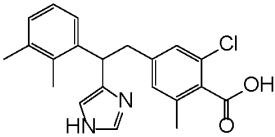
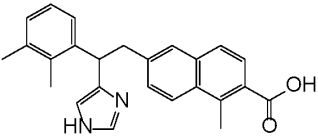
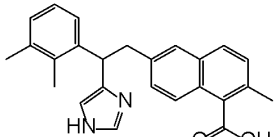
A99	A101	A102
		
A103	A104	A105
		
A107	A108	A109
		
A111	A112	A113
		
A117	A119	A120
		
A121	A122	A123
		
A124	A125	A131
		

A132	A134	A138
A141	A142	A143
144	145	149
151	152	153
A155	A157	A158
A161	A162	A165
A166	A167	A169

A170	A171	A172
		
A173	A176	A177
		
A178	A179	A180
		
A181	A186	A187
		
A189	A198	A200
		
A205	A212	A214
		

A233	A234	A706
A727	A906	A907
B1	B2	B3
B4	B7	B8
B9	B16	B17
B21	B22	B23
B24	B25	B26

B27	B28	B29
B30	B31	B32
B33	B34	B35
B36	B37	B38
B39	B40	B41
B42	B43	B44
B45	B46	B47
B48	B49	B50

B51	B52	B53
		

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.

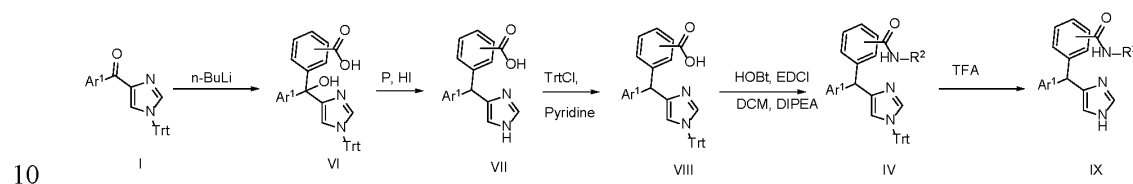
By way of illustration, but not as a limitation, compounds of formula (I-a) or (I-b) described herein can be prepared according to the following general preparation procedures shown in Scheme 1 and Scheme 2 as well as the examples shown in the present disclosure. One of ordinary skill in the art will recognize that, to obtain various compounds of formula (I-a) or (I-b) 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.

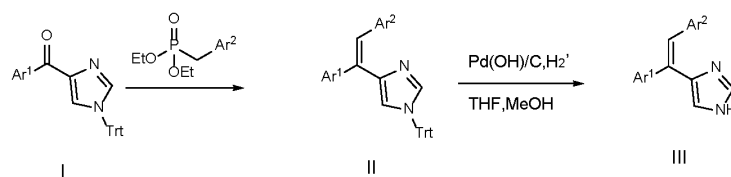
If no temperature or temperature range is stated, it is to be understood that the reaction is to be conducted at room temperature.

- 5 When isomerically pure samples are desired, isomeric mixtures of compounds synthesized according to Scheme 1 and Scheme 2 can be separated by chiral supercritical fluid chromatography (SFC) or high performance liquid chromatography (HPLC).

Scheme 1:



Scheme 2:



15 **Compositions**

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

- 20 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.,
- 25 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,

gencaps 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.

5 Compositions can be formulated in any matter 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,
10 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
15 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) or (I-b) or a stereoisomer, tautomer, pharmaceutically acceptable salt or solvate thereof, with at least one pharmaceutically acceptable
20 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) or (I-b) with one or more pharmaceutically acceptable carriers according to conventional
25 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 activating $\alpha 2AR$ and methods of treating or preventing a disease in a subject, using the compounds described herein or the composition
30 containing the compounds with one or more acceptable pharmaceutical carriers, describe herein.

 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 conditions, 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.

5 In some embodiments, the compounds of formula (I-a) or (I-b) can be useful for activating α 2AR.

In some embodiments, provided is a method of activating α 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.

10 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.

15 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.

20 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.

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

EXAMPLES

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

5 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;
- 10 “EA” or “EtOAc” refers to ethyl acetate;
- “PE” refers to petroleum ether;
- “r.t.” and “rt” refer to room temperature;
- “THF” refers to tetrahydrofuran;
- “DEAD” refers to diethyl azodicarboxylate;
- 15 “DIPEA” refers to diisopropylethylamine;
- “TBAB” refers to tetrabutylammonium bromide;
- “DCM” refers to dichloromethane;
- “HOBT” refers to hydroxybenzotriazole;
- “LAH” refers to lithium aluminum hydride;
- 20 “TLC” refers to thin layer chromatography;
- “Prep-TLC” refers to preparatory thin layer chromatography;
- “TMS-I” refers to trimethylsilyl iodide;
- “Hex” refers to hexanes;
- “DMF” refers to dimethylformamide;
- 25 “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;
- 30 “DHP” refers to dihydropyran;
- “DPPF” refers to 1,1'-Bis(diphenylphosphino)ferrocene; and
- “DIEA” refers to diisopropylethylamine.
- “NCS” refers to N-chlorosuccinimide.
- “TEA” refers to triethylamine.

“TFA” refers to trifluoroacetic acid.

“TES” refers to triethyl silane.

“Trt” refers to trityl group or triphenylmethyl group.

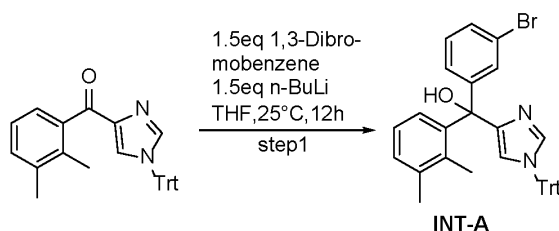
“m-CPBA” refers to meta-chloroperoxybenzoic acid.

5 “MeOH” refers to methanol.

“EtOH” refers to ethanol.

“i-PrOH” refers to isopropanol.

Synthesis of Intermediates

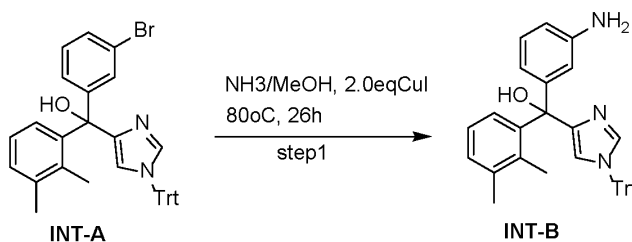


10

Step 1: A 500 mL reaction bottle was charged with THF (80 mL) and 1,3-dibromobenzene (8 g, 33.89 mmol, 1.5 eq). The reaction mixture was cooled to -78°C, and n-BuLi (13.56 mL, 33.89 mmol, 1.5 eq) was added dropwise. After stirring at -78°C for 1 hour, a solution of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (10 g, 22.6 mmol, 1.0 eq) in THF (100 mL) was added dropwise. The reaction was stirred at 28°C for 12 hours. LC-MS analysis confirmed the completion of the reaction. The reaction mixture was quenched with saturated NH₄Cl (200 mL), and the layers were separated. The aqueous phase was extracted with MTBE (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting crude product was purified by column chromatography to afford compound **INT-A** (12.4 g, 91.5% yield).

15

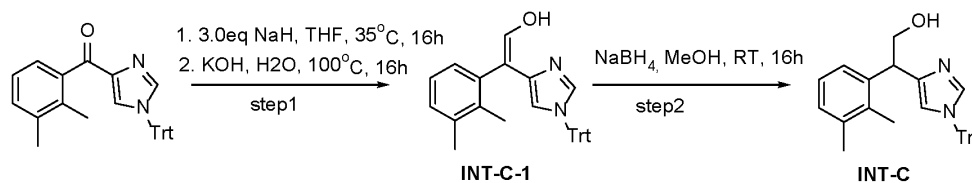
20



Step 1: A 200 mL hydrothermal reactor was charged with NH₃/MeOH (150 mL), INT-A (10 g, 16.68 mmol, 1.0 eq), and CuI (6.35 g, 33.36 mmol, 2.0 eq). The mixture was heated to 80°C and stirred for 26 hours. TLC analysis confirmed the completion of the reaction.

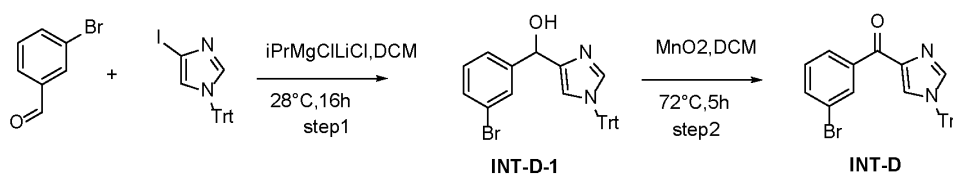
25 The reaction solution was poured into water (550 mL) and filtered. An additional batch using INT-A (4.3 g) was processed under the same conditions to prepare INT-B. The combined filter

cakes were dried overnight under infrared light. The crude product was purified by column chromatography (eluent: DCM/MeOH = 98:2 → 95:5 → 90:10) to obtain 4.8 g of compound **INT-B** as a light gray solid. **Yield: 37.57%.**



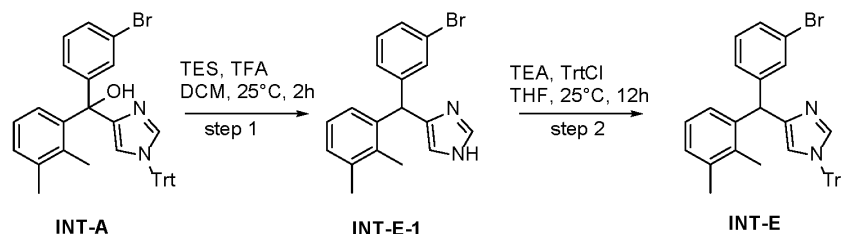
- 5 **Step 1:** A 250 mL single-neck flask was charged with THF (30 mL), (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (3 g, 6.8 mmol, 1.0 eq), ethyl chloroacetate (1.4 g, 10.9 mmol, 1.6 eq), and NaH (0.8 g, 20.4 mmol, 3.0 eq, 60% wt) under a nitrogen atmosphere. The reaction mixture was stirred at 35°C for 16 hours. LC-MS analysis confirmed the completion of the reaction. The mixture was concentrated under reduced pressure, and 10% KOH (50 mL) was
- 10 added. The resulting mixture was stirred at 100°C for 16 hours, then poured into water, extracted with ethyl acetate (EA), dried over Na₂SO₄, and purified by fast silica gel column chromatography to afford **INT-C-1** (1.7 g). **Yield: 57%.**

- Step 2:** A 250 mL single-neck flask was charged with THF (17 mL), MeOH (17 mL), and **INT-C-1** (1.7 g, 3.7 mmol, 1.0 eq) under a nitrogen atmosphere. NaBH₄ (0.43 g, 11.1 mmol, 3.0 eq)
- 15 was added, and the reaction mixture was stirred at 25°C for 16 hours. LC-MS analysis confirmed the completion of the reaction. The mixture was poured into water, extracted with EA, dried over Na₂SO₄, and purified by fast silica gel column chromatography to afford **INT-C** (1.4 g). **Yield: 82%.**



- 20 **Step 1:** A 100 mL reaction flask was charged with DCM (50 mL) and 4-iodo-1-tritylimidazole (11.8 g, 0.027 mol, 1.0 eq). The mixture was cooled to 0°C, and iPrMgCl·LiCl (1.3 mol/L, 20.7 mL, 0.027 mol, 1.0 eq) was added dropwise. The reaction mixture was stirred at 0°C for 2 hours, then 3-bromobenzaldehyde (5 g, 0.027 mol, 1.0 eq) was added. The mixture was stirred at 28°C for 16 hours. LC-MS analysis confirmed the completion of the reaction.
- 25 The reaction mixture was cooled to 0°C, and saturated ammonium chloride (44 mL) was added. The organic phase was separated and concentrated under vacuum. The residue was purified by column chromatography (eluent: ethyl acetate) to afford **INT-D-1** (7.1 g). **Yield: 53%.**

Step 2: A 200 mL high-pressure tube was charged with DCM (180 mL), **INT-D-1** (6.1 g, 12.35 mmol, 1.0 eq), and MnO₂ (6.44 g, 74.1 mmol, 6.0 eq). The reaction mixture was stirred at 72°C for 5 hours. LC-MS analysis confirmed the completion of the reaction. The mixture was filtered, and the residue was collected to afford **INT-D** (5.6 g). **Yield: 83.9%.**



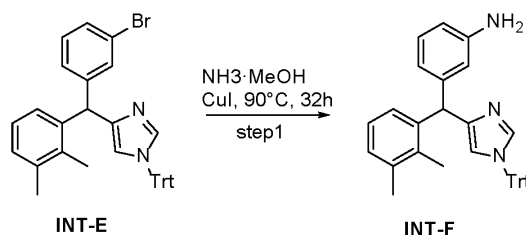
5

Step 1: A 250 mL reaction bottle was charged with DCM (70 mL), **INT-A** (15 g, 25.02 mmol, 1.0 eq), triethylsilane (TES, 32.69 mL, 0.25 mol, 10.0 eq), and trifluoroacetic acid (TFA, 19.16 mL, 0.25 mol, 10.0 eq). The mixture was stirred at 25°C for 2 hours. LC-MS analysis confirmed the completion of the reaction.

10 The reaction mixture was adjusted to pH 10 with 1 N NaOH and the aqueous phase was extracted with DCM (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography to afford **INT-E-1** (7 g). **Yield: 81.9%.**

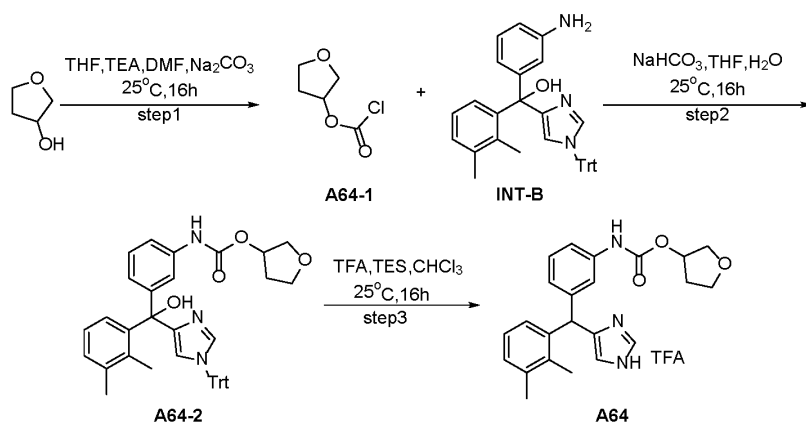
Step 2: A 250 mL reaction bottle was charged with DMF (50 mL), **INT-E-1** (5 g, 14.65 mmol, 1.0 eq), triethylamine (TEA, 2.97 g, 29.3 mmol, 2.0 eq), and trityl chloride (TrtCl, 4.9 g, 17.58 mmol, 1.2 eq). The mixture was stirred until LC-MS analysis confirmed completion of the reaction. The reaction was poured into water (20 mL) and the aqueous phase was extracted with ethyl acetate (EA, 20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography to afford **INT-E** (6 g). **Yield: 70%.**

20



Step 1: A 250 mL reaction bottle was charged with NH₃ in MeOH (10 mL), **INT-E** (0.6 g, 1.03 mmol, 1.0 eq), and CuI (587.43 mg, 3.08 mmol, 3.0 eq). The reaction mixture was stirred at 90°C for 32 hours. LC-MS analysis confirmed the completion of the reaction. The reaction mixture was poured into water (20 mL) and filtered. The solid was collected to afford **INT-F** (300 mg). **Yield: 56.17%.**

25

Example 1. Synthesis of Compound A64

Step 1: A 250 mL three-necked flask was charged with THF (100 mL), triphosgene (17 g,

5 0.0568 mol, 0.5 eq), and a drop of DMF. The mixture was cooled to 0°C, and sodium carbonate (12 g, 0.1136 mol, 1.0 eq) was added while maintaining the temperature at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. A solution of 3-hydroxytetrahydrofuran (10 g, 0.1136 mol, 1.0 eq) in THF (20 mL) was then added dropwise at 0°C. The reaction was stirred overnight at room temperature. GC analysis confirmed completion of the reaction.

10 The mixture was treated with water (100 mL) at 5°C, and the aqueous phase was extracted with ethyl acetate (EA). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **A64-1** (15 g) as a yellow oil. **Yield: 97%.**

Step 2: A 25 mL three-necked flask was charged with THF (10 mL), **INT-B** (500 mg, 0.934

15 mmol, 1.0 eq), sodium bicarbonate (172 mg, 2.053 mmol, 2.2 eq), and water (5 mL). The mixture was cooled to 0°C, and a solution of **A64-1** (210 mg, 1.4001 mmol, 1.5 eq) in THF (5 mL) was added at 0°C. The reaction mixture was stirred overnight at room temperature. LC-MS analysis confirmed the completion of the reaction.

The mixture was poured into water and extracted with EA. The organic phase was dried over

20 Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **A64-2** (461 mg). **Yield: 24.7%.**

Step 3: A 10 mL three-necked flask was charged with chloroform (3 mL), **A64-2** (270 mg,

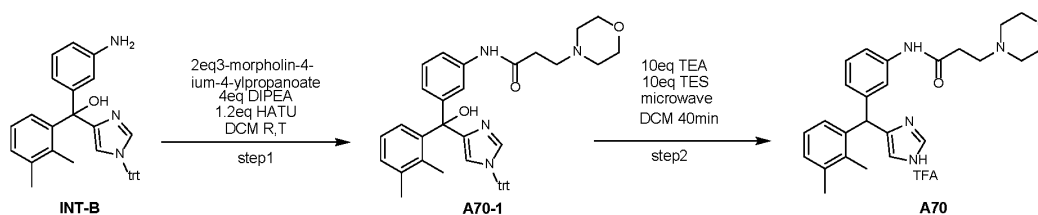
0.416 mmol, 1.0 eq), and trifluoroacetic acid (TFA, 711 mg, 6.24 mmol, 15.0 eq). The mixture was cooled to 0°C, and triethylsilane (TES, 121 mg, 1.04 mmol, 2.5 eq) was added at 10°C. The

25 reaction mixture was stirred overnight at room temperature. LC-MS analysis showed that the reaction was incomplete. An additional portion of triethoxysilane (60 mg, 0.5 mmol, 1.2 eq) was

added at 10°C, and the mixture was stirred overnight at room temperature. LC-MS analysis confirmed completion of the reaction.

The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **130 mg of crude product**. The crude product was further purified by preparative liquid chromatography to afford **A64** (54 mg) as a white solid. **Yield: 33.2%.**

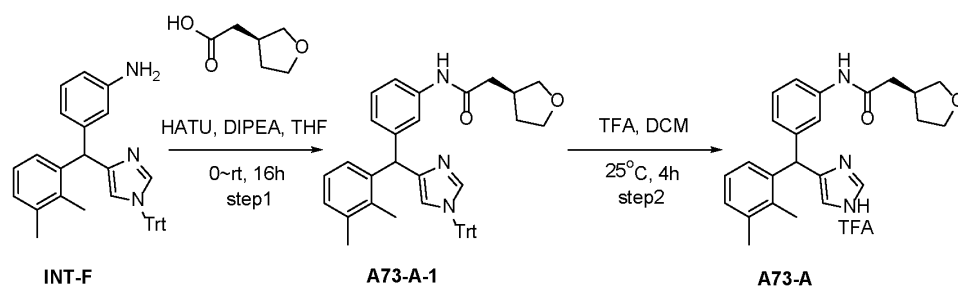
Example 2. Synthesis of Compound A70



Step 1: To a 25 mL three-port flask was added DCM (10 mL), **INT-B** (500 mg, 0.933 mmol, 1.0 eq), DIPEA (482 mg, 3.733 mmol, 4.0 eq), and 3-morpholin-4-ium-4-ylpropanoate (297 mg, 1.867 mmol, 2.0 eq). HATU (426 mg, 1.12 mmol, 1.2 eq) was added to the mixture at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 hours. LC-MS analysis confirmed the completion of the reaction. The mixture was poured into water and extracted with ethyl acetate (EA). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford a crude product. The crude was purified by column chromatography to afford **A70-1** (630 mg). **Yield: 99.7%.**

Step 2: To a 10 mL single-port flask was added DCM (5 mL), **A70-1** (240 mg, 0.35 mmol, 1.0 eq), TFA (404 mg, 3.54 mmol, 10.0 eq), and TES (412 mg, 3.54 mmol, 10.0 eq). The reaction mixture was stirred at 100°C for 40 minutes using a microwave reactor. LC-MS analysis confirmed the completion of the reaction. The solvent was then concentrated under reduced pressure. The residue was purified by preparative HPLC to afford **A70** (40 mg) as a white solid. **Yield: 17.4%.**

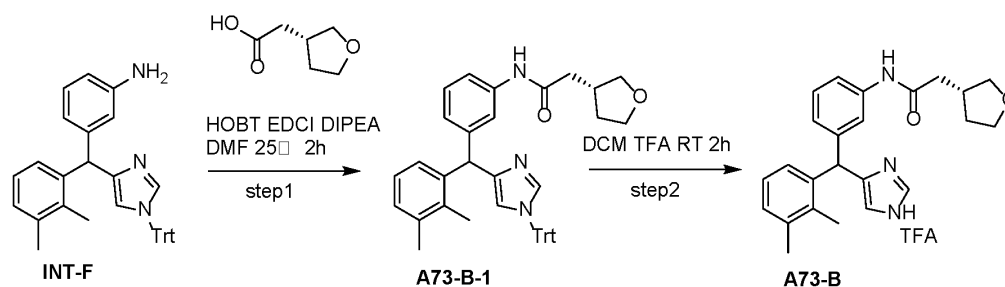
Overall yield: 17.3%.

Example 3. Synthesis of Compounds A73-A and A73-B

Step 1: A 25 mL single-mouth flask bottom was added with 10 mL THF, **INT-F** (0.2 g, 0.4 mmol, 1.0 eq), DIPEA (0.16 g, 1.2 mmol, 3.0 eq), and (S)-2-(tetrahydrofuran-3-yl)acetic acid (0.06 g, 0.4 mmol, 1.0 eq) under a nitrogen atmosphere. The reaction mixture was stirred to 0°C, followed by the addition of HATU (0.23 g, 0.6 mmol, 1.5 eq). After stirring at room temperature for 16 hours, LC-MS showed the reaction was completed. The mixture was poured into water, washed with ethyl acetate (EA), dried over Na₂SO₄, and purified by TLC to afford **A73-A-1** (0.4 g, crude).

Step 2: The reaction flask bottom was added with 12 mL DCM and **A73-A-1** (0.4 g, 0.44 mmol, 1.0 eq) under a nitrogen atmosphere. The reaction mixture was cooled to 0°C, followed by the addition of TFA (1 g, 8.8 mmol, 20 eq). The reaction was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the crude product was purified by preparative HPLC to afford **A73-A** (0.03 g). **Yield: 13.53%.**

Overall yield: 13.53%.

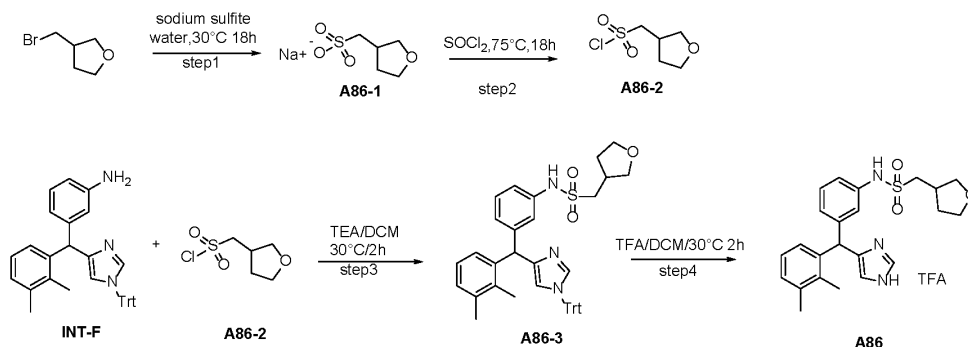


Step 1: A 10 mL three-necked flask was added 1 mL DMF, **INT-F** (100 mg, 0.19 mmol, 1.0 eq), (R)-2-(tetrahydrofuran-3-yl)acetic acid (30 mg, 0.23 mmol, 1.2 eq), HOBT (39 mg, 0.29 mmol, 1.5 eq), EDCI (56 mg, 0.29 mmol, 1.5 eq), and DIPEA (124 mg, 0.96 mmol, 5.0 eq). The reaction was stirred at 25°C for 1 h. LC-MS showed the reaction was completed. The solution was poured into water, extracted by EA, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (DCM: MeOH = 20:1) to afford 57 mg compound **A73-B-1**. **Yield: 47%.**

Step 2: A 25 mL reaction flask was added 1 mL DCM, **A73-B-1** (57 mg, 0.09 mmol, 1.0 eq), and TFA (1 mL). The reaction was stirred at 25°C for 2 h. LC-MS showed the reaction was completed. The mixture was concentrated under reduced pressure. The crude was purified by preparative HPLC to afford 27.4 mg compound **A73-B**. **Yield: 60%.**

5 **Overall yield: 28.2%.**

Example 4. Synthesis of Compound A86



10 **Step 1:** A 50 mL reaction bottle was added with 20 mL saturated sodium sulfite aqueous solution and 3-(bromomethyl)oxolane (2 g, 0.0122 mol, 1.0 eq). The reaction was stirred overnight at room temperature. After the reaction was completed, the mixture was concentrated under vacuum. The residue was added to 40 mL ethanol, stirred for 30 minutes at 50°C, filtered, and dried under vacuum at 50°C to afford **A86-1** (2.5 g). **Yield: 99.9%.**

15 **Step 2:** A 25 mL reaction flask was added with 8.5 mL thionyl chloride and **A86-1** (500 mg, 2.66 mmol, 1.0 eq). The mixture was stirred overnight at 80°C. The solution was concentrated four times with DCM and once with 10 mL to afford **A86-2** (590 mg). **Yield: 99.9%.**

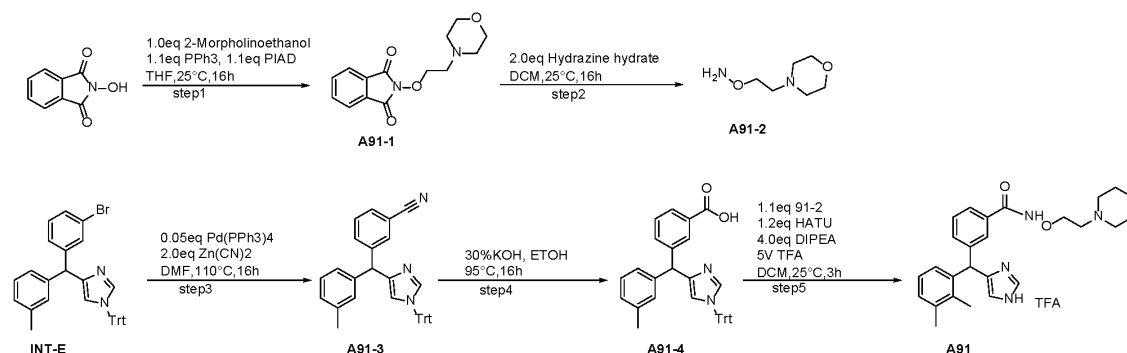
20 **Step 3:** A 5 mL reaction flask was added with 2 mL DCM, followed by **INT-F** (50 mg, 0.0962 mmol, 1.0 eq) and TEA (40 mg, 1.868 mmol, 4.0 eq). The mixture was cooled to 0°C, and **A86-2** (286 mg, 1.868 mmol, 2.0 eq) was added. The reaction was stirred at 30°C for 1.5 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to 0°C, and 1 mL water was added. The organic phase was separated and extracted once with 1 mL DCM. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to afford the crude product. The residue was purified by column chromatography to afford **A86-3** (52 mg). **Yield: 81.0%.**

25 **Step 4:** A 5 mL reaction flask was added with 1 mL DCM, 0.5 mL TFA, and **A86-3** (52 mg, 0.078 mmol, 1.0 eq). The reaction mixture was stirred at 28°C for 2 hours. LC-MS showed the

reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **A86** (20 mg). **Yield: 47.5%.**

Overall yield: 38.5%.

5 Example 5. Synthesis of Compound A91



Step 1: A 500 mL reaction flask was added with 250 mL THF, 2-morpholinoethanol (25 g, 0.19 mol, 1.0 eq), N-hydroxyphthalimide (31 g, 0.19 mol, 1.0 eq), and PPh₃ (55 g, 0.21 mol, 1.1 eq). After cooling to 0°C, DIAD (42.3 g, 0.21 mol, 1.1 eq) was added. The reaction mixture was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by column chromatography to afford **A91-1** (25 g). **Yield: 47.4%.**

Step 2: A 500 mL reaction flask was added with 250 mL DCM, **A91-1** (25 g, 0.09 mol, 1.0 eq), and hydrazine hydrate (10.6 g, 0.18 mol, 2.0 eq). The mixture was stirred at 27°C for 16 hours. LC-MS showed the reaction was completed. The mixture was filtered and concentrated to obtain 20 g of crude product. The crude was then dissolved in 200 mL DCM and 50 mL of 4 M HCl in dioxane. The resulting mixture was stirred at 25°C for 1 hour, then filtered to obtain **A91-2** (4.3 g). **Yield: 36.4%.**

Step 3: A 10 mL sealed tube was added with 5 mL DMF, **INT-E** (500 mg, 1.47 mmol, 1.0 eq), Zn(CN)₂ (343 mg, 2.93 mmol, 2.0 eq), and Pd(PPh₃)₄ (85 mg, 0.07 mmol, 0.05 eq). The mixture was heated to 110°C and stirred for 16 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by column chromatography to afford **A91-3** (320 mg). **Yield: 75.5%.**

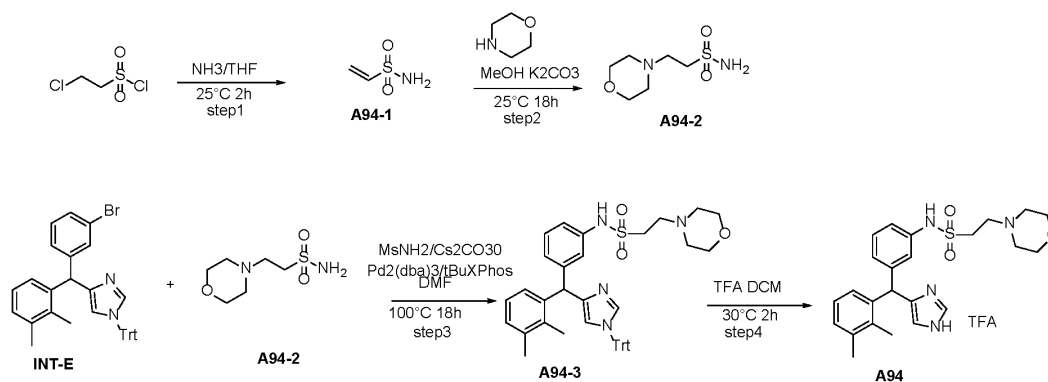
Step 4: A 25 mL reaction flask was added with 9.5 mL EtOH, 3.2 mL of 30% KOH in water, and **A91-3** (320 mg, 1.11 mmol, 1.0 eq). The mixture was heated to 105°C and stirred for 16 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and 2 mL of water was added. The pH was adjusted to 6-7 using 4 N HCl, and the mixture was filtered to obtain **A91-4** (250 mg). **Yield: 72.2%.**

Step 5: A 10 mL reaction flask was added with 2 mL DCM, **A91-4** (100 mg, 0.32 mmol, 1.0 eq), **A91-2** (78 mg, 0.36 mmol, 1.1 eq), and DIPEA (168 mg, 1.3 mmol, 4.0 eq). After cooling to 0°C, HATU (148 mg, 0.39 mmol, 1.2 eq) was added. The mixture was stirred at 25°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by column chromatography to obtain 120 mg of crude product. The crude was then dissolved in 1 mL DCM and 0.5 mL TFA, and the mixture was stirred at 27°C for 5 minutes. The mixture was concentrated, and the residue was purified by preparative HPLC to afford **A91** (10 mg). **Yield: 7.2%.**

Overall yield: 0.7%.

10

Example 6. Synthesis of Compound A94



Step 1: A 250 mL reaction bottle was added with 100 mL THF and 2-chloroethanesulfonyl chloride (10 g, 0.062 mol, 1.0 eq). Ammonia gas (NH₃) was bubbled slowly into the reaction mixture at 0°C for 2 hours. The mixture was then stirred at room temperature for an additional 2 hours. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to obtain **A94-1** (4.5 g). **Yield: 67.8%.**

Step 2: A 100 mL reaction flask was added with 20 mL MeOH, **A94-1** (2 g, 0.0187 mol, 1.0 eq), morpholine (1.3 g, 0.015 mol, 0.8 eq), and K₂CO₃ (5.16 g, 0.0374 mol, 2.0 eq). The mixture was stirred at 25°C overnight. LC-MS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 50 mL ice water and extracted four times with 50 mL chloroform:isopropanol (3:1). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to obtain **A94-2** (620 mg). **Yield: 17.1%.**

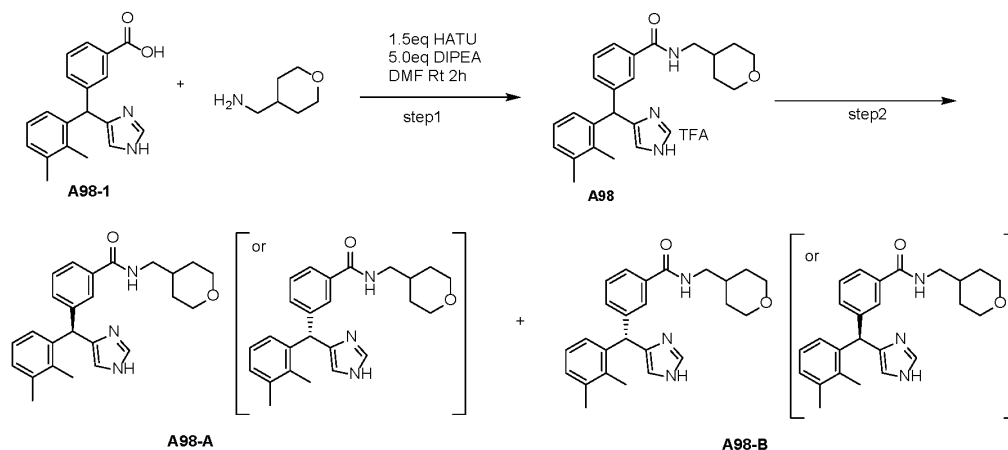
Step 3: A 5 mL reaction bottle was added with 2 mL DMF, **A94-2** (100 mg, 0.172 mmol, 1.0 eq), cesium carbonate (112 mg, 0.344 mmol, 2.0 eq), **INT-E** (140 mg, 0.72 mmol, 4.2 eq),

$\text{Pd}_2(\text{dba})_3$ (16 mg, 0.0172 mmol, 0.1 eq), and t-BuXPhos (68 mg, 0.0344 mmol, 0.2 eq). The mixture was stirred at 105°C overnight under a nitrogen atmosphere. LC-MS showed the reaction was completed. The reaction mixture was poured into 10 mL ice water and the aqueous phase was extracted four times with 10 mL ethyl acetate (EA). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography to afford **A94-3** (100 mg). **Yield: 83.5%.**

Step 4: A 5 mL reaction flask was added with 2 mL DCM, 1 mL TFA, and **A94-3** (100 mg, 0.144 mmol, 1.0 eq). The mixture was stirred at 28°C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **A94** (25 mg). **Yield: 45.2%.**

Overall yield: 4.4%.

Example 7. Synthesis of Compound A98



Step 1: A 10 mL reaction flask was added with 6 mL DMF, **98-1** (150 mg, 0.49 mmol, 1.0 eq), 4-(aminomethyl)tetrahydro-2H-pyran (112 mg, 0.98 mmol, 2.0 eq), DIPEA (317 mg, 2.45 mmol, 5.0 eq), and HATU (280 mg, 0.74 mmol, 1.5 eq). The reaction mixture was stirred at 25°C for 2 hours. LC-MS showed the reaction was completed. The crude residue was purified by column chromatography to obtain 64 mg of product. The obtained crude product was dissolved in 4 mL DCM and 2 mL TFA and stirred at 23.2°C. The reaction mixture was concentrated under vacuum, and the residue was further purified by preparative HPLC to afford **A98** (58 mg). **Yield: 29.44%.**

Step 2: **A98** (45 mg) was separated on a column packed with CHIRALPAK® IE (30 × 250 mm, 10 μm particle size). A mixture of mobile phase A (Hexane + 0.2% AMMN) and mobile phase B (EtOH + 0.2% AMMN) in a 50:50 ratio was used. The operation conditions were set at

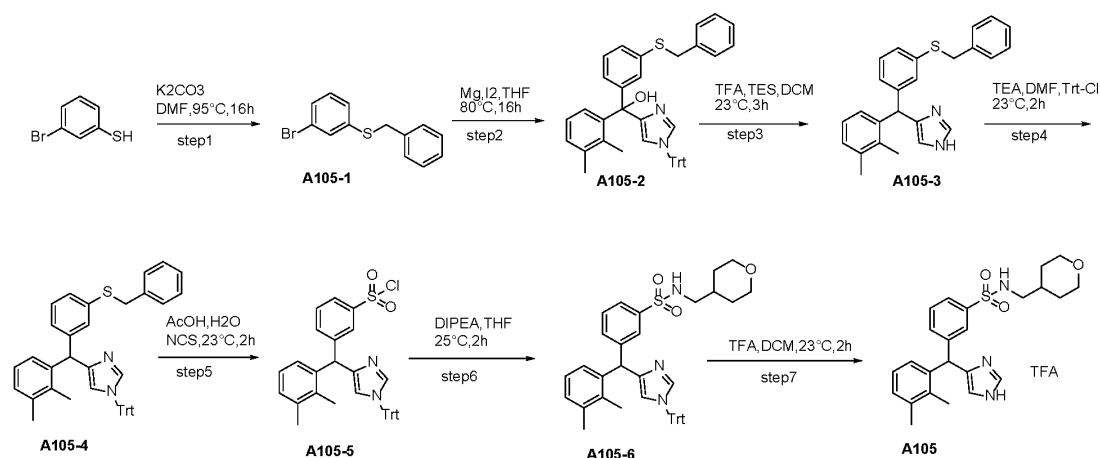
ambient temperature with a flow rate of 25 mL/min and UV detection at 214 nm/254 nm. The first eluting enantiomer, **A98-A** (16 mg), was isolated with a retention time of 5.090 min and an enantiomeric excess of 100%. **Yield: 71%.**

Overall yield: 21%.

- 5 The second eluting enantiomer, **A98-B** (15 mg), was isolated with a retention time of 7.540 min and an enantiomeric excess of 100%. **Yield: 66%.**

Overall yield: 21%.

Example 8. Synthesis of Compound A105



10

Step 1: A 500 mL reaction flask was added with 180 mL DMF, 3-bromothiophenol (20 g, 0.106 mol, 1.0 eq), benzyl bromide (21.72 g, 0.127 mol, 1.2 eq), and K₂CO₃ (17.53 g, 0.127 mol, 1.2 eq). The mixture was stirred at 95°C for 16 hours. GC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by column

- 15 chromatography (PE:EA = 6%) to give **A105-1** (23 g). **Yield: 77.7%.**

Step 2: A 25 mL reaction flask was added with 6 mL THF, Mg (208 mg, 8.55 mmol, 2.1 eq), and **A105-1** (2.26 g, 8.13 mmol, 2.0 eq). The mixture was stirred at 85°C for 1 hour. In another 50 mL reaction flask, 20 mL THF, (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (1.8 g, 4.07 mmol, 1.0 eq), and the Grignard reagent were added. The reaction mixture was stirred at

20 80°C for 16 hours. LC-MS showed the reaction was completed. The mixture was cooled to 0°C, and 10 mL saturated NH₄Cl was added. The organic phase was separated, and the aqueous phase was extracted with EA (30 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (PE:EA = 16%) to give **A105-2** (1.7 g). **Yield: 65%.**

Step 3: A 100 mL reaction flask was added with 30 mL DCM, **A105-2** (3 g, 4.67 mmol, 1.0 eq), and TES (5.42 g, 46.7 mmol, 10.0 eq). After cooling to 0°C, TFA (5.32 g, 46.7 mmol, 10.0 eq) was added. The reaction was stirred at 23°C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by column chromatography (DCM:MeOH = 7%) to give **A105-3** (2.9 g). **Yield: 100%.**

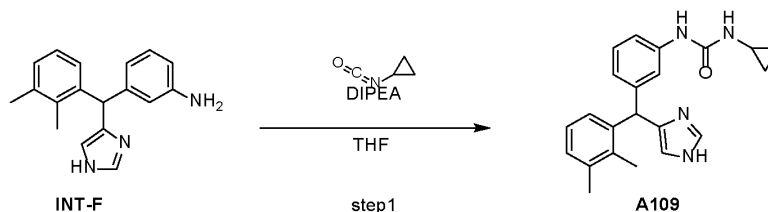
Step 4: A 100 mL reaction flask was added with 30 mL DMF, **A105-3** (2.9 g, 5.82 mmol, 1.0 eq), TEA (1.77 g, 17.46 mmol, 3.0 eq), and triphenylmethyl chloride (1.95 g, 6.98 mmol, 1.2 eq). The reaction was stirred at 23°C for 2 hours. LC-MS showed the reaction was completed. The mixture was poured into 300 mL ice water and extracted with EA (100 mL × 2). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (PE:EA = 16%) to give **A105-4** (2.1 g). **Yield: 57.6%.**

Step 5: A 25 mL reaction flask was added with 9 mL AcOH, 3 mL H₂O, and **A105-4** (600 mg, 0.958 mmol, 1.0 eq). After cooling to 0°C, NCS (640 mg, 4.79 mmol, 5.0 eq) was added. The reaction mixture was stirred at 23°C for 1.5 hours. LC-MS showed the reaction was completed. The mixture was quenched with 30 mL H₂O, and the aqueous phase was extracted with EA (20 mL × 2). The combined organic phase was dried over Na₂SO₄ and concentrated under vacuum to obtain the crude **A105-5**, which was used directly without further purification.

Step 6: A 25 mL reaction flask was added with 12 mL THF, 4-(aminomethyl)tetrahydro-2H-pyran (552 mg, 4.79 mmol, 5.0 eq), DIPEA (1.24 g, 9.58 mmol, 10.0 eq), and the crude **A105-5** (0.958 mmol, 1.0 eq). The reaction was stirred at 23°C for 1.5 hours. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by TLC (DCM:MeOH = 20:1) to give **A105-6** (126 mg). **Yield: 19.3%.**

Step 7: A 10 mL reaction flask was added with 3 mL DCM, 1.5 mL TFA, and **A105-6** (124 mg). The mixture was stirred at 28°C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to give **A105** (32 mg). **Yield: 31.3%.**

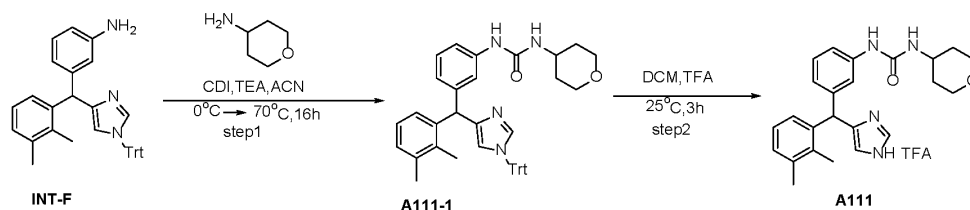
Overall yield: 0.7%.

Example 9. Synthesis of Compound A109

Step 1: To a solution of **INT-F** (120 mg, 0.43 mmol) in tetrahydrofuran (5 mL) was added DIPEA (83.86 mg, 0.65 mmol) and isocyanatocyclopropane (53.97 mg, 0.65 mmol). The reaction mixture was stirred at room temperature for 2 hours. Then, a 4 M NaOH aqueous solution (5 mL) was added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under vacuum.

The crude product was purified by preparative HPLC (Gemini 5 μ m C18 column, 150 $\times$ 21.2 mm) using a gradient elution from 5% to 95% acetonitrile/water containing 0.1% formic acid. The purification afforded **A109** as a white solid (9.32 mg). **Yield: 6.02%.**

Overall yield: 1.45%.

Example 10. Synthesis of Compound A111

Step 1: A 25 mL three-necked flask was added with 10 mL acetonitrile, CDI (250 mg, 1.54 mmol, 2.0 eq), and TEA (78 mg, 0.77 mmol, 1.0 eq). The mixture was cooled to 0°C, and 4-aminotetrahydropyran (78 mg, 0.77 mmol, 1.0 eq) was added at 0°C. The reaction mixture was stirred for 1 hour at 0°C. Then **INT-F** (400 mg, 0.77 mmol, 1.0 eq) was added, and the reaction was stirred overnight at 70°C. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography to afford **A111-1** (70 mg). **Yield: 48.2%.**

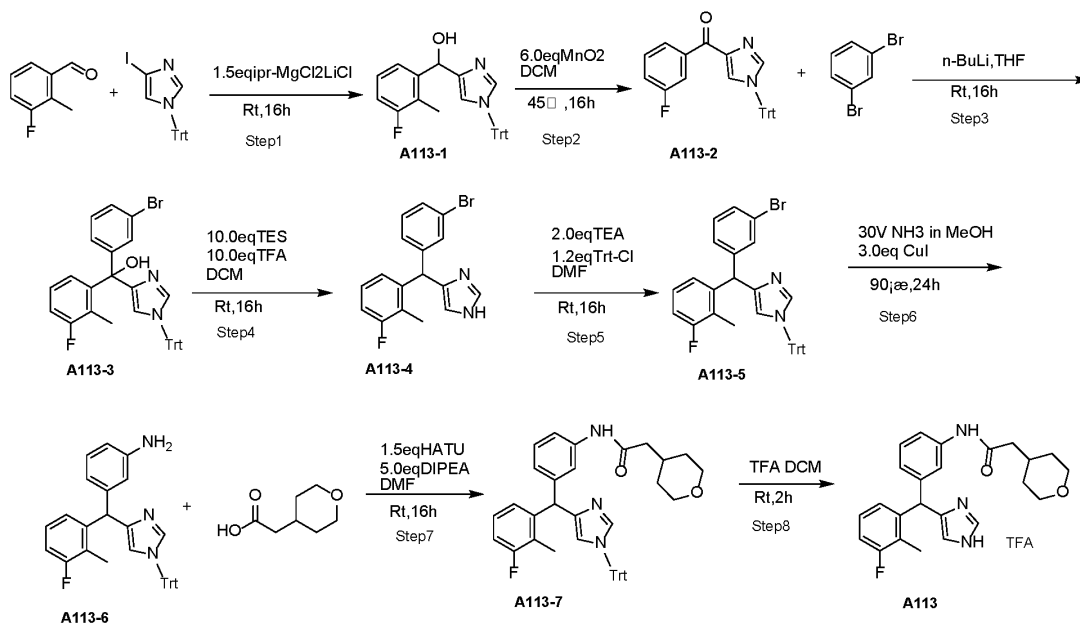
Step 2: A 25 mL single-necked flask was added with 0.7 mL DCM, **A111-1** (70 mg, 0.12 mmol, 1.0 eq), and 0.35 mL TFA. The reaction mixture was stirred at room temperature for 3 hours.

LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and

the residue was purified by silica gel column chromatography to obtain 45 mg of crude product. The crude was further purified by preparative HPLC to afford **A111** (6 mg). **Yield: 67%.**

Overall yield: 32.3%.

5 Example 11. Synthesis of Compound A113



- Step 1:** A 100 mL reaction flask containing 50 mL DCM and 4-Iodo-1-tritylimidazole (5 g, 0.0115 mol, 1.0 eq) was replaced with nitrogen three times. The mixture was cooled to 0-10°C, and iPrMgCl·LiCl (1.3 M, 14 mL, 0.0172 mol, 1.5 eq) was added dropwise. The reaction was stirred at 23.8°C for 1 hour. LC-MS showed the reaction was completed. The mixture was cooled again to 0-10°C, and 3-fluoro-2-methylbenzaldehyde (2.4 g, 0.0172 mol, 1.5 eq) was added dropwise. The reaction was stirred at 23.8°C for 16 hours. LC-MS showed the reaction was completed. The mixture was quenched with 50 mL NH₄Cl, extracted, and filtered to obtain 3.5 g of **A113-1** as a solid. **Yield: 67.96%.**
- Step 2:** A 100 mL reaction flask containing 70 mL DCM, **A113-1** (3.5 g, 0.0078 mol, 1.0 eq), and MnO₂ (4.1 g, 0.047 mol, 6.0 eq) was stirred at 45°C for 6 hours. LC-MS showed the reaction was completed. The mixture was filtered, and the residue was concentrated under reduced pressure. The crude product was purified by column chromatography to obtain 1.5 g of **A113-2**. **Yield: 42.86%.**
- Step 3:** A 50 mL reaction flask containing 8 mL THF and 1,3-dibromobenzene (0.8 g, 0.0034 mol, 1.5 eq) was cooled to -78°C, and n-BuLi (1.4 mL, 0.0034 mol, 1.5 eq) was added dropwise. After stirring at -78°C for 1 hour, a solution of **A113-2** (1 g, 0.0022 mol, 1.0 eq) in 10 mL THF

was added dropwise. The reaction was stirred at 23.8°C for 16 hours. LC-MS showed the reaction was completed. The mixture was quenched with 20 mL NH₄Cl, and the organic phase was separated. The aqueous phase was extracted with 50 mL EA, and the combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography to obtain 920 mg of **A113-3**. **Yield: 70.77%.**

Step 4: A 10 mL reaction flask containing 5 mL DCM, **A113-3** (920 mg, 0.00153 mol, 1.0 eq), TES (1.8 g, 0.0153 mol, 10.0 eq), and TFA (1.75 g, 0.0153 mol, 10.0 eq) was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The mixture was adjusted to pH 10 with 1 N NaOH and extracted with DCM (2 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography to obtain 403 mg of **A113-4**. **Yield: 76.62%.**

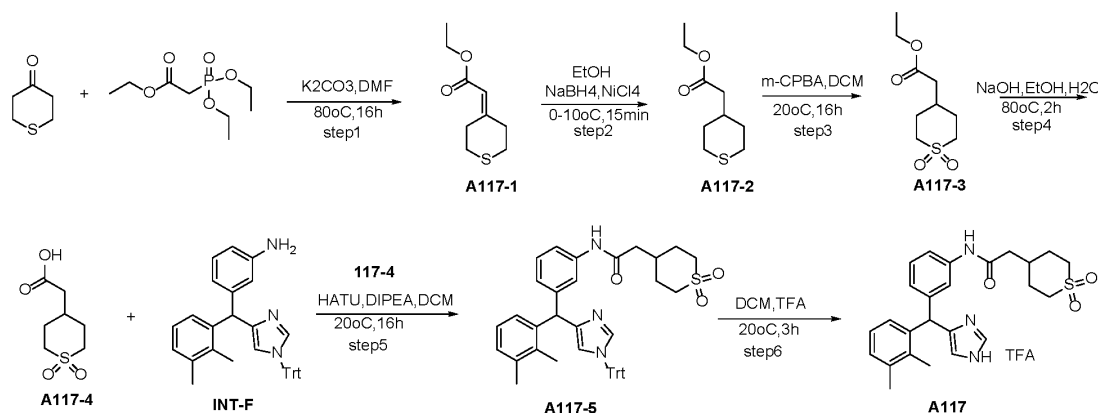
Step 5: A 10 mL reaction flask containing 4 mL DMF, **A113-4** (400 mg, 0.00116 mol, 1.0 eq), TEA (235 mg, 0.0023 mol, 2.0 eq), and TrtCl (390 mg, 0.0014 mol, 1.2 eq) was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was poured into 12 mL water and extracted with EA (2 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography to obtain 480 mg of **A113-5**. **Yield: 70.69%.**

Step 6: A 100 mL reaction flask containing 14.4 mL NH₃ in MeOH, **A113-5** (480 mg, 0.82 mmol, 1.0 eq), and CuI (470 mg, 2.4 mmol, 3.0 eq) was stirred at 90°C for 24 hours. LC-MS showed the reaction was completed. The mixture was poured into 30 mL water, and the aqueous phase was extracted with 50 mL DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography to obtain 152 mg of **A113-6**. **Yield: 36.19%.**

Step 7: A 10 mL reaction flask containing 5 mL DMF, **A113-6** (150 mg, 0.0029 mol, 1.0 eq), tetrahydropyranyl-4-acetic acid (82 mg, 0.00057 mol, 2.0 eq), HATU (166 mg, 0.00043 mol, 1.5 eq), and DIPEA (188 mg, 0.00145 mol, 5.0 eq) was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was poured into 12 mL water, and the aqueous phase was extracted with EA (2 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain 270 mg of **A113-7**. **Yield: 100%.**

Step 8: A 10 mL reaction flask containing 4 mL DCM, **A113-7** (270 mg, 0.00042 mol, 1.0 eq), and 2 mL TFA was stirred at 25°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford 35 mg of **A113**. **Yield: 20.46%.**

Overall yield: 1.16%.

Example 12. Synthesis of Compound A117

- Step 1:** A 500 mL three-necked flask containing 300 mL DMF, tetrahydrothiopyran-4-one (30 g, 0.26 mol, 1 eq), triethyl phosphonoacetate (64 g, 0.28 mol, 1.1 eq), and K_2CO_3 (54 g, 0.39 mol, 1.5 eq) was stirred overnight at $80^\circ C$. LC-MS showed the reaction was completed. The mixture was poured into water, extracted with ethyl acetate, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **A117-1** (45 g). **Yield: 93.1%.**
- Step 2:** A 100 mL three-necked flask containing 60 mL DCM and **A117-1** (5 g, 0.027 mol, 1 eq) was cooled to $0^\circ C$, and $NiCl_4$ (3.5 g, 0.027 mol, 1 eq) was added. $NaBH_4$ (5.1 g, 135 mmol, 5 eq) was added in portions at $0^\circ C$. The mixture was stirred for 15 minutes at $25^\circ C$. GC-MS showed the reaction was completed. The mixture was poured into water, extracted with MTBE, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **A117-2** (2.4 g). **Yield: 47.3%.**
- Step 3:** A 100 mL three-necked flask containing 60 mL DCM and **A117-2** (2 g, 0.011 mol, 1 eq) was cooled to $0^\circ C$, and $m\text{-CPBA}$ (4.6 g, 0.027 mol, 2.5 eq) was added. The reaction mixture was stirred overnight at room temperature. LC-MS showed the reaction was incomplete. The mixture was filtered, and the filtrate was washed with $Na_2S_2O_3$ and $NaHCO_3$ solutions. The organic phase was dried over Na_2SO_4 , concentrated under vacuum, and purified by silica gel column chromatography to afford **A117-3** (1.7 g). **Yield: 70.2%.**
- Step 4:** A 100 mL three-necked flask containing 17 mL EtOH, **A117-3** (1.7 g, 7.7 mmol, 1 eq), $NaOH$ (0.618 g, 15.5 mmol, 2 eq), and 17 mL H_2O was stirred at $80^\circ C$ for 2 hours. LC-MS showed the reaction was incomplete. The mixture was concentrated under vacuum, extracted with DCM, and adjusted to pH 1 using hydrochloric acid. The crude mixture was filtered, and

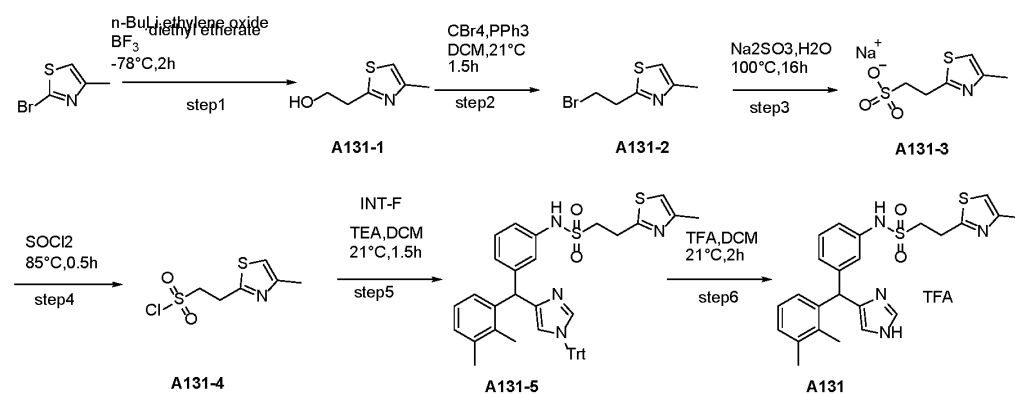
the filtrate was extracted with DCM:MeOH (10:1). The organic phase was dried over Na₂SO₄ and concentrated under vacuum to afford **A117-4** (1 g). **Yield: 66.9%.**

Step 5: A 10 mL single-necked flask containing 2 mL DCM, **INT-F** (200 mg, 0.385 mmol, 1 eq), **A117-4** (150 mg, 0.77 mmol, 2 eq), and DIPEA (199 mg, 1.54 mmol, 4 eq) was cooled to 0°C. HATU (176 mg, 0.462 mmol, 1.2 eq) was added at 0°C. The reaction mixture was stirred overnight at room temperature. LC-MS showed the reaction was completed. The mixture was purified by silica gel column chromatography to afford **A117-5** (217 mg). **Yield: 81.3%.**

Step 6: A 10 mL single-necked flask containing 2 mL DCM and **A117-5** (217 mg, 0.31 mmol, 1 eq) was stirred with 2 mL TFA for 3 hours at room temperature. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography to afford **A117** (100 mg). **Yield: 71.5%.**

Overall yield: 12.1%.

Example 13. Synthesis of Compound A131



Step 1: A 500 mL reaction flask containing 200 mL diethyl ether and **2-bromo-4-methylthiazole** (7.97 g, 0.0451 mol, 1.0 eq) was cooled to -78°C . $n\text{-BuLi}$ (2.5 M, 27 mL, 0.0677 mol, 1.5 eq) was added dropwise. The mixture was stirred at -78°C for 1.5 hours, then a solution of **ethylene oxide** (5 M, 135 mL, 0.677 mol, 15.0 eq) in Et₂O (135 mL) and **boron trifluoride diethyl etherate** (9.61 g, 0.0677 mol, 1.5 eq) in Et₂O (64 mL) was added. The reaction was stirred at -78°C for 2 hours. LC-MS showed the reaction was completed. The mixture was quenched with saturated ammonium chloride (30 mL) at 0°C , and the organic phase was separated, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by column chromatography (PE:EA = 1:1) to afford **A131-1** (1.32 g). **Yield: 20.4%.**

Step 2: A 50 mL sealing pot containing 26 mL DCM and **A131-1** (1.32 g, 9.23 mmol, 1.0 eq) was cooled to 0°C . **PPh₃** (3.63 g, 13.85 mmol, 1.5 eq) and **CBr₄** (4.59 g, 13.85 mmol, 1.5 eq) were added. The reaction was stirred at 22°C for 1.5 hours. LC-MS showed the reaction was

completed. The mixture was concentrated under vacuum, and the residue was purified by column chromatography (PE:EA = 92:8) to afford **A131-2** (1.28 g). **Yield: 67.3%.**

Step 3: A 25 mL reaction flask containing 6.5 mL H₂O, **A131-2** (1.28 g, 6.24 mmol, 1.0 eq), and Na₂SO₃ (786 mg, 6.24 mmol, 1.0 eq) was stirred at 105°C for 16 hours. LC-MS showed the reaction was completed. The mixture was dried by vacuum drying at 45°C for 19 hours to afford **A131-3** (1.85 g). **Yield: 100%.**

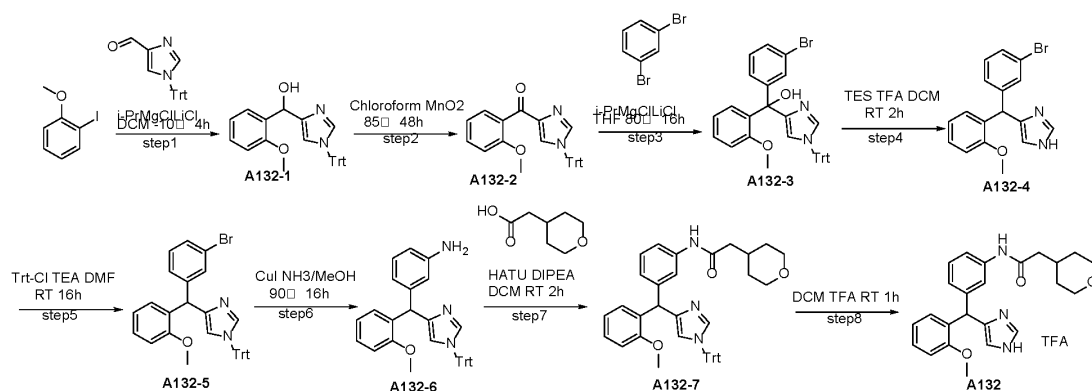
Step 4: A 10 mL reaction flask containing 4.5 mL SOCl₂ was cooled to -10°C. **A131-3** (264 mg, 1.156 mmol, 1.0 eq) was added, and the reaction was stirred at 85°C for 0.5 hours. The mixture was concentrated under vacuum, and the residue was used directly in the next step without further purification.

Step 5: A 10 mL reaction flask containing 1.5 mL DCM, **INT-F** (150 mg, 0.289 mmol, 1.0 eq), and **TEA** (292 mg, 2.89 mmol, 10.0 eq) was cooled to 0°C. The crude **A131-4** (1.156 mmol, 4.0 eq) in 1 mL DCM was added. The reaction was stirred at 16°C for 1.5 hours. HPLC showed the mixture contained 17% of the product. The mixture was filtered and concentrated under vacuum. The residue was purified by TLC (DCM:MeOH = 20:1) to afford **A131-5** (40 mg). **Yield: 19.5%.**

Step 6: A 5 mL reaction flask containing 1.2 mL DCM, **A131-5** (60 mg, 1.0 eq), and **TFA** (0.6 mL) was stirred at 22°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **A131** (16 mg). **Yield: 40.5%.**

Overall yield: 1.1%.

Example 14. Synthesis of Compound A132



Step 1: A 1 L three-necked flask containing 200 mL DCM and 2-iodoanisole (20 g, 0.085 mol, 1 eq) was cooled to -10°C. Isopropylmagnesium chloride lithium chloride (99 mL, 0.13 mol, 1.5 eq) was added dropwise. The reaction mixture was stirred at -10°C for 3 hours, then 1-

tritylimidazole-4-carboxaldehyde (35 g, 0.1 mol, 1.2 eq) was added. The mixture was stirred at 25°C for 1 hour. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **A132-1** (45 g, crude).

- 5 **Step 2:** A 2 L three-necked flask containing 800 mL chloroform, **A132-1** (45 g, 0.1 mol, 1 eq), and MnO₂ (52.5 g, 0.6 mol, 6 eq) was stirred at 85°C for 48 hours. LC-MS showed the reaction was completed. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:EA = 1:1) to afford **A132-2** (12.6 g).

Yield: 33%.

- 10 **Step 3:** A 500 mL reaction flask containing 120 mL THF and 1,3-dibromobenzene (6 g, 0.013 mol, 1.5 eq) was cooled to -10°C. Isopropylmagnesium bromide (16 mL, 0.02 mol, 1.5 eq) was added dropwise. The reaction mixture was stirred at -10°C for 2 hours, then a solution of **A132-2** (6 g, 0.02 mol, 1 eq) in THF (120 mL) was added. The mixture was stirred at 80°C for 16 hours. LC-MS showed the reaction was completed. The mixture was poured into water and
15 extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 3:1) to afford **A132-3** (1.2 g). **Yield: 15%.**

- Step 4:** A 50 mL single-port flask containing 24 mL DCM, **A132-3** (1.2 g, 0.002 mol, 1 eq), triethylsilane (12 mL), and TFA (12 mL) was stirred at 25°C for 2 hours. LC-MS showed the
20 reaction was completed. The mixture was concentrated under reduced pressure to afford **A132-4** (1.9 g, crude).

- Step 5:** A 100 mL flask containing 38 mL DMF, **A132-4** (1.9 g, 0.0055 mol, 1 eq), triphenylmethyl chloride (4.6 g, 0.017 mol, 3 eq), and TEA (4.5 g, 0.044 mol, 8 eq) was stirred at 25°C for 12 hours. LC-MS showed the reaction was completed. The mixture was poured into
25 water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 4:1) to afford **A132-5** (1 g). **Yield: 86%.**

- Step 6:** A 50 mL sealed pot containing **A132-5** (1 g, 0.0017 mol, 1 eq), CuI (0.97 g, 0.0051 mol, 3 eq), and NH₃/MeOH (30 mL) was stirred at 90°C for 48 hours. LC-MS showed the reaction
30 was completed. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 93:7) to afford **A132-6** (450 mg). **Yield: 51%.**

Step 7: A 10 mL three-necked flask containing 2 mL DMF, **A132-6** (100 mg, 0.19 mmol, 1 eq), tetrahydropyranyl-4-acetic acid (56 mg, 0.38 mmol, 2 eq), DIPEA (149 mg, 1.15 mmol, 6 eq),

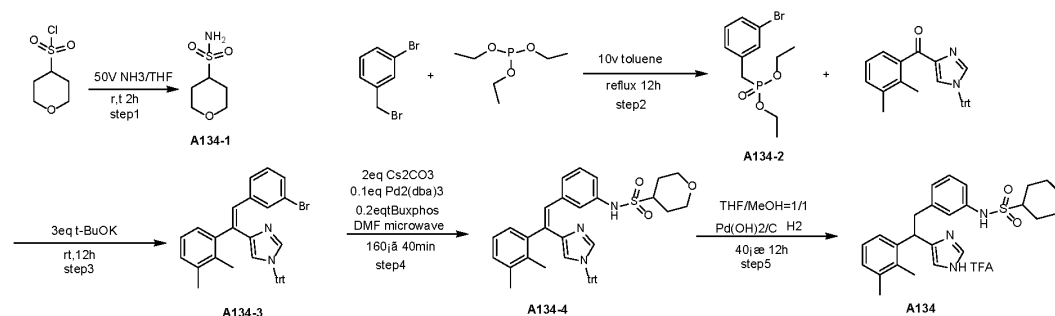
and HATU (87 mg, 0.23 mmol, 1.2 eq) was stirred at 25°C for 1 hour. LC-MS showed the reaction was completed. The solution was poured into water and extracted with EA, washed with brine, dried over Na₂SO₄, concentrated under vacuum, and purified by column chromatography (DCM:MeOH = 20:1) to afford **A132-7** (15 mg).

- 5 **Step 8:** A 50 mL reaction flask containing 1 mL DCM, **A132-7** (15 mg, 0.015 mmol, 1 eq), and TFA (1 mL) was stirred at room temperature for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford **A132** (11 mg). **Yield: 0.15%.**

Overall yield: 0.3%.

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Example 15. Synthesis of Compound A134



- Step 1:** A 50 mL reaction flask containing 10 mL NH₃/THF and tetrahydropyran-4-sulfonyl chloride (180 mg, 0.975 mmol, 1 eq) was stirred at 20°C for 2 hours. GC-MS showed the reaction was completed. The mixture was filtered and concentrated under reduced pressure to afford **A134-1** (160 mg). **Yield: 99.3%.**

- Step 2:** A 100 mL reaction flask containing 50 mL toluene, 3-bromobenzyl bromide (5 g, 20.00 mmol, 1 eq), and triethyl phosphite (3.65 g, 22.01 mmol, 1.1 eq) was stirred at 110°C for 12 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **A134-2** (5 g). **Yield: 81.4%.**

- Step 3:** A 100 mL reaction flask containing 58 mL THF, **A134-2** (2.9 g, 9.44 mmol, 1.1 eq), t-BuOK (2.89 g, 25.76 mmol, 3 eq), and (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (3.8 g, 8.58 mmol, 1 eq) was stirred at 15°C for 12 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced

pressure. The crude product was purified by column chromatography to afford **A134-3** (3 g).

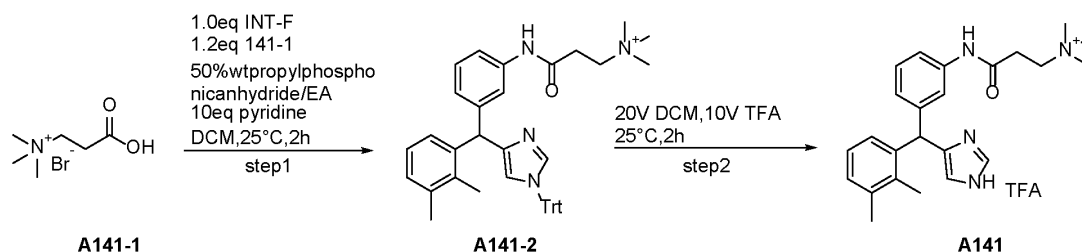
Yield: 58.7%.

Step 4: A 10 mL reaction flask containing 5 mL DMF, **A134-3** (240 mg, 0.403 mmol, 1 eq), Cs_2CO_3 (262 mg, 0.806 mmol, 2 eq), **A134-1** (200 mg, 1.21 mmol, 3 eq), $\text{Pd}_2(\text{dba})_3$ (37 mg, 0.040 mmol, 0.1 eq), and t-BuXphos (34 mg, 0.081 mmol, 0.2 eq) was stirred at 160°C for 40 minutes in a microwave. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **A134-4** (220 mg). **Yield: 80.4%.**

Step 5: A mixture of **A134-4** (100 mg), $\text{Pd}(\text{OH})_2/\text{C}$ (50 mg), MeOH (5 mL), and THF (5 mL) was stirred at 40°C for 15 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. DCM (10 mL) and TFA (5 mL) were added to the residue and stirred for 10 minutes. The solvent was evaporated under reduced pressure, and the residue was purified by preparative HPLC to afford **A134** (50 mg) as a white solid. **Yield: 61.3%.**

Overall yield: 23.4%.

Example 16. Synthesis of Compound A141



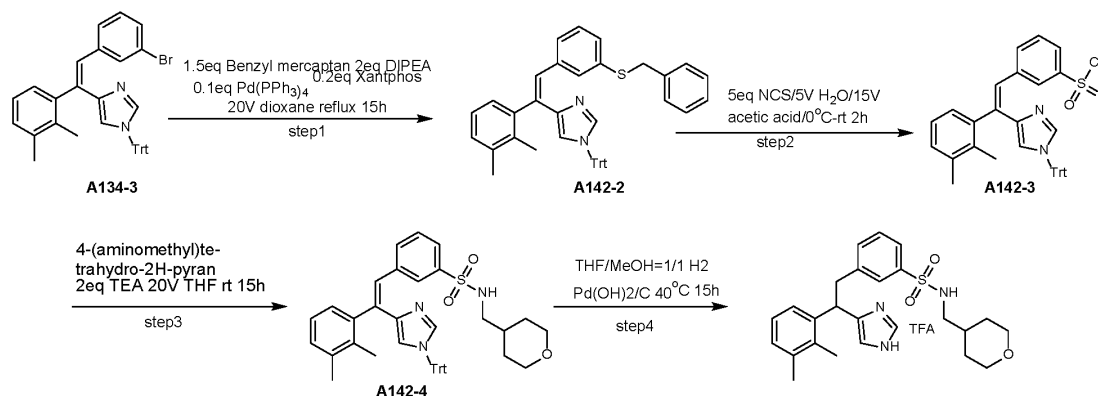
Step 1: A 10 mL reaction flask containing 2 mL DCM, compound **A141-1** (24 mg, 0.116 mmol, 1.2 eq), **INT-F** (50 mg, 0.096 mmol, 1.0 eq), and pyridine (77 mg, 0.963 mmol, 10 eq) was cooled to 0°C. Propylphosphonic anhydride in EA (50% wt, 368 mg, 0.578 mmol, 6.0 eq) was added. The reaction mixture was stirred at 25°C for 1 hour. LC-MS showed the reaction was completed. Then 1 mL TFA was added, and the reaction was stirred at 25°C for 15 minutes. The mixture was concentrated under vacuum to afford **A141-2** (600 mg) as a yellow oil crude. **Yield: 100%.**

Step 2: A 10 mL reaction flask containing 1 mL DCM and **A141-2** (600 mg, 0.096 mmol, 1.0 eq) was cooled to 0°C. TFA (1 mL, 10 V) was added. The reaction mixture was stirred at 25°C for 2

hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum. The residue was purified by preparative HPLC to afford **A141** (4 mg). **Yield: 10.7%.**

Overall yield: 10.7%.

5 Example 17. Synthesis of Compound A142



Step 1: A 50 mL reaction flask containing 18 mL 1,4-dioxane, compound **A134-3** (900 mg, 1.511 mmol, 1.0 eq), DIPEA (391 mg, 3.022 mmol, 2 eq), benzyl mercaptan (282 mg, 2.267 mmol, 1.5 eq), Pd(PPh₃)₄ (175 mg, 0.151 mmol, 0.1 eq), and Xantphos (175 mg, 0.302 mmol, 0.2 eq) was stirred at 100°C for 15 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **A142-2** (750 mg). **Yield: 77.8%.**

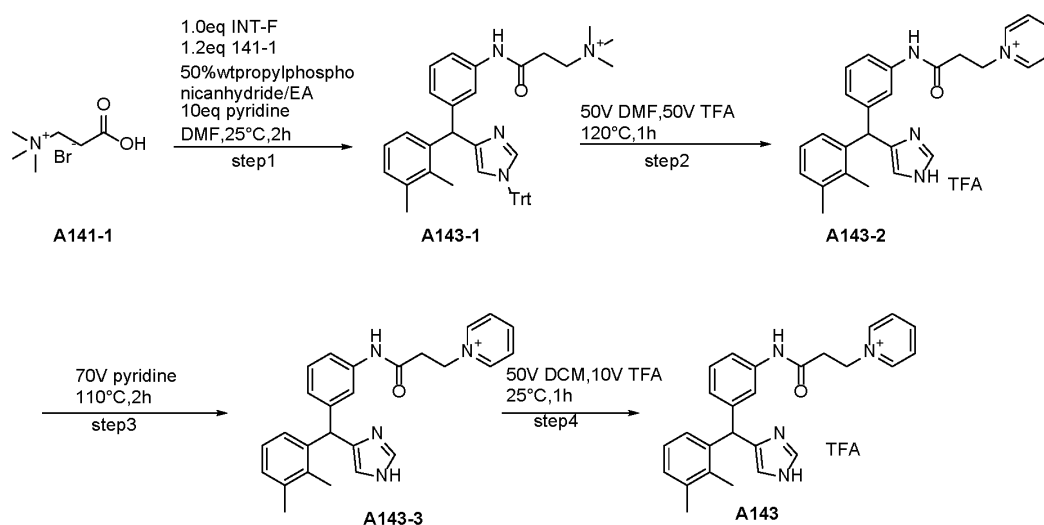
Step 2: A 10 mL reaction flask containing 3 mL acetic acid, 1 mL water, and compound **A142-2** (100 mg, 0.157 mmol, 1.0 eq) was cooled to 0°C. NCS (105 mg, 0.783 mmol, 5 eq) was added, and the reaction mixture was stirred at 20°C for 2 hours. LC-MS showed the reaction was completed. The mixture was poured into 10 mL water and extracted with EA (2 × 10 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **A142-3** (130 mg, crude). **Yield: 100%.**

Step 3: A 25 mL three-necked flask containing 5 mL THF, compound **A142-3** (130 mg, 0.211 mmol, 1 eq), TEA (43 mg, 0.423 mmol, 2 eq), and 4-(aminomethyl)tetrahydro-2H-pyran (37 mg, 0.317 mmol, 1.5 eq) was stirred at 25°C for 18 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **A142-4** (25 mg) as a white solid. **Yield: 23%.**

Step 4: A mixture of compound **A142-4** (25 mg), Pd(OH)₂/C (25 mg), MeOH (5 mL), and THF (5 mL) was stirred at 40°C for 18 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. DCM (10 mL) and TFA (5 mL) were added to the residue, stirred for 10 minutes, and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC to afford **A142** (3.5 mg) as a white solid. **Yield: 17%.**

Overall yield: 3.1%.

Example 18. Synthesis of Compound A143



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Step 1: A 10 mL reaction flask containing 2.5 mL DMF, compound **A141-1** (24 mg, 0.116 mmol, 1.2 eq), **INT-F** (50 mg, 0.096 mmol, 1.0 eq), and pyridine (77 mg, 0.963 mmol, 10 eq) was cooled to 0°C. Propylphosphonic anhydride in EA (50% wt, 368 mg, 0.578 mmol, 6.0 eq) was added. The reaction mixture was stirred at 25°C for 1 hour. LC-MS showed the reaction was completed. Then 1 mL TFA was added and stirred at 25°C for 5 minutes. The reaction mixture was concentrated under vacuum to afford 600 mg of a yellow oil mixture of **A143-1** and **A143-2**. It was used directly in the next step without further purification. **Yield: 100%.**

15

Step 2: A 10 mL reaction flask containing 1 mL DCM and **A143-1** (600 mg, 0.096 mmol, 1.0 eq) was cooled to 0°C. TFA (1 mL, 10 V) was added. The reaction mixture was stirred at 25°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **A143-2** (20 mg). **Yield: 52%.**

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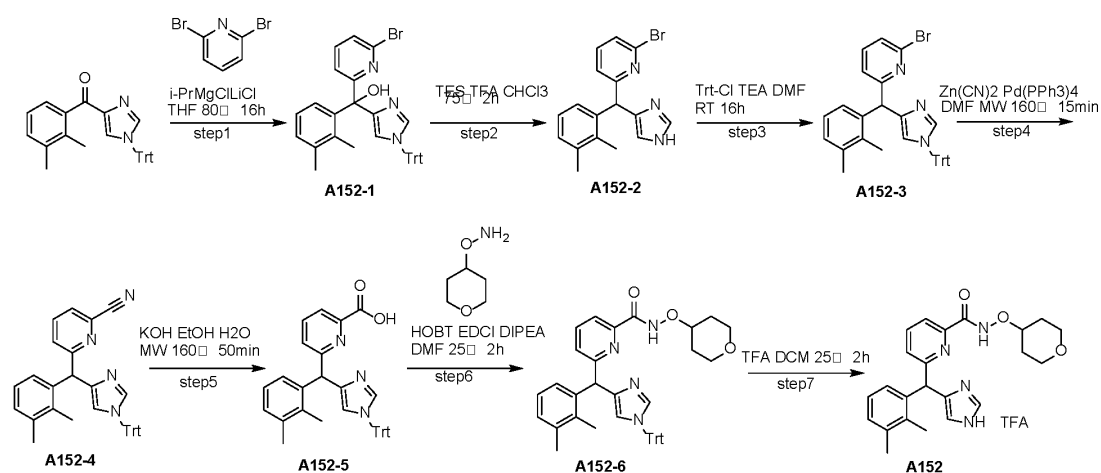
Step 3: A 10 mL reaction flask containing 2 mL pyridine and **A143-2** (20 mg, 0.05 mmol, 1.0 eq) was stirred at 110°C for 2 hours. LC-MS showed the reaction was completed. Then 2 mL TFA

was added and stirred at 25°C for 5 minutes. The reaction mixture was concentrated under vacuum to afford **A143-3** (40 mg) as a yellow oil crude. **Yield: 100%.**

Step 4: A 10 mL reaction flask containing 1 mL DCM and **A143-3** (40 mg, 0.05 mmol, 1.0 eq) was cooled to 0°C. TFA (1 mL, 10 V) was added. The reaction mixture was stirred at 25°C for 1 hour. The mixture was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **A143** (4 mg). **Yield: 19.5%.**

Overall yield: 10%.

Example 19. Synthesis of Compound A152



- Step 1:** A 250 mL three-necked flask containing 50 mL THF and 2,6-dibromopyridine (8.1 g, 0.034 mol, 1.5 eq) was cooled to -10°C. Isopropylmagnesium bromide (26 mL, 0.034 mol, 1.5 eq) was added. The reaction mixture was stirred at 40°C for 2 hours, then cooled to 0°C. (2,3-Dimethylphenyl)(1-trityl-4-imidazolyl)methanone (10 g, 0.023 mol, 1 eq) was added. The reaction mixture was stirred at 25°C for 16 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **A152-1** (4.8 g). **Yield: 36%.**
- Step 2:** A 250 mL sealed tank containing 96 mL chloroform, **A152-1** (4.8 g, 0.008 mol, 1 eq), TES (48 mL), and TFA (48 mL) was stirred at 75°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under reduced pressure, poured into a sodium bicarbonate solution, and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product

was purified by column chromatography (DCM:MeOH = 50:1) to afford **A152-2** (1.0 g). **Yield: 37%.**

Step 3: A 100 mL reaction flask containing 20 mL DMF, **A152-2** (1 g, 2.9 mmol, 1 eq), triphenylmethyl chloride (2.4 g, 8.8 mmol, 5 eq), and TEA (2.4 g, 2.3 mmol, 8 eq) was stirred at 25°C for 12 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:EA = 20:1) to afford **A152-3** (1.1 g). **Yield: 65%.**

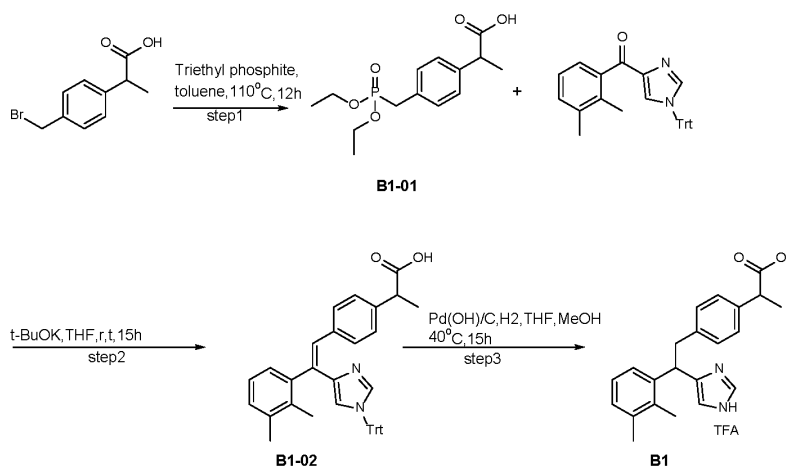
Step 4: A 30 mL single-port flask containing 10 mL DMF, **A152-3** (1 g, 1.7 mmol, 1 eq), zinc cyanide (600 mg, 5.1 mmol, 3 eq), and tetrakis(triphenylphosphine)palladium (590 mg, 5.1 mmol, 0.3 eq) was heated in a microwave at 160°C for 15 minutes. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:EA = 9:1) to afford **A152-4** (430 mg). **Yield: 48%.**

Step 5: A 10 mL sealed tank containing 1 mL EtOH, **A152-4** (100 mg, 0.19 mmol, 1 eq), and 30% potassium hydroxide aqueous solution (1 mL) was heated in a microwave at 160°C for 50 minutes. LC-MS showed the reaction was completed. The mixture was concentrated under reduced pressure, poured into water, and extracted with DCM. The aqueous phase was adjusted to pH 1 and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **A152-5** (110 mg). **Yield: 100%.**

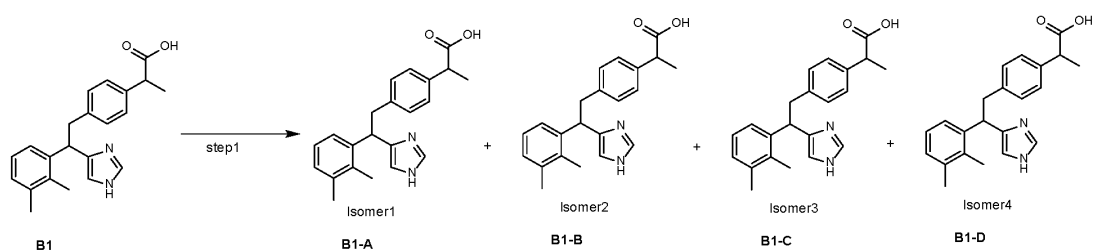
Step 6: A 10 mL three-necked flask containing 1 mL DMF, **A152-5** (110 mg, 0.24 mmol, 1 eq), HOBt (48 mg, 0.35 mmol, 1.5 eq), EDCI (68 mg, 0.35 mmol, 1.5 eq), O-(tetrahydro-2H-pyran-4-yl)hydroxylamine (56 mg, 0.47 mmol, 2 eq), and DIPEA (153 mg, 1.18 mmol, 6 eq) was stirred at 25°C for 1 hour. LC-MS showed the reaction was completed. The solution was poured into water and extracted with EA. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 50:1) to afford **A152-6** (80 mg). **Yield: 67%.**

Step 7: A 25 mL reaction flask containing 1 mL DCM and **A152-6** (80 mg, 0.13 mmol, 1 eq) was stirred with TFA (1 mL) at 25°C for 2 hours. LC-MS showed the reaction was completed. The mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford **A152** (10 mg). **Yield: 21.5%.**

Overall yield: 0.5%.

Example 20. Synthesis of Compound B1, and B1-A, B1-B, B1-C and B1-D

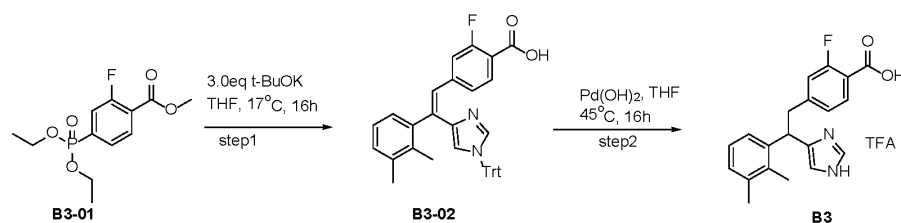
- Step 1:** To a 50 mL three-necked flask, 30 mL of toluene, 2-(4-bromomethyl)phenylpropionic acid (3 g, 12.34 mmol, 1.0 equiv), and triethyl phosphite (2.25 g, 13.57 mmol, 1.1 equiv) were added. The reaction mixture was stirred at 110°C for 12 hours. LC-MS analysis confirmed completion of the reaction. The organic phase was separated and concentrated under vacuum. The residue was purified by silica gel column chromatography (MeOH/DCM = 10%) to yield 2.3 g of compound **B1-01**. **Yield: 62.1%.**
- Step 2:** To a 50 mL three-necked flask, 10 mL of THF, compound **B1-01** (500 mg, 1.66 mmol, 1.1 equiv), t-BuOK (680 mg, 6.06 mmol, 4 equiv), and (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (670 mg, 1.51 mmol, 1.0 equiv) were added. The reaction mixture was stirred at 15°C for 15 hours. LC-MS analysis confirmed completion of the reaction. The mixture was poured into water and extracted with ethyl acetate. The residue was purified by preparative HPLC to give 160 mg of compound **B1-02** as a white solid. **Yield: 17.9%.**
- Step 3:** A mixture of compound **B1-02** (80 mg), Pd(OH)₂/C (40 mg), methanol (4 mL), and THF (4 mL) was stirred at 40°C for 15 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Then, 10 mL of DCM and 5 mL of TFA were added, and the mixture was stirred for 10 minutes. The solvent was removed by rotary evaporation. The residue was purified by preparative HPLC to afford 10 mg of compound **B1** as a white solid. **Yield: 15.9%.**



Step 4: A sample of compound **B1** (832 mg) was separated using a column packed with CHIRALPAK® IG (dimensions 30 × 250 mm, 10 μm particle size). A mobile phase consisting of 80% CO₂ (mobile phase A) and 20% methanol + 0.2% ammonia (mobile phase B) was used.

- 5 The separation was carried out under ambient conditions with a flow rate of 60 g/min, and detection at 214 nm and 254 nm. Compounds **B1-A**, **B1-B**, **B1-C** and **B1-D** was isolated with a retention time of 6.62 min, 7.65min, 6.28min, and 7.89min, respectively.

Example 21. Synthesis of Compound B3

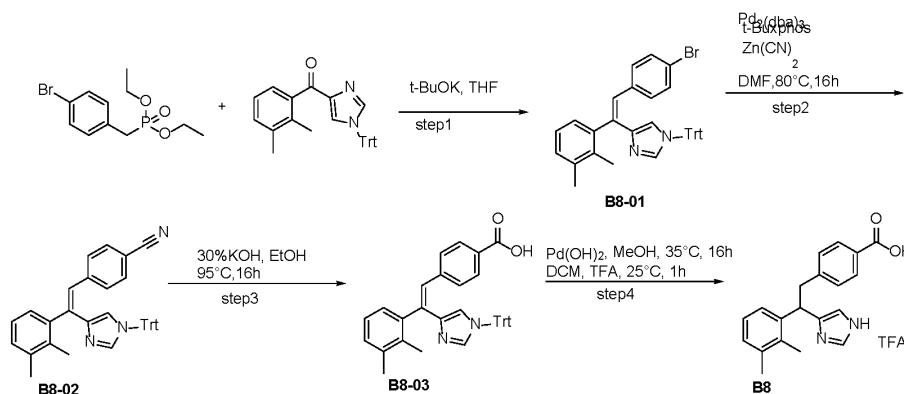


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Step 1: To a 250 mL three-necked flask, compound **B3-01** (1.78 g, 5.86 mmol, 1.0 equiv), (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (2.85 g, 6.45 mmol, 1.1 equiv), and 53 mL of THF were added. The reaction mixture was cooled to 0°C, and t-BuOK (1.97 g, 17.58 mmol, 3.0 equiv) was added. The mixture was stirred at 16°C for 16 hours under a nitrogen atmosphere.

- 15 LC-MS analysis confirmed completion of the reaction. The reaction mixture was filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (DCM/MeOH = 20:1 + 3% AcOH) to afford 875 mg of compound **B3-02** as a yellow solid. **Yield: 25.8%.**

- 20 **Step 2:** A mixture of compound **B3-02** (70 mg) and Pd(OH)₂ (70 mg) in 1 mL of THF was stirred at 45°C under a hydrogen atmosphere overnight. LC-MS analysis confirmed completion of the reaction. The reaction mixture was concentrated under vacuum, and the crude product was purified by preparative HPLC to afford 20.1 mg of compound **B3** as a white solid. **Yield: 36.8%.**

Example 22. Synthesis of Compound B8

Step 1: To a 250 mL three-necked flask, 500 mL of THF, diethyl(4-bromophenyl)phosphonate (17 g, 0.056 mol, 1.0 equiv), and (2,3-dimethylphenyl)[1-(trityl)-1H-imidazol-4-yl]methanone (24.6 g, 0.056 mol, 1.0 equiv) were added. The mixture was cooled to 0°C, and potassium tert-butoxide (18.9 g, 0.168 mol, 3.0 equiv) was added. The reaction mixture was stirred at 22.5°C for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was poured into 1 L of water and extracted with ethyl acetate (EA, 500 mL $\times$ 2). The organic phase was dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography to give 24.5 g of compound **B8-01**. **Yield: 64.05%.**

Step 2: A mixture of compound **B8-01** (400 mg, 0.67 mmol, 1.0 equiv), Zn(CN)_2 (95 mg, 0.81 mmol, 1.2 equiv), $\text{Pd}_2(\text{dba})_3$ (18 mg, 0.02 mmol, 0.03 equiv), and *t*-BuXPhos (17 mg, 0.04 mmol, 0.06 equiv) in 4 mL of DMF was stirred at 80°C for 16 hours under nitrogen. LC-MS showed the reaction was complete. The reaction mixture was poured into 50 mL of ice water and extracted with ethyl acetate (30 mL $\times$ 3). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (PE/EA = 100:0 to 85:15) to give 270 mg of compound **B8-02** as a white solid. **Yield: 74.6%.**

Step 3: A mixture of compound **B8-02** (270 mg, 0.5 mmol, 1.0 equiv) in 9 mL of ethanol and 3 mL of 30% KOH was stirred at 85°C for 16 hours under nitrogen. LC-MS showed the reaction was complete. The solution was concentrated under vacuum, and 30 mL of water was added. The aqueous phase was acidified with concentrated HCl until pH = 1 and then extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was dried over Na_2SO_4 , filtered, and concentrated under vacuum to afford 270 mg of compound **B8-03** as a white solid. **Yield: 96.4%.**

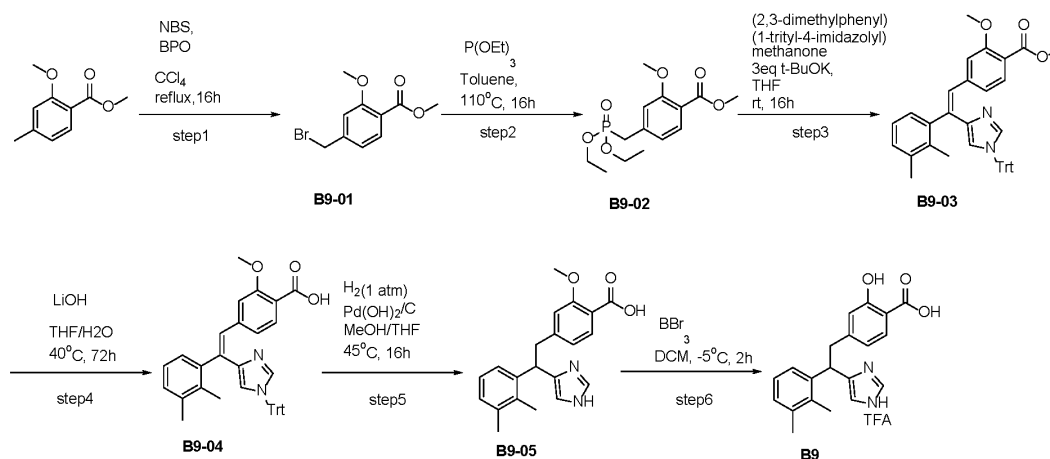
Step 4: A mixture of compound **B8-03** (80 mg, 0.14 mmol, 1.0 equiv) and Pd(OH)_2 (80 mg, 100%) in 3 mL of methanol/THF (1:1) was stirred at 35°C under a hydrogen atmosphere overnight. LC-MS showed the reaction was complete. The reaction mixture was concentrated

under vacuum, and the residue was dissolved in 1 mL of DCM and 0.5 mL of TFA. The mixture was stirred at 18°C for 15 minutes. The reaction was concentrated under vacuum, and the crude product was purified by preparative HPLC to give 40 mg of compound **B8** as a white solid.

Yield: 66.0%.

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Example 23. Synthesis of Compound B9



Step 1: To a 50 mL three-necked flask, 20 mL of CCl_4 and methyl 4-methyl-2-methoxybenzoate (2 g, 11.1 mmol, 1.0 equiv) were added. The reaction mixture was cooled to 0°C , and benzoyl peroxide (BPO, 0.145 g, 0.66 mmol, 0.05 equiv) and NBS (1.98 g, 11.1 mmol, 1.0 equiv) were added. The mixture was refluxed under a nitrogen atmosphere for 16 hours. LC-MS analysis confirmed completion of the reaction. The solvent was removed under vacuum, and the residue was purified by flash chromatography to give 2.6 g of compound **B9-01** as a colorless oil. **Yield: 90.44%.**

Step 2: To a 100 mL single-necked flask, 50 mL of toluene, compound **B9-01** (2.6 g, 10 mmol, 1.0 equiv), and triethyl phosphite (2.49 g, 15 mmol, 1.5 equiv) were added. The reaction mixture was stirred at 120°C for 16 hours under a nitrogen atmosphere. LC-MS analysis confirmed completion of the reaction. The solvent was removed under vacuum, and the residue was purified by flash chromatography to give 1.7 g of compound **B9-02** as a yellow oil. **Yield: 53.80%.**

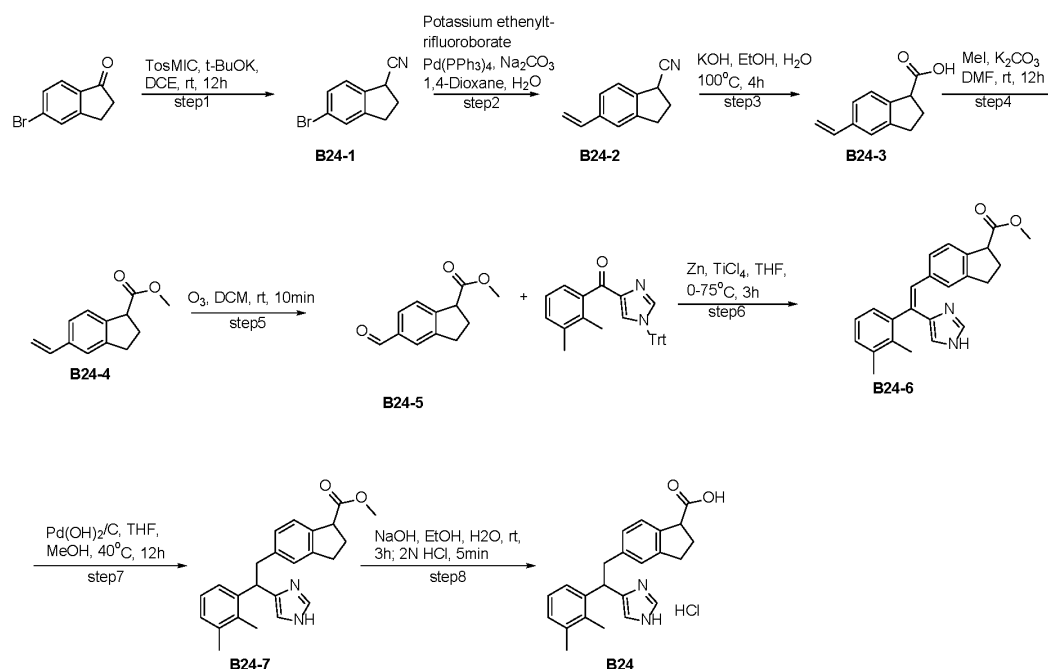
Step 3: To a 100 mL single-necked flask, 30 mL of THF, compound **B9-02** (1.5 g, 4.74 mmol, 1.3 equiv), and (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (1.5 g, 3.39 mmol, 1.0 equiv) were added. The reaction mixture was cooled to 0°C , and $t\text{-BuOK}$ (1.14 g, 10.17 mmol, 3.0 equiv) was added. The mixture was stirred at 11.6°C for 2 hours under a nitrogen atmosphere. LC-MS analysis confirmed completion of the reaction. The aqueous layer was

extracted twice with ethyl acetate, and the organic layer was dried and evaporated. The residue was purified by flash chromatography to give 2.5 g of compound **B9-03** as a yellow oil. **Yield: 87.32%.**

Step 4: To a 100 mL single-necked flask, 15 mL of THF, 15 mL of water, compound **B9-03** (0.5 g, 0.83 mmol, 1.0 equiv), and LiOH (0.177 g, 4.2 mmol, 5.0 equiv) were added. The reaction mixture was stirred at 40°C for 72 hours under a nitrogen atmosphere. LC-MS analysis confirmed completion of the reaction. The aqueous layer was extracted twice with ethyl acetate, and the organic layer was dried and evaporated. The residue was purified by flash chromatography to give 0.487 g of compound **B9-04** as a faint yellow solid. **Yield: 99.45%.**

Step 5: To a 100 mL single-necked flask, 4 mL of THF, 4 mL of methanol, compound **B9-04** (0.2 g, 0.339 mmol, 1.0 equiv), and Pd(OH)₂ (0.2 g, 1.0 wt equiv) were added. The reaction mixture was stirred at 45°C under a hydrogen atmosphere for 16 hours. LC-MS analysis confirmed completion of the reaction. The mixture was filtered through Celite, and the solvent was removed under vacuum. The residue was purified by flash chromatography to give 0.126 g of compound **B9-05** as a faint yellow solid. **Yield: 99.99%.**

Step 6: To a 25 mL single-necked flask, 5 mL of DCM and compound **B9-05** (0.106 g, 0.303 mmol, 1.0 equiv) were added. The reaction mixture was cooled to 0°C, and BBr₃ (0.114 g, 0.455 mmol, 1.5 equiv) was added. The reaction was stirred at 0°C for 2 hours under a nitrogen atmosphere. LC-MS analysis confirmed completion of the reaction. The solvent was removed under vacuum after adding 0.5 mL of TFA, and the residue was purified by preparative HPLC to give 0.017 g of compound **B9** as a faint yellow solid. **Yield: 12.47%.**

Example 24. Synthesis of Compound B24

Step 1: To a 500 mL three-necked flask, 180 mL of DCE, 20 mL of ethanol, 5-bromoindanone (10 g, 47.38 mmol, 1.0 equiv), and TosMIC (13.88 g, 71.07 mmol, 1.5 equiv) were added. The solution was stirred for 5 minutes, and then t-BuOK (10.63 g, 94.76 mmol, 2.0 equiv) was added at 25°C. The solution was stirred at ambient temperature for 12 hours. LC-MS analysis confirmed the reaction was complete. The solution was poured into 500 mL of ice water and extracted with DCM (200 mL $\times$ 2). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford a black oil. The crude product was purified by column chromatography (PE/EA = 90:10) to give 3.5 g of compound **B24-1** as an orange oil. **Yield: 33.26%.**

Step 2: To a 100 mL single-necked flask, 60 mL of dioxane, 6 mL of water, compound **B24-1** (3 g, 13.51 mmol, 1.0 equiv), potassium ethenyltrifluoroborate (2.71 g, 20.26 mmol, 1.5 equiv), Na₂CO₃ (2.15 g, 20.26 mmol, 1.5 equiv), and Pd(PPh₃)₄ (0.78 g, 0.68 mmol, 0.05 equiv) were added. The solution was stirred at 90°C under nitrogen for 12 hours. TLC analysis confirmed the reaction was complete. The mixture was poured into 300 mL of water and extracted with ethyl acetate (200 mL $\times$ 2). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford 5 g of **B24-2** as an orange oil, which was used in the next step without further purification. **Yield: 100%.**

Step 3: To a 100 mL single-necked flask, 50 mL of ethanol, compound **B24-2** (5 g, 13.53 mmol, 1.0 equiv), 7.59 g of water, and KOH (7.59 g, 135.32 mmol, 10.0 equiv) were added. The

reaction mixture was stirred at 100°C for 4 hours. LC-MS analysis confirmed the reaction was complete. The solution was poured into 300 mL of water and extracted with 100 mL of ethyl acetate. The aqueous phase was adjusted to pH 1 with concentrated HCl and then extracted with DCM (150 mL $\times$ 2). The DCM phase was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford 3.9 g of compound **B24-3** as an orange oil, which was used in the next step without further purification. **Yield: 100%.**

Step 4: To a 100 mL single-necked flask, 40 mL of DMF, compound **B24-3** (3.9 g, 13.55 mmol, 1.0 equiv), and K₂CO₃ (3.74 g, 27.10 mmol, 2.0 equiv) were added. Methyl iodide (3.85 g, 27.10 mmol, 2.0 equiv) was then added to the stirred solution. The mixture was stirred at ambient temperature for 12 hours. LC-MS analysis confirmed the reaction was complete. The mixture was poured into 300 mL of water and extracted with MTBE (100 mL $\times$ 2). The organic phase was washed with 100 mL of brine, dried over Na₂SO₄, filtered, and concentrated under vacuum to afford the crude oil. The crude product was purified by column chromatography (PE/EA = 95:5) to give 1.8 g of compound **B24-4** as a colorless liquid. **Yield: 65.69%.**

Step 5: To a 25 mL three-necked flask, 10 mL of DCM and compound **B24-4** (2 g, 9.89 mmol, 1.0 equiv) were added. Ozone was bubbled into the reaction mixture for 10 minutes. TLC analysis confirmed the reaction was complete. The solution was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford the crude oil. The crude product was purified by column chromatography (PE/EA = 90:10) to give 1.1 g of compound **B24-5** as a yellow oil. **Yield: 54.47%.**

Step 6: To a 25 mL three-necked flask, 100 mL of THF, (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (300 mg, 0.68 mmol, 1.0 equiv), compound **B24-5** (139 mg, 0.68 mmol, 1.0 equiv), and zinc powder (177 mg, 2.71 mmol, 4.0 equiv) were added. The solution was charged with nitrogen, and TiCl₄ (257 mg, 1.36 mmol, 2.0 equiv) was added dropwise at 10°C. The reaction mixture was stirred at 80°C for 3 hours. LC-MS analysis confirmed the reaction was complete. The mixture was cooled and poured into a mixture of 20 mL of ethyl acetate and 50 mL of saturated sodium bicarbonate solution. It was stirred for 5 minutes and filtered. The aqueous phase was extracted with ethyl acetate, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH = 90:10) to give 152 mg of compound **B24-6** as a yellow foam solid. **Yield: 36.47%.**

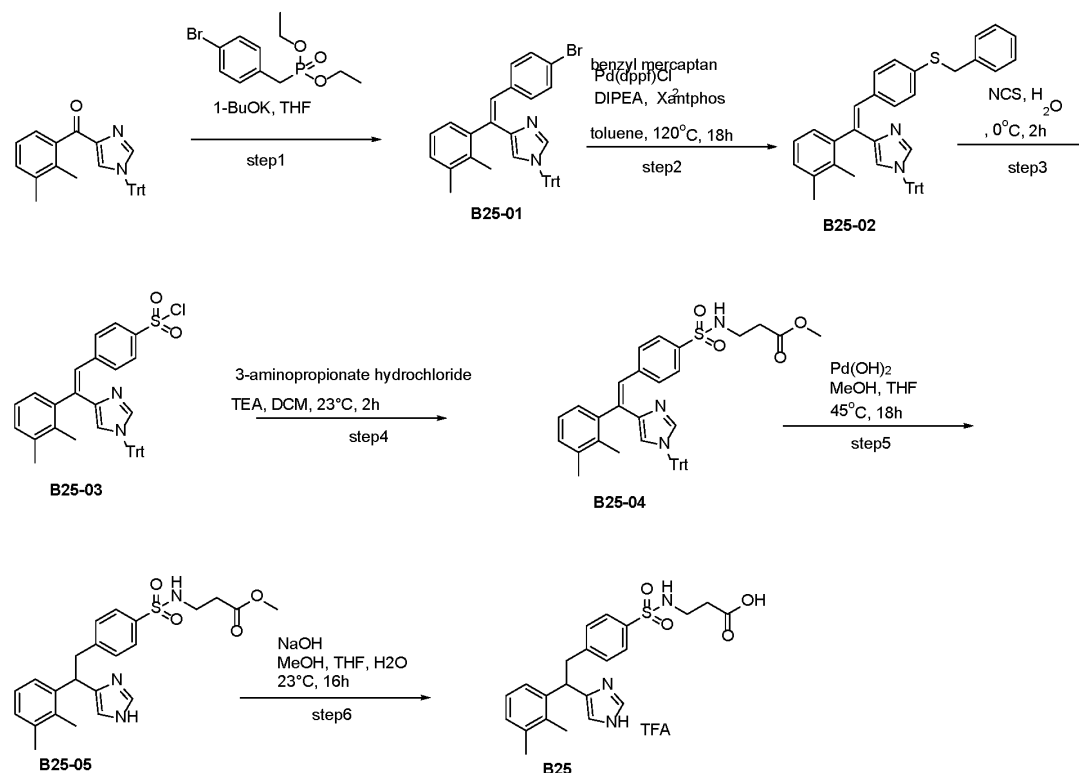
Step 7: To a 100 mL single-necked flask, 8 mL of THF, 8 mL of methanol, compound **B24-6** (150 mg, 0.40 mmol, 1.0 equiv), and Pd(OH)₂/C (80 mg) were added. The solution was stirred at 40°C under a hydrogen atmosphere for 12 hours. LC-MS analysis confirmed the reaction was

complete. The solution was filtered and concentrated under vacuum. The residue was purified by preparative TLC (ethyl acetate) to afford 72 mg of compound **B24-7** as a white solid. **Yield: 47.74%.**

Step 8: To a 10 mL single-necked flask, compound **B24-7** (72 mg, 0.19 mmol, 1.0 equiv), 0.1 mL of water, 1 mL of ethanol, and NaOH (23 mg, 0.58 mmol, 3.0 equiv) were added. The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis confirmed the reaction was complete. To the reaction mixture, 0.5 mL of 2 N HCl was added, and the mixture was stirred for 5 minutes. The solution was concentrated under vacuum, and the residue was purified by preparative HPLC to give 24 mg of compound **B24** as a white solid. **Yield: 31.45%.**

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Example 25. Synthesis of Compound B25



Step 1: To a 250 mL three-necked flask, 500 mL of THF, diethyl(4-bromophenyl)phosphonate (17 g, 0.056 mol, 1.0 equiv), and (2,3-dimethylphenyl)[1-(trityl)-1H-imidazol-4-yl]methanone (24.6 g, 0.056 mol, 1.0 equiv) were added. The mixture was cooled to 0°C, and potassium tert-butoxide (18.9 g, 0.168 mol, 3.0 equiv) was added. The reaction mixture was stirred at 22.5°C for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was poured into 1 L of water and extracted with ethyl acetate (EA, 500 mL × 2). The organic phase was dried over

Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography to give 24.5 g of **B25-01**. **Yield: 64.05%.**

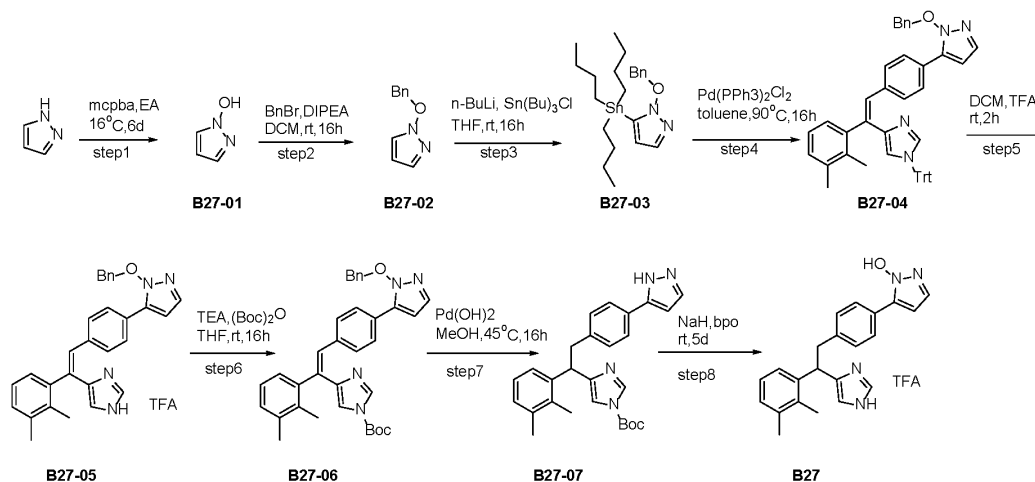
Step 2: A mixture of **B25-01** (500 mg, 0.84 mmol, 1.0 equiv), benzyl mercaptan (115 mg, 0.93 mmol, 1.1 equiv), DIPEA (217 mg, 1.68 mmol, 2.0 equiv), XantPhos (95 mg, 0.16 mmol, 0.2 equiv), and PdCl₂(dppf) (67 mg, 0.08 mmol, 0.1 equiv) in 10 mL of toluene was stirred at 120°C overnight under nitrogen. LC-MS analysis confirmed the reaction was complete. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (elution with DCM) to give 400 mg of **B25-02** as a faint yellow solid. **Yield: 66.7%.**

Step 3: To a mixture of **B25-02** (200 mg, 0.31 mmol, 1.0 equiv) in 1.2 mL of acetic acid and 3 mL of water, cooled to 0°C, NCS (210 mg, 1.57 mmol, 5.0 equiv) was added under nitrogen. The reaction mixture was stirred at 0°C for 2 hours under nitrogen. LC-MS analysis confirmed **B25-03** the reaction was complete. The reaction mixture was used directly for the next step. **Yield: 100%.**

Step 4: To a solution of methyl 3-aminopropionate hydrochloride (219 mg, 1.57 mmol, 5.0 equiv) and TEA (317 mg, 3.13 mmol, 10 equiv) in 10 mL of DCM, the crude **B25-03** from the previous step was added at 0°C under nitrogen. The reaction mixture was stirred at 23°C for 2 hours under nitrogen. LC-MS analysis confirmed the reaction was complete. The reaction mixture was concentrated under vacuum, and the crude product was purified by silica gel chromatography (DCM/MeOH = 20:1) to give 270 mg of **B25-04**. **Yield: 100%.**

Step 5: A mixture of **B25-04** (270 mg, 0.4 mmol, 1.0 equiv) and Pd(OH)₂ (270 mg) in 5 mL of THF and 5 mL of methanol was stirred at 45°C overnight under a hydrogen atmosphere. LC-MS analysis confirmed the reaction was complete. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to afford 57 mg of crude product. The crude product was purified by silica gel chromatography (DCM/MeOH = 10:1) to give 65 mg of **B25-05**. **Yield: 35.0%.**

Step 6: A mixture of **B25-05** (65 mg, 0.14 mmol, 1.0 equiv) and NaOH (11 mg, 0.27 mmol, 2.0 equiv) in a MeOH/THF/H₂O mixture (2:2:1, 6 mL) was stirred at 23°C for 16 hours under nitrogen. LC-MS analysis confirmed the reaction was complete. The reaction mixture was concentrated under vacuum, and 0.5 mL of TFA was added, followed by stirring at room temperature for 1 hour. The residue was concentrated under vacuum, and the crude product was purified by preparative HPLC to give 50 mg of **B25** as a white solid. **Yield: 65.9%.**

Example 26. Synthesis of Compound B27

Step 1: A mixture of pyrazole (60 g, 0.881 mol, 1.0 equiv) and 3-chloroperoxybenzoic acid (152.1 g, 0.881 mol, 1.0 equiv) in ethyl acetate (3 L) was stirred at room temperature for 10 days. LC-MS showed the reaction was incomplete. The reaction mixture was concentrated and quenched with saturated sodium sulfite solution. The organic layer was washed with saturated sodium bicarbonate solution, dried over Na₂SO₄, filtered, and concentrated to give compound **B27-01** (8 g) as a purple liquid. **Yield: 10.8%.**

Step 2: A mixture of compound **B27-01** (4.5 g, 0.0536 mol, 1.0 equiv), benzyl bromide (9.2 g, 0.0541 mol, 1.01 equiv), and DIPEA (7 g, 0.0541 mol, 1.01 equiv) in DCM (54 mL) was stirred at room temperature for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (PE/EA = 96:4) to give compound **B27-02** (7.57 g) as a colorless liquid. **Yield: 81.1%.**

Step 3: To a mixture of compound **B27-02** (1 g, 5.74 mmol, 1.0 equiv) in 15 mL of THF was added n-BuLi (2.5 M, 2.5 mL, 6.31 mmol, 1.1 equiv) at -78°C. The reaction was stirred at -78°C for 2 hours under nitrogen, then tributyltin chloride (2.06 g, 6.31 mmol, 1.1 equiv) was added at -78°C. The reaction was stirred at room temperature for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was quenched with saturated ammonium chloride (5 mL) and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EA = 92:8) to give compound **B27-03** (1.7 g) as a colorless liquid. **Yield: 63.8%.**

Step 4: A mixture of compound **B27-03** (1.16 g, 1.95 mmol, 1.0 equiv), (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (1 g, 2.15 mmol, 1.1 equiv), and Pd(PPh₃)₂Cl₂ (68 mg, 0.0975

mmol, 0.05 equiv) in toluene (10 mL) was stirred at 95°C for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was filtered, and the organic solution was concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EA = 3:1) to give compound compound **B27-04** (1.19 g) as a white solid.

5 **Yield: 88.7%.**

Step 5: A mixture of compound **B27-04** (1.19 g, 1.0 equiv) and TFA (5 mL) in DCM (10 mL) was stirred at room temperature for 1 hour. LC-MS showed the reaction was complete. The reaction mixture was concentrated under vacuum, and the crude product was purified by silica gel column chromatography (MeOH/DCM = 13:87) to give compound **B27-05** (550 mg) as a

10 white solid. **Yield: 56.8%.**

Step 6: A mixture of compound **B27-05** (290 mg, 0.518 mmol, 1.0 equiv), TEA (157 mg, 1.554 mmol, 3.0 equiv), and (Boc)₂O (169 mg, 0.777 mmol, 1.5 equiv) in THF (3 mL) was stirred at room temperature for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography

15 (PE/EA = 3:1) to give compound **B27-06** (243 mg) as a white solid. **Yield: 85.9%.**

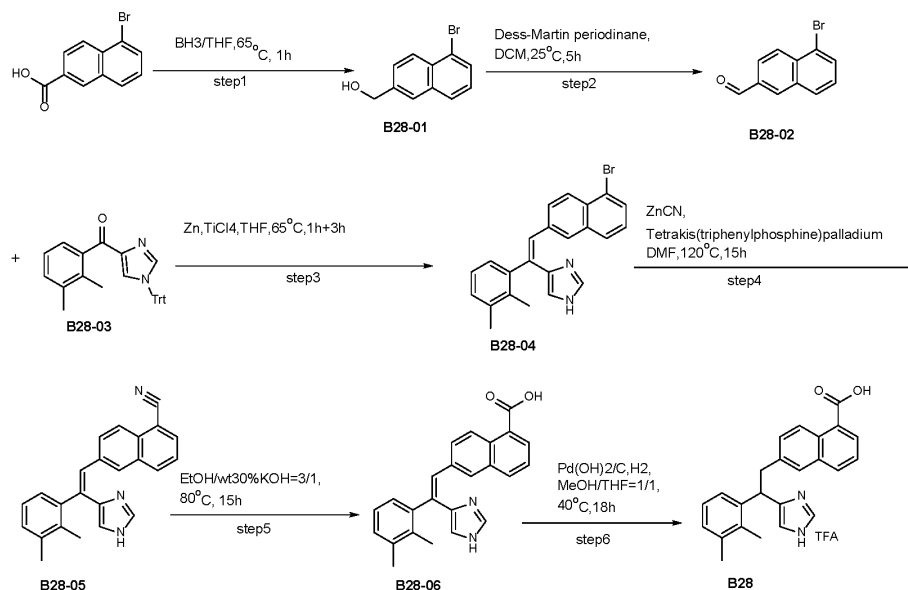
Step 7: A mixture of compound **B27-06** (243 mg) and Pd(OH)₂ (243 mg) in THF (2.5 mL) and methanol (2.5 mL) was stirred at 45°C for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was filtered, and the organic solution was concentrated under vacuum. The crude product was purified by preparative TLC (PE/EA = 5:1) to give compound **B27-07** (130

20 mg) as a colorless liquid. **Yield: 66.1%.**

Step 8: To a mixture of compound **B27-07** (110 mg, 0.249 mmol, 1.0 equiv) in 2.5 mL of THF, NaH (11 mg, 0.274 mmol, 1.1 equiv) was added at 0°C. The reaction was stirred at room temperature for 0.5 hours under nitrogen, then BPO (6 mg, 0.0249 mmol, 0.1 equiv) was added. The mixture was stirred at room temperature for 5 days. LC-MS showed the reaction was

25 incomplete. The reaction mixture was quenched with ice water (3 mL) and adjusted to pH 6 with 1 M HCl. The mixture was extracted with ethyl acetate, and the organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was added to 2 mL of DCM and 1 mL of TFA, then stirred at room temperature for 0.4 hours. The mixture was concentrated, and the crude product was purified by preparative HPLC to give compound **B27** (2 mg) as a white

30 solid. **Yield: 1.7%.**

Example 27. Synthesis of Compound B28

Step 1: A 50 mL reaction flask containing 10 mL THF and 5-bromo-2-naphthoic acid (1 g, 3.98 mmol, 1 eq) was cooled to 0°C . BH_3/THF (1 M, 9.9 mL, 9.96 mmol, 2.5 eq) was added dropwise. The mixture was stirred at 65°C for 1 hour. LC-MS analysis confirmed the reaction was complete. The solution was cooled to 0°C , and methanol (3 mL) was added dropwise to quench the reaction. The mixture was poured into water and extracted with EA. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **B28-01** (790 mg) as a white solid. **Yield: 83.7%.**

Step 2: A 50 mL reaction flask containing 14 mL DCM, **B28-01** (700 mg, 2.95 mmol, 1 eq), and Dess-Martin periodinane (1.5 g, 3.54 mmol, 1.2 eq) was stirred at 25°C for 1 hour. LC-MS analysis confirmed the reaction was complete. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography to afford **B28-02** (570 mg) as a white solid. **Yield: 82.1%.**

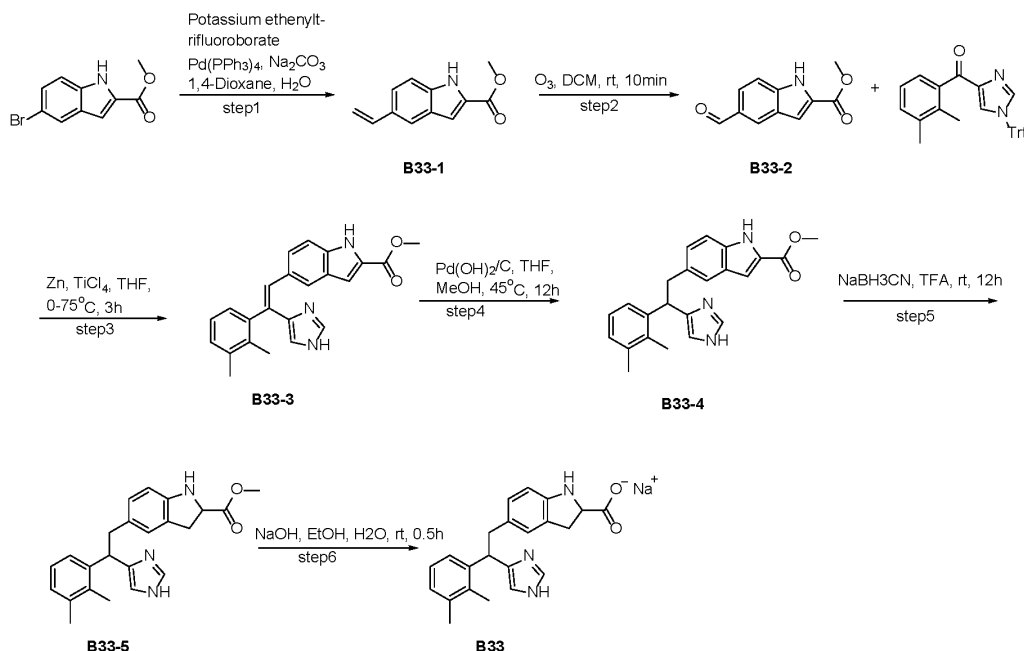
Step 3: A 50 mL reaction flask containing 10 mL THF and Zn (1.1 g, 16.84 mmol, 19 eq) was cooled to 0°C . TiCl_4 (1.61 g, 8.50 mmol, 9.6 eq) was added slowly while maintaining the temperature at $0-10^\circ\text{C}$. The mixture was refluxed for 1 hour, then cooled to room temperature. A solution of **B28-02** (500 mg, 2.13 mmol, 2.4 eq) and **B28-03** ((2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone, 392 mg, 0.886 mmol, 1 eq) in 5 mL THF was added slowly. The reaction mixture was refluxed for 3 hours. LC-MS analysis confirmed the reaction was complete. The mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **B28-04** (250 mg). **Yield: 70.0%.**

Step 4: A 25 mL reaction flask containing 5 mL DMF, **B28-04** (220 mg, 0.545 mmol, 1 eq), $\text{Zn}(\text{CN})_2$ (128 mg, 1.09 mmol, 2 eq), and tetrakis(triphenylphosphine)palladium (126 mg, 0.109 mmol, 0.2 eq) was stirred at 120°C for 15 hours. LC-MS analysis confirmed the reaction was complete. The mixture was poured into water and extracted with EA. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **B28-05** (100 mg) as a white solid. **Yield: 52.5%.**

Step 5: A 25 mL reaction flask containing 6 mL ethanol, 2 mL 30% KOH solution, and **B28-05** (100 mg, 1 eq) was stirred at 80°C for 15 hours. LC-MS analysis confirmed the reaction was complete. The mixture was adjusted to pH 4 and filtered to afford **B28-06** (240 mg) as a white solid. **Yield: 100%.**

Step 6: A mixture of **B28-06** (240 mg), $\text{Pd}(\text{OH})_2/\text{C}$ (50 mg), methanol (5 mL), and THF (5 mL) was stirred at 40°C for 15 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Then, 4 mL DCM and 2 mL TFA were added, and the mixture was stirred for 10 minutes. The solvent was evaporated, and the residue was purified by preparative HPLC to afford **B28** (22 mg) as a white solid. **Yield: 15.9%.**

Example 28. Synthesis of Compound B33



Step 1: A 250 mL single-necked flask containing 75 mL dioxane, 2.5 mL water, 5-bromoindole-2-carboxylic acid methyl ester (5 g, 19.68 mmol, 1.0 eq), potassium ethenyltrifluoroborate (5.27

g, 39.36 mmol, 2.0 eq), Na₂CO₃ (4.17 g, 39.36 mmol, 2.0 eq), and Pd(PPh₃)₄ (1.14 g, 0.98 mmol, 0.05 eq) was stirred at 100°C under nitrogen for 12 hours. TLC showed the reaction was complete. The mixture was filtered, poured into 150 mL water, and extracted with EA (150 mL × 3). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (PE/EA = 90:10) to afford **B33-1** (2.3 g) as a yellow solid. **Yield: 58.08%.**

Step 2: A 100 mL three-necked flask containing 50 mL DCM and **B33-1** (2.3 g, 11.43 mmol, 1.0 eq) was treated with ozone (O₃) bubbled into the reaction mixture for 10 minutes. TLC showed the reaction was complete. The solution was filtered, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford an oily crude product. The crude was purified by column chromatography (PE/EA = 85:15) to afford **B33-2** (410 mg) as a yellow oil. **Yield: 17.65%.**

Step 3: A 50 mL three-necked flask containing 10 mL THF, (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (458 mg, 1.03 mmol, 1.0 eq), **B33-2** (210 mg, 1.03 mmol, 1.0 eq), and Zn (270 mg, 4.13 mmol, 4.0 eq) was charged with nitrogen, and TiCl₄ (392 mg, 2.07 mmol, 2.0 eq) was added dropwise at 10°C. The reaction mixture was stirred at 80°C for 3 hours. LC-MS showed the reaction was complete. The solution was cooled and poured into a mixture of 50 mL EA and 60 mL saturated sodium bicarbonate solution, stirred for 5 minutes, and filtered. The aqueous phase was extracted with EA (25 mL × 2). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH = 90:10) to afford **B33-3** (350 mg) as a yellow foam solid. **Yield: 91.18%.**

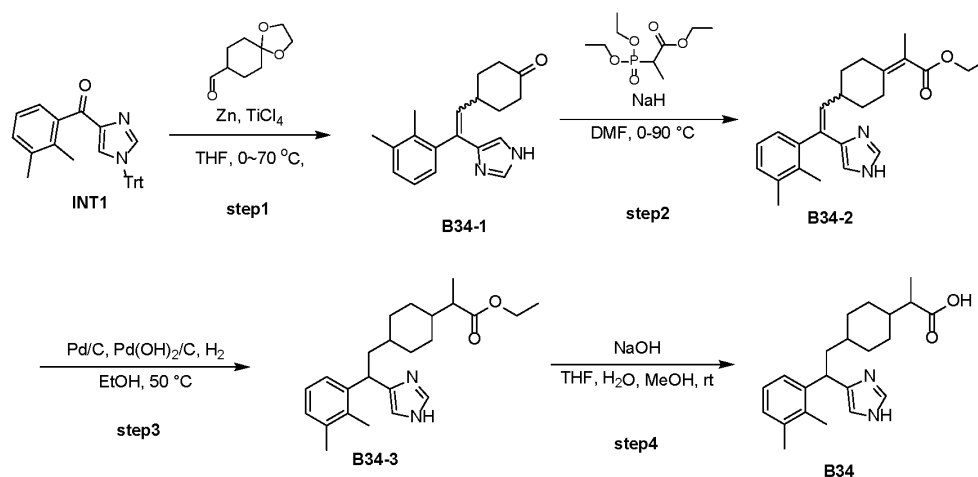
Step 4: A 50 mL single-necked flask containing 5 mL THF, 5 mL methanol, **B33-3** (350 mg, 0.94 mmol, 1.0 eq), and Pd(OH)₂/C (50 mg) was stirred at 45°C under a hydrogen atmosphere for 12 hours. LC-MS showed the reaction was complete. The solution was filtered and concentrated under vacuum. The residue was purified by preparative TLC (EA) to afford **B33-4** (165 mg) as a white solid. **Yield: 46.89%.**

Step 5: A 10 mL single-necked flask containing 1 mL TFA and **B33-4** (50 mg, 0.13 mmol, 1.0 eq) was treated with NaBH₃CN (42 mg, 0.67 mmol, 5.0 eq). The solution was stirred at room temperature for 12 hours. LC-MS showed the reaction was complete. The solution was concentrated under vacuum, and the residue was purified by preparative HPLC to afford **B33-5** (19 mg) as a white solid. **Yield: 37.80%.**

Step 6: A 10 mL single-necked flask containing **B33-5** (19 mg, 0.05 mmol, 1.0 eq), 0.5 mL ethanol, and NaOH (1 M, 0.1 mL, 0.1 mmol, 2.0 eq) was stirred at room temperature for 30

minutes. LC-MS showed the reaction was complete. The solution was purified by preparative HPLC to afford **B33** (2 mg) as a white solid. **Yield: 10.31%.**

Example 29. Synthesis of Compound B34



5

Step 1: A 50 mL reaction flask containing a mixture of 4-[(2,3-dimethylphenyl)carbonyl]-1-(triphenylmethyl)imidazole (500 mg, 1.12 mmol), 1,4-dioxaspiro[4.5]decane-8-carbaldehyde (192.30 mg, 1.12 mmol), and Zn (738.99 mg, 11.29 mmol) in THF (10 mL) was cooled to 0°C. TiCl₄ (1.2 mL, 11.29 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and then at 70°C for 4 hours. LC-MS analysis confirmed the reaction was complete. The mixture was diluted with water and extracted with EA. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude product was purified by flash column chromatography (DCM/MeOH = 50:1 to 5:1) to afford **B34-1** (160 mg) as a yellow solid. **Yield: 48.19%.**

Step 2: A 50 mL reaction flask containing NaH (407.61 mg, 10.19 mmol) in DMF (5 mL) was cooled to 0°C under a nitrogen atmosphere. Ethyl 2-(diethoxyphosphoryl)propanoate (2.43 g, 10.19 mmol) in DMF (7 mL) was added dropwise. The mixture was stirred at 0°C for 1 hour. A solution of **B34-1** (300 mg, 1.0191 mmol) in DMF (3 mL) was added dropwise at 0°C, and the reaction mixture was stirred at 90°C for 2 hours. LC-MS confirmed the reaction was complete. The mixture was quenched with saturated NH₄Cl solution (100 mL) and extracted with EA (3 × 50 mL). The combined organic phases were washed with brine (2 × 80 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography (MeOH/DCM = 4%) to afford **B34-2** (350 mg) as a yellow solid. **Yield: 83.4%.**

Step 3: A sealed tube containing a solution of **B34-2** (350 mg, 0.9247 mmol) in ethanol (10 mL), Pd/C (350 mg, 3.2889 mmol), and Pd(OH)₂/C (350 mg, 2.4923 mmol) was evacuated and

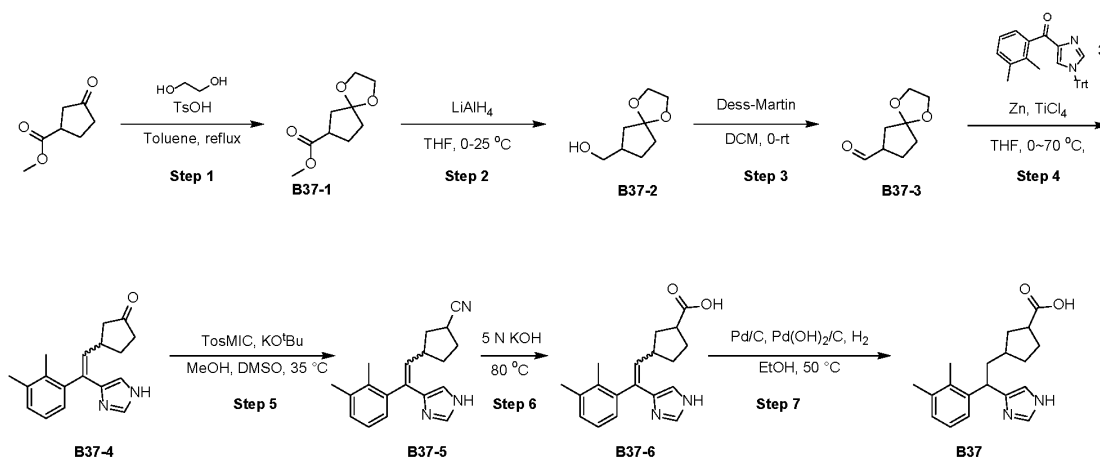
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backfilled with hydrogen three times, then charged with hydrogen (3 MPa). The reaction mixture was stirred at 50°C for 16 hours under a hydrogen atmosphere. LC-MS confirmed the reaction was complete. The mixture was filtered, and the filter cake was washed with ethanol (30 mL). The filtrate was concentrated to dryness to afford **B34-3** (300 mg) as a colorless oil. **Yield:**

5 **78.03%.**

Step 4: A 10 mL reaction flask containing a solution of **B34-3** (200 mg, 0.5228 mmol) in THF (3 mL), H₂O (1.5 mL), and methanol (3 mL) was stirred with NaOH (41.82 mg, 1.4056 mmol) at 25°C for 12 hours. LC-MS confirmed the reaction was complete. The solvent was removed, and the mixture was diluted with water (100 mL) and adjusted to pH 4 with 1 M HCl. The mixture
10 was extracted with EA (30 mL), and the organic phase was dried and concentrated. The crude product was purified by preparative HPLC (Gemini column, ACN-H₂O with 0.05% NH₄OH) to give **B34** (40 mg) as a white solid. **Yield: 20.7%.**

Example 30. Synthesis of Compound B37



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Step 1: A mixture of methyl 3-oxocyclopentane-1-carboxylate (CAS: 32811-75-9) (20 g, 140.7 mmol), ethane-1,2-diol (17.47 g, 281.4 mmol), and 4-methylbenzenesulfonic acid (2.42 g, 14 mmol) in toluene (200 mL) was heated at 110°C under a nitrogen atmosphere for 4 hours. After cooling to ambient temperature, the reaction mixture was quenched with NaHCO₃ (200 mL) and
20 extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (0–25% EtOAc in hexanes) to afford **B37-1** (3.2 g, 16.3 mmol) as a yellow oil. **Yield: 12%.**

Step 2: A solution of **B37-1** (3.7 g, 19.9 mmol) in THF (30 mL) was cooled to 0°C, and LAH
25 (39.8 mL, 39.8 mmol) was added dropwise. The mixture was stirred at 25°C for 3 hours. The

reaction was quenched with water (20 mL), 15% NaOH (20 mL), and water (60 mL). The organic phase was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under vacuum to afford **B37-2** (2.1 g, 12.6 mmol) as a yellow oil. **Yield: 63.32%.**

- 5 **Step 3:** A mixture of **B37-2** (1 g, 6.3 mmol) in DCM (10 mL) and Dess-Martin periodinane (3.21 g, 7.5 mmol) was stirred at 25°C for 2 hours. TLC showed the reaction was complete. The mixture was quenched with NaHCO₃ (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (0–30% EtOAc in hexanes) to afford **B37-3** (0.6 g, 3.6 mmol) as a yellow oil. **Yield: 57.14%.**

- 10 **Step 4:** A mixture of 4-[(2,3-dimethylphenyl)carbonyl]-1-(triphenylmethyl)imidazole (1700.15 mg, 3.84 mmol), **B37-3** (600 mg, 3.84 mmol), and Zn (1507.69 mg, 23.05 mmol) in THF (20 mL) was cooled to 0°C. TiCl₄ (4372.16 mg, 23.05 mmol) was added dropwise. The mixture was stirred for 1 hour at 0°C and then heated to 70°C for 3 hours. LC-MS showed the reaction was complete. The mixture was quenched with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (0–5% MeOH in DCM) to afford **B37-4** (200 mg, 0.57 mmol) as a yellow solid. **Yield: 15%.**

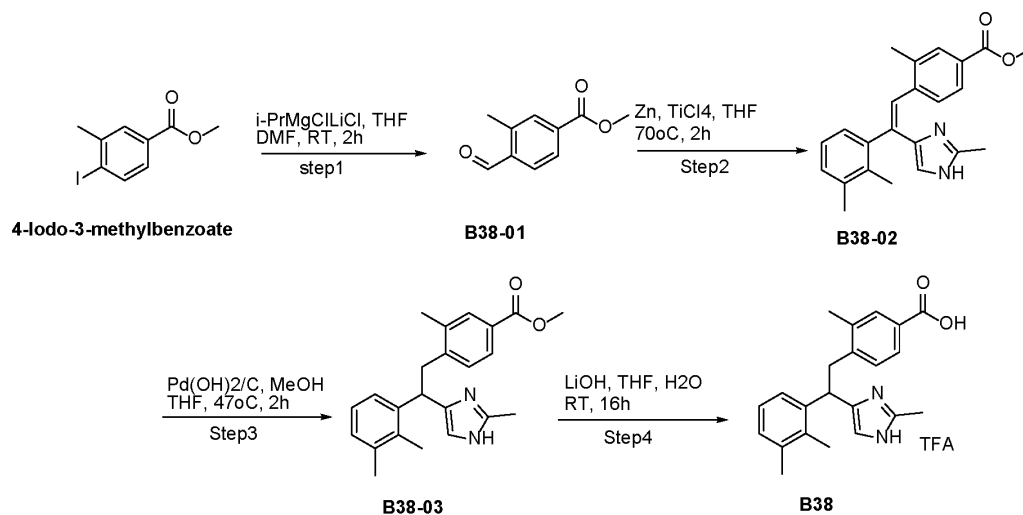
- 15 **Step 5:** A mixture of TosMIC (208.91 mg, 1.07 mmol) and t-BuOK (350.20 mg, 3.12 mmol) in DMSO (3 mL) was stirred at 25°C for 30 minutes. LC-MS showed the reaction was complete. The mixture was quenched with water, and MeOH (66.09 mg, 0.8917 mmol) and **B37-4** (250 mg, 0.8917 mmol) in DMSO (2 mL) were added dropwise. The reaction mixture was stirred at 25°C for 16 hours. LC-MS showed the reaction was complete. The mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under vacuum to afford **B37-5** (200 mg, 0.5834 mmol) as a yellow solid. **Yield: 65%.**

- 20 **Step 6:** A mixture of **B37-5** (120 mg, 0.4118 mmol) in 5 N KOH (5 mL) was heated at 80°C for 16 hours. LC-MS showed the reaction was complete. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried with sodium sulfate, and concentrated under vacuum to afford **B37-6** (90 mg, 0.2755 mmol) as a white solid. **Yield: 67%.**

- 25 **Step 7:** A mixture of **B37-6** (90 mg, 0.29 mmol), Pd/C (92.59 mg, 0.87 mmol), and Pd(OH)₂/C (122.17 mg, 0.87 mmol) in methanol (3 mL) was heated at 50°C under a hydrogen atmosphere (3 MPa) for 16 hours in a high-pressure reactor. After cooling to ambient temperature, the

mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified on a Biotage Isolera One (C18 column, eluting with 10–90% MeCN/H₂O containing 0.1% TFA) to provide **B37** (33.01 mg, 0.1046 mmol) as a white solid. **Yield: 36%.**

5 Example 31. Synthesis of Compound B38



Step 1: To a solution of methyl 4-iodo-3-methylbenzoate (5 g, 18 mmol, 1 equiv) in THF, isopropylmagnesium chloride lithium chloride complex (69.7 mL, 91 mmol, 5 equiv) was added at -10°C. The solution was stirred for 2 hours at -10°C under a nitrogen atmosphere. DMF (3.2 g, 43 mmol, 6 equiv) was then added at -10°C, and the solution was stirred for 2 hours at room temperature under nitrogen. LC-MS analysis confirmed the reaction was complete. The reaction mixture was diluted with 200 mL of water and extracted with ethyl acetate (EA, 200 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **B38-01** (3 g) as crude. The crude product was purified by silica gel column chromatography (EA/PE = 1/20) to afford 3 g of **B38-01**. **Yield: 93.7%.**

Step 2: To a solution of zinc (842 mg, 12.9 mmol, 19 equiv) in THF, titanium tetrachloride (1.2 g, 6.51 mmol, 9.6 equiv) was added at -10°C. The solution was stirred for 1 hour at 70°C under a nitrogen atmosphere. Then, (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (320 mg, 0.68 mmol, 1 equiv) and **B38-01** (362 mg, 2.03 mmol, 3 equiv) were added at room temperature, and the mixture was stirred for 2 hours at 70°C under nitrogen. LC-MS analysis confirmed the reaction was complete. The reaction mixture was diluted with 100 mL of water and extracted with EA (50 mL × 2). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel

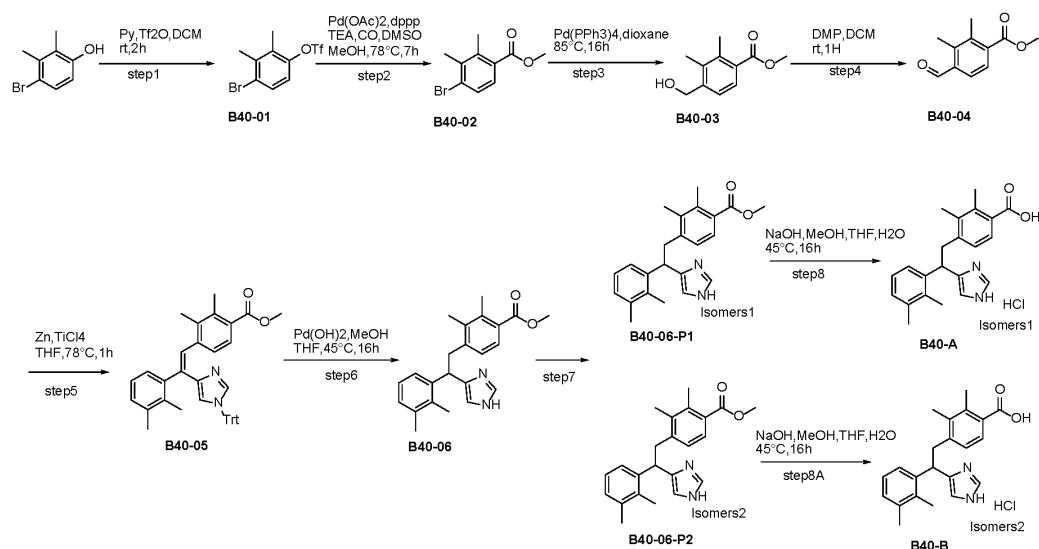
column chromatography (MeOH/DCM = 1/20) to afford 240 mg of **B38-02** as a white solid.

Yield: 100%.

Step 3: To a solution of **B38-02** (240 mg, 0.72 mmol, 1.0 equiv) in methanol and THF, Pd(OH)₂/C (240 mg, 1.0 wt%) was added at room temperature. The suspension was stirred at 47°C under a hydrogen atmosphere overnight. LC-MS analysis confirmed the reaction was complete. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product. The crude product was purified by preparative TLC to afford 100 mg of **B38-03** as a white solid. **Yield: 41%.**

Step 4: A mixture of **B38-03** (100 mg, 0.29 mmol, 1.0 equiv) and LiOH (36 mg, 0.86 mmol, 3 equiv) in methanol and water was stirred at room temperature for 2 hours under nitrogen. The reaction mixture was evaporated to dryness to provide 320 mg of crude **B39**. The crude product was purified by preparative HPLC to afford 67 mg of **B39** as a white solid. **Yield: 68.4%.**

Example 32. Synthesis of Compound B40-A and B40-B



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Step 1: A mixture of 4-bromo-2,3-dimethylphenol (10 g, 0.05 mol, 1.0 eq) and pyridine (11.87 g, 0.15 mol, 3.0 eq) in DCM (100 mL) was cooled to 0°C. Trifluoromethanesulfonic anhydride (23.97 g, 0.085 mol, 1.7 eq) was added at 0°C, and the mixture was stirred at room temperature for 2 hours under a nitrogen atmosphere. LC-MS analysis confirmed the reaction was complete. The reaction mixture was poured into 100 mL of ice water and extracted with DCM. The organic phase was washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford compound **B40-01** (15.53 g) as a colorless liquid. **Yield: 93.6%.**

Step 2: A mixture of **B40-01** (8 g, 0.024 mol, 1.0 eq), TEA (4.62 g, 0.0461 mol, 1.9 eq), Pd(OAc)₂ (1.1 g, 0.00482 mmol, 0.2 eq), and dppp (1.88 g, 0.0058 mmol, 0.24 eq) in a 1:1 mixture of DMSO and MeOH (260 mL) was stirred at 78°C under a 5 MPa CO atmosphere for 7 hours. LC-MS analysis confirmed the reaction was complete. The reaction mixture was poured
5 into 1.2 L of ice water and extracted with DCM. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford compound **B40-02**.

Step 3: A mixture of **B40-02** (3.357 g, 0.0139 mol, 1.0 eq), (tributylstannyl)methanol (6.68 g, 0.0208 mol, 1.5 eq), and Pd(PPh₃)₄ (1.2 g, 0.104 mmol, 0.075 eq) in dioxane (40 mL) was stirred
10 at 85°C for 16 hours under a nitrogen atmosphere. LC-MS analysis showed the reaction was incomplete. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography to afford compound **B40-03** (674 mg) as a white solid. **Yield: 25%.**

Step 4: A mixture of **B40-03** (610 mg, 3.14 mmol, 1.0 eq) and Dess-Martin periodinane (DMP) (2 g, 4.71 mmol, 1.5 eq) in DCM (6 mL) was stirred at room temperature for 1 hour under a
15 nitrogen atmosphere. LC-MS analysis confirmed the reaction was complete. The reaction mixture was poured into 6 mL of saturated sodium bicarbonate solution, filtered, and extracted with DCM. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford compound **B40-04** (496 mg) as a white solid. **Yield: 82.3%.**

Step 5: A mixture of **B40-04** (496 mg, 2.58 mmol, 1.0 eq), (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (1.14 g, 2.58 mmol, 1.0 eq), and Zn (1.26 g, 19.35 mmol, 7.5 eq) in THF (10 mL) was cooled to 0°C, and TiCl₄ (1.81 g, 9.55 mmol, 3.7 eq) was added dropwise. The mixture was stirred at 80°C for 1 hour under a nitrogen atmosphere. LC-MS analysis confirmed the reaction was complete. The mixture was poured into 50 mL of ice water, filtered, and
25 extracted with ethyl acetate (EA). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford compound **B40-05** (210 mg) as a white solid. **Yield: 13.5%.**

Step 6: A mixture of **B40-05** (210 mg, 1 eq) and Pd(OH)₂ (210 mg, 1.0 wt) in a 1:1 mixture of MeOH and THF (6 mL) was stirred at 45°C under a hydrogen atmosphere overnight. LC-MS
30 analysis confirmed the reaction was complete. The mixture was filtered and concentrated under vacuum to afford compound **B40-06** (82.5 mg) as a white solid. **Yield: 65.3%.**

Step 7: A total of 285 mg of **B40-06** was separated on a column with dimensions 30 × 250 mm packed with **CHIRALPAK® IB-10** (10 μm particle size). A mixture of 70% mobile phase A (CO₂) and 30% mobile phase B (0.2% ammonia in MeOH/EtOH) was used. The operational

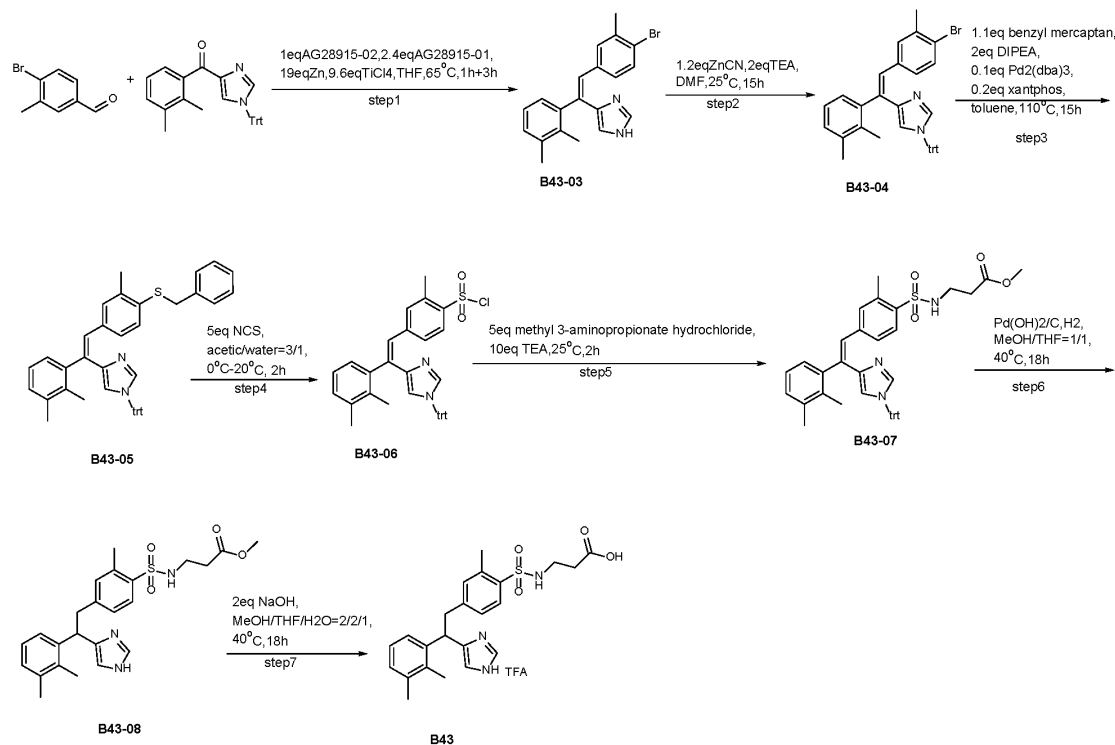
conditions were: 35°C, flow rate 3 g/min, detection at 214 nm and 254 nm. The first eluting enantiomer, **B40-06-P1** (125 mg), was isolated with an enantiomeric excess of 100%. **Yield: 87.7%**. The second eluting enantiomer, **B40-06-P2** (139 mg), was isolated with an enantiomeric excess of 100%. **Yield: 97.5%**.

- 5 **Step 8:** A mixture of **B40-06-P1** (125 mg, 0.345 mmol, 1.0 eq) and NaOH (55 mg, 1.38 mmol, 4.0 eq) in a 2:2:1 mixture of MeOH, THF, and H₂O (2 mL) was stirred at 45°C for 16 hours under a nitrogen atmosphere. LC-MS analysis confirmed the reaction was complete. The mixture was concentrated under vacuum, adjusted to pH 1 with 1 M HCl, and concentrated again under vacuum. The residue was purified by preparative HPLC to afford compound **B40-A**
 10 (86.1 mg) as a white solid. **Yield: 65%**.

Overall yield: 0.6%.

- Step8A: A mixture of **B41-06-P2** (109mg, 0.345mmol, 1.0eq), NaOH (55mg, 1.38mmol, 4.0eq) in MeOH/THF/H₂O=2/2/1 (2mL) was stirred at 45°C for 16h under N₂. LCMS showed the
 15 reaction was completed. The reaction was concentrated under vacuum. The crude was adjusted to pH=1 with 1M HCl. The mixture was concentrated under vacuum and the residue was purified by prep-Hplc to give the compound **B41-B** (80.8mg) as a white solid. Yield: 70%
 Overall yield: 0.7%

Example 33. Synthesis of Compound B43



Step1: To a 250 mL reaction flask was added 60 mL THF, Zn (6.4 g, 98.74 mmol, 19 eq), cooled to 0°C, slowly added TiCl₄ (9.5 g, 49.89 mmol, 9.6 eq) while controlling the temperature at 0-10°C. The mixture was refluxed for 1 hour, cooled to room temperature, and then a solution of 4-bromo-3-methyl-benzaldehyde (2.5 g, 12.56 mmol, 2.4 eq) and (2,3-dimethylphenyl)[1-(trityl)-1H-imidazol-4-yl]methanone (2.3 g, 5.23 mmol, 1 eq) in 40 mL THF was added slowly. The reaction was refluxed for 3 hours. LC-MS showed the reaction was completed. The mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (DCM/MeOH = 94/6) to afford **B43-03** (1.9 g). **Yield: 100%.**

Step2: To a 100 mL reaction flask was added 36 mL DMF, **B43-03** (1.85 g, 5.03 mmol, 1.0 eq), triphenylmethyl chloride (1.68 g, 6.04 mmol, 1.2 eq), and TEA (1.02 g, 10.07 mmol, 2 eq). The reaction mixture was stirred at 25°C for 15 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The residue was purified by silica gel column chromatography (PE/EA = 93/7) to afford **B43-04** (2.1 g). **Yield: 68.4%.**

Step3: To a 50 mL reaction flask was added 20 mL toluene, **B43-04** (1 g, 1.64 mmol, 1.0 eq), DIPEA (424 mg, 3.28 mmol, 2 eq), benzyl mercaptan (224 mg, 1.80 mmol, 1.1 eq), Pd₂(dba)₃ (150 mg, 0.164 mmol, 0.1 eq), and xantphos (190 mg, 0.328 mmol, 0.2 eq). The reaction mixture was stirred at 110°C for 15 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The residue was purified by silica gel column chromatography (PE/EA = 89/11) to afford **B43-05** (720 mg). **Yield: 67.2%.**

Step4: To a 25 mL reaction flask was added 6 mL acetic acid and 2 mL water, **B43-05** (400 mg, 0.612 mmol, 1 eq). After the mixture was cooled to 0°C, NCS (409 mg, 3.06 mmol, 5 eq) was added. The reaction mixture was stirred at 20°C for 2 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with EA. The organic phase was dried over Na₂SO₄ and concentrated under vacuum to afford **B43-06** (520 mg). **Yield: 100%.**

Step5: To a 25 mL three-necked flask was added 5 mL DCM, **B43-06** (theoretical yield: 385 mg, 0.612 mmol, 1 eq), TEA (620 mg, 6.12 mmol, 10 eq), and methyl 3-aminopropionate hydrochloride (427 mg, 3.06 mmol, 5 eq). The reaction mixture was stirred at 25°C for 2 hours. LC-MS showed the reaction was completed. The mixture was poured into water and extracted with DCM. The residue was purified by silica gel column chromatography to afford **B43-07** (130 mg). **Yield: 30.5%.**

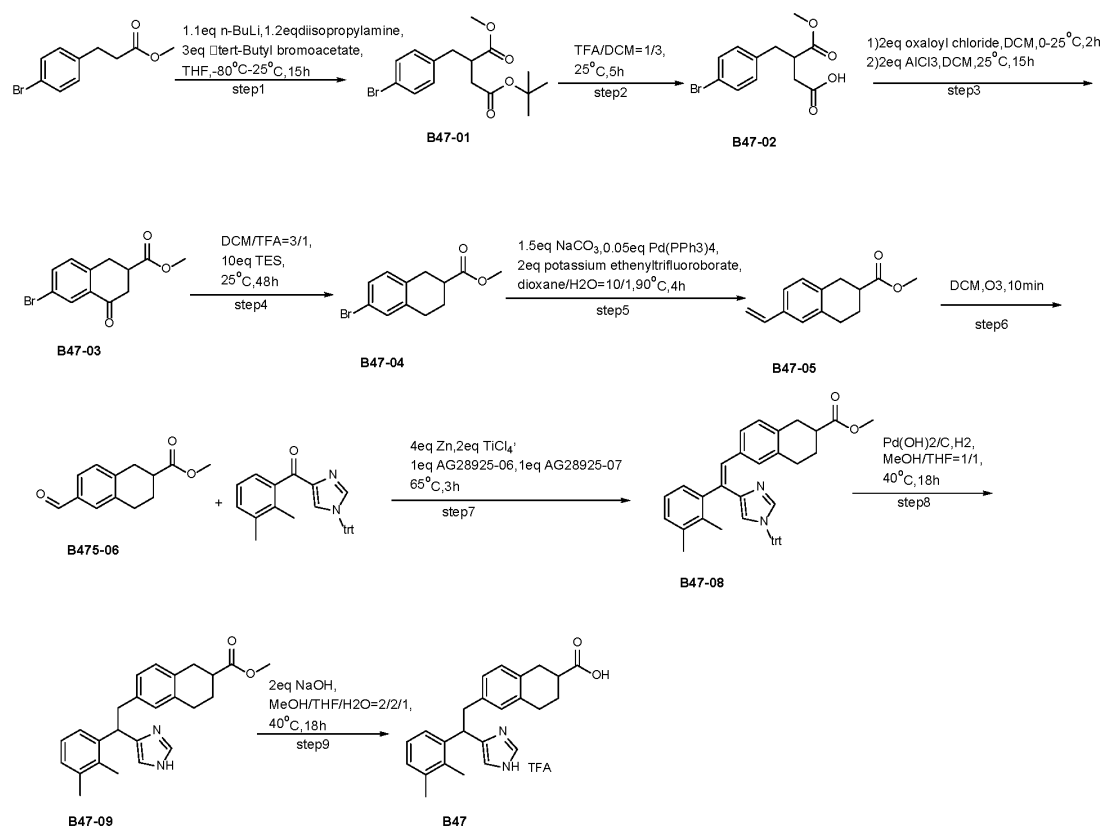
Step6: A mixture of **B43-07** (130 mg), Pd(OH)₂/C (50 mg), CH₃OH (7 mL), and THF (7 mL) was stirred at 40°C for 4 days under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **B43-08** (50 mg). **Yield: 58.7%.**

Step7: A mixture of **B43-08** (50 mg, 0.109 mmol, 1 eq), NaOH (9 mg, 0.219 mmol, 2 eq), CH₃OH (4 mL), THF (4 mL), and H₂O (2 mL) was stirred at 40°C for 18 hours. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum. Then 10 mL DCM and 5 mL TFA were added, and the solution was stirred for 10 minutes before evaporating the solvent. The residue was purified by preparative HPLC to give **B43** (25 mg) as a white solid.

Yield: 41.0%.

Overall yield: 3.37%.

Example 34. Synthesis of Compound B47



10

Step 1: To a 1 L three-necked flask, 480 mL THF, diisopropylamine (10 g, 98.72 mmol, 1.2 eq), and n-BuLi (2.5 M, 36.3 mL, 90.49 mmol, 1.1 eq) were added at 0°C and stirred for 30 minutes. The mixture was cooled to -78°C, and a solution of methyl 3-(4-bromophenyl)propanoate (20 g, 82.27 mmol, 1 eq) in THF (100 mL) was added slowly. The reaction was stirred at -78°C for 40 minutes. A solution of tert-butyl bromoacetate (48.1 g, 0.247 mol, 3 eq) in THF (60 mL) was then added. The reaction was stirred for 40 minutes at -78°C and warmed to room temperature overnight. LC-MS showed the reaction was complete. The mixture was poured into saturated NH₄Cl and extracted with EA. The residue was purified by silica gel column chromatography

15

(PE/EA = 92:8) to afford **B47-01** (19 g). **Yield: 64.6%.**

Step 2: To a 250 mL single-neck flask, 150 mL DCM, 50 mL TFA, and **B47-01** (19 g) were added. The reaction mixture was stirred at 25°C for 5 hours. LC-MS showed the reaction was complete. The solution was concentrated under vacuum, and the residue was purified by column chromatography (DCM/MeOH = 99:1) to afford **B47-02** (7.3 g) as a yellow oil. **Yield: 45.4%.**

Step 3: To a 250 mL three-neck flask, 70 mL DCM and **B47-02** (7 g, 23.24 mmol, 1.0 eq) were added, followed by three drops of DMF. Oxalyl chloride (5.9 g, 46.49 mmol, 2.0 eq) was added at 0°C, and the solution was stirred at 25°C for 2 hours. TLC showed the reaction was complete. The mixture was concentrated under vacuum, and the residue was dissolved in 70 mL DCM and cooled to 0–10°C. AlCl₃ (6.2 g, 46.49 mmol, 2.0 eq) was added, and the solution was stirred at 25°C overnight. LC-MS showed the reaction was complete. The mixture was poured into a mixture of 100 mL ice water and 100 mL 0.5 N HCl. It was extracted with DCM (100 mL × 2). The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (PE/EA = 93:7) to afford **B47-03** (4.2 g). **Yield: 63.8%.**

Step 4: To a 50 mL single-neck flask, 30 mL DCM, 10 mL TFA, **B47-03** (2 g, 7.06 mmol, 1.0 eq), and TES (8.2 g, 70.64 mmol, 10 eq) were added. The reaction mixture was stirred at 25°C for 48 hours. LC-MS showed the reaction was complete. The solution was concentrated under vacuum, and the residue was purified by column chromatography (PE/EA = 93:7) to afford **B47-04** (800 mg). **Yield: 42.1%.**

Step 5: To a 25 mL three-neck flask, 16 mL 1,4-dioxane, 1.6 mL water, **B47-04** (800 mg, 2.97 mmol, 1.0 eq), potassium ethenyltrifluoroborate (597 mg, 4.46 mmol, 2.0 eq), Na₂CO₃ (472 mg, 4.46 mmol, 1.5 eq), and Pd(PPh₃)₄ (172 mg, 0.148 mmol, 0.05 eq) were added. The reaction mixture was stirred at 90°C under N₂ for 4 hours. LC-MS showed the reaction was complete. The mixture was poured into water and extracted with EA. The residue was purified by silica gel column chromatography (PE/EA = 92:8) to afford **B47-05** (380 mg). **Yield: 59.1%.**

Step 6: To a 25 mL three-neck flask, 10 mL DCM and **B47-05** (380 mg) were added. O₃ was bubbled through the reaction mixture for 10 minutes. TLC showed the reaction was complete. The mixture was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford a crude oil. The crude product was purified by column chromatography (PE/EA = 92:8) to afford **B47-06** (100 mg) as a white solid. **Yield: 26.1%.**

Step 7: To a 50 mL three-neck flask, 10 mL THF, (2,3-dimethylphenyl)[1-(trityl)-1H-imidazol-4-yl]methanone (203 mg, 0.458 mmol, 1.0 eq), **B47-06** (100 mg, 0.458 mmol, 1.0 eq), and Zn (119 mg, 1.832 mmol, 4.0 eq) were added. The solution was charged with N₂, and TiCl₄ (174

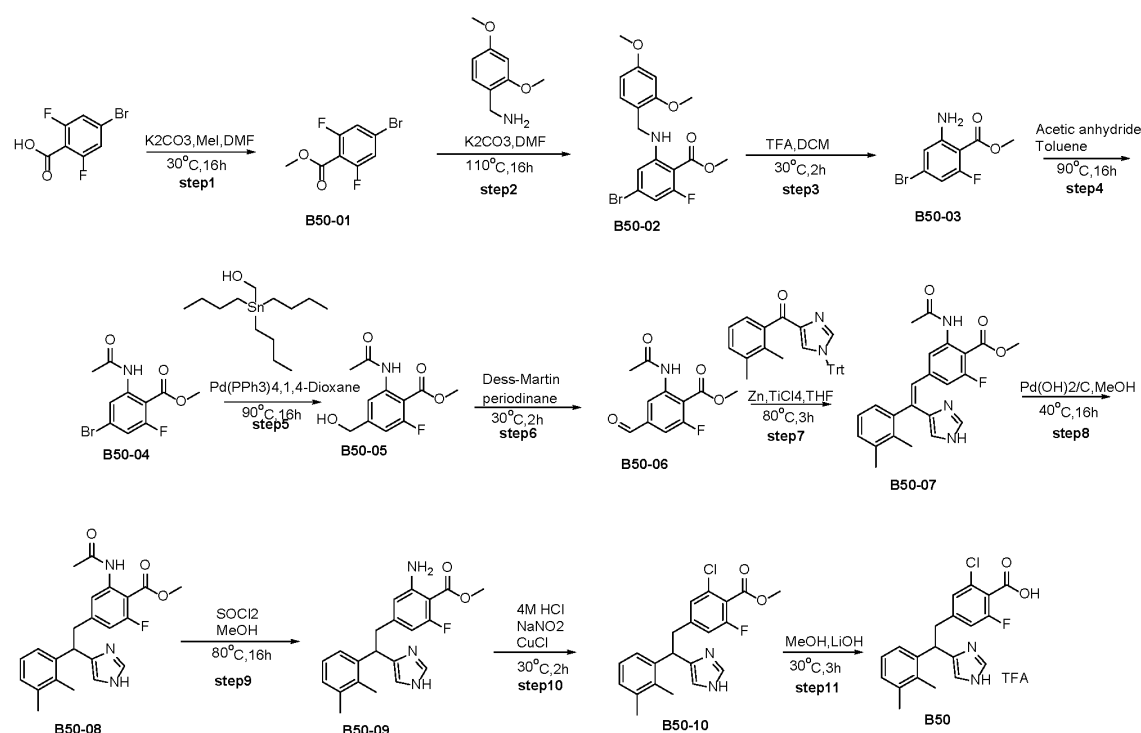
mg, 0.916 mmol, 2.0 eq) was added dropwise at 10°C. The reaction mixture was stirred at 65°C for 3 hours. LC-MS showed the reaction was complete. The mixture was poured into saturated sodium bicarbonate solution and extracted with EA. The residue was purified by silica gel column chromatography to afford **B47-08** (70 mg). **Yield: 39.5%.**

5 **Step 8:** To a 50 mL single-neck flask, 5 mL THF, 5 mL MeOH, **B47-08** (70 mg), and Pd(OH)₂/C (30 mg) were added. The reaction mixture was stirred at 40°C under H₂ for 15 hours. LC-MS showed the reaction was complete. The mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford **B47-09** (30 mg). **Yield: 42.6%.**

10 **Step 9:** A mixture of **B47-09** (30 mg, 0.077 mmol, 1 eq), NaOH (7 mg, 0.154 mmol, 2 eq), CH₃OH (4 mL), THF (4 mL), and H₂O (2 mL) was stirred at 40°C for 15 hours. LC-MS showed the reaction was complete. The mixture was concentrated under vacuum, then 5 mL DCM and 2 mL TFA were added. The mixture was stirred for 10 minutes and concentrated. The residue was purified by preparative HPLC to afford **B47** (18 mg) as a white solid. **Yield: 47.7%.**

15 **Overall yield: 0.25%. LC-MS: [M-C₂H₃O₂+1]⁺=375.2.**

Example 35. Synthesis of Compound B50



20 **Step1:** A mixture of 4-Bromo-2,6-difluorobenzoic Acid (5 g, 21 mmol, 1 eq), K₂CO₃ (9 g, 63 mmol, 3 eq), and MeI (6 g, 42 mmol, 2 eq) in DMF (50 mL) was stirred at 30°C overnight under

N₂. LC-MS showed the reaction was completed. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-01** (5 g). **Yield: 95.24%.**

- 5 **Step2:** A mixture of **B50-01** (5 g, 20 mmol, 1 eq), 2,4-Dimethoxyaniline (3.7 g, 22 mmol, 1.1 eq), and K₂CO₃ (4 g, 30 mmol, 1.5 eq) in DMF (50 mL) was stirred at 110°C overnight under N₂. LC-MS showed the reaction was completed. The reaction mixture was diluted with water (50 mL) and extracted with EA (50 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel
10 to afford **B50-02** (6 g). **Yield: 70%.**

- Step3:** A mixture of **B50-02** (5 g, 13 mmol, 1 eq) and TFA (40 mL) in DCM (50 mL) was stirred at 30°C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum. The mixture was diluted with saturated sodium carbonate solution and extracted with DCM (50 mL × 1). The organic phase was dried over Na₂SO₄ and
15 concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-03** (3.6 g). **Yield: 100%.**

- Step4:** A mixture of **B50-03** (3.6 g, 15 mmol, 1 eq) and acetic anhydride (2.2 g, 21 mmol, 1.5 eq) in toluene (40 mL) was stirred at 90°C for 16 hours under N₂. LC-MS showed the reaction was completed. The reaction mixture was diluted with saturated sodium bicarbonate solution (20
20 mL) and extracted with EA (20 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-04** (3.7 g). **Yield: 84.7%.**

- Step5:** A mixture of **B50-04** (3.7 g, 12.7 mmol, 1 eq), (tributylstannyl)methanol (6 g, 19 mmol, 1.5 eq), and Pd(PPh₃)₄ (733 mg, 0.635 mmol, 0.05 eq) in 1,4-dioxane (40 mL) was refluxed at
25 90°C overnight under N₂. LC-MS showed the reaction was incomplete. The mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-05** (3.8 g). **Yield: 77.6%.**

- Step6:** To a solution of **B50-05** (3.8 g, 15.8 mmol, 1 eq) in DCM (25 mL), Dess-Martin periodinane (8 g, 19 mmol, 1.2 eq) was added at 0°C. The reaction mixture was stirred for 2
30 hours at room temperature. LC-MS showed the reaction was completed. The mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-06** (2.4 g). **Yield: 63.6%.**

Step7: To a solution of **B50-06** (2.2 g, 9.2 mmol, 2.4 eq), Zn (1.7 g, 26.6 mmol, 7 eq), and (2,3-Dimethylphenyl)(1-trityl-4-imidazolyl)methanone (1.7 g, 3.8 mmol, 1 eq) in THF (170 mL),

titanium tetrachloride (2.5 g, 13.3 mmol, 3.5 eq) was added at 0°C. The reaction mixture was stirred for 3 hours at 80°C. LC-MS showed the reaction was completed. The reaction mixture was diluted with water (300 mL) and extracted with EA (100 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column

5 chromatography on silica gel to afford **B50-07** (920 mg). **Yield: 51.6%.**

Step8: A mixture of **B50-07** (800 mg, 1.96 mmol, 1 eq), Pd(OH)₂/C (700 mg), TFA (200 mg), and water (10 drops) in MeOH (16 mL) was stirred at 50°C for 16 hours under H₂. LC-MS showed the reaction was completed. The mixture was filtered and concentrated under vacuum to afford **B50-08** (848 mg) as a crude product. It was used for the next step without further

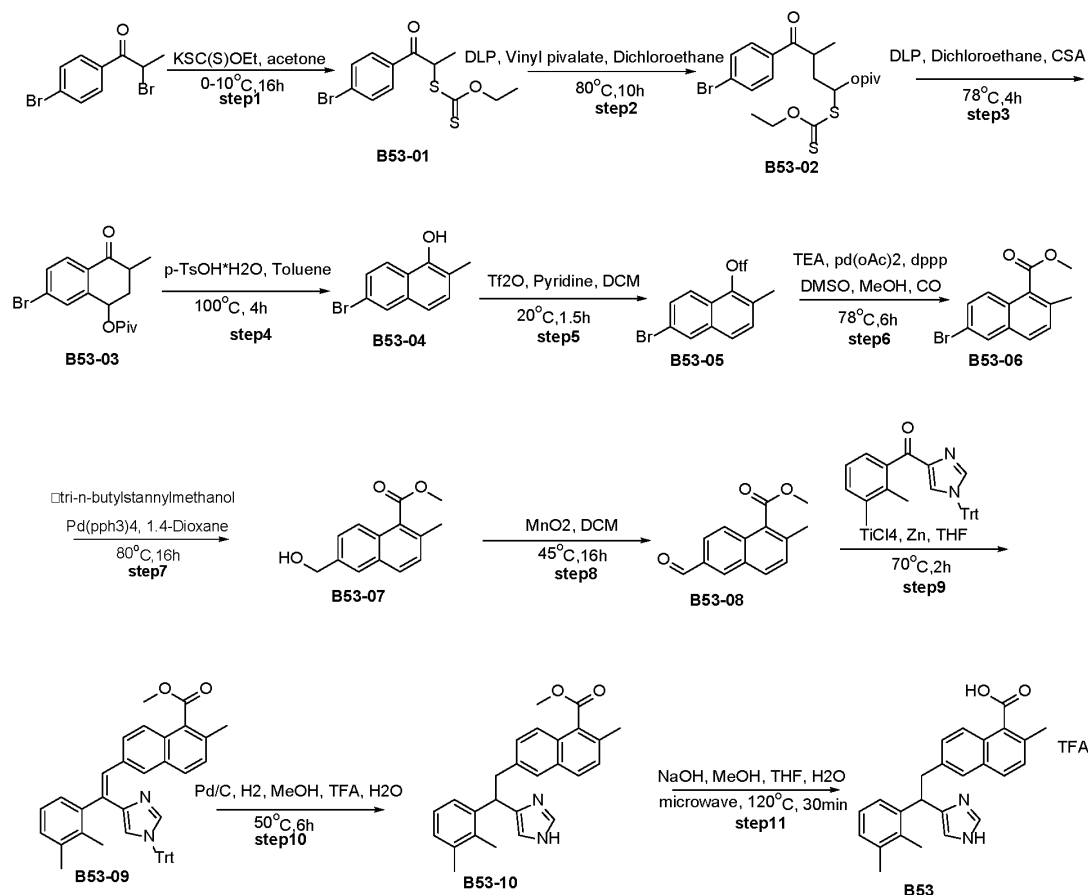
10 purification. **Yield: 100%.**

Step9: A mixture of **B50-08** (848 mg, 2.07 mmol, 1 eq) and SOCl₂ (400 mg, 4.1 mmol, 2 eq) in MeOH (16 mL) was stirred at 80°C for 16 hours under N₂. LC-MS showed the reaction was completed. The reaction mixture was concentrated under vacuum. The mixture was diluted with saturated sodium bicarbonate solution and extracted with EA (20 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-09** (330 mg). **Yield: 41.3%.**

15 **Step10:** A mixture of **B50-09** (200 mg, 0.54 mmol, 1 eq) in 4 M HCl (6 mL) was stirred at 45°C for 0.5 hours. NaNO₂ (45 mg, 0.65 mmol, 1.2 eq) in water (0.5 mL) was added at 0°C. The reaction mixture was stirred for 1 hour at 0°C. CuCl (270 mg, 2.7 mmol, 5 eq) in water (0.5 mL) was added at 0°C. The reaction mixture was stirred for 2 hours at 30°C. LC-MS showed the reaction was completed. The mixture was diluted with saturated sodium bicarbonate solution and extracted with EA (20 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **B50-10** (90 mg). **Yield: 40.7%.**

25 **Step11:** A mixture of **B50-10** (85 mg, 0.22 mmol, 1 eq), LiOH (28 mg, 0.66 mmol, 3 eq), and water (1 mL) in MeOH (1 mL) was stirred at 30°C for 3 hours under N₂. LC-MS showed the reaction was completed. The mixture was concentrated under vacuum as a crude product. DCM:TFA = 2:1 (3 mL) was added, and the mixture was concentrated under vacuum. The residue was purified by preparative HPLC to afford **B50** (30 mg). **Yield: 36.7%.**

30

Example 36. Synthesis of Compound B53

- Step 1:** A 250 mL three-necked flask containing 100 mL acetone and 2-bromo-1-(4-bromophenyl)propan-1-one (10 g, 0.0343 mol, 1 eq) was cooled to 0°C. Potassium O-ethyl xanthate (6.05 g, 0.03773 mol, 1.1 eq) was added. The reaction mixture was stirred until the starting material disappeared. Acetone was evaporated, and the resulting mixture was partitioned between water and DCM. The organic phase was dried with brine and Na₂SO₄. The crude product was purified by flash chromatography on silica gel to obtain 9 g of **B53-01**. **Yield: 78.95%.**
- Step 2:** A 100 mL three-necked flask containing 45 mL dichloroethane, **B53-01** (9 g, 0.0271 mol, 1 eq), and vinyl pivalate (6.95 g, 0.0542 mol, 2 eq) was refluxed under nitrogen. Lauroyl peroxide (DLP) (540 mg, 1.36 mmol, 0.05 eq) was then added to the refluxing solution followed by additional portions (0.03 eq every 1-1.5 hours). When TLC monitoring showed that the starting material was consumed (after seven additions of DLP), the solution was cooled to room temperature. The reaction mixture was purified by a fast silica gel column to give 14 g (crude) of **B53-02**. **Yield: 100%.**

Step 3: A 500 mL three-necked flask containing 140 mL dichloroethane, **B53-02** (14 g, 0.0271 mol, 1 eq), and camphorsulfonic acid (629 mg, 0.00271 mol, 0.1 eq) was refluxed under nitrogen. Lauroyl peroxide (DLP) was then added to the refluxing solution followed by additional portions (2.16 g, 5.42 mmol, 0.2 eq, every 1-1.5 hours). When TLC monitoring showed that the starting material was consumed (after 1 eq of DLP), the solution was cooled to room temperature. The organic phase was evaporated. The crude product was purified by flash chromatography on silica gel to obtain 1.1 g of **B53-03**. **Yield: 12.02%.**

Step 4: A 100 mL three-necked flask containing 19 mL toluene, **B53-03** (1.1 g, 4.66 mmol, 1 eq), and p-TsOH·H₂O (3.1 g, 16.3 mmol, 2.9 eq) was refluxed for 4 hours. When the starting material was totally consumed, the mixture was allowed to cool to room temperature, neutralized with saturated Na₂CO₃, extracted with DCM, dried, and evaporated under reduced pressure. The residue was purified by a fast silica gel column to give 1.1 g of **B53-04**. **Yield: 83.33%.**

Step 5: A 100 mL three-necked flask containing 11 mL DCM, **B53-04** (1.1 g, 4.66 mmol, 1 eq), pyridine (1.11 g, 13.98 mmol, 3 eq), and trifluoromethanesulfonic anhydride (Tf₂O) (2.23 g, 7.92 mmol, 1.7 eq) was stirred for 1.5 hours at room temperature. TLC showed the reaction was complete. The organic phase was washed with water, and the aqueous phase was extracted with DCM. The organic phases were combined, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by a fast silica gel column to give 1.33 g of **B53-05**. **Yield: 77.78%.**

Step 6: A 200 mL autoclave containing 22 mL MeOH, 22 mL DMSO, **B53-05** (1.3 g, 3.53 mmol, 1 eq), TEA (679.2 mg, 6.71 mmol, 1.9 eq), dppp (274.75 mg, 0.847 mmol, 0.24 eq), and Pd(OAc)₂ (159.92 mg, 0.706 mmol, 0.2 eq) was stirred for 6 hours at 78°C under CO (5 MPa). GC-MS showed the reaction was complete. The mixture was diluted with water and extracted with EA. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by a fast silica gel column to give 690 mg of **B53-06**. **Yield: 70.34%.**

Step 7: A 25 mL three-necked flask containing 7 mL 1,4-dioxane, **B53-06** (683 mg, 2.46 mmol, 1 eq), tri-n-butylstannylmethanol (1.183 g, 3.69 mmol, 1.5 eq), and Pd(PPh₃)₄ (142.14 mg, 0.123 mmol, 0.05 eq) was stirred for 16 hours at 80°C under nitrogen. LC-MS showed the reaction was complete. The mixture was diluted with water (20 mL) and extracted with EA (40 mL × 2). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by a fast silica gel column to give 377 mg of **B53-07**. **Yield: 66.61%.**

Step 8: A 25 mL three-necked flask containing 7.5 mL DCM, **B53-07** (370 mg, 1.61 mmol, 1 eq), and MnO₂ (1.4 g, 16.1 mmol, 10 eq) was stirred for 16 hours at 45°C. The mixture was

filtered and evaporated to dryness. The residue was purified by a fast silica gel column to give 287 mg of **B53-08**. **Yield: 78.20%**.

Step 9: A 50 mL three-necked flask containing 14 mL THF and powdered Zn (763 mg, 11.67 mmol, 19 eq) was cooled to 0°C under nitrogen. TiCl₄ (1.12 g, 5.89 mmol, 9.6 eq) was added dropwise, and the mixture was stirred for 1 hour at 70°C. The mixture was cooled to 0°C. A solution of (2,3-dimethylphenyl)(1-trityl-4-imidazolyl)methanone (280 mg, 0.614 mmol, 1 eq) and **B53-08** (280 mg, 1.23 mmol, 2 eq) in 14 mL THF was added. The reaction mixture was stirred for 3 hours at 70°C. LC-MS showed the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EA (30 mL × 3). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by a fast silica gel column to give 200 mg of **B53-09**. **Yield: 25.48%**.

Step 10: A 10 mL single-necked flask containing 1 mL MeOH, 4 drops of water, 4 drops of TFA, **B53-09** (100 mg, 0.252 mmol, 1 eq), and 10% Pd/C (100 mg) was stirred for 6 hours at 50°C under a hydrogen atmosphere. LC-MS showed the reaction was complete. The mixture was evaporated to dryness to give 154 mg of **B53-10**. **Yield: 100%**.

Step 11: A 10 mL single-necked flask containing 5 mL of a solution (MeOH:THF:H₂O = 2:2:1), NaOH (77.4 mg, 1.9 mmol, 5 eq), and **B53-10** (154 mg, 0.387 mmol, 1 eq) was stirred in a microwave at 120°C for 30 minutes. LC-MS showed the reaction was complete. A mixture of 1 mL MeCN, 1 mL TFA, and the residue was stirred at 15°C for 5 minutes under nitrogen. The mixture was concentrated under vacuum. The residue was purified by preparative HPLC to afford **B53** (13.6 mg). **Yield: 9.19%**.

Overall yield: 0.053%. LCMS: [M-C₂H₃O₂+1]⁺=385.2

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

Table 2

Comp. No.	Characterization Data
A64	[M-C ₂ H ₃ O ₂ +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).
A70	[M-C ₄ H ₂ F ₆ O ₄ +1] ⁺ =419.2, 1H NMR (400 MHz, DMSO-D ₂ O) 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).

A73	[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).
A73-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).
A73-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).
A79	[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).
A80	[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).
A81	[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).
A82	[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).
A84	[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).

A86	[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).
A87	[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).
A88	[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).
A89	[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).
A90	[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).
A91	[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).
A94	[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).
A95	[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).
A96	[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).

A98	LC-MS: [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 (qd, J = 12.1, 4.4 Hz, 2H).
A98-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 (dtd, J = 15.2, 7.5, 3.6 Hz, 1H), 1.67 (d, J = 12.9 Hz, 2H), 1.42 – 1.19 (m, 3H).
A98-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).
A99	[M-C2HF3O2+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).
A101	[M-C2HF3O2+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).
A102	[M-C2HF3O2+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).
A103	[M-C2HF3O2+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).
A104	[M-C2HF3O2+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).

A105	[M-C2HF3O2+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).
A107	[M-C2HF3O2+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).
A108	[M-C2HF3O2+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).
A109	[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).
A111	[M-C2HF3O2+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).
A112	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).
A112-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).
A112-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).
A113	[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).

A117	[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).
A119	[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).
A120	[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).
A121	[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).
A121-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).
A121-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).
A124	[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).
A124-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).
A124-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).

A131	[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).
A132	[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).
A134	[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).
A138	[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).
A141	[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).
A142	[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).
A143	[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).
A144	[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).
A145	[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).
A149	[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).

A151-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).
A151-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).
A152	[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).
A153	[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).
A155-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 = 11.1 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).
A155-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).
A157	[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).
A157-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).
A157-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).

A158	[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).
A161	[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).
A162	[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).
A165	LC-MS: [M-C2HF3O2+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).
A166	LC-MS: [M-C2HF3O2+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).
A167	[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).
A169	LC-MS: [M-C2HF3O2+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).
A170	LCMS=[M-C2HF3O2+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).
A171	LC-MS: [M-C2HF3O2+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).

A172	[M-C2HF3O2+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).
A173	LC-MS: [M-C2HF3O2+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).
A176	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).
A177	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).
A178	[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).
A179	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).
A180	[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).
A181	[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).
A186	LC-MS: [M-C2HF3O2+1] ⁺ =405.21, 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).

A187	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =422.2, ¹ H 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).
A189	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =448.2, ¹ H 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).
A198	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =405.2, ¹ H 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).
A200	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =376.2, ¹ H 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).
A205	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =419.3, ¹ H 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).
A212	[M+1] ⁺ =420.2, ¹ H 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).
A214	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =391.2, ¹ H 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).
A233	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =420.2, ¹ H 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).
A234	LCMS: [M-C ₂ HF ₃ O ₂ +1] ⁺ = 376.2, ¹ H 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).

A706	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =392.2, 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 9.74 (s, 1H), 7.76 (s, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 7.4 Hz, 1H), 7.04 – 6.93 (m, 4H), 6.89 (s, 1H), 5.45 – 5.32 (m, 1H), 4.79 (t, J = 7.0 Hz, 2H), 4.57 – 4.45 (m, 3H), 3.27 (d, J = 8.2 Hz, 1H), 3.00 (dd, J = 13.7, 7.3 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H).
A727	LC-MS: [M+1] ⁺ =412.2, 1H NMR (400 MHz, DMSO) δ 11.94 (s, 1H), 9.76 (s, 1H), 7.55 (s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 6.98 (ddd, J = 18.4, 16.3, 7.8 Hz, 6H), 6.78 (s, 1H), 4.76 – 4.59 (m, 2H), 4.58 – 4.40 (m, 4H), 3.34 (d, J = 6.1 Hz, 1H), 3.01 (dd, J = 13.7, 7.6 Hz, 1H), 2.17 (s, 3H), 2.09 (d, J = 6.7 Hz, 3H).
A906	LC-MS: [M+1] ⁺ =394.2, 1H NMR (400 MHz, DMSO) δ 11.92 (d, J = 38.3 Hz, 1H), 8.47 (s, 1H), 7.59 (s, 1H), 7.51 – 7.39 (m, 1H), 7.23 – 6.93 (m, 4H), 6.82 – 6.63 (m, 1H), 6.41 (d, J = 114.5 Hz, 1H), 5.85 (d, J = 34.5 Hz, 1H), 4.60 (dd, J = 7.7, 6.1 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 3.13 (dt, J = 13.6, 6.8 Hz, 1H), 2.23 (s, 3H), 2.12 (s, 3H).
A907	LC-MS: [M+1] ⁺ =380.2, 1H NMR (400 MHz, DMSO) δ 11.93 (d, J = 40.4 Hz, 1H), 9.04 (d, J = 6.5 Hz, 1H), 7.60 (s, 1H), 7.43 (d, J = 4.2 Hz, 1H), 7.26 – 6.93 (m, 4H), 6.86 – 6.63 (m, 1H), 6.42 (d, J = 114.7 Hz, 1H), 5.86 (d, J = 32.2 Hz, 1H), 4.94 (dt, J = 13.8, 7.0 Hz, 1H), 4.73 (t, J = 6.9 Hz, 2H), 4.53 (t, J = 6.4 Hz, 2H), 2.24 (s, 3H), 2.12 (s, 3H).
B1	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).
B1-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).
B1-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).
B1-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).
B1-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).
B2	[M+1] ⁺ =345.17, 1 H 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).

B3	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =339.2, ¹ H 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).
B3-A	LC-MS: [M+1] ⁺ =339.2, ¹ H NMR (400 MHz, DMSO) δ 7.66 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 0.9 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.13 – 6.94 (m, 4H), 6.79 (s, 1H), 4.58 (t, J = 7.8 Hz, 1H), 3.44 (dd, J = 13.7, 8.2 Hz, 1H), 3.15 (dd, J = 13.7, 7.5 Hz, 1H), 2.19 (s, 3H), 2.15 (s, 3H).
B3-B	LC-MS: [M+1] ⁺ =339.2, ¹ H NMR (400 MHz, DMSO) δ 7.72 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.98 (d, J = 7.1 Hz, 1H), 6.86 (s, 1H), 4.61 (t, J = 7.9 Hz, 1H), 3.44 (dd, J = 13.8, 8.1 Hz, 1H), 3.17 (dd, J = 13.7, 7.7 Hz, 1H), 2.19 (s, 3H), 2.14 (s, 3H).
B4	LC-MS: [M+1] ⁺ =357.2, ¹ H 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).
B7	LC-MS: [M-C ₂ HF ₃ O ₂ -1] ⁻ =333.1, ¹ H 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).
B8	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =321.2, ¹ H 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).
B8-A	LC-MS: [M+1] ⁺ =321.2, ¹ H 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).
B8-B	LC-MS: [M+1] ⁺ =321.2, ¹ H 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).
B9	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =337.2, ¹ H 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).
B16	LC-MS: [M-C ₂ HF ₃ O ₂ -1] ⁻ =361.2, ¹ H 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).
B17	LC-MS: [M-HCl+1] ⁺ =322.2, ¹ H NMR (400 MHz, DMSO) δ 12.74 (s, 2H), 8.40 (d, J = 1.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.69 (dd, J = 8.0, 2.1 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.00 – 6.92 (m, 2H), 4.59 (t, J = 7.8 Hz, 1H), 3.49 (dd, J = 13.7, 8.3 Hz, 1H), 3.20 (dd, J = 13.7, 7.5 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H).
B21	LCMS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =360.2, ¹ H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 11.36 (s, 1H), 8.95 (s, 1H), 7.75 – 7.56 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 7.08 (dt, J = 9.6, 6.2 Hz, 3H), 6.47 (s, 1H), 4.75 (t, J = 7.8 Hz, 1H), 3.43 (d, J = 5.4 Hz, 1H), 3.20 (dd, J = 13.7, 7.5 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).

B22	LCMS: [M+1] ⁺ =332.2, 1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 12.84 (s, 1H), 8.95 (d, J = 0.9 Hz, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.61 (s, 1H), 7.35 (dt, J = 14.9, 7.6 Hz, 2H), 7.08 (dt, J = 13.3, 7.2 Hz, 3H), 4.73 (t, J = 7.9 Hz, 1H), 3.47 – 3.41 (m, 1H), 3.21 (dd, J = 13.7, 7.6 Hz, 1H), 2.20 (s, 3H), 2.08 (d, J = 7.5 Hz, 3H).
B23	LC-MS: [M-Na] ⁺ =348.1, 1H NMR (400 MHz, DMSO+D ₂ O) δ 7.45 (s, 1H), 7.13 (s, 1H), 7.01 – 6.88 (m, 2H), 6.82 – 6.68 (m, 3H), 6.29 (d, J = 8.4 Hz, 2H), 4.40 (t, J = 7.4 Hz, 1H), 3.21 – 3.13 (m, 3H), 2.87 (dd, J = 13.8, 7.2 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H).
B24	LC-MS: [M-HCl+1] ⁺ =361.2, 1H NMR (400 MHz, DMSO+D ₂ O) δ 7.53 (d, J = 0.8 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.02 (s, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.0 Hz, 2H), 6.77 (s, 1H), 4.53 (t, J = 7.6 Hz, 1H), 3.86 (t, J = 7.4 Hz, 1H), 3.31 (dd, J = 13.9, 8.4 Hz, 1H), 3.02 (dd, J = 13.8, 7.0 Hz, 1H), 2.86 (dd, J = 15.2, 7.6 Hz, 1H), 2.73 (dt, J = 19.3, 5.6 Hz, 1H), 2.19 (dd, J = 16.0, 11.3 Hz, 8H).
B25	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =428.2, 1H NMR (400 MHz, DMSO) δ 14.24 (s, 2H), 12.30 (s, 1H), 8.96 (d, J = 1.2 Hz, 1H), 7.75 – 7.53 (m, 4H), 7.34 (d, J = 8.3 Hz, 2H), 7.18 – 6.97 (m, 3H), 4.74 (t, J = 7.8 Hz, 1H), 3.50 – 3.43 (m, 1H), 3.22 (dd, J = 13.6, 7.8 Hz, 1H), 2.86 (dd, J = 13.0, 7.0 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 2.19 (s, 3H), 2.05 (s, 3H).
B26	[M+1] ⁺ =327.15, 1H NMR (400 MHz, MeOD) δ 8.76 (d, J = 1.6 Hz, 1H), 7.36 (s, 1H), 7.09 – 7.05 (m, 2H), 6.98 – 6.94 (m, 1H), 4.56 (t, J = 7.6 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.24 – 2.17 (m, 1H), 2.01 – 1.94 (m, 3H), 1.89 – 1.82 (m, 3H), 1.34 – 1.19 (m, 3H), 1.14 – 1.00 (m, 2H).
B27	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =359.2, 1H NMR (400 MHz, DMSO) δ 8.90 (d, J = 1.0 Hz, 1H), 7.64 – 7.56 (m, 4H), 7.17 (d, J = 8.2 Hz, 2H), 7.14 – 7.03 (m, 3H), 6.59 (d, J = 2.3 Hz, 1H), 4.74 (t, J = 7.9 Hz, 1H), 3.36 (dd, J = 13.7, 8.2 Hz, 1H), 3.16 (dd, J = 13.7, 7.6 Hz, 1H), 2.21 (s, 3H), 2.11 (d, J = 13.4 Hz, 3H).
B28	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =371.2, 1H NMR (400 MHz, DMSO+D ₂ O) δ 8.87 (s, 1H), 8.68 (d, J = 8.9 Hz, 1H), 8.12 – 8.05 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.61 – 7.53 (m, 2H), 7.49 (dd, J = 8.9, 1.6 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 7.1 Hz, 1H), 4.89 (t, J = 7.9 Hz, 1H), 3.56 (dd, J = 13.9, 8.2 Hz, 1H), 3.37 (dd, J = 13.8, 7.6 Hz, 1H), 2.18 (s, 3H), 2.13 (s, 3H).
B29	LC-MS: [M-C ₂ HF ₃ O ₂ +1] ⁺ =339.2, 1H NMR (400 MHz, DMSO) δ 14.29 (s, 2H), 12.87 (s, 1H), 8.96 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.64 (s, 1H), 7.35 (t, J = 9.1 Hz, 1H), 7.33 – 7.17 (m, 4H), 5.56 – 5.44 (m, 1H), 5.44 – 5.29 (m, 1H), 4.79 (t, J = 7.9 Hz, 1H), 3.47 (dd, J = 13.7, 8.3 Hz, 1H), 3.25 (dd, J = 13.7, 7.5 Hz, 1H), 2.21 (s, 3H).
B30	[M-C ₂ HF ₃ O ₂ +1] ⁺ =350.2 1H NMR (400 MHz, DMSO) δ 14.21 (s, 3H), 8.88 (s, 1H), 8.65 (s, 2H), 7.57 (s, 1H), 7.36 – 7.23 (m, 4H), 7.05 (dt, J = 9.3, 4.6 Hz, 3H), 5.02 (s, 1H), 4.73 (t, J = 7.8 Hz, 1H), 3.41 (d, J = 5.7 Hz, 1H), 3.15 (dd, J = 13.9, 7.4 Hz, 1H), 2.20 (s, 3H), 2.10 (s, 3H).
B31	1H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 13.27 (s, 1H), 8.96 (s, 1H), 7.68 (s, 1H), 7.59 (dd, J = 15.7, 9.2 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.09 (dt, J = 16.6, 7.5 Hz, 3H), 4.79 (t, J = 8.0 Hz, 1H), 3.48 – 3.43 (m, 1H), 3.28 (dd, J = 13.8, 7.3 Hz, 1H), 2.20 (s, 3H), 2.12 (s, 3H).
B32	[M-C ₂ HF ₃ O ₂ +1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 12.09 (s, 1H), 8.93 (s, 1H), 7.61 (s, 1H), 7.10 – 7.01 (m, 7H), 4.67 (t, J = 7.8 Hz, 1H), 3.31 (d, J = 5.3 Hz, 1H), 3.08 (dd, J = 13.8, 7.0 Hz, 1H), 2.73 (t, J = 7.6 Hz, 2H), 2.46 (d, J = 7.5 Hz, 2H), 2.21 (s, 3H), 2.11 (s, 3H).

B33	LC-MS: [M-Na] ⁺ =360.2, ¹ H NMR (400 MHz, DMSO) δ 11.72 (s, 1H), 7.45 (s, 1H), 7.17 (s, 1H), 6.94 (d, J = 16.9 Hz, 2H), 6.72 (d, J = 19.7 Hz, 2H), 6.61 (dd, J = 22.9, 7.5 Hz, 1H), 6.36 (d, J = 6.6 Hz, 1H), 4.97 (s, 1H), 4.40 (s, 1H), 3.58 (d, J = 8.1 Hz, 1H), 3.16 (s, 2H), 2.90 (dd, J = 14.4, 9.6 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H).
B34	[M+1] ⁺ =355.1, ¹ H NMR (400 MHz, DMSO) δ 7.68 - 7.64 (m, 1H), 7.07 - 6.99 (m, 3H), 6.78 - 6.74 (m, 1H), 4.48 - 4.36 (m, 1H), 2.34 - 2.28 (m, 6H), 2.16 - 2.07 (m, 1H), 2.03 - 1.87 (m, 2H), 1.85 - 1.70 (m, 3H), 1.58 - 1.42 (m, 3H), 1.20 (s, 1H), 1.14 - 1.08 (m, 3H), 1.06 - 0.87 (m, 3H).
B35	LC-MS: [M-C2HF3O2+1] ⁺ =371.2, ¹ H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 13.03 (s, 1H), 8.95 (d, J = 1.1 Hz, 1H), 8.53 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.93 (dd, J = 8.6, 1.6 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.44 (dd, J = 8.5, 1.4 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 4.86 (t, J = 7.8 Hz, 1H), 3.57 (m, J = 5.3 Hz, 1H), 3.38 - 3.32 (m, 1H), 2.18 (s, 3H), 2.13 (s, 3H).
B36	[M-C2HF3O2+1] ⁺ =364.2, ¹ H NMR (400 MHz, DMSO) δ 14.21 (s, 3H), 8.88 (s, 1H), 8.65 (s, 2H), 7.57 (s, 1H), 7.36 - 7.23 (m, 4H), 7.05 (dt, J = 9.3, 4.6 Hz, 3H), 5.02 (s, 1H), 4.73 (t, J = 7.8 Hz, 1H), 3.41 (d, J = 5.7 Hz, 1H), 3.15 (dd, J = 13.9, 7.4 Hz, 1H), 2.20 (s, 3H), 2.10 (s, 3H).
B37	[M+1] ⁺ =313.2, ¹ H NMR (400 MHz, MeOD) δ 8.76 (d, J = 1.2 Hz, 1H), 7.40 - 7.32 (m, 1H), 7.07 (dd, J = 8.4, 4.0 Hz, 2H), 7.03 - 6.96 (m, 1H), 4.48 (t, J = 7.6 Hz, 1H), 2.90 - 2.65 (m, 1H), 2.31 (d, J = 4.0 Hz, 6H), 2.17 - 1.99 (m, 4H), 1.95 - 1.71 (m, 4H), 1.58 - 1.26 (m, 2H).
B38	[M-C2HF3O2+1] ⁺ =335.2 ¹ H NMR (400 MHz, DMSO) δ 14.23 (s, 2H), 12.79 (s, 1H), 8.96 (d, J = 1.1 Hz, 1H), 7.67 (d, J = 15.4 Hz, 2H), 7.55 (dd, J = 7.9, 1.5 Hz, 1H), 7.21 - 6.94 (m, 4H), 4.75 (t, J = 7.7 Hz, 1H), 3.46 (dd, J = 14.1, 7.4 Hz, 1H), 3.22 (dd, J = 14.1, 8.2 Hz, 1H), 2.25 (s, 3H), 2.17 (s, 3H), 1.96 (s, 3H).
B39	LCMS: [M-C2HF3O2+1] ⁺ =335.2, ¹ H NMR (400 MHz, D2O) δ 11.00 (s, 1H), 9.84 (d, J = 8.4 Hz, 1H), 9.70 (s, 1H), 9.27 (t, J = 8.4 Hz, 5H), 6.94 (t, J = 7.9 Hz, 1H), 5.55 (dd, J = 13.8, 8.0 Hz, 1H), 5.36 (dd, J = 13.8, 7.9 Hz, 1H), 4.60 (s, 3H), 4.38 (s, 3H), 4.28 (s, 3H).
B39-A	LCMS: [M-HCL+1] ⁺ =335.2, ¹ H NMR (400 MHz, DMSO) δ 12.12 (d, J = 292.4 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.20 (d, J = 7.1 Hz, 1H), 6.99 (ddd, J = 25.4, 12.8, 5.2 Hz, 4H), 6.75 (s, 1H), 4.54 (t, J = 7.6 Hz, 1H), 3.37 (dd, J = 12.3, 6.9 Hz, 1H), 3.07 (dd, J = 13.7, 7.2 Hz, 1H), 2.41 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H).
B39-B	LCMS: [M-HCL+1] ⁺ =335.2, ¹ H NMR (400 MHz, DMSO) δ 11.86 (s, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.20 (d, J = 7.4 Hz, 1H), 6.99 (ddd, J = 25.4, 12.7, 5.0 Hz, 4H), 6.75 (s, 1H), 4.54 (t, J = 7.6 Hz, 1H), 3.38 (d, J = 6.7 Hz, 1H), 3.07 (dd, J = 13.7, 7.3 Hz, 1H), 2.41 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H).
B40	[M-C2HF3O2+1] ⁺ =349.2, ¹ H NMR (400 MHz, DMSO) δ 8.87 (d, J = 1.3 Hz, 1H), 7.60 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.15 - 7.02 (m, 2H), 6.80 (d, J = 8.1 Hz, 1H), 4.69 (t, J = 7.7 Hz, 1H), 3.48 (dd, J = 14.0, 7.4 Hz, 1H), 3.24 (dd, J = 14.0, 8.1 Hz, 1H), 2.36 (s, 3H), 2.17 (d, J = 5.0 Hz, 3H), 2.15 (s, 3H), 1.94 (s, 3H).
B40-A	LC-MS: [M-HCL+1] ⁺ =349.2, ¹ H NMR (400 MHz, DMSO) δ 12.41 (s, 2H), 7.64 (s, 1H), 7.27 (dd, J = 12.5, 7.8 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.86 - 6.70 (m, 2H), 4.50 (t, J = 7.5 Hz, 1H), 3.49 (dd, J = 14.0, 7.3 Hz, 1H), 3.13 (dd, J = 14.0, 7.6 Hz, 1H), 2.36 (s, 3H), 2.17 (d, J = 3.6 Hz, 6H), 2.01 (s, 3H).

B40-B	LC-MS: [M-HCl+1] ⁺ =349.2, ¹ H NMR (400 MHz, DMSO) δ 7.76 (s, 1H), 7.27 (t, J = 6.9 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.91 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 4.55 (t, J = 7.5 Hz, 1H), 3.48 (dd, J = 14.0, 7.2 Hz, 1H), 3.16 (dd, J = 14.0, 7.9 Hz, 1H), 2.36 (s, 3H), 2.17 (d, J = 5.0 Hz, 6H), 2.00 (s, 3H).
B41	[M-C2HF3O2+1] ⁺ = 349.2, ¹ H NMR (400 MHz, DMSO) δ 14.15 (s, 2H), 13.02 (s, 1H), 8.93 (d, J = 0.8 Hz, 1H), 7.60 (s, 1H), 7.14 – 7.02 (m, 3H), 6.87 (s, 2H), 4.71 (t, J = 7.8 Hz, 1H), 3.29 – 3.24 (m, 1H), 3.07 (dd, J = 13.9, 6.8 Hz, 1H), 2.23 (s, 3H), 2.17 (d, J = 5.2 Hz, 9H).
B41-A	LC-MS: [M-HCl+1] ⁺ = 349.2, ¹ H NMR (400 MHz, DMSO) δ 13.22 (s, 2H), 8.26 (s, 1H), 7.20 (s, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.07 – 6.97 (m, 2H), 6.85 (s, 2H), 4.62 (t, J = 7.8 Hz, 1H), 3.25 (s, 1H), 3.03 (dd, J = 13.9, 6.9 Hz, 1H), 2.22 (s, 3H), 2.17 (s, 9H).
B41-B	LC-MS: [M-HCl+1] ⁺ = 349.2, ¹ H NMR (400 MHz, DMSO) δ 12.95 (s, 2H), 8.03 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.10 – 6.95 (m, 3H), 4.59 (t, J = 7.7 Hz, 1H), 3.25 (s, 1H), 3.02 (dd, J = 13.8, 6.9 Hz, 1H), 2.21 (s, 3H), 2.17 (d, J = 2.7 Hz, 9H).
B42	[M-C2HF3O2+1] ⁺ =355.1/357.1, ¹ H NMR (400 MHz, DMSO) δ 14.16 (s, 2H), 13.28 (s, 1H), 8.94 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.59 (s, 1H), 7.34 (s, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.12 – 7.02 (m, 3H), 4.75 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.4, 8.3 Hz, 1H), 3.20 (dd, J = 13.8, 7.5 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H).
B42-A	LCMS: [M-HCl+1] ⁺ =355.1/357.1, ¹ H NMR (400 MHz, DMSO) δ 12.86 (s, 2H), 7.79 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 1.3 Hz, 1H), 7.18 (dd, J = 12.7, 4.7 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 6.9 Hz, 1H), 6.93 (s, 1H), 4.57 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.1, 7.7 Hz, 1H), 3.13 (dd, J = 13.7, 7.2 Hz, 1H), 2.20 (s, 3H), 2.15 (s, 3H).
B42-B	LCMS: [M-HCl+1] ⁺ =355.1/357.1, ¹ H NMR (400 MHz, DMSO) δ 12.91 (s, 2H), 7.83 (s, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 1.3 Hz, 1H), 7.18 (dt, J = 8.1, 4.0 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.1 Hz, 1H), 6.95 (s, 1H), 4.58 (t, J = 7.8 Hz, 1H), 3.41 (dd, J = 13.7, 8.4 Hz, 2H), 3.13 (dd, J = 13.7, 7.3 Hz, 1H), 2.20 (s, 3H), 2.15 (s, 3H).
B43	LC-MS: [M-C2HF3O2+1] ⁺ =442.2, ¹ H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 12.24 (s, 1H), 8.95 (d, J = 1.2 Hz, 1H), 7.74 – 7.54 (m, 3H), 7.19 – 7.00 (m, 5H), 4.73 (t, J = 7.8 Hz, 1H), 3.40 (dd, J = 13.7, 8.1 Hz, 1H), 3.16 (dd, J = 13.6, 7.7 Hz, 1H), 2.89 (dd, J = 13.0, 7.0 Hz, 2H), 2.45 (s, 3H), 2.32 (dd, J = 9.1, 5.2 Hz, 2H), 2.20 (s, 3H), 2.07 (d, J = 9.8 Hz, 3H).
B44	LCMS: [M-C2HF3O2+1] ⁺ =389.2, ¹ H NMR (400 MHz, DMSO) δ 14.19 (s, 2H), 13.47 (s, 1H), 8.97 (d, J = 1.2 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.53 – 7.46 (m, 2H), 7.11 (dd, J = 6.7, 3.3 Hz, 2H), 7.09 – 7.04 (m, 1H), 4.75 (t, J = 7.9 Hz, 1H), 3.52 (dd, J = 13.6, 7.7 Hz, 1H), 3.28 (dd, J = 13.6, 8.0 Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H).
B45	[M-C2HF3O2+1] ⁺ =405.1, ¹ H NMR (400 MHz, DMSO) δ 14.21 (s, 2H), 13.29 (s, 1H), 8.96 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.16 – 7.01 (m, 4H), 4.74 (t, J = 7.9 Hz, 1H), 3.50 (d, J = 5.8 Hz, 1H), 3.29 – 3.22 (m, 1H), 2.19 (s, 3H), 2.05 (s, 3H).
B46	LC-MS: [M-C2HF3O2+1] ⁺ =385.2, ¹ H NMR (400 MHz, DMSO) δ 13.39 (d, J = 311.6 Hz, 3H), 8.45 (s, 1H), 7.90 (ddd, J = 14.7, 12.7, 8.3 Hz, 4H), 7.53 – 7.42 (m, 2H), 7.16 – 7.03 (m, 3H), 4.78 (t, J = 7.8 Hz, 1H), 3.52 (d, J = 3.5 Hz, 1H), 3.34 – 3.29 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H).
B47	LC-MS: [M-C2HF3O2+1] ⁺ =375.2, ¹ H NMR (400 MHz, DMSO+D2O) δ 8.85 (s, 1H), 7.54 (s, 1H), 7.12 – 7.03 (m, 3H), 6.90 (dt, J = 29.4, 10.6 Hz, 3H), 4.70 (td, J = 7.8, 2.8 Hz, 1H), 3.26 (dd, J = 13.9, 8.4 Hz, 1H), 3.07 (dd, J = 13.8, 7.2 Hz, 1H), 2.86 (dd, J = 16.7, 5.4 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.71 – 2.59 (m, 3H), 2.22 (s, 3H), 2.12 (t, J = 6.1 Hz, 3H), 2.04 (d, J = 12.7 Hz, 1H), 1.74 – 1.60 (m, 1H).

B48	[M-C2HF3O2+1] ⁺ =349.2, 1H NMR (400 MHz, DMSO) δ 14.22 (s, 2H), 12.61 (s, 1H), 8.95 (s, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.78 (s, 1H), 4.73 (t, J = 7.7 Hz, 1H), 3.42 – 3.37 (m, 1H), 3.18 – 3.11 (m, 1H), 2.32 (s, 3H), 2.17 (d, J = 3.1 Hz, 6H), 1.95 (s, 3H).
B49	LC-MS: [M-C2HF3O2+1] ⁺ =350.2, 1H NMR (400 MHz, DMSO) δ 14.08 (s, 2H), 8.95 (s, 1H), 7.60 (s, 1H), 7.10 – 6.92 (m, 4H), 5.07 (t, J = 7.6 Hz, 1H), 3.43 – 3.38 (m, 1H), 3.25 – 3.19 (m, 1H), 2.42 (s, 3H), 2.30 – 2.12 (m, 9H).
B50	[M-C2HF3O2+1] ⁺ =373.1/375.1, 1H NMR (400 MHz, DMSO) δ 14.18 (s, 3H), 8.95 (s, 1H), 7.59 (s, 1H), 7.23 – 7.06 (m, 5H), 4.78 (t, J = 7.9 Hz, 1H), 3.40 (dd, J = 13.9, 8.5 Hz, 1H), 3.21 (dd, J = 13.8, 7.4 Hz, 1H), 2.22 (s, 3H), 2.15 (s, 3H).
B51	LCMS: [M-C2HF3O2+1] ⁺ = 369.1/371.1, 1H NMR (400 MHz, DMSO) δ 14.17 (s, 3H), 8.96 (s, 1H), 7.61 (s, 1H), 7.19 – 6.96 (m, 5H), 4.75 (dd, J = 18.2, 10.3 Hz, 1H), 3.35 – 3.29 (m, 1H), 3.13 (dd, J = 13.9, 7.1 Hz, 1H), 2.22 (d, J = 9.7 Hz, 6H), 2.15 (s, 3H).
B52	LCMS: [M-C2HF3O2+1] ⁺ = 385.2, 1H NMR (400 MHz, DMSO) δ 14.16 (s, 2H), 13.01 (s, 1H), 8.94 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.75 – 7.59 (m, 4H), 7.49 – 7.43 (m, 1H), 7.16 (d, J = 6.9 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 6.9 Hz, 1H), 4.86 (t, J = 7.8 Hz, 1H), 3.59 – 3.53 (m, 1H), 3.38 – 3.32 (m, 1H), 2.81 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H).
B53	[M-C2HF3O2+1] ⁺ =385.2, 1H NMR (400 MHz, DMSO) δ 14.13 (s, 2H), 13.42 (s, 1H), 8.93 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.43 – 7.35 (m, 2H), 7.22 – 7.02 (m, 3H), 4.82 (t, J = 7.8 Hz, 1H), 3.52 (d, J = 5.3 Hz, 1H), 3.34 – 3.29 (m, 1H), 2.43 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H).

Biological Assays

Example 1. a2A AR FLIPR assay

This experimental protocol involved cell seeding and a FLIPR assay using the a2A AR 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 tests 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 DirectTM loading buffer
5 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.
10 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. The results were then fitted using specific models to determine EC₅₀ for agonists.

The experimental protocol utilized various reagents and apparatus, including Penicillin/Streptomycin (100x) (SV30010, Hyclone), Poly-L-lysine hydrobromide (P1399,
15 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. a₂A AR binding assay

The a₂A AR Binding Assay was conducted using a stable HEK293 cell line, specifically
20 constructed by WuXi AppTec for targeting a₂A AR. This assay primarily focused on the binding activity of the radioligand [3H]-RX 821002 (PerkinElmer, NET1153250UC) to a₂A AR, 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
25 (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
30 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 (0.5µg/well) and 100 µL 0.5nM 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 μ L 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- (Assay well Average_LC)/ (Average_HC-Average_LC)) * 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 α 2A AR.

The result of the α 2A AR FLIPR assay and binding assay result are listed in Table 3 below.

Table 3

Compound No.	α 2A AR agonist activity (EC50, nM)	α 2A AR affinity (Ki, nM)	Compound No.	α 2A AR agonist activity (EC50, nM)	α 2A AR affinity (Ki, nM)
A64	A	A	A178	A	
A70	A	A	A179	A	A
A73	A	A	A180	A	A
A73-A	A	A	A181	B	A
A73-B	A		A186	A	A
A79	B	A	A187	A	A
A80	A	A	A189		A
A81	A	A	A198	A	A
A82		D	A200	A	A
A84	A	A	A205	A	A
A86	A	A	A212	A	A
A87		B	A214	A	A
A88	B	A	A233	A	A
A89	B	A	A234	A	A
A90	B	B	A706		A
A91		B	A727	A	A
A94	B	B	A906	A	A
A95	A	A	A907	A	A
A96	A	A	B1	A	
A98	A	A	B1-A	D	
A98-A		C	B1-B	A	B
A98-B	A	A	B1-C	C	
A99	A	A	B1-D	A	A
A101	A	A	B2	A	A
A102	A	A	B3	A	B

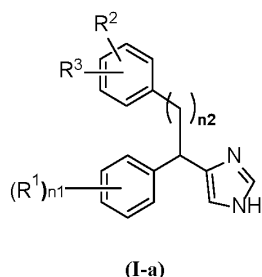
A103	A	A	B3-A	D	D
A104	A	A	B3-B	A	A
A105	A	A	B4		D
A107		B	B7	B	B
A108	A	A	B8	A	
A109	A	A	B8-A		D
A111	A	A	B8-B	A	
A112	A	A	B9	A	B
A112-A		C	B16	A	B
A112-B	A	A	B17		D
A113		B	B21	B	
A117	A	A	B22	B	
A119	A	A	B23	A	A
A120	A	A	B24	A	A
A121	A	A	B25	A	A
A121-A	D		B26	B	C
A121-B	A	A	B27	A	
A124	A	A	B28	A	A
A124-A	A	A	B29	B	
A124-B		C	B30	A	
A131		A	B31	A	B
A132		B	B32	C	
A134	A	A	B33	A	
A138	A	A	B34	A	B
A141	C	A	B35	A	A
A142	A	A	B36	B	
A143	B	A	B37	C	
A144		B	B38	A	B
A145	A	A	B39	A	A
A149	A	A	B39-A	D	
A151-A	A	A	B39-B	A	A
A151-B	A		B40	A	A
A152	A	A	B40-A	D	
A153	A	A	B40-B	A	A
A155-A	A	A	B41	A	A
A155-B	A		B41-A	D	
A157	A	A	B41-B	A	A
A157-A	D		B42	A	A
A157-B	A	A	B42-A	A	A
A158	A	A	B42-B	C	
A161	A	A	B43	A	A
A162	A	A	B44		B
A165	A	A	B45		B
A166	A	A	B46		B
A167	A	A	B47	B	
A169	A	A	B48	A	
A170	B		B49	B	
A171	A	A	B50	A	
A172	A		B51	A	

A173	A		B52	A	A
A176	A	A	B53	A	
A177	A	A			

A: <10nM
B: 10nM-50nM
C: 50nM-250nM
D: 250nM-1000nM
E: >1000nM

CLAIMS

1. A compound of formula (I-a):



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

each R^1 is independently selected from the group consisting of hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and $-COOH$;

R^2 is selected from the group consisting of hydrogen, halogen, and hydroxyl;

R^3 is selected from the group consisting of $-C(O)-NHR^4$, $-SO_2-NHR^4$, $-NH-C(O)-R^5$, 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 C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally substituted with one or more R^{4a} ;

each R^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and ketone;

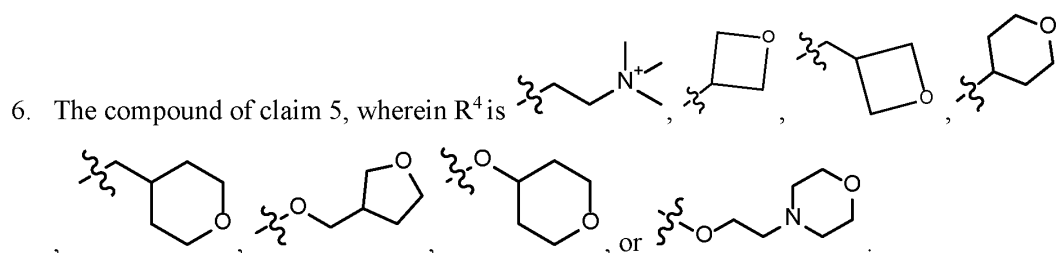
each R^{6a} is independently selected from the group consisting of $-C_{0-12}$ alkylene- C_{3-12} cycloalkyl, $-C_{0-12}$ alkylene- C_{2-12} heterocyclyl, and $-C_{0-12}$ alkylene- C_{1-12} heteroaryl; wherein each of the C_{3-12} cycloalkyl, C_{2-12} heterocyclyl, and C_{1-12} heteroaryl is optionally 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- $C(=S)-R^5$;

n_1 is 1 or 2; and

n_2 is 0 or 1.

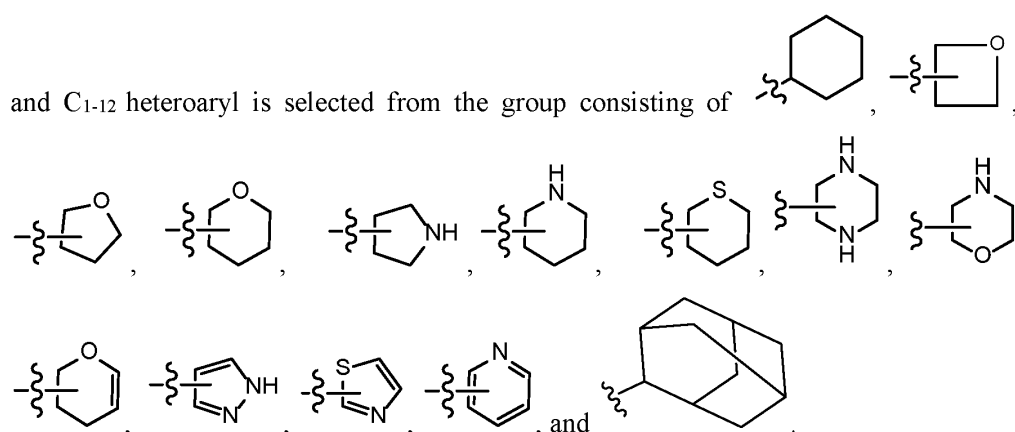
2. The compound of claim 1, wherein R¹ is alkyl, such as methyl.
3. The compound of claim 1 or 2, wherein n1 is 2.
4. The compound of any one of claims 1-3, wherein R² is hydrogen or halogen.
5. The compound of any one of claims 1-4, wherein R³ is -C(O)-NHR⁴ or -SO₂-NHR⁴, wherein R⁴ is -C₀₋₁₂ alkylene-NHR^{6a}, -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}.



7. The compound of any one of claims 1-6, wherein 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}.

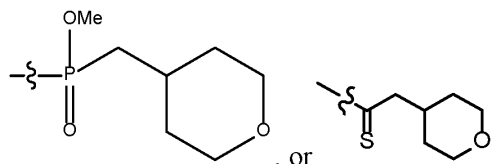
8. The compound of claim 7, wherein R⁵ is alkyl substituted with trialkylammonium.

9. The compound of claim 7, when R⁵ is -C₀₋₁₂ alkylene-C₃₋₁₂ cycloalkyl, -C₀₋₁₂ alkylene-C₂₋₁₂ heterocyclcyl, or -C₀₋₁₂ alkylene-C₁₋₁₂ heteroaryl, the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclcyl,

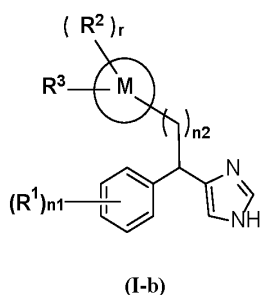


10. The compound of claim 9, wherein each of the C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, and C₁₋₁₂ heteroaryl is substituted with one or more R^{4a}, and R^{4a} is hydroxyl, methyl, oxo, or -C(O)-Me.
11. The compound of any one of claims 1-10, wherein R³ is -NH-R⁷, and R⁷ is C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-N(R⁴)-SO₂-R⁵, -C₀₋₁₂ alkylene-P(=O)(R⁴)(alkoxy), or -C₀₋₁₂ alkylene-C(=S)-R⁵.

12. The compound of claim 11, wherein R⁷ is



13. A compound of formula (I-b):



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

each R¹ is independently selected from the group consisting of hydrogen, halogen, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkyl, and -COOH;

ring M is C₃₋₁₂ cycloalkyl, C₂₋₁₂ heterocyclyl, C₆₋₁₂ aryl, or C₁₋₁₂ heteroaryl;

R² is selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, haloalkyl, and haloalkoxy;

R³ is selected from the group consisting of -C₀₋₁₂ alkylene-COOH, -C₁₋₁₂ heteroaryl, -C₀₋₁₂ alkylene-P(=O)(R⁴)(R⁴), and -(SO₂)₀₋₁-NH-C₀₋₁₂ alkylene-COOH; wherein the -C₀₋₁₂ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino, and the C₁₋₁₂ heteroaryl is optionally substituted with one or more R^{4a};

each R^{4a} is independently selected from the group consisting of hydroxy, alkyl, oxo, and ketone;

each of R^4 and $R^{4'}$ is independently hydrogen, alkyl, alkoxy, $-C_{0-12}$ alkylene- $N(R^{6a})_t$, $-C_{0-12}$ 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, wherein 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} ;

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

each R^{6a} is independently selected from the group consisting of 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, 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} ;

n_1 is 1 or 2;

n_2 is 1 or 2;

$r = 0, 1, \text{ or } 2$; and

t is 2 or 3.

14. The compound of claim 13, wherein R^1 is alkyl, such as methyl.
15. The compound of claim 13 or 14, wherein n_1 is 2.
16. The compound of any one of claims 13-15, wherein M is C_{6-12} aryl or C_{1-12} heteroaryl, such as phenyl, thiophenyl, pyrimidinyl, pyridinyl, or naphthyl.
17. The compound of any one of claims 13-15, wherein M is C_{3-12} cycloalkyl or C_{2-12} heterocyclyl, such as cyclopentyl, cyclohexyl, pyrrolidinyl, indolinyl, or 2,3-dihydro-1H-indenyl.
18. The compound of any one of claims 13-17, wherein n_2 is 1.
19. The compound of any one of claims 13-18, wherein R^2 is hydrogen, halogen, alkyl, hydroxy, haloalkyl, or haloalkoxy.
20. The compound of any one of claims 13-19, wherein at least one R^2 is alkyl, haloalkyl, or haloalkoxy.
21. The compound of any one of claims 13-20, wherein R^3 is $-C_{0-12}$ alkylene-COOH, and the $-C_{0-12}$ alkylene-COOH is optionally substituted with one or more substitutes chosen from amino and alkylamino.

22. The compound of any one of claims 13-20, wherein R^3 is $-C_{1-12}$ heteroaryl that is optionally substituted with one or more R^{4a} .
23. The compound of any one of claims 13-20, wherein R^3 is $-C_{0-12}$ alkylene- $P(=O)(R^4)(R^{4'})$.
24. The compound of any one of claims 13-20, wherein R^3 is $-(SO_2)_{0-1}-NH-C_{0-12}$ alkylene-COOH.
25. A compound chosen from Table 1, or a stereoisomer, tautomer, pharmaceutically acceptable salt or a solvate thereof.
26. A pharmaceutical composition comprising the compound of any one of preceding claims, and a pharmaceutically acceptable carrier.
27. 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 1-25 or the pharmaceutical composition of claim 26.
28. The method of claim 24, wherein the disease is pain, glaucoma, spasticity, nasal congestion, rosacea, rhinitis, anesthesia, presbyopia, acute kidney injury, insomnia, inflammatory disease, or cancer.
29. A method of activating alpha2 adrenergic receptor ($\alpha 2AR$) in a subject in need thereof, the method comprising administering to the subject the compound of any one of claims 1-25 or the pharmaceutical composition of claim 26.